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

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A highly enantio- and regio-selective Markovnikov hydromonofluoroalkylation 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. In particular, the installation of a monofluoromethyl (CH2F) 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. Typical drugs or inhibitors featuring a CH2F unit are shown in Scheme 1a. However, despite the significant progress made in selective fluoralkylation, the efficient incorporation of a CH2F group in a highly enantioselective manner remains challenging and very much in demand.

While the hydrofluoroalkylation of alkenes is a powerful strategy to introduce a fluoroalkyl group selectively, catalytic enantioselective incorporation of a monofluoroalkyl group is unexplored. Notably, most known monokfluoroalkylations are based on radical processes, affording linear adducts with anti-Markovnikov regioselectivity. 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). Following our interest in selective fluoroalkylation, we recently developed the出来。
first Markovnikov hydrodi- and hydromonofluoroallylation of simple alkenes using fluorinated enol silyl ethers, via an acid-catalyzed carboxation process (Scheme 1c).\textsuperscript{6a} Herein, we disclose a highly regio- and enantio-selective Markovnikov hydromonofluoro(methyl)allylation reaction of 1,3-dienes by redox-neutral Ni catalysis (Scheme 1d).

Transition-metal-catalyzed regio- and enantio-selective hydrofunctionalization of 1,3-dienes \textit{I} offers an efficient and atom-economical method to access chiral functionalized allylic compounds from readily available starting materials.\textsuperscript{10,11} Over the past few years, various highly enantioselective protocols have been used: hydroamination,\textsuperscript{11} hydroalkylation,\textsuperscript{12,13} hydroarylation,\textsuperscript{13} and hydroboration,\textsuperscript{14} among others.\textsuperscript{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,\textsuperscript{16} 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.\textsuperscript{12,13} Despite ongoing achievements, the catalytic enantio- and regio-selective hydrofunctionalizations of 1,3-dienes are relatively rare.\textsuperscript{10,16}"n

Inspired by these elegant advances, we speculated that the implementation of catalytic asymmetric 1,3-dienes hydrofunctionalization 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, fluoro(phenyl-sulfonyl)methane (FBSM)\textsuperscript{17a,b} proves to be a robust one in developing catalytic enantioselective monofluoromethylation reactions,\textsuperscript{18,19} since the landmark work of Shibata.\textsuperscript{18e} On this basis, we determined to use FBSM 2a as a latent monofluoromethyl agent to explore the asymmetric Markovnikov hydromonofluoromethylation of 1,3-dienes \textit{I} 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)\textsubscript{2} (10 mol%) and \textit{N,N}-disopropylethylamine (DIPEA) (20 mol%). As shown in Table 1, a series of axially chiral bisphosphine ligands were used: hydroamination,\textsuperscript{11} hydroalkylation,\textsuperscript{12,13} hydroarylation,\textsuperscript{13} and hydroboration.\textsuperscript{14} Among others.\textsuperscript{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,\textsuperscript{16} 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.\textsuperscript{12,13} Despite ongoing achievements, the catalytic enantio- and regio-selective hydrofunctionalizations of 1,3-dienes are relatively rare.\textsuperscript{10,16} In this context, 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.

**Table 1** Selected conditions for optimization\textsuperscript{a}

| Entry | Ligand | DIPEA (mol%) | Solvent | Time (h) | Yield\textsuperscript{b} (%) | ee\textsuperscript{c} (%) |
|-------|--------|--------------|---------|---------|--------------------------|---------------------|
| 1     | L1     | 20           | EtOH    | 14      | 98                       | 37                  |
| 2     | L2     | 20           | EtOH    | 48      | 9                        | 27                  |
| 3     | L3     | 20           | EtOH    | 24      | 66                       | 72                  |
| 4     | L4     | 20           | EtOH    | 26      | 70                       | 80                  |
| 5     | L5     | 20           | EtOH    | 14      | 99                       | 86                  |
| 6     | L6a    | 20           | EtOH    | 89      | 86                       | 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\textsubscript{2}Cl\textsubscript{2} | 24 | Trace | — |
| 14    | L8     | 0            | MeOH    | 24      | Trace | — |
| 15    | L8     | 0            | ProH     | 24      | Trace | — |
| 16\textsuperscript{e} | L8 | 0 | EtOH | 72 | 86 | 96 |

\textsuperscript{a} Reaction conditions: 1a (0.15 mmol), 2a (0.1 mmol), Ni(COD)\textsubscript{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. \textsuperscript{b} Determined by \textit{H} NMR analysis of the crude product using 1,3,5-trimethoxybenzene as the internal standard. \textsuperscript{c} Determined by chiral HPLC. \textsuperscript{d} No reaction. \textsuperscript{e} Run on a 0.25 mmol scale using Ni(COD)\textsubscript{2} (5 mol%) and L8 (5.5 mol%).

In the ee values (entry 8, see the ESI\textsuperscript{f} for details). Subsequently, we turned our attention to exploring P-chiral phosphine ligands because they usually exhibit distinct chirality-inducing ability.\textsuperscript{17} To our delight, P-chiral (\textit{S,S})-Quinox\textsuperscript{P+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)-QuinoxPh 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, 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).

#### Table 2 Scope of hydromono-fluoromethylation of dienes with 2

| Entry | 1a: substituent (●) | 2: Time (d) | 3: Yield (%) | ee (%) |
|-------|---------------------|-------------|--------------|--------|
| 1     | CH₂H₂               | 2a          | 3a           | 86     | 96    |
| 2     | 4-MeC₆H₄            | 2b          | 3b           | 99     | 94    |
| 3     | 4-MeC₆H₄            | 2c          | 3c           | 97     | 98    |
| 4     | 4-MeC₆H₄            | 2d          | 3d           | 95     | 98    |
| 5     | 4-MeC₆H₄            | 2e          | 3e           | 93     | 96    |
| 6     | 4-MeC₆H₄            | 2f          | 3f           | 94     | 97    |
| 7     | 4-MeC₆H₄            | 2g          | 3g           | 93     | 97    |
| 8     | 4-MeC₆H₄            | 2h          | 3h           | 98     | 95    |
| 9     | 4-MeC₆H₄            | 2i          | 3i           | 95     | 98    |
| 10    | 4-MeC₆H₄            | 2j          | 3j           | 96     | 97    |
| 11    | 4-MeC₆H₄            | 2k          | 3k           | 98     | 98    |
| 12    | 4-MeC₆H₄            | 2l          | 3l           | 99     | 95    |
| 13    | 4-MeC₆H₄            | 2m          | 3m           | 90     | 90    |
| 14    | 4-MeC₆H₄            | 2n          | 3n           | 97     | 97    |
| 15    | 4-MeC₆H₄            | 2o          | 3o           | 97     | 97    |
| 16    | 4-MeC₆H₄            | 2p          | 3p           | 95     | 95    |
| 17    | 4-MeC₆H₄            | 2q          | 3q           | 98     | 98    |
| 18    | 4-MeC₆H₄            | 2r          | 3r           | 99     | 99    |
| 19    | 4-MeC₆H₄            | 2s          | 3s           | 97     | 97    |
| 20    | 4-MeC₆H₄            | 2t          | 3t           | 99     | 99    |
| 21    | 4-MeC₆H₄            | 2u          | 3u           | 98     | 98    |
| 22    | 4-MeC₆H₄            | 2v          | 3v           | 98     | 98    |
| 23    | 4-MeC₆H₄            | 2w          | 3w           | 99     | 99    |
| 24    | 4-MeC₆H₄            | 2x          | 3x           | 97     | 97    |
| 25    | 4-MeC₆H₄            | 2y          | 3y           | 91     | 91    |
| 26    | 4-MeC₆H₄            | 2z          | 3z           | 94     | 94    |

Unsurprisingly, the FBSM adduct 3a could efficiently undergo a reductive desulfonylation to access chiral \( \alpha \)-mono-fluoromethyl (CH₂F) 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 (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. 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. To
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 desulfonation step.

Furthermore, a tandem Ni-catalyzed asymmetric hydromonofluoro bis(phenylsulfonyl)methylation/reductive desulfonation 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 hydromonofluoroalkylation inspired us to explore the realization of enantioselective hydromonofluoroalkylation with diethyl fluoromalonate5,6,16,25 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 6y–6x 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.13 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.
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, 12:1 dr, 96% ee (major)) and 8 (73%, 14:1 dr, 96% ee (major)) 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 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 pig 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(OtBu)3 or NaBH4, 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 hydrofluoroalkyl(methyl)ation of 1,3-dienes by using chiral Ni catalysis, allowing access to various functionalyzed chiral allylic compounds bearing a CH2F, CD2FO 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-diienes, 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 ESL† 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-diienes. 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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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 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.

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.