

Photoredox Catalyzed Site-Selective Generation of Carbanions from C(sp³)-H bonds in Amines

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Abstract:

The selective activation of sp³ carbon-hydrogen bonds in presence of multiple C-H bonds is challenging and remains of supreme importance in chemical research. Herein, we describe the activation of a C(sp³)-H bond in α -position to an amine *via* a carbanion intermediate. In the presence of several α -amine sites, only one specific position is selectively activated. Applying this protocol, the proposed carbanion intermediate was effectively trapped with different electrophiles such as deuterium (D⁺), tritium (T⁺), or carbonyl compounds compiling over 50 examples. Further, this methodology was used to install deuterium or tritium in different drug-derivatives (> 10 drugs) at a selected position in a late-stage functionalization. In addition, the protocol is suitable for a gram-scale synthesis and a detailed mechanistic investigation has been carried out to support our hypothesis.

Introduction:

Owing to their ubiquity, the activation of C-H bonds at sp³ carbon centers represents a continuous challenge with great interest in organic synthesis.^{1,2} Over the years, a wealth of methods for their activation in various positions has been developed, the majority of which relies on transition metal catalysis.³⁻⁷ Recently, photocatalysis has proven to be a valuable tool for C-H functionalization as well, offering novel approaches *via* single-electron transfer (SET) and hydrogen atom transfer mechanisms (HAT), in some cases including the aid of a metal catalyst.⁸⁻²³

While photocatalysis is most commonly known for radical reactivity,^{18,19} carbanion or carbocation species can be generated via a radical-polar crossover as well.²⁴⁻²⁹ In particular, the formation of carbanion^{28,29} intermediates in a photocatalytic and redox neutral fashion offers several advantages compared to traditional methods,^{30,31} such as full atom economy, no stoichiometric amount of metal waste (low valent Mg, Zn, or Li metals), and high functional group tolerance (limitation of classical methods; Fig. 1a).

Recently, our group³²⁻³⁴ and others^{35,36} have developed photocatalytic procedures for the activation of C(sp³)-H bonds to carbanion (equivalents) without the need of stoichiometric organometallic reagents. However, only C(sp³)-H bonds in benzylic^{32,34} and allylic position^{35,36} or in α -position to two sulfur atoms could so far be activated,³³ while C(sp³)-H bonds in aliphatic systems require a stoichiometric amount of chromium.³⁷ In spite of recent advances in this field, the regioselective generation of a carbanion intermediate in the presence of more than one potentially reactive site, using either this photocatalytic approach or a classical deprotonation, remains underdeveloped.

The late-stage transformation of pharmaceutically active compounds is of prime importance and continues to be in demand for novel organic transformations. In particular, amines are among the most important motives in natural products, agrochemicals, polymers, biologically active compounds, materials, and pharmaceuticals, with the majority of the commercially available drugs containing an amine or nitrogen moiety.^{38,39} In general, the generation of a carbanion in the α -amino position^{40,41} is exceedingly difficult due to the high pK_a, because of the low electronegativity of nitrogen and

destabilization from the lone pair interaction (Fig. 1a-b). In addition, in presence of multiple C-H bonds with similar pK_a values, all positions can be deprotonated using an organolithium base. Further, several functional groups are sensitive to harsh bases and cannot withstand these conditions.

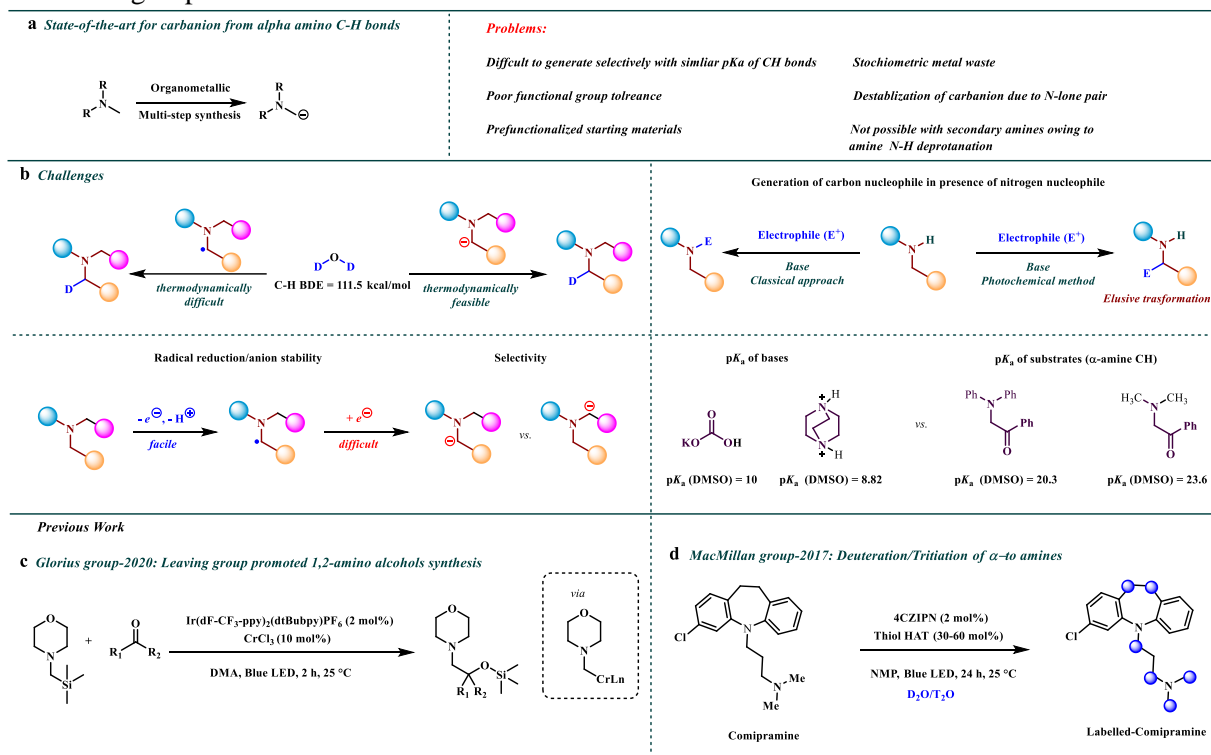


Fig. 1: Functionalization of α -amino C-H bonds. a, State-of-the-art for carbanion generation α to amine. b, Challenges to overcome in this proposed work. c, Radical chain process for indirect carbanion generation. d, Previous work on hydrogen isotope exchange on α to amines.

The group of Glorius⁴² solved this problem by using an anion stabilizing chromium catalyst (Fig. 1c). Unfortunately, the reactive carbanion equivalent cannot be generated directly from the C-H bond, yet requires a silicon pre-functionalization and is limited to primary alkyl nucleophiles due to chromium. A direct, site-selective carbanion generation from α -amino C-H bonds remains thus far elusive.

The preparation of deuterated organic compounds is fundamentally important in drug discovery research, as deuterated drugs can change the metabolism and improve the pharmacokinetics and toxicological properties.⁴³ An instance is deutetrabenazine, used for the treatment of Huntington's disease. The incorporation of deuterium within the methoxy groups resulted in improved metabolic properties and fewer adverse effects compared to the non-deuterated analogue.⁴⁴ A catalytic method for the direct conversion of C-H bonds into C-D bonds with a high degree of selectivity is thus of high interest in the area of drug discovery research. Accordingly, significant advances have been made in the deuteration/tritiation of organic compounds via metal- and photocatalysis.⁴⁵⁻⁵³ A notable example is the deuteration and tritiation of aromatic $C(sp^2)$ -H bond using a homogeneous iron catalyst, reported by the Chirik group.⁴⁸ This method shows an orthogonal selectivity to the traditional ortho-directing Crabtree iridium catalyst. There are only a few reports on the photocatalytic deuteration of $C(sp^3)$ -H bonds.^{50,51} In 2017, the MacMillan group⁵⁴ published the first photocatalytic approach for the deuteration/tritiation of α -amino C-H bonds. While this method features impressive isotope incorporation, it is not designed to do so in a regioselective manner (Fig. 1d).

Labelled amino acids are essential for biological *in vivo* and *in vitro* studies. The installation of deuterium in the α -position of amino acids can reduce the rate of epimerization and enhance the efficacy for elucidating biosynthetic pathways.^{54,55} Although these factors are of crucial interest for scientists in research and development, the preparation of deuterated amino acids or peptides with one-pot synthesis remains an elusive, yet an urgent task.^{51,56} In this regard, we herein describe a practically simple protocol for the site-selective generation of carbanions from α -amino $C(sp^3)$ -H bonds via a reductive radical-

polar crossover, without a HAT catalyst. This method was successfully implemented in a site-specific deuteration, tritiation, and 1,2-amino alcohols synthesis (Fig. 2). To the best of our knowledge, this is the first example of a photocatalytic, regioselective generation of an α -amino carbanion from a C(sp³)-H bond.

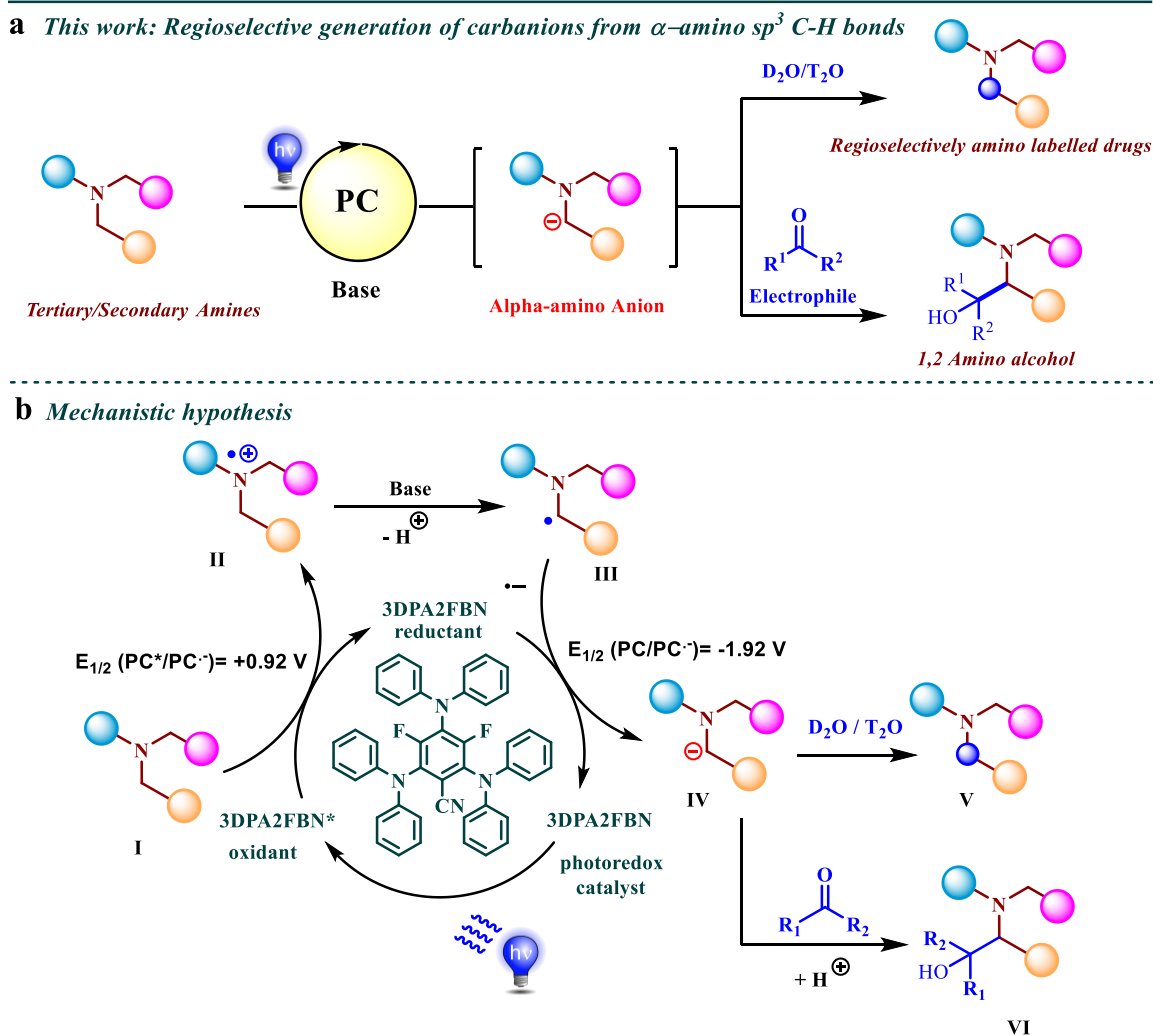


Fig. 2: Photoredox catalyzed carbanion generation and reaction development. **a**, The present work to regioselective carbanion generation. **b**, Mechanistic proposal, redox potentials are reported with SCE.

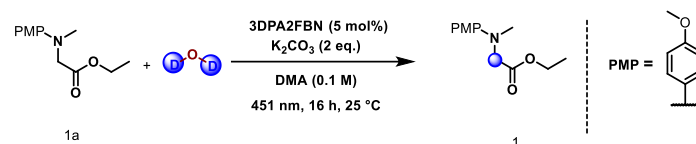
Results

Reaction discovery and developments:

Our envisioned catalytic cycle (**Fig. 2b**) starts with the oxidation of the amine (**I**) by the excited photocatalyst. Analogous to previously reported mechanisms,²² the thus formed amino radical cation (**II**) triggers rapid α -amino deprotonation, yielding a carbon-centered α -amino radical (**III**). This radical should then be converted to the desired carbanion intermediate (**IV**) by the reduced photocatalyst species, facilitated by the presence of an electron-withdrawing group. In accordance with this, *N*-(4-methoxyphenyl)-*N*-methyl glycinate (**1a**) was chosen as a simple model substrate. The *para*-methoxy phenyl group (PMP) was selected as the amine protecting group, as it should not hamper the initial oxidation. Additionally, PMP can be easily removed in a subsequent step to yield the corresponding free amine. A methyl group was adopted as the second *N*-substituent to introduce another α -amino position in order to test the anticipated selectivity. Finally, D₂O was employed as a potent carbanion trap and reasonably priced deuterium source to obtain the isotopically labelled compound. Gratifyingly, 5 mol% of 3DPA2FBN as photocatalyst in combination with 2 equivalents of K₂CO₃ as a mild base and DMA

(0.1 M) as solvent gave the desired deuterated compound **1** in high yield (85% NMR-yield) and excellent deuterium incorporation (1.80 D/molecule) within 16 h (Table 1, entry 1). As designed and desired, the α -amino position of the amino ester is exclusively deuterated, while the primary α -amino position remains untouched. This is exceedingly difficult to achieve using a photocatalytic HAT process, where both positions are likely to be deuterated.⁵⁴

Table 1: Control experiments



Entry	Deviation from the standard condition	D/molecule	Yield of 1a + 1 (%)
1	none	1.80	85
2	absence of PC	0	98
3	absence of base	0	97
4	absence of light	0	98
5	At 60 °C (dark)	0.12	94
6	At 60 °C (dark), DABCO as a base	0.01	95
7	24 h instead of 16 h	1.85	87

Reaction conditions: ^a0.1 mmol substrate, 5 mol% 3DPA2FBN, 2 eq. K₂CO₃, 15 eq. D₂O, 1 mL dry DMA (0.1 M), 451 nm, 25 °C, 16-24 h, ¹H NMR yield using dibromomethane as internal standard. Deuterium incorporation was measured by HRMS.

Control experiments revealed that photocatalyst, light, and base are essential for this transformation (Table 1, entries 2-4). Even at elevated temperature (60 °C), the absence of light leads to an insignificant deuterium incorporation, which clearly indicates that the reaction is of photocatalytic rather than thermal nature (Table 1, entries 5 and 6). Increasing the reaction time to 24 h slightly increases the deuterium incorporation further to 1.85 D/molecule. The complete optimization process, including photocatalyst, base, solvent, and time screening is given in the SI (Table S1-S8).

With the optimized conditions in hand, various amines, including complex structures were tested for hydrogen isotope exchange (HIE). All tested compounds shown in Fig. 3 gave good to excellent yields with excellent selectivity (> 95%) for the α -amino ester position. Substrates bearing an *N*-methyl, ethyl, and propyl substituent, gave the respective product in high yields with a selectivity of up to 99% for the deuterium incorporation (1-3). The same is true for cyclic amines (4) even in presence of a benzylic position. Sterically hindered amines underwent an efficient deuterium labelling as well (5-6). Opposed to a classical deprotonation with harsh bases, the here presented method offers a high functional group tolerance, with functionalities such as carboxylic esters, boronic esters (8), amides (9), and nitriles (10) remaining inert. A benzene ring can be placed between the α -amino position and the electron-withdrawing ester functionality (11), yet the deuterium incorporation decreases in this case. Replacing the PMP protecting group with a different aromatic substituent like toluene is possible as well (12). In addition to tertiary amines, secondary amines (R₂NH) are viable substrates, too (13-16). Notably, even electron-deficient secondary amines, bearing potential protic hydrogen are suitable substrates using this method (14-16).

The late-stage site-selective activation of C-H bonds in structurally complex, bioactive molecules is a crucial and challenging task.^{9,39,45} In this context, our protocol could be employed for the selective isotope labelling of more than 10 pharmaceutical analogues of antibiotic, antiviral, antidepressant, and

seizure drugs, rendering the desired product in good to excellent yields with a selectivity of up to 99% (**Fig. 4**). Remarkably, the targeted selectivity could be achieved in the presence of various other α -amine or α -hetero atom positions (**17-25**), *e.g.* present in the prominent morpholine (**17**), piperidine (**18-19**), and piperazine (**20-22**) moieties, which would likely be affected in a photocatalytic hydrogen atom abstraction approach. Along the same line, sugar derivatives could be deuterated in good yield and remarkable selectivity as well (**23-24**). Besides this, drug analogues bearing a glutarimide group (**25**), adamantane (**26**) functionality or an extended conjugated system (**27**) are accepted, too. Functionalized amino acids (**28**) and more challenging short peptide chains (**29**) can be deuterated, likewise. In this case, it is worth mentioning that untargeted chiral centers stay untouched (**29**), while a classical approach of employing a strong base is expected to lead to a racemization.

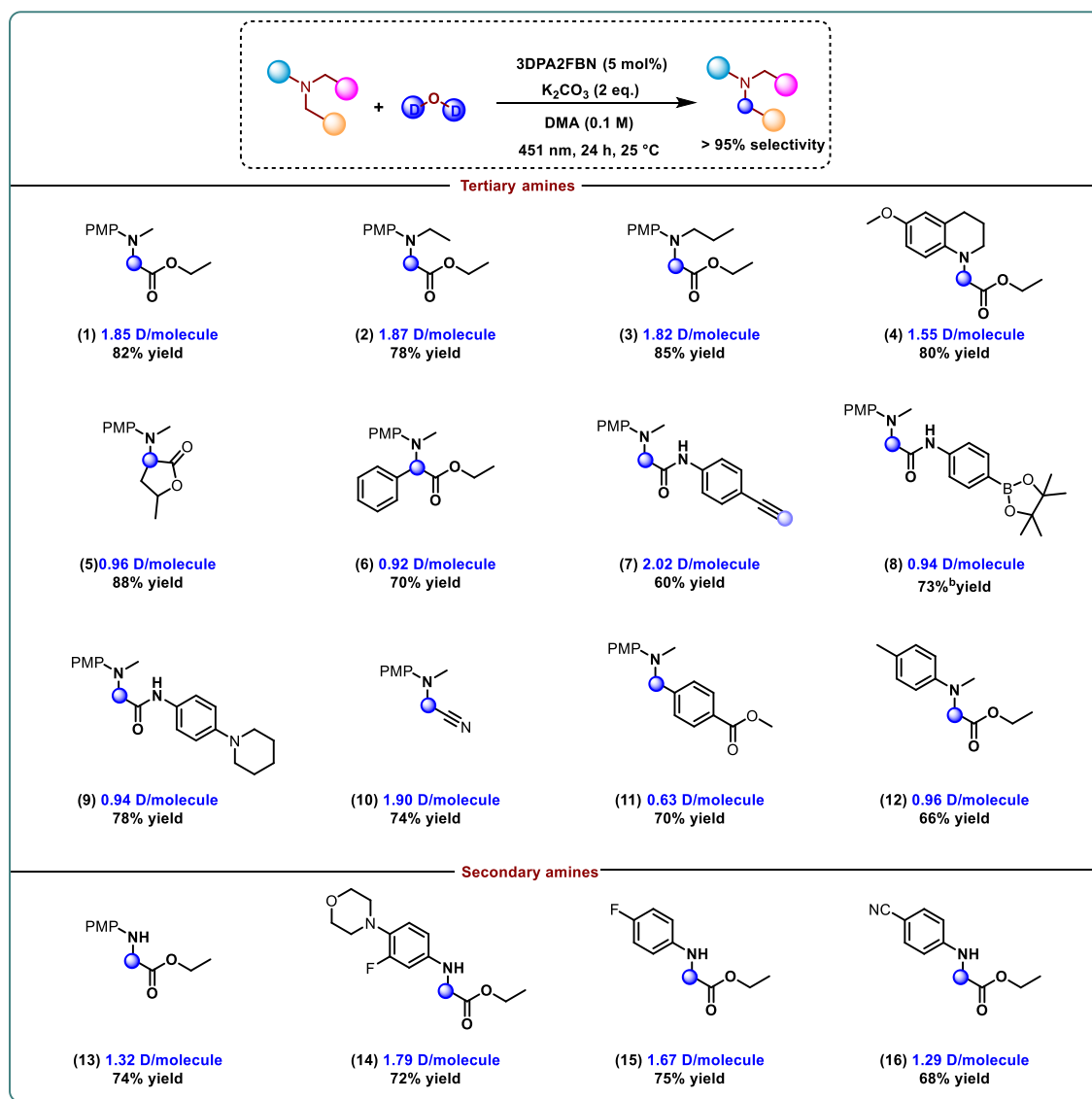


Fig. 3: Modular incorporation of deuterium to amines.

Reaction conditions: a 0.1 mmol substrate, 5 mol% PC (3DPA2FBN), 2 eq. K_2CO_3 , 15 eq. D_2O , 1 mL DMA (0.1 M), 451 nm, 25 $^\circ\text{C}$, 24 h, isolated yields. Deuterium incorporation was calculated based on ESI-MS and ^1H NMR. Selectivity was determined by ESI-MS, ^1H - and ^2H -NMR. PMP = *para* methoxy phenyl. b same as “a” with a reaction time of 48 h.

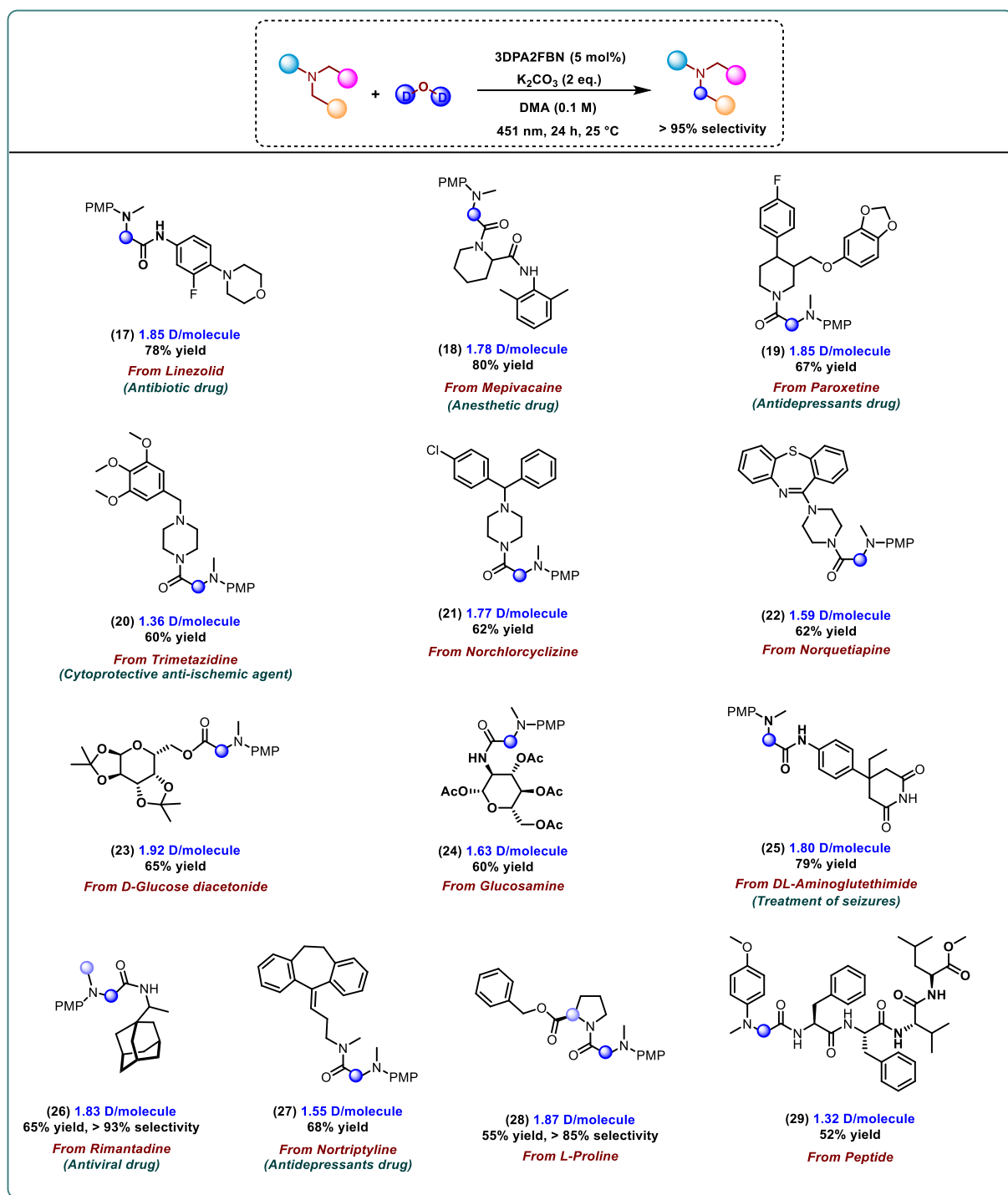


Fig. 4: Late-stage functionalization of pharmaceutically relevant molecules.

Reaction conditions: ^{18}O 0.1 mmol substrate, 5 mol% PC (3DPA2FBN), 2 eq. K_2CO_3 , 15 eq. D_2O , 1 mL DMA (0.1 M), 451 nm, 25 °C, 24 h, isolated yields. Deuterium incorporation was calculated based on ESI-MS and 1H NMR. Selectivity determined by ESI-MS, 1H - and 2H -NMR. PMP = *para* methoxy phenyl.

Tritiated compounds play a vital role in pharmaceutical research, as they can be used as a radiotracer for absorption, distribution, metabolism, and excretion (ADME) studies.^{45,48,54} Hence, we showcased the applicability of our protocol for the site-selective tritiation in one example (**Fig. 5**). In this case, an excellent selectivity together with high tritium incorporation was observed.

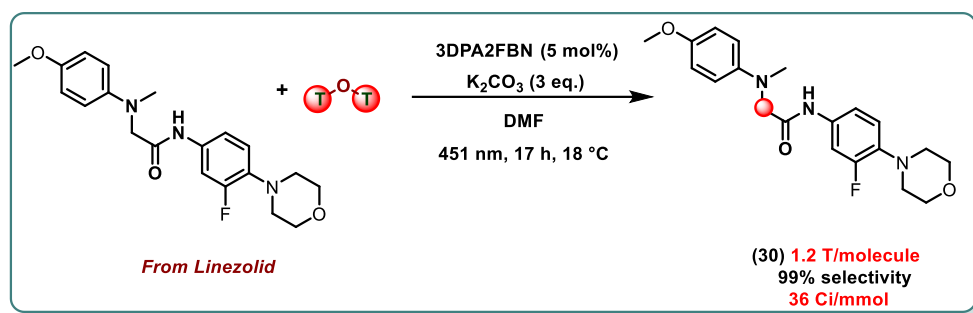


Fig. 5: Site-specific tritiation of complex molecules.

Reaction conditions: ^a6.7 μmol substrate, 5 mol% PC (3DPA2FBN), 3 eq. K₂CO₃, 5 eq. T₂O, 100 μL DMF, 451 nm, 18 °C, 17 h, isolated yields. Please see SI for detailed procedure.

Beside the application in isotope labelling the newly obtained carbanions bear the opportunity to expand the scope to late-stage functionalization towards C-C connection. Using *e.g.* carbonyl compounds as electrophiles, amino alcohols can be formed under mild conditions.

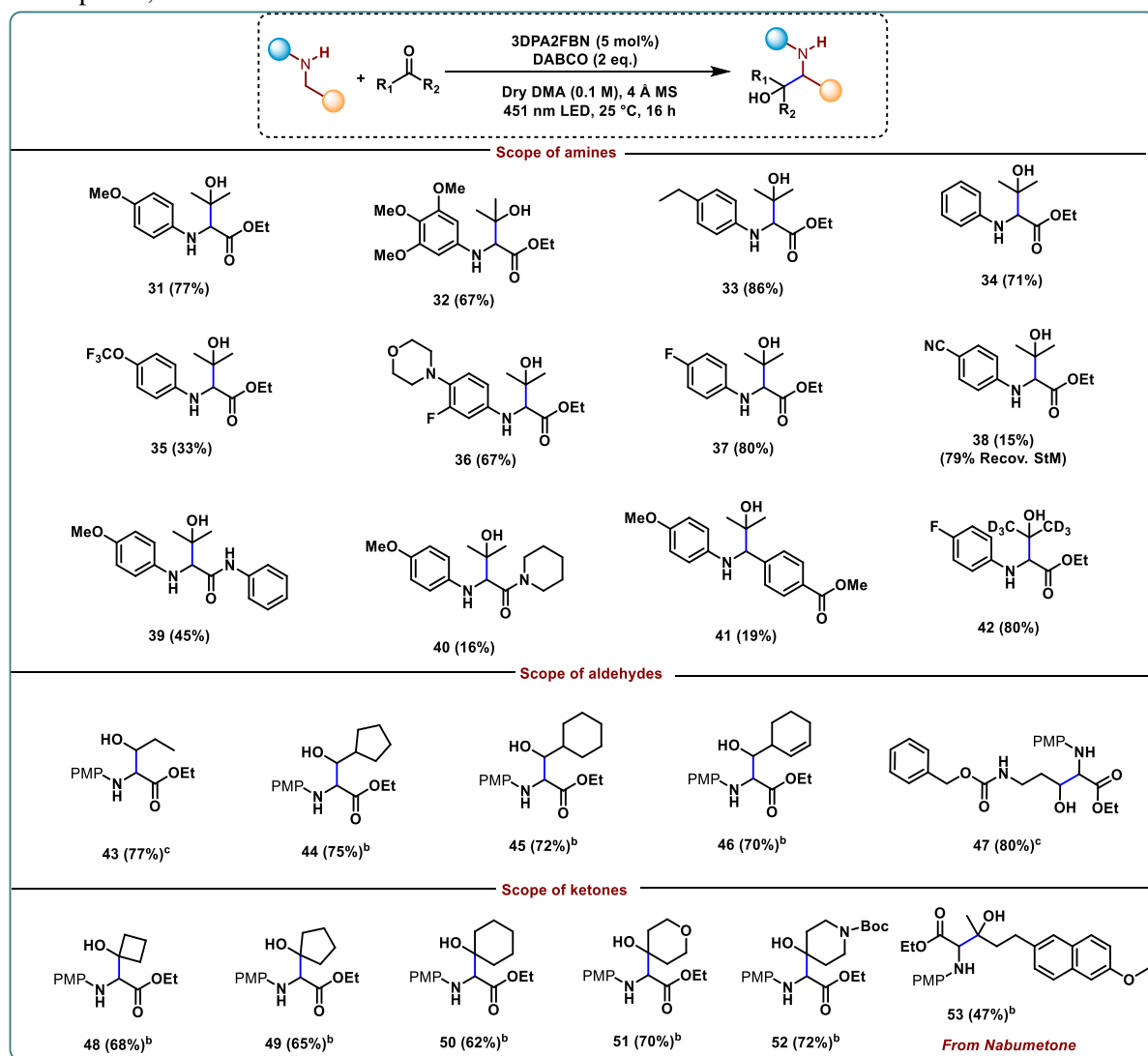


Fig. 6: Divergent synthesis of 1,2-amino alcohols with different carbonyl compounds. Reaction conditions for scope of amines: ^a0.1 mmol substrate, 5 mol% PC (3DPA2FBN), 2 eq. DABCO, 1 mL DMA:acetone (1:1) (0.1 M), 451 nm, 25 °C, 16 h, isolated yields. Reaction conditions for scope of aldehydes and ketones: ^b0.1 mmol substrate, 5 mol% PC (3DPA2FBN), 2 eq. DABCO, 3 eq. carbonyl compounds, 1 mL DMA (0.1 M), 451 nm, 25 °C, 16 h, isolated yield. Products were obtained as diastereomeric mixtures (7:3 to 1:1 according to ¹H-NMR). ^csame as “a” 2 eq. of carbonyl compounds. PMP= *para* methoxy phenyl.

Traditionally, 1,2-amino alcohols are prepared by a nucleophilic attack of an amine to an epoxide. However, the limited availability and difficulties in the synthesis of epoxides in a late-stage application calls for an alternative method.⁴² The development of a complementary method using commercially available starting materials for 1,2-amino alcohol synthesis is highly desired. Accordingly, secondary amines were used as nucleophilic C-H carbanion precursors with various carbonyl compounds as electrophiles to give the corresponding 1,2-amino alcohol in moderate to good yields (Fig. 6). The reaction conditions were only slightly changed, with DABCO proving to be superior to K_2CO_3 as a base (Table S7-S8). With acetone as an electrophile, substrates bearing electron-donating and -withdrawing substituents on the aromatic ring gave the respective amino alcohol in good yields up to 80% (Fig. 6, 31-38). The low yield in case of the strong electron-withdrawing cyano group (37) could be ascribed to an incomplete conversion, where most of the remaining starting material was recovered after the completed reaction time. Aromatic (39) and aliphatic (40) amides instead of esters could be used as carbanion stabilizing groups as well. Similarly, a conjugated electron-withdrawing moiety (41) was viable, too. Unfortunately, products 40 and 41 were only obtained in low yields of 16 and 19%, respectively. The diminished yield in these cases may be attributed to the decomposition of the products at room temperature. In the scope of amines shown in Fig. 6, acetone was used as a co-solvent in order to achieve the optimal yield. However, the use of comparatively less equivalents (10 equivalents) of acetone lowers to yield only slightly. As an example, a good yield of 70% could still be obtained in case of compound 31. Notably, deuterated acetone could be used as an electrophile to give the corresponding amino alcohol 42 in an isolated yield of 80%, too.

Besides acetone, different aliphatic aldehydes and ketones can be employed as electrophiles to give the corresponding product (Fig. 6). Aromatic carbonyl compounds were not included in this study, as they may be directly reduced by the radical anion of the photocatalyst. With a reduction potential of -1.92 V vs. SCE,³³ the reduced 3DPA2FBN species is in reach of *e.g.* benzaldehyde ($E_{red}^{1/2} = -1.93$ V vs. SCE) and benzophenone ($E_{red}^{1/2} = -1.83$ V vs. SCE). A potential product formation would hence likely involve a radical-radical cross-coupling mechanism rather than a carbanion formation.⁵⁷ Noteworthy, 2-3 equivalents of carbonyl compound are sufficient to give the desired product in good yields (Fig. 6). Cyclic (43-46), as well as linear (47) aldehydes, gave the desired products in a yield of 70-80%. Similarly, the use of cyclic ketones (48-52) led to good yields of 62-72%. Interestingly, Nabumetone as an example for a linear ketone is a viable electrophile, yielding 53 in 47%.

In order to demonstrate the applicability of this method further, compounds 1, 31, and 42 were prepared in a bulk-scale (1-2 g scale). A yield of 60-70% was obtained (Scheme S4-S6), which is comparable to the small-scale synthesis. Moreover, the cleavage of the PMP protecting group was tested for the deuterated model compound 1, applying a previously reported cerium ammonium nitrate method.⁵⁸ Gratifyingly, the corresponding secondary amine was obtained, retaining the same deuterium incorporation (Scheme S7). In this context, alpha deuterated/tritiated secondary or primary amines can be synthesized by this pathway.

Mechanistic Investigation:

To support the proposed hypothesis (Fig. 2b), emission quenching studies were performed, showing an interaction between the excited 3DPA2FBN* photocatalyst and the amine substrate (ethyl (4-methoxyphenyl)glycinate; $K_{SV} = 30.4$ M⁻¹). According to the oxidation potentials of the excited photocatalyst ($E_{1/2}(PC^*/PC^{\cdot-}) = +0.92$ V) and substrate ($E_{1/2} = +0.63$ V vs SCE) (see SI), the interaction is likely to be an oxidation (Fig. 2b, I to II). To exclude that the interaction is dependent on a pre-complexation of substrate and photocatalyst (*e.g.* an EDA complex), UV-VIS and NMR spectra of both were measured separately and in mixture (Fig. S13 and S14). No significant changes of the single components upon mixing were detected, rendering a pre-complexation unlikely. For the synthesis of amino alcohols, DABCO was employed as a base. Emission quenching reveals an interaction of the excited photocatalyst with DABCO as well ($K_{SV} = 14.3$ M⁻¹). However, comparing the Stern-Volmer constants, the amine is a significantly more potent quencher than DABCO (Fig. 7a and b).

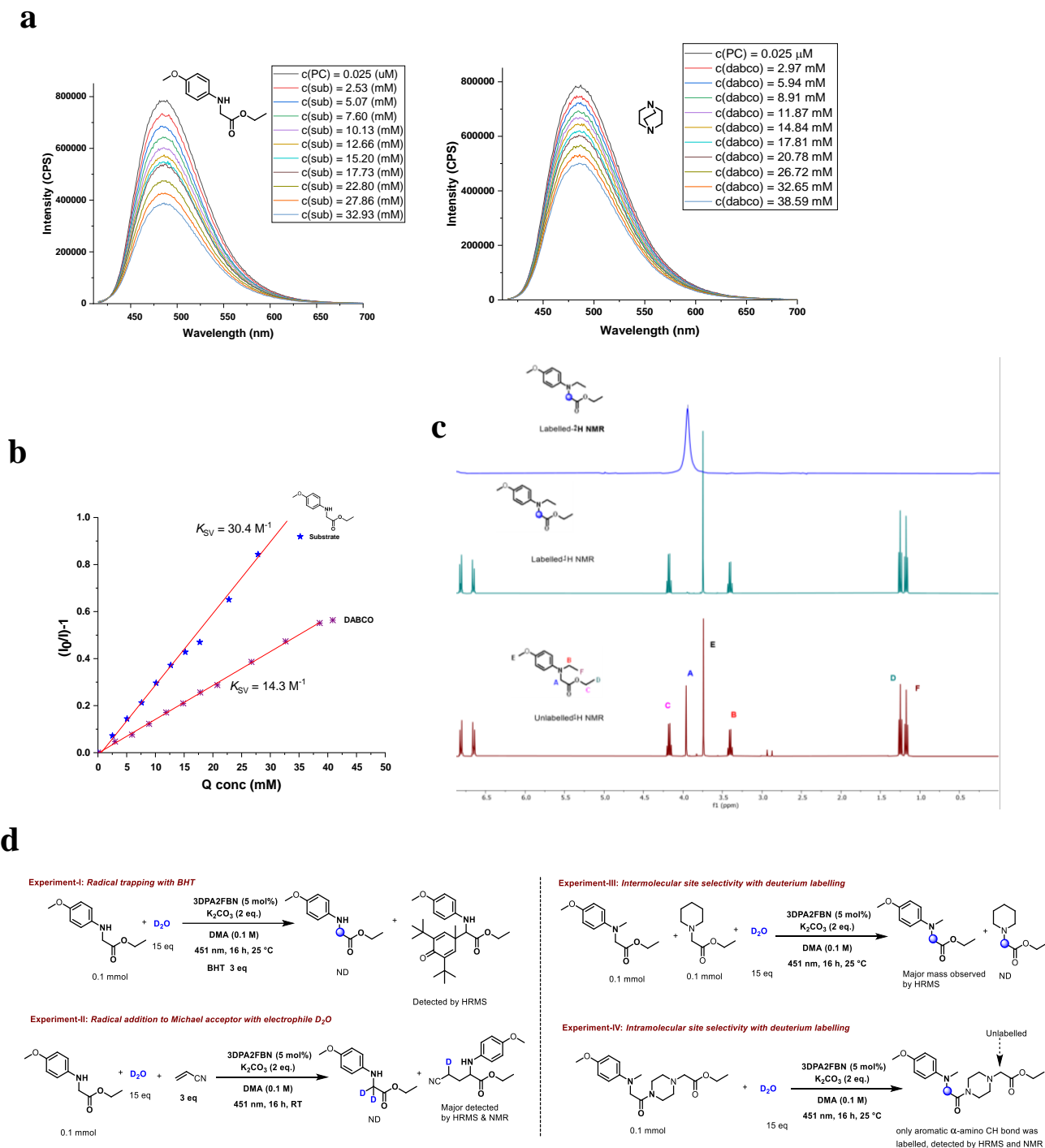


Fig. 7: Mechanistic studies. **a**, Left: Emission quenching of 3DPA2FBN with a substrate. Right: 3DPA2FBN with DABCO. **b**, Stern-Volmer plot. **c**, NMR analysis for site selectivity with and W/O labelled compound. **d**, Mechanistic experiments.

A single electron oxidation of the amine results in the formation of the corresponding radical cation (**II**). In the presence of base, this species can undergo rapid deprotonation to generate α -amino radical **III**. To support the presence of radical intermediates, the reaction was conducted in the presence of radical scavengers such as TEMPO or BHT, leading to no product formation in both cases (Scheme S8, Experiment-1 to 3). In presence of BHT, the coupling product between the α -amino radical (**III**) and BHT was detected to a small extent by HRMS (Fig. 7d, Experiment-I), further confirming its formation. Moreover, the α -amino radical could be efficiently trapped with Michael acceptors such as acrylonitrile (Scheme-S8, Experiment-4 to 5). In presence of D_2O , deuterium was, as expected, incorporated in α -position to the nitrile, supported by HRMS and NMR (Fig. S23 and Fig. 7d, Experiment-II).

The α -amino radical (**III**) is thereafter proposed to be transformed to the corresponding carbanion **IV**. Due to the stabilization of the adjacent electron-withdrawing group, the reduced photocatalyst ($E_{1/2}(3\text{DPA2FBN}/3\text{DPA2FBN}^{\cdot-}) = -1.92 \text{ V vs. SCE}$) should be capable to accomplish this *via* the transfer of an electron to **III**. The formation of this anionic nucleophile is indicated by the successful trapping with D_2O , T_2O , and carbonyl compounds, which should all not efficiently react with a radical intermediate such as **III**.²⁸

The site-selectivity of the deuteration was confirmed by ^1H - and ^2H -NMR (Fig. 7c and SI). As an example, unlabelled starting material **2** holds two potentially reactive α -amino C-H bonds. In the ^1H -NMR, the α -amino ester CH_2 -group shows a singlet resonance signal at δ 3.95 ppm (**A**), whereas the α -amino CH_2 -group of the ethylene substituent shows as a quartet resonance signal at δ 3.41 ppm (**B**), respectively. After the completed HIE reaction, singlet **A** disappears in the ^1H -NMR, while the quartet **B** stays unchanged, indicating a complete and selective deuteration of the α -amino ester position. The ^2H -NMR further supports this selectivity, with only a broad singlet resonance signal at δ 3.95 ppm corresponding to position **A** being observed (Fig. 7c).

Lastly, the effect of the aromatic protecting group was investigated. Interestingly, secondary or tertiary amino esters with solely aliphatic substituents on the nitrogen do not incorporate deuterium (Scheme S8, Experiment-7). The inactivity of purely aliphatic amino esters does not seem to be mainly due to a higher oxidation potential, hindering its initial activation by the excited photocatalyst. Using acrylonitrile as a coupling partner, the corresponding amino radical could still be trapped, confirming that aliphatic amino esters can be oxidized by the excited 3DPA2FBN photocatalyst (Scheme S8, Experiment-8-9). Hence, we assume that the aromatic group is stabilizing the carbanion intermediate, presumably *via* a conjugation effect. This observation could be exploited for an intermolecular selectivity, where a PMP-protected amino ester is selectively deuterated in the presence of an aliphatic one (Fig. 7d, Experiment-III). The idea could be further extended to an intramolecular selectivity (Fig. 7d, Experiment-IV). A substrate containing both, a PMP-protected and an aliphatic amino ester/amide, was selectively labelled at the PMP-protected site, confirmed by ^2H -NMR (Fig. S26-27). This is exceedingly difficult to achieve using other known methods.

Conclusions:

In conclusion, we have developed a practically simple and sustainable process for the site-selective carbanion generation from $\text{C}(\text{sp}^3)\text{-H}$ bonds in the α -amine position. Applying this methodology, numerous amines have been selectively deuterated/tritiated with a high degree of regioselectivity. In addition, the methodology was further extended to the synthesis of various 1,2-amino alcohols, including drug molecules. The practical utility of this method was further demonstrated by conducting bulk scale reactions. Based on several mechanistic experiments, including spectroscopic analysis, we propose a possible reaction pathway and offer a rationale for the observed selectivity.

Acknowledgements:

The German Science Foundation (DFG, KO 1537/18-1) supported this work. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 Research and Innovation Programme (grant agreement No. 741623). We thank Dr. Rudolf Vasold for GC-MS measurements, Regina Hoheisel for Cyclic Voltammetry measurements and Willibald Stockerl for *in-situ* NMR measurements. We further thank Remo Weck for performing the tritium experiments and Dr. Martin Sandvoss for analytical support. We also thank the Mass and NMR Analytic department of the University of Regensburg for assistance with HRMS and NMR analysis.

Author contributions:

B.K. guided the research. B.K. and K.M. conceived and designed the project. K.M. and B.K. wrote the manuscript, with input from all authors. K.M., K.D. and R.N. performed and analyzed the experiments. V.D. and A.B. performed tritium experiments at Sanofi. All authors discussed the results and commented on the manuscript.

Competing interests:

Volker Derdau and Armin Bauer are Sanofi employees and may hold shares and/or stock options in the company.

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