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Accessing (Multi)Fluorinated Piperidines Using Heterogeneous Hydrogenation

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hydrogenation • nitrogen heterocycles • fluorine • heterogeneous catalysis • palladium

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 heterogenous catalyst. Fluorinated derivatives of important drug compounds are prepared and a straightforward strategy for the synthesis of enantioenriched fluorinated piperidines is disclosed.

Fluorine has become recognized as a potent substituent in medicinal, agricultural, and material science over the last decades.(1) Owing to their high polarity, carbon–fluorine bonds are deliberately installed in drug candidates to optimize their physicochemical properties.(2) 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.(3) For instance, fluorine's strong preference for *gauche* orientation is widely utilized to establish conformationally-defined building blocks.(4) Besides fluorine, nitrogen-containing heterocycles are an outstandingly important moiety commonly found in natural products and pharmaceuticals.(5)

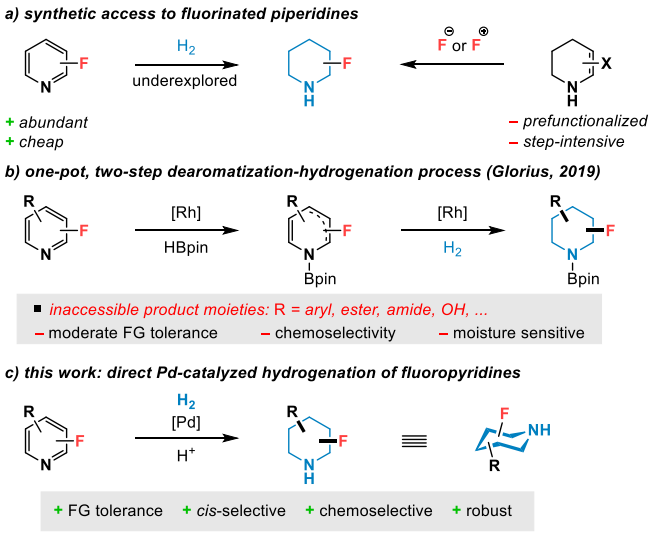
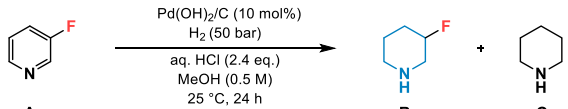


Figure 1. Synthetic strategies to access fluorinated piperidines.

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

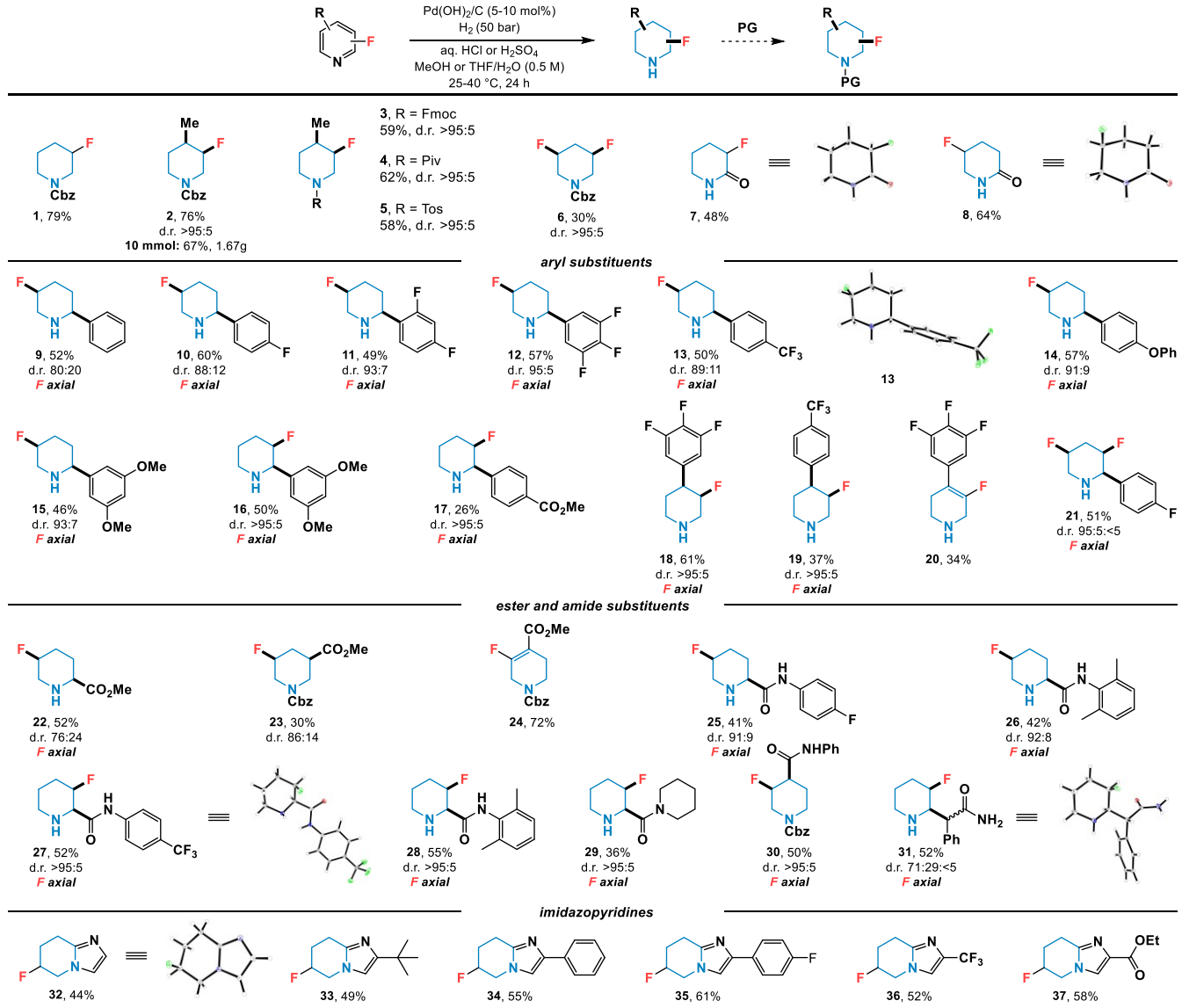
An alternative retrosynthetic strategy is the formation of piperidines from fluorinated precursors.(10) Given the broad availability of fluorinated pyridines, metal-catalyzed hydrogenation is recognizable as a powerful tool to transform these to the desired saturated building blocks (Figure 1a).(11)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

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_2O_3 (5 wt%)	traces	<5%
4	Pt/C (5 wt%)	6%	>99%
5	Ru/Al_2O_3 (5 wt%)	traces	<5%
6	Pd/C (10 wt%)	83%	>99%
7	no acid	17%	78%

Chart 1. Substrate scope for the palladium-catalyzed hydrogenation of fluoropyridines. See Supporting Information for full experimental details.



To address this problem, our group recently reported the development of a dearomatization-hydrogenation (DAH) process (Figure 1b).[13] Although this process allowed access to a series of fluorinated piperidines for the first time, the synthetic utility is limited. Firstly, 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.

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.[14] 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 a 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).[15]

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.[16] To our delight, we found that the combination of $Pd(OH)_2$ 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 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 towards small deviations of concentration, pressure, temperature and the presence

of oxygen or moisture (see Supporting Information for further details).[17]

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.

Further, 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.

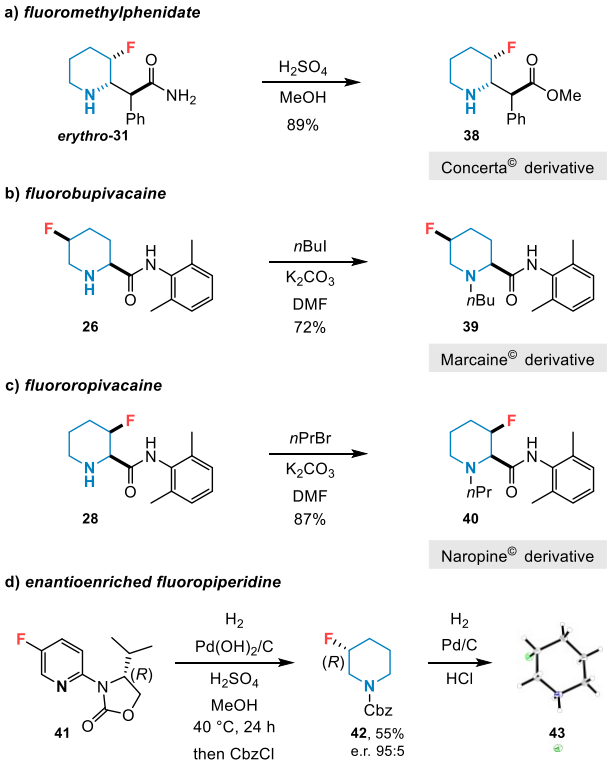
In contrast to our previous study,[13] free hydroxy groups were tolerated under the reaction conditions and led to the isolation of valuable δ-lactam products **7** and **8** in good yields, respectively. Our catalytic system facilitated the *cis*-selective reduction of fluoropyridines over benzene rings and enabled the synthesis of 5-fluoro-2-phenylpiperidine (**9**) in good diastereoselectivity.[18] A series of multi-fluorinated 2-aryl-5-fluoropiperidines **10**–**13** were 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, respectively. Furthermore, multifluorinated 4-aryl-3-fluoropiperidines **18** and **19** were synthesized in THF/H_2O 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-dilfluoropiperidine **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.[19] 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 β-amino acid **23** and tetrahydropyridine γ-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. 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 non-fluorinated piperidines. This is due to remaining hydrodefluorination reactions, which are not completely suppressed by our new catalytic system.



Scheme 1. Synthesis of fluorinated methylphenidate (a), bupivacaine (b), ropivacaine (c), and enantioenriched 3-fluoropiperidine (d).

Preliminary mechanistic investigations indicate that hydrodefluorination occurs on dearomatized intermediates (see Supporting Information for further details). The beneficial role of the Brønsted acid on reactivity towards hydrogenation has been investigated in the literature[20] 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.[21] A recent, detailed study investigated the fundamental interactions of fluorinated piperidines.[22] NMR analysis of the free NH piperidines synthesized in this study proved the *gauche* conformation of the products in $CDCl_3$.

To further show the utility of our developed method, several fluorinated drug derivates 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_2SO_4. 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,[23] oxazolidine-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 a 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.

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallographic data 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.

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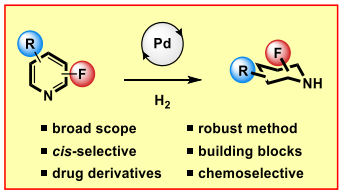
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NH
broad scope
cis-selective
drug derivatives
robust method
building blocks
chemoselective