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

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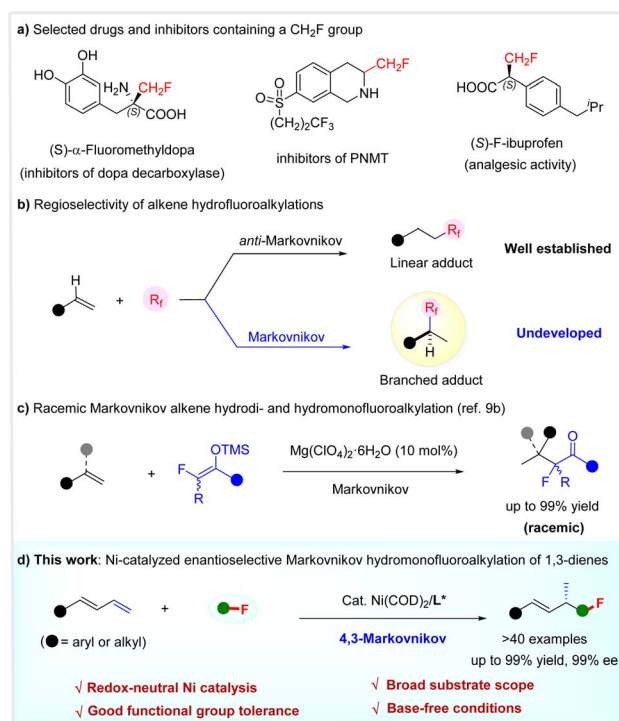
A highly enantio- and regio-selective Markovnikov hydromonofluoro(methyl)alkylation of 1,3-dienes was developed using redox-neutral nickel catalysis. It provided a facile strategy to construct diverse monofluoromethyl- or monofluoroalkyl-containing chiral allylic molecules. Notably, this represents the 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.

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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 CH₂F 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 ₂ Cl 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 ¹H 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



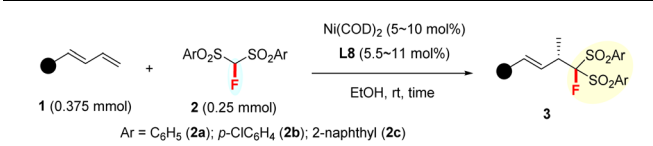
EtOH under the catalysis of a 5 mol% or 10 mol% *P*-chiral (*S,S*)-QuinoxP* decorated Ni(COD)₂ complex (Table 2).

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

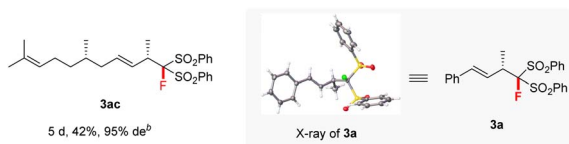
alkene (**3h**), ester (**3j**), nitrile (**3k**), ketone (**3l**), and aldehyde (**3m**). Naphthyl-, 2-furyl-, and 2-thienyl-substituted 1,3-dienes all worked smoothly with **2a** to afford **3s–3v** in excellent yields and ee values (entries 19–22). A conjugated triene was also tolerated; it afforded 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 (CH₂F) allylic compound **4a** with 96% ee under the action of Mg/MeOH¹⁹ (Scheme 2A). This result stimulated us to explore the assembly of deuterated monofluoromethyl (CD₂F)-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 CD₂F 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

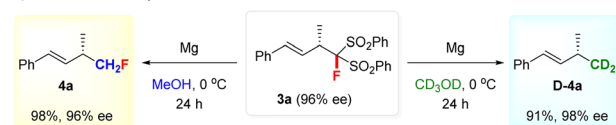


Entry	1: substituent (●)	2	Time (d)	3	Yield (%)	ee (%)
1	1a : C ₆ H ₅	2a	3	3a	86	96
2	1b : 4-MeC ₆ H ₄	2a	4	3b	99	94
3	1c : 4-MeOC ₆ H ₄	2a	3	3c	97	97
4 ^b	1d : 3-MeOC ₆ H ₄	2a	3	3d	86	98
5 ^b	1e : 2-MeOC ₆ H ₄	2a	3	3e	93	98
6	1f : 3,5-MeO ₂ C ₆ H ₃	2a	3	3f	98	99
7 ^b	1g : 4-Me ₂ NC ₆ H ₄	2a	4	3g	48	93
8	1h : 4-CH ₂ =CH(CH ₂) ₂ C ₆ H ₄	2a	3	3h	68	95
9	1i : 4-CF ₃ C ₆ H ₄	2a	4	3i	94	97
10	1j : 4-EtO ₂ CC ₆ H ₄	2a	3	3j	82	96
11	1k : 4-CNC ₆ H ₄	2a	3	3k	90	98
12	1l : 4-COMeC ₆ H ₄	2a	3	3l	90	98
13	1m : 4-CHOC ₆ H ₄	2a	3	3m	71	90
14	1n : 4-ClC ₆ H ₄	2a	4	3n	87	97
15	1o : 4-FC ₆ H ₄	2a	4	3o	74	99
16 ^c	1p : 3-FC ₆ H ₄	2a	4	3p	92	96
17 ^c	1q : 2-FC ₆ H ₄	2a	4	3q	99	94
18	1r : 3,5-(CF ₃) ₂ C ₆ H 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 : (<i>E</i>)-Ph-CH=CH	2a	5	3w	99	97
24 ^d	1x : <i>n</i> -C ₅ H ₁₁	2a	3	3x	67	93
25 ^d	1y : PhCH ₂ CH ₂	2a	5	3y	81	90
26 ^d	1z :	2a	4	3z	69	94
27 ^b	1a : C ₆ H ₅	2b	5	3aa	94	97
28 ^b	1a : C ₆ H ₅	2c	5	3ab	99	95

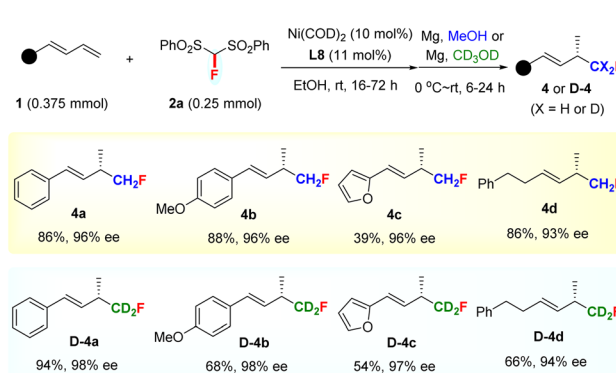


^a Conditions: **1** (0.375 mmol), **2** (0.25 mmol), and EtOH (2.5 mL), at rt, unless otherwise noted; yields of the isolated products are reported; the ee values were determined by chiral HPLC analysis. For **3a**, **3c**, **3o**, and **3s**: Ni(COD)₂ (5 mol%) and **L8** (5.5 mol%) were used; for the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

A) Reductive desulfonylation of **3a**



B) Tandem synthesis of chiral α -CH₂F or α -CD₂F molecules **4** or **D-4**



Scheme 2 Synthetic applications of hydromonofluoromethylation.

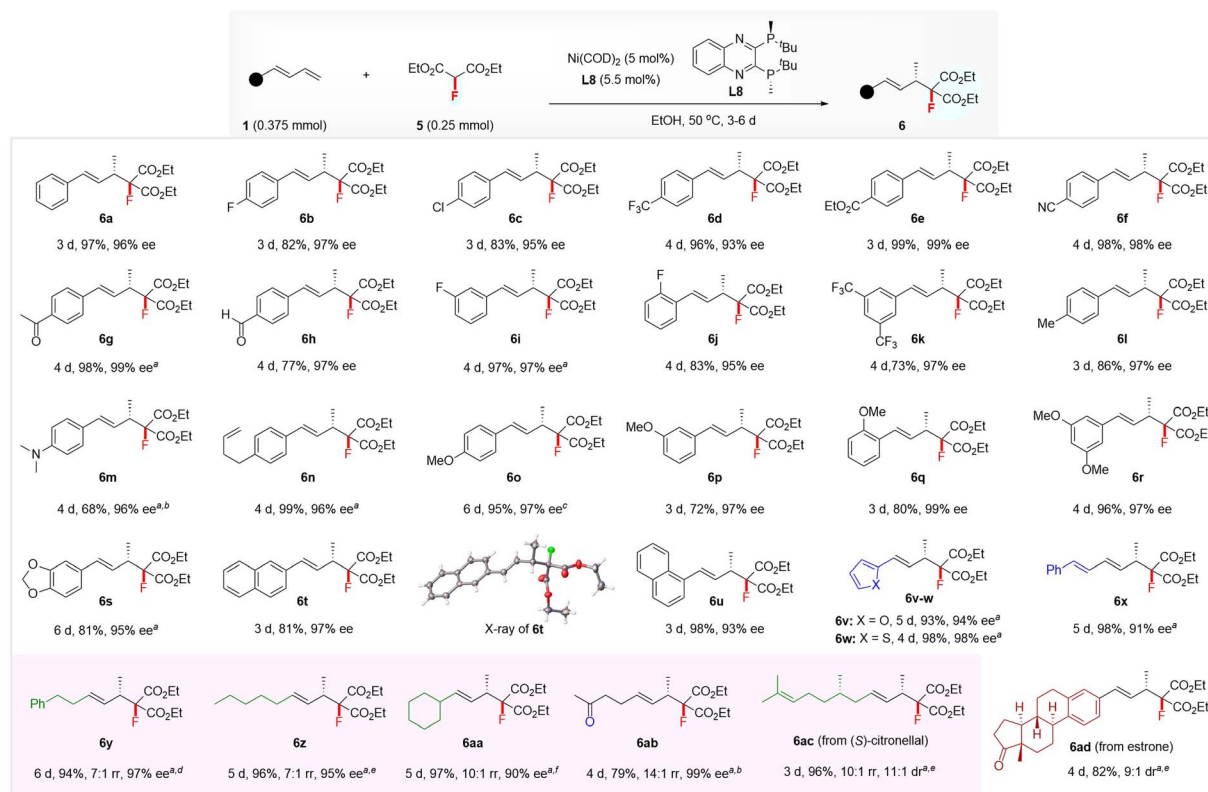


our delight, chiral deuterated allylic product **D-4a** featuring a CD₂F group at the stereocenter, difficult to access by other methods, could be obtained smoothly by using CD₃OD as the solvent in the desulfonylation step.

Furthermore, a tandem Ni-catalyzed asymmetric hydromonofluoro bis(phenylsulfonyl)methylation/reductive desulfonylation sequence was developed for the direct access of α -CH₂F and α -CD₂F 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 CD₂F-substituted stereocenter justified the use of FBSM as the monofluoromethylation reagent and further highlighted the value of our method.

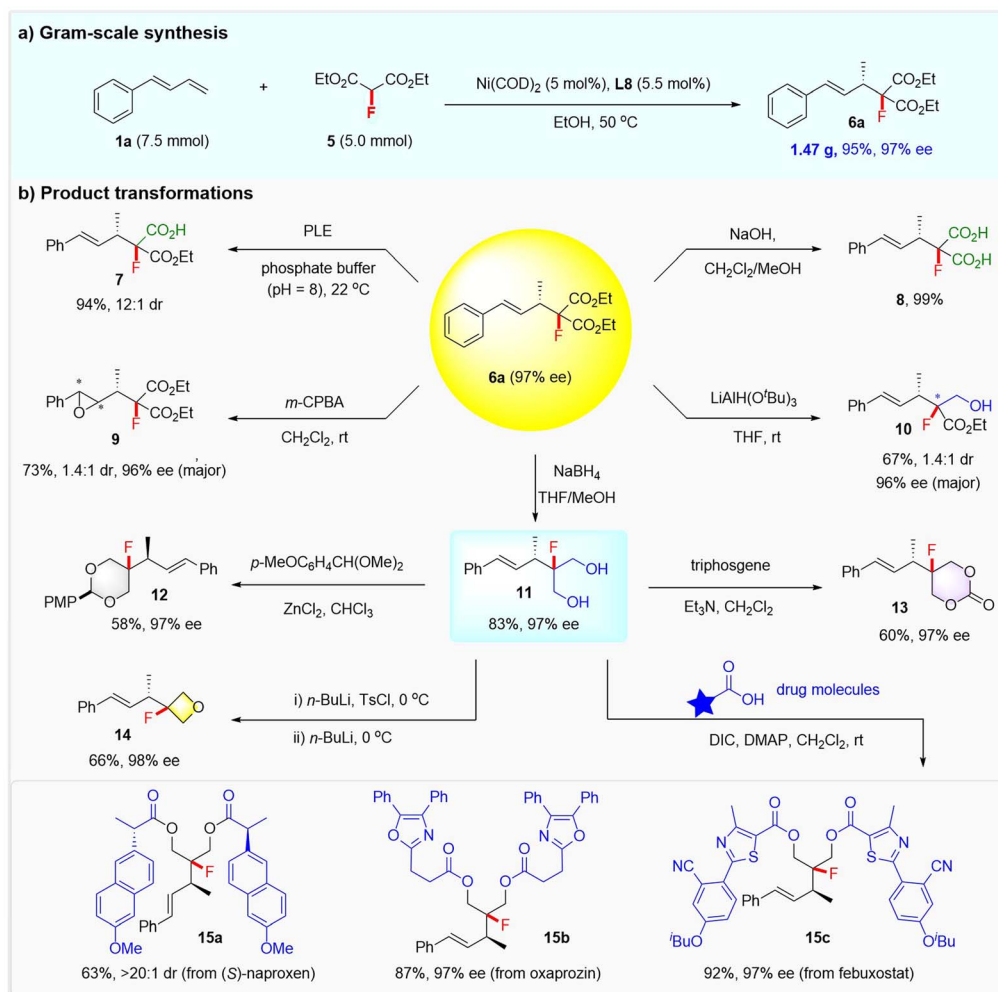
The excellent regio- and enantio-selectivity of the above hydromonofluoromethylation inspired us to explore the realization of enantioselective hydromonofluoroalkylation with diethyl fluoromalonate^{4p,16d} **5** because of its ability to simultaneously incorporate a fluorine atom and two convertible 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 ¹⁹F 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 $\text{LiAlH}(\text{O}^t\text{Bu})_3$ 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 mechanism²⁵ 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.

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