Iron(III)-Mediated Rapid Radical-Type Three-Component Deuteration of Quinoxalinones With Olefins and NaBD\textsubscript{4}

Wanmei Li*\textsuperscript{,} Heng Cai, Lin Huang, Lei He, Yilan Zhang, Jun Xu and Pengfei Zhang

College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou, China

Iron(III)-promoted rapid three-component deuteration of quinoxalinones with olefins and NaBD\textsubscript{4} is reported for the first time, which provides a novel, economic, and efficient method for the rapid synthesis of deuterated quinoxalinones. In this transformation, a radical pathway is involved according to the results of control experiments.

Keywords: deuteration, quinoxalinones, alkenes, three-component, radical pathway

INTRODUCTION

In recent years, deuterium-labeled compounds have received much attention because they play an important role in studying chemical and biological processes (Mutlib, 2008; Gómez-Gallego and Sierra, 2011; Konermann et al., 2011; Simmons and Hartwig, 2012; Atzrodt et al., 2018; Pirali et al., 2019). The incorporation of deuterium is a very efficient strategy not only to measure the kinetic isotope effect and track the reaction path in synthetic chemistry but also to change the absorption, distribution, metabolism, and excretion (ADME) properties of drug candidates in pharmaceutical chemistry (Atzrodt et al., 2007; Meanwell, 2011; Guengerich, 2012; Katsnelson, 2013; Gant, 2014). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018). Since the first deuterated drug, deutetrabenazine, for the treatment of chorea associated with Huntington’s disease was approved by the Food and Drug Administration in 2017 (Schmidt, 2017), which clearly proved a route for the development of deuterated drugs in clinical medicine (Scheme 1A) (Junk and Catallo, 1997; Gowrisankar et al., 2012; Tolnai et al., 2014; Ray et al., 2018), considerable interests have been devoted to developing novel and efficient methods for the synthesis of such compounds (Yu et al., 2016; Kerr et al., 2017; Liang et al., 2017; Ray et al., 2018).
In 2019, Wasa and coworkers demonstrated a B(C₆F₅)₃-catalyzed α-deuteration of carbonyl compounds with D₂O, providing an efficient protocol for the synthesis of deuterium labeling carbonyl-based pharmaceuticals (Chang et al., 2020). Despite their utilities, there is still a substantial interest in developing novel and efficient methods for the synthesis of such organic compounds.

Multicomponent reactions have become a hot field in modern organic chemistry in recent years because multicomponent reaction can form multiple chemical bonds in one step in comparison with the traditional synthesis method, thus realizing the simple, efficient, and atomic economic synthesis of structural diversity compounds. Quinoxalines and their derivatives are one of the important organic compounds because they have been widely applied in organic synthesis, material chemistry, agrochemical industries, and pharmaceutical chemistry (TenBrink et al., 1994; Monge et al., 1995; Badran et al., 2003; Refaat et al., 2004; Hoogewijs et al., 2013; Nakane et al., 2015; Renault et al., 2017). Although a plenty of two-component reactions for the synthesis of quinoxalinones were achieved (Hong et al., 2019; Jin et al., 2019; Ke et al., 2019; Liu et al., 2019; Wang et al., 2019, 2020; Wei et al., 2019; Xie et al., 2019; Xue et al., 2019; Yan et al., 2019; Zhang H. et al., 2019; Zhang W. et al., 2019; Bao et al., 2020).

Multicomponent transformations were rarely reported. In 2019, Studer and coworkers demonstrated a visible-light-initiated three-component reaction of quinoxalinones, olefins, and perfluoroalkyl iodides (Zheng and Studer, 2019). In the same year, Koley’s group disclosed a metal-free domino three-component radical cascade reaction of quinoxalinones, olefins, and sulfonic acids (Dutta et al., 2019).

We also achieved a useful method for the rapid synthesis of quinoxalinone-containing organoazides using three-component cascade reaction of quinoxalinones with olefins and TMSN₃ (Shen et al., 2020). Keeping on our interests in developing simple
and efficient methods for the synthesis of quinoxalinones (Xu et al., 2019; Zhang H. et al., 2019; Shen et al., 2020), herein, we demonstrated a radical-type three-component deuteration of quinoxalinones with olefins and NaBD₄ mediated by Fe(NO₃)₃•9H₂O for the first time (Scheme 1C).

RESULTS AND DISCUSSION

Initially, we commenced three-component deuteration of quinoxalinones by the reaction of 1-methylquinoxalin-2(1H)-one (1a), 2.0 equiv of styrene (2a), 1.0 equiv of NaBD₄ (3) 4.0 equiv of Fe(NO₃)₃•9H₂O in ethanol at room temperature for 10 min, providing the desired product 4a in 55% yield (Table 1, entry 1). This reaction could not take place if other solvents (MeCN, dichloromethane (DCM), dioxane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO)) [Table 1, entries 2–6] or catalysts (Table 1, entries 12–17) [FeBr₃, CuCl₂, CuO, (NH₄)₂Ce(NO₃)₆, Fe₂(ox)₃, FeF₃], or no catalyst (Table 1, entry 18) were used. However, it surprised us that using the mixed solvent of ethanol and acetonitrile (v/v = 1:1) could improve the reaction yield to 65% (Table 1, entry 7 among entries 7–11). Subsequently, the dosage of styrene 2a and NaBD₄ 3 were screened (Table 1, entries 19–23). The yield was decreased to 40% when amount of 2a was reduced from 2.0 to 1.0 equiv (Table 1, entry 19). By increasing the amount of NaBD₄ 3 from 1.0 to 2.0 equiv, a highest yield (73%) was observed (Table 1, entry 23). Furthermore, the product yield could also not be further improved no matter changing the amount of Fe(NO₃)₃•9H₂O (Table 1, entries 24–25) or reaction time (Table 1, entries 26–27). Thus, the highest yield could be obtained when the mixture of 1-methylquinoxalin-2(1H)-one (1a), 2.0 equiv of styrene (2a), 2.0 equiv of NaBD₄ (3) in EtOH/CH₃CN (4.0 ml, v/v = 1:1) were reacted at 4.0 equiv of Fe(NO₃)₃•9H₂O as oxidant at room temperature for 10 min.

With the optimized reaction conditions in hand, the substrate scope of the three-component deuteration was subsequently explored by using various quinoxalinones (1) with styrene (2a) and NaBD₄ (3) (Table 2). To our delight, a wide range of N-protecting groups including N-methyl, N-ethyl, N-buty1, N-cyclopropylmethyl, and N-esterly groups could work well under standard conditions, affording the target products (4a–4e) in 70–77% yields. Quinoxalinones with various N-benzyl groups or the methoxyl, chloro, bromo, and methyl groups on the benzene ring were also tolerated in this reaction, as demonstrated with products 4f–4q, or 4r–4u in good yields. It was noteworthy that the N-free protecting quinoxalino1ne was also suitable for the transformation; the product (4v) was obtained in 66% yield. Unfortunately, other N-heterocycles, such as theophylline and 4-hydroxyquinazoline, could not undergo the reaction (see SI).

Some other olefins were then tested by the reaction with 1-methylquinoxalin-2(1H)-one (1a) and NaBD₄ (3) (Table 3). It was found that aromatic olefins bearing electron-rich or electron-poor substituents (4aa–4ai) could react smoothly, affording the desired products in good yields. The transformation with nonfunctionalized olefin was also successful, giving the corresponding product 4aj in 75% yield. The multiple substituted olefin (4ak) and cyclic olefin (4al) were also compatible, providing the target products in 60 and 76% yields, respectively (Tang et al., 2015; Yi et al., 2017). In addition, olefins with various ester substituents were also well tolerated, affording the target products (4am–4aq) in good yields. More interestingly, olefins with high-activity functional groups including halo (4ar) and alcohol substituents (4as–4av) also could be converted into corresponding products in good yields (65–79%). However, other olefins containing heteroaromatic ring, such as 2-vinylpyridine, 4-vinylpyridine, and 1-vinyl-2-pyrrolidone could not be transformed into corresponding products (see SI).

### Table 1 | Optimization of reaction conditions.a

| Entry | 2a (x) | 3(y) | Oxidant | Solvent | Yield (%)b |
|-------|--------|------|---------|---------|------------|
| 1     | 2      | 1    | Fe(NO₃)₃•9H₂O | EtOH     | 55         |
| 2     | 2      | 1    | Fe(NO₃)₃•9H₂O | MeCN     | 0          |
| 3     | 2      | 1    | Fe(NO₃)₃•9H₂O | DCM      | 0          |
| 4     | 2      | 1    | Fe(NO₃)₃•9H₂O | Dioxane  | 0          |
| 5     | 2      | 1    | Fe(NO₃)₃•9H₂O | DMF      | 0          |
| 6     | 2      | 1    | Fe(NO₃)₃•9H₂O | DMSO     | 0          |
| 7     | 2      | 1    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 65  |
| 8     | 2      | 1    | Fe(NO₃)₃•9H₂O | DCM/EtOH | 60         |
| 9     | 2      | 1    | Fe(NO₃)₃•9H₂O | Dioxane/EtOH | 30  |
| 10    | 2      | 1    | Fe(NO₃)₃•9H₂O | DMF/EtOH | Trace      |
| 11    | 2      | 1    | Fe(NO₃)₃•9H₂O | DMSO/EtOH | Trace      |
| 12    | 2      | 1    | FeBr₃      | MeCN/EtOH | 0          |
| 13    | 2      | 1    | CuCl₂      | MeCN/EtOH | 0          |
| 14    | 2      | 1    | CuO        | MeCN/EtOH | 0          |
| 15    | 2      | 1    | (NH₄)₂Ce(NO₃)₆ | MeCN/EtOH | 0          |
| 16    | 2      | 1    | Fe₂(ox)₃  | MeCN/EtOH | 0          |
| 17    | 2      | 1    | FeF₃       | MeCN/EtOH | 0          |
| 18    | 2      | 1    | –          | MeCN/EtOH | 0          |
| 19    | 1      | 1    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 40         |
| 20    | 3      | 1    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 65         |
| 21    | 3      | 2    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 71         |
| 22    | 3      | 3    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 72         |
| 23    | 2      | 2    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 73         |
| 24    | 2      | 2    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 55         |
| 25    | 2      | 2    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 73         |
| 26    | 2      | 2    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 73         |
| 27    | 2      | 2    | Fe(NO₃)₃•9H₂O | MeCN/EtOH | 59         |

a Reaction conditions: 1a (0.2 mmol), 2a (x equiv), 3 (y equiv), oxidant (4.0 equiv), solvent (4.0 ml, v/v = 1:1), room temperature, open flask, 10 min.
b Isolated yields.

Frontiers in Chemistry | www.frontiersin.org 4 August 2020 | Volume 8 | Article 606
TABLE 2 | Substrate scope of quinoxalinones<sup>a,b</sup>.

| R<sup>1</sup> | R<sup>2</sup> | Substrate | Yield |
|---|---|---|---|
| Ph | R<sup>1</sup> | 4a | 73% |
| Me | CH₂CO₂Bu | 4e | 71% |
| Me | R<sup>1</sup> | 4f | 61% |
| Et | R<sup>1</sup> | 4g | 78% |
| nBu | R<sup>1</sup> | 4h | 60% |
| R<sup>1</sup> | R<sup>1</sup> | 4i | 61% |
| R<sup>1</sup> | R<sup>1</sup> | 4j | 70% |
| R<sup>1</sup> | R<sup>1</sup> | 4k | 73% |
| R<sup>1</sup> | R<sup>1</sup> | 4l | 70% |
| R<sup>1</sup> | R<sup>1</sup> | 4m | 69% |
| R<sup>1</sup> | R<sup>1</sup> | 4n | 61% |
| R<sup>1</sup> | R<sup>1</sup> | 4o | 60% |
| R<sup>1</sup> | R<sup>1</sup> | 4p | 60% |
| R<sup>1</sup> | R<sup>1</sup> | 4q | 59% |

<sup>a</sup> Reaction conditions: 1 (0.2 mmol), 2a (2.0 equiv), 3 (2.0 equiv), Fe(NO₃)₃·9H₂O (4.0 equiv), MeCN/EtOH (4.0 ml, v/v = 1:1), room temperature, open flask, 10 min.

<sup>b</sup> Isolated yields.

To demonstrate the synthetic utility of our method, a gram-scale experiment was performed to synthesize 1-methyl-3-(1-phenylethyl-2-d)quinoxalin-2(1H)-one (4a) in 66% yield (Scheme 2A). It was worth mentioning that the modification of estrone derivative further demonstrated its synthetic utility (Scheme 2B).

To understand the reaction mechanism, the preliminary mechanistic studies was proceeded (Scheme 3). When 2.0 equiv of TEMPO (2,2,6,6-tetramethyl-piperidin-1-oxyl) were used as radical inhibitor, the reaction was completely inhibited (Scheme 3A). In addition, the transformation of 1-methylquinoxalin-2(1H)-one (1a) and diethyl 2,2-diallylmalonate (5a) with NaBD₄ (3) performed to give product 6a in 70% yield (Scheme 3B). All these results clearly implied that a radical pathway was responsible for the three-component reaction.

Based on the above experimental results and previous reports (Yi et al., 2017; Yan et al., 2019; Shen et al., 2020), a probable radical mechanism for the three-component reaction was proposed (Scheme 4). First, deuterium radical (A) was generated from NaBD₄ in the presence of Fe(III). Second, the generated deuterium radical (A) attacked olefin 2a to afford alkyl radical (B). Third, alkyl radical (B) then attacked quinoxalinone 1a to give nitrogen radical (C), which underwent a 1,2-hydrogen shift process to produce carbon radical (D). After the generation of carbon cation (E) from carbon radical (D) by the oxidation of Fe(III), the final product 4a was obtained through a deprotonation process.

**EXPERIMENTAL SECTION**

**General Information**

All reagents and deuterated solvents were commercially available and used without further purification. All products were separated by silica gel (200–300 mesh) column chromatography with petroleum ether (PE) (60–90°C) and ethyl acetate (EA). ¹H, ¹³C, and ¹⁹F NMR spectra were recorded on a
TABLE 3 | Substrate scope of olefins$^{a,b}$. 

| Substrates | Reagents | Yields |
|------------|----------|--------|
| R = 4-CH$_3$, 73% | Fe(NO$_3$)$_3$•9H$_2$O (4.0 equiv) | OPEN FLASK |
| R = 4-F, 70% | MeCN/EtOH, rt, 10 min |
| R = 4-Cl, 78% |
| R = 4-BR, 80% |
| R = 4-CF$_3$, 70% |
| R = 3-CH$_3$, 72% |
| R = 3-F, 75% |
| R = 3-CF$_3$, 65% |
| R = 2-Cl, 63% |
| R = PhCO$_2$, n = 4, 78% |
| R = PhCO$_2$, n = 8, 80% |
| R = PhCO$_2$, n = 9, 82% |
| R = Br, n = 4, 79% |
| R = OH, n = 3, 73% |
| R = OH, n = 4, 70% |
| R = OH, n = 8, 69% |
| R = OH, n = 9, 65% |

$^a$Reaction conditions: 1 (0.2 mmol), 2 (2.0 equiv), 3 (2.0 equiv), Fe(NO$_3$)$_3$•9H$_2$O (4.0 equiv), MeCN/EtOH (4.0 ml, v/v = 1:1), room temperature, open flask, 10 min.

$^b$Isolated yields.

Bruker Advance 500 spectrometer at ambient temperature with CDCl$_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Melting points were determined on an X-5 Data microscopic melting point apparatus. Analytical thin layer chromatography (TLC) was performed on Merk precoated TLC (silica gel 60 F254) plates. Compounds for high-resolution mass spectrometry (HRMS) were analyzed by positive mode electrospray ionization (ESI) using Agilent 6530 QTOF mass spectrometer.

Typical Reaction Procedure for the Cascade Reaction of Quinoxalinones With Unactivated Alkenes and NaBD$_4$

A mixture of quinoxalinones (1) (0.2 mmol), olefins (2) (2.0 equiv), Fe(NO$_3$)$_3$•9H$_2$O (4.0 equiv), and MeCN/EtOH (4.0 ml, v/v = 1:1) in a 15-ml tube was stirred at room temperature for 5 min to make all the components dissolved. Then, NaBD$_4$ (2.0 equiv) was slowly added. The resulting mixture was stirred for another 5 min. After the completion (as indicated by TLC), the reaction mixture was quenched with aqueous NH$_3$•H$_2$O (2 ml) and extracted with EtOAc (5 ml × 3). The collected organic layer was washed with brine and dried with MgSO$_4$. Finally, the organic solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (200–300 mesh silica gel, PE/EA = 3:1).

Gram-Scale Synthesis of 1-methyl-3-(1-phenylethyl-2-d)quinoxalin-2(1H)-one

A mixture of quinoxalinones (1) (6.0 mmol), olefins (2) (2.0 equiv), Fe(NO$_3$)$_3$•9H$_2$O (4.0 equiv), and MeCN/EtOH (100 ml, v/v = 1:1) in a 250-ml flask was stirred at room temperature.
for 5 min to make all the components dissolved. Then, NaBD₄ (2.0 equiv) was slowly added. The resulting mixture was stirred for another 5 min. After the completion (as indicated by TLC), the reaction mixture was quenched with aqueous NH₃•H₂O (50 ml) and extracted with EtOAc (50 ml × 3). The collected organic layer was washed with brine and dried with MgSO₄. Finally, the organic solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (200–300 mesh silica gel, PE/EA = 3:1) to provide product 4a in 66% yield (1.05 g).

**CONCLUSION**

In conclusion, a rapid three-component deuteration of quinoxalinones with olefins and NaBD₄ was reported for the first time. Quinoxalinones or olefins bearing...
various functional groups could undergo the reaction smoothly, producing the target products in moderate to good yields. This transformation gave a novel and efficient method for the synthesis of previously unknown deuterated quinoxalinones.

DATA AVAILABILITY STATEMENT
All datasets presented in this study are included in the article/Supplementary Material.

AUTHOR CONTRIBUTIONS
WL and PZ contributed conception and design of the study. HC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

REFERENCES
Atzrodt, J., Derdau, V., Kerr, W. J., and Reid, M. (2018). Deuterium- and tritium-labelled compounds: applications in the life sciences. Angew. Chem. Int. Ed. 57, 1758–1784. doi: 10.1002/anie.201704146
Atzrodt, J., Derdau, V., Fey, T., and Zimmermann, J. (2007). The Renaissance of H/D exchange. Angew. Chem. Int. Ed. 46, 7744–7765. doi: 10.1002/anie.200700039
Badran, M. M., Abouzid, K. A. M., and Hussein, M. H. M. (2003). Synthesis of certain substituted quinoxalines as antimicrobial agents (Part II). Arch. Pharm. Res. 26, 107–113. doi: 10.1007/BF02976653

FUNDING
This work was supported by General Scientific Research Projects of Zhejiang Education Department-Special Project on Training Mode Reform of Master of Engineering in Universities (Y201840022).

ACKNOWLEDGMENTS
We thank the National Natural Science Foundation of China (No. 21871071) and the Key Research and Development Project of Zhejiang (No. 2019C01081) for financial support.

SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2020.00606/full#supplementary-material

Bao, P., Liu, F., Lv, Y., Yue, H., Li, J.-S., and Wei, W. (2020). Visible-light-promoted acridine red catalyzed aerobic oxidative decarboxylative acylation of α-oxo-carboxylic acids with quinoxalin-2(1H)-ones. Org. Chem. Front. 7, 492–498. doi: 10.1039/C9QQ01334B
Barker, T., and Boger, D. (2012). Fe(III)/NaBH₄-mediated free radical hydrofluorination of unactivated alkenes. J. Am. Chem. Soc. 134, 13588–13591. doi: 10.1021/ja3063716
Chang, Y., Myers, T., and Wasa, M. (2020). B(C₆F₅)₃-catalyzed α-deuteration of bioactive carbonyl compounds with D₂O. Adv. Synth. Catal. 362, 360–364. doi: 10.1002/adsc.201901419
Li et al. Radical-Type Three-Component Deuteration

Yi, H., Zhang, G., Wang, H., Huang, Z., Wang, J., Singh, A. K., et al. (2017). Recent advances in radical C-H activation/radical cross-coupling. Chem. Rev. 117, 9016–9085. doi: 10.1021/acs.chemrev.6b00620

Yu, R. P., Hesk, D., Rivera, N., Pelczer, I., and Chirik, P. J. (2016). Iron-catalysed tritiation of pharmaceuticals. Nature 529, 195–199. doi: 10.1038/nature16464

Zhang, H., Xu, J., Zhou, M., Zhao, J., Zhang, P., and Li, W. (2019). The visible-light-triggered regioselective alkylation of quinoxalin-2(1H)-ones via decarboxylation coupling. Org. Biomol. Chem. 17, 10201–10208. doi: 10.1039/C9OB02203A

Zhang, W., Pan, Y.-L., Yang, C., Chen, L., Li, X., and Cheng, J.-P. (2019). Metal-free direct C-H cyanoalkylation of quinoxalin-2(1H)-ones by organic photoredox catalysis. J. Org. Chem. 84, 7786–7795. doi: 10.1021/acs.joc.9b00657

Zhao, L.-L., Liu, W., Zhang, Z., Zhao, H., Wang, Q., and Yan, X. (2019). Ruthenium-catalyzed ortho- and meta-H/D exchange of arenes. Org. Lett. 21, 10023–10027. doi: 10.1021/acs.orglett.9b03955

Zheng, D., and Studer, A. (2019). Photoinitiated three-component α-perfluoroalkyl-β-heteroarylation of unactivated alkenes via electron catalysis. Org. Lett. 21, 325–329. doi: 10.1021/acs.orglett.8b03849

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Li, Cai, Huang, He, Zhang, Xu and Zhang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.