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2020

Zhang, X., Chen, Q., Song, R., Xu, J., Tian, W., Li, S., Jin, Z. & Chi, R. Y. (2020).
Carbene-catalyzed α,γ -deuteration of enals under oxidative conditions. ACS Catalysis,
10(10), 5475-5482. <https://dx.doi.org/10.1021/acscatal.0c00636>

<https://hdl.handle.net/10356/148639>

<https://doi.org/10.1021/acscatal.0c00636>

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Carbene-Catalyzed α,γ -Deuteration of Enals under Oxidative Conditions

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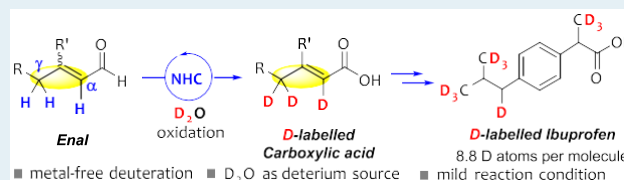


Supporting Information

ABSTRACT: Organic compounds with deuterated allyl groups are very attractive for drug entities to enhance pharmacokinetic properties, since allylic C–H bonds are prone to metabolic oxidation and the deuterated versions can be less prone to such metabolism. However, direct deuteration at allylic C–H moieties is still a challenge. Few examples have been reported by transition-metal catalysis and no such reports have been documented in an

organocatalytic fashion. Herein, a carbene-catalyzed C–H deuteration of enal at allylic C(sp³) and C(sp²) centers is disclosed. Addition of the carbene catalyst to the aldehyde moiety of enals to eventually activate the α - and γ -carbon atom under oxidative conditions is critical to achieve high deuterium incorporation. Key mechanistic steps of our reaction include carbene catalyst addition, azolium ester formation, remote γ -carbon activation, reversible α - and γ -carbon enolization, and iterative H/D exchanges. The reaction is performed under mild conditions using D₂O as the deuterium source to efficiently afford α,γ -deuterated 2-alkenoic acids and their derivatives in good to excellent yields and high deuterium incorporation. These labeled products containing carbonyl and allyl bifunctionalities are valuable building blocks for further transformations, eventually leading to otherwise challenging labeled targets including deuterated allylic derivatives, aliphatic derivatives and polydeuterated drugs (e.g., Ibuprofen). The convenient and scalable synthesis has application potential for materials and pharmaceuticals.

KEYWORDS: carbene catalysis, C–H deuteration, allyl group, enal, polydeuteration



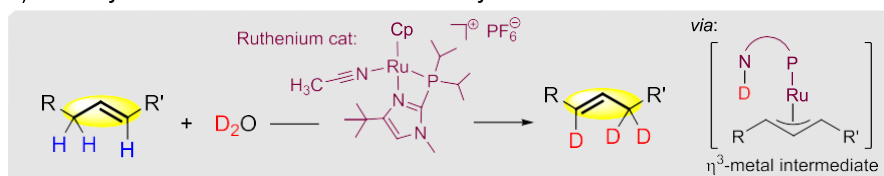
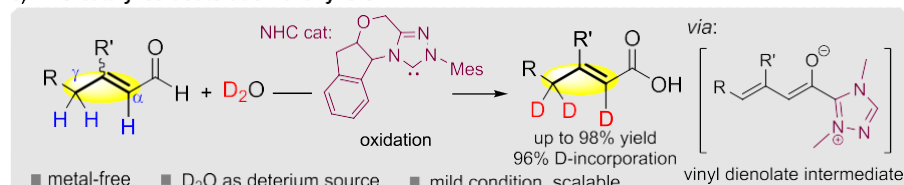
INTRODUCTION

Deuterium-labeled compounds exhibit distinct properties and offer significant value for both fundamental research and practical applications.^{1–3} In chemistry, study of kinetic isotope effects (KIE) using deuterium-labeled compounds provides mechanistic insights on reaction pathways.^{4,5} In biology and medicinal sciences, deuterium-labeled compounds are frequently used for metabolism elucidation^{6,7} and drug discovery.^{8–10} Pharmaceutical molecules with part of the protium atoms replaced by the deuterium isotopes can show improved pharmacological effects.^{8–10} Not surprisingly, the development of catalytic H/D exchange methods for direct conversion of carbon–hydrogen (C–H) bonds to carbon–deuterium (C–D) bonds has received considerable attention.^{11–25} Although there are many reports of H/D exchange at aromatic,^{12–17} aliphatic,^{18–21} and olefinic^{22–25} C–H bonds, there are surprisingly few such reports for allylic C–H bonds.^{26,27} Considering the fact that allylic C–H bonds are prone to metabolic oxidation,⁶ direct H/D exchange reactions at allyl groups are highly desirable for drug entities to improve pharmacokinetic properties.^{8–10} Particularly, Grotjahn and co-workers have reported, in 2009, a ruthenium-catalyzed method for selective deuteration and isomerization of nonactivated alkenes at allyl groups (see Chart 1a).²⁶ However, in addition to limited functional group tolerance, the side reactions, such

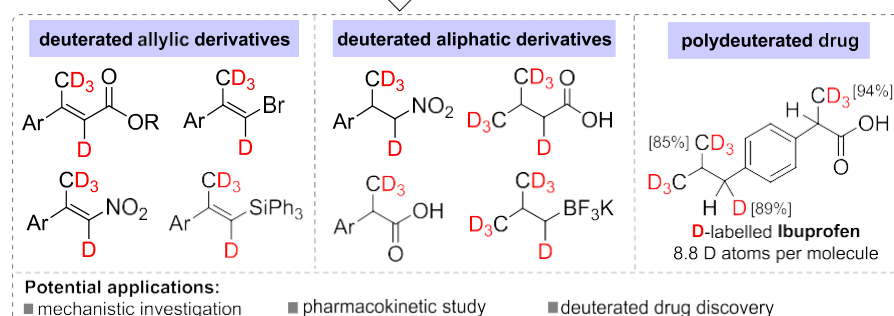
as C–C bond migration mediated by η^3 -allyl-metal intermediate, increases the challenges associated with metal-catalyzed allylic C–H deuteration reactions.

Here, we disclose an organocatalytic method for highly efficient conversion of multiple protons at the α - and γ -carbon atoms of enals to deuterium isotopes (Chart 1b). Our reaction involves addition of N-heterocyclic carbene (NHC) catalyst to the aldehyde moiety of enals to eventually activate the α - and γ -carbon atoms.^{28,29} The reactions are performed under mild conditions with D₂O as the deuterium source. As an important note, previous efforts in using NHC as a base or covalent catalyst to facilitate H/D exchanges mainly involved the α -carbons of carbonyl compounds^{30,31} or the formyl groups of aldehydes.^{32,33} Specifically, Vora and Rovis described an NHC-catalyzed α -carbon deuteration of α,α -dichloro aldehyde at ambient temperature.³¹ Very recently, the Yan group³² and the Wang group³³ independently reported the H/D exchange of formyl groups using NHC catalysis to provide C1 deuterated

Chart 1. Direct Deuteration of Allylic C–H Bonds

Previous work:**a) Ru-catalyzed isomerization and deuteration of allylic C–H bonds**^{ref. 26}**This work:****b) NHC-catalyzed deuteration of allylic C–H bonds**

downstream derivatization

**Potential applications:**

mechanistic investigation

pharmacokinetic study

deuterated drug discovery

aldehydes. To the best of our knowledge, to date, NHC-catalyzed H/D exchange at allylic C–H bonds has not been disclosed.

Our method is scalable and affords deuterium-enriched unsaturated carboxylic acids/esters (or termed as α,γ -deuterated 2-alkenoic acids) containing labeled allyls. Although H/D exchange at the α -position of carboxylic acids has been documented by Stuart and co-workers, extension to γ -position remains challenging.³⁴ Commonly practiced routes to these labeled compounds involve multistep synthesis, the use of expensive deuterated starting materials, and suffer from functional group tolerance.³⁵ These products are stable for storage and, more importantly, valuable for further transformations at either carbonyl or allyl functional groups, eventually leading to labeled targets. For example, deuterated allyl derivatives can be easily accessed by harnessing the decarboxylative functionalization methodologies, which may have potential in mechanistic investigations or pharmacokinetic studies. In addition, hydrogenation of the C=C bond can give rise to polydeuterated aliphatic derivatives, which are difficult to access by direct H/D exchange on the inert aliphatic C–H bonds. Lastly, polydeuterated drug molecules (such as Ibuprofen) can be accessed, thus proving an additional synthetic tool in the growing field of deuterated drug discovery.

RESULTS AND DISCUSSION

We started by using cinnamaldehyde with a β -methyl substituent (1a) as a model enal substrate and D_2O as the deuterium source. Selected results from relatively intensive

condition screenings are summarized in Table 1. With DABCO as the base, nitrobenzene as the oxidant, and CH_3CN as the solvent, triazolium-based NHC precatalysts with an *N*-phenyl (A)³⁶ or pentafluorophenyl (B)³⁷ substituent were ineffective in converting 1a to the corresponding carboxylic acid (2a) (see Table 1, entries 1 and 2). When triazolium NHC precatalyst with an *N*-mesityl substituent (C)³⁸ was used, 2a was obtained in 81% yield with a very encouraging degree of deuteration on both α - and γ -carbon atoms (see Table 1, entry 3). Specifically, 74% and 80% of the proton atoms were replaced by deuterium isotopes on the α - and γ -carbon atoms, respectively. Extensive additional studies with achiral triazoliums (A–D³⁹), imidazolium⁴⁰ (E), and thiazolium⁴¹ (F)-based NHC precatalysts did not lead to satisfactory product yields or deuteration levels (Table 1, entries 1–6; also see the Supporting Information (SI)). We then found that the use of aminoindanol-derived precatalyst G⁴² could lead to much better results, with 2a being formed in 91% isolated yield, 77% α -deuteration (D_α), and 90% γ -deuteration (D_γ) (see Table 1, entry 7). We next further optimized the reaction conditions using G (racemic form) as the NHC precatalyst (Table 1, entries 8–13). Several oxidants (DQ, phenazine, hexachloroethane) previously used in NHC oxidative catalysis^{43–47} were then evaluated, among which the use of phenazine offered the best results based on the yield, deuterium incorporation (D_α , D_γ), and the content of unlabeled CH_3 residue (see Table 1, entry 9; 90% yield, 73% D_α , 92% D_γ , and 1.7% unlabeled CH_3 moiety (see Figure S1 in the SI)). Elevated temperature (80 °C) further improved the degree of α -deuteration to 88% (Table 1, entry 12). Increasing

Table 1. Reaction Optimization.^a

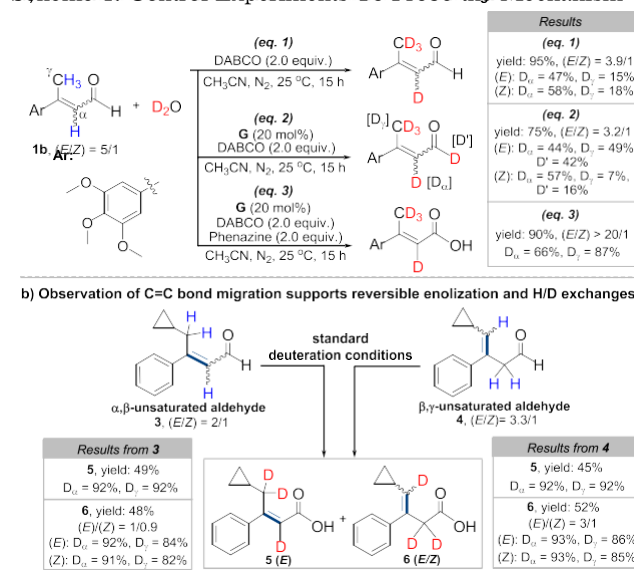
NHC precursor: 					
Oxidant: 					
entry	NHC	oxidant	temperature, T [°C]	yield ^b [%]	D _α /D _γ ^c [%]
1	A	nitrobenzene	25	trace	—
2	B	nitrobenzene	25	trace	—
3	C	nitrobenzene	25	81	74/80
4	D	nitrobenzene	25	70	68/85
5	E	nitrobenzene	25	n.d.	—
6	F	nitrobenzene	25	43	72/83
7	G	nitrobenzene	25	91	77/90 ^d
8	G	DQ	25	31	53/56
9	G	phenazine	25	90	73/92 ^e
10	G	C ₂ Cl ₆	25	n.d.	—
11	G	phenazine	40	95	83/92
12	G	phenazine	80	96	88/91
13 ^f	G	phenazine	80	98	91/93 ^g

^aConditions: 1a (0.1 mmol, *E/Z* = 3/1), D₂O (40 equiv), NHC precursor (20 mol %), DABCO (1.0 equiv), oxidant (2.0 equiv), CH₃CN (1 mL), 25 °C, N₂ atmosphere and 24 h. ^bIsolated yield after workup. n.d. = not detected. ^cDeuterium incorporations (D_α and D_γ) were determined by ¹H NMR analysis of the product. ^dWith 4.3% unlabeled CH₃. ^eWith 1.7% unlabeled CH₃. ^f2.0 equiv of DABCO. ^gWith 0.3% unlabeled CH₃.

the loading of DABCO (2.0 equiv) resulted in 2a with almost quantitative yield and 91% D_α and 93% D_γ deuteration (Table 1, entry 13).

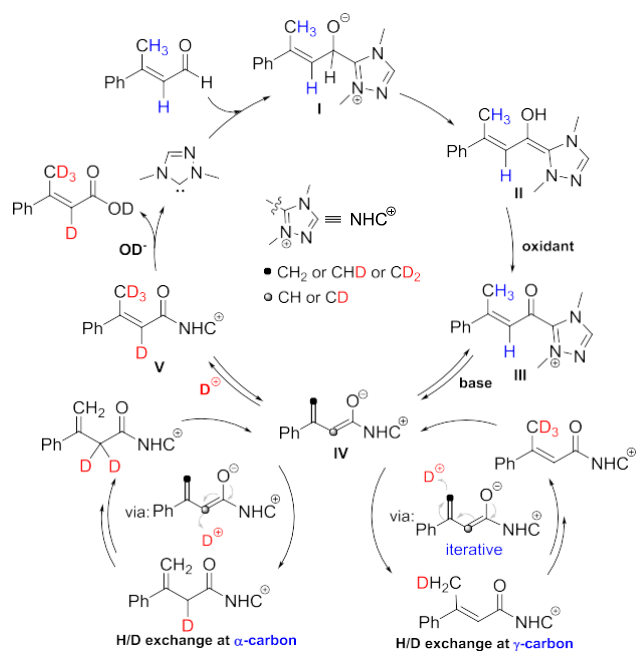
In metal-catalyzed allylic C–H deuteration reactions, the allyl can directly react with the metal center to activate the C–H bonds for subsequent H/D exchange.²⁶ Although it has been established that nucleophilic addition of a carbene to an aldehyde moiety of enal can activate the allylic γ -C–H bonds under oxidative conditions,⁴⁷ this activation has been used mainly for C–C bond formation, and it has not been developed for C–D bond formation. Control experiments were conducted to gain mechanistic insights into the reaction pathways (see Scheme 1). In the absence of carbene catalyst, H/D exchange of 1b at α - and γ -carbon is ineffective in the presence of DABCO, especially at the γ -position (D_α = 47–58%, D_γ = 15%–18%; see Scheme 1a, eq 1). Interestingly, the addition of a catalytic amount (20 mol %) of carbene precursor (G) promoted the γ -deuteration (D_γ = 49%) for the (*E*)-isomer but caused a low degree of deuteration (D_γ = 7%) for the (*Z*)-isomer, which indicated that the γ -deprotonation of the (*E*)-isomer might be more favored over the (*Z*)-isomer. The distinct reactivity of (*E*)- and (*Z*)-enals in NHC-catalyzed reactions has been previously documented by our group.⁴⁸ Deuteration at the aldehyde site (D' = 16%–42%, Scheme 1a, eq 2) could also be detected in the presence of the carbene

Scheme 1. Control Experiments To Probe the Mechanism



catalyst (likely via reversible Breslow intermediate formation).⁴⁹ When the external oxidant (phenazine) was added, (*E*)-carboxylic acid was isolated as the thermodynamically stable product with significantly enhanced deuteration at the γ -carbon position (D_γ = 87%; see Scheme 1a, eq 3). These control experiments indicate that formation of an azolium ester intermediate⁴⁴ under the oxidative conditions is responsible for the effective H/D exchange. When γ -cyclopropyl-substituted enal (3) was used as a substrate, C=C bond isomerization/migration was observed with the formation of β,γ -unsaturated carboxylic acid (6) as one of the products (Scheme 1b). Independent treatment of β,γ -unsaturated aldehyde (4) under an otherwise identical condition also afforded products 5 and 6 in almost full conversion and high deuterium incorporations (Scheme 1b). In both cases (using 3 or 4 as the substrate), no cyclopropane ring opening products were detected. The results support a reversible enolization, deprotonation, and deuterium-protonation processes during our catalytic H/D exchange reaction. No H/D exchanges were observed for the α,β -unsaturated carboxylic acid under current deuteration conditions.

A plausible pathway of our NHC-catalyzed deuteration reaction involving oxidation, reversible enolization, and iterative H/D exchange is illustrated in Scheme 2. The nucleophilic addition of the NHC to the aldehyde group of enal leads to intermediate I^{50,51} and the subsequently formation of a Breslow intermediate II,⁴⁹ which undergoes an oxidation to generate an α,β -unsaturated triazolium ester intermediate III.⁴⁴ γ -C–H deprotonation and enolization of III under basic conditions affords a vinyl dienolate intermediate IV^{28,29} that behaves as a key intermediate for iterative H/D exchange at both α - and γ -carbon atoms. Finally, hydrolysis of the deuterated α,β -unsaturated triazolium ester intermediate V yields the corresponding unsaturated carboxylic acid with regeneration of the carbene catalyst. This hydrolysis step appears to be much slower than the enolization and H/D exchange steps, which is consistent with our previous study on NHC-catalyzed dynamic kinetic resolution of carboxylic esters.⁵² Alkene positional isomerization/migration was observed in transition-metal-catalyzed allylic deuteration

Scheme 2. Proposed Mechanism for NHC-Catalyzed Deuteration of α - and γ -Carbon Atoms of Enal

reactions via η^3 -allylic-metal intermediates.²⁶ In our organic catalytic reaction, this type of C–C bond migration is likely attributed to the competing hydrolysis pathway of the β,γ -unsaturated triazolium ester intermediate in the presence of D₂O. It is worth mentioning that NHC-catalyzed reactions in water have been reported by our group,⁵³ and we believe that the utilization of nonexpensive D₂O as the deuterium source can add additional values for the carbene-catalyzed incorporation of deuterium into organic molecules.

With acceptable conditions in hand, the scope of this transformation was investigated using electronically and structurally diverse enals as substrates (see Table 2). The reactions afforded (*E*)- α,β -unsaturated carboxylic acids (or esters) with simultaneous deuteration on both α - and γ -carbon atoms. We first evaluated enals bearing β -aryl substituents (2a–2r). Generally, substituents on the β -aryl ring of enals with both electronic-donating and electronic-withdrawing groups were well-tolerated, as exemplified by methoxyl (2b–2d), acetal (2e), and methyl (2f) as electronic-donating substituents and trifluoromethyl (2g) and fluoro (2k) as electronic-withdrawing groups. The reactions generally afforded excellent yields and high degrees of deuteration at the α - and γ -positions (see Table 2). An enal with a 2-naphthyl substituent could also be effectively deuterated to afford 2h, which is a useful synthon for naphthopyran-2-ones.⁵⁴ Slightly decreased yields of 2i and 2j (84% and 85% yields) were observed for enals bearing *ortho*-substituents at the β -aryl ring, likely due to steric effects. Notably, our metal-free protocol is compatible with halogen substituents in the substrates (2k–2n). These halogen substituents can be directly utilized for further derivatizations such as cross couplings. Replacing the hydrogen atom on the γ -carbon with phenyl (Ph) or CH₃ led to an erosion on product yield for 2o and 2p (85% and 60%, respectively) with negligible effects on deuterium incorporations. Conformationally constrained enals (with the γ - and phenyl-substituents connected to form a ring) were also well-tolerated, affording deuterated derivatives of cinnamic acids

Table 2. Substrate Scope of Enals with β -Aryl and γ -Substituents^a

Reaction scheme: Enal 1 + D₂O $\xrightarrow[\text{Phenazine (2.0 equiv.)}]{\text{G (20 mol %), DABCO (2.0 equiv.)}}$ Product 2a-2r (yields and D_α, D_γ values).

Legend: R' = $\text{C}_6\text{H}_4\text{NO}_2$

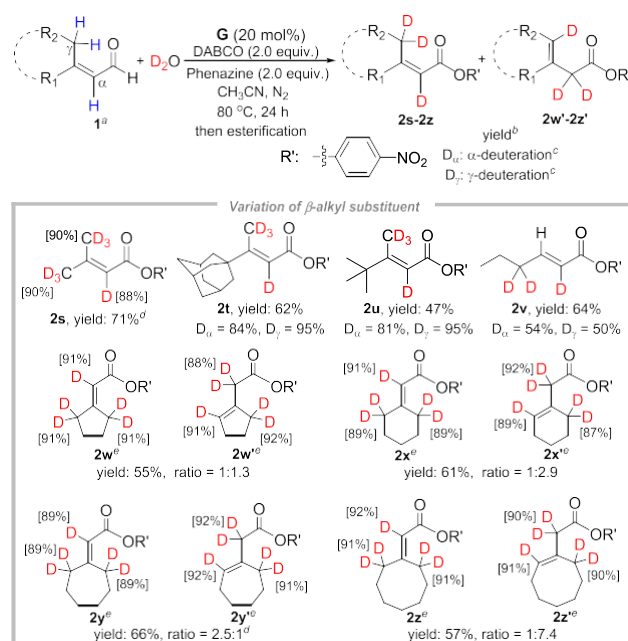
Variation of β -aryl and γ -substituent

Product	Yield (%)	D _α (%)	D _γ (%)
2a	98%	91%	93%
2b	95%	91%	95%
2c	90%	92%	94%
2d	88%	90%	96%
2e	96%	92%	96%
2f	94%	91%	93%
2g	94%	90%	94%
2h	96%	89%	94%
2i	84% ^d	90%	94%
2j	85% ^d	92%	94%
2k	95%	91%	94%
2l	92%	90%	96%
2m	90%	92%	95%
2n	90%	92%	95%
2o	85%	94%	94%
2p	60% ^{d,e}	90%	91%
2q	95%	93%	93%
2r	83% ^e	92%	94%

^aConditions: 1 (0.2 mmol), D₂O (40 equiv), G (20 mol %), DABCO (2.0 equiv), phenazine (2.0 equiv), CH₃CN (2 mL), 80 °C, N₂ atmosphere and 24 h. The *E*-isomer of enal is used except for 1a (*E*/*Z* = 3/1) and 1b (*E*/*Z* = 5/1). ^bIsolated yields after workup. ^cDeuterium incorporations (D_α and D_γ) were determined by ¹H NMR analysis of the product. ^dIsolated as *para*-nitrophenyl esters. ^eReacted at 40 °C.

(2q and 2r) exhibiting interesting bioactivities in regulating plant growth.⁵⁵

We next studied enals bearing β -alkyl substituents (2s–2z) (see Table 3). Enals with the β -substituent as methyl, 1-adamantan-1-yl, or *tert*-butyl unit could all be effectively D-labeled, albeit with a moderate reduction in product yields (47%–71%). A β -monosubstituted enal afforded a moderate level of deuteration at the α - and γ -carbons (2v), probably because of the less-favored dienolization pathway for the β -monosubstituted α,β -unsaturated acyl triazolium intermediate.⁴⁷ Interestingly, the cyclo-alkylated substituted enals gave rise to two types of products as α,β - and β,γ -unsaturated carboxylic esters (2w–2z, 2w'–2z') in moderate combined yields (55%–66%) and high degrees of deuterium incorporations (87%–92%). This C–C bond migration (2w'–2z') operates via a pathway similar to that of enal substrates 3 and 4 (see Scheme 2b). As a technical note, here, the reaction products (2w–2z, 2w'–2z') were isolated and characterized as the corresponding carboxylic esters in pure form after

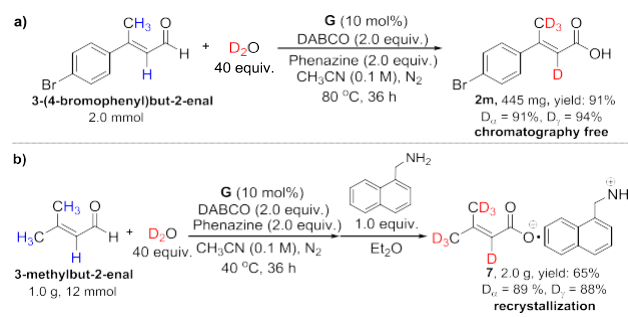
Table 3. Substrate Scope of Enals with β -Alkyl Substituents^a

^aConditions: 1 (0.2 mmol), D₂O (40 equiv), G (20 mol %), DABCO (2.0 equiv.), phenazine (2.0 equiv.), CH₃CN (2 mL), 80 °C, N₂ atmosphere and 24 h. ^bIsolated yields after workup. ^cDeuterium incorporations (D_α and D_γ) were determined by ¹H NMR analysis of the product. ^dReacted at 40 °C. ^eIsolated and characterized in pure form.

esterification with *p*-nitrophenol. This is because the carboxylic acid adducts are volatile or only weakly visible under ultraviolet (UV) illumination during thin-layer chromatography. Noteworthy that α -methyl-substituted enal, α,β -unsaturated carboxylic acid, and β -ester substituted enal are noneffective substrates under the current deuteration conditions (see the general procedure section in the SI).

Our method is amenable for scale-up via simple operations without the need of column chromatography (see Scheme 3).

Scheme 3. Scale-Up Reactions



For example, deuteration of 3-(4-bromophenyl)but-2-enal on a 2.0 mmol scale under standard conditions could provide 2m (445 mg) in 91% yield, 91% D_α, and 94% D_γ (Scheme 3a) after a simple acid-base workup process. Deuteration of 3-methylbut-2-enal was performed on a gram scale using 10 mol % of NHC catalyst at 40 °C. A chromatography-free process was developed via recrystallization of the acid product with naphthalen-1-ylmethanamine (1.0 equiv) to afford the

corresponding salt 7 (2.0 g) in 65% isolated yield, 89% D_α, and 88% D_γ (see Scheme 3b).

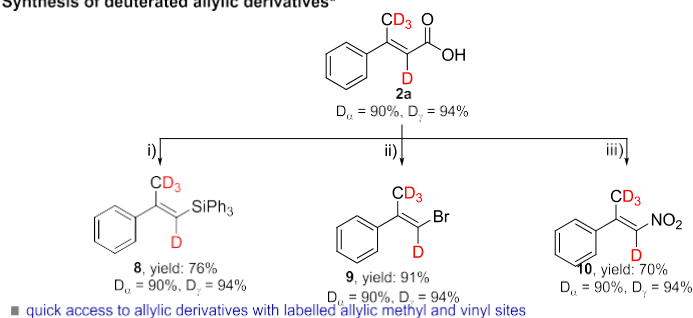
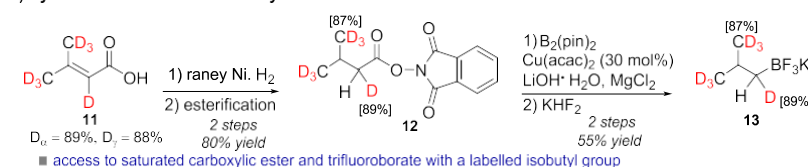
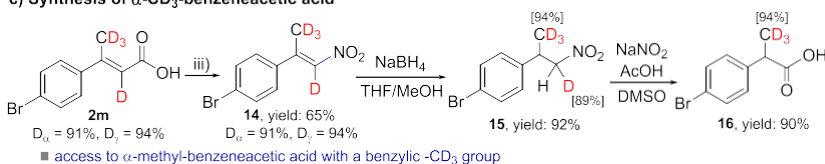
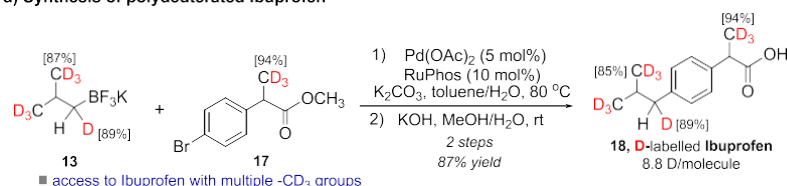
The deuterium-enriched products from our reactions can be readily transformed to other functional molecules at either carbonyl sites or allylic sites (see Scheme 4). For example, deuterated carboxylic acids could undergo decarboxylative silylation,⁵⁶ bromination,⁵⁷ and nitration⁵⁸ to afford vinylsilane (8), vinyl bromide (9), and nitroolefin (10), respectively (see Scheme 4a). These labeled allyl derivatives may have potential in pharmacokinetic studies or mechanism investigations. Moreover, hydrogenation of the C=C bond of a labeled allyl group can give rise to deuterated aliphatic moieties, which are difficult to access by direct H/D exchange on the inert aliphatic C-H bonds. As shown in Scheme 4b, the fully deuterated 3-methyl-2-butenic acid with two allylic -CD₃ substituents at the β -carbon (11) could be converted to the saturated carboxylic ester (12) and trifluoroborate (13), which contain a deuterated isobutyl group. Specifically, hydrogenation⁵⁹ of 11 catalyzed with Raney nickel followed by esterification with *N*-hydroxyphthalimide generated a redox-active ester 12 in 80% yield. Decarboxylative borylation⁶⁰ of 12, followed by treatment with KHF₂, furnished the deuterated isobutyl trifluoroborate 13 in appreciable yields (55% yields over two steps). Furthermore, selectively labeled α -CD₃-benzeneacetic acid 16 can be obtained from 2m via a three-step process (with 54% overall yield) involving decarboxylative nitration,⁵⁸ reduction,⁶¹ and oxidation⁶² (see Scheme 4c). In all of these transformations, the deuterium isotopes were retained. Notably, isobutyl and α -methyl-acetic moieties are widely presented in pharmaceuticals and nature products.⁶³ These deuterated molecule architectures might have applications in organic synthesis, mechanistic studies, and medicinal sciences.

To further demonstrate the utility of these products, we developed a concise route for access to polydeuterated Ibuprofen by using the deuterated synthons generated from our catalytic reactions and downstream derivatizations (Scheme 4d). Briefly, Suzuki coupling⁶⁴ of 13 and 17, followed by hydrolysis, afforded deuterium-labeled ibuprofen (18) in 87% yield over two steps. The multi deuterium isotope-labeled Ibuprofen contains 8.8 deuterium atoms per molecule at the aliphatic carbon atoms with <0.1% unlabeled compound, as confirmed by ¹H NMR and mass spectrum. Our approach provides a unique route toward the selective incorporation of one or multiple -CD₃ groups into pharmaceuticals and other functional molecules, which can benefit the discovery of deuterated drugs.

CONCLUSION

In summary, we have developed a metal-free method for efficient H/D exchange of enals at allylic C(sp³) and C(sp²) sites. The utilization of the NHC catalyst is essential to activate the γ -carbon atom and to achieve high deuterium incorporation. Our method involves mild reaction conditions with D₂O as a readily available, convenient-to-use, and inexpensive deuterium source. It offers a unique solution toward α,γ -deuterated 2-alkenoic acids/esters with allylic functionality that allows for wide synthetic transformations. A vast class of labeled molecules, including allylic derivatives, aliphatic derivatives, and polydeuterated drugs, can be readily accessed. These deuterated targets are otherwise difficult to access. The synthetic method is convenient and amenable for scale-up and

Scheme 4. Synthetic Applications

a) Synthesis of deuterated allylic derivatives^ab) Synthesis of deuterated isobutyl derivatives^bc) Synthesis of α -CD₃-benzeneacetic acid^bd) Synthesis of polydeuterated Ibuprofen^b

^aConditions: (i) CuCl (10 mol%), Ph₃SiH, *t*-BuOOH, *t*-BuOH, 110 °C; (ii) Dess-Martin periodinane, Et₄NBr, CH₂Cl₂, 25 °C; (iii) CuCl (20 mol %), *tert*-butyl nitrite, CH₃CN, 80 °C, air. ^bFor reaction details, see the SI.

may find applications in the field of materials science and pharmaceuticals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at

Experimental details and compound characterizations (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge financial support by National Research Foundation (NRF) Singapore, under its NRF Investigatorship (No. NRF-NRFI2016-06); the Ministry of Education of Singapore (Nos. MOE2016-T2-1-032, MOE2018-T3-1-003, RG108/16, and RG1/18); A*STAR Individual Research Grants (Nos. A1783c0008; A1783c0010); GSK-EDB Trust Fund; Nanyang Research Award Grant, Nanyang Technological University; the National Natural Science Foundation of China (Nos. 21772029 and 21472028); National Key Technologies R&D Program (No. 2014BAD23B01); The 10 Talent Plan (Shicengci) of Guizhou Province (No. [2016] 5649); the Natural Science Foundation of Guizhou Province (No. [2018]2802); the Guizhou Province First-Class Disciplines Project (No. GNYL(2017)008); Guizhou University of Traditional Chinese Medicine (China); and Guizhou University (China).

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