

Decarboxylative C–C and C–N Bond Formation via Ligand-Accelerated Iron Photocatalysis

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ABSTRACT: Through iron photocatalysis, a mild and effective protocol for the decarboxylative C–C and C–N bond formation has been achieved. The carboxylic acids readily underwent radical decarboxylation in the presence of Fe₂(SO₄)₃ and di-(2-picolyl)amine with visible light irradiation. The resultant alkyl radicals then reacted with Michael acceptors or azodicarboxylates to furnish the adducts.

Since iron is the second most abundant metal on earth, a vast array of seminal work (prior 1970) in the area of the photochemistry and photophysics was based upon its complexes.¹ More recently, Ru(II) and Ir(III) homoleptic and heteroleptic complexes have gained prominence as photocatalysts in organic transformation, thanks to their long-lived excited states.² The latter profiles provided opportunities for photoredox catalysis to activate organic compounds via intermolecular single-electron transfer (SET) pathway.³ Chemists have had a long-standing interest in replacing the precious metals in photoactive coordination complexes with earth-abundant elements.⁴ Particularly in recent years, there is increasing awareness of green chemistry principles and practice in both academic labs and industrial setting.⁵ However, the photoexcitable charge-transfer states of most iron complexes were deactivated through low-lying metal-centered states at picosecond time scale, resulting in inefficient electron-transfer reactivity. Despite that, the Cozzi, and Collins groups achieved high-level application of [Fe(bpy)₃]Br₂ and [Fe(phen)₃](NTf₂)₂ in photocatalysis.⁶ Increasing the ligand field strength can raise energies of the metal-centered states. Recently, the use of strong donor ligands such as *N*-heterocyclic carbenes (NHCs) to increase the excited state lifetimes of iron complexes has become a fruitful strategy. The Wärnmark group successfully synthesized an Fe(III) complex with a relatively long-lived (2 nanosecond) doublet ligand-to-metal charge-transfer (²LMCT) state.⁷ In combination with advances from other research groups,⁸ it renders iron photoredox catalysis a promising area for further development. On the other side, the intramolecular charge-transfer mode via coordination of organic substrates directly to iron species is also catching chemists' attention (Figure 1A). In this approach, long-lived excited states of iron complexes are not necessarily essential. Parker firstly reported the photo-induced decarboxylation of ferrioxalate in 1953.⁹ Following that, the mechanism of the Fe(III) photoreduction, which is accompanied by degradation of the carboxylate lig-

and, has been investigated intensively.¹⁰ Nevertheless, the photoreactivity of the Fe(III) carboxylate complexes so far has been rarely recognized in synthetic organic chemistry. Therefore, we envisioned to take advantage of the photoreactivity of the Fe(III) carboxylates and use the resultant alkyl radicals from this process to realize various C–C and C–N bond formation reactions.

Radical decarboxylative alkylation strategy sounds appealing in practical application since carboxylic acids are typically stable, inexpensive, and non-toxic, and are the second largest group only after amines among commercially available organic building blocks (Figure 1B).¹¹ The approaches for radical decarboxylation could be traced back to 1848 when Kolbe reported the first electrochemical decarboxylation (Figure 1B, path A).¹² Ag-mediated decarboxylation is another classic method employed extensively (Figure 1B, path B).¹³ Since the last decade, several photochemical alternatives for decarboxylation have been developed using visible light.¹⁴ In 2014, MacMillan published a decarboxylative arylation with iridium photocatalyst (Figure 1B, path C).¹⁵ In 2019, König reported a cerium photocatalyzed decarboxylative hydrazination via ligand-to-metal charge transfer (LMCT) pathway (Figure 1B, path D).¹⁶

We have been pursuing visible light-promoted organic synthesis for years.¹⁷ The earth-abundant iron offers an inexpensive and sustainable alternative to precious metals like silver and iridium. Very recently, we developed an iron photocatalytic decarboxylation method for the alkylation of heteroarenes (Figure 1C).¹⁸ In this preliminary work, however, an excess amount of the carboxylic acid was used to achieve a high level of reactivity, and it required a terminal oxidant to turn over the Fe(II)/Fe(III) catalytic cycle. We wondered if a redox-neutral process with higher decarboxylation efficiency could be achieved by the ligand modulation. Herein, we describe on the latest progress from our lab in iron photocatalysis, and its ap-

plication to the decarboxylative C–C and C–N bond formation.^{19,20}

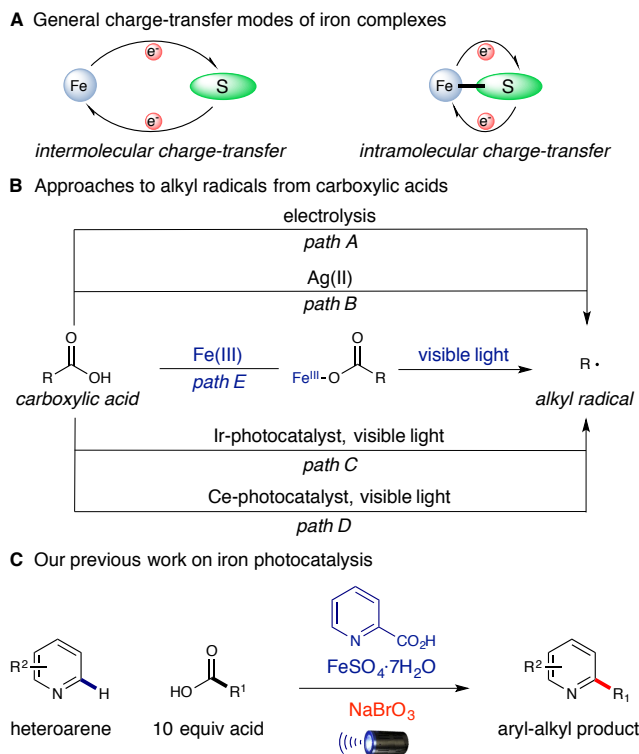
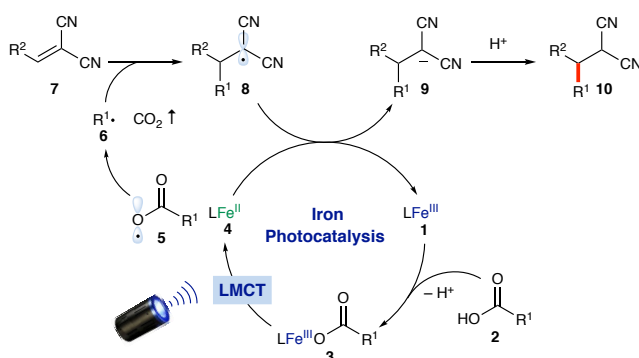


Figure 1. Photochemistry of Iron Complexes.

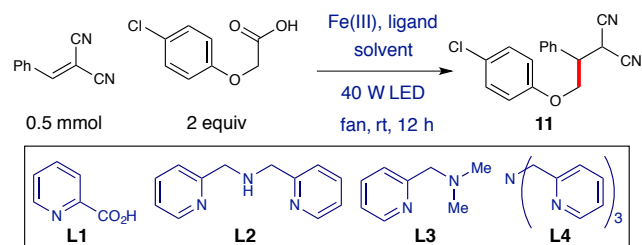
A detailed description of the possible mechanism for decarboxylative C–C bond formation is outlined in Scheme 1. We expected that Fe(III) **1** would coordinate with a carboxylic acid **2** to form Fe(III)-carboxylate complex **3**. Upon visible light irradiation, iron complex **3** should get photoexcited and an intramolecular charge-transfer event would occur to generate reduced Fe(II) **4**.⁹ At the meantime, it afforded carboxyl radical **5** which after CO₂ extrusion would furnish desired alkyl radical **6**. The nucleophilic alkyl radical **6** then could react with Michael acceptor **7** to provide the electron-deficient radical adduct **8**, which should be capable of oxidizing Fe(II) back to Fe(III) to close the catalytic cycle. Finally, the resultant anion **9** could be protonated to yield the desired alkylated product **10**.

Scheme 1. Possible Mechanism for the Decarboxylative C–C Bond Formation



We started our exploration into this decarboxylative C–C bond formation with 2-(4-chlorophenoxy)acetic acid and 2-benzylidenemalononitrile as the model substrates, with Kessil 40 W 427 nm LED lamps as the visible light source in the presence of Fe₂(SO₄)₃ (Table 1). Surprisingly, with 2-picolinic acid **L1**, the superior ligand for our previous work, there was no desired product (entries 1 and 2). Then we tried the other 2-substituted pyridines as the ligand. To our delight, a dramatic ligand acceleration effect was observed (entries 3–6). It afforded the alkylation product **11** in quantitative yield when ligand **L2** was added into the reaction at 1:1 ratio of iron to ligand. The high yield was maintained with 2 equivalents of **L2**. Ligand **L3** furnished a 95% yield while ligand **L4** only rendered the transformation moderately. The critical roles of iron, ligand and light were demonstrated through the control experiments (entries 7–9). The reduction of the amount of carboxylic acid to 1 equivalent still resulted in a satisfactory yield (79%) (entry 10). Moreover, the reaction also proceeded smoothly in MeCN and DMSO (entries 11 and 12).

Table 1. Optimization of the Reaction Conditions^a

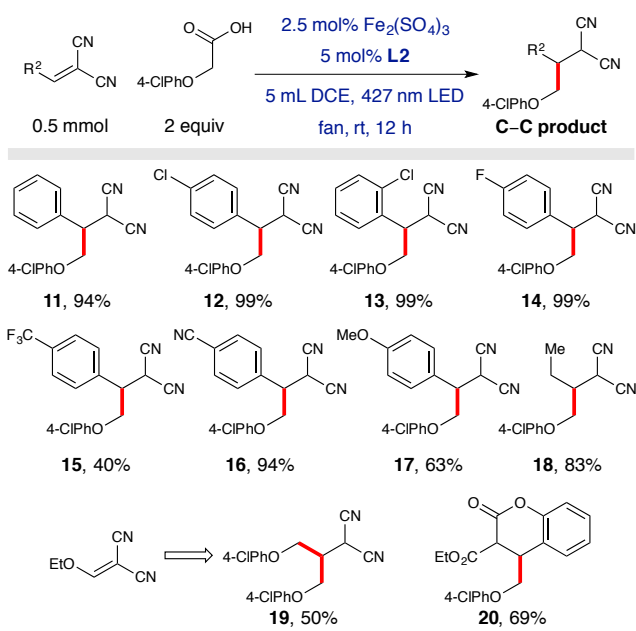


entry	Fe ₂ (SO ₄) ₃	ligand	solvent	wavelength	yield [%]
1	2.5 mol %	L1 (5%)	DCE (5 mL)	427 nm	0
2	2.5 mol %	L1 (10%)	DCE (5 mL)	427 nm	0
3	2.5 mol %	L2 (5%)	DCE (5 mL)	427 nm	99
4	2.5 mol %	L2 (10%)	DCE (5 mL)	427 nm	99
5	2.5 mol %	L3 (5%)	DCE (5 mL)	427 nm	95
6	2.5 mol %	L4 (5%)	DCE (5 mL)	427 nm	35
7	–	L2 (5%)	DCE (5 mL)	427 nm	0
8	2.5 mol %	–	DCE (5 mL)	427 nm	0
9	2.5 mol %	L2 (5%)	DCE (5 mL)	dark	0
10 ^b	2.5 mol %	L2 (5%)	DCE (5 mL)	427 nm	79
11	2.5 mol %	L2 (5%)	MeCN (5 mL)	427 nm	93
12	2.5 mol %	L2 (5%)	DMSO (5 mL)	427 nm	80

^aYields determined by ¹H NMR using 1,3-benzodioxole as the internal standard. ^b1 equiv carboxylic acid used.

Upon identification of the optimal conditions, we began to evaluate the generality of this decarboxylative radical addition protocol. As shown in Scheme 2, a broad array of Michael acceptors can be alkylated in this reaction. 2-Benzylidenemalononitriles with electron-withdrawing and -donating substituents on the phenyl ring were well tolerated (**11**–**17**). 2-Alkylidenemalononitriles also could participate in this transformation effectively (**18**). Interestingly, when 2-(ethoxymethylene)malononitrile was subjected to the reaction conditions, the first alkylation sequence was followed by elimination of EtOH and then a second alkyl addition to furnish the bis-alkylated product **19**. Moreover, malonate-type Michael acceptors could readily undergo the alkylation in good yield (**20**).

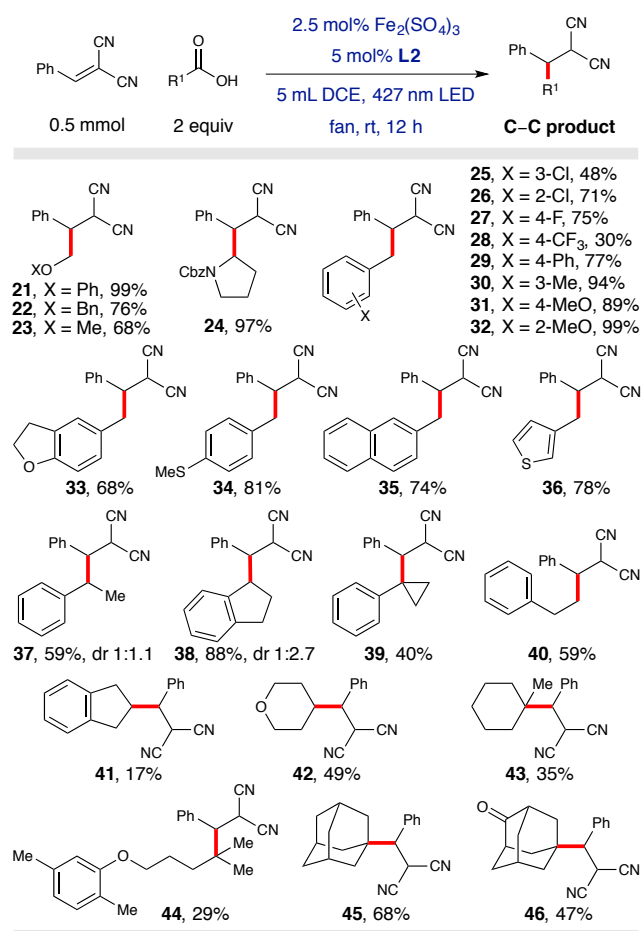
Scheme 2. Scope of the Michael Acceptors^a



^aIsolated yields, see Supporting Information for details.

Next, we investigated the scope of the radical C–C bond formation with regard to the carboxylic acids (Scheme 3). A broad array of cyclic and acyclic alkyl radical precursors could be employed with good levels of efficiency. The α -oxy and -amino acids provided the corresponding conjugate adducts in good to excellent yields (**21–24**). A variety of α -aryl acetic acids readily participated in this decarboxylative addition effectively (**25–36**). Importantly, secondary and tertiary benzyl radicals were compatible with the reaction conditions (**37–39**). It is gratifying that unactivated carboxylic acids are amenable to the decarboxylative addition through the generation of primary, secondary and tertiary alkyl radicals (**40–46**).

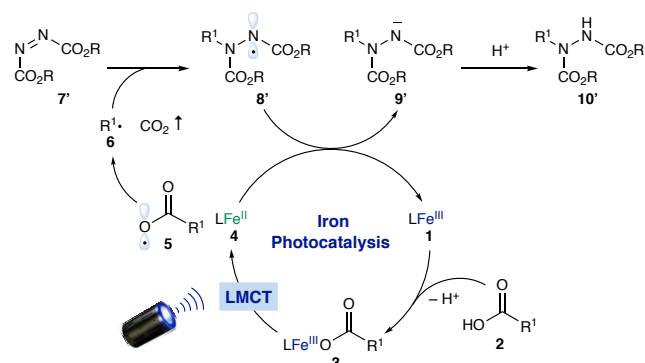
Scheme 3. Scope of the Carboxylic Acids^a



^aIsolated yields, see Supporting Information for details.

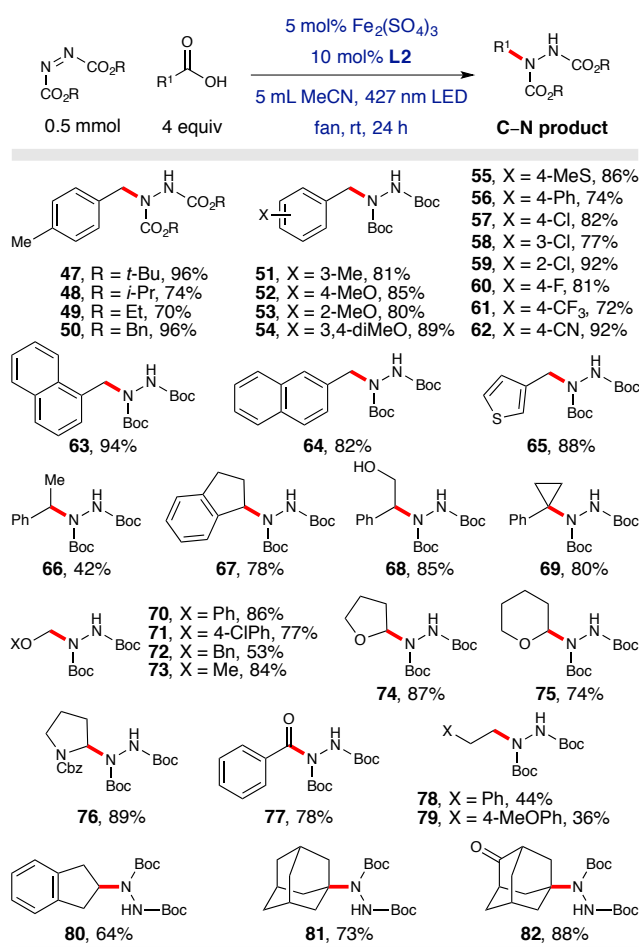
Within the realm of organic chemistry, the construction of C–N bonds has been in the spotlight for decades owing to the prevalence of nitrogen-containing motifs in a diverse range of pharmaceuticals, natural products and functional materials. Encouraged by the results of decarboxylative C–C bond formation, we sought to apply this iron photocatalytic method to C–N bond formation. We started the exploration into this transformation with azodicarboxylates as the nitrogen source, which should share a similar mechanism with the C–C bond formation reaction (Scheme 4).

Scheme 4. Possible Mechanism for the Decarboxylative C–N Bond Formation



After the identification of optimal conditions for the C–N bond formation (see Supporting Information), we examined the generality of this decarboxylative amination by investigating the scope of azodicarboxylates and carboxylic acids (Scheme 5). The four common dialkyl azodicarboxylates were converted into the corresponding *N*-benzylated hydrazine products effectively (**47–50**). α -Aryl acetic acids with various substituents readily underwent the decarboxylative amination with di-*tert*-butyl azodicarboxylate (DTBAD) in high yields (**51–65**). Moreover, secondary and tertiary benzyl radicals were compatible with the reaction conditions (**51–69**). The α -oxy, -amino and -oxo acids afforded the hydrazine products in good to high yields (**70–77**). Notably, unactivated carboxylic acids also performed well in this C–N bond formation protocol (**78–82**).

Scheme 5. Scope of the Azodicarboxylates and Carboxylic Acids for the C–N Bond Formation^a



^aIsolated yields, see Supporting Information for details.

The results of preliminary mechanistic studies (see Supporting Information) well supported the possible mechanism outlined in Schemes 1 and 4. The free radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) completely inhibited the decarboxylative alkylation, indicating a radical mechanism (Figure S1A). The constant irradiation of visible light was necessary to drive the alkylation to completion, which was demonstrated by the light on/off experiments using alternating

intervals of light on and off (Figure S1B). The UV-vis spectra illustrated that the solution of 1:1 iron and ligand exhibited a significant optical absorption in the visible range while the iron salt or ligand had minimal absorption of visible light separately (Figure S1C). We speculate that the redox potentials of iron salts should be modulated by the ligand coordination after light absorption. Control experiments with related transition metal salts such as Mn(III), Ni(II), Co(III), Cu(II), and Ru(III) showed no reactivity (Figure S2). Further investigation into the precise role of ligands are undergoing in our lab.

In conclusion, a mild and effective protocol for the decarboxylative radical C–C and C–N bond formation has been achieved via iron photocatalysis. The broad scopes with respect to both the carboxylic acids and the alkyl radical acceptors have been demonstrated. Different from the oxidative procedure reported by us previously, the current protocol is redox-neutral and it shows that the oxidation of Fe(II) back to Fe(III) by the electron-deficient radical intermediates should be feasible. Moreover, the amount of carboxylic acid can be reduced significantly under the Fe₂(SO₄)₃/di-(2-picolyl)amine system.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the website.

General experimental procedures, mechanistic studies, reaction setup, characterization data and spectra for all key compounds (PDF).

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) (a) Balzani, V.; Carassiti, V. *Photochemistry of Coordination Compounds*; Academic Press: New York: 1970. (b) Šima, J.; Makáňová, J. Photochemistry of Iron(III) Complexes. *Coord. Chem. Rev.* **1997**, *160*, 161-189. (c) Chen, J.; Browne, W. R. Photochemistry of Iron Complexes. *Coord. Chem. Rev.* **2018**, *374*, 15-35.
- (2) Balzani, V.; Ceroni, P.; Juris, A. *Photochemistry and Photophysics*; Wiley-VCH; Weinheim: 2014.
- (3) (a) Stephenson, C. R. J.; Yoon, T. P.; MacMillan, D. W. C. *Visible Light Photocatalysis in Organic Chemistry*; Wiley-VCH; Weinheim: 2018. (b) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Visible-Light

- Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem. Int. Ed.* **2018**, *57*, 10034-10072.
- (4) (a) Larsen, C. B.; Wenger, O. S. Photoredox Catalysis with Metal Complexes Made from Earth-Abundant Elements. *Chem. Eur. J.* **2018**, *24*, 2039-2058. (b) Wenger, O. S. Photoactive Complexes with Earth-Abundant Metals. *J. Am. Chem. Soc.* **2018**, *140*, 13522-13533. (c) Qiao, Y.; Schelter, E. J. Lanthanide Photocatalysis. *Acc. Chem. Res.* **2018**, *51*, 2926-2936. (d) Hockin, B. M.; Li, C.; Robertson, N.; Zysman-Colman, E. Photoredox Catalysts Based on Earth-Abundant Metal Complexes. *Catal. Sci. Technol.* **2019**, *9*, 889-915. (e) Wenger, O. S. Is Iron the New Ruthenium. *Chem. Eur. J.* **2019**, *25*, 6043-6052. (f) Hossain, A.; Bhattacharyya, A.; Reiser, O. Copper's Rapid Ascent in Visible-Light Photoredox Catalysis. *Science* **2019**, *364*, eaav9713. (5) Horváth, I. T.; Anastas, P. T. Innovations and Green Chemistry. *Chem. Rev.* **2007**, *107*, 2169-2173.
- (6) (a) Gualandi, A.; Marchini, M.; Mengozzi, L.; Natali, M.; Lucarini, M.; Ceroni, P.; Cozzi, P. G. Organocatalytic Enantioselective Alkylation of Aldehydes with [Fe(bpy)₃]Br₂ Catalyst and Visible Light. *ACS Catal.* **2015**, *5*, 5927-5931. (b) Parisien-Collette, S.; Hernandez-Perez, A. C.; Collins, S. K. Photochemical Synthesis of Carbazoles Using an [Fe(phen)₃](NTf₂)₂/O₂ Catalyst System: Catalysis toward Sustainability. *Org. Lett.* **2016**, *18*, 4994-4997. (c) Gualandi, A.; Mengozzi, L.; Cozzi, P. G. Iron-Promoted Radical Reactions: Current Status and Perspectives. *Asian. J. Org. Chem.* **2017**, *6*, 1160-1179.
- (7) Kjær, K. S.; Kaul, N.; Prakash, O.; Chábera, P.; Rosemann, N. W.; Honarfar, A.; Gordivska, O.; Fredin, L. A.; Bergquist, K.-E.; Häggström, L.; Ericsson, T.; Lindh, L.; Yartsev, A.; Styring, S.; Huang, P.; Uhlig, J.; Bendix, J.; Strand, D.; Sundström, V.; Persson, P.; Lomoth, R.; Wärnmark, K. Luminescence and Reactivity of a Charge-Transfer Excited Iron Complex with Nanosecond Lifetime. *Science* **2019**, *363*, 249-253.
- (8) Liu, L.; Duchanois, T.; Etienne, T.; Monari, A.; Beley, M.; Assfeld, X.; Haacke, S.; Gros, P. C. A New Record Excited State ³MLCT Lifetime for Metalorganic Iron(II) Complexes. *Phys. Chem. Chem. Phys.* **2016**, *18*, 12550-12556.
- (9) (a) Parker, C. A. A New Sensitive Chemical Actinometer. I. Some Trials with Potassium Ferrioxalate. *Proc. R. Soc. Lond. A* **1953**, *220*, 104-116. (b) Hatchard, C. G.; Parker, C. A. A New Sensitive Chemical Actinometer. II. Potassium Ferrioxalate as a Standard Chemical Actinometer. *Proc. R. Soc. Lond. A* **1956**, *235*, 518-536.
- (10) (a) Weller, C.; Horn, S.; Herrmann, H. Photolysis of Fe(III) Carboxylate Complexes: Fe(III) Quantum Yields and Reaction Mechanisms. *J. Photochem. Photobiol. A Chem.* **2013**, *268*, 24-36. (b) O'Neil, G. C.; Miaja-Avila, L.; Joe, Y. II; Alpert, B. K.; Balasubramanian, M.; Sagar, D. M.; Doriese, W.; Fowler, J. W.; Fullagar, W. K.; Chen, N.; Hilton, G. C.; Jimenez, R.; Ravel, B.; Reintsema, C. D.; Schmidt, D. R.; Silverman, K. L.; Swetz, D. S.; Uhlig, J.; Ullom, J. N. Ultrafast Time-Resolved X-ray Absorption Spectroscopy of Ferrioxalate Photolysis with a Laser Plasma X-ray Source and Microcalorimeter Array. *J. Phys. Chem. Lett.* **2017**, *8*, 1099-1104. (c) Mangiante, D. M.; Schaller, R. D.; Zarzycki, P.; Banfield, J. F.; Gilbert, B. Mechanism of Ferric Oxalate Photolysis. *ACS Earth Space Chem.* **2017**, *1*, 270-276. (d) Vernia, J. E.; Warmin, M. R.; Krause, J. A.; Tierney, D. L.; Baldwin, M. J. Photochemistry and Anion-Controlled Structure of Fe(III) Complexes with an α -Hydroxy Acid-Containing Tripodal Amine Chelate. *Inorg. Chem.* **2017**, *56*, 13029-13034. (e) Straub, S.; Brünker, P.; Lindner, J.; Vöhringer, P. An Iron Complex with a Bent, O-Coordinated CO₂ Ligand Discovered by Femtosecond Mid-Infrared Spectroscopy. *Angew. Chem. Int. Ed.* **2018**, *57*, 5000-5005.
- (11) Kalliokoski, T. Price-Focused Analysis of Commercially Available Building Blocks for Combinatorial Library Synthesis. *ACS Comb. Sci.* **2015**, *17*, 600-607.
- (12) Vijh, A. K.; Conway, B. E. Electrode Kinetic Aspects of the Kolbe Reaction. *Chem. Rev.* **1967**, *67*, 623-664.
- (13) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinunno, M. Nucleophilic Character of Alkyl Radicals-VI: A New Convenient Selective Alkylation of Heteroaromatic Bases. *Tetrahedron*, **1971**, *27*, 3575-3579.
- (14) (a) Xuan, J.; Zhang, Z.-G.; Xiao, W.-J. Visible-Light-Induced Decarboxylative Functionalization of Carboxylic Acids and Their Derivatives. *Angew. Chem. Int. Ed.* **2015**, *54*, 15632-15641. (b) Schwarz, J.; König, B. Decarboxylative Reactions with and without Light – A Comparison. *Green Chem.* **2018**, *20*, 323-361.
- (15) Zuo, Z.; MacMillan, D. W. C. Decarboxylative Arylation of α -Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014**, *136*, 5257-5260.
- (16) Yatham, V. R.; Bellotti, P.; König, B. Decarboxylative Hydrazination of Unactivated Carboxylic Acids by Cerium Photocatalysis. *Chem. Commun.* **2019**, *55*, 3489-3492.
- (17) (a) Zhao, H.; Jin, J. Visible Light-Promoted Aliphatic C-H Arylation Using Selectfluor as a Hydrogen Atom Transfer Reagent. *Org. Lett.* **2019**, *21*, 6179-6184. (b) Zhao, H.; Li, Z.; Jin, J. Green Oxidant H₂O₂ as a Hydrogen Atom Transfer Reagent for Visible Light Mediated Minisci Reaction. *New J. Chem.* **2019**, *43*, 12533-12537.
- (18) Li, Z.; Wang, X.; Xia, S.; Jin, J. Ligand-Accelerated Iron Photocatalysis Enabling Decarboxylative Alkylation of Heteroarenes. *Org. Lett.* **2019**, *21*, 4259-4265.
- (19) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of (\pm)-Pregabalin. *J. Am. Chem. Soc.* **2014**, *136*, 10886-10889.
- (20) (a) Lang, S. B.; Cartwright, K. C.; Welter, R. S.; Locascio, T. M.; Tunge, J. A. Photocatalytic Aminodecarboxylation of Carboxylic Acids. *Eur. J. Org. Chem.* **2016**, 3331-3334. (b) Zhang, M.-J.; Schroeder, G. M.; He, Y.-H.; Guan, Z. Visible Light-Mediated decarboxylative Amination of Indoline-2-Carboxylic Acids Catalyzed by Rose Bengal. *RSC Adv.* **2016**, *6*, 96693-96699.