Iron(III)-Mediated Rapid Radical-Type Three-Component Deuteration of Quinoxalinones With Olefins and NaBD₄

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Iron(III)-promoted rapid three-component deuteration of quinoxalinones with olefins and NaBD₄ 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; Li et al., 2017; Liu et al., 2018; Yang et al., 2018; Han et al., 2019; Shen et al., 2019; Xu et al., 2019; Zhao et al., 2019; Chang et al., 2020; Dong et al., 2020). For instances, in 2016, Chirik and coworkers reported an iron-catalyzed transformation for the deuteration and tritiation of pharmaceuticals (Yu et al., 2016). Kerr's group developed an iridium-catalyzed hydrogen isotope exchange method for the site-selective deuteration of *N*-heterocycles (Kerr et al., 2017). In 2012, Fe(III)/NaBH₄-mediated free radical hydrofluorination of unactivated alkenes was reported by Boger's group (Barker and Boger, 2012) (**Scheme 1B**). Subsequently, Liu and coworkers reported a similar method with Fe(III)-promoted free-radical hydroheteroarylation of alkenes (Liang et al., 2017) (**Scheme 1B**). Dai and Yan, respectively developed novel methods for the synthesis of deuterated arenes by a palladium-catalyzed, pyridine-directed remote *meta*-C–H bond deuteration of arenes (Xu et al., 2019) or ruthenium catalysis (Zhao et al., 2019).
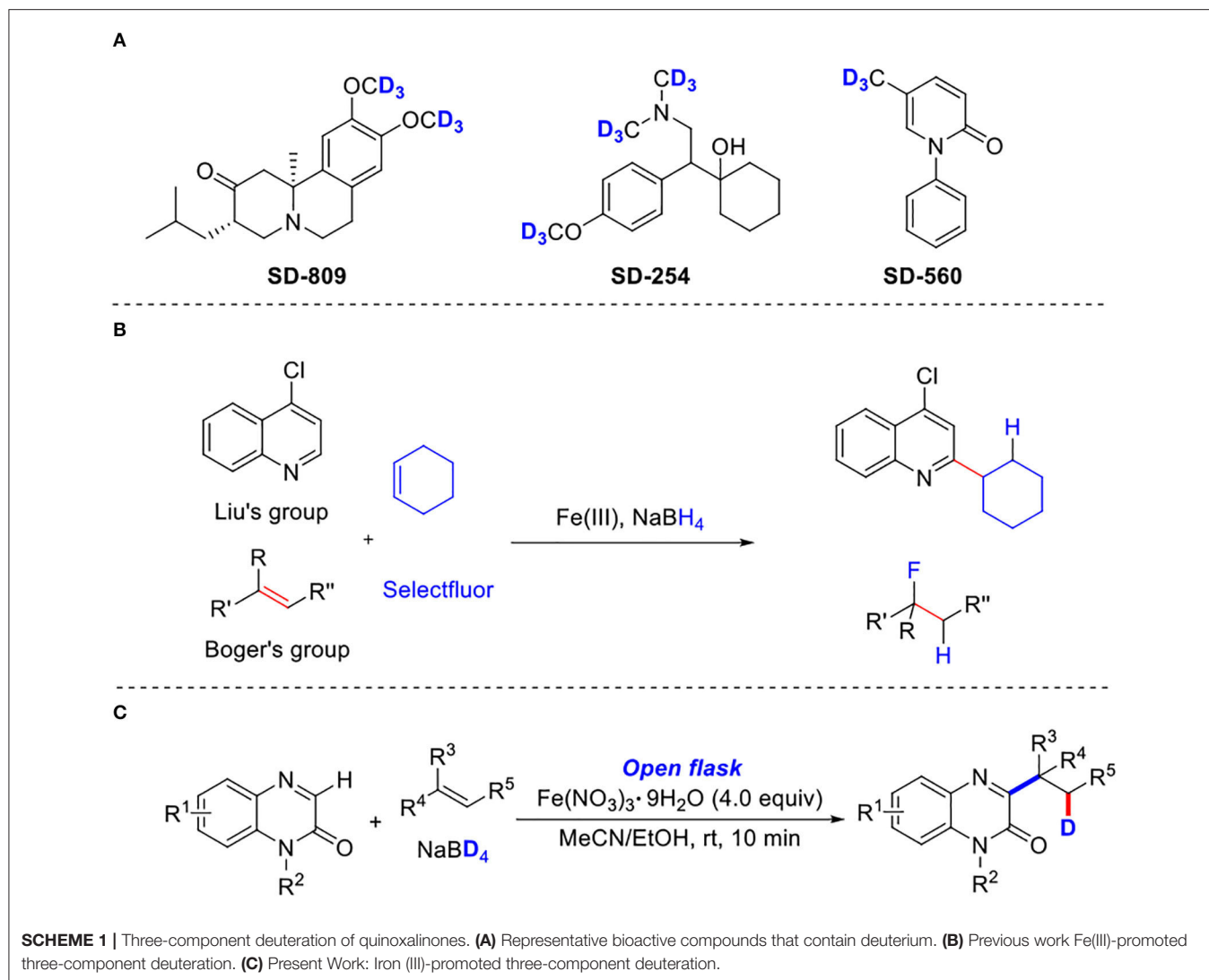
SCHEME 1 | Three-component deuteration of quinoxalinones. **(A)** Representative bioactive compounds that contain deuterium. **(B)** Previous work Fe(III)-promoted three-component deuteration. **(C)** Present Work: Iron (III)-promoted three-component deuteration.

In 2019, Wasa and coworkers demonstrated a $B(C_6F_5)_3$-catalyzed α-deuteration of carbonyl compounds with D_2O, 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 cascde reaction of quinoxalinones, olefins, and sulfinic 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 $TMSN_3$ (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 NaBD$_4$ mediated by Fe(NO$_3$)$_3 \bullet$9H$_2$O 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 NaBD$_4$ (**3**) 4.0 equiv of Fe(NO$_3$)$_3\bullet$9H$_2$O in ethanol at room temperature for 10 min, providing the desired product **4a** in 55% yield (**Table 1**, entry 1). This reaction could not take place if other solvents (MeCN, dichloromethane (DCM), dioxane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO)] (**Table 1**, entries 2–6) or catalysts (**Table 1**, entries 12–17) [FeBr$_3$, CuCl$_2$, CuO, (NH$_4$)$_2$Ce(NO$_3$)$_6$, Fe$_2$(ox)$_3$, FeF$_3$], or no catalyst (**Table 1**, entry 18) were used. However, it surprised us that using the mixed solvent of ethanol and acetonitrile ($v/v = 1{:}1$) could improve the reaction yield to 65% (**Table 1**, entry 7 among entries 7–11). Subsequently, the dosage of styrene **2a** and NaBD$_4$ **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 NaBD$_4$ **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(NO$_3$)$_3\bullet$9H$_2$O (**Table 1**, entries 24–25) or reaction time (**Table 1**, entries 26–27). Thus, the highest yield could be obtained when the mixture of 1-methylquinoxalin-2(1H)-one (**1a**), 2.0 equiv of styrene (**2a**), 2.0 equiv of NaBD$_4$ (**3**) in EtOH/CH$_3$CN (4.0 ml, $v/v = 1{:}1$) were reacted at 4.0 equiv of Fe(NO$_3$)$_3\bullet$9H$_2$O 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 NaBD$_4$ (3) (**Table 2**). To our delight, a wide range of N-protecting groups including N-methyl, N-ethyl, N-butyl, N-cyclopropylmethyl, and N-esteryl 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 quinoxalinone 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 NaBD$_4$ (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

TABLE 1 | Optimization of reaction conditions[a].
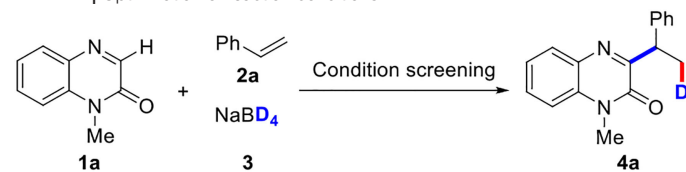
Entry	2a (x)	3(y)	Oxidant	Solvent	Yield (%)[b]
1	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	EtOH	55
2	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN	0
3	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	DCM	0
4	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	Dioxane	0
5	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	DMF	0
6	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	DMSO	0
7	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	65
8	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	DCM/EtOH	60
9	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	Dioxane/EtOH	30
10	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	DMF/EtOH	Trace
11	2	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	DMSO/EtOH	Trace
12	2	1	FeBr$_3$	MeCN/EtOH	0
13	2	1	CuCl$_2$	MeCN/EtOH	0
14	2	1	CuO	MeCN/EtOH	0
15	2	1	(NH$_4$)$_2$Ce(NO$_3$)$_6$	MeCN/EtOH	0
16	2	1	Fe$_2$(ox)$_3$	MeCN/EtOH	0
17	2	1	FeF$_3$	MeCN/EtOH	0
18	2	1	–	MeCN/EtOH	0
19	1	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	40
20	3	1	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	65
21	3	2	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	71
22	3	3	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	72
23	2	2	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	73
24[c]	2	2	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	55
25[d]	2	2	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	73
26[e]	2	2	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	59
27[f]	2	2	Fe(NO$_3$)$_3\bullet$9H$_2$O	MeCN/EtOH	72

[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.
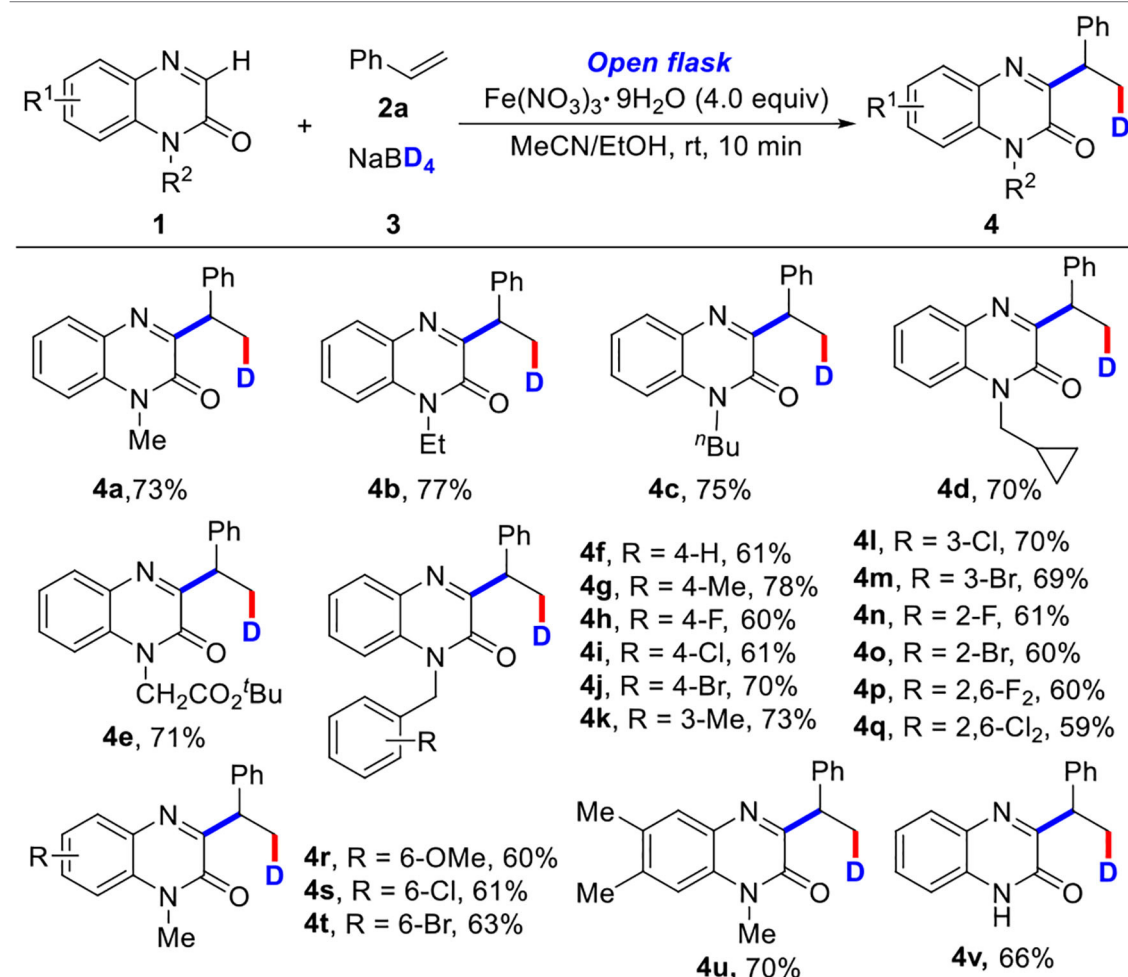[b] Isolated yields.
[c] Fe(NO$_3$)$_3\bullet$9H$_2$O (3.0 equiv).
[d] Fe(NO$_3$)$_3\bullet$9H$_2$O (5.0 equiv).
[e] The reaction was performed in 5 min.
[f] The reaction was performed in 20 min.

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 2 | Substrate scope of quinoxalinones[a,b].

[a]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.
[b]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(1*H*)-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(1*H*)-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). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a

TABLE 3 | Substrate scope of olefins[a,b].
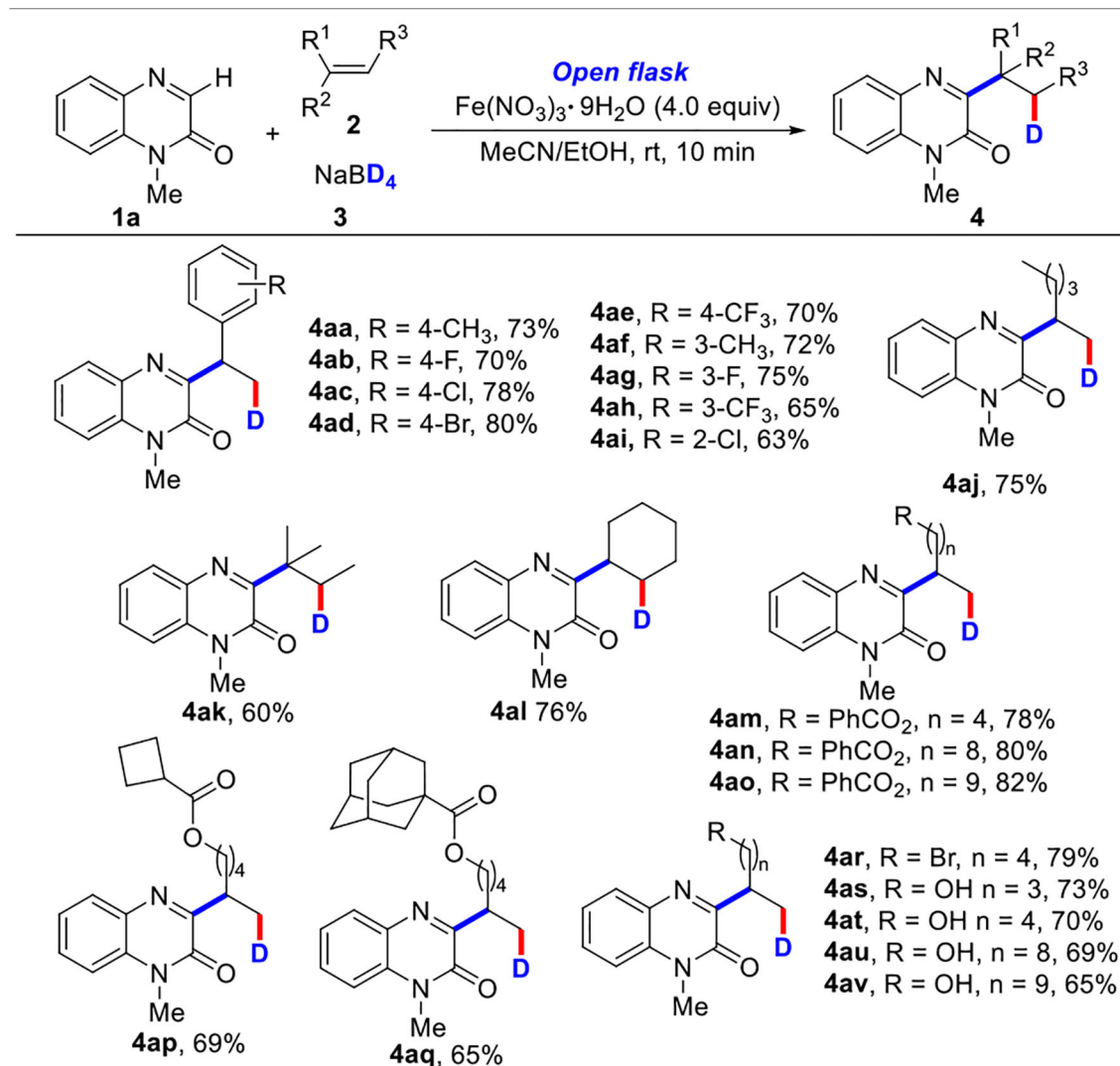
[a] Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv), **3** (2.0 equiv), Fe(NO$_3$)$_3$•9H$_2$O (4.0 equiv), MeCN/EtOH (4.0 ml, v/v = 1:1), room temperature, open flask, 10 min.
[b] Isolated yields.

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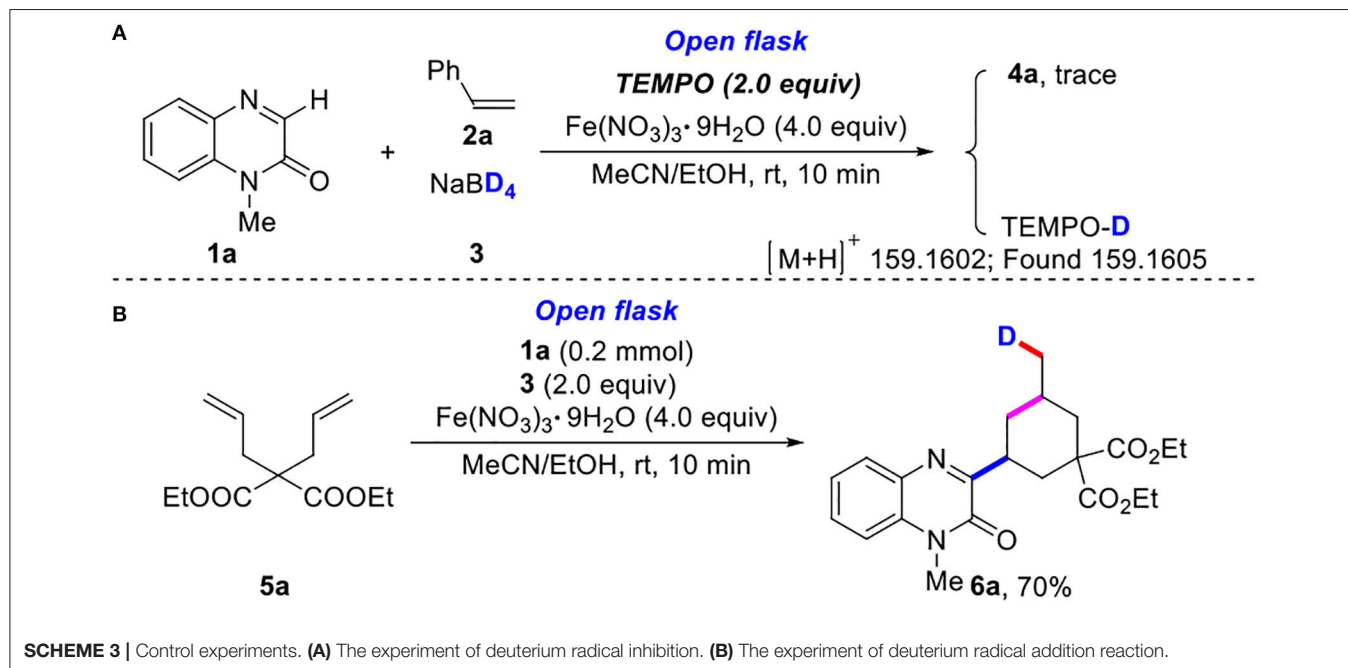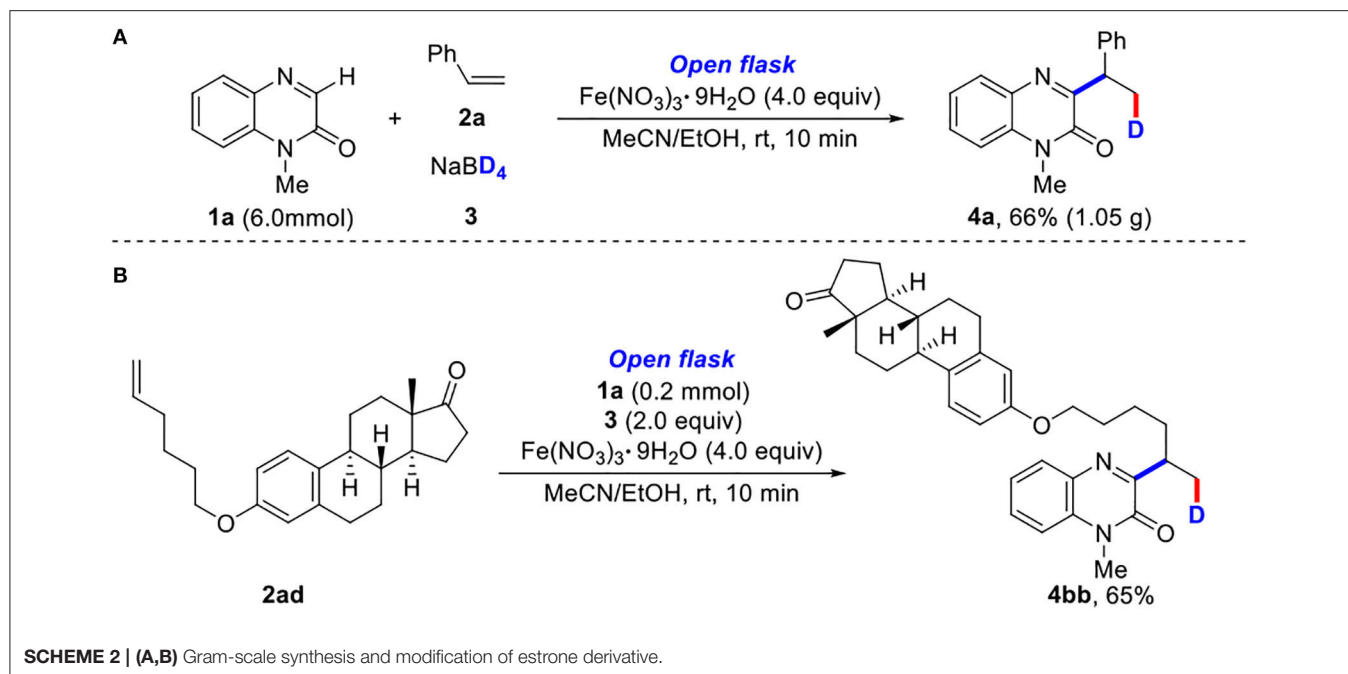
Typical Reaction Procedure for the Cascade Reaction of Quinoxalinones With Unactivated Alkenes and NaBD$_4$

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

SCHEME 2 | (A,B) Gram-scale synthesis and modification of estrone derivative.

SCHEME 3 | Control experiments. (A) The experiment of deuterium radical inhibition. (B) The experiment of deuterium radical addition reaction.

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 $NH_3 \bullet H_2O$ (50 ml) and extracted with EtOAc (50 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) to provide product 4a in 66% yield (1.05 g).

CONCLUSION

In conclusion, a rapid three-component deuteration of quinoxalinones with olefins and $NaBD_4$ was reported for the first time. Quinoxalinones or olefins bearing

SCHEME 4 | Plausible mechanism.
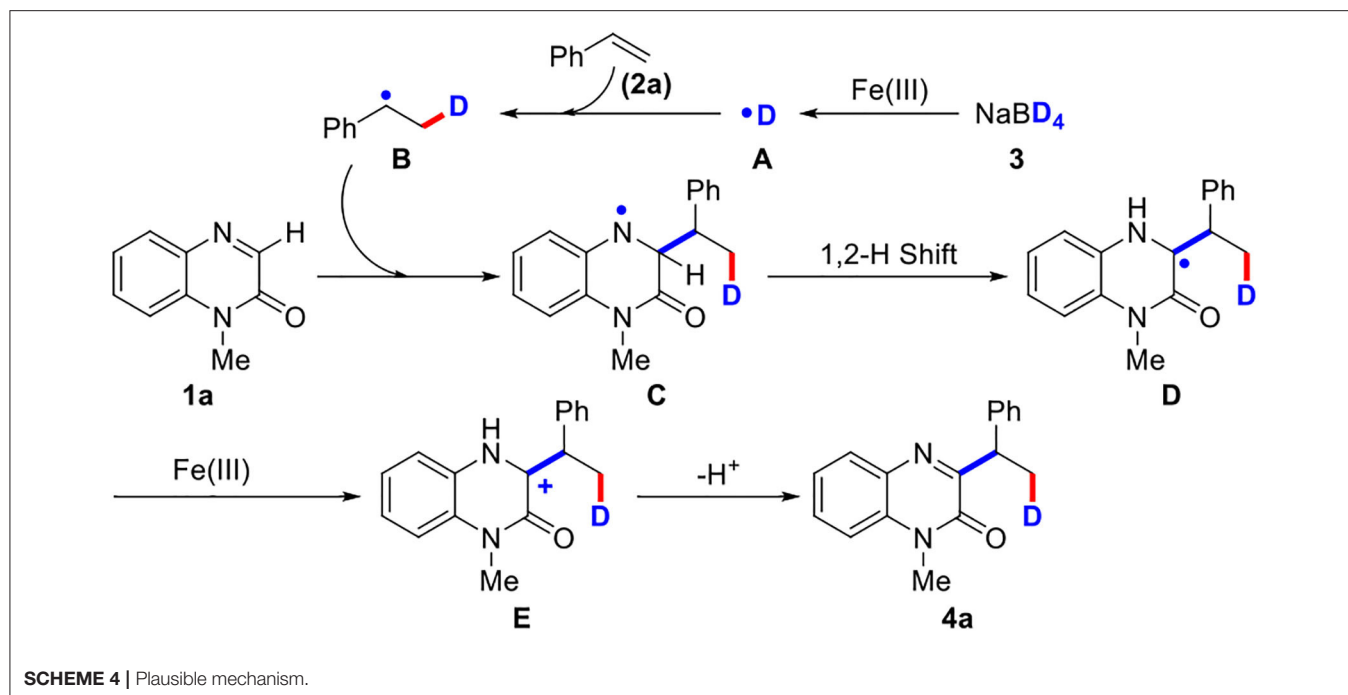
various functional groups could undergo the reaction smoothly, producing the target products in moderate to good yields. This transformation gave a novel and efficient method for the synthesis of previously unknown deuterated quinoxalinones.

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.

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

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

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/C9QO01334B

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.2019 01419

Dong, J., Wang, X., Wang, Z., Song, H., Liu, Y., and Wang, Q. (2020). Formyl-selective deuteration of aldehydes with D2O via synergistic organic and photoredox catalysis. *Chem. Sci.* 11, 1026–1031. doi: 10.1039/C9SC05132E

Dutta, H. S., Ahmad, A., Khan, A. A., Kumar, M., and Raziullah, K. D. (2019). Metal free benzylation and alkylation of quinoxalin-2(1*H*)-ones with alkenes triggered by sulfonyl radical generated from sulfinic acids. *Adv. Synth. Catal.* 361, 5534–5539. doi: 10.1002/adsc.201901212

Gant, T. G. (2014). Using deuterium in drug discovery: leaving the label in the drug. *J. Med. Chem.* 57, 3595–3611. doi: 10.1021/jm4007998

Gómez-Gallego, M., and Sierra, M. A. (2011). Kinetic isotope effects in the study of organometallic reaction mechanisms. *Chem. Rev.* 111, 4857–4963. doi: 10.1021/cr100436k

Gowrisankar, S., Neumann, H., and Beller, M. (2012). A convenient and practical synthesis of anisoles and deuterated anisoles by palladium-catalyzed coupling reactions of aryl bromides and chlorides. *Chem. Eur. J.* 18, 2498–2502. doi: 10.1002/chem.201103347

Guengerich, F. P. (2012). Introduction: use of radioactive compounds in drug discovery and development. *Chem. Res. Toxicol.* 25, 511–512. doi: 10.1021/tx3000522

Han, X., Yuan, Y., and Shi, Z. (2019). Rhodium-catalyzed selective C-H trideuteromethylation of indole at C7 position using acetic-d6 anhydride. *J. Org. Chem.* 84, 12764–12772. doi: 10.1021/acs.joc.9b01114

Hong, G., Yuan, J., Fu, J., Pan, G., Wang, Z., Yang, L., et al. (2019). Transition-metal-free decarboxylative C3-difluoroarylmethylation of quinoxalin-2(1*H*)-ones with α,α-difluoroarylacetic acids. *Org. Chem. Front.* 6, 1173–1182. doi: 10.1039/C9QO00105K

Hoogewijs, K., Buyst, D., Winne, J. M., Martins, J. C., and Madder, A. (2013). Exploiting furan's versatile reactivity in reversible and irreversible orthogonal peptide labelling. *Chem. Commun.* 49, 2927–2929. doi: 10.1039/C3CC40588E

Jin, C., Zhuang, X., Sun, B., Li, D., and Zhu, R. (2019). Merging visible-light photoredox and organoamine catalysis for the C-3 difluoroalkylation of quinoxalin-2(1*H*)-ones. *Asian J. Org. Chem.* 8, 1490–1494. doi: 10.1002/ajoc.201900369

Junk, T., and Catallo, W. J. (1997). Hydrogen isotope exchange reactions involving C-H (D, T) bonds. *Chem. Soc. Rev.* 26, 401–406. doi: 10.1039/CS9972600401

Katsnelson, A. (2013). Heavy drugs draw heavy interest from pharma backers. *Nat. Med.* 19:656. doi: 10.1038/nm0613-656

Ke, Q., Yan, G., Yu, J., and Wu, X. (2019). Recent advances in the direct functionalization of quinoxalin-2(1*H*)-ones. *Org. Biomol. Chem.* 17, 5863–5881. doi: 10.1039/C9OB00782B

Kerr, W. J., Lindsay, D. M., Owens, P. K., Reid, M., Tuttle, T., and Campos, S. (2017). Site-selective deuteration of N-heterocycles via iridium-catalyzed hydrogen isotope exchange. *ACS Catal.* 7, 7182–7186. doi: 10.1021/acscatal.7b02682

Konermann, L., Pan, J., and Liu, Y. H. (2011). Hydrogen exchange mass spectrometry for studying protein structure and dynamics. *Chem. Soc. Rev.* 40, 1224–1234. doi: 10.1039/C0CS00113A

Li, W., Wang, M.-M., Hu, Y., and Werner, T. (2017). B(C$_6$F$_5$)$_3$-catalyzed regioselective deuteration of electron-rich aromatic and heteroaromatic compounds. *Org. Lett.* 19, 5768–5771. doi: 10.1021/acs.orglett.7b02701

Liang, B., Wang, Q., and Liu, Z.-Q. (2017). A Fe(III)/NaBH$_4$-promoted free-radical hydroheteroarylation of alkenes. *Org. Lett* 19, 6463–6465. doi: 10.1021/acs.orglett.7b03313

Liu, C., Chen, Z., Su, C., Zhao, X., Gao, Q., Ning, G.-H., et al. (2018). Controllable deuteration of halogenated compounds by photocatalytic D$_2$O splitting. *Nat. Commun.* 9:80. doi: 10.1038/s41467-017-02551-8

Liu, L. X., Pan, N., Sheng, W., Su, L., Liu, L., Dong, J. Y., et al. (2019). Visible light-induced regioselective decarboxylative alkylation of the C(sp^2)-H bonds of non-aromatic heterocycles. *Adv. Synth. Catal.* 361, 4126–4132. doi: 10.1002/adsc.201900572

Meanwell, N. A. (2011). Synopsis of some recent tactical application of bioisosteres in drug design. *J. Med. Chem.* 54, 2529–2591. doi: 10.1021/jm1013693

Monge, A., Martinez-Crespo, F. J., Cerai, A. L., Palop, J. A., Narro, S., Senador, V., et al. (1995). Hypoxia-selective agents derived from 2-quinoxalinecarbonitrile 1,4-Di-iV-oxides. *J. Med. Chem.* 38, 4488–4494. doi: 10.1021/jm00022a014

Mutlib, A. E. (2008). Application of stable isotope-labeled compounds in metabolism and in metabolism-mediated toxicity studies. *Chem. Res. Toxicol.* 21, 1672–1689. doi: 10.1021/tx800139z

Nakane, Y., Takeda, T., Hoshino, N., Sakai, K.-I., and Akutagawa, T. (2015). Cation–anion dual sensing of a fluorescent quinoxalinone derivative using lactam–lactim tautomerism. *J. Phys. Chem. A* 119, 6223–6231. doi: 10.1021/acs.jpca.5b02850

Pirali, T., Serafini, M., Cargnin, S., and Genazzani, A. A. (2019). Applications of deuterium in medicinal chemistry. *J. Med. Chem.* 62, 5276–5279. doi: 10.1021/acs.jmedchem.8b01808

Ray, P. G., Pawar, Y. D., Singare, D. T., Deshpande, T. N., and Singh, G. P. (2018). Novel process for preparation of tetrabenazine and deutetrabenazine. *Org. Process Res. Dev.* 22, 520–526. doi: 10.1021/acs.oprd.8b00011

Refaat, H. M., Moneer, A. A., and Khalil, O. M. (2004). Synthesis and antimicrobial activity of certain novel quinoxalines. *Arch. Pharm. Res.* 27, 1093–1098. doi: 10.1007/BF02975110

Renault, K., Renard, P.-Y., and Sabot, C. (2017). Photophysical properties of quinoxalin-2(1*H*)-ones: application in the preparation of an azide-based fluorogenic probe for the detection of hydrogen sulphide, *New J. Chem.* 41, 10432–10437. doi: 10.1039/C7NJ01893B

Schmidt, C. (2017). First deuterated drug approved. *Nat. Biotechnol.* 35, 493–494. doi: 10.1038/nbt0617-493

Shen, J., Xu, J., Cai, H., Shen, C., and Zhang, P. (2019). Platinum(II)-catalyzed selective para C–H alkoxylation of arylamines through a coordinating activation strategy. *Org. Biomol. Chem.* 17, 490–497. doi: 10.1039/C8OB02942C

Shen, J., Xu, J., Huang, L., Zhu, Q., and Zhang, P. (2020). Hypervalent iodine(III)-promoted rapid cascade reaction of quinoxalinones with unactivated alkenes and TMSN3. *Adv. Synth. Catal.* 362, 230–241. doi: 10.1002/adsc.201901314

Simmons, E. M., and Hartwig, J. F. (2012). On the interpretation of deuterium kinetic isotope effects in c-h bond functionalizations by transition-metal complexes. *Angew. Chem. Int. Ed.* 51, 3066–3072. doi: 10.1002/anie.201107334

Tang, S., Liu, K., Liu, C., and Lei, A. (2015). Olefinic C-H functionalization through radical alkenylation. *Chem. Soc. Rev.* 44, 1070–1082. doi: 10.1039/C4CS00347K

TenBrink, R. E., Im, W. B., Sethy, V. H., Tang, A. H., and Carter, D. B. (1994). Antagonist, partial agonist, and full agonist imidazo[1,5-a]quinoxaline amides and carbamates acting through the GABAA/benzodiazepine receptor. *J. Med. Chem.* 37, 758–768. doi: 10.1021/jm00032a008

Tolnai, G. L., Pethö, B., Králl, P., and Novák, Z. (2014). Palladium-catalyzed methoxylation of aromatic chlorides with borate salts. *Adv. Synth. Catal.* 356, 125–129. doi: 10.1002/adsc.201300687

Wang, J., Sun, B., Zhang, L., Xu, T., Xie, Y., and Jin, C. (2020). Transition-metal-free direct C-3 cyanation of quinoxalin-2(1H)-ones with ammonium thiocyanate as the "CN" source. *Org. Chem. Front.* 7, 113–118. doi: 10.1039/C9QO01055F

Wang, L., Liu, H., Li, F., Zhao, J., Zhang, H.-Y., and Zhang, Y. (2019). copper-catalyzed C3-H difluoroacetylation of quinoxalinones with ethyl bromodifluoroacetate. *Adv. Synth. Catal.* 361, 2354–2359. doi: 10.1002/adsc.201900066

Wei, Z., Qi, S., Xu, Y., Liu, H., Wu, J., Li, H.-S., et al. (2019). Visible light-induced photocatalytic C-H perfluoroalkylation of quinoxalinones under aerobic oxidation condition. *Adv. Synth. Catal.* 361, 5490–5498. doi: 10.1002/adsc.201900885

Xie, L.-Y., Peng, S., Fan, T.-G., Liu, Y.-F., Sun, M., Jiang, L.-L., et al. (2019). Metal-free C3-alkoxycarbonylation of quinoxalin-2(1*H*)-ones with carbazates as ecofriendly ester sources. *Sci. Chin. Chem.* 62, 460–464. doi: 10.1007/s11426-018-9446-1

Xu, H., Liu, M., Li, L.-J., Cao, Y.-F., Yu, J.-Q., and Dai, H.-X. (2019). Palladium-catalyzed remote meta-C–H bond deuteration of arenes using a pyridine template. *Org. Lett.* 21, 4887–4891. doi: 10.1021/acs.orglett.9b01784

Xue, W., Su, Y., Wang, K.-H., Zhang, R., Feng, Y., Cao, L., et al. (2019). Visible-light induced decarboxylative alkylation of quinoxalin-2(1*H*)-ones at the C3-position. *Org. Biomol. Chem.* 17, 6654–6661. doi: 10.1039/C9OB01169B

Yan, Z., Sun, B., Zhang, X., Zhuang, X., Yang, J., Su, W., et al. (2019). Construction of C(sp^2)-C(sp^3) Bond between quinoxalin-2(1*H*)-ones and N-hydroxyphthalimide esters via photocatalytic decarboxylative coupling. *Chem. Asian J.* 14, 3344–3349. doi: 10.1002/asia.201900904

Yang, H., Zarate, C., Palmer, W. N., Rivera, N., Hesk, D., and Chirik, P. J. (2018). Site-selective nickel-catalyzed hydrogen isotope exchange in N-heterocycles and its application to the tritiation of pharmaceuticals. *ACS Catal.* 8, 10210–10218. doi: 10.1021/acscatal.8b03717

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(1*H*)-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