

# Accessing (Multi)Fluorinated Piperidines Using Heterogeneous Hydrogenation

Tobias Wagener, Arne Heusler, Zackaria Nairoukh, Klaus Bergander, Constantin G. Daniliuc, and Frank Glorius\*

Cite This: *ACS Catal.* 2020, 10, 12052–12057

Read Online

ACCESS |

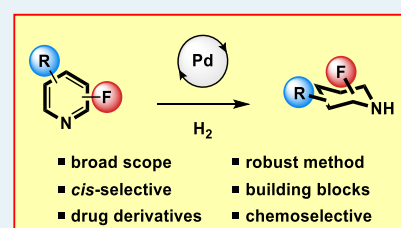
Metrics & More

Article Recommendations

Supporting Information

**ABSTRACT:** Fluorinated piperidines are desirable motifs for pharmaceutical and agrochemical research. Nevertheless, general synthetic access remains out of reach. Herein, we describe a simple and robust *cis*-selective hydrogenation of abundant and cheap fluoropyridines to yield a broad scope of (multi)fluorinated piperidines. This protocol enables the chemoselective reduction of fluoropyridines while tolerating other (hetero)-aromatic systems using a commercially available heterogeneous catalyst. Fluorinated derivatives of important drug compounds are prepared, and a straightforward strategy for the synthesis of enantioenriched fluorinated piperidines is disclosed.

**KEYWORDS:** hydrogenation, nitrogen heterocycles, fluorine, heterogeneous catalysis, palladium



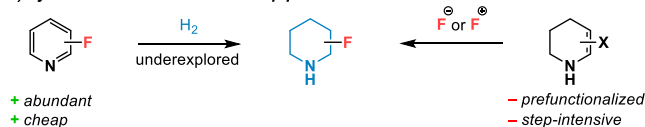
Fluorine has become recognized as a potent substituent in medicinal, agricultural, and material science over the last decades.<sup>1</sup> Owing to their high polarity, carbon–fluorine bonds are deliberately installed in drug candidates to optimize their physicochemical properties.<sup>2</sup> Although fluorine is barely found in natural products, almost one-quarter of all small-molecule drugs in the market contain at least one fluorine atom.<sup>3</sup> For instance, fluorine's strong preference for *gauche* orientation is widely utilized to establish conformationally defined building blocks.<sup>4</sup> Besides fluorine, nitrogen-containing heterocycles are an outstandingly important moiety commonly found in natural products and pharmaceuticals.<sup>5</sup>

A recent investigation revealed that 59% of all small-molecule drugs approved by the FDA contain at least one N-heterocycle.<sup>6</sup> Undoubtedly, the combination of both fluorine substituents and N-heterocycles is of great interest to pharmaceutical and agricultural researchers.<sup>7</sup> Although piperidine is the most abundant heterocycle in pharmaceuticals, straightforward and general synthesis of fluorinated piperidines remains challenging.<sup>8</sup> Common synthetic fluorination pathways such as electrophilic and nucleophilic substitution offer only limited access to fluorinated piperidines.<sup>9</sup>

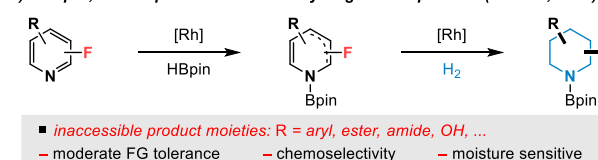
An alternative retrosynthetic strategy is the formation of piperidines from fluorinated precursors.<sup>10</sup> Given the broad availability of fluorinated pyridines, metal-catalyzed hydrogenation is recognizable as a powerful tool to transform these to the desired saturated building blocks (Figure 1a).<sup>11</sup> This synthetic approach, however, is hampered by the competing hydrodefluorination pathway, leading to undesired nonfluorinated piperidines.<sup>12</sup>

To address this problem, our group recently reported the development of a dearomatization–hydrogenation (DAH) process (Figure 1b).<sup>13</sup> Although this process allowed access to

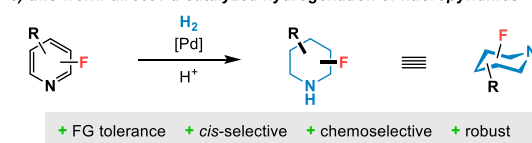
## a) synthetic access to fluorinated piperidines



## b) one-pot, two-step dearomatization-hydrogenation process (Glorius, 2019)



## c) this work: direct Pd-catalyzed hydrogenation of fluoropyridines



**Figure 1.** Synthetic strategies to access fluorinated piperidines.

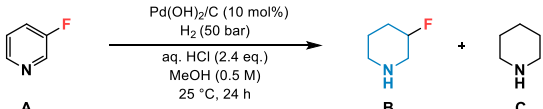
a series of fluorinated piperidines for the first time, the synthetic utility is limited. First, owing to the use of hydridic HBpin, polar and/or protic functional groups such as esters, amides, alcohols, and free amines are not tolerated under the reaction conditions.

Received: July 27, 2020

Revised: September 10, 2020

Published: September 18, 2020



**Table 1. Standard Reaction Conditions and Selected Deviations**


entry	deviation	yield B	conv. A (%)
1	none	88%	>99
2	Rh/C (5 wt %)	53%	>99
3	Rh/Al <sub>2</sub> O <sub>3</sub> (5 wt %)	traces	<5
4	Pt/C (5 wt %)	6%	>99
5	Ru/Al <sub>2</sub> O <sub>3</sub> (5 wt %)	traces	<5
6	Pd/C (10 wt %)	83%	>99
7	no acid	17%	78

Moreover, since rhodium is one of the most active transition metals for arene reduction, a general chemoselective hydrogenation of pyridines over other (hetero)arenes such as benzene or imidazole was not possible.<sup>14</sup> Additionally, the

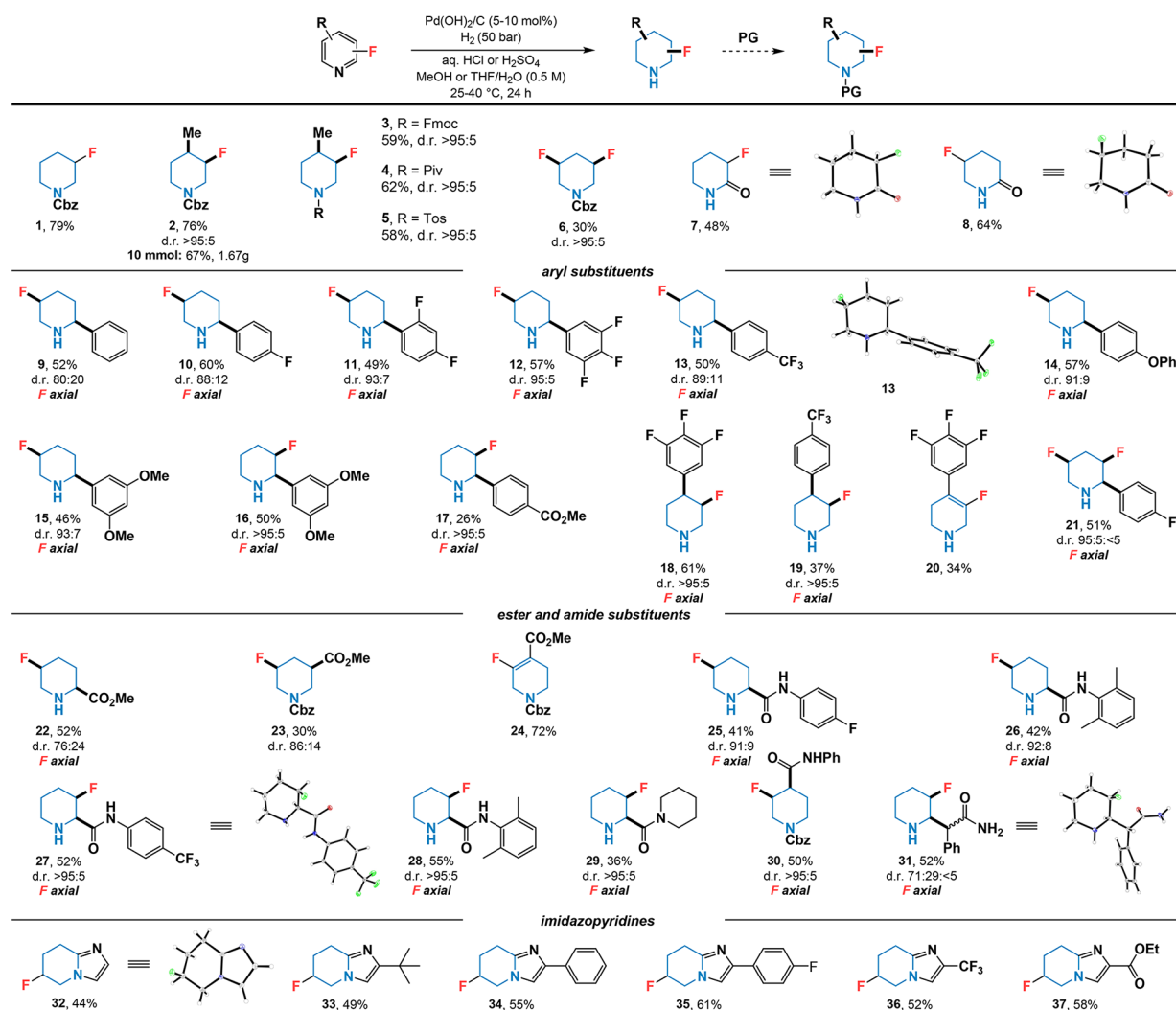
reactivity of the DAH process is highly dependent on the purity of reagents and solvents applied.

With these drawbacks in mind, we were searching for direct hydrogenation without the need for a dearomatizing agent to circumvent the functional group incompatibility and sensitivity problems affiliated with the DAH process (Figure 1c).<sup>15</sup>

To start our investigations, we studied the reduction of 3-fluoropyridine in organic solvents using various heterogeneous catalysts. Early experiments indicated that many catalysts are not sufficiently active under these conditions. Thus, we tried to solve both issues through protonation of both the substrate and product with Brønsted acid.<sup>16</sup> To our delight, we found that the combination of Pd(OH)<sub>2</sub> on carbon (20 wt %) with aqueous HCl in MeOH is a suitable and simple system for the hydrogenation of fluorinated pyridines (Table 1, entry 1). In contrast, several common heterogeneous catalysts gave less or only traces of the desired fluorinated product B (entries 2–6). Omitting the strong Brønsted acid results in diminished conversion and formation of the defluorinated side product C dominates (entry 7). Notably, no special care was taken to

**Chart 1. Substrate Scope for the Palladium-Catalyzed Hydrogenation of Fluoropyridines<sup>a</sup>**

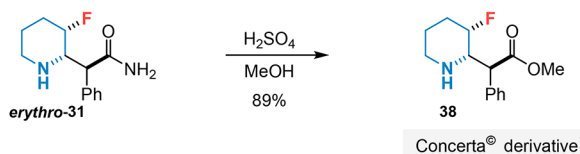
experimental details.



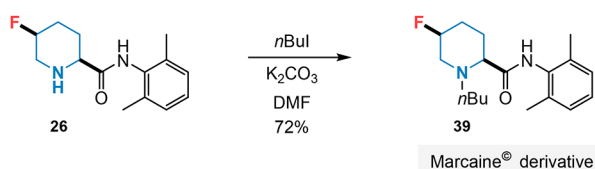
<sup>a</sup>See the Supporting Information for full experimental details.

**Scheme 1. Synthesis of Fluorinated Methylphenidate (a), Bupivacaine (b), Ropivacaine (c), and Enantioenriched 3-Fluoropiperidine (d)**

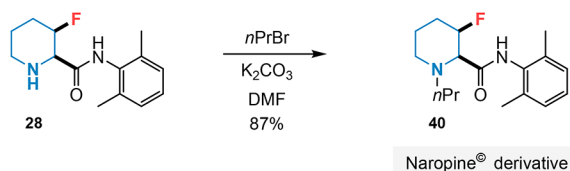
**a) fluoromethylphenidate**



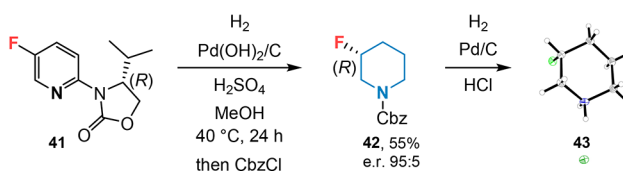
**b) fluorobupivacaine**



**c) fluororopivacaine**



**d) enantioenriched fluoropiperidine**



exclude air and moisture during reaction setup within this study—an attractive feature.

A recently described reaction-condition-based sensitivity screen revealed that our procedure is insensitive toward small deviations of concentration, pressure, temperature, and the presence of oxygen or moisture (see the [Supporting Information](#) for further details).<sup>17</sup>

Having optimized reaction conditions in hand, we then investigated the substrate scope of the protocol ([Chart 1](#)). Since purification of volatile, unprotected fluorinated piperidines is challenging, we investigated the trapping with different protecting groups. Fluorinated piperidines **1** and **2** were isolated in high yields after in situ benzyloxycarbonyl (Cbz) protection. Performing the synthesis of piperidine **2** in a gram-scale reaction afforded the desired product in 67% yield. Likewise, Fmoc-protected fluorinated piperidine **3** was obtained in good yield and excellent diastereoselectivity after in situ trapping.

Furthermore, amide- (**4**) and sulfonamide-protecting groups (**5**) could also be employed and in both cases the products were isolated in good yield and excellent diastereoselectivity. Difluorinated piperidine **6** was isolated in 30% yield after Cbz protection, owing to significant formation of single- and double-defluorinated side products.

In contrast to our previous study,<sup>13</sup> free hydroxy groups were tolerated under the reaction conditions and led to the isolation of valuable  $\delta$ -lactam products **7** and **8** in good yields. Our catalytic system facilitated the *cis*-selective reduction of fluoropyridines over benzene rings and enabled the synthesis of 5-fluoro-2-phenylpiperidine (**9**) in good diastereoselectivity.<sup>18</sup> A series of multifluorinated 2-aryl-5-fluoropiperidines

**10–13** was synthesized in good to moderate yields and high diastereoselectivities.

Moreover, aryl- and alkyl- ether-substituted aryl-fluoropiperidines **14–16** and ester-substituted piperidine **17** were synthesized in good yield and excellent diastereoselectivity. Furthermore, multifluorinated 4-aryl-3-fluoropiperidines **18** and **19** were synthesized in tetrahydrofuran/H<sub>2</sub>O while not fully reduced fluorinated tetrahydropyridine **20** was obtained in moderate yield when changing the solvent to MeOH. To our delight, 2-aryl-3,5-difluoropiperidine **21** was synthesized after elongated reaction time in good yield and diastereoselectivity.

Fluorinated, unnatural amino acids are of high interest, but synthetic access remains difficult.<sup>19</sup> Our protocol allows the isolation of **22** after a single reaction step from a commercially available starting material in 62% yield. Moreover, this method reveals access to  $\beta$ -amino acid **23** and tetrahydropyridine  $\gamma$ -amino acid **24**. Besides esters, a series of amide-substituted fluorinated piperidines **25–30** was synthesized. 2-Phenylacetamide-substituted piperidine **31** was isolated in 52% yield and only two diastereomers in a 71:29 ratio were observed. Nuclear magnetic resonance (NMR) and X-ray analyses revealed *cis*-configuration for both isolated isomers with the erythro isomer as the main component.

To further investigate the selective reduction of fluorinated pyridines over other (hetero)arenes, we tested the hydrogenation of various imidazo[1,2-*a*]pyridines. To our delight, 6-fluoro-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (**32**) was isolated without reduction of the imidazole ring being observed. A series of 2-substituted (multi)fluorinated tetrahydroimidazo[1,2-*a*]pyridines **33–37** were synthesized in good yields tolerating alkyl, aryl, trifluoromethyl, and ester substituents.

Many of the products listed in [Chart 1](#) were isolated in diminished yields and accompanied with nonfluorinated piperidines. This is due to remaining hydrodefluorination reactions, which are not completely suppressed by our new catalytic system. Preliminary mechanistic investigations indicate that hydrodefluorination occurs on dearomatized intermediates (see the [Supporting Information](#) for further details). The beneficial role of the Brønsted acid on reactivity toward hydrogenation has been investigated in the literature,<sup>20</sup> yet the influence on hydrodefluorination remains unclear. Further mechanistic investigations are ongoing but beyond the scope of this study.

The conformational behavior of fluorinated piperidines aroused the interest of physical-organic chemists.<sup>21</sup> A recent, detailed study investigated the fundamental interactions of fluorinated piperidines.<sup>22</sup> NMR analysis of the free NH piperidines synthesized in this study proved the *gauche* conformation of the products in CDCl<sub>3</sub>.

To further show the utility of our developed method, several fluorinated drug derivatives have been prepared ([Scheme 1](#)). Fluorinated methylphenidate (Ritalin, Concerta) **38** was obtained in 89% yield from **31** after stirring in MeOH in the presence of H<sub>2</sub>SO<sub>4</sub>. Free NH piperidines **26** and **28** were prepared applying our new protocol and were transformed into fluorinated derivatives of bupivacaine **39** and ropivacaine **40**, respectively.

Our method can be further expanded to the synthesis of enantioenriched fluorinated piperidines. Adopting a strategy which was previously established in our lab,<sup>23</sup> oxazolidinone-substituted pyridine **41** was prepared. Under acidic conditions, pyridine **41** was hydrogenated to the corresponding

oxazolidine-substituted piperidine in a diastereoselective fashion. In situ cleavage of the auxiliary followed by reduction of the imine intermediate gave the enantioenriched piperidine **42** in 55% yield and 95:5 e.r. after Cbz protection. After the protecting group was removed, the absolute configuration of 3-fluoropiperidine·HCl was determined using X-ray analysis.

In summary, we have developed a new method to access highly valuable fluorinated piperidines based on palladium-catalyzed hydrogenation. This protocol enables the transformation of cheap and abundant fluoropyridines to sought-after fluorinated piperidines in a robust and simple manner. Using a common heterogeneous palladium catalyst, a selective reduction of fluoropyridines over benzene and imidazole systems was established. The robustness of our method was demonstrated by applying a reaction-condition-based sensitivity assessment, revealing high tolerance for the presence of air and moisture. The products are obtained in good yields and high diastereoselectivities, and the synthetic utility was highlighted by the synthesis of fluorinated drug derivatives. Furthermore, this method was expanded to the synthesis of highly enantioenriched fluorinated piperidines in a straightforward fashion.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.0c03278>.

Experimental procedures and characterization data; mechanistic experiments; sensitivity screen (PDF)

X-ray crystallographic data (CIF) for compounds **7** (CCDC Nr.: 1999050), **8** (CCDC Nr.: 1999051), **13** (CCDC Nr.: 1999052), **27** (CCDC Nr.: 1999053), **31** (CCDC Nr.: 1999054), **32** (CCDC Nr.: 1999055), and **43** (CCDC Nr.: 2026631) can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)

## ■ AUTHOR INFORMATION

### Corresponding Author

**Frank Glorius** – Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany; [orcid.org/0000-0002-0648-956X](https://orcid.org/0000-0002-0648-956X); Email: [glorius@uni-muenster.de](mailto:glorius@uni-muenster.de)

### Authors

**Tobias Wagener** – Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany

**Arne Heusler** – Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany

**Zackaria Nairoukh** – Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany

**Klaus Bergander** – Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany

**Constantin G. Daniliuc** – Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany; [orcid.org/0000-0002-6709-3673](https://orcid.org/0000-0002-6709-3673)

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acscatal.0c03278>

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors acknowledge financial support from the European Research Council (ERC Advanced Grant Agreement no. 788558), the Deutsche Forschungsgemeinschaft (Leibniz Award), and the Alfred Krupp von Bohlen und Halbach Foundation. The authors also thank Toryn Dalton, Daniel Moock, J. Luca Schwarz, and Marco Wollenburg for many helpful discussions.

## ■ REFERENCES

- (1) (a) Jeschke, P. The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection. *ChemBioChem* **2004**, *5*, 570–589. (b) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881–1886. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330.
- (2) (a) Smart, B. E. Fluorine substituent effects (on bioactivity). *J. Fluorine Chem.* **2001**, *109*, 3–11. (b) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (c) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506.
- (3) (a) O'Hagan, D. Fluorine in health care: Organofluorine containing blockbuster drugs. *J. Fluorine Chem.* **2010**, *131*, 1071–1081. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals to Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* **2014**, *57*, 2832–2842. (c) Walker, M. C.; Chang, M. C. Y. Natural and engineered biosynthesis of fluorinated natural products. *Chem. Soc. Rev.* **2014**, *43*, 6527–6536.
- (4) For selected reviews and examples, see: (a) Gooseman, N. E. J.; O'Hagan, D.; Peach, M. J. G.; Slawin, A. M. Z.; Tozer, D. J.; Young, R. J. An Electrostatic *Gauche* Effect in  $\beta$ -Fluoro- and  $\beta$ -Hydroxy-*N*-ethylpyridinium Cations. *Angew. Chem., Int. Ed.* **2007**, *46*, 5904–5908. (b) Silla, J. M.; Silva, W. G. D. P.; Cormanich, R. A.; Rittner, R.; Tormena, C. F.; Freitas, M. P. *Gauche* Preference of  $\beta$ -Fluoroalkyl Ammonium Salts. *J. Phys. Chem. A* **2014**, *118*, 503–507. (c) Rey, Y. P.; Zimmer, L. E.; Sparr, C.; Tanzer, E.-M.; Schweizer, W. B.; Senn, H. M.; Lakhdar, S.; Gilmour, R. Molecular Design Exploiting a Fluorine *gauche* Effect as a Stereoelectronic Trigger. *Eur. J. Org. Chem.* **2014**, *2014*, 1202–1211. (d) Thiehoff, C.; Rey, Y. P.; Gilmour, R. The Fluorine *Gauche* Effect: A Brief History. *Isr. J. Chem.* **2017**, *57*, 92–100. (e) Aufiero, M.; Gilmour, R. Informing Molecular Design by Stereoelectronic Theory: The Fluorine *Gauche* Effect in Catalysis. *Acc. Chem. Res.* **2018**, *51*, 1701–1710.
- (5) For selected reviews, see: (a) O'Hagan, D. Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Nat. Prod. Rep.* **2000**, *17*, 435–446. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845–5859.
- (6) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.
- (7) For a hydrogenation of trifluoromethylated pyridines, see: (a) Zhang, X.; Ling, L.; Luo, M.; Zeng, X. Accessing Difluoromethylated and Trifluoromethylated *cis*-Cycloalkanes and Saturated Heterocycles: Preferential Hydrogen Addition to the Substitution Sites for Dearomatization. *Angew. Chem., Int. Ed.* **2019**, *58*, 16785–16789. For a hydrogenation of fluorinated isoquinolines, see: (b) Guo, R.-N.; Cai, X.-F.; Shi, L.; Ye, Z.-S.; Chen, M.-W.; Zhou, Y.-G. An efficient route to chiral *N*-heterocycles bearing a C–F stereogenic center via asymmetric hydrogenation of fluorinated isoquinolines. *Chem. Commun.* **2013**, *49*, 8537–8539. (c) Chen, M.-W.; Ji, Y.; Wang, J.; Chen, Q.-A.; Shi, L.; Zhou, Y.-G. Asymmetric Hydrogenation of Isoquinolines and Pyridines Using Hydrogen Halide Generated in Situ as Activator. *Org. Lett.* **2017**, *19*, 4988–4991.

(8) For selected examples, see ref 13 and: (a) Kajimoto, T.; Liu, K. C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A., Jr.; Wong, C. H. Enzyme-Catalyzed Aldol Condensation for Asymmetric Synthesis of Azasugars: Synthesis, Evaluation, and Modeling of Glycosidase Inhibitors. *J. Am. Chem. Soc.* **1991**, *113*, 6187–6196. (b) Yang, Y.; Zheng, F.; Bols, M.; Marinescu, L. G.; Qing, F.-L. Synthesis of monofluorinated isofagomine analogues and evaluation as glycosidase inhibitors. *J. Fluorine Chem.* **2011**, *132*, 838–845. (c) Bhumra, N.; Burade, S. S.; Louat, T.; Herman, J.; Kawade, S.; Doshi, P. J.; Dhavale, D. D. Fluorinated piperidine iminosugars and their *N*-alkylated derivatives: Synthesis, conformational analysis, immunosuppressive and glycosidase inhibitory activity studies. *Tetrahedron* **2018**, *74*, 852–858. (d) Sarver, P. J.; Bacauanu, V.; Schultz, D. M.; DiRocco, D. A.; Lam, Y.-h.; Sherer, E. C.; MacMillan, D. W. C. The merger of decarboxylation and copper catalysis to enable aliphatic C(sp<sup>3</sup>)–H trifluoromethylation. *Nat. Chem.* **2020**, *12*, 459–467.

(9) For selected reviews, see: (a) Katcher, M. H.; Doyle, A. G. Palladium-Catalyzed Asymmetric Synthesis of Allylic Fluorides. *J. Am. Chem. Soc.* **2010**, *132*, 17402–17404. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **2011**, *473*, 470–477. (c) Campbell, M. G.; Ritter, T. Modern Carbon–Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis. *Chem. Rev.* **2015**, *115*, 612–633. (d) Szpera, R.; Moseley, D. F. J.; Smith, L. B.; Sterling, A. J.; Gouverneur, V. The Fluorination of C–H Bonds: Developments and Perspectives. *Angew. Chem., Int. Ed.* **2019**, *58*, 14824–14848.

(10) (a) Wu, T.; Yin, G.; Liu, G. Palladium-Catalyzed Intramolecular Aminofluorination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2009**, *131*, 16354–16355. (b) Wang, Q.; Zhong, W.; Wei, X.; Ning, M.; Meng, X.; Li, Z. Metal-free intramolecular amino-fluorination of alkenes mediated by PhI(OPiv)<sub>2</sub>/hydrogen fluoride–pyridine system. *Org. Biomol. Chem.* **2012**, *10*, 8566–8569.

(11) For selected reviews, see: (a) De Vries, J. G.; Elsevier, C. J. *The Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, 2006; pp 455–485. (b) Gual, A.; Godard, C.; Castillón, S.; Claver, C. Soluble transition-metal nanoparticles-catalysed hydrogenation of arenes. *Dalton Trans.* **2010**, *39*, 11499–11512. (c) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. Asymmetric Hydrogenation of Heteroarenes and Arenes. *Chem. Rev.* **2012**, *112*, 2557–2590. (d) Qi, S.-C.; Wei, X.-Y.; Zong, Z.-M.; Wang, Y.-K. Application of supported metallic catalysts in catalytic hydrogenation of arenes. *RSC Adv.* **2013**, *3*, 14219–14232. (e) Giustra, Z. X.; Ishibashi, J. S. A.; Liu, S.-Y. Homogeneous metal catalysis for conversion between aromatic and saturated compounds. *Coord. Chem. Rev.* **2016**, *314*, 134–181. (f) Gualandi, A.; Savoia, D. Substrate induced diastereoselective hydrogenation/reduction of arenes and heteroarenes. *RSC Adv.* **2016**, *6*, 18419–18451. (g) Zhao, D.; Candish, L.; Paul, D.; Glorius, F. *N*-Heterocyclic Carbenes in Asymmetric Hydrogenation. *ACS Catal.* **2016**, *6*, 5978–5988. (h) Wiesenfeldt, M. P.; Nairoukh, Z.; Dalton, T.; Glorius, F. Selective Arene Hydrogenation for Direct Access to Saturated Carbo- and Heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 10460–10476.

(12) For selected reviews, see: (a) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. Activation of Carbon–Fluorine Bonds by Metal Complexes. *Chem. Rev.* **1994**, *94*, 373–431. (b) Kuehnel, M. F.; Lentz, D.; Braun, T. Synthesis of Fluorinated Building Blocks by Transition-Metal-Mediated Hydrodefluorination Reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 3328–3348. (c) Whittlesey, M. K.; Peris, E. Catalytic Hydrodefluorination with Late Transition Metal Complexes. *ACS Catal.* **2014**, *4*, 3152–3159.

(13) Nairoukh, Z.; Wollenburg, M.; Schleppehorst, C.; Bergander, K.; Glorius, F. The formation of all-*cis*-(multi)fluorinated piperidines by a dearomatization-hydrogenation process. *Nat. Chem.* **2019**, *11*, 264–270.

(14) (a) Wei, Y.; Rao, B.; Cong, X.; Zeng, X. Highly Selective Hydrogenation of Aromatic Ketones and Phenols Enabled by Cyclic (Amino)(alkyl)carbene Rhodium Complexes. *J. Am. Chem. Soc.* **2015**, *137*, 9250–9253. (b) Wiesenfeldt, M. P.; Nairoukh, Z.; Li, W.;

Glorius, F. Hydrogenation of fluoroarenes: Direct access to all-*cis*-(multi)fluorinated cycloalkanes. *Science* **2017**, *357*, 908–912. (c) Wiesenfeldt, M. P.; Knecht, T.; Schleppehorst, C.; Glorius, F. Silylarene Hydrogenation: A Strategic Approach that Enables Direct Access to Versatile Silylated Saturated Carbo- and Heterocycles. *Angew. Chem., Int. Ed.* **2018**, *57*, 8297–8300. (d) Tran, B. L.; Fulton, J. L.; Linehan, J. C.; Lercher, J. A.; Bullock, R. M. Rh(CAAC)-Catalyzed Arene Hydrogenation: Evidence for Nanocatalysis and Sterically Controlled Site-Selective Hydrogenation. *ACS Catal.* **2018**, *8*, 8441–8449. (e) Wollenburg, M.; Mook, D.; Glorius, F. Hydrogenation of Borylated Arenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 6549–6553. (f) Ling, L.; He, Y.; Zhang, X.; Luo, M.; Zeng, X. Hydrogenation of (Hetero)aryl Boronate Esters with a Cyclic (Alkyl)(amino)carbene-Rhodium Complex: Direct Access to *cis*-Substituted Borylated Cycloalkanes and Saturated Heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 6554–6558.

(15) The direct hydrogenation of 2-propyl-5-fluoropyridine was reported in the patent literature: WO: 2007/071358. However, only a mixture of fluorinated and defluorinated product was obtained, which was neither purified nor completely characterized. Thus, the obtained yield of the desired fluorinated piperidine is unclear. When we employed the reported conditions to the hydrogenation of 3-fluoropyridine, a mixture of fluorinated and non-fluorinated piperidine resulted, leading to 36% yield of the desired 3-fluoropyridine.

(16) Yu, Z.; Jin, W.; Jiang, Q. Bronsted Acid Activation Strategy in Transition-Metal Catalyzed Asymmetric Hydrogenation of *N*-Unprotected Imines, Enamines, and *N*-Heteroaromatic Compounds. *Angew. Chem., Int. Ed.* **2012**, *51*, 6060–6072.

(17) (a) Pitzer, L.; Schäfers, F.; Glorius, F. Rapid Assessment of the Reaction-Condition-Based Sensitivity of Chemical Transformations. *Angew. Chem., Int. Ed.* **2019**, *58*, 8572–8576. See also: (b) Gensch, T.; Glorius, F. The straight dope on the scope of chemical reactions. *Science* **2016**, *352*, 294–295.

(18) Kuduk, S. D.; Chang, R. K.; Ng, C.; Murphy, K. L.; Ransom, R. W.; Tang, C.; Prueksaranont, T.; Freidinger, R. M.; Pettibone, D. J.; Bock, M. G. Bradykinon B<sub>1</sub> antagonists: SAR studies in the 2,3-diaminopyridine series. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3925–3929.

(19) (a) Tarui, A.; Sato, K.; Omote, M.; Kumdaki, I.; Ando, A. Stereoselective Synthesis of  $\alpha$ -fluorinated Amino Acid Derivatives. *Adv. Synth. Catal.* **2010**, *352*, 2733–2744. (b) Qiu, X.-L.; Qing, F.-L. Recent Advances in the Synthesis of Fluorinated Amino Acids. *Eur. J. Org. Chem.* **2011**, *2011*, 3261–3278.

(20) (a) Geraty, S. M.; Harkin, P.; Vos, J. G. A kinetic investigation of the hydrogenation of acetone by [Ru(2,2'-bipyridyl)<sub>2</sub>(CO)H]PF<sub>6</sub>·0.5acetone. *Inorg. Chim. Acta* **1987**, *131*, 217–220. (b) Song, J.-S.; Szalda, D. J.; Bullock, R. M.; Lawrie, C. J. C.; Rodkin, M. A.; Norton, J. R. Hydride Transfer by Hydrido Transition-Metal Complexes. Ionic Hydrogenation of Aldehydes and Ketones, and Structural Characterization of an Alcohol Complex. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1233–1235. (c) Bullock, R. M.; Song, J.-S. Ionic Hydrogenations of Hindered Olefins at Low Temperature. Hydride Transfer Reactions of Transition Metal Hydrides. *J. Am. Chem. Soc.* **1994**, *116*, 8602–8612.

(21) (a) Lankin, D. C.; Chandrakumar, N. S.; Rao, S. N.; Spangler, D. P.; Snyder, J. P. Protonated 3-Fluoropiperidines: An Unusual Fluoro Directing Effect and a Test for Quantitative Theories of Solvation. *J. Am. Chem. Soc.* **1993**, *115*, 3356–3357. (b) Snyder, J. P.; Chandrakumar, N. S.; Sato, H.; Lankin, D. C. The Unexpected Diaxial Orientation of *cis*-3,5-Difluoropiperidine in Water: A Potent CF<sub>2</sub>-NH Charge-Dipole Effect. *J. Am. Chem. Soc.* **2000**, *122*, 544–545. (c) Sun, A.; Lankin, D. C.; Hardcastle, K.; Snyder, J. P. 3-Fluoropiperidines and *N*-Methyl-3-fluoropiperidinium Salts: The Persistence of Axial Fluorine. *Chem.—Eur. J.* **2005**, *11*, 1579–1591.

(22) Nairoukh, Z.; Strieth-Kalthoff, F.; Bergander, K.; Glorius, F. Understanding the Conformational Behavior of Fluorinated Piperidines: The Origin of the Axial-F Preference. *Chem.—Eur. J.* **2020**, *26*, 6141–6146.

(23) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. Efficient Asymmetric Hydrogenation of Pyridines. *Angew. Chem., Int. Ed.* **2004**, *43*, 2850–2852.