Accessing (Multi)Fluorinated Piperidines Using Heterogeneous Hydrogenation

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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.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

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, 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 nonfluorinated piperidines.12

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. 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.
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. 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). 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. 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

| entry | deviation | yield B (%) | conv. A (%) |
|-------|-----------|-------------|-------------|
| 1     | none      | 88%         | >99         |
| 2     | Rh/C (5 wt %) | 53%         | >99         |
| 3     | Rh/Al$_2$O$_3$ (5 wt %) | traces | <5 |
| 4     | Pt/C (5 wt %) | 6%          | >99         |
| 5     | Ru/Al$_2$O$_3$ (5 wt %) | traces | <5 |
| 6     | Pd/C (10 wt %) | 83%         | >99         |
| 7     | no acid   | 17%         | 78          |

See the Supporting Information for full experimental details.

ACS Catal. 2020, 10, 12052–12057
excludes 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).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 benzoxycarbonyl (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 sulfonyl-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. 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 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, trifluoromethylated 4-aryl-3-fluoropiperidines 18 and 19 were synthesized in tetrahydrofuran/H₂O while notably 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.19 Our protocol allows the isolation of 22 after a single reaction step from a commercially available starting material in 62% yield. Moreover, the 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-Phenylacetyl amide-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-tetrahydromidazo[1,2-a]pyridine (32) was isolated without reduction of the imidazole ring being observed. A series of 2-substituted (multi)fluorinated tetrahydromidazo[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 Bronsted acid on reactivity toward 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 intermediates (see the Supporting Information for further details). The beneficial role of the Bronsted acid on reactivity toward 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.

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 H₂SO₄. 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...
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catalyzed hydrogenation. This protocol enables the trans-
formation of cheap and abundant fluoroypyridines to sought-
after fluorinated piperidines in a robust and simple manner. Using a common heterogeneous palladium catalyst, a selective reduction of fluoroypyridines over benzene and imidazole systems was established. The robustness of our method was demonstrated by applying a reaction-condition-based sensi-
tivity 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

1 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

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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 Taryn Dalton, Daniel Moock, J. Luca Schwarz, and Marco Wollenburg for many helpful discussions.

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