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The formation of all-*cis*-(multi)fluorinated piperidines by a dearomatization–hydrogenation process

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Piperidines and fluorine substituents are both independently indispensable components in pharmaceuticals, agrochemicals and materials. Logically, the incorporation of fluorine atoms into piperidine scaffolds is therefore an area of tremendous potential. However, synthetic approaches towards the formation of these architectures are often impractical. The diastereoselective synthesis of substituted monofluorinated piperidines often requires substrates with pre-defined stereochemistry. That of multifluorinated piperidines is even more challenging, and often needs to be carried out in multistep syntheses. In this report, we describe a straightforward process for the one-pot rhodium-catalysed dearomatization–hydrogenation of fluoropyridine precursors. This strategy enables the formation of a plethora of substituted all-*cis*-(multi)fluorinated piperidines in a highly diastereoselective fashion through pyridine dearomatization followed by complete saturation of the resulting intermediates by hydrogenation. Fluorinated piperidines with defined axial/equatorial orientation of fluorine substituents were successfully applied in the preparation of commercial drugs analogues. Additionally, fluorinated PipPhos as well as fluorinated ionic liquids were obtained by this dearomatization–hydrogenation process.

The predictable and modular assembly of complex molecular structures is one of the main challenges in synthetic organic chemistry, which therefore necessitates the development of new synthetic strategies with improved selectivity and efficiency[1–4]. Among the many elegant chemical transformations that have been developed to meet this end, the metal-catalysed hydrogenation of unsaturated compounds is arguably one of the most powerful methods. However, there remain many unsolved challenges related to reactivity and selectivity for the hydrogenation of simple planar aromatic ring systems[5–8].

Saturated nitrogen heterocycles are among the most significant structural components of pharmaceuticals and natural products[9]. To this end, a recent analysis of FDA-approved drugs revealed that 59% of small molecule drugs contain at least one N-heterocycle, of which saturated piperidine is the most prevalent (Fig. 1a)[10]. In a similar fashion to N-heterocycles, fluorine substituents are frequently found in drugs, agrochemicals and materials science (Fig. 1a). Furthermore, the incorporation of fluorine into lead drug candidates has been recognized as a powerful strategy to improve their pharmacokinetic and physicochemical properties and hence increase the likelihood of success in clinical trials[11–14]. Therefore, it is not surprising that around 20% of all marketed drugs and 40% of the current top ten best-selling drugs today contain at least one fluorine substituent[15,16]. With these considerations in mind, it seems only logical to assume that the incorporation of fluorine into aliphatic N-heterocycles is therefore of significant interest to the scientific community (Fig. 1a). For instance, it was recently shown that the pK_a of a kinesin spindle protein (KSP) inhibitor could be altered by the introduction of an axial or equatorial fluorine substituent into the piperidine core[16]. From these studies, the axial diastereomer (MK-0731) was selected for clinical trials over the equatorial homologue (Fig. 1a).

Current synthetic routes for the synthesis of relatively simple monofluorinated piperidine derivatives are usually based on electrophilic fluorination and thus require the careful preparation of pre-functionalized precursors. The diastereoselective synthesis of substituted monofluorinated piperidines can be achieved by nucleophilic substitution (Fig. 1b). However, the difficult pre-decoration of substrates with defined stereochemistry is required[17,18]. Other synthetic routes based on radical intermediates have been reported recently, with a minor focus on the generation of fluorinated piperidines[19,20]. Furthermore, the preparation of multifluorinated piperidines is rarely disclosed in the literature and often requires tedious multistep syntheses[21]. It should also be noted that, to the best of our knowledge, there are no known methods for the direct diastereoselective synthesis of multifluorinated piperidines (Fig. 1c). In light of the above, we considered that a more straightforward synthetic route to access these motifs via the hydrogenation of fluoropyridine precursors would represent a significant synthetic advancement. However, this strategy would require several challenges to be overcome, such as avoiding catalyst deactivation by the Lewis-basic heterocycles and the hydrodefluorination side reactions[7]. Strategies to circumvent catalyst poisoning by employing pyridinium salts instead of pyridines are known[22,23]. However, the extension of this method to fluorinated compounds has yet to be disclosed, presumably due to competing hydrodefluorination side reactions[24]. Thus, a direct synthetic protocol for the hydrogenation of fluorinated nitrogen-containing heteroarenes, in particular fluoropyridine derivatives, remains elusive.

Herein, we describe a protocol for the highly selective one-pot dearomatization–hydrogenation (DAH) of fluorinated pyridines, providing convenient and diastereoselective access to *cis*-fluorinated piperidine building blocks (Fig. 1d). Furthermore, this synthetic protocol was successfully extended to multifluorinated

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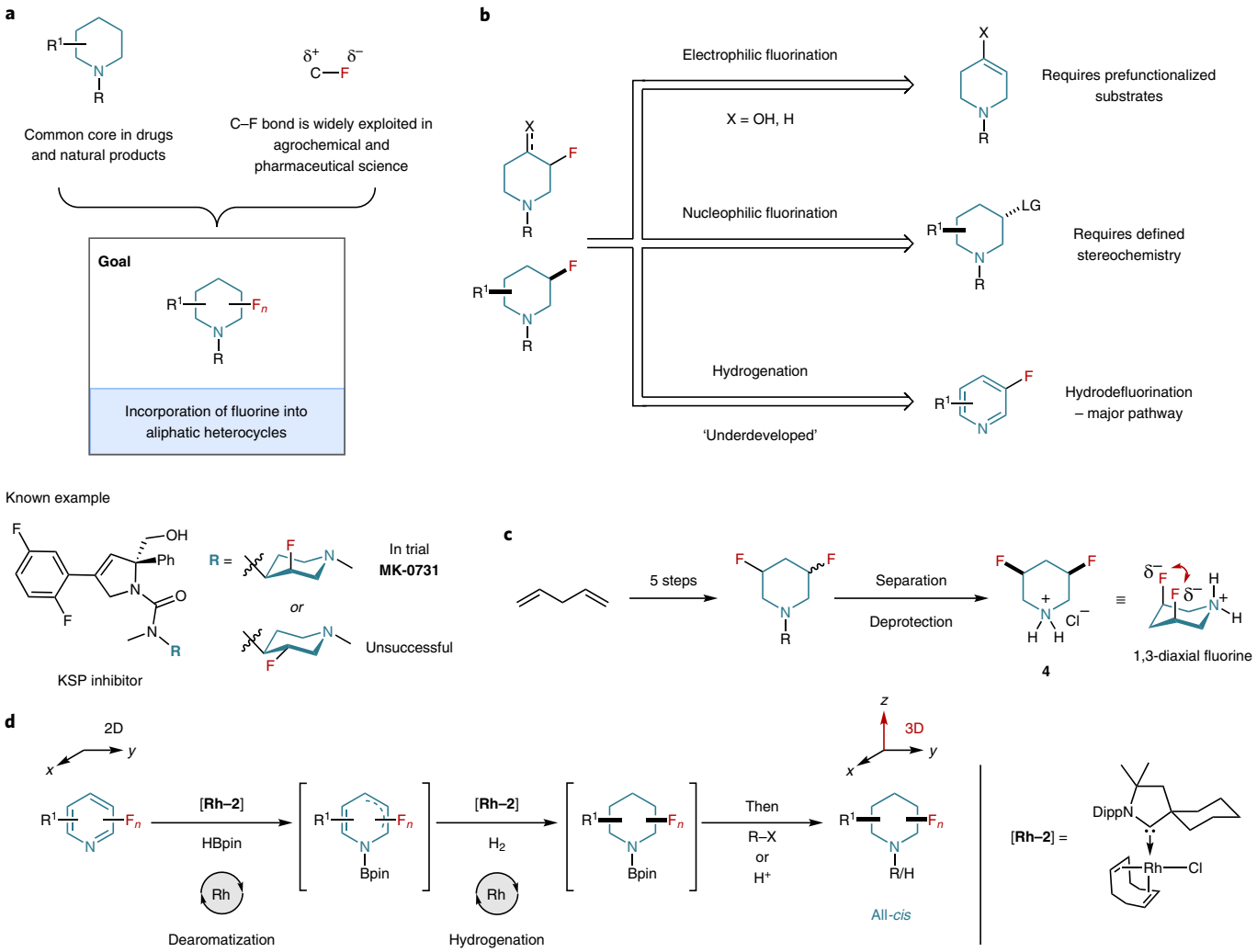


Fig. 1 | Preparation of all-*cis*-(multi)fluorinated piperidines by the dearomatization–hydrogenation process. a, Merging common elements of drugs. The goal is the incorporation of fluorine into piperidine derivatives. The basicity of the KSP inhibitor was affected by the orientation of the fluorine atom. The more basic axial isomer (MK-0731) was selected for clinical evaluation. **b**, Known retrosynthetic routes for the preparation of monofluorinated piperidines. LG, leaving group. **c**, The multistep synthesis of *cis*-3,5-difluoropiperidine hydrochloride. A 1,3-diaxial behaviour of the fluorine atoms was observed. **d**, Our proposed DAH process is a combined dearomatization and hydrogenation that gives access to all-*cis*-(multi)fluorinated piperidine building blocks.

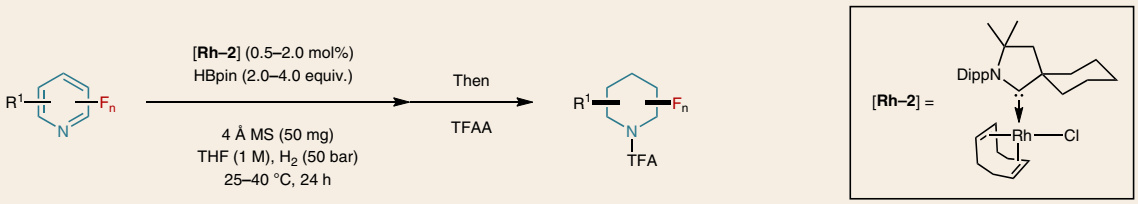
pyridines to access the all-*cis*-multifluorinated piperidines with excellent diastereoselectivity.

Results and discussion

Our studies regarding the hydrogenation of fluoropyridines began by testing a variety of catalysts known to be capable of arene hydrogenation for the reduction of 3-fluoro- and 3,5-difluoropyridine[6,7,25]. However, these initial attempts were unsuccessful due to either catalyst poisoning or uncontrolled hydrodefluorination side reactions (Supplementary Section 3). We therefore tried to develop an efficient process that could both prevent catalyst poisoning and enable fluoropyridine hydrogenation without the loss of the fluorine atoms. Considering this, we envisioned that a borane reagent could be used to first dearomatize the pyridine ring system by forming a mixture of dienes that could be more easily hydrogenated while also preventing catalyst poisoning by protecting the Lewis-basic nitrogen.

Initial studies towards our envisioned approach were conducted using 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin), a known additive in the rhodium-catalysed dearomatization of pyridine[26,27], and $[Rh(COD)Cl]_2$ [**Rh-1**] as catalyst for the hydrogenation of 3-fluoropyridine in THF at 25 °C. Indeed, the desired product was obtained in both good yield and chemoselectivity (Supplementary Table 2). Other rhodium complexes were then examined, from which the Rh–CAAC (ref. [6,28]) complex [**Rh-2**] was found to be optimal. The reaction conditions were further optimized utilizing complex [**Rh-2**] by screening different solvents and concentrations. The influence of different hydride sources as well as the reaction pressure to ensure high efficiency were also investigated (Supplementary Section 3). With the optimized conditions in hands, we began scoping studies for the hydrogenation of fluoropyridines (Table 1). Notably, the substrates were obtained either from commercial sources or via a single-step synthesis following literature procedures. On completion of the reactions, trifluoroacetic anhydride was added as a trapping agent to prevent loss of the volatile fluorinated piperidine derivatives. For less reactive substrates, an increase in catalyst loading and/or reaction temperature improved the yield of the final product. We also observed that, in some cases, an excess of pinacol borane could reduce the amount of the undesired hydrodefluorinated side product. Generally, high yields and excellent diastereomeric ratios were obtained. Furthermore, the

Table 1 | Scope and conformational behaviour of all-*cis*-(multi)fluorinated piperidines



TFA-analogues	HCl-analogues[a]	TFA-analogues	HCl-analogues[a]
1, 81% (92%)[b]	**2**, 70%	**3**, 79% (95%)[b], d.r. >99:1 **Gram-scale**, 1.57 g, 72%, d.r. >99:1	**4**, 95%, d.r. >99:1
5, 81% (97%)[b], d.r. 90:10	**6**, 89%, d.r. >99:1	**7**, 90%, d.r. 95:5	**8**, 99%, d.r. >99:1
9, 77% (89%)[b], d.r. 95:5	**10**, 99%, d.r. >99:1	**11**, 84% (95%)[b], d.r. 90:10	**12**, 99%, d.r. >99:1
13, 79% (93%)[b], d.r. 93:7	**14**, 80%, d.r. >99:1	**15**, 70%, d.r. 95:5:0	**16**, 99%, d.r. 95:5:0
17, 72%, d.r. 97:2:1	**18**, 97%, d.r. 99:1:0		

Reactions were carried out on a 0.25–10.0 mmol scale. Yields were determined after column chromatography (TFA-analogues) or precipitation (HCl-analogues). d.r. values were determined by ^{19}F NMR or gas chromatography (GC) analysis before purification. The conformational behaviour was determined by NMR studies. For details concerning catalyst loading, amount of HBpin and temperature, see Supplementary Section 4. [a]The given yields correspond to the deprotection step of the TFA-fluoropiperidines to generate the fluoropiperidine HCl-analogues, see general procedure B in Supplementary Section 4 for more details. [b]NMR yields are provided in parentheses and were determined by ^{19}F NMR spectroscopy with hexafluorobenzene as internal standard before the addition of TFAA. HBpin, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane; Dipp, 2,6-diisopropylphenyl; THF, tetrahydrofuran; TFAA, trifluoroacetic anhydride; TFA, trifluoroacetyl; MS, molecular sieves; Me, methyl.

isolation of the major diastereomer by standard column chromatography was often possible. Deprotection of the TFA-analogues afforded the piperidine hydrochlorides almost quantitatively. Accordingly, the *cis*-3,5-difluoropiperidine hydrochloride (**4**), previously requiring a six-step synthesis[21], is now obtained in a two-step process as a single diastereomer (d.r. > 99:1) after deprotection of TFA-analogue **3**. This reaction was also readily carried out on a gram scale, affording 1.57 g of **3** in good yield and with excellent diastereoselectivity (72%, d.r. > 99:1, Sigma-Aldrich product no. 903817). The *cis*-selectivity as well as the 1,3-diaxial behaviour of the fluorine atoms in **4** was confirmed by NMR studies and was consistent with previously published reports (Supplementary Section 4).

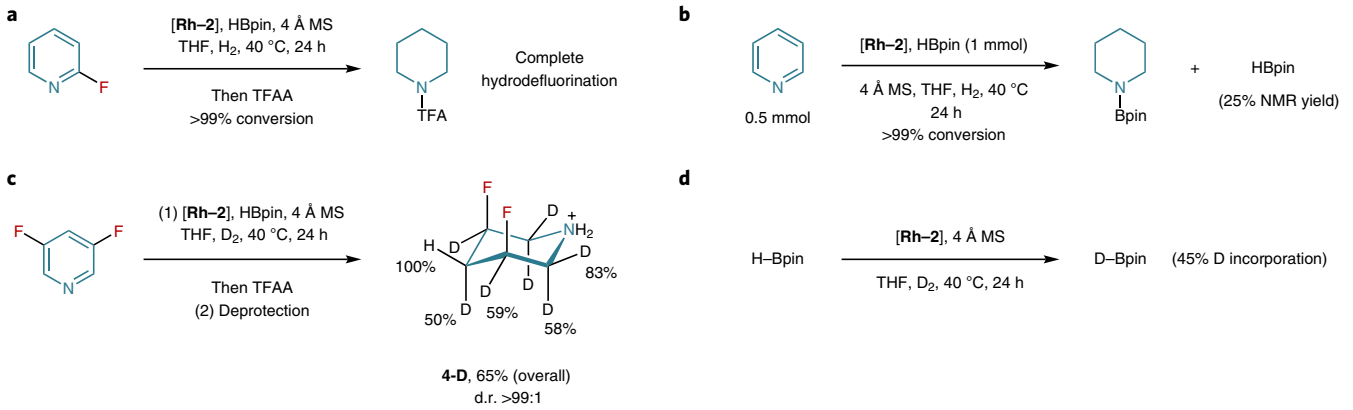
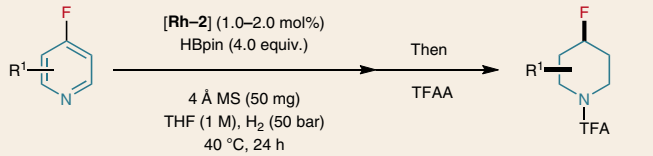
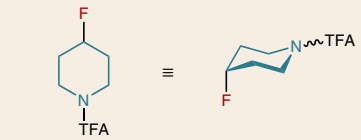
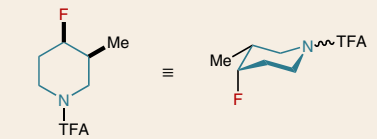
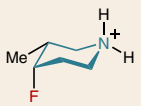
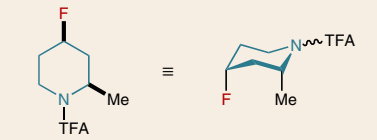
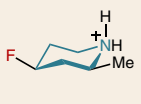


Fig. 2 | Selected mechanistic experiments for the DAH process. a, Complete hydrodefluorination of 2-fluoropydrine was observed. **b**, The amount of HBpin was determined after the reaction by NMR analysis using benzene as the internal standard. **c**, Deuterium scrambling was observed by employing molecular deuterium. The structure of **4-D** was confirmed by NMR and electrospray ionization mass spectrometry (ESI-MS) studies. **d**, D-incorporation for HBpin was observed under the reaction conditions. For more details concerning additional mechanistic studies, see Supplementary Section 6.

Table 2 | Scope and conformational behaviour of all-*cis*-4-fluoropiperidines



TFA-analogues	HCl-analogues[a]
 **19**, 20%	 **20**, 93%
 **21**, 31%, d.r. 97:3	 **22**, 99%, d.r. 97:3
 **23**, 23%, d.r. 92:8	 **24**, 99%, d.r. 92:8

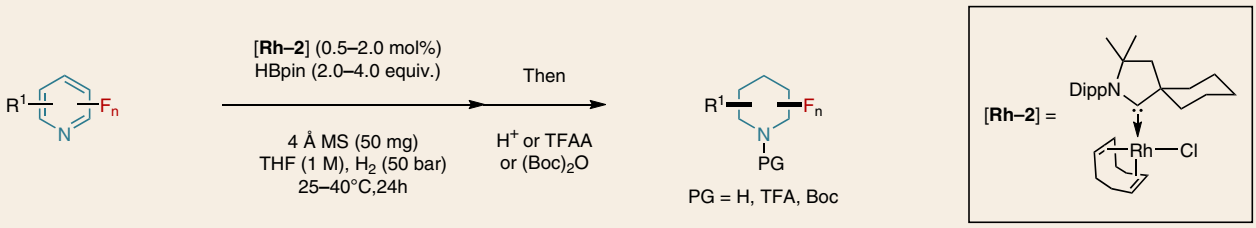
Reactions were carried out on a 0.5–1.0 mmol scale. Yields were determined after column chromatography (TFA-analogues) or precipitation (HCl-analogues). d.r. values were determined by ^{19}F NMR or GC analysis before purification. The conformational behaviour was determined by NMR studies. For details concerning catalyst loading, see Supplementary Section 4.
[a]The given yields correspond to the deprotection step of the TFA-fluoropiperidines to generate the fluoropiperidine HCl-analogues, see general procedure B in Supplementary Section 4 for more details.

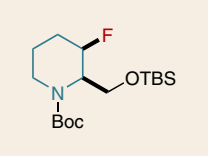
The same behaviour was also observed for the hydrochloride (HCl)-analogue of **1**. Observation of the large axial preference for 3-fluoro- and 3,5-difluoropiperidine hydrochloride ring systems was first discussed by Lankin and colleagues and was rationalized by the occurrence of charge dipole interactions (C–F···HN$^+$)[21,29]. As our protocol provides access to a variety of new substituted fluorinated piperidines, we wondered whether the axial preference will also be preserved in the presence of bulky substituents on the piperidine ring system (Table 1). Comprehensive NMR studies (including nuclear Overhauser effect (NOE), HetNOE, high and low temperature experiments) for the TFA-analogues as well as the HCl-analogues revealed that in most cases the axial preference is preserved (see Supplementary Section 4 for more details). Interestingly, even in highly crowded ring systems (**15**–**18**), fluorine atoms still prefer occupying axial positions (Table 1). However, when the TFA-analogue of the piperidine ring system contains a substituent adjacent to the nitrogen, the conformers favour equatorial fluorine (**9**, **11** and **13**), in sharp contrast to the conformational behaviour of their HCl-analogues (**10**, **12** and **14**). Notably, in both the TFA- and HCl-analogues of *cis*-3-fluoro-5-methylpiperidine (**5** and **6**), the equatorial orientation is dominant. It should be noted that the vicinal ^3J(F,H) coupling constants provide useful insight into the conformational structure, as large values of $^3J(F,H_a)$ indicate axial preference and small values of $^3J(F,H_a)$ indicate equatorial preference (for more details, see Supplementary Section 4)[30].

Despite the generality of the reaction, we also discovered some limitations. For example, while 2- and 4-fluoropyridine derivatives readily underwent hydrogenation, the hydrodefluorinated products were identified as the major species, presumably due to unavoidable defluorination of the unstable conjugated intermediates. Further optimization of 4-fluoropyridine precursors allowed access to a variety of all-*cis*-4-fluoropiperidine derivatives (**19**–**24**) with high diastereoselective ratios but in reduced yields. Their conformation was also determined by comprehensive NMR studies for both TFA- and HCl-analogues (Table 2). Interestingly, in most cases the axial orientation is dominant.

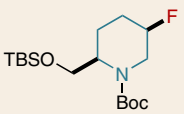
We next sought to demonstrate the utility of this methodology for the preparation of highly valuable and versatile fluorinated building blocks, and at the same time to demonstrate the mild nature of the conditions employed (Table 3). A variety of functional groups, which allow further elaboration of the molecular structure, were well-tolerated. Among these are *tert*-butyl(dimethyl)silyl

Table 3 | Scope of all-*cis*-(multi)fluorinated piperidine building blocks

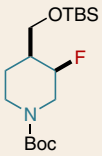




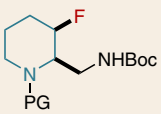
25, 84%
d.r. 99:1



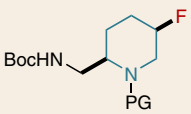
26, 94%
d.r. 97:3



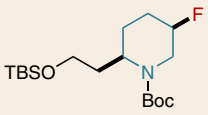
27, 85%
d.r. 95:5



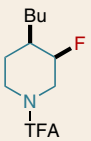
28, PG = Boc, 88%, d.r. 99:1
29, PG = TFA, 24%, d.r. 99:1



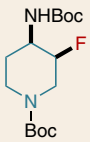
30, PG = Boc, 75%, d.r. 97:3
31, PG = TFA, 61% (95%)[a], d.r. 97:3



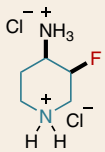
32, 92%
d.r. 95:5



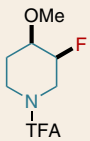
33, 80%
d.r. 99:1



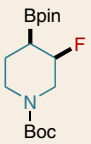
34, 94%
d.r. 97:3



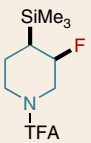
35, 99%[b]
d.r. 97:3



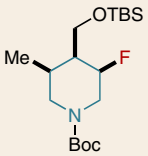
36, 70%
d.r. 99:1



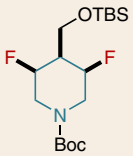
37, 73%
d.r. 96:4



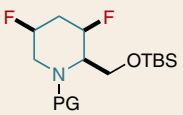
38, 71% (83%)[a]
d.r. >99:1



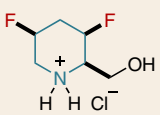
39, 64% (91%)[a]
d.r. 93:7:0



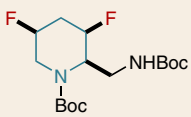
40, 80%
d.r. 90:10:0



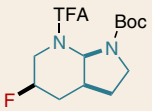
41, PG = Boc, 80%, d.r. 99:1:0
42, PG = H, 46%, d.r. 99:1:0



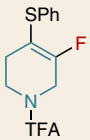
43, 99%[b]
d.r. 99:1:0



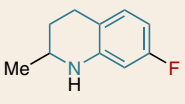
44, 60%
d.r. 99:1:0



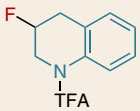
45, 44% (91%)[a]
d.r. 86:14:0



46, 41%[c]



47, 91%



48, 78%

Reactions were carried out on a 0.25–0.5 mmol scale. Yields were determined after column chromatography (TFA- or Boc-analogues) or precipitation (HCl-analogues). d.r. values were determined by ^{19}F NMR or GC analysis before purification. The conformational behaviour was determined by NMR studies. For details concerning catalyst loading, amount of HBpin and temperature, see Supplementary Section 4. [a]NMR yields are provided in parentheses and were determined by ^{19}F NMR spectroscopy with hexafluorobenzene as internal standard before addition of the trapping agent. [b]See general procedure C in Supplementary Section 4 for the deprotection of Boc-fluoropiperidines to generate the fluoropiperidine HCl-analogues. [c]60% conversion. PG, protecting group; $(Boc)_2O$, di-*tert*-butyl dicarbonate; Boc, *tert*-butyloxycarbonyl; TBS, *tert*-butyl(dimethyl)silyl; Bpin, 4,4,5,5-tetramethyl-1,3,2-dioxaboroyl; Bu, *n*-butyl; Ph, phenyl.

(TBS)-protected alcohols (**25**–**27**), *tert*-butyloxycarbonyl (Boc)-protected amines (**28**–**31**), methoxy (**36**), pinacol boronic ester (**37**) and trimethylsilyl groups (**38**). Different trapping agents, such as TFAA and $(Boc)_2O$, or simple addition of MeOH, were chosen to ensure straightforward isolation of the final products. The fluorinated analogues of the (Boc)-protected 4-aminopiperidine (**34**) and its HCl-analogue (**35**), a common core in pharmaceuticals, were also obtained in high yields and diastereoselectivities. The conformational behaviour in solution of the new fluorinated building blocks was determined by NMR and was found to be consistent with the simplified substitution analogues in Table 1 (Supplementary Section 4). The *cis*-selectivity and equatorial preference of the fluorine in **29** were also confirmed by X-ray crystallographic analysis. Orthogonally protected building blocks can be obtained through our strategy, albeit in low yields due to the deprotection of the Boc group upon addition of TFAA (**29**,**31**). The multi-substituted monofluorinated piperidine (**39**) as well as multi-fluorinated moieties bearing additional functional groups (**40**–**44**) were all obtained in a highly diastereoselective manner. In all of these cases, the axial orientation of the fluorine atoms is dominant.

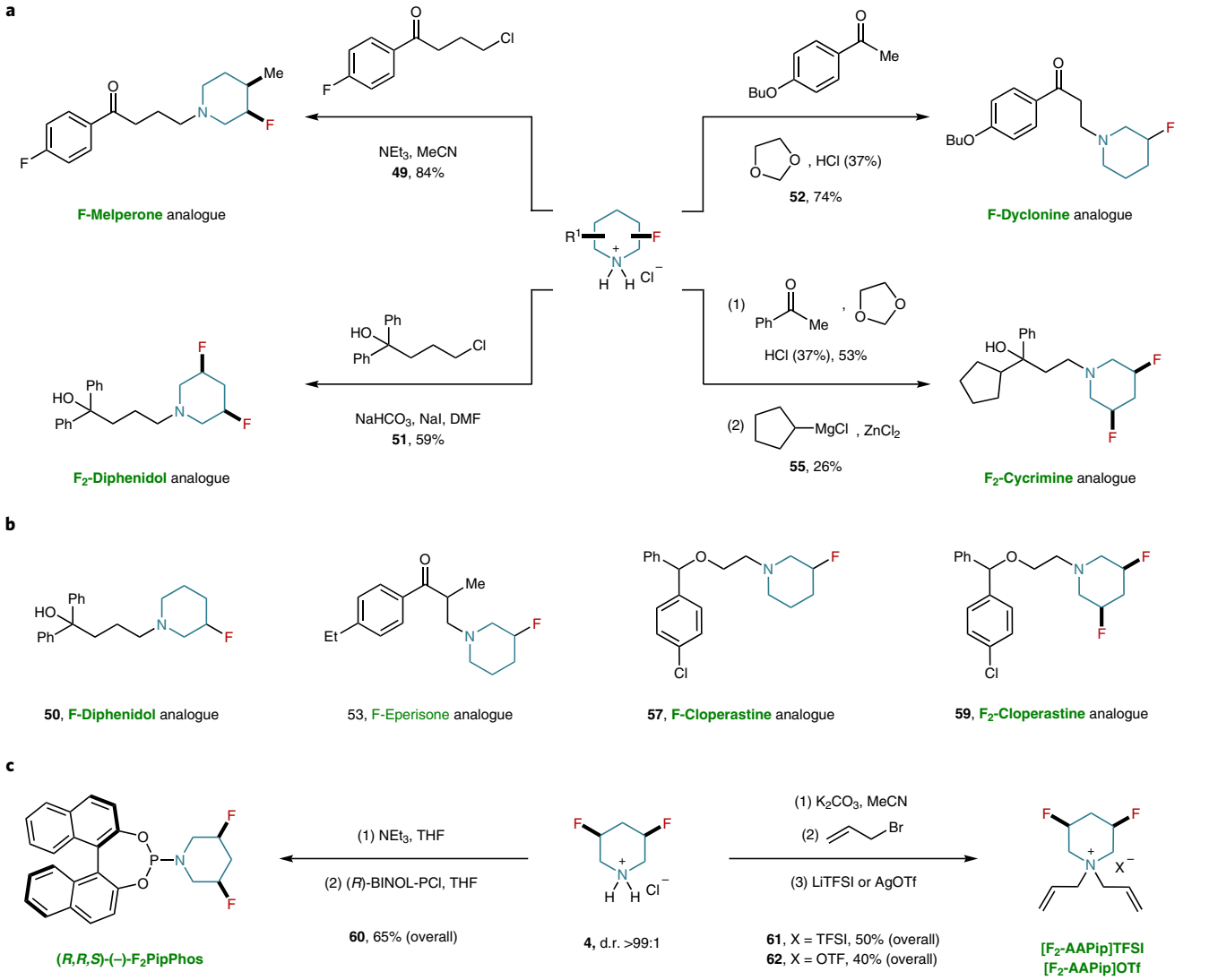


Fig. 3 | Application of the all-*cis*-(multi)fluorinated piperidine building blocks. a, Preparation of fluorinated analogues of commercial drugs starting from fluoropiperidine hydrochloride derivatives. **b**, Fluorinated analogues of additional commercial drugs. For reaction conditions, see Supplementary Section 7. **c**, Preparation of fluorinated analogues of PipPhos and ionic liquids. For detailed reaction conditions see Supplementary Section 7. NEt_3, triethylamine; MeCN, acetonitrile; DMF, dimethylformamide; (*R*)-BINOL-PCl, (*R*)-1,1′-binaphthyl-2,2′-dioxychlorophosphine; LiTFSI, bis(trifluoromethane)sulfonimide lithium salt; AgOTf, silver trifluoromethanesulfonate.

The scope of this reaction was also extended to other heterocycles (**45**–**48**). Interestingly, we could even selectively reduce the pyridine ring system in the presence of other phenyl rings (**46**–**48**).

Preliminary mechanistic experiments were performed to gain a better understanding of the DAH process (Fig. 2). In the absence of pinacol borane, no product was detected (Supplementary Section 3). Traces of the proposed borylated-dearomatized intermediates could be observed by ^{1}H and ^{19}F NMR studies of the crude reaction mixture of 3,5-difluoropyridine after 5 h. However, our attempts to isolate the intermediates were unsuccessful, presumably due to their rapid hydrogenation. On the other hand, NMR analysis of the crude reaction showed that HBpin was consumed during the reaction (Fig. 2b), suggesting that it has a crucial role in the DAH process. Hydrogenation of 3,5-difluoropyridine using molecular deuterium was also performed generating the isotopologues of the 3,5-difluoropiperidine **4-D** (Fig. 2c). Deuterium scrambling can be rationalized due to the formation of imine-enamine intermediates as well as the D-incorporation into HBpin that was also observed under our reaction conditions (Fig. 2d).

To illustrate the utility of our method and further demonstrate the value of the prepared building blocks, we synthesized several fluorinated analogues of commercially available drugs, the PipPhos ligand and ionic liquids (Fig. 3a–c). The monofluorinated analogue of Melperone (**49**) as well as mono- and difluorinated analogues of Diphenidol (**50**,**51**) were prepared using the corresponding piperidinium salts by nucleophilic substitution. The monofluorinated analogues of Dyclonine (**52**), Eperisone (**53**) and Cycrimine (**55**) were all prepared starting from fluorinated piperidine hydrochloride derivatives utilizing a modified Mannich reaction with 1,3-dioxolane. Moreover, the synthesis of mono- and difluorinated analogues of Cloperastine (**57**,**59**) were also achieved (Fig. 3a,b; see Supplementary Section 7 for more details). Additionally, the difluorinated phosphoramidite analogue of PipPhos (**60**) was accessed starting from 3,5-difluoropiperidine hydrochloride (**4**) in a one-pot process (Fig. 3c). Interestingly, NMR analysis of **60** revealed that the fluorine atoms adopt the equatorial orientation in polar and non-polar solvents. However, X-ray crystallographic analysis of F_2-PipPhos (**60**) showed that the 1,3-diaxial behaviour is dominant

in the solid state. In materials science, fluorinated ionic liquids (FILs) are gaining attention due to their unique physical properties[31]. Therefore, we incorporated our new building blocks into analogues of previously known ionic liquids (**61**,**62**) (Fig. 3c).

Conclusions

In conclusion, we have developed a straightforward strategy to access all-*cis*-(multi)fluorinated piperidines from the corresponding fluoropyridine precursors in a highly diastereoselective manner. This process proceeds via a rhodium-catalysed pyridine dearomatization event followed by complete saturation of the resulting intermediates by hydrogenation. We envision that the newly developed methodology will be of immediate interest in medicinal, agrochemical and materials science.

Methods

General procedure for DAH of fluoropyridine derivatives. An oven-dried reaction vessel (4 or 9 ml screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Activated 4 Å molecular sieves (crushed, 50 mg), [**Rh-2**] (and solid substrates, 1.0 equiv.), were added under air. The vial was then depressurized and pressurized with argon gas three times before the addition of dry THF (1 M) (and liquid substrates, distilled over CaH_2, 1.0 equiv.). Following the addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.0–4.0 equiv. as indicated), the glass vial was placed in a 150 ml stainless-steel autoclave under an argon atmosphere. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at 25–40 °C for 24 h. After the autoclave was carefully depressurized, trifluoroacetic anhydride (3.0 equiv.) and CH_2Cl_2 (0.5 ml) were added to the crude mixture and stirring was continued for 10 min at room temperature. Alternatively, di-*tert*-butyl dicarbonate (3.0 equiv.), triethyl amine (3.0 equiv.) and CH_2Cl_2 (0.5 ml) were added to the reaction mixture and stirring was continued for 2 h at room temperature. The crude was then filtered over fritted funnel and the remaining solid was washed with ethyl acetate (2×5 ml). The combined solution was concentrated under reduced pressure and submitted to column chromatography (pentane/ethyl acetate or pentane/dichloromethane) to obtain the final product. The indicated diastereoselectivities were determined by GC analysis or from the ^{19}F NMR spectrum immediately after the reaction. NMR yield was calculated using hexafluorobenzene (20 µl, 0.173 mmol) as internal standard.

Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers CCDC 1845054 (**29**) and 1845055 (**60**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. All other data supporting the findings of this study are available within the Article and its Supplementary Information, or from the corresponding author upon reasonable request.

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References

1. Trost, B. M. Selectivity: a key to synthetic efficiency. *Science* **219**, 245–250 (1983).
2. Baran, P. S., Maimone, T. J. & Richter, J. M. Total synthesis of marine natural products without using protecting groups. *Nature* **446**, 404–408 (2007).
3. Young, I. S. & Baran, P. S. Protecting-group-free synthesis as an opportunity for invention. *Nat. Chem.* **1**, 193–205 (2009).
4. Wender, P. A. & Miller, B. L. Synthesis at the molecular frontier. *Nature* **460**, 197–201 (2009).
5. Zhao, D., Candish, L., Paul, D. & Glorius, F. N-Heterocyclic carbenes in asymmetric hydrogenation. *ACS Catal.* **6**, 5978–5988 (2016).
6. 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.* **137**, 9250–9253 (2015).
7. Wiesenfeldt, M. P., Nairoukh, Z., Li, W. & Glorius, F. Hydrogenation of fluoroarenes: direct access to all-*cis*-(multi)fluorinated cycloalkanes. *Science* **357**, 908–912 (2017).
8. Wiesenfeldt, M. P., Knecht, T., Schlepphorst, C. & Glorius, F. Silylarene hydrogenation: a strategic approach enabling direct access to versatile silylated saturated carbo- and heterocycles. *Angew. Chem. Int. Ed.* **57**, 8297–8300 (2018).
9. O'Hagan, D. Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Nat. Prod. Rep.* **17**, 435–446 (2000).
10. Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals. *J. Med. Chem.* **57**, 10257–10274 (2014).
11. Müller, K., Faeh, C. & Diederich, F. Fluorine in pharmaceuticals: Looking beyond intuition. *Science* **317**, 1881–1886 (2007).
12. Shah, P. & Westwell, A. D. The role of fluorine in medicinal chemistry. *J. Enzyme Inhib. Med. Chem.* **22**, 527–540 (2007).
13. O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **37**, 308–319 (2008).
14. Thiehoff, C., Rey, Y. P. & Gilmour, R. The fluorine gauche effect: a brief history. *Isr. J. Chem.* **57**, 92–100 (2017).
15. Wang, J. et al. Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001–2011). *Chem. Rev.* **114**, 2432–2506 (2014).
16. Gillis, E. P., Eastman, K. J., Hill, M. D., Donnelly, D. J. & Meanwell, N. A. Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **58**, 8315–8359 (2015).
17. Li, X. et al. Process development for scale-up of a novel 3,5-substituted thiazolidine-2,4-dione compound as a potent inhibitor for estrogen-related receptor 1. *Org. Process Res. Dev.* **18**, 321–330 (2014).
18. Goldberg, N. W., Shen, X., Li, J. & Ritter, T. AlkylFluor: deoxyfluorination of alcohols. *Org. Lett.* **18**, 6102–6104 (2016).
19. Liu, W. et al. Oxidative aliphatic C–H fluorination with fluoride ion catalyzed by a manganese porphyrin. *Science* **337**, 1322–1325 (2012).
20. Ventre, S., Petronijevic, F. R. & MacMillan, D. W. C. Decarboxylative fluorination of aliphatic carboxylic acids via photoredox catalysis. *J. Am. Chem. Soc.* **137**, 5654–5657 (2015).
21. 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- - -NH charge-dipole effect. *J. Am. Chem. Soc.* **122**, 544–545 (2000).
22. Glorius, F., Spielkamp, N., Holle, S., Goddard, R. & Lehmann, C. W. Efficient asymmetric hydrogenation of pyridines. *Angew. Chem. Int. Ed.* **43**, 2850–2852 (2004).
23. Zhou, Y.-G. Asymmetric hydrogenation of heteroaromatic compounds. *Acc. Chem. Res.* **40**, 1357–1366 (2007).
24. Whittlesey, M. K. & Peris, E. Catalytic hydrodefluorination with late transition metal complexes. *ACS Catal.* **4**, 3152–3159 (2014).
25. Dyson, P. J. Arene hydrogenation by homogeneous catalysts: fact or fiction? *Dalton Trans.* **2003**, 2964–2974 (2003).
26. Park, S. & Chang, S. Catalytic dearomatization of N-heteroarenes with silicon and boron compounds. *Angew. Chem. Int. Ed.* **56**, 7720–7738 (2017).
27. Oshima, K., Ohmura, T. & Suginome, M. Regioselective synthesis of 1,2-dihydropyridines by rhodium-catalyzed hydroboration of pyridines. *J. Am. Chem. Soc.* **134**, 3699–3702 (2012).
28. Jazzar, R. et al. Intramolecular 'hydroiminiumation' of alkenes: application to the synthesis of conjugate acids of cyclic alkyl amino carbenes (CAACs). *Angew. Chem. Int. Ed.* **46**, 2899–2902 (2007).
29. 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.* **115**, 3356–3357 (1993).
30. Silla, J. M. et al. Gauche preference of β-fluoroalkyl ammonium salts. *J. Phys. Chem. A* **118**, 503–507 (2014).
31. Pereiro, A. B. et al. Fluorinated ionic liquids: properties and applications. *ACS Sustain. Chem. Eng.* **1**, 427–439 (2013).

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Author contributions

Z.N., M.W., C.S. and F.G. designed, performed and analysed experiments. K.B. performed and analysed NMR data. Z.N. and F.G. prepared the manuscript with contributions from all authors.

Competing interests

Z.N., C.S. and F.G. are inventors on German patent application DE 10 2018 104 201.9 held by WWU Muenster, which covers the DAH process for the synthesis of all-*cis*-(multi)fluorinated aliphatic heterocycles.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41557-018-0197-2.

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