Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2022, **13**, 12519

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 15th July 2022
Accepted 13th September 2022

DOI: 10.1039/d2sc03958c

rsc.li/chemical-science

Nickel-catalyzed regio- and enantio-selective Markovnikov hydromonofluoroalkylation of 1,3-dienes†

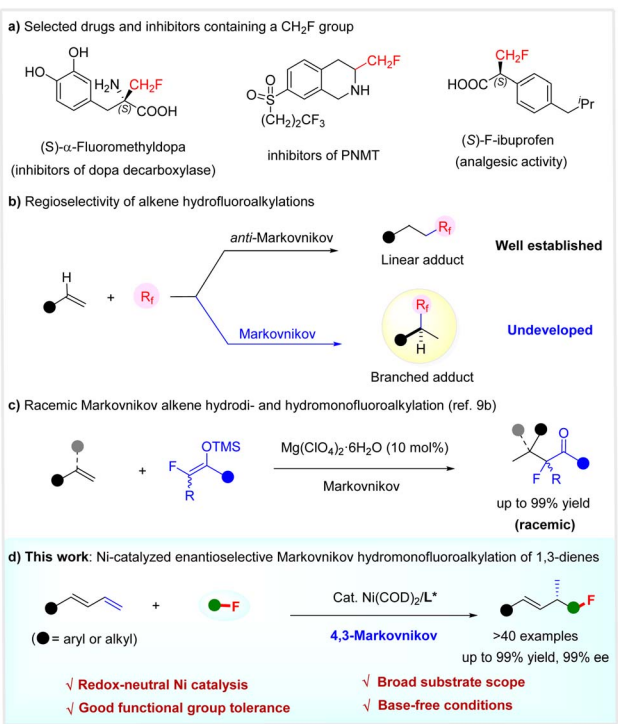
Ling Liao,‡[a] Ying Zhang,‡[a] Zhong-Wei Wu,[a] Zhong-Tian Ye,[a] Xue-Xin Zhang,[a] Guangying Chen[b] and Jin-Sheng Yu *[ab]

A highly enantio- and regio-selective Markovnikov hydromonofluoro(methyl)alkylation of 1,3-dienes was developed using redox-neutral nickel catalysis. It provided a facile strategy to construct diverse monofluoromethyl- or monofluoroalkyl-containing chiral allylic molecules. Notably, this represents the first catalytic asymmetric Markovnikov hydrofluoroalkylation of olefins. The practicability of this methodology is further highlighted by its broad substrate scope, mild base-free conditions, excellent enantio- and regio-selectivity, and diversified product elaborations to access useful fluorinated building blocks.

Introduction

The selective introduction of a fluorine or fluoroalkyl moiety into molecules often results in improved physical, chemical, and biological properties.[1] In particular, the installation of a monofluoromethyl (CH_2F) group as a bioisostere of various functional groups, such as methyl and hydroxymethyl, has been established as a robust and routine tactic in pharmaceutical chemistry and agrochemistry to tune the properties of bioactive compounds, including bioavailability and metabolic stability.[2] Typical drugs or inhibitors featuring a CH_2F unit are shown in Scheme 1a.[3] However, despite the significant progress made in selective fluoroalkylation,[4] the efficient incorporation of a CH_2F group in a highly enantioselective manner remains challenging and very much in demand.[5]

While the hydrofluoroalkylation of alkenes is a powerful strategy to introduce a fluoroalkyl group selectively,[6] the catalytic enantioselective incorporation of a monofluoroalkyl group is unexplored. Notably, most known alkene hydrofluoroalkylations are based on radical processes, affording linear adducts with anti-Markovnikov regioselectivity.[6,7] It is considered both interesting and urgent to develop the Markovnikov hydrofluoroalkylation of olefins. This not only offers the potential to develop catalytic enantioselective versions, but would afford branched adducts with a chemical space shape distinct from linear products, which are interesting targets for drug discovery because of the intimate relationship between the shape and their properties of organic molecules (Scheme 1b).[8] Following our interest in selective fluoroalkylation,[9] we recently developed the



Scheme 1 Regioselective hydrofluoroalkylation of alkenes.

[a]*Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, Shanghai Key Laboratory of Green Chemistry and Chemical Processes, East China Normal University, Shanghai 200062, China. E-mail: jsyu@chem.ecnu.edu.cn*

[b]*Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, Hainan Normal University, Haikou 571158, China*

† Electronic supplementary information (ESI) available. CCDC 2130032 and 2130034. For ESI and crystallographic data in CIF or other electronic format see https://doi.org/10.1039/d2sc03958c

‡ L. Liao and Y. Zhang contributed equally to this work.

first Markovnikov hydrodi- and hydromonofluoroalkylation of simple alkenes using fluorinated enol silyl ethers, *via* an acid-catalyzed carbocationic process (Scheme 1c).[9b] Herein, we disclose a highly regio- and enantio-selective Markovnikov hydromonofluoro(methyl)alkylation reaction of 1,3-dienes by redox-neutral Ni catalysis (Scheme 1d).

Transition-metal-catalyzed regio- and enantio-selective hydrofunctionalization of 1,3-dienes **1** offers an efficient and atom-economical method to access chiral functionalized allylic compounds from readily available starting materials.[10] Over the past few years, various highly enantioselective protocols have been used: hydroamination,[11] hydroalkylation,[12] hydroarylation,[13] and hydrosulfonylation,[14] among others.[15] Despite the advances made, these reactions mainly rely on using chiral precious metal Pd and Rh catalysts. Since the landmark work of the Zhou group in 2018,[12c] the use of earth-abundant and low-cost chiral Ni catalysts for developing the asymmetric hydrofunctionalization of acyclic 1,3-dienes has gained increasing attention.[12c,e,f,13b,c] Despite ongoing achievements, the catalytic enantio- and regio-selective Markovnikov hydromonofluoromethylation of 1,3-dienes to construct functionalized chiral allylic compounds with a CH_2F at the stereocenter is unexplored.

Inspired by these elegant advances, we speculated that the implementation of catalytic asymmetric 1,3-dienes hydromonofluoromethylation would provide a new direction for enantioselective monofluoromethylation and constitutes a new branch for the hydrofunctionalizations of 1,3-dienes. To reach this goal, the quest for a suitable monofluoromethyl reagent would be the key to success. Among various monofluoromethyl agents, fluorobis(phenyl-sulfonyl)methane (FBSM)[16a,b] **2a** proves to be a robust one in developing catalytic enantioselective monofluoromethylation reactions,[5,16] since the landmark work of Shibata.[16a] On this basis, we determined to use FBSM **2a** as a latent monofluoromethyl agent to explore the asymmetric Markovnikov hydromonofluoromethylation of 1,3-dienes **1** under the action of chiral nickel catalysis.

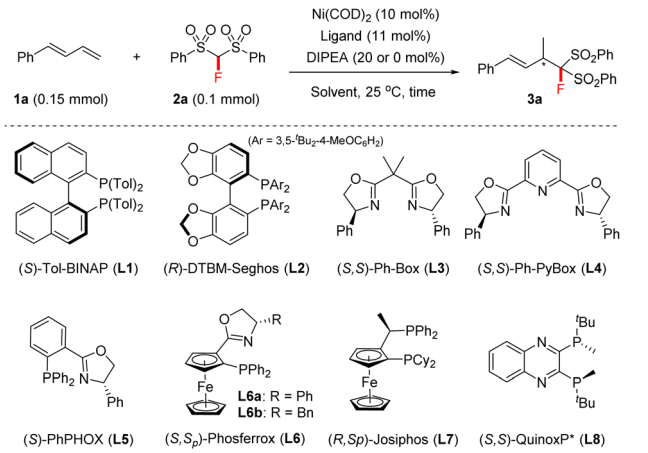
Results and discussion

Optimization of the reaction conditions

We commenced this study with 1-phenylbuta-1,3-diene **1a** and FBSM **2a** as the model substrates, in the presence of $Ni(COD)_2$ (10 mol%) and *N*,*N*-diisopropylethylamine (DIPEA) (20 mol%). As shown in Table 1, a series of axially chiral bisphosphine ligands were first investigated. The use of (*S*)-Tol-BINAP afforded the 4,3-Markovnikov adduct **3a** in 98% NMR yield with 37% ee within 14 h (entry 1), whilst the bulky (*R*)-DTBM-Segphos **L2** afforded product **3a** in only 9% NMR yield and 27% ee after 48 h (entry 2).

Encouraged by these results, we then tested the performance of chiral bisoxazoline ligands and *P*,*N*-based PHOX (entries 3–6), and found that the use of (*S*,*Sp*)-Ph-Phosferrox **L6a** could improve the ee of product **3a** to 68% (entry 6). Interestingly, base DIPEA proved to be unnecessary in the current reaction. A comparable result was obtained in the absence of DIPEA (entries 6 *vs.* 7). The focus of further optimization was on chiral ferrocene-based chiral ligands, but there was no improvement

Table 1 Selected conditions for optimization[a]



Entry	Ligand	DIPEA (mol%)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**L1**	20	EtOH	14	98	37
2	**L2**	20	EtOH	48	9	27
3	**L3**	20	EtOH	24	4	22
4	**L4**	20	EtOH	24	nr[d]	—
5	**L5**	20	EtOH	14	79	22
6	**L6a**	20	EtOH	10	89	68
7	**L6a**	0	EtOH	10	90	67
8	**L6b**	0	EtOH	22	50	64
9	**L7**	0	EtOH	22	50	78
10	**L8**	0	EtOH	16	95	96
11	**L8**	0	Toluene	24	84	70
12	**L8**	0	THF	24	99	86
13	**L8**	0	CH_2Cl_2	24	Trace	—
14	**L8**	0	MeOH	24	Trace	—
15	**L8**	0	^{i}PrOH	24	Trace	—
16[e]	**L8**	0	EtOH	72	86	96

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), $Ni(COD)_2$ (10 mol%), ligand (11 mol%), and DIPEA (20 or 0 mol%), run at 25 °C in the indicated solvent (1.0 mL), unless otherwise noted. [b] Determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by chiral HPLC. [d] No reaction. [e] Run on a 0.25 mmol scale using $Ni(COD)_2$ (5 mol%) and **L8** (5.5 mol%).

in the ee values (entry 8, see the ESI† for details). Subsequently, we turned our attention to exploring *P*-chiral phosphine ligands because they usually exhibit distinct chirality-inducing ability.[17] To our delight, *P*-chiral (*S*,*S*)-QuinoxP*[18] **L8**, never before used in hydrofunctionalizations of 1,3-dienes, proved to be efficient; it afforded **3a** in 95% NMR yield with 96% ee within 16 h (entry 10). An examination of the solvent effect revealed that EtOH was still the best solvent (entries 10 *vs.* 11–15), although the use of THF also afforded the desired product **3a** in 99% NMR yield, but with a slightly lower ee (entry 12). Moreover, the use of a 5 mol% Ni catalyst afforded the product **3a** in 86% isolated yield with 96% ee, albeit within 72 h (entry 16).

Evaluation of substrate scope

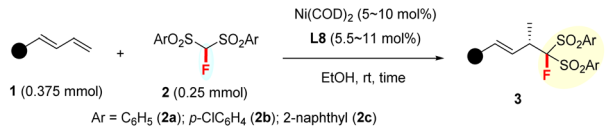
With the optimized conditions in hand, we explored the generality of this Markovnikov hydromonofluoromethylation in

EtOH under the catalysis of a 5 mol% or 10 mol% *P*-chiral (*S*,*S*)-QuinoxP* decorated $Ni(COD)_2$ complex (Table 2).

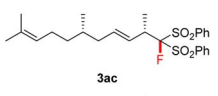
Various aromatic 1,3-dienes with different electron-donating and -withdrawing groups on the aryl ring were viable substrates, affording the corresponding 4,3-Markovnikov adducts **3b–3r** in 48–99% yields with 90–99% ee (entries 2–18). The increase in reaction temperature was necessary to ensure full conversion in the cases of *ortho*- or *meta*-substituted aromatic 1,3-dienes. Of note is that the current reaction tolerated various functional groups on the aryl ring of 1,3-dienes: amine (**3g**), non-conjugated alkene (**3h**), ester (**3j**), nitrile (**3k**), ketone (**3l**), and aldehyde (**3m**). Naphthyl-, 2-furyl-, and 2-thienyl-substituted 1,3-dienes all worked smoothly with **2a** to afford **3s–3v** in excellent yields and ee values (entries 19–22). A conjugated triene was also tolerated; it afforded product **3w** in 99% yield and with 97% ee (entry 23). Remarkably, the aliphatic 1,3-dienes, which are generally very challenging in terms of controlling both regio- and enantio-selectivity due to the small steric hindrance of the alkyl group,[12c] proved to be compatible in our reaction system. They afforded the adducts **3x–3z** with up to 81% yields and 94% ee at slightly elevated temperatures (entries 24–26). Notably, the ketone functionalities attached in aliphatic 1,3-diene were also compatible well (**3z**). The differently substituted FBSM **2b** and **2c** also reacted efficiently with 1-phenylbuta-1,3-diene **1a** at 50 °C to afford the targets **3aa** (94% yield and 97% ee) and **3ab** (99% yield and 95% ee). Furthermore, (*S*)-citronellal-derived alkyl 1,3-diene also reacted smoothly to afford adduct **3ac** in moderate yield and with 95% de. X-ray diffraction (XRD) analysis revealed that the absolute configuration of **3a** was (*S*). Subsequently, (*S*) was assigned to all other products **3** by analogy.

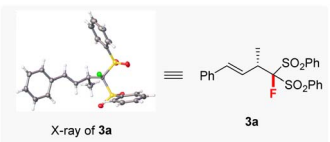
Unsurprisingly, the FBSM adduct **3a** could efficiently undergo a reductive desulfonylation to access chiral α-monofluoromethyl (CH_2F) allylic compound **4a** with 96% ee under the action of Mg/MeOH[19] (Scheme 2A). This result stimulated us to explore the assembly of deuterated monofluoromethyl (CD_2F)-containing chiral allylic molecules, given that the incorporation of a deuterium atom in the bioactive molecules is emerging as a promising tactic to modulate the bioactivity or pharmacological properties in drug discovery programs since the first deuterated drug, Austedo, was approved by FDA in 2017.[20a] However, while the development of efficient approaches for preparing deuterated compounds is of current interest, the selective introduction of a CD_2F group into the stereogenic center is still a challenging task and remains unexplored.[21] To

Table 2 Scope of hydromonofluoromethylation of dienes with **2** [a]

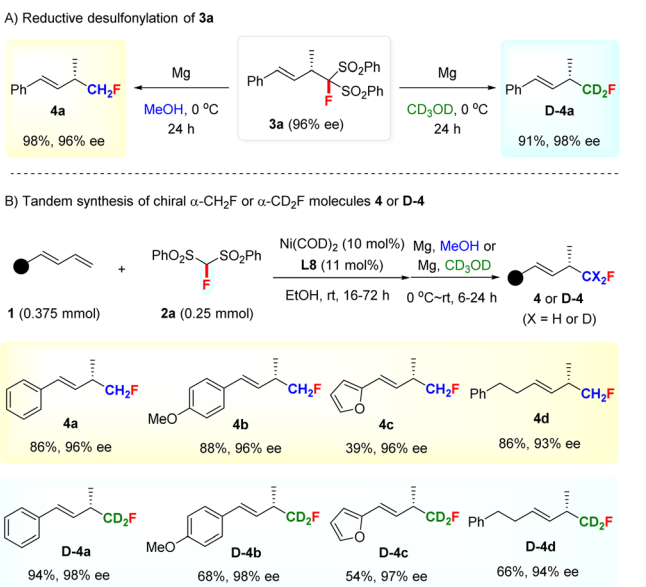


Entry	1: substituent (●)	2	Time (d)	3	Yield (%)	ee (%)
1	**1a**: C_6H_5	**2a**	3	**3a**	86	96
2	**1b**: 4-MeC_6H_4	**2a**	4	**3b**	99	94
3	**1c**: 4-$MeOC_6H_4$	**2a**	3	**3c**	97	97
4[b]	**1d**: 3-$MeOC_6H_4$	**2a**	3	**3d**	86	98
5[b]	**1e**: 2-$MeOC_6H_4$	**2a**	3	**3e**	93	98
6	**1f**: 3,5-$Me_2O_2C_6H_3$	**2a**	3	**3f**	98	99
7[b]	**1g**: 4-$Me_2NC_6H_4$	**2a**	4	**3g**	48	93
8	**1h**: 4-CH_2=$CH(CH_2)_2C_6H_4$	**2a**	3	**3h**	68	95
9	**1i**: 4-$CF_3C_6H_4$	**2a**	4	**3i**	94	97
10	**1j**: 4-$EtO_2CC_6H_4$	**2a**	3	**3j**	82	96
11	**1k**: 4-CNC_6H_4	**2a**	3	**3k**	90	98
12	**1l**: 4-$COMeC_6H_4$	**2a**	3	**3l**	90	98
13	**1m**: 4-$CHOC_6H_4$	**2a**	3	**3m**	71	90
14	**1n**: 4-ClC_6H_4	**2a**	4	**3n**	87	97
15	**1o**: 4-FC_6H_4	**2a**	4	**3o**	74	99
16[c]	**1p**: 3-FC_6H_4	**2a**	4	**3p**	92	96
17[c]	**1q**: 2-FC_6H_4	**2a**	4	**3q**	99	94
18	**1r**: 3,5-$(CF_3)_2C_6H_3$	**2a**	3	**3r**	49	95
19	**1s**: 2-naphthyl	**2a**	3	**3s**	97	99
20[c]	**1t**: 1-naphthyl	**2a**	3	**3t**	98	91
21[b]	**1u**: 2-furyl	**2a**	3	**3u**	85	93
22[b]	**1v**: 2-thienyl	**2a**	3	**3v**	98	98
23	**1w**: (*E*)-Ph-CH=CH	**2a**	5	**3w**	99	97
24[d]	**1x**: *n*-C_5H_{11}	**2a**	3	**3x**	67	93
25[d]	**1y**: $PhCH_2CH_2$	**2a**	5	**3y**	81	90
26[d]	**1z**: 	**2a**	4	**3z**	69	94
27[b]	**1a**: C_6H_5	**2b**	5	**3aa**	94	97
28[b]	**1a**: C_6H_5	**2c**	5	**3ab**	99	95





[a] Conditions: **1** (0.375 mmol), **2** (0.25 mmol), and EtOH (2.5 mL), at rt, unless otherwise noted; yields of the isolated products are reported; the ee values were determined by chiral HPLC analysis. For **3a**, **3c**, **3o**, and **3s**: $Ni(COD)_2$ (5 mol%) and **L8** (5.5 mol%) were used; for the others: $Ni(COD)_2$ (10 mol%) and **L8** (11 mol%) were used. [b] At 50 °C. [c] At 60 °C. [d] At 70 °C.

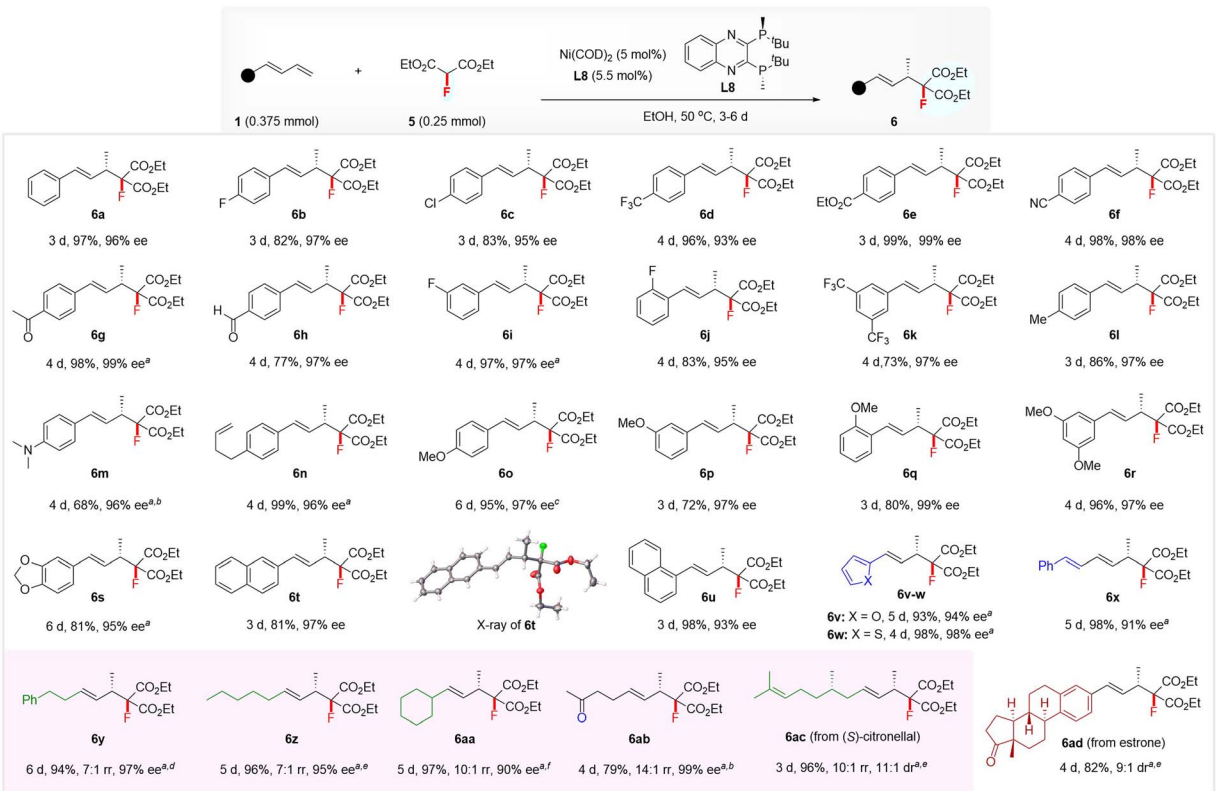


Scheme 2 Synthetic applications of hydromonofluoromethylation.

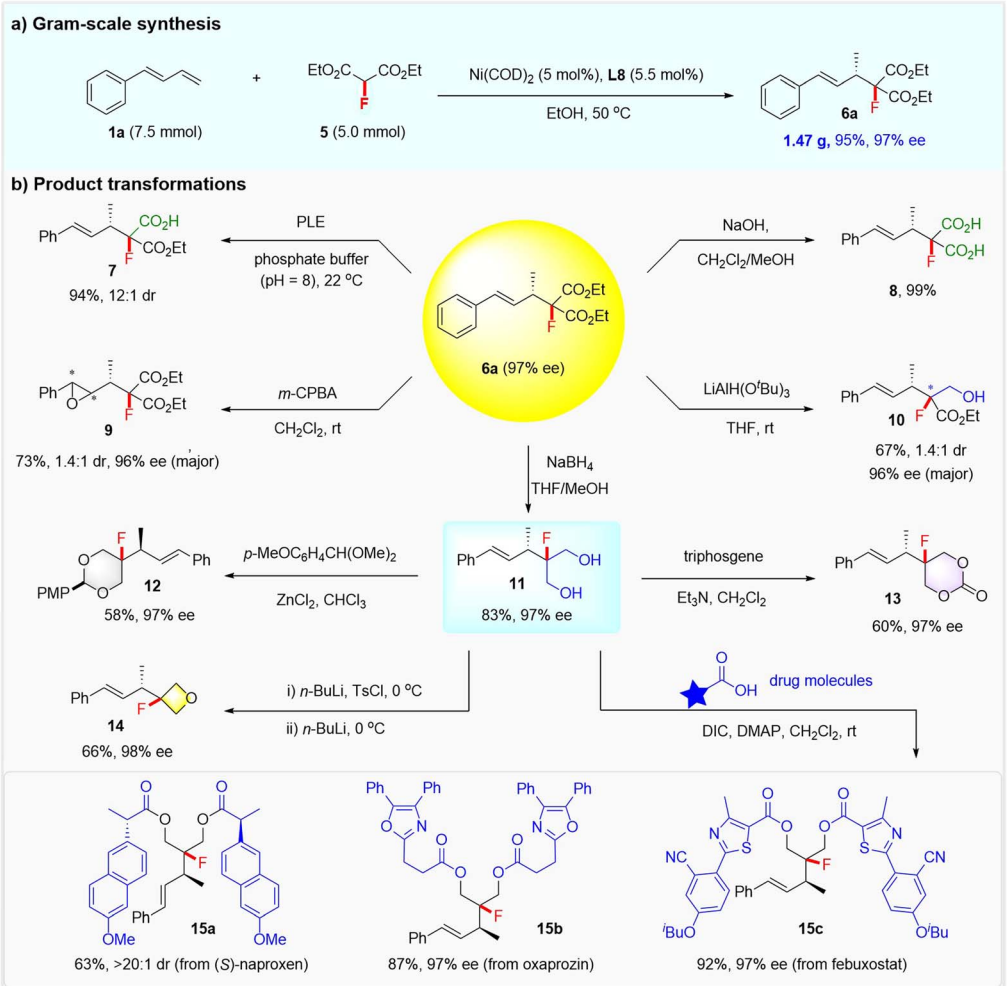
our delight, chiral deuterated allylic product **D-4a** featuring a CD_2F group at the stereocenter, difficult to access by other methods, could be obtained smoothly by using CD_3OD as the solvent in the desulfonylation step.

Furthermore, a tandem Ni-catalyzed asymmetric hydromonofluoro bis(phenylsulfonyl)methylation/reductive desulfonylation sequence was developed for the direct access of α-CH_2F and α-CD_2F substituted chiral allylic compounds **4** and **D-4** (Scheme 2B). Both aryl- and alkyl-substituted 1,3-dienes were suitable partners for this tandem sequence, as exemplified by the preparation of **4a–4d** and **D-4a–4d** with excellent ee values. It is worth mentioning that the facile synthesis of chiral allylic compounds bearing a CD_2F-substituted stereocenter justified the use of FBSM as the monofluoromethylation reagent and further highlighted the value of our method.

The excellent regio- and enantio-selectivity of the above hydromonofluoromethylation inspired us to explore the realization of enantioselective hydromonofluoroalkylation with diethyl fluoromalonate[4p,16d] **5** because of its ability to simultaneously incorporate a fluorine atom and two convertible ester groups,[22] which allows the construction of functionalized chiral monofluorinated molecules with high structural complexity. After optimization of the reaction conditions (see the ESI† for details), the combination of $Ni(COD)_2$ and (*S*,*S*)-QuinoxP* **L8** still proved to be an optimal catalytic system.[23] As illustrated in Scheme 3, the substrate scope was examined by running the reaction in EtOH at 50 °C using 5 mol% of $Ni(COD)_2$-ligated (*S*,*S*)-QuinoxP* as the catalyst. Both (hetero)aromatic and aliphatic 1,3-dienes were suitable substrates, affording the 4,3-Markovnikov adducts **6** with excellent regio- and enantio-selectivity. Regardless of the nature and position of the substituent on the phenyl ring of aryl 1,3-dienes, all reacted well with **5** to afford the products **6a–6u** in 68–99% yields with 93–99% ee. The XRD analysis of **6t** confirmed its absolute configuration to be (*S*), and that of other products was assigned by analogy. Various functional groups, such as ester (**6e**), nitrile (**6f**), ketone (**6g**), aldehyde (**6h**), amine (**6m**), and non-conjugated alkene (**6n**), on the aryl ring of aromatic 1,3-dienes were well-tolerated under this hydromonofluoroalkylation as well. Heteroaromatic 2-furyl- and 2-thienyl-substituted 1,3-dienes, as well as conjugated triene, also afforded the adducts **6v–6x** in 93–98% yields and 91–98% ee. Moreover, linear and branched alkyl-substituted 1,3-dienes were tolerated, affording 4,3-Markovnikov adducts **6y–6ab** in 79–97% yields and 90–97% ee, with high to excellent regioselectivity, albeit with the generation of a small amount of 4,1-addition isomer in these cases.[13c] The use of a 10 mol% Ni catalyst was required to ensure excellent yields in the case of heteroaryl and alkyl 1,3-dienes. The protocol was also applied to the late-stage hydromonofluoroalkylation of (*S*)-



Scheme 3 Scope of enantioselective hydromonofluoroalkylation of 1,3-dienes **1** with diethyl fluoromalonate **5**. Conditions: **1** (0.375 mmol), **2** (0.25 mmol), $Ni(COD)_2$ (5 mol%), and **L8** (5.5 mol%) at 50 °C in EtOH (1.5 mL), unless otherwise noted. Yields of isolated products were reported and ee was determined by chiral HPLC analysis. [a] Using $Ni(COD)_2$ (10 mol%) and **L8** (11 mol%). [b] At 70 °C. [c] At 50–70 °C. [d] At 60 °C. [e] At 80 °C. [f] At 75 °C. The rr indicates the regioselectivity ratio of 4,3-Markovnikov isomer with another isomer, which was determined by ^1H NMR analysis. The ee value of **6z** and **6aa** was determined by their derivatives; see the ESI† for details. The dr value of **6ac** and **6ad** was determined by ^{19}F NMR analysis.



Scheme 4 Synthetic utility.

citronellal and estrone derivatives, affording **6ac** in 96% yield with 11 : 1 dr and **6ad** in 82% yield with 9 : 1 dr.

Synthetic utility

To further highlight the practicality of the reaction, a gram-scale synthesis of product **6a** and its synthetic elaborations toward structurally diversified fluorine-containing molecules was conducted. As shown in Scheme 4, starting from **1a** (7.5 mmol) and **5** (5 mmol), 1.47 g of **6a** could be readily generated in 95% yield and with 97% ee under the standard conditions. The two ester groups of **6a** could be selectively hydrolyzed to fluorinated carboxylic acid or dicarboxylic acid, as demonstrated by the synthesis of **7** (94% yield and 12 : 1 dr) *via* a porcine liver esterase (PLE) enabled hydrolytic desymmetrization, and **8** (99% yield) *via* NaOH-mediated hydrolysis. The treatment of **6a** with *m*-CPBA led to the epoxidation of the alkenyl and afforded chiral fluorinated epoxide **9** in 73% yield, albeit with modest dr. Compound **6a** could also be selectively reduced with $LiAl(O^tBu)_3$ or $NaBH_4$, affording a fluorinated hydroxy ester **10** in 67% yield with 1.4 : 1 dr and 96% ee, or a fluorinated diol **11** in 83% yield with 97% ee, respectively.

Notably, diol **11** was readily converted into a synthetically useful fluorinated 1,3-dioxane **12** or 1,3-dioxan-2-one **13** (ref.[24]) under the action of 1-(dimethoxymethyl)-4-methoxybenzene or triphosgene. A fluorinated oxetane **14** was also obtained from diol **11** *via* a selective monotosylation and sequential cyclization process. The versatile diol **11** proved to be a very useful linker that can merge two drugs to form complex fluorine-containing molecules, as exemplified by the efficient installation of fluorinated compounds **15a–15c** from drugs (*S*)-naproxen, oxaprozin, and febuxostat.

Conclusions

In summary, we have developed a highly enantioselective Markovnikov regioselective hydromonofluoroalkyl(methyl)ation of 1,3-dienes by using chiral Ni catalysis, allowing access to various functionalized chiral allylic compounds bearing a CH_2F, CD_2F or monofluoroalkyl group at the stereocenter. Remarkably, such a methodology provides a new direction for enantioselective monofluoroalkyl(methyl)ation, and it constitutes a new branch of asymmetric 1,3-diene hydrofunctionalizations. Moreover, this

represents the first enantio- and regio-selective Markovnikov hydrofluoroalkylation of olefins. The salient features include broad substrate scope for both aromatic and aliphatic 1,3-dienes, excellent enantio- and regio-selectivity, good functional group tolerance, mild base-free conditions, and diverse product transformations. Further studies in our laboratory will focus on elucidating the reaction mechanism[25] and developing other asymmetric Markovnikov regioselective hydrofluoroalkylation reactions.

Data availability

All of the experimental data have been included in the ESI.† Crystallographic data can be obtained from the CCDC (2130032 and 2130034).

Author contributions

L. Liao and Y. Zhang performed the experiments, and collected and analyzed the data; Z.-W. Wu, Z.-T. Ye, and X.-X. Zhang synthesized some of the 1,3-dienes. J.-S. Yu conceived the idea and directed the project; J.-S. Yu and G. Chen co-wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge Prof. Dr Jian Zhou at ECNU for his kind and valuable discussion. The financial support from the National Key Research and Development Program of China (2021YFC2102400), the National Natural Science Foundation of China (22171087 and 21901074), the Shanghai Science and Technology Innovation Action Plan (21N41900500 and and 20JC1416900), the Fundamental Research Funds for the Central Universities, and the Open Foundation of Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education (rdzh2020003) is highly appreciated. J.-S. Y. also acknowledges financial support from the "Zijiang Scholar Program" of East China Normal University.

Notes and references

1 (*a*) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, 2009; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*c*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (*d*) K. Müller, C. Faeh and F. Diederich, *Science*, 2017, **317**, 1881–1886.

2 (*a*) R. E. Banks, B. E. Smart and J. C. Tatlow, *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum, New York, 1994, ch. 3; (*b*) V. P. Reddy, *Organofluorine Compounds in Biology and Medicine*, Elsevier, Amsterdam, 2020; (*c*) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3–11; (*d*) P. Jeschke, *ChemBioChem*, 2004, **5**, 570–589; (*e*) W. K. Hagmjann, *J. Med. Chem.*, 2008, **51**, 4359–4369; (*f*) J. Wang, M. Sánchez-Roselló, J. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (*g*) M. Reichel, B. Krumm, Y. V. Vishnevskiy, S. Blomeyer, J. Schwabedissen, H.-G. Stammler, K. Karaghiosoff and N. W. Mitzel, *Angew. Chem., Int. Ed.*, 2019, **58**, 18557–18561; (*h*) M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633–10640; (*i*) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, *iScience*, 2020, **23**, 101467.

3 (*a*) J. Kollonitsch, A. A. Patchett, S. Marburg, A. L. Maycock, L. M. Perkins, G. A. Doldouras, D. E. Duggan and S. D. Aster, *Nature*, 1978, **274**, 906–908; (*b*) G. L. Grunewald, M. R. Seim, R. C. Regier, J. L. Martin, C. L. Gee, N. Drinkwater and K. R. Criscione, *J. Med. Chem.*, 2006, **49**, 5424–5433; (*c*) H. Su, Y. Xie, W.-B. Liu and S.-L. You, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3578–3582.

4 For selected reviews:(*a*) G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757–786; (*b*) K. Uneyama, T. Katagiri and H. Amii, *Acc. Chem. Res.*, 2008, **41**, 817–829; (*c*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455–529; (*d*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477; (*e*) G. Valero, X. Companyó and R. Rios, *Chem.–Eur. J.*, 2011, **17**, 2018–2037; (*f*) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598–6608; (*g*) L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513–1522; (*h*) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650–682; (*i*) X. Yang, T. Wu, R. J. Phipps and F. D. Toste, *Chem. Rev.*, 2015, **115**, 826–870; (*j*) C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765–825; (*k*) C. Alonso, E. M. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935; (*l*) X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683–730; (*m*) V. Gouverneur and K. Seppelt, *Chem. Rev.*, 2015, **115**, 563–565; (*n*) Z. Feng, Y.-L. Xiao and X. Zhang, *Acc. Chem. Res.*, 2018, **51**, 2264–2278; (*o*) A. D. Dilman and V. V. Levin, *Acc. Chem. Res.*, 2018, **51**, 1272–1280; (*p*) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho and F. D. Toste, *Chem. Rev.*, 2018, **118**, 3887–3964; (*q*) D. Cahard and J.-A. Ma, *Emerging Fluorinated Motifs: Synthesis, Properties, and Applications*. Wiley-VC, 1st edn, 2020; (*r*) T. W. Butcher, W. M. Amberg and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2021, **61**, e202112251.

5 For the leading review, see:M. Reichel and K. Karaghiosoff, *Angew. Chem., Int. Ed.*, 2020, **59**, 12268–12281.

6 (*a*) T. Chatterjee, N. Iqbal, Y. You and E. J. Cho, *Acc. Chem. Res.*, 2016, **49**, 2284–2294; (*b*) S. Barata-Vallejo, M. V. Cooke and A. Postigo, *ACS Catal.*, 2018, **8**, 7287–7307; (*c*) R. D. Laishram, J. Chen and B. Fan, *Chem. Rec.*, 2021, **21**, 69–86; (*d*) T. Koike and M. Akita, *Chem*, 2018, **4**, 409–437; (*e*) D. E. Yerien, S. Barata-Vallejo and A. Postigo, *Chem.–Eur. J.*, 2017, **23**, 14676–14701.

7 For selected examples of perfluoroalkylations:(*a*) C.-M. Hu and Y.-L. Qiu, *J. Org. Chem.*, 1992, **57**, 3339; (*b*) Z.-Y. Long and Q.-Y. Chen, *J. Org. Chem.*, 1999, **64**, 4775–4782; (*c*)

T. Yajima and S. Shigenaga, *Org. Lett.*, 2019, **21**, 138–141; (*d*) C.-L. Tong, X.-H. Xu and F.-L. Qing, *Org. Lett.*, 2019, **21**, 9532–9535; (*e*) W. Zhang, Z. Zou, Y. Wang, Y. Wang, Y. Liang, Z. Wu, Y. Zheng and Y. Pan, *Angew. Chem., Int. Ed.*, 2019, **58**, 624–627, for selected examples of trifluoromethylations:; (*f*) S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheel-house, G. Rassias, M. Médebielle and V. Gouverneur, *J. Am. Chem. Soc.*, 2013, **135**, 2505–2508; (*g*) X. Wu, L. Chu and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2013, **52**, 2198–2202; (*h*) D. J. Wilger, N. J. Gesmundo and D. A. Nicewicz, *Chem. Sci.*, 2013, **4**, 3160–3165; (*i*) P. Yu, J.-S. Lin, L. Li, S.-C. Zheng, Y.-P. Xiong, L.-J. Zhao, B. Tan and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 11890–11894; (*j*) N. J. W. Straathof, S. E. Cramer, V. Hessel and T. Noël, *Angew. Chem., Int. Ed.*, 2016, **55**, 15549–15553; (*k*) J.-X. Xiang, Y. Ouyang, X.-H. Xu and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2019, **58**, 10320–10324, for selected difluoroalkylations:; (*l*) C. Yu, N. Iqbal, S. Park and E. Cho, *Chem. Commun.*, 2014, **50**, 12884–12887; (*m*) G. Ma, W. Wan, J. Li, Q. Hu, H. Jiang, S. Zhu, J. Wang and J. Hao, *Chem. Commun.*, 2014, **50**, 9749–9752; (*n*) Q.-Y. Lin, X.-H. Xu and F.-L. Qing, *Org. Biomol. Chem.*, 2015, **13**, 8740–8749; (*o*) X.-J. Tang, Z. Zhang and W. R. Dolbier Jr, *Chem.–Eur. J.*, 2015, **21**, 18961–18965; (*p*) J. Yu, J.-H. Lin, Y.-C. Cao and J.-C. Xiao, *Org. Chem. Front.*, 2019, **6**, 3580–3583; (*q*) W. Huang, W. Chen, G. Wang, J. Li, X. Cheng and G. Li, *ACS Catal.*, 2016, **6**, 7471–7474; (*r*) W. Shu, E. Merino and C. Nevado, *ACS Catal.*, 2018, **8**, 6401–6406; (*s*) H. Wang and N. T. Jui, *J. Am. Chem. Soc.*, 2018, **140**, 163–166; (*t*) D. B. Vogt, C. P. Seath, H. Wang and N. T. Jui, *J. Am. Chem. Soc.*, 2019, **141**, 13203–13211.

8 (*a*) D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458; (*b*) K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191.

9 For a review, see:(*a*) X.-S. Hu, J.-S. Yu and J. Zhou, *Chem. Commun.*, 2019, **55**, 13638–13648; (*b*) X.-S. Hu, J.-X. He, S.-Z. Dong, Q.-H. Zhao, J.-S. Yu and J. Zhou, *Nat. Commun.*, 2020, **11**, 5500; (*c*) J.-S. Yu, F.-M. Liao, W.-M. Gao, K. Liao, R.-L. Zuo and J. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 7381–7385.

10 For leading reviews:(*a*) G.-L. Li, X.-H. Huo, X.-Y. Jiang and W.-B. Zhang, *Chem. Soc. Rev.*, 2020, **49**, 2060–2118; (*b*) N. J. Adamson and S. J. Malcolmson, *ACS Catal.*, 2020, **10**, 1060–1076.

11 Hydroamination:(*a*) O. Löber, M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 4366–4367; (*b*) X.-H. Yang and V. M. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 1774–1777; (*c*) N. J. Adamson, E. Hull and S. J. Malcolmson, *J. Am. Chem. Soc.*, 2017, **139**, 7180–7183; (*d*) G. Tran, W. Shao and C. Mazet, *J. Am. Chem. Soc.*, 2019, **141**, 14814–14822.

12 Hydroalkylation:(*a*) A. Leitner, J. Larsen, C. Steffens and J. F. Hartwig, *J. Org. Chem.*, 2004, **69**, 7552–7557; (*b*) N. J. Adamson, K. C. E. Wilbur and S. J. Malcolmson, *J. Am. Chem. Soc.*, 2018, **140**, 2761–2764; (*c*) L. Cheng, M.-M. Li, L.-J. Xiao, J.-H. Xie and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2018, **140**, 11627–11630; (*d*) Q. Zhang, H. Yu, L. Shen, T. Tang, D. Dong, W. Chai and W. Zi, *J. Am. Chem. Soc.*, 2019, **141**, 14554–14559; (*e*) W. Shao, C. Besnard, L. Guénée and C. Mazet, *J. Am. Chem. Soc.*, 2020, **142**, 16486–16492; (*f*) J. Xia, T. Hirai, S. Katayama, H. Nagae, W. Zhang and K. Mashima, *ACS Catal.*, 2021, **11**, 6643–6655; (*g*) H. Wang, R. Zhang, Q. Zhang and W. Zi, *J. Am. Chem. Soc.*, 2021, **143**, 10948–10962.

13 Hydroarylation:(*a*) C. C. Roberts, J. S. Marcum, C. C. Roberts, R. S. Manan, T. N. Cervarich and S. J. Meek, *J. Am. Chem. Soc.*, 2017, **139**, 15580–15583; (*b*) X.-Y. Lv, C. Fan, L.-J. Xiao, J.-H. Xie and Q.-L. Zhou, *CCS Chem.*, 2019, **1**, 328–334; (*c*) L. Cheng, M.-M. Li, M.-L. Li, L.-J. Xiao, J.-H. Xie and Q.-L. Zhou, *CCS Chem.*, 2021, **3**, 3260–3267.

14 (*a*) Q. Zhang, D. Dong and W. Zi, *J. Am. Chem. Soc.*, 2020, **142**, 15860–15869; (*b*) M.-M. Li, L. Cheng, L.-J. Xiao, J.-H. Xie and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2021, **60**, 2948–2951.

15 (*a*) J. W. Han and T. Hayashi, *Tetrahedron: Asymmetry*, 2010, **21**, 2193–2197; (*b*) M. Shirakura and M. Suginome, *Angew. Chem., Int. Ed.*, 2010, **49**, 3827–3829; (*c*) S.-Z. Nie, R. T. Davison and V. M. Dong, *J. Am. Chem. Soc.*, 2018, **140**, 16450–16454; (*d*) X.-H. Yang, R. T. Davison and V. M. Dong, *J. Am. Chem. Soc.*, 2018, **140**, 10443–10446; (*e*) X.-H. Yang, R. T. Davison, S.-Z. Nie, F. A. Cruz, T. M. McGinnis and V. M. Dong, *J. Am. Chem. Soc.*, 2019, **141**, 3006–3013; (*f*) J. Long, Y.-Q. Li, W.-N. Zhao and G.-Y. Yin, *Chem. Sci.*, 2022, **13**, 1390–1397.

16 For pioneering work on the synthesis and application of FBSM:(*a*) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura and T. Toru, *Angew. Chem., Int. Ed.*, 2006, **45**, 4973–4977; (*b*) C. Ni, Y. Li and J. Hu, *J. Org. Chem.*, 2006, **71**, 6829–6833, for reviews:; (*c*) A.-N. R. Alba, X. Companyo and R. Rios, *Chem. Soc. Rev.*, 2010, **39**, 2018–2033; (*d*) C. Ni, L. Zhu and J. Hu, *Acta Chim. Sin.*, 2015, **73**, 90–115, see selected examples for the application of FBSM in asymmetric reactions:; (*e*) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura and T. Toru, *J. Am. Chem. Soc.*, 2007, **129**, 6394–6395; (*f*) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem., Int. Ed.*, 2008, **47**, 8051–8054; (*g*) T. Furukawa, J. Kawazoe, W. Zhang, T. Nishimine, E. Tokunaga, T. Matsumoto, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2011, **50**, 9684–9688; (*h*) A. N. Alba, X. Companyó, A. Moyano and R. Rios, *Chem.–Eur. J.*, 2009, **15**, 7035–7038; (*i*) S. Zhang, Y. Zhang, Y. Ji, H. Li and W. Wang, *Chem. Commun.*, 2009, 4886–4888; (*j*) F. Ullah, G. L. Zhao, L. Deiana, M. Zhu, P. Dziedzic, I. Ibrahem, P. Hammar, J. Sun and A. Córdova, *Chem.–Eur. J.*, 2009, **15**, 10013–10017; (*k*) W. B. Liu, S. C. Zheng, H. He, X. M. Zhao, L. X. Dai and S. L. You, *Chem. Commun.*, 2009, 6604–6606; (*l*) X. Companyó, G. Valero, V. Ceban, T. Calvet, M. Font-Bardia, A. Moyano and R. Rios, *Org. Biomol. Chem.*, 2011, **9**, 7986–7989; (*m*) W. Yang, X. Wei, Y. Pan, R. Lee, B. Zhu, H. Liu, L. Yan, K.-W. Huang, Z. Jiang and C.-H. Tan, *Chem.–Eur. J.*, 2011, **17**, 8066–8070, also see ref. 5.

17 (*a*) M. Dutartre, J. Bayardon and S. Jugé, *Chem. Soc. Rev.*, 2016, **45**, 5771–5794; (*b*) R.-Y. Zhu, K. Liao, J.-S. Yu and J. Zhou, *Acta Chim. Sin.*, 2020, **78**, 193–216.

18 T. Imamoto, K. Sugita and K. Yoshida, *J. Am. Chem. Soc.*, 2005, **127**, 11934–11935.

19 (*a*) G. K. S. Prakash, S. Chacko, S. Alconcel, T. Stewart, T. Mathew and G. A. Olah, *Angew. Chem., Int. Ed.*, 2007, **46**, 4933–4936; (*b*) G. K. S. Prakash, S. Chacko, H. Vaghoo, N. Shao, L. Gurung, T. Mathew and G. A. Olah, *Org. Lett.*, 2009, **11**, 1127–1130.

20 (*a*) C. Schmidt, First Deuterated Drug Approved, *Nat. Biotechnol.*, 2017, **35**, 493–494; (*b*) S. H. DeWitt and B. E. Maryanoff, *Biochemistry*, 2018, **57**, 472–473; (*c*) V. Jacques, A. W. Czarnik, T. M. Judge, L. H. T. Van der Ploeg and S. H. DeWitt, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, E1471–E1479.

21 Shen and Lu installed a CD_2F group in a few achiral molecules using their developed electrophilic CD_2F-substituted sulfonium ylides:Y. Liu, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2017, **56**, 9930–9934.

22 P. Xu and Z. Huang, *Nat. Chem.*, 2021, **13**, 634–642.

23 An obvious fluorine effect was observed in the current reaction, though the origin is still unclear. In the presence of 10 mol% $Ni(COD)_2$/**L8**, the use of diethyl 2-fluoromalonate **5** afforded the hydromonofluoroalkylated product **6a** in 94% with 96% ee; in sharp contrast, under the same conditions, no reaction occurred at all when replacing **5** with diethyl 2-chloromalonate and only 74% ee of the corresponding product with 98% yield was obtained in the case of diethyl 2-methylmalonate.

24 The utility of fluorinated rings:(*a*) P. Kirsch, A. Hahn, R. Fröhlich and G. Haufe, *Eur. J. Org. Chem.*, 2006, **2006**, 4819–4824; (*b*) R. Mondal, M. Agbaria and Z. Nairoukh, *Chem.–Eur. J.*, 2021, **27**, 7193–7213.

25 To gain some insight into the reaction mechanism, we conducted preliminary experimental investigation and also proposed a reaction mechanism; see Section 7 of the ESI† for details.