nature catalysis

Article

https://doi.org/10.1038/s41929-025-01420-8

Silicon frustrated Lewis pairs catalyse α-deuteration of amides and esters

Received: 25 October 2024

Accepted: 4 September 2025

Published online: 24 October 2025

Check for updates

Y. Koga[1], I. Fukumoto[1], K. Masui[1], T. Tanaka[1], Y. Naganawa[2], M. Hayashi[3] ✉, T. Ohshima[1] ✉ & R. Yazaki[1,4,5] ✉

Deuterium-labelled compounds play a crucial role in drug discovery as both diagnostic tools and deuterated pharmaceuticals. While hydrogen isotope exchange is well established for activated substrates, the catalytic deuteration of unactivated amides and esters remains underdeveloped, particularly under mild conditions suitable for sensitive pharmaceuticals and polymers. This limitation hampers the late-stage modification of pharmaceutical molecules and functional materials. Here we report a catalytic hydrogen isotope exchange method using cooperative catalysts—a silicon Lewis acid and a tertiary amine base—functioning as a frustrated Lewis pair. This approach enables highly selective deuteration under mild conditions. Our method achieves high deuterium incorporation in various functionalized pharmaceuticals and polyesters, including those typically unstable under basic conditions, demonstrating its broad applicability.

The demand for deuterated molecules has recently increased in drug discovery research, not only for internal standards for liquid chromatography mass spectrometry analysis of clinical samples but also for the development of deuterated drugs (Fig. 1a)[1,2]. Additionally, deuterated molecules have long been widely utilized to elucidate reaction mechanisms[3,4] and enhance the stability of protective groups[5] in synthetic organic chemistry. Furthermore, deuterium labelling in polymer science is not only valuable as a structural analysis technique using neutron scattering but is also gaining attention as a method for modifying polymer properties[6]. Hydrogen isotope exchange is widely recognized as a highly efficient approach for synthesizing deuterated molecules[7–13]. While various late-stage catalytic deuteration methods have been developed using transition metal catalysts via the hydrogen isotope exchange processes, many of them target aromatic C–H bonds rather than aliphatic C–H bonds. Aliphatic C–H bond-selective deuteration remains an important challenge due to the concomitant deuteration of aromatic C–H bonds. Although several catalytic deuteration methods targeting aliphatic C–H bonds have been developed, the deuteration position is limited to C–H bonds around heteroatoms[14–22]. Furthermore, achieving a selective and high deuteration ratio under mild conditions is regarded as a formidable task[23–28].

Amides and esters are universal functional groups found in various pharmaceuticals as well as functional bulk chemicals. Despite a number of methods for the α-deuteration of readily enolizable aldehydes, ketones and amino acids[29–35], a catalytic approach to α-deuteration of unmodified amides and esters is lacking, due to the inherent low acidity of their α-protons. Traditionally, strong base-mediated methods were adopted for the α-deuteration of amides and esters (Fig. 1b)[36–39]. Although radical-based strategies have enabled α-deuteration at the nitrogen atom of amides[40], recent methods utilizing deprotonative activation under mild conditions are limited in substrate scope, being applicable only to activated amides. Maulide and co-workers reported a stoichiometric retro-ene reaction, achieving chemoselective α-deuteration of tertiary amides under mild conditions (Fig. 1c)[41]. Xiang and co-workers developed an electrochemical method for the α-deuteration of activated amides, such as lactams, anilides and

[1]Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan. [2]Research Institute for Chemical Process Technology, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Japan. [3]Department of Life Science and Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology, Nagoya, Japan. [4]Institute for Advanced Study, Kyushu University, Fukuoka, Japan. [5]Deuterium Science Research Unit, Center for the Promotion of Interdisciplinary Education and Research, Kyoto University, Kyoto, Japan. ✉e-mail: hayashi.mikihiro@nitech.ac.jp; ohshima@phar.kyushu-u.ac.jp; yazaki@phar.kyushu-u.ac.jp

https://doi.org/10.1038/s41929-025-01420-8

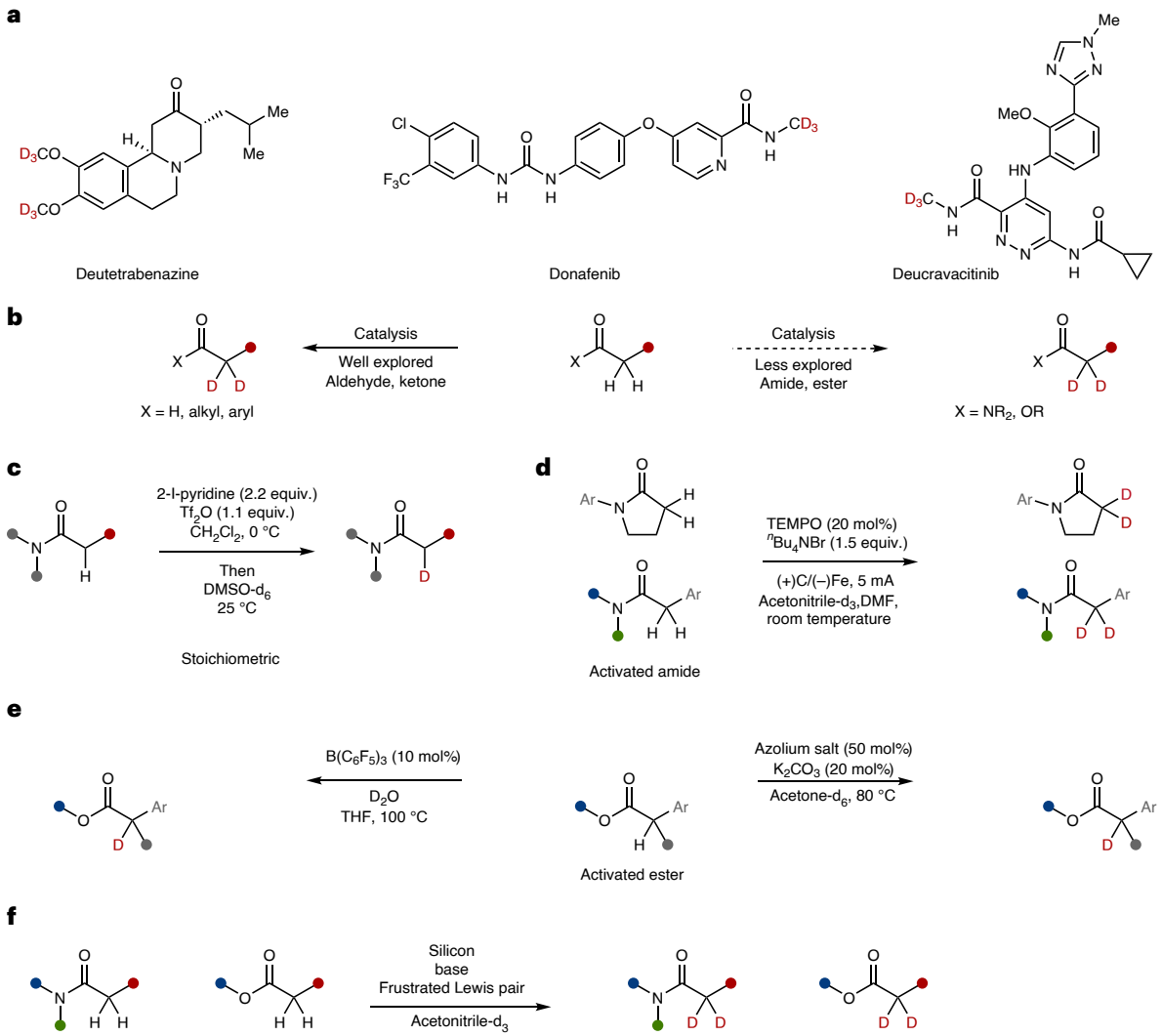


Fig. 1 | Practical examples of deuterated pharmaceuticals and deuteration of carbonyl compounds. a, Examples of deuterated pharmaceuticals. **b**, Deuteration of carbonyl compounds. **c**, Chemoselective α-deuteration under stoichiometric conditions. **d**, α-Deuteration of activated amides under electrochemical conditions. **e**, α-Deuteration of activated esters. **f**, This work: silicon catalysed deuteration of amides and esters. DMSO, dimethyl sulfoxide; TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl free radical.

α-arylamide derivatives (Fig. 1d)[42]. The catalytic α-deuteration of esters remains particularly challenging[43,44]. Wasa and co-workers developed frustrated Lewis acid/Brønsted base catalysis for the α-deuteration of activated esters (Fig. 1e, left)[45–47]. Ananikov and co-workers also reported azolium salt-catalysed α-deuteration of activated esters as a part of their substrate scope (Fig. 1e, right)[48]. However, the development of a general catalytic method with a broad substrate scope has remained an unresolved issue.

Organosilicon compounds have long played an important role in organic chemistry[49]. The versatile properties of silicon are exploited in transformations, as exemplified by silicon enolate chemistry[50–52]. Pioneering work on catalytic nucleophilic activation of tertiary amides by addition to imines was achieved by Kobayashi and co-workers[53,54]. While an efficient catalytic nucleophilic addition of amides was achieved using a silicon Lewis acid combined with weakly basic amines, the range of applicable amides was confined to less functionalized molecules such as acetamides, propionamides and lactams. Moreover, the nucleophilic activation of simple esters using a catalytic amount of Lewis acid with weakly basic amine has never been achieved.

In this Article, we show the α-deuteration of amides and esters using a silicon Lewis acid/Brønsted base cooperative catalyst, functioning as a frustrated Lewis pair (Fig. 1f). A silicon frustrated Lewis pair-catalysed hydrogen isotope exchange process enables the synthesis of versatile deuterated amides and esters bearing various functional groups with high deuteration ratios. The present strategy is applied to the direct and selective deuteration of polymers (for example, polyesters) and this will be experimentally demonstrated in the final section 'Direct catalytic deuteration of polymers'.

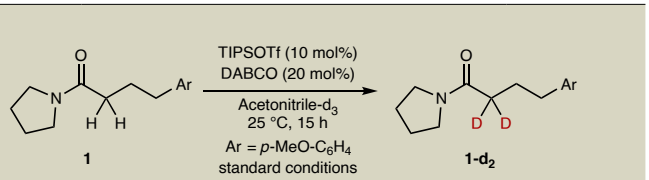
Results

Optimization study of silicon frustrated Lewis pair-catalysed deuteration

We recently developed a catalytic α-deuteration of carboxylic acids using a ternary catalyst system comprising a commonplace potassium carbonate, pivalic anhydride and 4-dimethylaminopyridine[55]. The previous investigation prompted us to use acetonitrile-d_3 as a deuterium source whose α-proton pK_a value is similar to that of amides and esters[56]. Initially, we envisioned that soft Lewis basic acetonitrile-d_3 would be efficiently activated by soft Lewis acidic transition metals[57–62]. Soft Lewis acid screening under intensive conditions revealed that a silicon Lewis acid could activate acetonitrile-d_3 as well as an amide substrate could[63]. The combination of triisopropylsilyl triflate (TIPSOTf) and 1,4-diazabicyclo[2.2.2]octane (DABCO) delivered deuterated product **1-d$_2$** with a high deuteration ratio (Table 1, entry 1). Trimethylsilyl triflate

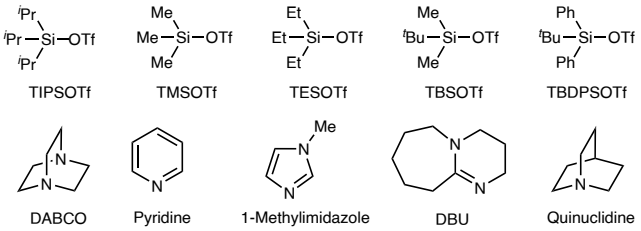
https://doi.org/10.1038/s41929-025-01420-8

Table 1 | Effect of reaction parameters on the silicon-catalysed deuteration of an amide



Entry	Variation from the standard conditions	Yield (%)
1	None	99
2	TMSOTf instead of TIPSOTf	4
3	TESOTf instead of TIPSOTf	83
4	TBSOTf instead of TIPSOTf	97
5	TBDPSOTf instead of TIPSOTf	0
6	Pyridine instead of DABCO	0
7	1-Methylimidazole instead of DABCO	0
8	$^{i}Pr_2EtN$ instead of DABCO	0
9	DBU instead of DABCO	90
10	Quinuclidine instead of DABCO	99
11	D_2O instead of acetonitrile-d3	0
12	Methanol-d4 instead of acetonitrile-d3	0
13	Chloroform-d instead of acetonitrile-d3	0
14	DMSO-d6 instead of acetonitrile-d3	0
15	Acetone-d6 instead of acetonitrile-d3	0

Reaction conditions were on a 0.10 mmol scale. D incorporations were determined by ^{1}H NMR spectroscopic analysis.



(TMSOTf) exhibited quite low catalytic performance, presumably due to the α-silylation of acetonitrile-d_3 (entry 2)[64]. A large silyl triflate such as triethylsilyl triflate (TESOTf) and *tert*-butyldimethylsilyl triflate (TBSOTf) provided **1-d$_2$** with a high deuteration ratio (entries 3 and 4). Highly hindered *tert*-butyldiphenylsilyl triflate (TBDPSOTf) completely terminated the catalysis (entry 5). Commonly used weakly basic amines such as pyridine, 1-methylimidazole and diisopropylethylamine did not afford **1-d$_2$** (entries 6–8). A satisfactory deuteration ratio was observed using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entry 9). Quinuclidine showed the same efficiency as DABCO, and **1-d$_2$** was achieved with a 99% deuteration ratio (entry 10). A survey of deuterium sources revealed that acetonitrile-d_3 specifically provided **1-d$_2$** (entries 11–15).

Substrate scope of amides

Having determined the optimized conditions, we explored the substrate scope for catalytic α-deuteration of amides (Table 2). A co-solvent, either tetrahydrofuran (THF) or PhCl, was added to substrates with poor solubility. A broad array of substrates was successfully deuterated with a high deuteration ratio (average deuteration ratio >98% across 36 substrates). Various tertiary amides derived from both cyclic and acyclic amines were efficiently deuterated (**1**–**8**). Heterocyclic amine-derived amides were well tolerated under the optimal reaction conditions (**9**–**11**). The secondary amide, activated in a catalytic manner, was successfully applied with gentle heating, yielding product **12-d$_2$** with a 99% deuteration ratio. Additionally, more challenging substrates possessing an acidic N–H proton, anilide **13** and primary amide **14**, also afforded the products with a high deuteration ratio, although stoichiometric amounts of TIPSOTf and DABCO were required. α-Aryl amides bearing an oxidatively labile benzylic site could be deuterated with the same efficiency (**15, 16**). Sterically hindered α,α-disubstituted amide **17** was efficiently activated by the use of less-hindered TESOTf as a catalyst. Deuteration of metabolically and oxidatively labile carbon atoms bearing a heteroatom (N, O, S) was also achieved (**18**–**20**). Substrates containing a ketone or ester functionality afforded the product with a high deuteration ratio, although competitive α-deuteration was observed (**21, 22**) (chemoselective deuteration of amide over ester, see Fig. 3c). Furthermore, lactams that are commonly found in natural products could be applied to the present catalysis (**23**). The labile monomer of polyvinylpyrrolidone **24** was well tolerated under optimal conditions, and the terminal vinyl position was concomitantly deuterated. Natural products possessing various Lewis basic sites, including linoleic acid derivatives, sophoridine, brucine, melatonin and Gly-Gly derivatives were also applicable, and the products were isolated with a high deuteration ratio (**25**–**29**). Pharmaceuticals bearing various functional groups, such as chloromezanone, ramelteon, aniracetam, ketoconazole and aripiprazole, were efficiently transformed into their α-deuterated forms (**30**–**34**). Substrates bearing free hydroxyl groups, such as acetaminophen and capsaicin, were successfully deuterated with the hydroxy group protected in situ using stoichiometric amounts of TISPOTf and DABCO (**35, 36**). These results clearly demonstrate the potential of the present protocol for late-stage deuteration of complex carbon skeletons and multifunctional molecules, underscoring its broad applicability and versatility.

Substrate scope of esters

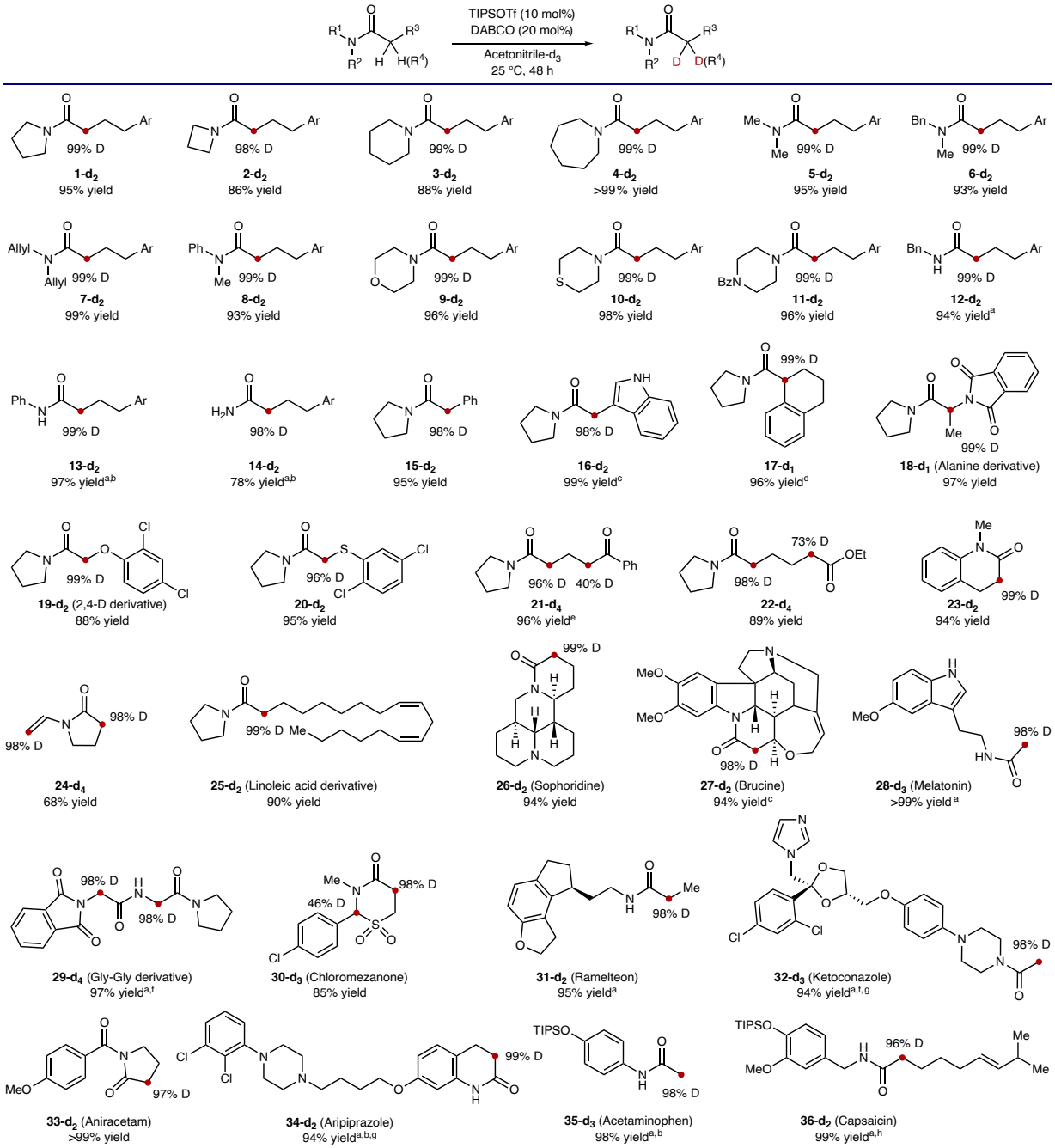
Our catalyst system was not limited to the deuteration of amides and was also applied to the unmodified esters (Table 3). Deuteration of esters is traditionally conducted under strongly basic conditions, leading to concomitant undesired hydrolysis[39]. In sharp contrast, the present method delivered α-deuterated esters under almost neutral conditions without the formation of any hydrolysed products (**37**–**42**). The mildness of the present catalysis was demonstrated using phenol-derived ester **43**, which is easily hydrolysable. The congested phenolic hydroxyl group had no detrimental effect (**44**). Lactone was also compatible under the optimized conditions (**45, 46**). Deuteration of redox-active *N*-hydroxyphthalimide ester **47** also proceeded efficiently, and the resulting deuterated ester can serve as a radical precursor[55]. Our method was successfully applied to late-stage deuteration of natural products and pharmaceuticals, such as ethyl linoleate, tricaprylin, an indomethacin derivative, mycophenolate mofetil and famciclovir (**48**–**52**), although protecting group-free phenol **50** and aniline **51** required stoichiometric amounts of TIPSOTf and DABCO. We further established the enhanced metabolic stability of deuterated antiviral drug **52-d$_7$** using mouse liver microsomes (clearance: **52** = 591 µl per min per mg, **52-d$_7$** = 479 µl per min per mg), confirming the usefulness of the present deuteration method. The **52-d$_6$** compound also exhibited improved metabolic stability (395 µl per min per mg), presumably due to its enhanced resistance to enzymatic hydrolysis[65]. Deuterated acetylcholine **53-d$_3$** was also prepared through a deuteration/alkylation sequence. The deuteration of **53** proceeded without the addition of DABCO under gentle heating conditions. Diethyl adipate (**54**) was a suitable substrate for deuteration without concomitant generation of the Dieckmann condensation product. These results demonstrate the high applicability of the present method, which is completely distinct from reactions involving strong bases.

Application of silicon/DABCO-catalysed deuteration

The practicality of this catalytic method was demonstrated by gram-scale synthesis using a reduced amount of catalyst and

https://doi.org/10.1038/s41929-025-01420-8

Table 2 | Scope of catalytic α-deuteration of amides



Reactions were conducted on 0.20 mmol scale using 1.0 ml acetonitrile-d_3. Isolated yields are shown. [a]60 °C. [b]TIPSOTf (3.0 equiv.), DABCO (6.0 equiv.). [c]THF was added as co-solvent. [d]TESOTf (20 mol%), DABCO (40 mol%). [e]Quinuclidine was used. [f]TIPSOTf (30 mol%), DABCO (60 mol%). [g]Chlorobenzene was added as co-solvent. [h]TIPSOTf (1.1 equiv.), DABCO (2.2 equiv.). Ar, *p*-$MeOC_6H_4$.

acetonitrile-d_3 (Fig. 2a). A survey of co-solvents revealed that less coordinating solvents, such as toluene and hexane, were more effective for the present silicon-catalysed deuteration (Supplementary Table 9). The desired deuterated product was obtained in high yield with a high deuteration ratio (99% yield, 7.44 g, 93% D). The deuterated amides and esters prepared through the present silicon-catalysed protocol are particularly attractive due to their ready transformation into useful deuterated synthons (Fig. 2b). The deuterated *N*-acylazetidines could be converted into ketones using lithium reagents (**55-d$_2$**, **56-d$_2$**)[66]. The readily enolizable aldehyde could also be synthesized using Schwartz's reagent without compromising the deuteration ratio (**57-d$_2$**). Treatment with Lawesson's reagent delivered deuterated thioamide **58-d$_2$**, which serves as a precursor for the synthesis of various heterocyclic compounds[67]. β-Deuterated alcohol **59-d$_2$** and amine **60-d$_2$** were easily obtained through reduction[68]. Furthermore, diverse reactions using ester **38-d$_2$** delivered deuterated synthons such as β-deuterated ether **61-d$_2$** (ref. 69) and tertiary alcohol **62-d$_2$** (ref. 70).

Proposed catalytic cycle and mechanistic studies

The proposed catalytic cycle is shown in Fig. 3a. Amides or esters **I** would be enolized by the cooperative actions of a silicon Lewis acid and Brønsted basic DABCO, delivering silicon enolate **II** along with

https://doi.org/10.1038/s41929-025-01420-8

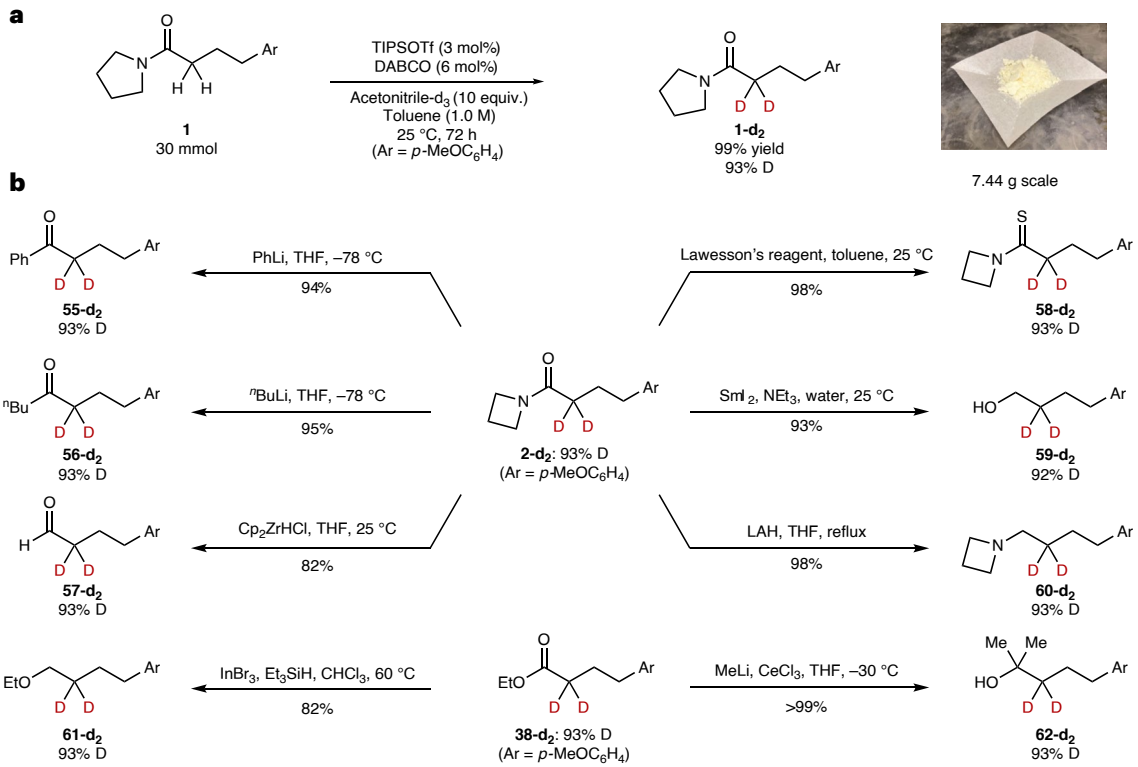


Fig. 2 | Utility of the silicon/DABCO-catalysed deuteration. a, Large-scale synthesis of deuterated amide. **b**, Divergent transformation of the deuterated amide and ester. LAH, lithium aluminum hydride.

the generation of a TfOH salt. At the same time, the enolate derived from acetonitrile-d_3 **IV** would also be formed by the TIPSOTf/DABCO system with concomitant generation of a TfOD salt. Silicon enolate **II** would be deuterated by the TfOD generated from acetonitrile-d_3 **III**, delivering deuterated product **V**. To confirm the envisioned catalytic cycle, we conducted a mechanistic investigation. We first performed ^{29}Si NMR analysis of a mixture of silyl triflates and various Lewis bases (Fig. 3b)[71]. The coordination of DABCO to TMSOTf was inferred from the significant upfield shift of the silicon signals (42.9 ppm and 7.6 ppm). By contrast, no peak shift was observed with sterically hindered TIPSOTf (40.7 ppm), indicating that TIPSOTf and DABCO could serve as a cooperative Lewis acid/Brønsted base catalyst through the formation of a frustrated Lewis pair[46,47,72,73]. The formation of frustrated Lewis pairs was also confirmed by heterolytic bond cleavage of the amine–borane adduct by the TIPSOTf/DABCO system (Supplementary Methods)[74]. An upfield shift was observed using DBU instead of DABCO, indicating the formation of classical Lewis adducts and supporting a lower deuteration ratio (Table 1, entry 9). The attenuated reactivity of the catalyst comprising TIPSOTf and DBU was exploited to achieve chemoselective deuteration of the amide over the ester (Fig. 3c), which TIPSOTf/DABCO could not achieve (Table 2, **22-d$_4$**). Isolated classical Lewis adduct **63** (calculated $\Delta G^{\ddagger} = 14.6$ kcal mol^{-1}, $\Delta G^{0} = -9.2$ kcal mol^{-1}) exhibited no catalytic activity (Fig. 3d)[75]. We further conducted a series of control experiments to gain insight into the intermediate. Imidate **64** was efficiently deuterated under optimized conditions. This delivered **64-d$_2$** with a high deuteration ratio after quenching with CsF (ref. 51), indicating that an imidate would be an intermediate for the enolization (Fig. 3e). Silicon enolate **65** was also deuterated under optimized conditions (Fig. 3f). During this experiment, the enolate of acetonitrile-d_3 **66** was detected by high-resolution mass spectrometry. A similar result was observed using DABCO·$(TfOH)_2$ as a catalyst (Fig. 3g), indicating that the triflate salt of the base is the actual deuterium source.

Direct catalytic deuteration of polymers

Finally, we applied our deuteration method to polymer deuteration, specifically for site-selective deuteration of the polymer. In general, deuterated polymers are synthesized using the corresponding deuterated monomers[76]. On the other hand, in this study, direct deuteration was achieved (Fig. 4a). Polycaprolactone (PCL) **67**, with a number average molecular weight of 24,000 (according to poly(methyl methacrylate) standards), was efficiently deuterated under slightly modified catalytic conditions, using a 35 mol% catalyst for the ester functionality. The α-selective deuterated polycaprolactone **67-d** was isolated in 46% yield with a 99% deuteration ratio, as confirmed by ^{1}H NMR analysis (see the ^{1}H NMR spectra in Supplementary Fig. 6). The deuteration was further corroborated by Fourier transform infrared spectroscopy (see the Fourier transform infrared spectra in Supplementary Fig. 7); the red shift of the carbonyl (C=O) signal and spectral changes in the 900–1,400 cm^{-1} region support successful deuteration, in accordance with the literature[6,76]. Moreover, we assessed potential main chain degradation during the deuteration process using size exclusion chromatography (Fig. 4b). The number average molecular weight values before (24,600) and after (22,000) deuteration indicated minimal change, and the polydispersity index was similar for the samples before (1.47) and after (1.41) deuteration. These minor changes in polydispersity index and peak shape are likely to be attributable to the purification process. These polymeric characterizations demonstrate that our method enables selective deuteration of polyesters without causing undesirable chain scission. We further evaluated the thermal and crystalline properties using differential scanning calorimetry (DSC) and thermogravimetric analysis. Figure 4c,d shows the DSC spectra for PCL-H and PCL-D during the first cooling and second heating cycles. In the cooling spectra, the crystallization temperature was 32.1 °C for PCL-H and 41.0 °C for PCL-D. In the heating spectra, the melting temperature was 55.5 °C for PCL-H and 53.3 °C for PCL-D, with melting enthalpies of 66.9 J g^{-1}

https://doi.org/10.1038/s41929-025-01420-8

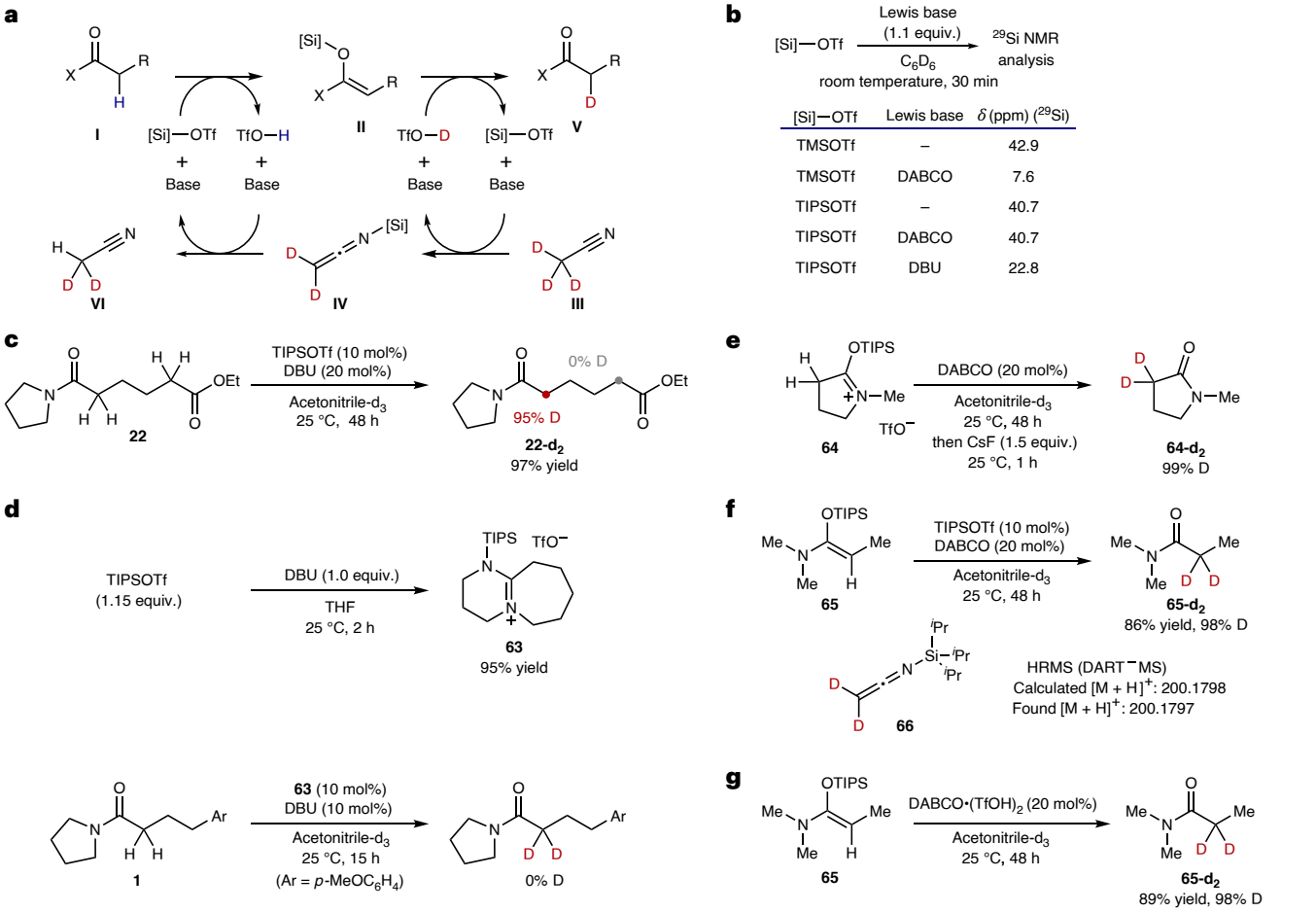


Fig. 3 | Mechanistic investigation of silicon/DABCO-catalysed deuteration. **a**, Proposed catalytic cycle. Silicon enolate **II** would be generated by the cooperative actions of a silicon Lewis acid and DABCO. The formed enolate **II** would be deuterated by TfOD generated from acetonitrile-d_3 to afford deuterated amide **V**. **b**, ^{29}Si NMR analysis using a silicon catalyst and Lewis base. **c**, Chemoselective deuteration of amide over ester using an attenuated catalyst system comprising TIPSOTf with DBU. **d**, Isolation and catalytic activity of TIPSOTf/DBU complex **63**. No deuterated product was observed using **63** as a catalyst. **e**, Reactivity of imidate **64**. Imidate **64** was efficiently deuterated under the optimized reaction conditions. **f**, A silicon enolate as a starting material. A high deuteration ratio was observed and the enolate derived from acetonitrile-d_3 **66** was detected by high-resolution mass spectrometry. **g**, Deuteration of a silicon enolate using DABCO·$(TfOH)_2$. A high deuteration ratio was observed.

for PCL-H and 59.9 J g^{-1} for PCL-D. These results suggest slightly lower crystallinity in PCL-D, which may be attributed to the weaker intermolecular interactions in deuterated polymers[77]. The minor decrease in melting temperature following deuteration is consistent with previous reports on the effect of deuteration on the crystallization behaviour of PCL (ref. 78). The thermogravimetric analysis and derivative thermogravimetry (DTG) curves (Fig. 4e) show that the thermal stability remained virtually unchanged after deuteration, indicating that selective replacement of hydrogen with deuterium did not negatively impact thermal stability. Overall, these results confirm that our direct deuteration method preserves both the polymer chain structure and the related properties. We are currently exploring the extension of this synthetic approach to other polymers with ester functionalities. This could broaden the application range of deuterated polymers and potentially reveal functional advantages.

Conclusion

In summary, we have successfully developed a synthetic method for the deuteration of amides and esters under mild conditions. The cooperative catalyst system comprising TIPSOTf and DABCO, which functions as a frustrated Lewis pair efficiently activated unmodified amides, esters and acetonitrile-d_3. The present catalysis enabled not only late-stage deuteration of complex carbon skeletons and multifunctional molecules but also direct deuteration of polymer materials. Mechanistic investigations showed that TIPSOTf and DABCO operated independently, the former as a Lewis acid and the latter as a Brønsted base. This operationally simple and practical catalytic protocol allows for rapid access to various deuterated molecules, including pharmaceuticals and functional polymer materials.

Methods

General

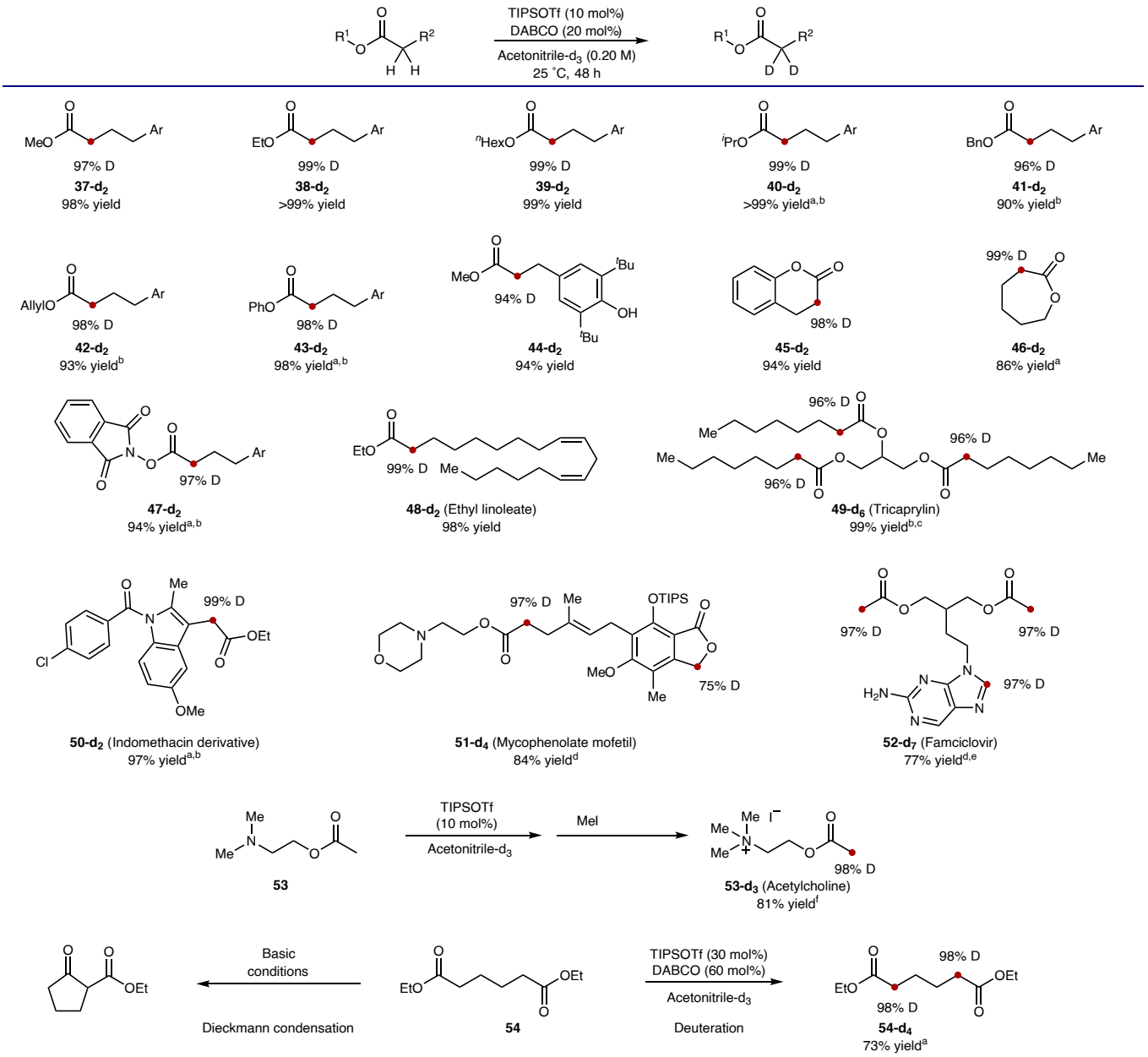
All reactions were carried out using heat-gun-dried glassware under a positive pressure of dry argon unless otherwise noted. Catalytic reactions were run under an argon atmosphere. Air- and moisture-sensitive liquids were transferred via a syringe and a stainless steel needle. Reactions were magnetically stirred and monitored by thin-layer chromatography. All workup and purification procedures were carried out with reagent-grade solvents under an ambient atmosphere. Flash chromatography was performed using silica gel. See Supplementary Methods for detailed conditions and the characterization data.

General procedure for silicon-mediated α-deuteration of amides and esters

DABCO (4.5 mg, 0.04 mmol) was added to a 4-ml vial equipped with a magnetic stir bar containing an amide or ester (0.20 mmol). This was

https://doi.org/10.1038/s41929-025-01420-8

Table 3 | Scope of catalytic α-deuteration of esters



Reactions were conducted on 0.20 mmol scale using 1.0 ml acetonitrile-d_3. Isolated yields are shown. [a]TIPSOTf (30 mol%), DABCO (60 mol%). [b]60 °C. [c]TIPSOTf (90 mol%), DABCO (180 mol%). [d]TIPSOTf (3.0 equiv.), DABCO (6.0 equiv.). [e]Isolated after treatment with $NEt_3{\cdot}HF$ (3.0 equiv.). [f]40 °C. Ar, *p*-$MeOC_6H_4$.

followed by the addition of acetonitrile-d_3 (1.0 ml, 19.2 mmol, 0.20 M) and triisopropylsilyl trifluoromethanesulfonate (5.4 µl, 0.02 mmol). The reaction mixture was stirred under argon at 25 °C for 48 h. The reaction mixture was then directly subjected to silica gel flash chromatography to afford the product.

Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information. Data are available from the corresponding authors upon request.

References

1. Gant, T. G. Using deuterium in drug discovery: leaving the label in the drug. *J. Med. Chem.* **57**, 3595–3611 (2014).
2. Pirali, T., Serafini, M., Cargnin, S. & Genazzani, A. A. Applications of deuterium in medicinal chemistry. *J. Med. Chem.* **62**, 5276–5297 (2019).
3. Gómez-Gallego, M. & Sierra, M. A. Kinetic isotope effects in the study of organometallic reaction mechanisms. *Chem. Rev.* **111**, 4857–4963 (2011).
4. Simmons, E. M. & Hartwig, J. F. On the interpretation of deuterium kinetic isotope effects in C–H bond functionalizations by transition-metal complexes. *Angew. Chem. Int. Ed.* **51**, 3066–3072 (2012).
5. Miyashita, M., Sasaki, M., Hattori, I., Sakai, M. & Tanino, K. Total synthesis of norzoanthamine. *Science* **305**, 495–499 (2004).
6. Li, L., Jakowski, J., Do, C. & Hong, K. Deuteration and polymers: rich history with great potential. *Macromolecules* **54**, 3555–3584 (2021).

https://doi.org/10.1038/s41929-025-01420-8

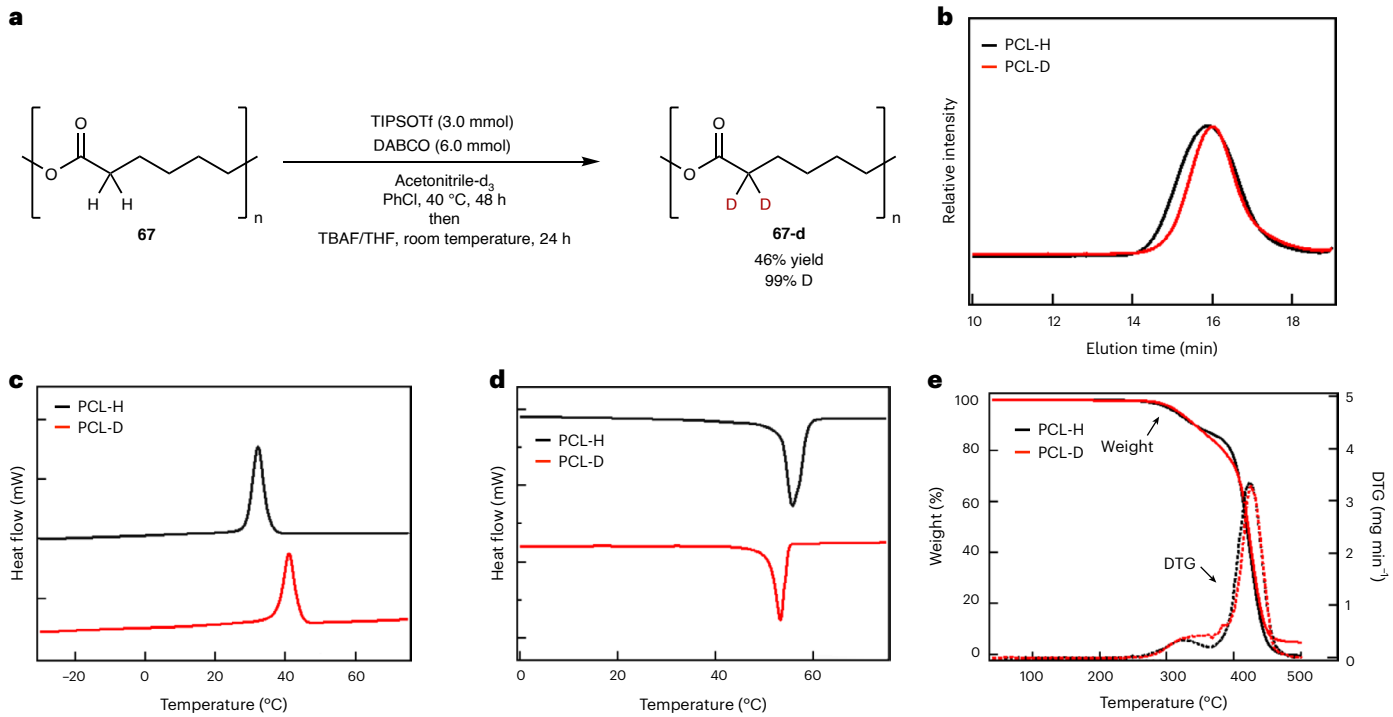


Fig. 4 | Direct deuteration of PCL and the characterization of physical properties. a, The scheme of deuteration for PCL. **b**, Size exclusion chromatography data. **c**, 1st cooling DSC thermogram. **d**, 2nd heating DSC thermogram. In **c** and **d**, the interval between the ticks represents 2 mW. **e**, Thermogravimetric analysis curve. For **b**–**e**, the data are compared for PCL-H and PCL-D (see the measurement conditions in Supplementary Fig. 7).

7. Atzrodt, J., Derdau, V., Fey, T. & Zimmermann, J. The renaissance of H/D exchange. *Angew. Chem. Int. Ed.* **46**, 7744–7765 (2007).
8. Atzrodt, J., Derdau, V., Kerr, W. J. & Reid, M. C–H functionalisation for hydrogen isotope exchange. *Angew. Chem. Int. Ed.* **57**, 3022–3047 (2018).
9. Prakash, G., Paul, N., Oliver, G. A., Werz, D. B. & Maiti, D. C–H deuteration of organic compounds and potential drug candidates. *Chem. Soc. Rev.* **51**, 3123–3163 (2022).
10. Kopf, S. et al. Recent developments for the deuterium and tritium labeling of organic molecules. *Chem. Rev.* **122**, 6634–6718 (2022).
11. Dey, J. & Van Gemmeren, M. Late-stage C–H deuteration of organic compounds via ligand-enabled palladium-catalyzed hydrogen isotope exchange. *Synlett* **35**, 2191–2200 (2024).
12. Li, H., Shabbir, M., Li, W. & Lei, A. Recent advances in deuteration reactions. *Chin. J. Chem.* **42**, 1145–1156 (2024).
13. Ogasahara, R., Ban, K., Mae, M., Akai, S. & Sawama, Y. Deuterated alkyl sulfonium salt reagents; importance of H/D exchange methods in drug discovery. *ChemMedChem* **19**, e202400201 (2024).
14. Takahashi, M., Oshima, K. & Matsubara, S. Ruthenium catalyzed deuterium labelling of α-carbon in primary alcohol and primary/secondary amine in D_2O. *Chem. Lett.* **34**, 192–193 (2005).
15. Neubert, L. et al. Ruthenium-catalyzed selective α,β-deuteration of bioactive amines. *J. Am. Chem. Soc.* **134**, 12239–12244 (2012).
16. Loh, Y. Y. et al. Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. *Science* **358**, 1182–1187 (2017).
17. Chang, Y. et al. Catalytic Deuterium incorporation within metabolically stable β-amino C–H bonds of drug molecules. *J. Am. Chem. Soc.* **141**, 14570–14575 (2019).
18. Itoga, M. et al. Iridium-catalyzed α-selective deuteration of alcohols. *Chem. Sci.* **13**, 8744–8751 (2022).
19. Ban, K. et al. Sulfonium salt reagents for the introduction of deuterated alkyl groups in drug discovery. *Angew. Chem. Int. Ed.* **62**, e202311058 (2023).
20. Meng, X., Dong, Y., Liu, Q. & Wang, W. Organophotocatalytic α-deuteration of unprotected primary amines via H/D exchange with D_2O. *Chem. Commun.* **60**, 296–299 (2023).
21. Tatoueix, K. et al. Unlocking the potential of hydrogen deuterium exchange via an iterative continuous-flow deuteration process. *Nat. Commun.* **16**, 1314 (2025).
22. Valero, M., Weck, R., Güssregen, S., Atzrodt, J. & Derdau, V. Highly selective directed iridium-catalyzed hydrogen isotope exchange reactions of aliphatic amides. *Angew. Chem. Int. Ed.* **57**, 8159–8163 (2018).
23. Uttry, A., Mal, S. & Van Gemmeren, M. Late-Stage β-C(sp3)–H Deuteration of Carboxylic Acids. *J. Am. Chem. Soc.* **143**, 10895–10901 (2021).
24. Suzuki, A. et al. Photocatalytic deuterium atom transfer deuteration of electron-deficient alkenes with high functional group tolerance. *Angew. Chem. Int. Ed.* **62**, e202214433 (2023).
25. Jiao, M., Zhang, J., Wang, M., Lu, H. & Shi, Z. Metallaphotoredox deuteroalkylation utilizing thianthrenium salts. *Nat. Commun.* **15**, 5067 (2024).
26. Zhang, J. et al. Hydrodeuteroalkylation of unactivated olefins using thianthrenium salts. *Angew. Chem. Int. Ed.* **63**, e202409862 (2024).
27. Suzuki, A., Higashida, K., Yoshino, T. & Matsunaga, S. Multiple deuterium atom transfer perdeuteration of unactivated alkenes under base-assisted cobalt/photoredox dual catalysis. *Angew. Chem. Int. Ed.* **64**, e202500233 (2025).
28. Xiao, W. et al. Thianthrenium-enabled chromium-catalyzed deuterated alkyl addition to aldehydes via a photoactive electron donor–acceptor complex. *Org. Lett.* **27**, 1112–1117 (2025).
29. Kunick, C. & Messinger, P. Deuterierung enolisierbarer Ketone mit Deuterochloroform [Deuteration of enolizable ketones with deuterated chloroform]. *Chem. Ber.* **119**, 1429–1431 (1986).

30. Berthelette, C. & Scheigetz, J. Base-catalyzed deuterium and tritium labelling of 1-biphenyl-4-ylpropane-1, 2-dione and deuteration of aryl methyl ketones. *J. Label. Compd. Radiopharm.* **47**, 891–894 (2004).
31. Sabot, C., Kumar, K. A., Antheaume, C. & Mioskowski, C. Triazabicyclodecene: an effective isotope exchange catalyst in $CDCl_3$. *J. Org. Chem.* **72**, 5001–5004 (2007).
32. Ariza, X. et al. Preparation of α-labeled aldehydes by base-catalyzed exchange reactions. *J. Label. Compd. Radiopharm.* **53**, 556–558 (2010).
33. Zhan, M., Zhang, T., Huang, H., Xie, Y. & Chen, Y. A simple method for α-position deuterated carbonyl compounds with pyrrolidine as catalyst. *J. Label. Compd Radiopharm.* **57**, 533–539 (2014).
34. Xiao, G. et al. Binary Catalytic hydrogen/deuterium exchange of free α-amino acids and derivatives. *Chem. Eur. J.* **30**, e202402045 (2024).
35. Zheng, J. et al. Site-selective deuteration of α-amino esters with 2-hydroxynicotinaldehyde as a catalyst. *ACS Omega* **9**, 26963–26972 (2024).
36. Duffield, A. M., Budzikiewicz, H. & Djerassi, C. Mass spectrometry in structural and stereochemical problems. LVIII. A study of the fragmentation processes of some lactams. *J. Am. Chem. Soc.* **86**, 5536–5541 (1964).
37. Deslongchamps, P., Barlet, R. & Taillefer, R. J. Hydrolysis and carbonyl-oxygen exchange in tertiary amides. Estimation of the free energy changes for breakdown and conformational changes of tetrahedral intermediates. *Can. J. Chem.* **58**, 2167–2172 (1980).
38. Maryanoff, B. E., McComsey, D. F. & Duhl-Emswiler, B. A. Stereochemistry of intramolecular amidoalkylation reactions in the synthesis of polycyclic isoquinoline derivatives. *J. Org. Chem.* **48**, 5062–5074 (1983).
39. Peng, S. et al. Synthesis of isotopically labeled arachidonic acids to probe the reaction mechanism of prostaglandin H synthase. *J. Am. Chem. Soc.* **124**, 10785–10796 (2002).
40. Meng, X., Che, C., Dong, Y., Liu, Q. & Wang, W. Organophotocatalytic selective deuteration of metabolically labile heteroatom adjacent C–H Bonds via H/D exchange with D_2O. *Org. Lett.* **26**, 8961–8966 (2024).
41. Porte, V., Di Mauro, G., Schupp, M., Kaiser, D. & Maulide, N. Chemoselective alpha-deuteration of amides via retro-ene reaction. *Chem. Eur. J.* **26**, 15509–15512 (2020).
42. Ning, S. et al. Electrochemical α-deuteration of amides. *Green Chem.* **25**, 9993–9997 (2023).
43. Esaki, H. et al. Efficient H/D exchange reactions of alkyl-substituted benzene derivatives by means of the Pd/C–H_2–D_2O system. *Chem. Eur. J.* **13**, 4052–4063 (2007).
44. Watanabe, A. et al. Controlled tetradeuteration of straight-chain fatty acids: synthesis, application, and insight into the metabolism of oxidized linoleic acid. *Angew. Chem. Int. Ed.* **61**, e202202779 (2022).
45. Chang, Y., Myers, T. & Wasa, M. $B(C_6F_5)_3$-catalyzed α-deuteration of bioactive carbonyl compounds with D_2O. *Adv. Synth. Catal.* **362**, 360–364 (2020).
46. Chan, J. Z., Yao, W., Hastings, B. T., Lok, C. K. & Wasa, M. Direct Mannich-type reactions promoted by frustrated Lewis acid/Brønsted base catalysts. *Angew. Chem. Int. Ed.* **55**, 13877–13881 (2016).
47. Shang, M. et al. Frustrated Lewis acid/Brønsted base catalysts for direct enantioselective α-amination of carbonyl compounds. *J. Am. Chem. Soc.* **139**, 95–98 (2017).
48. Galkin, K. I., Gordeev, E. G. & Ananikov, V. P. Organocatalytic deuteration induced by the dynamic covalent interaction of imidazolium cations with ketones. *Adv. Synth. Catal.* **363**, 1368–1378 (2021).
49. Dilman, A. D. & Ioffe, S. L. Carbon–carbon bond forming reactions mediated by silicon Lewis acids. *Chem. Rev.* **103**, 733–772 (2003).
50. Gilman, H. & Clark, R. N. Ethyl β-triethylsiloxycrotonate and tetra-n-butylsilane. *J. Am. Chem. Soc.* **69**, 967–968 (1947).
51. Krüger, C. R. & Rochow, E. G. O-silyl-substituted enols. *J. Organomet. Chem.* **1**, 476–483 (1964).
52. Mukaiyama, T., Banno, K. & Narasaka, K. New cross-aldol reactions. Reactions of silyl enol ethers with carbonyl compounds activated by titanium tetrachloride. *J. Am. Chem. Soc.* **96**, 7503–7509 (1974).
53. Kobayashi, S., Kiyohara, H. & Yamaguchi, M. Catalytic silicon-mediated carbon-carbon bond-forming reactions of unactivated amides. *J. Am. Chem. Soc.* **133**, 708–711 (2011).
54. Li, X. et al. Selective α-oxyamination and hydroxylation of aliphatic amides. *Angew. Chem. Int. Ed.* **56**, 12307–12311 (2017).
55. Tanaka, T. et al. Ternary catalytic α-deuteration of carboxylic acids. *Nat. Synth.* **1**, 824–830 (2022).
56. Zhang, X. M., Bordwell, F. G., Van Der Puy, M. & Fried, H. E. Equilibrium acidities and homolytic bond dissociation energies of the acidic C–H bonds in *N*-substituted trimethylammonium and pyridinium cations. *J. Org. Chem.* **58**, 3060–3066 (1993).
57. Suto, Y., Kumagai, N., Matsunaga, S., Kanai, M. & Shibasaki, M. Direct catalytic aldol-type reactions using RCH_2CN. *Org. Lett.* **5**, 3147–3150 (2003).
58. Kumagai, N., Matsunaga, S. & Shibasaki, M. Cooperative catalysis of a cationic ruthenium complex, amine base, and Na salt: catalytic activation of acetonitrile as a nucleophile. *J. Am. Chem. Soc.* **126**, 13632–13633 (2004).
59. Suto, Y., Tsuji, R., Kanai, M. & Shibasaki, M. Cu(I)-catalyzed direct enantioselective cross aldol-type reaction of acetonitrile. *Org. Lett.* **7**, 3757–3760 (2005).
60. Saito, A., Kumagai, N. & Shibasaki, M. Direct catalytic asymmetric addition of acetonitrile to aldimines. *Org. Lett.* **21**, 8187–8190 (2019).
61. Saito, A., Adachi, S., Kumagai, N. & Shibasaki, M. Direct catalytic asymmetric addition of alkylnitriles to aldehydes with designed nickel–carbene complexes. *Angew. Chem. Int. Ed.* **60**, 8739–8743 (2021).
62. Sun, M., Wei, L. & Li, C. Regio- and enantioselective allylic cyanomethylation by synergistic rhodium and silane catalysis. *J. Am. Chem. Soc.* **145**, 3897–3902 (2023).
63. Olah, G. A. & Narang, S. C. Iodotrimethylsilane—a versatile synthetic reagent. *Tetrahedron* **38**, 2225–2277 (1982).
64. Emde, H. & Simchen, G. Silylierung von Nitrilen mit Trimethylsilyl-trifluoromethansulfonat (Trimethylsilyl-triflat) [Silylation of nitriles with trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate)]. *Synthesis* **1977**, 636–637 (1977).
65. Belz, T. F. et al. Enhancement of a heroin vaccine through hapten deuteration. *J. Am. Chem. Soc.* **142**, 13294–13298 (2020).
66. Liu, C., Achtenhagen, M. & Szostak, M. Chemoselective ketone synthesis by the addition of organometallics to *N*-acylazetidines. *Org. Lett.* **18**, 2375–2378 (2016).
67. Jagodziński, T. S. Thioamides as useful synthons in the synthesis of heterocycles. *Chem. Rev.* **103**, 197–227 (2003).
68. Tong, X., Schneck, F. & Fu, G. C. Catalytic enantioselective α-alkylation of amides by unactivated alkyl electrophiles. *J. Am. Chem. Soc.* **144**, 14856–14863 (2022).
69. Sakai, N., Moriya, T. & Konakahara, T. An efficient one-pot synthesis of unsymmetrical ethers: a directly reductive deoxygenation of esters using an $InBr_3/Et_3SiH$ catalytic system. *J. Org. Chem.* **72**, 5920–5922 (2007).
70. Liu, Y. et al. Divergent enantioselective synthesis of hapalindole-type alkaloids using catalytic asymmetric hydrogenation of a ketone to construct the chiral core structure. *Chem. Sci.* **7**, 4725–4729 (2016).

71. Klare, H. F. T. et al. Silylium Ions: from elusive reactive intermediates to potent catalysts. *Chem. Rev.* **121**, 5889–5985 (2021).
72. Stephan, D. W. "Frustrated Lewis pairs": a concept for new reactivity and catalysis. *Org. Biomol. Chem.* **6**, 1535–1539 (2008).
73. Stephan, D. W. Frustrated Lewis pairs. *J. Am. Chem. Soc.* **137**, 10018–10032 (2015).
74. Whittell, G. R. et al. Reactions of amine-and phosphane-borane adducts with frustrated Lewis pair combinations of group 14 triflates and sterically hindered nitrogen bases. *Eur. J. Inorg. Chem.* **2010**, 3967–3975 (2010).
75. A. Soderquist, J. et al. Selective triisopropylsilylation of α-amino acids: protection without racemization. *Heterocycles* **80**, 409 (2010).
76. Chang, D. et al. Selectively deuterated poly(ε-caprolactone) s: synthesis and isotope effects on the crystal structures and properties. *Macromolecules* **51**, 9393–9404 (2018).
77. Li, L. et al. Isotope effects on the crystallization kinetics of selectively deuterated poly(ε-caprolactone). *J. Polym. Sci. B* **57**, 771–779 (2019).
78. Bates, F. S., Keith, H. D. & Mcwhan, D. B. Isotope effect on the melting temperature of nonpolar polymers. *Macromolecules* **20**, 3065–3070 (1987).

Acknowledgements

This work was financially supported by the JST-FOREST programme (grant number JPMJFR2229), the Environment Research and Technology Development Fund (grant number JPMEERF20231R02) of the Environmental Restoration and Conservation Agency provided by the Ministry of the Environment of Japan, KAKENHI (grant number JP24H01777) for the Grant-in-Aid for Transformative Research Areas (A) Latent Chemical Space from MEXT, grant numbers JP21A204, JP21H05207 and JP21H05208 for the Grant-in-Aid for Transformative Research Areas (A) Digitalization-driven Transformative Organic Synthesis (Digi-TOS) from MEXT, the JST-PRESTO programme (grant number JPMJPR2277), the Joint Usage/Research Center for Catalysis (grant numbers 22AY0129, 23AY0157, 23DS0418, 23DS0456 and 24ES0544), the Network Joint Research Center for Materials and Devices Cooperative Research Program, a Grant-in-Aid for Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS) (grant numbers JP20am0101091, JP22ama121031) and AMED (grant numbers JP21ak0101167, JP22ak0101167, JP23ak0101167). Y.K. and T.T. thank the JSPS for a predoctoral fellowship. Y.K. is grateful for the support from the Japan Science Technology Agency (JST) SPRING (grant number JPMJSP2136) and the Academic Challenge Program 2023 of Kyushu University. T.O. thanks the NAGASE Science Technology Foundation for financial support. R.Y. thanks the Inamori Foundation, the Shorai Foundation for Science and Technology and the Noguchi Institute for financial support. We are grateful to T. Niwa (Kyushu University) for liquid chromatography mass spectrometry measurements and to H. Naka (Kyoto University) and K. Oka (Tohoku University) for fruitful discussions.

Author contributions

Y.K. and R.Y. conceived the work and all of the authors analysed the data, discussed the results and co-wrote the paper. Y.K., I.F. and K.M. designed and carried out the experiments. Y.N. performed ^{29}Si NMR analysis. M.H. evaluated the deuterated polymers.

Competing interests

Y.K., T.O. and R.Y. are listed as inventors on patent no. PCT/JP2024/29718 filed by Kyushu University in Japan covering the silicon frustrated Lewis pair catalyst class and its application in deuteration. I.F., K.M., T.T., Y.N. and M.H. declare no competing interests.

Additional information

Supplementary information The online version contains supplementary m0aterial available at https://doi.org/10.1038/s41929-025-01420-8.

Correspondence and requests for materials should be addressed to M. Hayashi, T. Ohshima or R. Yazaki.

Peer review information *Nature Catalysis* thanks Grégory Pieters and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.