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Photocatalytic deuterocarboxylation of alkynes with oxalate†

Pei Xu,‡ Hao-Qiang Jiang,‡ Hui Xu,‡ Sai Wang, Hui-Xian Jiang, Song-Lei Zhu, Long Yin,* Dong Guo* and Xu Zhu*

Herein, a catalytic photoredox-neutral strategy for alkyne deuterocarboxylation with tetrabutylammonium oxalate as the carbonyl source and D_2O as the deuteration agent was described. For the first time, the oxalic salt acted as both the reductant and carbonyl source through single electron transfer and subsequential homolysis of the C–C bond. The strongly reductive CO_2 radical anion species *in situ* generated from oxalate played significant roles in realizing the global deuterocarboxylation of terminal and internal alkynes to access various tetra- and tri-deuterated aryl propionic acids with high yields and deuteration ratios.

Introduction

Hydrocarboxylation of unsaturated hydrocarbons, such as C–C double and triple bonds, to forge thermodynamically and kinetically stable C–C bonds and yield value-added propionic acid derivatives is an attractive research topic.[1] Although the alkene carboxylation reactions were disclosed by many research groups,[2] carboxylation of alkynes is rarely reported as the C–C triple bond is relatively stable and inert.[3] In addition, introduction of deuterium into pharmaceutical drugs could potentially improve the metabolic stability and pharmacokinetics of the original molecules.[4] For example, deutetrabenazine (Austedo®) was approved as the first deuterium-labeled drug in 2017 by the FDA for the treatment of choreas associated with Huntington's disease.[5] Recently, d_4-butyric acids[6] and d_3-L-DOPA[7] were investigated in clinical trials for treatment of narcolepsy and Parkinson's disease, respectively (Fig. 1a). The development of deuterated analogues of the original drugs was proved to be the effective drug discovery process in medicinal chemistry and therefore attracted more and more attention in the synthetic chemistry community.[4,8] For reductive carboxylation of alkynes, since 2018, a number of examples were reported utilizing various deuteration reagents, such as C_2H_5OD, D_2O, TfOD, or deuterated silanes (Fig. 1b).[9] In 2021, Evano and co-workers reported an elegant selective deuteration reaction with electron-poor alkynes as the substrate to access diverse di- and tetra-deuterated alkylamines.[9e] However, development of direct protocols for alkyne deuterocarboxylation to access multi-deuterated propionic acid derivatives is challenging yet highly desired.

Traditional strategies to access d_4-propionic acids from alkynes relied on multi-step manipulations and tedious conditions (Fig. 1c). The terminal alkynes could be carboxylated with different carbonyl sources, such as CO or CO_2, in the presence of transition metals[10] or basic conditions,[11] respectively. Afterward, the alkynyl carboxylic acids/esters could undergo hydrogenation with D_2 (ref. 12) or reductive deuteration with D_2O

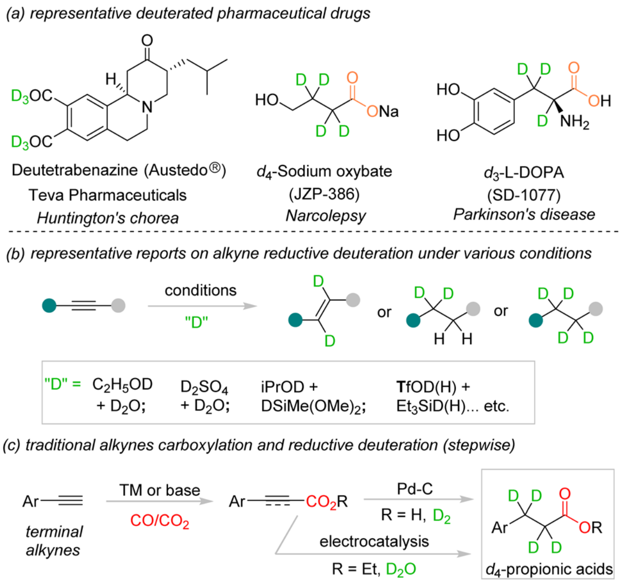

Fig. 1 (a) Representative deuterated drugs on the market and in clinical trials. (b) Well developed reductive deuteration of alkynes. (c) Traditional procedures for alkyne deutero-carboxylation.

Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, School of Pharmacy, Xuzhou Medical University, 209 Tongshan Road, Xuzhou 221004, China. E-mail: longyin@xzhmuedu.cn; guo@xzhmu.edu.cn; xuzhu@xzhmu.edu.cn

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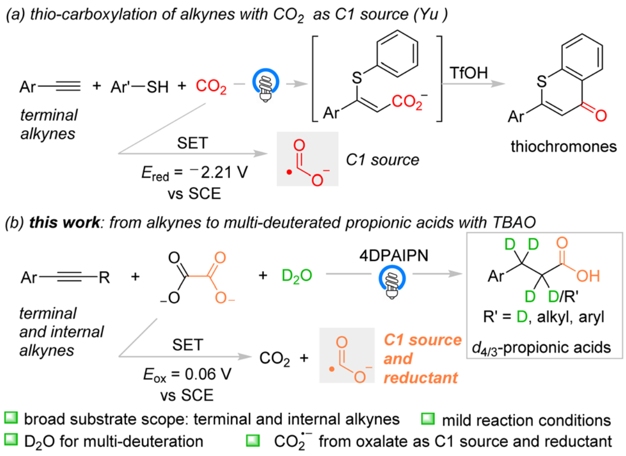
‡ These authors contributed equally.

under transition metal mediated[13] or electrochemical[14] conditions to access deuterated propionic acids. To date, direct conversion of either terminal or internal alkynes to the corresponding fully deuterated propionic acids in one step is still not realized. Development of a new protocol with a new carbonyl source is crucial to solve the above problem.

Compared with the commonly used carbon dioxide as the carbonyl source under photocatalytic conditions,[15] the carbon dioxide radical anion ($CO_2^{\bullet -}$),[2b,15b,c,e,16] with reversed polarity, was recently developed as a novel carbonyl source for carboxylation of alkenes *via* Giese radical addition in synthetic organic chemistry.[17] Interestingly, in 2023, Yu and co-workers reported that $CO_2^{\bullet -}$ generated from CO_2 ($E_{red} = -2.21$ V *vs.* SCE) *via* single electron transfer (SET) was able to undergo radical addition to the terminal alkynes and install the carboxy group (Scheme 1a).[18a] In the presence of aryl thiol, the C–S bond was formed *via* radical–radical coupling and the subsequential cyclization afforded thiochromones as the final products. This is the first example which showcased the possibility of the carboxylation of alkynes with $CO_2^{\bullet -}$ under photo-induced conditions, which encouraged us to devote efforts to alkyne carboxylation reactions under mild reaction conditions. Herein we disclose our recent discovery of deuterocarboxylation of various terminal and internal alkynes with tetrabutylammonium oxalate (TBAO) as the $CO_2^{\bullet -}$ precursor under photoredox-neutral conditions to access diverse aryl $d_{4/3}$-propionic acids (Scheme 1b).

There are a couple of obstacles to overcome for regio- and chemoselective deuterocarboxylation of alkynes with D_2O as the cheapest deuteration agent. Existence of any protonic agents, solvents, or hydrogen atom transfer process could decrease the deuteration ratio. In addition, realizing the high α- or β-selectivity of the carboxylation step is also challenging.[19]

We noticed that TBAO, previously exploited as a co-reductant in electrogenerated chemiluminescence (ECL),[20] could be used as a new $CO_2^{\bullet -}$ precursor for carboxylation under mild reaction conditions.[21] The reaction mechanism involves the single-electron-oxidation of the oxalic dianion ($E_{ox} = 0.06$ V *vs.* SCE) by the oxidant or photocatalyst, followed by the subsequential homolytic C–C bond cleavage to produce $CO_2^{\bullet -}$.[22] Neither the protonic agent nor HAT process is involved during the generation of $CO_2^{\bullet -}$ from TBAO. Therefore, the deuterocarboxylation of terminal alkyne **1a** with TBAO and D_2O was used as a template reaction and initially investigated.



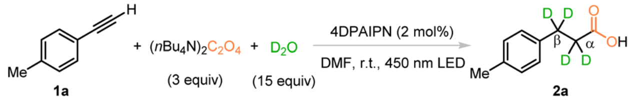
Scheme 1 Reported carboxylation of terminal alkynes and the reaction design for this study.

Results and discussion

After careful screening of various reaction parameters (see the ESI† for details), the best reaction conditions are showcased in Table 1, entry 1, namely, the treatment of the terminal alkyne 1-ethynyl-4-methylbenzene (**1a**) with 3 equivalents of TBAO and 15 equivalents of D_2O in the presence of 2 mol% 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile (4DPAIPN) in DMF under 450 nm blue LED irradiation yielded d_4-propionic acid **2a** in 85% isolated yield. The counter cations of the ammonium salt, such as NH_4^+ and Na^+, were tested and no conversion of the substrate was observed due to the poor solubility of these salts in organic solvent (Table 1, entries 2 and 3). Amounts of D_2O were also screened and the results showed that 15 equivalents of D_2O was optimal (Table 1, entries 4 and 5). Reactions conducted in DMSO provided product **2a** in slightly decreased yield and deuteration ratios at both the α- and β-positions (Table 1, entry 6). When DMA was used as the solvent, the reaction yield was increased to 96%; however the deuteration ratios dropped at each position (Table 1, entry 7). Without visible-light irradiation or a photocatalyst, the reaction did not occur and only the starting material **1a** was recovered (Table 1, entries 8 and 9). No reaction was observed in the absence of TBAO under a CO_2 atmosphere (Table 1, entry 10).

With the optimized reaction conditions in hand, the substrate scope of this novel deuterocarboxylation process of alkynes was investigated as shown in Table 2. Various terminal

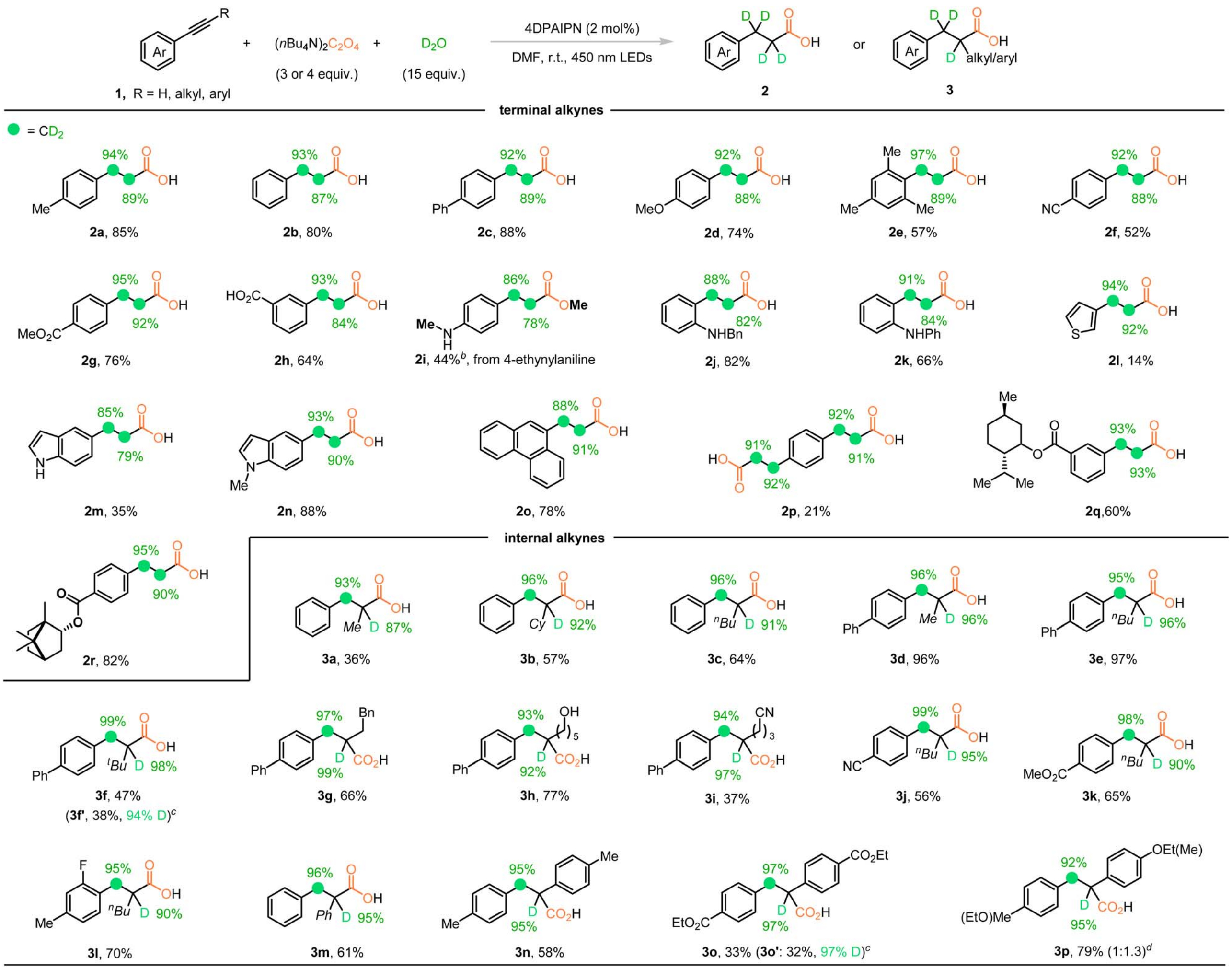
Table 1 Variation of the standard reaction conditions[a]



Entry	Variations	Yield of **2a**[b] (%)	Deuteration ratio (α/β)
1	None	91 (85)[c]	89%/94%
2	$(NH_4)_2C_2O_4$	0	—
3	$Na_2C_2O_4$	0	—
4	D_2O (8 equiv.)	91	75%/86%
5	D_2O (20 equiv.)	94	85%/92%
6	Anhydrous DMSO	85	82%/78%
7	Anhydrous DMA	96	85%/89%
8	In dark	0	—
9	W/o 4DPAIPN	0	—
10[d]	W/o TBAO	0	—

[a] Reaction conditions: **1a** (0.2 mmol), 4DPAIPN (2 mol%), TBAO (3 equiv.), in anhydrous DMF (0.1 M), r.t., 12 h under a N_2 atmosphere. [b] Crude ^1H NMR yield. [c] Isolated yield. [d] Under a CO_2 atmosphere.

Table 2 Substrate scope of various *N*-aryl acrylamides **1**[a]

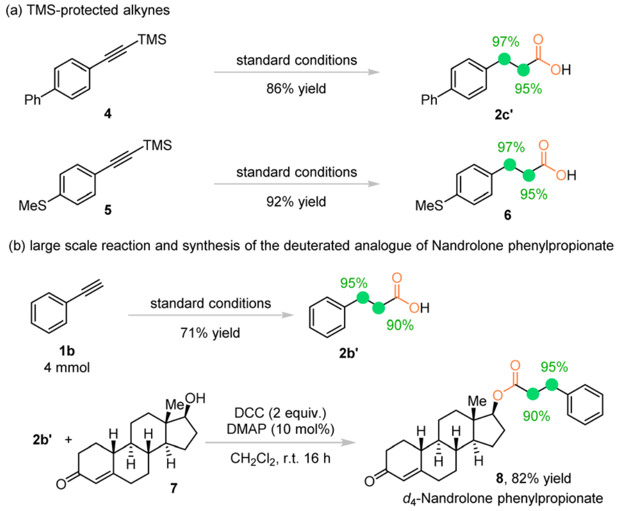


[a] Reaction conditions: **1** (0.2 mmol), 4CzIPN (2 mol%), TBAO (3 or 4 equiv.), anhydrous DMF (0.1 M), r.t., 12–48 h, under a N_2 atmosphere. [b] MeI was added after completion of the reaction. [c] Reductive deuteration product was isolated. [d] Two regioisomers were isolated as an inseparable mixture.

aryl alkynes were first investigated. Ethynylbenzene (**1b**) gave d_4-propionic acid **2b** smoothly in 80% yield. The ratios of 87% and 93% for deuteration at the α- and β-positions, respectively, were obtained. The terminal aryl alkynes tethering electron-donating groups, such as Ph and MeO groups, delivered the desired product **2c** and **2d** in good yields and deuteration ratios. Alkyne **1e** with two methyl substitutions at the *ortho* position provided d_4-propionic acid **2e** with a decreased yield of 57% due to the steric hindrance. The CN group could also be tolerated to give product **2f** in moderate yield and no decrease in the deuterium ratio at both α- and β-positions was detected. The ester moiety, which is vulnerable under reductive conditions, was also tolerated during the transformation to give product **2g** in 76% yield and high deuteration ratios up to 95%. Interestingly, substrate **1h** with a carboxy group on the aryl ring also worked well to give the corresponding product **2h** in 64% yield. 4-ethynylaniline (**1i**) was converted to the corresponding methylated propionic acid product **2i** in 44% yield after treatment with MeI before workup of the reaction, although the reaction yield and deuteration ratios were moderate. *Ortho-N*-benzyl substitution (**1j**) improved both the reaction yield and the deuteration ratios (**2j**). The more sterically hindered *ortho-N*-phenyl group led to better deuteration ratios with moderate yield (**2k**). Afterward, the sensitive heteroarene thiophene was examined. Although the reaction generated the desired product **2l** in only 14% yield, an average deuteration ratio of 93% was obtained. The instability of the thiophene ring under our reaction conditions caused the low yield. The other indole substituted alkynes also worked well to give moderate to good yields and deuteration ratios (**2m**, **2n**). The polyaromatic substrate 9-ethynylphenanthrene was converted to the corresponding aryl d_4-propionic acid **2o** in 78% yield and 90% average deuteration ratio. When 1,4-diethynylbenzene with two symmetric C–C triple bonds was employed under the reaction conditions, the d_8-diacid **2p** was isolated in high deuteration ratios, although a low yield was obtained. The alkynyl substrates derived from natural products, such as menthol and borneol, were investigated next and the corresponding d_4-propionic acids were produced in good yields and high deuteration ratios over 90% (**2q** and **2r**).

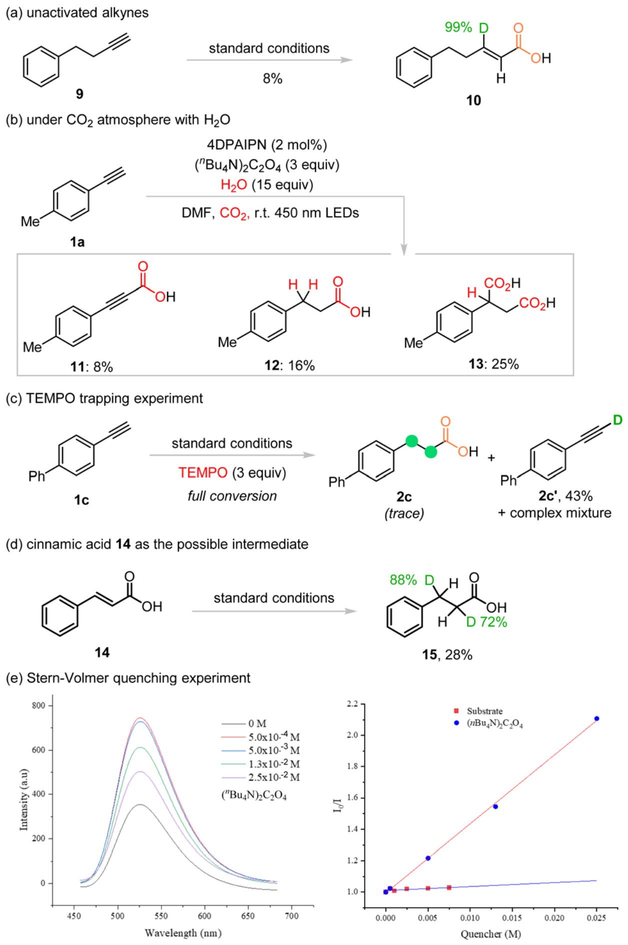
Compared with the terminal alkynes, deuterocarboxylation of internal alkynes under photocatalysis is also challenging and has never been reported before.[2h] With our established protocol, various internal alkynes were next investigated. As shown in the second part in Table 2, when the hydrogen on the terminal alkyne was replaced by alkyl groups such as Me, Cy, *n*-Bu, and phenethyl, the corresponding d_3-propionic acids **3a–3e** and **3g** were obtained, respectively, in up to 96% yield and over 90% deuteration ratios. Product **3a** was obtained in 36% yield, along with inseparable complex mixtures. When the steric hindered *t*-Bu group was incorporated, the reaction yield dropped to 47%, but extremely high deuteration ratios around 99% were observed (**3f**). In the meantime, almost equal amounts of reduction product **3f′** were isolated with a 94% deuteration ratio because the steric hindrance of the *t*-Bu group interrupted the carboxylation step. To further test the functional group tolerance of this reaction, the substrates tethering a free hydroxyl or cyano group on the alkyl chain were examined to give the corresponding functionalized d_3-propionic acids in moderate to good yields and high deuteration ratios (**3h**, **3i**). The cyano, ester, and fluoro substituents on the aryl ring were also investigated and the desired products **3j–3l** were obtained in good yields and deuteration ratios. Afterward, the 1,2-diaryl substituted internal alkynes were exploited and the deuterocarboxylation processes proceeded smoothly to give the desired products **3m** and **3n**. For an electron deficient substrate with an ester moiety as the substituent, direct reduction and deuteration was observed as a side reaction. A synthetically useful yield and high deuteration ratios were obtained for both products (**3o** and **3o′**). The unsymmetric 1,2-diaryl alkyne substrate provided the corresponding acid **3p** in 79% yield and high deuteration ratios up to 95% but poor regioselectivity was observed.

Interestingly, under our reaction conditions, the TMS protected alkyne **4** could be converted to the d_4-propionic acid **2c′** in even higher yield and deuteration ratios compared with the corresponding free terminal alkyne **1c**. The thiol ether substrate **5** underwent deutero-carboxylation smoothly to give acid **6** in 92% yield and 96% average deuteration ratio (Scheme 2a). Furthermore, the deuterium-labeled analogue of nandrolone phenylpropionate was synthesized in good yield and stable deuteration ratios from d_4-propionic acid **2b′** synthesized from a scaled-up reaction with increased deuteration ratios, proving it to be a practical method for synthesis of the deuterated version of biologically active molecules (Scheme 2b).



Scheme 2 (a) Further application of the protocol. (b) Synthesis of the deuterated analogue of nandrolone phenylpropionate.

To gain further insights into the reaction mechanism, several control experiments were conducted as shown in Scheme 3. Firstly, the unactivated alkyne **9** was utilized as the substrate to probe any possible intermediate during the Giese radical addition of $CO_2^{\bullet-}$ to the alkyne. When unactivated alkyne **9** was treated under the standard reaction conditions, the β-deuterated vinyl carboxylic acid **10** was observed in only 8% isolated yield with a very high deuteration ratio of 99%, along with inseparable complex mixtures (Scheme 3a). This result indicated that the alkenyl radical generated *via* Giese radical addition of $CO_2^{\bullet-}$ was reduced to the anion form and subsequently deuterated in the presence of excess amounts of D_2O. However, lack of a conjugated π-system caused low

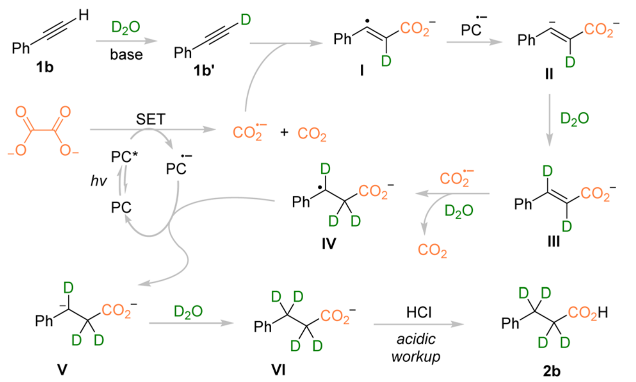


Scheme 3 Mechanistic studies.

reactivity and poor mass balance. Secondly, the template reaction of **1a** was investigated with normal H_2O under a CO_2 atmosphere (Scheme 3b). In the presence of CO_2, the reaction was disturbed and a complex mixture was observed. After careful investigation, byproducts **11**, **12**, and **13** were isolated and each of them was characterized by using NMR spectra and HRMS analysis.

Formation of **11** clearly showed that the alkyne **1a** underwent deprotonation under basic conditions and the anion form of **1a** trapped CO_2 to form the carboxylic acid. Therefore, under a N_2 atmosphere, proton–deuterium exchange occurred first in the presence of excess amounts of D_2O in our reaction to give the deuterated **1a**, which could accept the attack by $CO_2^{\bullet -}$ to establish the first carboxy group. Product **12** could be derived from either **11** or the cinnamic acid intermediate. For product **13**, incorporation of the second carboxy group at the benzyl position indicated formation of the benzyl anion intermediate during the transformation. When 3 equivalents of TEMPO were added to the reaction mixture, full conversion could be observed, but only trace amounts of the desired product **2c** were detected, along with H–D exchanged product **2c′** in 43% isolated yield. This result indicates that the formation of radical species during the transformation and the deuterocarboxylation process was disturbed (Schemes 3c). To determine if cinnamic acid was one of the intermediates, **14** was treated under standard reaction conditions and the desired product **15** was obtained in 28% yield and good deuteration ratios (Scheme 3d). Next, the Stern–Volmer quenching analysis was conducted with substrate **1a** and TBAO; the results showed that the excited state of photocatalyst 4DPAIPN was quenched by TBAO effectively (Scheme 3e, see the ESI† for more details).

As shown in Scheme 4, on the basis of the control experiments and reported literature,[20–22] we proposed that the reaction was first initiated by photo-exciting 4DPAIPN to form 4DPAIPN* ($E^*_{\text{red}} = 1.53$ V *vs.* SCE) that could oxidize TBAO ($E_{\text{ox}} = 0.06$ V *vs.* SCE) and generate the oxalic radical anion ($C_2O_4^{\bullet -}$), which subsequently underwent homolysis of the C–C bond to give $CO_2^{\bullet -}$ and CO_2. Under basic conditions, alkyne **1b** was deprotonated and deuterated rapidly to give **1b′** and underwent the Giese radical addition of $CO_2^{\bullet -}$ to give intermediate **I**. The vinyl radical **I** was reduced by 4DPAIPN$^{\bullet -}$ ($E_{1/2} = -1.52$ V *vs.* SCE) to produce anion intermediate **II**, which was deuterated by D_2O to yield intermediate **III**. Afterward, the anion form of vinyl acid **III** could be further reduced by $CO_2^{\bullet -}$ (or 4DPAIPN$^{\bullet -}$) to generate the benzyl radical species **IV**, which could be reduced by 4DPAIPN$^{\bullet -}$ (or $CO_2^{\bullet -}$), producing intermediate **V**. Finally, deuteration of intermediate **V** provided d_4-propionic anion **VI** that could be protonated upon acidic workup to give the desired product **2b**.



Scheme 4 Proposed mechanism for deuterocarboxylation of alkyne 1b.

Conclusions

In summary, a visible-light-induced photoredox-neutral alkyne deuterocarboxylation reaction using TBAO as both the C1 source and reductant was developed. This study provides a novel approach for $d_{4/3}$-propionic acid synthesis with super stoichiometric D_2O as the cheapest deuteration agent. The reaction is mild, clean, and sustainable, with broad substrate scope and a novel reaction mechanism. Most of the deuteration ratios are over 90%, which is close to the requirement of pharmaceutical drugs, indicating the application potential of our synthetic method. Further applications of TBAO as the $CO_2^{\bullet -}$ precursor in synthetic organic chemistry under sustainable reaction conditions are currently under investigation.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Pei Xu, Hao-Qiang Jiang, and Hui Xu performed the experiments and data collections, including $^1H/^{13}C$ NMR data, HRMS, and Stern–Volmer quenching experiments. Sai Wang and Hui-Xian Jiang prepared all the starting materials. Song-Lei Zhu assisted in the measurements of the above experiments and helped to supervise the project. Long Yin and Dong Guo assisted in the project design and preparation of the manuscript. Xu Zhu conceived the project, supervised the research, wrote the manuscript, and provided guidance for the analysis of the results.

Conflicts of interest

There are no conflicts to declare.

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