Electrochemical Trideuteromethylation with AcOD-d*4*: A Route to CD_3-Labelled Building Blocks.

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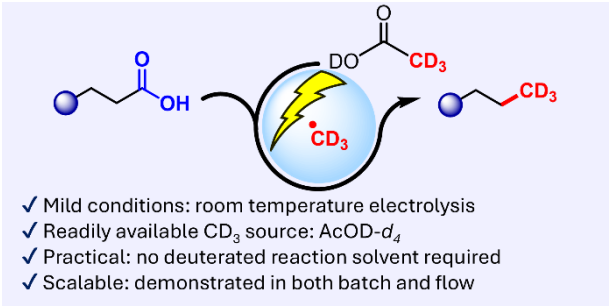


ABSTRACT: Deuterium substitution ($CH_3 \rightarrow CD_3$) can enhance metabolic stability via the kinetic isotope effect and enable bioanalytical mass shifts. We report an electrochemical Kolbe heterocoupling that installs CD_3 at aliphatic positions by coupling carboxylic acids with AcOD-d_4. The reaction proceeds at room temperature under constant current with Pt electrodes and base. Diverse CD_3-labeled building blocks are obtained in moderate to good yields, and the method avoids CD_3I and deuterated solvents.

Site-selective methylation is a powerful strategy in medicinal chemistry, with approximately 80% of top-selling drugs containing at least one methyl group.[1–4] This seemingly simple modification can deliver substantial gains in potency,[5] selectivity,[6–10] and pharmacokinetics, a phenomenon often referred to as the "magic methyl effect".[11] Methyl groups can modulate receptor binding through stereoelectronic and conformational effects, while also tuning solubility without significantly increasing lipophilicity.[11]

Replacing CH_3 with CD_3 can further enhance these benefits. The increased mass strengthens the C–D bond relative to C–H, reducing bond cleavage rates via the kinetic isotope effect (KIE).[12–14] As a result, CD_3 substitution can slow oxidative metabolism and improve metabolic stability, half-life, and toxicity profiles. In addition, site-selective deuteration can redirect metabolic pathways ("metabolic shunting"), stabilise otherwise labile stereoisomers, reduce drug–drug interactions, and enhance bioavailability.[15]

Beyond pharmacology, deuterium labels are highly valuable in analytical chemistry. With modern ultrasensitive mass spectrometry, stable-isotope tags provide unambiguous mass shifts that enable precise identification and quantitation in complex matrices, facilitating studies of drug distribution, metabolism, and target engagement in vivo.[16]

These advantages have driven sustained demand for CD_3-containing molecules and for robust, selective methods to access deuterated active pharmaceutical ingredients (APIs). Traditional strategies rely on the "deuterated pool", such as CD_3I, DMSO-d_6, MeOH-d_4, CD_3OH, DMF-d_7, or Ac_2O-d_6.[17] While these approaches can deliver high selectivity at activated positions, including α-methylation of ketones,[18] the transition-metal-catalyzed methylation of aryl halides,[19] C7 trideuteromethylation of indoles,[20] and azido-enabled trideuteromethylation of olefins,[21] they often depend on expensive deuterium sources or toxic reagents such as CD_3I (**Figure 1**). In addition, their scope rarely extends to unactivated aliphatic sites.[18,19] As a result, general solutions for CD_3 installation remain limited, particularly for unactivated aliphatic positions.

We therefore sought a complementary and sustainable approach to introduce CD_3 groups onto aliphatic frameworks at positions that are difficult to access using conventional methods. We turned to Kolbe electrolysis, in which anodic decarboxylation of carboxylates generates alkyl

radicals that couple at the anode surface.[22–25] Although homodimer formation is classical, unsymmetrical coupling can be achieved when one coupling partner is used in excess. On this basis, we envisioned trideuteromethylation via heterocoupling of an aliphatic carboxylic acid with a readily available CD_3 source, namely acetic acid-d_4 (AcOD-d_4), used in excess (**Figure 1**). The reaction proceeds cleanly under non-degassed, non-dried conditions, exhibits useful, although substrate-dependent, functional-group tolerance and is readily scalable up to 500 mg, positioning it as a practical method for laboratory use and for the preparation of deuterated building blocks for discovery and analytical studies.

Recently, transition-metal-catalyzed and photochemical doubly decarboxylative cross-couplings have emerged as powerful tools for Csp^3- Csp^3 bond formation.[26–28] While these methods achieve high selectivity, our electrochemical Kolbe approach offers a highly complementary, catalyst-free "plug-and-play" alternative. It operates under ambient atmosphere without the need for specialized ligands, photocatalysts, or rigorously anhydrous/degassed conditions, prioritizing practical laboratory utility.

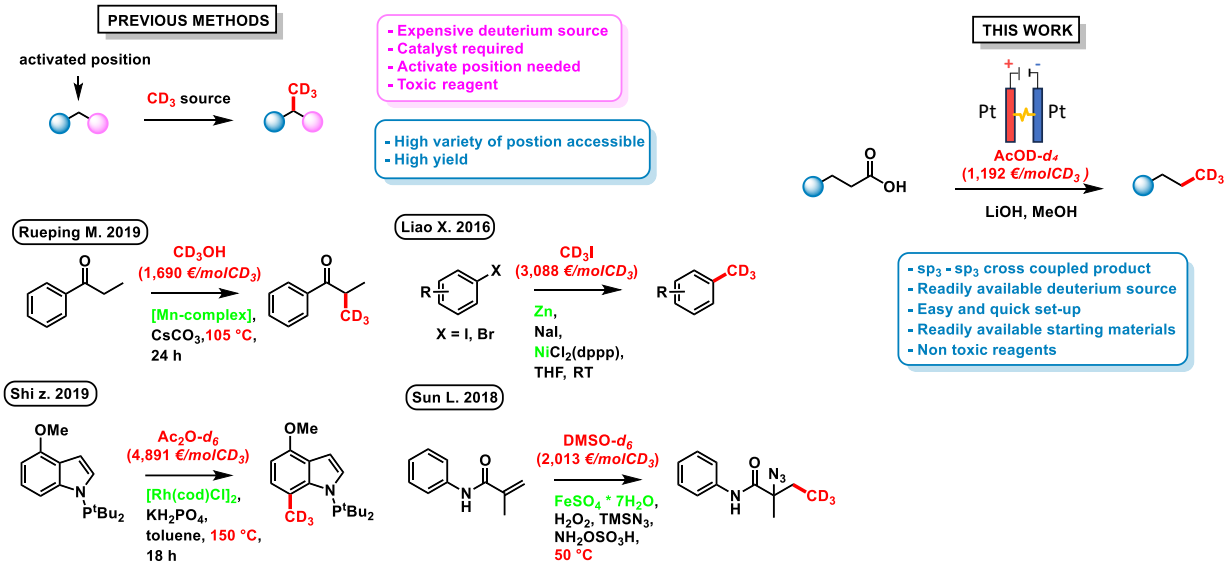
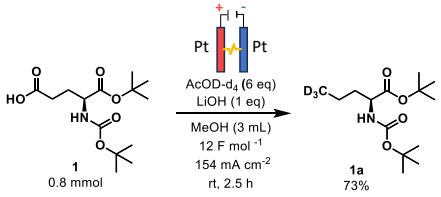


Figure 1. Previous trideuteromethylation methods reported in literature compared with this work. Prices of deuterated sources were calculated from reference prices obtained from Sigma-Aldrich (last accessed 06.05.2026).

We initiated our investigation with the anodic decarboxylation of Boc-L-glutamic acid 1-tert-butyl ester (**1**, **Table 1**, Boc-Glu-OtBu), selected as a model substrate for reaction optimisation. It is well established that partial deprotonation of carboxylic acids, combined with electrolysis in a protic medium using platinum electrodes at relatively high current densities, favours Kolbe-type radical cross-coupling over Hofer–Moest oxidation pathways.[26] Under the optimised conditions, the corresponding CD_3-substituted product **1a** was obtained in 70% yield using 1.0 equiv of base, which provided sufficient carboxylate for both electrolyte conductivity and efficient anodic decarboxylation (**Table 1**).

The reaction was conducted in methanol under constant current (154 mA cm^{-2}) using platinum electrodes and an excess of AcOD-d_4 (6.0 equiv), partially deprotonated with lithium hydroxide monohydrate ($LiOH{\cdot}H_2O$, 1.0 equiv). Base choice proved critical: alternative bases led to inferior outcomes, except for CsOH, which afforded a comparable yield (**Table 1**, entry 6). Nevertheless, lithium hydroxide was selected as a practical and readily available base. A full optimisation study, including different bases, AcOD-d4 equivalents, and current densities, is provided in the Supporting Information (Table S1), with selected results summarised in Table 1. Control experiments conducted in the absence of base or applied current yielded no conversion, confirming the electrochemical nature of the transformation.

Table 1. Selected results from the optimisation experiments. Reactions were carried out on a 0.8 mmol scale. The full optimisation table is provided in the Supporting Information. [a] Yields were determined by NMR spectroscopy using $CHBr_3$ as an internal standard. [b] Representative analyses of possible side products contributing to reduced yields are provided in the Supporting Information (**Table S2 and Figures S2-S4**).



Entry	Deviation from the standard condition	Yield[a]
1	none	73%[b]
2	NaOMe (1 eq.)	48%
3	NaOMe (1 eq.), AcOD-d_4 (10 eq.)	37%

4	KOH (1 eq.)	51%
5	NaOH (1 eq.)	30%
6	CsOH in H_2O 50% (1 eq.)	63%

With the optimised conditions in hand, we explored the scope of this Kolbe-based CD_3-labelling method. A diverse range of aliphatic carboxylic acids was evaluated to access CD_3-tagged building blocks suitable for late-stage functionalisation and as analytical standards (**Scheme 1**).

Linear aliphatic chains furnished the desired products in yields of up to 63% (**1b**, **1c**). Protected amino acid derivatives were also competent substrates: Boc-L-glutamic acid 1-tert-butyl ester afforded **1a** in 73% yield, while an aspartic acid derivative gave the corresponding CD_3-substituted product (**1i**) in 47% yield. In contrast, N-Boc-L-leucine delivered only 5% yield (**1g**), likely due to overoxidation of the α-heteroatom-adjacent radical intermediate to the corresponding, more stable iminium species under the reaction conditions.[29] Additional Boc-protected amino acids were compatible with the reaction, yielding products (**1k**, **1l**) up to 47%, highlighting the potential applicability of this method in medicinal chemistry.

Benzylic esters proved susceptible to transesterification in methanol during the electrolysis. When Boc-L-aspartic acid 1-benzyl ester was subjected to the reaction conditions, two products were noted: the desired benzyl-retaining derivative **1j** (52%) and the corresponding transesterified methyl ester **1ja** (39%). Boc-protected amines and benzylic ketones were tolerated, delivering **1h** (38%) and **1n** (44%), respectively.

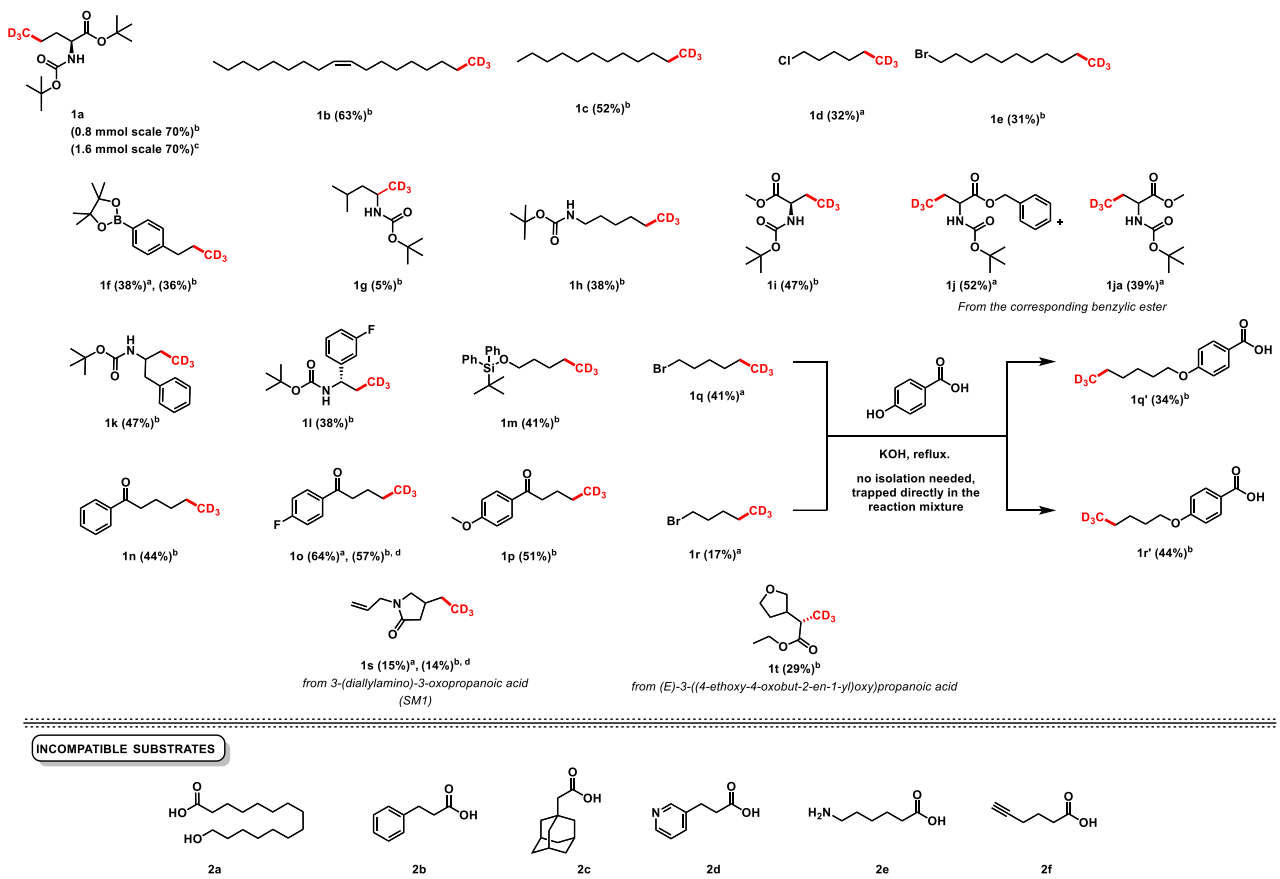
Halogenated aliphatic chains (**1d**, **1e**, **1q**, **1r**) were obtained in moderate yields (up to 41%). Notably, the volatile bromo derivatives were used directly from the crude reaction mixture to functionalise a deactivated phenol such as 4-hydroxybenzoic acid, thereby avoiding isolation of low-boiling intermediates. This one-pot, two-step sequence furnished the coupled products (**1q′**, **1r′**) in up to 44% overall yield.

More sensitive substrates, including a silyl ether and a protected boronic acid, were also compatible, providing the corresponding CD_3-labelled products (**1f**, **1m**) in moderate yield and underscoring the utility of this method for preparing versatile building blocks amenable to downstream diversification.

Finally, a one-pot CD_3 labelling and cyclisation to access pyrrolidine and furan derivatives was investigated, yielding 14% (**1s)** and 29% (**1t**) of the respective deuterated products, illustrating the potential synthetic utility of this method.

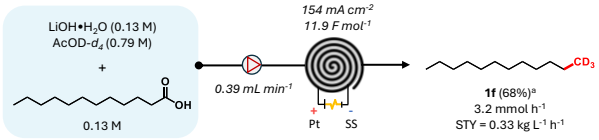
To evaluate scalability, Boc-Glu-OtBu was subjected to the reaction on a 1.6 mmol scale, delivering **1a** in 73% isolated yield, identical to that obtained on a 0.8 mmol scale. Full conversion was observed by GC–MS; minor overoxidation by-products were detected but did not affect the isolated yield.

Several functional groups were incompatible under the standard conditions. Alcohol-containing substrates (**2a**) gave no or only trace amounts of the desired CD_3-labelled products, despite the use of methanol as solvent. Substrate **2b** showed negligible formation of the desired product, with signals consistent with elimination products observed in the crude mixture. Substrate **2c** also failed to provide the desired product by GC-MS or NMR analysis, due to rearrangement of the generated radical as seen via GC-MS analysis of the reaction mixture. Pyridines (**2d**), free amines (**2e**), and terminal alkynes (**2f**) were also not tolerated under the present conditions. A full list of incompatible substrates is provided in the Supporting Information (**Figure S5**).



Scheme 1. Substrate scope for Kolbe electrochemical trideuteromethylation of carboxylic acids to CD_3 derivatives. *Reaction conditions*: 0.8 mmol scale, Pt/Pt electrodes, 154 mA cm^{-2}, 12 F mol^{-1}, AcOD-d_4 (6 eq.), LiOH·H_2O (1 eq.), MeOH (3 mL), r.t (**Table 1**). [a] NMR yield of the crude product after acidic workup (1 M HCl) followed by basic washing (1 M NaOH). [b] Isolated yield after column chromatography. [c] A 1.6 mmol scale reaction was performed in a 5 cm^3 ElectraSyn 2.0 vial. Electrolysis was conducted under constant current (154 mA cm^{-2}, 12 F mol^{-1}) until full conversion of the carboxylic acid was confirmed by GC–MS. [d] Trace impurities present in sample post purification via flash column chromatography.

The modest yields observed for certain substrates are attributed to competing radical and non-Kolbe pathways, which are well documented features of Kolbe electrolysis. In mixed Kolbe reactions, the desired cross-coupling event must compete with homocoupling of each radical partner, radical disproportionation, and further oxidation of the radical intermediate to carbocationic species. While cross-coupling is promoted here by the excess of AcOD-d_4, we observed minor amounts of alkene byproducts arising from disproportionation of the alkyl radical intermediate, a known characteristic of Kolbe electrolysis.[30] Furthermore, in cases where the mass balance was lower than expected despite high conversion, we hypothesise the formation of highly polar, water-soluble byproducts arising from Hofer-Moest-type two-electron oxidation to carbocationic intermediates.[30] To avoid overlooking products that could be lost during the standard aqueous workup, selected crude reaction mixtures were analysed directly before workup. Even under these conditions, only limited quantities of identifiable low-molecular-weight byproducts were detected, suggesting that the remaining mass balance may arise from poorly soluble, highly retained, or oligomeric/polymeric material. This behaviour is consistent with the established limitations of mixed Kolbe electrolysis, particularly under the relatively high current densities required to favour radical recombination, which can also limit tolerance of easily oxidisable functional groups. As a proof-of-concept for scalability, the reaction was adapted for continuous-flow electrolysis using dodecanoic acid as the model substrate (**Figure S1**). To ensure complete solubility of the reactants, the concentration was halved relative to the batch conditions. After screening current and flow-rate parameters, product **1f** was obtained in 68% yield with a productivity of 3.2 mmol h^{-1} (**Scheme 2**), representing a substantial increase compared to the batch productivity of 0.16 mmol h^{-1}. These results demonstrate that the methodology is well-suited to scale-up using continuous-flow electrochemical systems.



Scheme 2: Standard reaction conditions for the continuous flow. Kolbe trideuteromethylation of carboxylic acids to CD_3-derivatives. Reactor details are available in the supporting information. In summary, we have developed a practical electrochemical method for installing CD_3 groups using AcOD-d_4 as a readily available CD_3 source. The protocol avoids CD_3I and deuterated solvents, operates under ambient conditions, and provides direct access to CD_3-labelled building blocks from carboxylic acid precursors,

including compounds useful as reference standards and in discovery and analytical applications. Overall, this user-friendly methodology offers a valuable and complementary alternative to conventional strategies for trideuteromethylation.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Safety Statement

No unexpected or unusually significant hazards were encountered during these studies beyond those noted here. All electrochemical reactions were performed in a well-ventilated fume hood using appropriate shielding and standard laboratory precautions. Because the electrolysis process can evolve flammable gases (such as H_2), and because the sealed flow setup operates under pressure, these experiments were strictly conducted behind a safety shield and monitored to ensure system integrity. Corrosive, volatile, or toxic reagents, including acetic acid-d_4 (AcOD-d_4), methanol, $LiOH{\cdot}H_2O$, and aqueous HCl, were handled with appropriate personal protective equipment (lab coat, safety glasses, and chemical-resistant gloves) to avoid skin contact and inhalation.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Materials and methods; optimisation studies; experimental procedures; continuous-flow reactor details; full characterisation data for all compounds; list of incompatible substrates tested; and copies of ^1H and ^{13}C NMR spectra (PDF)

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K.L.: Conceptualisation, Funding acquisition, Methodology, Investigation, Supervision, Project administration, Writing, review and editing. F.P.: Investigation, Methodology, Formal analysis, Data curation, Validation, Writing, original draft, Writing, review and editing. C.M.: Investigation, Methodology, Formal analysis, Data curation, Validation, Writing, original draft, Writing, review and editing. M.G.: Investigation, Formal analysis, Writing, review and editing. S.X.: Investigation, Formal analysis, Writing, review and editing. K.M.P.W.: Validation, Formal analysis, Writing, review and editing. L.J.E.: Validation, Formal analysis, Writing, review and editing. All authors contributed to the manuscript and approved the final version.

Notes

‡F.P. and C.M. contributed equally to this work.

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