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Nickel-Catalyzed, Enantioselective Hydrofluoromethylation of Olefins: Access to Chiral α-Fluoromethylated Amides and Esters

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Cite This: *Org. Lett.* 2023, 25, 2218–2222 Read Online

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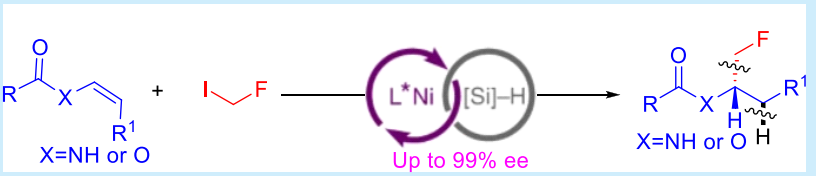


ABSTRACT: We herein report the nickel-catalyzed enantioselective hydrofluoromethylation of enamides and enol esters with CH_2FI as the fluoromethyl source to enable the diversity-oriented synthesis (DOS) of chiral α-fluoromethylated amides as well as esters with features of wide functional group compatibility as well as excellent enantioselectivity. The synthetic value of this protocol was demonstrated by transformations of the resulted α-fluoromethylated amides to different scaffolds including amine, oxazoline, thiazoline, and α-fluoromethylated tetrahydroquinoline.

Despite its small size and simplicity, the CH_2F motif is of particular interest due to the special fluorine effects on regulating the biological and physicochemical properties of parent molecules.[1] Moreover, the CH_2F group could work as competent bioisosteres of methyl (CH_3), hydroxymethyl (CH_2OH), and methoxymethyl (CH_2OCH_3) groups in various biorelevant molecules.[2] In this context, the α-fluoromethyl amine group is recognized as a pharmaceutically important motif, as demonstrated by its prevalence in many bioactive compounds (**1a**, Scheme 1).[3] Therefore, development of straightforward catalytic platforms to access enantioenriched α-fluoromethyl amines is in high demand.[4] However, to date only limited indirect strategies have been reported, which require subsequent reductive desulfonylation steps to release the CH_2F group.[5] Hu and co-workers pioneeringly disclosed the diastereoselective fluoromethylation reactions of the *N-tert*-(butanesulfinyl) imines with LiCFH-SO_2Ph (Path I, Scheme 1b),[6] while Toru elegantly developed the catalytic enantioselective fluoromethylation of α-amido sulfones with fluorobis(phenylsulfonyl)methane (FBSM) (Path II, Scheme 1b).[7] Thus, despite all these dedicated efforts, direct access to the enantioenriched α-fluoromethylated amines is far from straightforward and well-developed, and a robust platform for the diversity-oriented synthesis (DOS) of the enantioenriched α-fluoromethylated amines needs more intensive investigation.

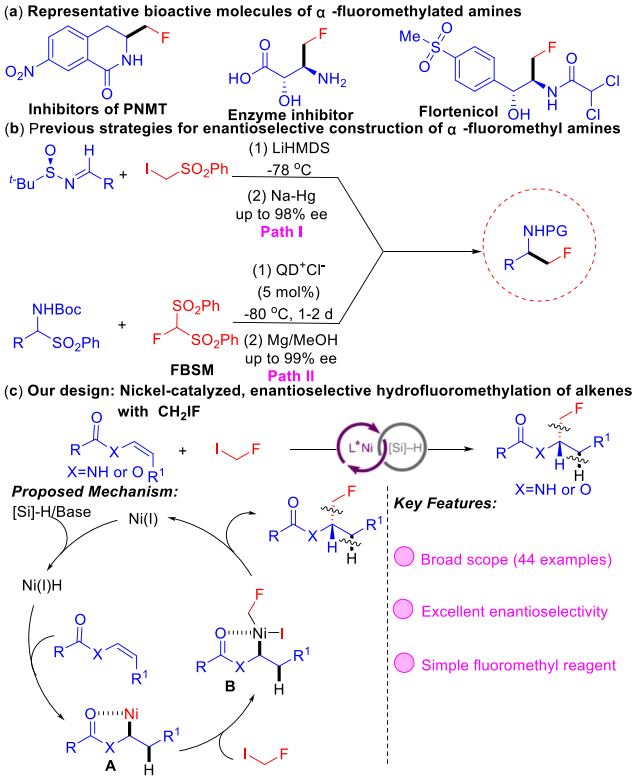
Our group[8] and others[9] have used ICH_2F in a variety of fluoromethylation reactions. With our continued interest in developing new fluoroalkylation methodologies,[10] we then further sought to employ the ICH_2F system in combination with a suitable chiral nucleophile species to realize the enantioselective fluoromethylation. Hydrofluoromethylation is an appealing strategy for the enantioselective introduction of a fluoromethyl group to an olefin. Although significant progress has been achieved on the enantioselective hydrofunctionalization of olefins, no report has ever been disclosed for the direct installation of the much smaller fluoromethyl group.[11,12] We thus further proposed that the reaction of ligated Ni(I) precursor with a silane and a base affords the chiral NiH species, which could undergo regio- and enantioselective hydrometalation to generate stabilized alkyl nickel intermediate **A** with the more favorable 5-membered ring. Then **A** could react with ICH_2F to form Ni(III) intermediate **B**. Final reductive elimination of **B** would deliver the desired product and regenerate Ni(I) catalyst. Herein, we disclose the nickel-catalyzed, enantioselective hydrofluoromethylation of enamides and enol esters with the simple CH_2IF as a fluoromethylation reagent (**1c**, Scheme 1), which enables the diversity-oriented synthesis (DOS) of enantioenriched α-fluoromethylated amides as well as esters in a robust route.

Our initial research started from the investigation of terminal hydrofluoromethylation of alkenes, and results showed that the combination of NiI_2 and KF could afford the desired products in good yields.[13,14] Motivated by this result, we then moved further to explore the possibility of the enantioselective

Received: February 4, 2023
Published: March 24, 2023

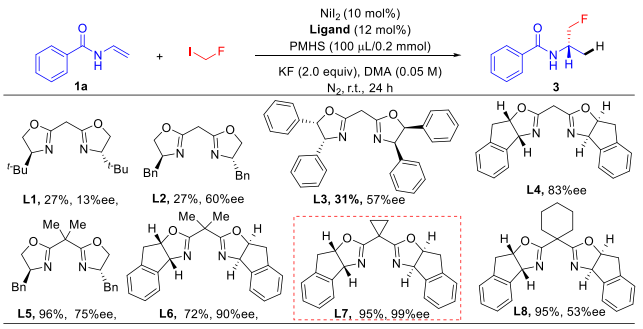
https://doi.org/10.1021/acs.orglett.3c00357
Org. Lett. 2023, 25, 2218–2222

Scheme 1. Design of the Diversity-Oriented Synthesis (DOS) of Enantioenriched α-Fluoromethylated Amides



hydrofluoromethylation of enamides, and the vinyl benzamide (**1a**) and CH_2FI were selected as model substrates in the presence of PMHS, KF, and NiI_2 to identify the chiral ligand (Scheme 2, and see SI for details). First, the Box ligand **L1**

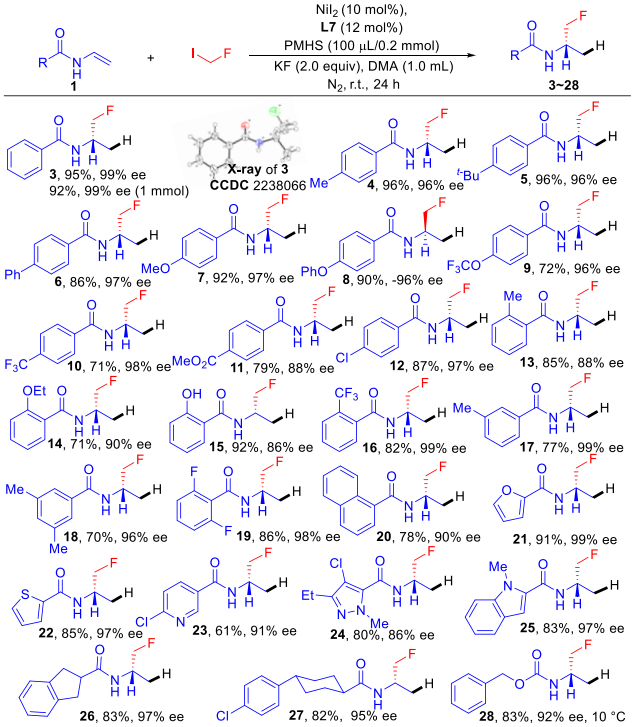
Scheme 2. Optimization of Chiral Ligands



with *tert*-butyl group on the oxazoline ring was evaluated, which exhibited low enantioselectivity but inspired us to test other substituted Box ligands **L2**–**L4**. Pleasingly, the indane moiety-substituted ligand **L4** could improve both the enantioselectivity and the yield efficiently, delivering more promising results than benzyl- and phenyl-substituted ligands **L2** and **L3**. We thus inferred that a bulky Box ligand might be beneficial for the final reductive elimination of Ni(III) species to form the targeted product. And indeed, increasing the steric hindrance of the linkage group through the use of dimethyl (**L5** and **L6**) or cyclopropanyl (**L7**) moieties could increase the enantioselectivity distinctly. However, cyclopropanyl-substutited Box ligand **L8** led to poor enantioselectivity, perhaps due to less steric hindrance. Thus, the desired chiral α-fluoromethylated amide **3** could be isolated with the best yield of 95% with 99% ee when performing the reaction of **1a** with CH_2FI in DMA (*c* 0.2 M) with NiI_2 (10 mol %) as the catalyst, **L7** (12 mol %) as the ligand, PMHS (100 uL/0.2 mmol) as the hydrogen source, and KF (2.0 equiv) as the base at room temperature for 24 h.

After establishing viable conditions, we set out to examine the scope of terminal vinyl amides (Scheme 3). Gratifyingly,

Scheme 3. Scope of Terminal Enamides Structures



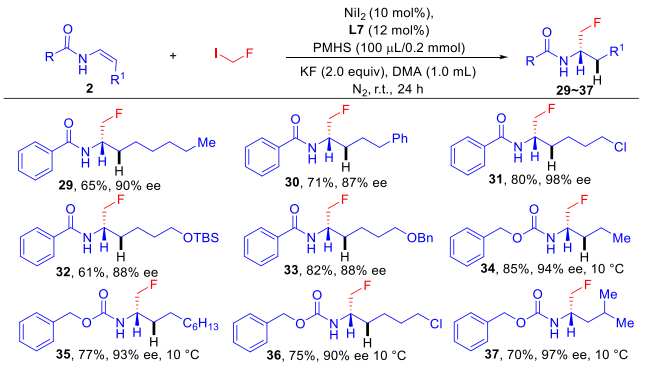
vinyl benzamides with both electron-donating and electron-withdrawing substituents at the *para* position could be transformed to the desired α-fluoromethylated amides (**3**–**12**) in 71–96% yields with 88–99% ee. Specifically, when the enantiomer of **L7** was used as ligand, **8** could be afforded in 90% yield and −96% ee. To our delight, the reaction also proceeded smoothly with *ortho*-substituted vinyl benzamides, delivering **13**–**16** with good efficiency and excellent enantioselectivity. Particularly noteworthy is the product **15** in which the reactive OH group could be kept intact, although it could react with ICH_2F under basic conditions. In addition, the methodology is also amenable to both *meta*- and polysubstituted vinyl benzamides with an electron-donating (Me) or electron-withdrawing group (F), furnishing the α-fluoromethylated amides **17**–**19** with similar efficiency in terms of both yield and absolute stereocontrol. Moreover, fused aromatics and heteroaromatics including naphthalene, furan, thiophene, pyridine, and indole could all engage in this transformation nicely to afford chiral α-fluoromethylated amides **20**–**25** in 61–91% yields with 86–99% ee. The reaction of alkyl vinyl amides was also competent, producing amides **26** and **27** in 83% and 82% yield and 97% and 95% ee, respectively. Interestingly, enecarbamate could also be efficiently functionalized by this protocol to produce **28** in 83% yield and 92% ee at 10 °C. High chemoselectivity could be observed in this protocol, and various functional groups,

https://doi.org/10.1021/acs.orglett.3c00357
Org. Lett. 2023, 25, 2218−2222

such as the ether (**7**, **8**, **9**), trifluoromethyl (**10**), ester (**11**), and halides (**12**, **19**, **23**, **24**, **27**), were all well tolerated. Finally, **3** was isolated in 92% yield and 99% ee at 1.0 mmol scale. The absolute configuration of **3** was confirmed as *S* by the X-ray diffraction analysis, and all analogous products except **8** were assigned the same absolute configuration.

We then extended this catalytic platform to internal enamides for the construction of more complexed α-fluoromethylated amides (Scheme 4). However, compared

Scheme 4. Scope of Internal Enamides Structures

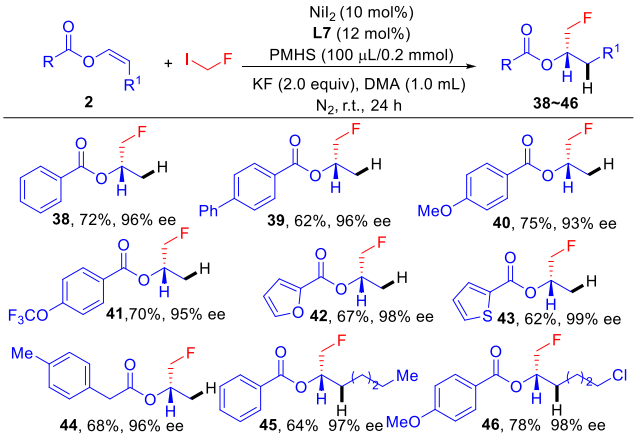


with terminal counterparts, reaction of internal enamides would be problematic due to the fact that metal-mediated insertions to olefins are normally sensitive to steric hindrance. Indeed, when (*E*)-enamides were evaluated, only reduction products were produced. Thus, a wide range of alkyl substituted (*Z*)-enamides were evaluated, which could be well accommodated by this protocol to yield the α-fluoromethylated amides **29**−**33** in 61−82% yields with 87−98% ee. Moreover, this protocol could also be competently applied to (*Z*)-enecarbamates, and the desired products **34**−**36** were afforded in 70−85% yields with 90−94% ee. Functional groups including the terminal phenyl group (**30**), alkyl halide (**31**, **36**), silyl ether (**32**), and ether (**33**) were all well compatible with the reaction conditions. Specifically, the reaction conditions were amenable to the fluoromethylation of (*Z*)- enecarbamate with a steric isopropyl group, producing **37** in 70% yield and 97% ee at 10 °C.

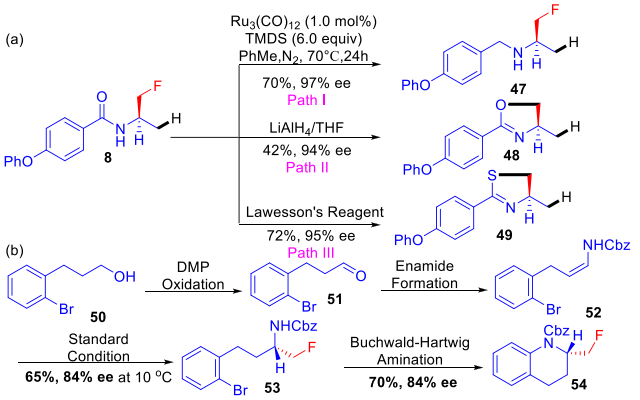
Encouraged by the success of constructing enantioenriched α-fluoromethylated amides, we questioned the possibility of the hydrofluoromethylation of enol esters, which would facilitate the direct synthesis of α-fluoromethylated esters (Scheme 5).[15] Fortunately, this catalytic platform could be efficiently extended to both aromatic or aliphatic acid derived enol esters, and the enantioenriched α-fluoromethylated esters (**38**−**46**) which are difficult to access otherwise, could be delivered with an excellent level of enantiocontrol (62−78% yields with 93−99% ee). The success of hydrofluoromethylation of enol esters might contribute to the design and discovery of new fluorinated lead pharmaceuticals.[16]

Final manipulation was performed to elaborate the synthetic applicability of this protocol. While hydrolysis of the resulted α-fluoromethylated amides and esters failed (see SI for details), we finally found that reduction of **8** with TMDS using $Ru_3(CO)_{12}$ as catalyst could afford the α-fluoromethylated amine **47** in 70% yield and 97% ee (Path I, Scheme 6a). Treatment of **8** with $LiAlH_4$ in THF furnished oxazoline **48** in 42% yield with 94% ee (Path II, Scheme 6a). And in the presence of Lawesson's reagent, thiazoline **49** was produced in

Scheme 5. Scope of Enol Esters Structures



Scheme 6. Synthetic Applicability



72% yield with 95% ee (Path III, Scheme 6a). In particular, the α-fluoromethylated tetrahydroquinoline **54** was efficiently constructed via the consecutive alcohol oxidation, enamide formation, enantioselective hydrofluoromethylation, and Buchwald−Hartwig amination in 70% yield and 84% ee (Scheme 6b).

In conclusion, we have disclosed the nickel-catalyzed enantioselective hydrofluoromethylation of enamides and enol esters with CH_2FI as the fluoromethyl reagents. This operationally convenient platform streamlines the diversity-oriented synthesis (DOS) of the enantioenriched α-fluoromethylated amides as well as esters, giving more than 40 examples in mild conditions with features of wide functional group compatibility as well as excellent enantioselectivity. The synthetic value of this protocol was demonstrated by the diverse transformations of the resulted α-fluoromethylated amides to different scaffolds, including enantioenriched amine, oxazoline, thiazoline, and the α-fluoromethylated tetrahydroquinoline.

■ ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00357.

https://doi.org/10.1021/acs.orglett.3c00357
Org. Lett. 2023, 25, 2218−2222

Screening data, experimental details, NMR spectra of new compounds and X-ray crystallographic data of **3**. (PDF)

Accession Codes

CCDC 2238066 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (22001080), Guangdong Basic and Applied Basic Research Foundation 2021 (A1515012433), Science and Technology Program of Guangzhou (202102020321), and the National Key Research and Development Program of China (No. 2021YFD1800600). We acknowledge our sincere thanks for Prof. Bi-Jie Li from Tsinghua University and Prof. Shou-Guo Wang from Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences for their generous support. We also thank editors and reviewers for their valuable suggestions for the publication of this work.

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https://doi.org/10.1021/acs.orglett.3c00357
Org. Lett. 2023, 25, 2218−2222