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Synthesis of Perfluoroalkyl-Substituted Azines via Nucleophilic Substitution of Hydrogen with Perfluoroisopropyl Carbanions

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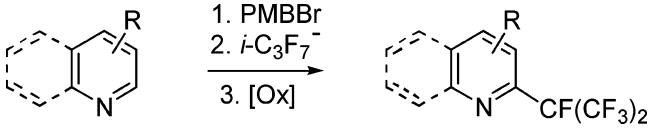

Perfluoroisopropyl carbanions generated *in situ* by treatment of perfluoropropene (HFP) with solid KF in the appropriate solvents add to *N*-alkylpyridinium, quinolinium, and other azinium salts to give reasonably stable *N*-alkyldihydroazines containing a perfluoroisopropyl group. In most cases, addition proceeds in position 2 of the heterocyclic ring. Stability of these dihydroazines depends on the nature of the *N*-alkyl group and other substituents present in the azine ring. The least stable of them were converted into their stable C-trifluoroacetyl derivatives in reaction with trifluoroacetic anhydride. Treatment of *N*-benzyl- or *N*-*p*-methoxybenzyl-2-perfluoroisopropyl dihydroazines with oxidizing agents such as DDQ or cerium(IV) ammonium nitrate results in cleavage of the benzylic C−N bond followed by oxidation of the ring, giving pyridines or quinolines with a perfluoroisopropyl group in the aromatic ring. On the basis of these findings, a new protocol for introduction of perfluoroalkyl substituents into azine rings was elaborated via oxidative nucleophilic substitution of hydrogen. It involves three chemical steps: (i) alkylation of azine with *p*-$MeOC_6H_4CH_2Br$, (ii) reaction of the resulting salt with fluorinated carbanions generated in situ from HFP and KF, and (iii) N-deprotection and aromatization of the isolated dihydroazine on treatment with CAN. The first two reactions, (i) and (ii), can be performed as a one-pot operation.

Introduction

Perfluoroalkyl-substituted heterocyclic compounds are of prominent importance among currently used pharmaceuticals, agrochemical agents, and liquid crystalline compounds.[1−3] They owe their unique properties to the special character of perfluoroalkyl groups—low polarizability, high lipophilicity and electronegativity, and significant metabolic stability. For many years, the most widely used methods of introduction of perfluoroalkyl substituents into aromatic systems were transformations of CCl_3 and CO_2H groups into CF_3 upon treatment with fluorinated Lewis acids (SbF_3, SbF_5, etc.—the Swarts process) or SF_4[4] and reactions of aryl halides (primarily iodides) with perfluoroalkylcopper reagents or with perfluoroalkylzinc reagents in the presence of palladium catalysts.[4,5] Procedures that allow direct introduction of a perfluoroalkyl group into aromatic rings but are applicable mainly on a laboratory scale include (i) nucleophilic oxidative substitution of hydrogen in nitroarenes by a trifluoromethyl carbanion (from the Ruppert reagent, CF_3SiMe_3 and $(Me_2N)_3S^+Me_2SiF_3^-$, TASF) with dimethyldioxirane (DMD) as an oxidant, affording trifluoromethylated phenols[6] (this procedure was recently developed in our laboratory); (ii) a reaction of electron-rich arenes with perfluoroalkylphenyliodonium[7] or trifluoromethyldibenzothiophenium and similar reagents;[8] and (iii) addition of *n*-perfluoroalkyllithiums to BF_3-complexed azaarenes, leading to 1,2-dihydro-2-*n*-perfluoroalkylquinolines and diazines (but to pyridines only in very low

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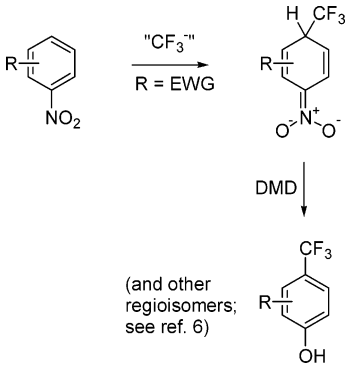
yields), followed by a spontaneous air oxidation to the corresponding perfluoroalkyl-containing heteroaromatic derivatives.[9] Attempts to replace halogens or a nitro group in halodinitrobenzenes or halocyanonitrobenzenes with CF_3^-, generated from the Ruppert reagent without a metal catalyst, gave mixtures of the expected trifluoromethylnitroarenes in low yields.[10] Oxidative nucleophilic replacement of hydrogen in trinitrobenzene by a trifluoromethyl carbanion was also reported.[11]

The limitations of most of the methods mentioned above are either the harsh conditions needed to effect the desired transformations or the application of expensive, high molecular weight or not environmentally benign reagents. For these reasons, alternative ways to synthesize perfluoroalkylated aromatic compounds should be of significant interest. We thus turned our attention to the process of generation of perfluorocarbanions from simpler perfluoroolefins and potassium fluoride and their possible use for direct nucleophilic perfluoroalkylation of aromatic compounds. We envisioned that these carbanions could react with electrophilic arenes to provide products of the aromatic nucleophilic substitution of hydrogen (vicarious or oxidative)[12] in a manner analogous to trifluoromethylation of nitroarenes by a CF_3SiMe_3/TASF system (Scheme 1).[6]

Polyfluorinated alkenes readily add fluoride anions and other nucleophiles leading to the formation of perfluorocarbanions.[1,13] Synthetic application of these intermediates is partially impeded by the competing fluoride-catalyzed oligomerization of the starting fluoroalkenes; however, there are reports on their successful reactions with electrophiles such as alkyl[14] and acyl[15]

SCHEME 1. Oxidative Nucleophilic Substitution of Hydrogen in Nitroarenes by Trifluoromethyl Carbanions



halides, chloromethyl ethers,[16] carbon dioxide,[17] $HgCl_2$,[18] etc. Their potential use in nucleophilic perfluoroalkylation of heteroaromatic compounds was explored only in a very specific case of perfluorinated aromatics (mainly pyridines) by Chambers and co-workers.[19] These highly electrophilic arenes are very prone to undergo a nucleophilic aromatic displacement of fluorine. They were reported to react with tetrafluoroethylene, hexafluoropropene, and, to some extent, with CF_2═CFX (X = H, Cl, Br) in the presence of KF or CsF at high temperatures or tetrakis(dimethylamino)ethylene (TDAE) at room temperature in solvents like sulfolane or tetraglyme to provide mixtures of mono- and polysubstituted products. However, this approach suffers from low selectivity and narrow applicability; all positions of the aromatic ring of the product are occupied by either a fluorine atom or a fluoroalkyl group.

Herein, we report results of our investigation of the reactions of perfluoroisopropyl carbanions generated from hexafluoropropene (HFP, a fluoroolefin manufactured at an industrial scale) and solid potassium fluoride with electrophilic arenes. In preliminary experiments, we have found that nitroarenes, even those as active as 1,3-dinitrobenzene, do not react with the $(CF_3)_2CF^-$ carbanion; no products were formed with HFP and KF(s) in various solvents, at various temperatures, and in the presence of crown ethers or tetraalkylammonium salts. Presumably, due to a strong stabilization of these carbanions by two CF_3 substituents, they are not sufficiently nucleophilic to add to nitroarenes and form σ-adducts.

Introduction of substituents into azine rings via *N*-acylation followed by addition of nucleophiles to such activated *N*-acylazinium rings is a methodology widely used in organic synthesis. There are several reports on addition of nucleophiles to *N*-acylpyridinium salts and subsequent oxidation of the resulting 1-acyl-1,2- and 1-acyl-1,4-dihydropyridines with dichlorodicyanobenzoquinone (DDQ) to obtain readily hydrolyzable, ring-substituted N-acylated salts.[20,21] Aromatization of such 1-acyldihydropyridines was also effected using chloranil,[22] sulfur,[23] atmospheric oxygen,[24] triphenylcarbenium tetrafluoro-

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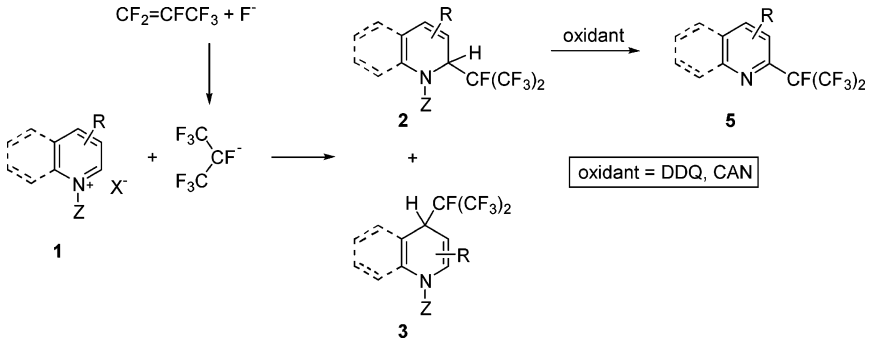
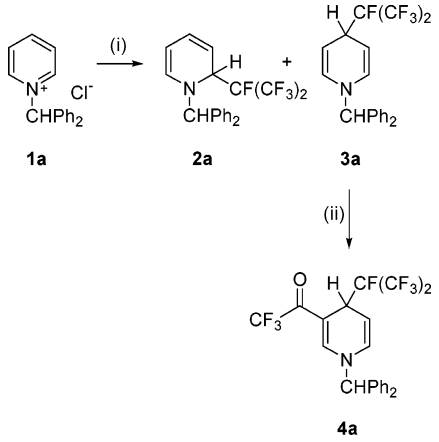
SCHEME 2. Oxidative Nucleophilic Substitution of Hydrogen in *N*-Alkylazinium Salts by Perfluoroisopropyl Carbanions



borate,[22d] or anodic oxidation.[25] However, perfluorocarbanions have never been used in these reactions as nucleophiles. Our attempts of reactions of a perfluoroisopropyl carbanion generated from KF(s) and HFP with *N*-acylpyridinium salts were unsuccessful; only acyl fluorides, perfluoroisopropyl ketones, and unreacted pyridines were recovered from such experiments. Apparently, F^- and $(CF_3)_2CF^-$ anions reacted preferentially with the activated carbonyl group of the *N*-acylazinium salts rather than with the heterocyclic ring.

On the other hand, preliminary experiments indicated that *N*-alkylazinium salts **1**, which are much more stable entities, undergo addition of such carbanions when exposed to HFP and KF(s) and afford the respective dihydro adducts **2** and **3** (Scheme 2). Furthermore, we have found that the 1,2-dihydroazine derivatives **2** yield the perfluoroisopropyl-substituted azaarenes **5** when treated with appropriate oxidants, thus completing a process of formal oxidative aromatic substitution of hydrogen by a perfluorinated carbanion. Herein, we provide an account of the scope and limitations of this novel and potentially useful synthesis of perfluoroalkylated heterocycles. The intermediate dihydroazines[20] are interesting by themselves since they can be potentially transformed into a multitude of other fluoroalkylated heterocyclic systems, for example, via reduction, cycloaddition, reactions with electrophiles, etc.[20a,26]

SCHEME 3. Addition of $C_3F_7^-$ Carbanions to a Simple *N*-Alkylpyridinium Salt 1a and Stabilization of the Product by Acylation with TFAA[a]



[a] Conditions: (i) 5.0 equiv of KF(s), ca. 4 equiv of HFP, rt, CH_2Cl_2, 24 h; (ii) TFAA, *i*-Pr_2NEt, 0 °C, 30 min.

Results and Discussion

Initial Studies. Reactions of *N*-Benzyl and *N*-Benzhydryl Salts. Reaction of *N*-benzylpyridinium chloride with perfluoroisopropyl carbanions generated from hexafluoropropene and solid potassium fluoride gave the expected adduct in low yield (<5%). Although the addition proceeded, the product was very unstable and decomposed rapidly during the reaction.

In our previous studies on reactions of trichloromethyl carbanions generated at the interface between chloroform and aqueous NaOH, we observed that adducts of these carbanions to *N*-benzylpyridinium chloride decomposed rapidly, whereas the adducts to *N*-benzhydrylpyridinium chloride **1a** were more stable and could be isolated in high yields.[27] Indeed, treatment of **1a** with an excess of HFP and KF(s) in CH_2Cl_2 in a closed pressure tube at room temperature for 24 h (Scheme 3) provided the expected adducts **2a** and **3a**. The 1,4-dihydropyridine isomer **3a** was the major product, and only traces of 1,2-dihydropyridine isomer **2a** were detected by the ^1H NMR analysis of the crude reaction mixture. Compound **3a** could be isolated in 58% yield, but it decomposed rapidly during chromatographic purification on silica gel and was rather unstable on standing at room temperature (dark-red products of decomposition appeared after less than 24 h). 1,2-Dihydropyridine **2a** was also unstable and was not isolated in pure form.

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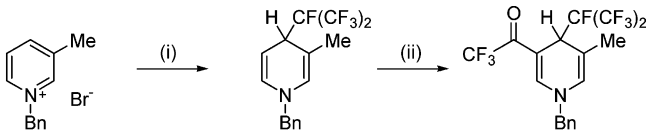
SCHEME 4. Reaction of 3-Methylpyridinium Salt 1b with HFP and KF(s) under Various Conditions[a]



	3b	4b
CH_2Cl_2, 2 h	23 %	(-)
CH_2Cl_2, 13 h	54 %	23 %
DME, 2.5 h	13 %	(-)
DME, 13 h	90 %	31 %

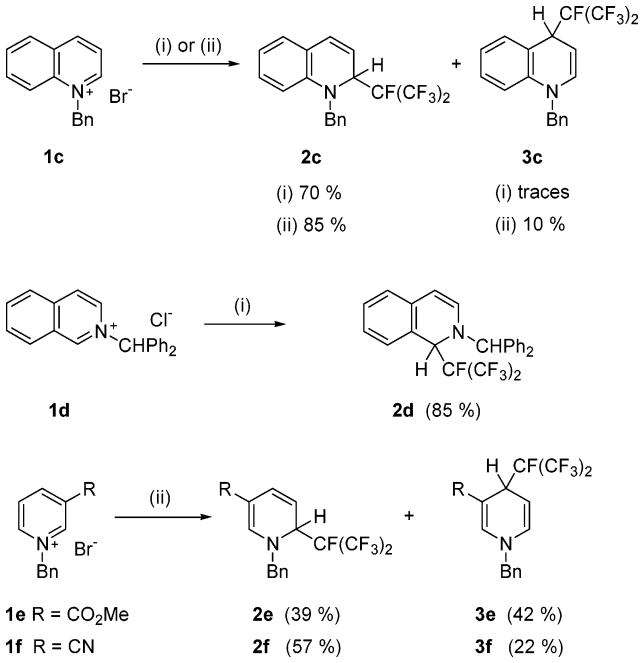
[a] Conditions: (i) 5.0 equiv of KF(s), ca. 4 equiv of HFP, rt; (ii) TFAA, *i*-Pr_2NEt, 0 °C, 30 min.

These results clearly demonstrate that perfluoroisopropyl carbanions generated via addition of fluoride anions to HFP under relatively mild conditions add efficiently to pyridinium cations, providing the respective adducts in a synthetically useful yield; however, the problem of stability of the products still remained to be solved. Since it is known that dihydropyridines containing electron-withdrawing substituents in position 3 are reasonably stable compounds,[20] we acylated crude **3a** with trifluoroacetic anhydride (TFAA) directly after the reaction with HFP and KF (performed in CH_2Cl_2 for 4.5 h) to obtain compound **4a** with an overall yield of 49% (Scheme 3).[28] Indeed, the presence of the strongly electron-withdrawing trifluoromethylcarbonyl group made this product sufficiently stable to obtain an analytical sample. The yield of the two-step procedure (reaction with KF(s) and HFP and then with TFAA) is lower than the yield of the initial dihydropyridine, presumably because of partial decomposition upon treatment with the acylating agent.

In an attempt to improve the yield of the process, we increased the time of the reaction of **1a** with HFP and KF(s), but it turned out to be slightly detrimental for the yield, presumably due to decomposition of dihydropyridine **3a** (45% of **4a** after 24 h of reaction with HFP and KF and subsequent acylation). We also tried to use DMF instead of CH_2Cl_2, as it is a much better solvent for pyridinium salts, and it can also partially dissolve solid KF. Indeed, the reaction in DMF was significantly faster (46% of **4a** after 1.5 h and acylation); however, under these conditions, decomposition of **3a** is also faster (only 35% of **4a** obtained after 24 h of reaction with HFP and KF(s)).

We then turned our attention to the reactions of *N*-benzyl-3-methylpyridinium bromide **1b**, as we expected that the adducts to this salt might be more stable, owing to the ring substituent. Unfortunately, reaction in DMF resulted in complete decomposition and formation of unidentified tarry material, whereas reaction in CH_2Cl_2 afforded only 23% of compound **3b** as one regioisomer (Scheme 4). Product **3b**, once isolated by flash column chromatography, was significantly more stable at room temperature than **2a** or **3a**. This prompted us to perform the reaction of the salt **1b** with HFP and KF(s) over a longer time. Indeed, after 13 h at room temperature, **3b** was isolated in a 54% yield. An even better result was obtained with 1,2-dimethoxyethane (DME) as the solvent; 90% of **3b** was obtained after 13 h. In each case, the reaction proceeded with complete regioselectivity. Similar to the case of 1,4-dihydropyridine adduct **3a**, compound **3b** could be acylated in situ with TFAA, giving completely stable **4b** in a 23 or 31% yield in two steps, depending on the solvent.

SCHEME 5. Reactions of *N*-Benzhydryl- and *N*-Benzylazinium Salts with Perfluoroisopropyl Carbanions[a]



[a] Conditions: (i) HFP, KF(s), CH_2Cl_2, rt, 24 h; (ii) HFP, KF(s), DMF, rt, 2 h.

Encouraged by the results obtained with **1a** and **1b**, we performed similar reactions with *N*-benzyl and benzhydryl salts **1c**−**f**, obtaining the respective C_3F_7-substituted dihydroazines in high yields as mixtures of readily separable 1,2- and 1,4-dihydro isomers **2** and **3** (with the 1,2-dihydro isomers favored in most cases, Scheme 5). The solvent of choice for these reactions was DMF rather than CH_2Cl_2; the reactions were much faster because of better solubility of salts **1**, and the addition products obtained from **1c**−**f** did not decompose, in contrast to **2a**, **3a**, and **3b**. The products of the addition at the position adjacent to the nitrogen atom of quinoline, isoquinoline, and pyridines containing an EWG substituent (CO_2Me, CN) in position 3 were stable and readily characterizable compounds; their stability is also increased by the bulky and electron-withdrawing perfluoroisopropyl substituent. The 1,4-dihydro isomers **3** decomposed very slowly upon standing at ambient temperature and could also be readily isolated and characterized.

In addition to standard ^1H, ^{13}C, and ^{19}F NMR 1D spectra, the structures of the products **2**, **3**, and **4** (described previously and in the next sections) were confirmed using COSY, DEPT, HMBC, and HSQC NMR experiments. A simple ^1H NMR spectrum does not allow one to distinguish between the isomeric products obtained in the reactions of quinolinium and 3-substituted pyridinium salts. The signals of the proton α of the perfluoroisopropyl group and of one of the vinyl protons have structures of apparent triplets or poorly resolved doublets of doublets and have very similar chemical shifts in the spectra of both 1,2- and 1,4-dihydro isomers. On the other hand, it is possible to assign the ^{13}C NMR signals of the benzylic and of the ring sp^3 carbon atoms (the former with the help of a DEPT

(28) Acylation of dihydropyridines with trifluoroacetic or trichloroacetic anhydride: (a) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1995**, *60*, 4280. (b) Bennasar, M.-L.; Roca, T.; Monerris, M.; Juan, C.; Bosch, J. *Tetrahedron* **2002**, *58*, 8099. (c) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597.

spectrum) and then to determine, unambiguously, the connectivity of the whole molecule based on the 2D $^{1}H-^{13}C$ HSQC and HMBC correlation spectra. An interesting feature of the ^{13}C NMR spectra of compounds **2**, **3**, and **4** is that the doublet of the sp^3 ring carbon atom (the one connected to the perfluoroisopropyl group) of 1,4-dihydropyridines **3** and **4** always appears in a lower chemical shift range (33−44 ppm) than that in the spectra of 1,2-dihydropyridines **2** (57−63 ppm). This observation is in agreement with literature reports,[21c] and it provides a simpler means of discriminating the 1,2- and 1,4-dihydro isomers.

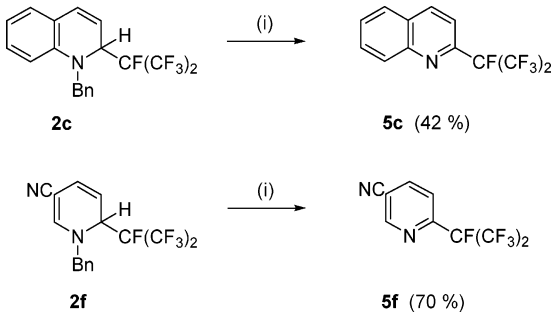
We have not observed any isomerization of 1,2- to 1,4-dihydropyridines during chromatographic purification[27] or after several months of storage.

The success of the addition reaction of carbanions generated from HFP and solid KF performed in a polar solvent like DMF could be explained by the partial solubility of potassium fluoride; fluoride anions present in a low concentration in the organic phase can add to the fluoroalkene leading to the formation of perfluoroisopropyl carbanions, which in turn add to the pyridinium cations giving the final product. On the other hand, the solubility of KF in apolar solvents like CH_2Cl_2 is negligible. A different type of mechanism must be operating for the addition process in such solvents. Perfluorocarbanions are formed on the surface of solid potassium fluoride and, via interfacial ion exchange, form ion pairs with pyridinium cations, which subsequently collapse to the addition products in the organic phase; thus, the pyridinium salt itself acts as a kind of a phase-transfer catalyst in a solid−liquid system. A similar "autocatalytic" effect of such salts in the process of dihydropyridine formation was studied in our laboratory for the case of the addition of trichloromethyl carbanion to the *N*-benzhydryl- and *N*-(2,4,6-trimethylbenzyl)pyridinium salts in a $CHCl_3$/50% NaOH(aq) system.[27] It was also proposed by Lavilla, Bosch, and co-workers for the reaction of *N*-benzylpyridine bromides with 2-methylindole in CH_2Cl_2 or PhMe/50% NaOH.[21c] In the case of DMF, simple solubility of KF (formation of $(CF_3)_2CF^-$ in the bulk of the organic phase) and phase-transfer (PT) catalysis may be of comparable importance. It has been reported that the rate of alkylation of chloromethyl ethers with carbanions generated from perfluoro-2-methyl-2-pentene and KF/DMF increased significantly in the presence of tetrabutylammonium chloride, but it could proceed without a PT catalyst as well.[16]

The addition of perfluorocarbanions to azinium salts proceeds readily when they contain a variety of substituents, but a methyl group in position 2 or 4 hinders the reaction. For example, reaction of 1-benzyl-2-methylpyridinium bromide with perfluoroisopropyl carbanions generated under standard conditions did not give any addition products, although the reaction mixture rapidly turned violet and an exothermic effect was noticed. These observations can probably be ascribed to a facile proton abstraction from the methyl substituent by a highly basic fluoride or perfluorocarbanion and formation of an exomethylene pyridine derivative.[29]

Oxidative Deprotection/Aromatization of 1,2-Dihydroazines. Although the C_3F_7-substituted dihydroazine derivatives described in the preceding sections were, in most cases, stable and could be of interest by themselves, our primary goal was to elaborate a new synthetic way toward perfluoroalkyl-substituted aromatic heterocycles by a process of a formal substitution of hydrogen by a perfluorocarbanion. While the first step of this process, that is, a nucleophilic addition to the aromatic ring, could be performed successfully, we still sought for a method of transforming these adducts into the aromatic and completely stable final products. To this end, we subjected the dihydroazine adducts **2**−**4** to oxidizing conditions. In general, *N*-alkylated dihydroazines are known to give the corresponding *N*-alkyl-substituted salts upon treatment with oxidizing agents.[20] On the other hand, oxidants like DDQ or cerium(IV) ammonium nitrate (CAN) are widely applied for deprotection of benzylic ethers and amines.[30] We therefore attempted a reaction of a *N*-benzyl compound **2c** with 4 equiv of DDQ in CH_2Cl_2, as depicted in Scheme 6. After 24 h, we were pleased to observe formation of aromatized, perfluoroisopropyl-substituted quinoline **5c**[31] isolated in 42% yield. Other widely used oxidizing reagents were not applicable for this transformation; chloranil did not react, trichloroisocyanuric acid (TCCA)[32] gave only poor conversion, whereas $KMnO_4$ led to a complete decomposition of the substrate. The reaction could also be successfully performed in the pyridine series (conversion of **2f** into **5f** in 70% yield).

SCHEME 6. Oxidative Deprotection/Aromatization of *N*-Benzyl-1,2-dihydroazines in the Presence of DDQ[a]



[a] Conditions: (i) 4.0 equiv of DDQ, CH_2Cl_2, 0 °C to rt, 24 h.

Unfortunately, 1,4-dihydro isomers **3** failed to undergo a similar reaction, although they were totally consumed in the presence of DDQ. We suppose that, in this case, the final product is a C_3F_7-substituted azinium salt. However, we were unable to separate it in a pure form from the mixture of products of DDQ decomposition or to liberate a free azine upon treatment with nucleophiles like triphenylphosphine or to transform this salt into a pyridone derivative upon treatment with NaOH. According to the literature data, 1,2-dihydropyridines undergo oxidation much slower than their 1,4-dihydro isomers.[20b,33] We suppose that, in our case, 1,2-dihydropyridines **2** in the presence of DDQ are first deprotected and subsequently oxidized to pyridines, while isomers **3** are quickly oxidized to the corre-

(29) For a similar deprotonation of a 2-alkylquinolinium salt under basic conditions, see: Diaba, F.; Lewis, I.; Grignon-Dubois, M.; Navarre, S. *J. Org. Chem.* **1996**, *61*, 4830.

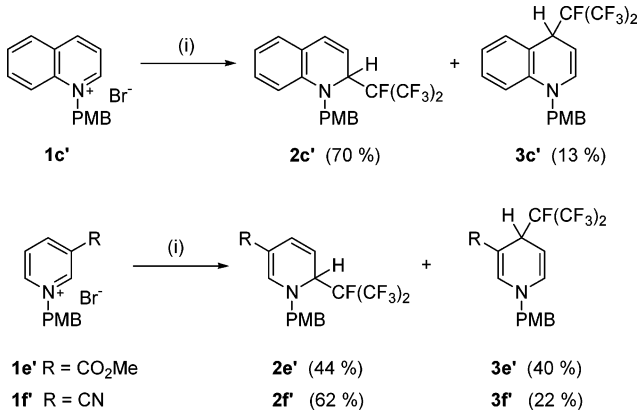
(30) (a) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291. (b) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885. (c) Murakata, C.; Ogawa, T. *Carbohydr. Res.* **1992**, *234*, 75. (d) Bull, S. D.; Davies, S. G.; Fenton, G. A.; Mulvaney, W.; Prasad, R. S.; Smith, A. D. *Chem. Commun.* **2000**, 337. (e) Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3106.

(31) Kobayashi, Y.; Kumadaki, I.; Hanzawa, Y.; Mimura, M. *Chem. Pharm. Bull.* **1975**, *23*, 2044.

(32) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384.

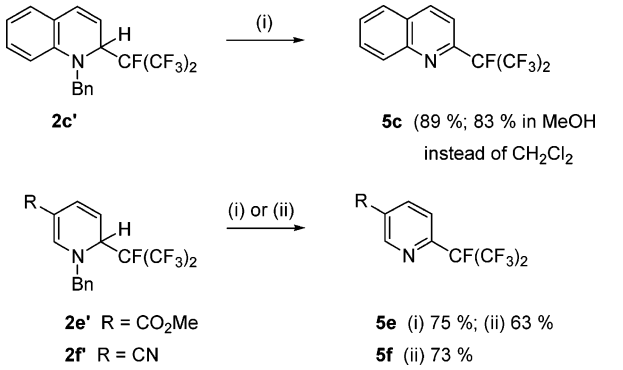
(33) (a) Wallenfels, K.; Gellrich, M. *Justus Liebigs Ann. Chem.* **1959**, *621*, 149. (b) Eisner, U.; Sadeghi, M. M.; Hambright, W. P. *Tetrahedron Lett.* **1978**, *3*, 303. (c) Bodor, N.; Kamiński, J. J. *THEOCHEM* **1988**, *163*, 315.

SCHEME 7. Reactions of *N*-*p*-Methoxybenzylazinium Bromides with Perfluoroisopropyl Carbanions[a]



[a] Conditions: (i) HFP, KF(s), DMF, rt, 2 h.

SCHEME 8. Oxidative Deprotection/Aromatization of *N*-*p*-Methoxybenzyl-1,2-dihydroazines with DDQ[a]



[a] Conditions: (i) 4.0 equiv of DDQ, CH_2Cl_2, 0 °C to rt, 30 min; (ii) 2.2 equiv of DDQ, CH_2Cl_2, 0 °C to rt, 30 min.

sponding salts, which in turn cannot undergo deprotection of the benzylic group.

Compound **4a**, bearing an *N*-benzhydryl substituent, was inert toward DDQ oxidation.

Oxidative cleavage of the N−C bond by DDQ is particularly facile for a *N*-*p*-methoxybenzyl (PMB) substituent.[30c] In order to elaborate a more efficient overall process of nucleophilic substitution of hydrogen in azines by perfluorocarbanions, we prepared compounds **2c′**, **2e′**, and **2f′** in a manner analogous to that of their *N*-benzylated counterparts (Scheme 7). Indeed, deprotection and aromatization of perfluoroisopropyl-substituted *N*-*p*-methoxybenzyl-1,2-dihydroazines **2c′**, **2e′**, and **2f′** by DDQ was complete in good yields within 30 min instead of 24 h as required for **2c** and **2f** (Scheme 8). Similar to the case of *N*-benzyl-1,4-dihydroazines, the compounds **3c′**, **3e′**, and **3f′** could not be transformed into the 4-perfluoroisopropylazines upon the action of DDQ.

The facile deprotection−aromatization of 1,2-dihydroazines **2** upon the action of DDQ is somewhat unexpected in the view of the report of Lau and co-workers,[34] who failed to affect a similar transformation with 1-*p*-methoxybenzyl-2-phenyl-1,2-dihydroquinoline; they observed no reaction with DDQ even after 24 h under forcing conditions.

(34) Wiebe, J. M.; Caillé, A. S.; Trimble, L.; Lau, C. K. *Tetrahedron* **1996**, *52*, 11705.

A serious drawback of the DDQ oxidation of the perfluoroisopropyl-substituted dihydroazines is problems with separation of the resulting perfluoroisopropyl azaarenes from the products of DDQ reduction and decomposition. Compounds **5** are not sufficiently basic to be extracted from the organic phase with concentrated aqueous HCl, whereas chromatographic purification is also ineffective. These problems are completely eliminated when CAN is used as an oxidizing agent. After some experimentation, we found that slow addition of an aqueous solution of 2.2 equiv of CAN to a solution of 2-perfluoroisopropyl-1,2-dihydropyridine **2** in MeOH at room temperature results in a clean and almost instantaneous formation of **5**. For example, CAN oxidation of dihydropyridine **2e′** gave **5e** in the isolated yield of 81%. Simple extraction of the product with Et_2O, evaporation, and chromatographic purification on silica gel using hexanes or hexanes−Et_2O as the eluent allows one to obtain pure perfluoroisopropyl azaarenes. In some cases, chromatography on neutral aluminum oxide was necessary to remove the side products of oxidation, that is, *p*-methoxybenzyl aldehyde and alcohol. An additional attractive feature of CAN is its lower price and better stability than DDQ.

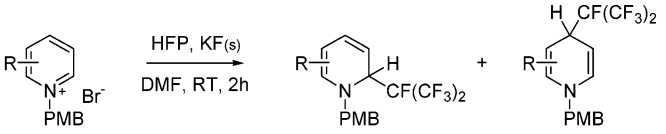
In the course of the experiments described so far, we established that the optimal way of preparation of perfluoroisopropyl-substituted azines from the corresponding azinium salts is to use a *N*-PMB salt as a substrate for the perfluoroisopropyl carbanion addition and CAN as an oxidant in the subsequent step of deprotection/aromatization. Along with this scheme, we prepared a series of C_3F_7-containing azines, as described in the following sections.

Reactions of *N*-*p*-Methoxybenzyl Salts with Perfluoroisopropyl Carbanions. Addition of perfluoroisopropyl carbanions to the *N*-PMB pyridinium and quinolinium salts **1c′**−**1m′** proceeded with a comparable efficiency as with their *N*-benzylated counterparts, as summarized in Scheme 7 and Table 1. The yields are good to very good, and regioselectivity is usually high, in most cases in favor of 1,2-dihydroazine. Only in the case of the 3-benzoylpyridinium salt **1g′** (entry 5) was it impossible to separate the resulting 1,2- and 1,4-dihydropyridines by column chromatography. Formation of compounds **2g′** and **3g′** in a very high combined yield is particularly notable considering that the carbonyl group is a widely used electrophile in reactions with fluorinated carbanions, especially for nucleophilic trifluoromethylation. In order to test the scalability of the reaction of azinium salts with HFP and KF(s), we also performed a reaction with 10.0 mmol of the salt **1e′** (instead of the usual 0.95 mmol) and obtained compounds **2e′** and **3e′** in the combined yield of 92% (1:1 from ^{1}H NMR).

N-PMB salts are somewhat easier to obtain, owing to a greater reactivity of PMBBr than BnBr. In fact, we were able to perform the salt preparation *in situ* by mixing the starting heterocycle and PMBBr in DMF and, after the appropriate time at room temperature, by reacting it with KF and HFP, thus effecting a one-pot transformation of an azine into a perfluoroalkylated dihydroazine (Table 1, entries 1, 3, 4, and 6−10).

Pyridines containing electron-withdrawing substituents in position 2 (like **6** and **7**) are weak nucleophiles and do not react with PMBBr even at high temperatures. Fortunately, this problem could be overcome by *in situ* alkylation in the presence of a stoichiometric amount of silver tetrafluoroborate in MeCN (Scheme 9). The resulting pyridinium tetrafluoroborates were subjected to the reaction with HFP and KF(s) without isolation and underwent addition of perfluoroisopropyl carbanions in

TABLE 1. Reactions of *N*-*p*-Methoxybenzylazinium Bromides with $(CF_3)_2CF^-$ Carbanions[a]



1 2 3

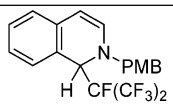
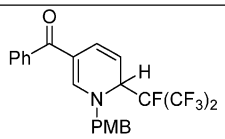
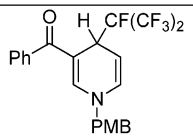
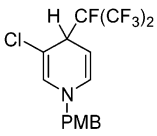
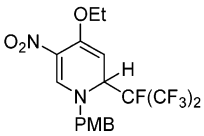
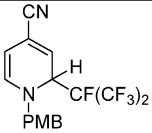
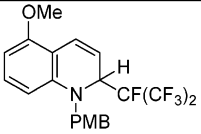
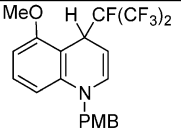
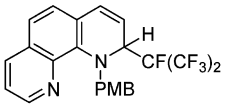
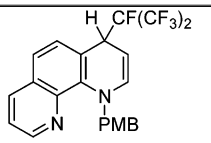
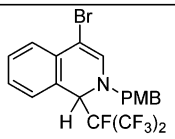
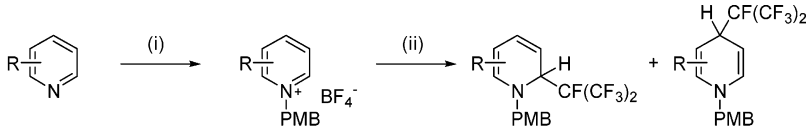
	substrate (R)	product(s) and yield(s)		yield(s) and time[b] for one-pot procedure
1	**1c'** quinoline	see Scheme 7.		**2c'** (85 %) **3c'** (5 %) 48 h[c]
2	**1d'** isoquinoline	 **2d'** (36 %)		
3	**1e'** 3-CO_2Me	see Scheme 7.		**2e'** (39 %) **3e'** (33 %) 24 h
4	**1f'** 3-CN	see Scheme 7.		**2f'** (67 %) **3f'** (22 %) 20 h
5	**1g'** 3-COPh	 **2g'** (81 %)	 **3g'** (18 %)	
6	**1h'** 3-Cl	 **3h'** (-)[d]		74 % 24 h
7	**1i'** 3-NO_2-4-OEt	 **2i'** (74 %)		36 % 30 min
8	**1j'** 4-CN	 **2j'** (50 %)		53 % 20 h
9	**1k'** 5-methoxy-quinoline	 **2k'** (66 %)	 **3k'** (16 %)	**2k'** (59 %) **3k'** (10 %) 24 h

Table 1 (Continued)

	substrate (R)	product(s) and yield(s)		yield(s) and time[b] for one-pot procedure
10	**1l'** phenanthroline	 **2l'** (79 %)	 **3l'** (13 %)	**2l'** (87 %) **3l'** (10 %) 14 h
11	**1m'** 4-bromo-isoquinoline	 **2m'** (87 %)		

[a] Conditions: 5.0 equiv of KF(s), ca. 4 equiv of HFP, DMF, rt. [b] Time needed for salt formation in DMF at rt, followed by TLC. [c] Azinium chloride was used instead of bromide. [d] Reaction of this salt was performed only according to a "one-pot" procedure.

SCHEME 9. Reaction of Pyridinium Salts Formed from Weakly Nucleophilic Pyridines 6 and 7 via Alkylation Promoted by Silver Tetrafluoroborate[a]



6 R = 2-CO_2Me — **2n'** (37 %) — **3n'** (-)

7 R = 2-CO_2Me, 5-CO_2Me — **2o'** (32 %) — **3o'** (10 %)

[a] Conditions: (i) PMBBr, $AgBF_4$, MeCN, rt; (ii) 5.0 equiv of KF(s), HFP, MeCN, rt, 2 h.

moderate overall yields due to incomplete conversion of the starting pyridines.

Regioselectivity of Perfluorocarbanion Addition. On the basis of the results summarized in Schemes 3, 4, 5, 7, and 9 and Table 1, it is possible to draw some conclusions on the regioselectivity of perfluoroisopropyl carbanions addition to azinium salts. Due to the special character of these carbanions, it is difficult to compare the regioselectivity of the reaction with other nucleophilic additions to *N*-alkylazinium salts described in the literature. In general, soft nucleophiles like sodium or potassium enolates, bis(*O*-trialkylsilyl)ketene acetals,[35] highly nucleophilic arenes,[36] alkyl- and arylcopper[28b,37] and organotitanium[21a] reagents, or sulfur nucleophiles attack predominantly at the 4 position, while hard nucleophiles like organolithium and organomagnesium[28b] compounds, hydroxide, alkoxide, and cyanide anions, ammonia, and secondary amines add preferentially at the position adjacent to the nitrogen atom.[20,38,39] In many cases (most heteroatom nucleophiles and highly stabilized carbon nucleophiles), the addition is reversible, and the kinetic product 1,2-dihydropyridine rearranges, at least at higher temperatures or after a prolonged period of time, to the more stable 1,4-dihydropyridine, which is the observed or predominant product of the reaction. The example of a trichloromethyl carbanion is perhaps the most relevant for the present discussion; it undergoes a reversible addition almost exclusively to the C-2 atom of the pyridinium ring.[20b,27,40] In our case, preferential formation of 1,2-dihydroazines **2** indicates that the $(CF_3)_2CF^-$ carbanion belongs to the hard nucleophiles like trifluoromethyl[6] or difluoro(phenylsulfonyl)methyl carbanions.[41] Despite a significant stabilizing effect of the two CF_3 groups, the process is irreversible, as we have not observed any interconversion between 1,2- and 1,4-dihydropyridines even after several months of storage. Moreover, pure compound **2e′** did not isomerize to **3e′** when subjected to standard reaction conditions (KF(s), HFP, DMF, rt).

The only examples of opposite regioselectivity are reactions in which 1,4-dihydropyridines **3a**, **3b**, and **3h′** were formed. The first of these results can be explained by steric factors; due to bulkiness of the perfluoroisopropyl carbanion, it does not attack the position vicinal to the large *N*-benzhydryl substituent.[28b] The two other cases are less obvious, but they both involve pyridinium salts with an electron-donating or weakly accepting substituent at C-3. Formation of their respective 1,4-dihydro

(35) Rudler, H.; Denise, B.; Parlier, A.; Daran, J.-C. *Chem. Commun.* **2002**, 940.
(36) Volochnyuk, D. M.; Kostyuk, A. N.; Pinchuk, A. M.; Tolmachev, A. A. *Tetrahedron Lett.* **2003**, *44*, 391.
(37) (a) Bennasar, M.-L.; Juan, C.; Bosch, J. *Tetrahedron Lett.* **1998**, *39*, 9275. (b) Bennasar, M.-L.; Juan, C.; Bosch, J. *Tetrahedron Lett.* **2001**, *42*, 585.
(38) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156.
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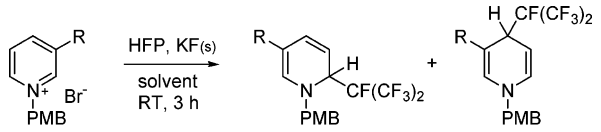
TABLE 2. Regioselectivity of the Reaction of 3-Methoxycarbonyl- (1e′) and 3-Cyanopyridinium (1f′) Salts with Perfluorocarbanions in Various Solvents



1 2 3

	substrate	solvent	2:3[a]	yield
1	**1e′**	toluene	(>20:1)[b]	5%
2	(3-CO_2Me)	CH_2Cl_2	31.4:1	10%
3		THF	20.6:1	11%
4		DME	12.6:1	22%
5		DME (24h)	11.0 1[c]	72%
6		MeCN	5.2:1	34%
7		DMF	1.1:1[c]	84%
8	**1f′** (3-CN)	DME (24h)	6.9:1	56%
9		DMF	2.8:1[c]	83%

[a] Ratio of isomers was established using ^{1}H and ^{19}F NMR spectroscopy. [b] No 1,4-isomer **3e′** was detected. [c] Ratio of isomers from chromatographic separation.

adducts is in agreement with a literature report about addition of a lithium enolate of 2-acetylindole to 3-substituted *N*-methylpyridinium salts with subsequent trapping of the resulting dihydropyridines by acylation with trichloroacetic anhydride (TCAA).[28a] While 3-COMe-, 3-CO_2Me-, 3-CH=CHCO$_2$Me-, 3-CN-, and 3-CONEt$_2$-substituted salts all afforded mainly 1,2-dihydropyridines, the only product detected after the reaction of 3-ethylpyridinium salt and treatment with TCAA was a trichloroacylated 1,4-dihydropyridine.

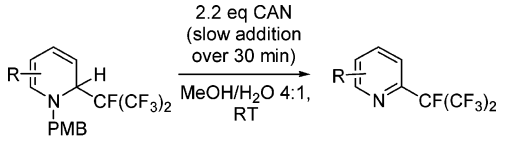
Exclusive formation of only one of the two possible regioisomeric 1,6-dihydropyridines in the reactions of unsymmetrically substituted 3-CN, 3-CO_2Me, and 3-COPh pyridinium salts is probably for steric reasons; the bulky perfluoroisopropyl group cannot enter the most hindered position between *N*-benzyl and the substituent already present in the ring.

From the preceding discussion, it follows that the regioselectivity of addition of a hard $(CF_3)_2CF^-$ carbanion is determined by the positive charge distribution in the azinium ring, the highest partial charge being localized on the two carbon atoms adjacent to nitrogen. It should then depend on the polarity of the reaction medium. Indeed, it was clearly demonstrated for the case of substrates **1e′** and **1f′** (Table 2). In solvents of low polarity (toluene, CH_2Cl_2, or THF), highly regioselective formation of the 1,2-isomer **2e′** was observed, but the overall yield was very poor due to low solubility of the substrates and a low reaction rate. From the synthetic point of view, it was interesting to find that using 1,2-dimethoxyethane (DME), a solvent of a slightly higher polarity and capable of dissolving some amount of potassium fluoride, allowed us to obtain **2e′** in a much better yield without a significant loss of regioselectivity. Since HFP oligomerization in DME in the presence of KF is much slower than that in DMF, it was possible to extend the reaction time to 24 h to obtain 2-perfluoroisopropyl-1,2-dihydropyridines **2e′** and **2f′** both selectively and in good yields.

In the case of quinoline derivatives, the influence of solvent on regioselectivity was insignificant. For example, for the reactions of **1l′** in toluene (24 h), DME (24 h), and DMF (3 h), the ratio of regioisomers **2l′** and **3l′** was, respectively, 8.0:1, 4.1:1, and 6.1:1 with total yields of 10, 55, and 92%.

The observed influence of reaction medium polarity on the regioselectivity of nucleophilic addition to pyridinium salts is somewhat in contradiction to the results reported by Lavilla, Bosch, and co-workers who investigated addition reactions of 2-methylindole anions to similar salts; in toluene, they always observed the highest preference for 1,4-dihydropyridine formation.[21c] This difference may probably be ascribed to a different nature of the nucleophiles.

TABLE 3. Preparation of Perfluoroisopropyl-Substituted Azines from 1,2-Dihydroazines Using CAN as the Oxidant



2 5

	substrate (R)	product, yield
1	**2e′** (5-CO_2Me)	**5e** (81%)
2	**2f′** (5-CN)	**5f** (99%)
3	**2g′** (5-COPh)	**5 g** (86%)
4	**2i′** (4-OEt-5-NO_2)	**5i** (87%)
5	**2j′** (4-CN)	**5j** (99%)
6	**2k′** (5-methoxy-1,2-dihydroquinoline)	**5k** (98%)
7	**2l′** (1,2-dihydrophenanthroline)	**5l** (52%; 37% recovered **2l′**)
8	**2o′** (3-CO_2Me-6-CO_2Me)	**5o** (68%; 24% recovered **2o′**)

Oxidative Deprotection/Aromatization of *N*-PMB-1,2-Dihydroazines with CAN. This reaction was performed using the previously described optimal conditions, and it proceeded in high yields to give a variety of substituted azines **5** containing a perfluoroisopropyl group in position 2 (in some cases, almost quantitatively, Table 3). Reaction of 1,2-dihydropyridine **2n′** proceeded reluctantly and afforded a complicated mixture of products, one of which was the expected 2-methoxycarbonyl-6-heptafluoroisopropylpyridine (identified by ^{1}H NMR analysis of the mixture after workup and evaporation). Unfortunately, on treatment with either CAN or DDQ, 1,2-dihydroisoquinoline derivatives **2d′** or **2m′** decomposed into complex mixtures of products instead of giving the expected 1-perfluoroisopropyl-isoquinolines.

Summary and Conclusions

Substituted *N*-alkylazinium salts were shown to efficiently add perfluoroisopropyl carbanions generated *in situ* from hexafluoropropene and solid potassium fluoride, leading to perfluoroalkyl-substituted dihydro derivatives that, in turn, are readily oxidized to perfluoroisopropyl azaarenes. The whole process can be viewed as an example of a nucleophilic aromatic substitution of hydrogen. Since it utilizes readily available substrates and proceeds under mild conditions, it may be a novel, valuable method of direct introduction of perfluoroalkyl groups into heterocyclic rings, either simple or already functionalized with other substituents; other fluoroolefins may probably be employed instead of HFP. For example, preliminary experiments show that chlorotrifluoroethene and 2*H*-pentafluoropropene enter similar reactions.

Considering the central role of dihydropyridines and dihydroquinolines in the synthesis of heterocyclic compounds,[20,21,26] our contribution may open new, versatile synthetic pathways, leading to previously unknown fluorinated heterocyclic systems.

Experimental Section

General Procedure for Reactions of *N*-Alkylazinium Salts 1 with HFP and KF(s). Preparation of Dihydroazines 2 and 3.

HFP (ca. 0.6 g, 4 mmol) was condensed in a glass pressure tube (ca. 3.5 mL volume) at −75 °C under an argon atmosphere. DMF (2.75 mL; or other solvent, see text), azinium salt (0.95 mmol), and spray-dried KF(s) (276 mg, 4.75 mmol) were introduced, and the pressure tube was closed with a teflon valve. The contents of the tube were stirred vigorously at room temperature for 3 h. After opening of the tube, the reaction mixture was poured into water (10 mL), and the products were extracted with CH_2Cl_2 (3 × 5 mL). Combined organic layers were washed with water (5 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated. The products were purified by column chromatography on silica gel using 10:1 or 5:1 mixtures of hexanes/AcOEt as the eluent (when two isomeric products were formed, mixtures of hexanes and Et_2O of similar composition were sometimes more effective to separate them, see below).

Preparation of Trifluoroacetylated 1,4-Dihydropyridines 4a and 4b. These reactions were performed as described in the previous paragraph, but after the reaction with HFP and KF (after the time specified in the text), the contents of the pressure tube was cooled to 0 °C, and *i*-Pr_2NEt (129 mg, 174 μL, 1.00 mmol) was added. Trifluoroacetic anhydride (210 mg, 139 μL, 1.00 mmol) was then added dropwise with vigorous stirring, and the reaction mixture was allowed to warm to room temperature over about 30 min. Isolation and purification of products was then performed, analogous to the general procedure described above.

1-Benzhydryl-4-heptafluoroisopropyl-1,4-dihydropyridine (3a). Yellow oil, becomes dark red after a few hours at rt: ^{1}H NMR (200 MHz) δ 4.22−4.38 (1H, m, CHCF), 4.45 (2H, dd, $^3J_{HH}$ = 7.9, 3.6 Hz, NCH=C*H*), 6.12 (2H, d, $^3J_{HH}$ = 8.2 Hz, NC*H*=CH), 7.19−7.30 (4H, m, H_{arom}), 7.30−7.50 (6H, m, H_{arom}); ^{13}C NMR (50 MHz) δ 37.5 (d, $^2J_{CF}$ = 22.0 Hz), 69.3, ok. 89 (m), 91.9 (d, $^3J_{CF}$ = 7.7 Hz), 121.2 (qd, $^1J_{CF}$ = 288.6 Hz, $^2J_{CF}$ = 27.5 Hz), 127.8, 128.4, 128.6, 133.0, 139.6.

1-Benzhydryl-4-heptafluoroisopropyl-3-trifluoroacetyl-1,4-dihydropyridine (4a). Pale yellow solid: mp 87−88 °C; IR (film, ν_{max}/cm^{-1}) 3093, 3068, 3035, 2923, 1667, 1573, 1497, 1454, 1430, 1386, 1291, 1261, 1218, 1129, 993, 975, 924, 876, 789, 750, 724, 700, 672, 607; ^{1}H NMR (400 MHz) δ 4.82 (1H, t, ^3J = 5.5 Hz, CHCF), 5.06 (1H, t, $^3J_{HH}$ = 6.9 Hz, NCH=C*H*), 5.94 (1H, s, $NCHPh_2$), 6.31 (1H, d, $^3J_{HH}$ = 7.8 Hz, NC*H*=CH), 7.13−7.19 (4H, m, Ph), 7.36−7.45 (6H, m, Ph), 7.46 (1H, s, NCH=CCOCF_3); ^{13}C NMR (100 MHz) δ 33.5 (d, $^2J_{CF}$ = 21.5 Hz), 71.2, 90.5 (m), 98.0, 101.5, 117.0 (q, $^1J_{CF}$ = 291.4 Hz), 121.0 (dm, $^1J_{CF}$ = 288.0 Hz), 128.2, 128.4, 128.9, 128.9, 129.2, 129.3, 131.6, 136.8, 137.0, 146.6 (d, $^4J_{CF}$ = 5.1 Hz), 177.5 (q, $^2J_{CF}$ = 33.7 Hz); ^{19}F NMR (376 MHz) δ −183.27 (1F, m, C*F*(CF_3)$_2$), −75.62 (3F, m, $^3J_{FF}$ = 8.3 Hz, CF-(C*F*$_3$)$_2$), −73.24 (3F, m, $^3J_{FF}$ = 7.6 Hz, CF(C*F*$_3$)$_2$), −69.7 (3F, *s*, COC*F*$_3$); MS (EI 70 eV, *m*/*z*, %) 511 (M^+, <1), 342 (10), 167 (100), 165 (17), 152 (9); HRMS (EI) calcd for $C_{23}H_{15}NOF_{10}$ (M^+), 511.0994; found, 511.0996. Anal. Calcd for $C_{23}H_{15}NOF_{10}$: C, 54.02; H, 2.96; N, 2.74; F, 37.15. Found: C, 54.05; H, 2.84; N, 2.73; F, 36.51.

1-Benzyl-4-heptafluoroisopropyl-3-methyl-1,4-dihydropyridine (3b). Yellow oil, becomes dark red after a few days at rt: ^{1}H NMR (200 MHz) δ 1.73 (3H, dd, $^4J_{HH}$ = 3.0, 1.4 Hz, Me), 4.02 (1H, m, CHCF), 4.29 (2H, s, NCH_2), 4.33 (1H, m, NCH=C*H*), 5.97 (1H, t, $^4J_{HH}$ = 1.2 Hz, NC*H*=CMe), 6.13 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.0 Hz, NC*H*=CH), 7.10−7.26 (2H, m, Ph), 7.26−7.48 (3H, m, Ph); ^{13}C NMR (50 MHz) δ 21.0 (d, $^4J_{CF}$ = 5.5 Hz), 42.5 (d, $^2J_{CF}$ = 20.9 Hz), 57.1, 89.5 (d, $^3J_{CF}$ = 9.5 Hz), 101.5, 127.2, 127.6, 128.7, 130.3, 134.0, 137.9.

1-Benzyl-4-heptafluoroisopropyl-3-methyl-5-trifluoroacetyl-1,4-dihydropyridine (4b). Colorless oil, solidified after several months at −15 °C: mp 39−40 °C; IR (film, ν_{max}/cm^{-1}) 3071, 3036, 2930, 1667, 1575, 1439, 1299, 1225, 1195, 1146, 1004, 735, 718, 676; ^{1}H NMR (400 MHz) δ 1.84 (3H, s, Me), 4.62 (2H, AB, $^2J_{HH}$ = 15.0 Hz, NCH_2), 4.69 (1H, d, $^3J_{HF}$ = 3.5 Hz, CHCF), 6.14 (1H, d, $^4J_{HH}$ = 0.9 Hz, NC*H*=CMe), 7.19−7.25 (2H, m, Ph), 7.36−7.45 (3H, m, Ph), 7.60 (1H, d, $^4J_{HH}$ = 1.1 Hz, NCH=CCOCF_3); ^{13}C NMR (100 MHz) δ 20.5, 37.6 (d, $^2J_{CF}$ = 21.6 Hz), 59.0, 91.7 (dm, $^1J_{CF}$ = 206.9 Hz, $^2J_{CF}$ = 31.0 Hz), 96.6 (d, $^3J_{CF}$ = 7.7 Hz), 111.8 (d, $^3J_{CF}$ = 5.2 Hz), 117.2 (q, $^1J_{CF}$ = 291.4 Hz), 120.7 (qd, $^1J_{CF}$ = 290.5 Hz, $^2J_{CF}$ = 28.5 Hz), 120.8 (qd, $^1J_{CF}$ = 287.9 Hz, $^2J_{CF}$ = 28.5 Hz), 127.7, 127.8, 128.9, 129.3, 134.1, 145.8 (q, $^4J_{CF}$ = 5.1 Hz), 177.1 (q, $^2J_{CF}$ = 33.6 Hz); ^{19}F NMR (376 MHz) δ −181.77 (1F, m, C*F*(CF_3)$_2$), −74.96 (3F, m, CF(C*F*$_3$)$_2$), −74.84 (3F, m, CF(C*F*$_3$)$_2$), −69.4 (3F, s, COCF_3); MS (EI 70 eV, *m*/*z*, %) 449 (M^+, <1), 380 (4), 280 (100); HRMS (EI) calcd for $C_{18}H_{13}NOF_{10}$ (M^+), 449.0838; found, 449.0832. Anal. Calcd for $C_{18}H_{13}NOF_{10}$: C, 48.12; H, 2.92; N, 3.12; F, 42.28. Found: C, 48.17; H, 2.98; N, 3.01; F, 41.52.

1-Benzyl-2-heptafluoroisopropyl-1,2-dihydroquinoline (2c). Pale yellow oil: IR (film, ν_{max}/cm^{-1}) 3066, 3033, 2884, 1650, 1601, 1495, 1453, 1295, 1254, 1224, 1155, 1109, 974, 944, 791, 748, 707, 525; ^{1}H NMR (400 MHz) δ 4.46 (1H, d, $^2J_{HH}$ = 16.3 Hz, NCH_2), 4.98 (1H, d, $^2J_{HH}$ = 16.2 Hz, NCH_2), 5.09 (1H, ddm, $^3J_{HF}$ = 10.8 Hz, $^3J_{HH}$ = 6.0 Hz, CHCF), 5.57 (1H, ddm, $^3J_{HH}$ = 9.6, 6.0 Hz, C*H*CHCF), 6.67 (1H, d, $^3J_{HH}$ = 9.2 Hz, C*H*=HCHCF), 6.65−6.73 (2H, m, H_{arom}), 6.99 (1H, dd, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.6 Hz, H_{arom}), 7.06 (1H, ddd, $^3J_{HH}$ = 9.0, 7.5 Hz, $^4J_{HH}$ = 1.6 Hz, H_{arom}), 7.18−7.24 (3H, m, H_{arom}), 7.25−7.30 (2H, m, H_{arom}); ^{13}C NMR (100 MHz) δ 55.9 (d, $^4J_{CF}$ = 4.3 Hz), 60.1 (d, $^2J_{CF}$ = 19.8 Hz), 92.1 (dm, $^1J_{CF}$ = 207.8 Hz, $^2J_{CF}$ = 30.2 Hz), 114.2 (d, $^3J_{CF}$ = 6.9 Hz), 114.4, 118.5, 120.7 (qd, $^1J_{CF}$ = 287.5 Hz, $^2J_{CF}$ = 28.0 Hz), 120.8 (qd, $^1J_{CF}$ = 287.5 Hz, $^2J_{CF}$ = 27.2 Hz), 122.1, 127.2, 127.4, 127.4, 128.7, 129.6, 130.9, 137.0, 142.8; ^{19}F NMR (376 MHz) δ −179.49 (1F, m, C*F*(CF_3)$_2$), −74.15 (3F, m, $^3J_{FF}$ = 7.9 Hz, CF-(C*F*$_3$)$_2$), −72.84 (3F, m, $^3J_{FF}$ = 8.6 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 389 (M^+, 2), 220 (100), 91 (41); HRMS (EI) calcd for $C_{19}H_{14}NF_7$ (M^+), 389.1014; found, 389.1007. Anal. Calcd for $C_{19}H_{14}NF_7$: C, 58.62; H, 3.62; N, 3.60; F, 34.16. Found: C, 58.29; H, 3.77; N, 3.53; F, 34.14.

1-Benzyl-4-heptafluoroisopropyl-1,4-dihydroquinoline (3c). Yellow oil, decomposes after a few days at rt: IR (film, ν_{max}/cm^{-1}) 3038, 2922, 1672, 1601, 1492, 1220, 974, 756, 740, 716, 706; MS (EI 70 eV, *m*/*z*, %) 389 (M^+, 2), 220 (43), 91 (100); HRMS (EI) calcd for $C_{19}H_{14}NF_7$ (M^+), 389.1014; found, 389.1026. Anal. Calcd for $C_{19}H_{14}NF_7$: C, 58.62; H, 3.62; N, 3.60; F, 34.16. Found: C, 58.84; H, 3.69; N, 3.53; F, 34.02.

2-Benzhydryl-1-heptafluoroisopropyl-1,2-dihydroisoquinoline (2d). White solid: mp 99−100 °C; IR (KBr, ν_{max}/cm^{-1}) 3069, 3036, 1624, 1492, 1284, 1234, 1107, 982, 771, 732, 697; ^{1}H NMR (400 MHz) δ 5.57 (1H, d, $^3J_{HH}$ = 7.4 Hz, NCH=C*H*), 5.61 (1H, d, $^3J_{HF}$ = 7.0 Hz, CHCF), 5.81 (1H, s, $CHPh_2$), 5.99 (1H, dd, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.2 Hz, NC*H*=CH), 6.87 (1H, d, $^3J_{HH}$ = 7.7 Hz, H_{arom}), 6.98−7.11 (4H, m, H_{arom}), 7.15−7.25 (6H, m, H_{arom}), 7.26−7.36 (3H, m, H_{arom}); ^{13}C NMR (100 MHz) δ 62.6 (d, $^2J_{CF}$ = 20.7 Hz), 71.7 (d, $^4J_{CF}$ = 2.6 Hz), 90.7 (dm, $^1J_{CF}$ = 204.3 Hz, $^2J_{CF}$ = 30.2 Hz), 102.3, 118.7 (d, $^3J_{CF}$ = 4.3 Hz), 120.5 (qd, $^1J_{CF}$ = 288.0 Hz, $^2J_{CF}$ = 27.6 Hz), 123.4, 125.4, 127.4, 127.8, 128.1, 128.6, 128.6, 129.0, 130.1, 131.7, 134.3, 138.4, 140.6; ^{19}F NMR δ (ppm) −179.31 (1F, m, C*F*(CF_3)$_2$), −71.72 (3F, m, $^3J_{FF}$ = 8.2 Hz, CF(C*F*$_3$)$_2$), −71.57 (3F, m, $^3J_{FF}$ = 8.2 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 465 (M^+, 2), 296 (43), 167 (100), 152 (12); HRMS (EI) calcd for $C_{25}H_{18}NF_7$ (M^+), 465.1328; found, 465.1338. Anal. Calcd for $C_{25}H_{18}NF_7$: C, 64.52; H, 3.90; N, 3.01; F, 28.57. Found: C, 64.57; H, 3.66; N, 2.80; F, 28.60.

1-Benzyl-2-heptafluoroisopropyl-5-methoxycarbonyl-1,2-dihydropyridine (2e). Separated from **3e** by chromatography using 10:1 hexanes/Et_2O as the eluent; pale yellow solid: mp 60−61 °C; IR (KBr, ν_{max}/cm^{-1}) 2953, 1702, 1646, 1578, 1442, 1387, 1320, 1288, 1257, 1219, 1185, 1157, 1112, 991, 955, 745, 705; ^{1}H NMR (400 MHz) δ 3.73 (3H, s, OCH_3), 4.50 (1H, AB, $^2J_{HH}$ = 15.6 Hz, NCH_2), 4.93 (1H, m, C*H*CHCF), 5.06 (1H, m, CHCF), 6.73 (1H, dm, $^3J_{HH}$ = 9.9 Hz, C*H*=CHCHCF), 7.21−7.26 (2H, m, Ph), 7.32−7.42 (3H, m, Ph), 7.47 (1H, d, $^4J_{HH}$ = 0.9 Hz, NC*H*=CCO_2Me); ^{13}C NMR (100 MHz) δ 51.1, 58.7 (d, $^2J_{CF}$ = 18.9 Hz), 60.5 (d, $^4J_{CF}$ = 6.0 Hz), 91.7 (dm,^{1} J_{CF} = 208.6 Hz, $^2J_{CF}$ = 29.4 Hz), 101.5,

103.7 (dd, $^3J_{CF}$ = 7.7 Hz, $^4J_{CF}$ = 1.7 Hz), 120.4 (qd, $^1J_{CF}$ = 287.1 Hz, $^2J_{CF}$ = 25.9 Hz), 120.6 (qd, $^1J_{CF}$ = 287.1 Hz, $^2J_{CF}$ = 27.6 Hz), 127.3, 127.4, 128.5, 129.2, 135.1, 146.8, 166.1; ^{19}F NMR (376 MHz) δ −177.59 (1F, m, C*F*(CF_3)$_2$), −73.76 (3F, m, CF(C*F*$_3$)$_2$), −72.63 (3F, m, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 397 (M^+, <1), 366 (5), 228 (41), 91 (100); HRMS (ESI, MeOH) calcd for $C_{17}H_{14}NO_2F_7Na$ (M + Na^+), 420.0805; found, 420.0822. Anal. Calcd for $C_{17}H_{14}NO_2F_7$: C, 51.39; H, 3.55; N, 3.53; F, 33.47. Found: C, 51.23; H, 3.56; N, 3.62; F, 33.28.

1-Benzyl-4-heptafluoroisopropyl-3-methoxycarbonyl-1,4-dihydropyridine (3e). Separated from **2e** by chromatography using 10:1 hexanes/Et_2O as the eluent; pale yellow oil: IR (film, ν_{max}/cm^{-1}) 3069, 3034, 2953, 1704, 1593, 1416, 1304, 1255, 1218, 1172, 1088, 977, 721; ^{1}H NMR (400 MHz) δ 3.73 (3H, s, OCH_3), 4.48 (2H, s, NCH_2), 4.71 (1H, tm, ^3J = 5.3 Hz, CHCF), 4.79 (1H, m, NCH=C*H*), 6.16 (1H, d, $^3J_{HH}$ = 7.8 Hz, NC*H*=CH), 7.18−7.22 (2H, m, Ph), 7.30−7.41 (3H, m, Ph), 7.47 (1H, d, $^4J_{HH}$ = 1.1 Hz, NC*H*=CCO_2Me); ^{13}C NMR (100 MHz) δ 35.2 (d, $^2J_{CF}$ = 21.6 Hz), 51.3, 58.0, 91.2 (dm, $^1J_{CF}$ = 207.8 Hz, $^2J_{CF}$ = 28.4 Hz), 93.7 (d, $^3J_{CF}$ = 5.2 Hz), 97.7 (d, $^3J_{CF}$ = 6.0 Hz), 120.9 (qd, $^1J_{CF}$ = 288.8 Hz, $^2J_{CF}$ = 28.4 Hz), 121.3 (qd, $^1J_{CF}$ = 288.0 Hz, $^2J_{CF}$ = 27.6 Hz), 127.3, 128.3, 129.0, 132.4, 135.9, 143.1, 168.2; ^{19}F NMR (376 MHz) δ −183.99 (1F, m, ^3J = 7.3 Hz, C*F*(CF_3)$_2$), −75.66 (3F, m, $^3J_{FF}$ = 7.3 Hz, CF(C*F*$_3$)$_2$), −73.14 (3F, m, $^3J_{FF}$ = 8.1 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 366 (4), 228 (42), 91 (100); HRMS (ESI, MeOH) calcd for $C_{17}H_{15}NO_2F_7$ (M + H^+), 398.0986; found, 398.0986. Anal. Calcd for $C_{17}H_{14}NO_2F_7$: C, 51.39; H, 3.55; N, 3.53; F, 33.47. Found: C, 51.20; H, 3.49; N, 3.63; F, 33.41.

1-Benzyl-3-cyano-6-heptafluoroisopropyl-1,6-dihydropyridine (2f). Pale yellow oil: IR (film, ν_{max}/cm^{-1}) 3066, 3033, 2210, 1646, 1577, 1385, 1292, 1258, 1226, 1111, 958, 750; ^{1}H NMR (400 MHz) δ 4.50 (2H, s, NCH_2), 4.98 (1H, m, C*H*CHCF), 5.08 (1H, m, CHCF), 6.24 (1H, d, $^3J_{HH}$ = 9.6 Hz, C*H*=CHCHCF), 6.98 (1H, m, NCH=CCN), 7.20−7.25 (2H, m, Ph), 7.35−7.44 (3H, m, Ph); ^{13}C NMR (100 MHz) δ 58.2 (d, $^2J_{CF}$ = 19.8 Hz), 60.7 (d, $^4J_{CF}$ = 6.0 Hz), 82.3, 91.5 (dm, $^1J_{CF}$ = 208.6 Hz, $^2J_{CF}$ = 29.3 Hz), 105.4 (d, $^3J_{CF}$= 6.0 Hz), 119.1, 120.2 (qd, $^1J_{CF}$ = 287.9 Hz, $^2J_{CF}$ = 25.0 Hz), 120.5 (qd, $^1J_{CF}$ = 287.1 Hz, $^2J_{CF}$ = 27.6 Hz), 126.6, 127.7, 128.9, 129.4, 134.3, 147.8; ^{19}F NMR (376 MHz) δ −178.24 (1F, m, C*F*(CF_3)$_2$), −73.91 (3F, m, CF(C*F*$_3$)$_2$), −72.80 (3F, m, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 364 (M^+, <1), 195 (24), 91 (100); HRMS (EI) calcd for $C_{16}H_{11}N_2F_7$ (M^+), 364.0810; found, 364.0820. Anal. Calcd for $C_{16}H_{11}N_2F_7$: C, 52.76; H, 3.04; N, 7.69; F, 36.51. Found: C, 52.76; H, 3.00; N, 7.60; F, 35.82.

1-Benzyl-3-cyano-4-heptafluoroisopropyl-1,4-dihydropyridine (3f). Yellow solid: mp 49−50 °C; IR (CH_2Cl_2, ν_{max}/cm^{-1}) 3068, 3036, 2935, 2205, 1679, 1594, 1418, 1295, 1257, 1223, 1122, 978, 748, 728; ^{1}H NMR (400 MHz) δ 4.31 (1H, tm, ^3J = 6.4 Hz, $^4J_{HF}$ = 0.8 Hz, CHCF), 4.42 (2H, s, NCH_2), 4.72 (1H, m, NCH=C*H*), 6.12 (1H, d, $^3J_{HH}$ = 8.1 Hz, NC*H*=CH), 6.89 (1H, d, $^4J_{HH}$ = 1.5 Hz, NCH=CCN), 7.16−7.20 (2H, m, Ph), 7.33−7.45 (3H, m, Ph); ^{13}C NMR (100 MHz) δ 37.5 (d, $^2J_{CF}$ = 21.6 Hz), 58.0, 74.7 (d, $^3J_{CF}$ = 6.2 Hz), 91.2 (dm, $^1J_{CF}$ = 206.9 Hz, $^2J_{CF}$ = 28.4 Hz), 96.5 (d, $^3J_{CF}$ = 6.9 Hz), 119.9, 120.7 (qd, $^1J_{CF}$ = 287.9 Hz, $^2J_{CF}$ = 27.6 Hz), 120.7 (qd, $^1J_{CF}$ = 287.9 Hz, $^2J_{CF}$ = 28.4 Hz), 127.4, 128.6, 129.2, 132.1, 135.0, 145.6; ^{19}F NMR (376 MHz) δ −179.76 (1F, md, $^3J_{FF}$ = 7.4 Hz, $^4J_{FH}$ = 1.4 Hz, C*F*(CF_3)$_2$), −74.62 (3F, m, CF(C*F*$_3$)$_2$), −72.58 (3F, m, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 364 (M^+, 1), 195 (29), 91 (100); HRMS (ESI, MeOH) calcd for $C_{16}H_{11}N_2F_7Na$ (M + Na^+), 387.0703; found, 387.0715. Anal. Calcd for $C_{16}H_{11}N_2F_7$: C, 52.76; H, 3.04; N, 7.69; F, 36.51. Found: C, 52.44; H, 3.03; N, 7.43; F, 36.45.

Oxidation of 2-Heptafluoroisopropyl-1,2-dihydroazines 2 with DDQ. Dihydroazine **2** (0.40 mmol) was dissolved in CH_2Cl_2 (4.0 mL), and DDQ (363 mg, 1.6 mmol) was added in one portion at 0 °C. The reaction mixture was stirred at rt for 24 h for *N*-benzyl-containing dihydroazines and for 30 min in the case of *N*-*p*-methoxybenzyldihydroazines. After evaporation, the product was purified using column chromatography on silica gel.

Oxidation of 2-Heptafluoroisopropyl-1,2-dihydroazines 2 with CAN. Dihydroazine **2** (0.40 mmol) was dissolved in MeOH (2.0 mL), and a solution of CAN (439 mg, 0.80 mmol) in water (0.5 mL) was added dropwise at rt with vigorous stirring. The reaction mixture was then diluted with H_2O (10 mL), and the product was extracted with Et_2O (3 × 10 mL). Combined organic layers were washed with H_2O (ca. 20 mL), dried (Na_2SO_4), and evaporated. The product was purified by column chromatography or distillation as specified below.

2-Heptafluoroisopropylquinoline (5c).[31] Purified by column chromatography on silica gel using hexanes as the eluent; colorless oil: IR (film, ν_{max}/cm^{-1}) 3070, 2924, 1597, 1505, 1296, 1280, 1233, 1219, 1167, 1137, 1114, 981, 935, 828, 754; ^{1}H NMR (400 MHz) δ 7.66 (1H, ddd, $^3J_{HH}$ = 8.2, 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, H_{arom}), 7.75 (1H, dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.9 Hz, H_{arom}), 7.81 (1H, ddd, $^3J_{HH}$ = 8.4, 6.9 Hz, $^4J_{HH}$ = 1.5 Hz, H_{arom}), 7.89 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.4 Hz, H_{arom}), 8.19 (1H, dm, $^3J_{HH}$ = 8.5 Hz, H_{arom}), 8.34 (1H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 0.7 Hz, H_{arom}); ^{13}C NMR (100 MHz) δ 91.1 (dm, $^1J_{CF}$ = 202.6 Hz, $^2J_{CF}$ = 31.9 Hz), 117.7 (d, $^3J_{CF}$ = 8.6 Hz), 120.3 (qd, $^1J_{CF}$ = 287.9 Hz, $^2J_{CF}$ = 27.6 Hz), 127.6, 128.1, 128.4, 130.2, 130.6, 137.6 (d, $^4J_{CF}$ = 2.6 Hz), 147.1 (d, $^4J_{CF}$ = 2.6 Hz), 147.2 (d, $^2J_{CF}$ = 25.9 Hz); ^{19}F NMR (376 MHz) δ −182.54 (1F, sept. of d, $^3J_{FF}$ = 6.7 Hz, $^4J_{FH}$ = 2.7 Hz, C*F*(CF_3)$_2$), −74.74 (6F, d, $^3J_{FF}$ = 6.7 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 297 (M^+, 100), 278 (16), 228 (60), 178 (39), 128 (43); HRMS (EI) calcd for $C_{12}H_6NF_7$ (M^+), 297.0388; found, 297.0382.

2-Heptafluoroisopropyl-5-methoxycarbonylpyridine (5e). Purified by chromatography on silica gel using hexanes and then 10:1 hexanes/AcOEt; colorless liquid: IR (film, ν_{max}/cm^{-1}) 3009, 2961, 2854, 1739, 1599, 1440, 1313, 1294, 1279, 1235, 1216, 1169, 1125, 1027, 984, 966, 739, 711; ^{1}H NMR (400 MHz) δ 4.00 (3H, s, OCH_3), 7.82 (1H, ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 2.8 Hz, $^5J_{HH}$ = 0.7 Hz, CHC=N), 8.50 (1H, dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.0 Hz, C*H*=CHC=N), 9.31 (1H, dm, $^4J_{HH}$ = 2.0 Hz, C*H*=CCO_2Me); ^{13}C NMR (100 MHz) δ 52.8, 90.9 (dm, $^1J_{CF}$ = 203.5 Hz, $^2J_{CF}$ = 32.8 Hz), 120.0 (qd, $^1J_{CF}$ = 287.1 Hz, $^2J_{CF}$ = 26.7 Hz), 121.6 (d, $^3J_{CF}$ = 9.5 Hz), 127.7, 138.5 (d, $^4J_{CF}$ = 2.6 Hz), 150.5 (d, $^4J_{CF}$ = 2.6 Hz), 151.0 (d, $^2J_{CF}$ = 25.9 Hz), 164.6; ^{19}F NMR (376 MHz) δ −182.87 (1F, sept. of d, $^3J_{FF}$ = 6.8 Hz, $^4J_{FH}$ = 2.7 Hz, C*F*(CF_3)$_2$), −74.94 (6F, d, $^3J_{FF}$ = 6.8 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 305 (M^+, 46), 286 (19), 274 (100), 246 (62); HRMS (EI) calcd for $C_{10}H_6NO_2F_7$ (M^+), 305.0287; found, 305.0281. Anal. Calcd for $C_{10}H_6NO_2F_7$: C, 39.36; H, 1.98; N, 4.59; F, 43.58. Found: C, 39.62; H, 1.84; N, 4.63; F, 43.63.

3-Cyano-6-heptafluoroisopropylpyridine (5f). Purified by chromatography on neutral aluminum oxide using pentane as the eluent and by subsequent distillation under reduced pressure (bp 77 °C at 22 mmHg); colorless liquid: IR (film, ν_{max}/cm^{-1}) 3077, 2929, 2241, 1595, 1567, 1478, 1319, 1295, 1273, 1237, 1219, 1196, 1171, 1121, 986, 967, 849, 751, 713; ^{1}H NMR (400 MHz) δ 7.88 (1H, ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 2.4 Hz, $^5J_{HH}$ = 0.8 Hz, CHC=N), 8.20 (1H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.1 Hz, C*H*=CHC=N), 9.00 (1H, dm, $^4J_{HH}$ = 2.0 Hz, C*H*=*CCN*); ^{13}C NMR (100 MHz) δ ca. 92 (m), 112.2, 115.3, 119.8 (qd, $^1J_{CF}$ = 286.2 Hz, $^2J_{CF}$ = 28.5 Hz), 122.0 (d, $^3J_{CF}$ = 10.4 Hz), 140.9 (d, $^4J_{CF}$ = 2.5 Hz), 151.0 (d, $^2J_{CF}$ = 25.9 Hz), 151.9 (d, $^4J_{CF}$ = 2.6 Hz); ^{19}F NMR (376 MHz) δ −182.76 (1F, sept. of d, $^3J_{FF}$ = 7.0 Hz, $^4J_{FH}$ = 2.4 Hz, C*F*(CF_3)$_2$), −74.67 (6F, d, $^3J_{FF}$ = 7.0 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 272 (M^+, 35), 253 (12), 203 (72), 153 (100), 103 (89), 69 (64); HRMS (EI) calcd for $C_9H_3N_2F_7$ (M^+), 272.0184; found, 272.0187. Anal. Calcd for $C_9H_3N_2F_7$: C, 39.72; H, 1.11; N, 10.29; F, 48.87. Found: C, 38.90; H, 1.15; N, 10.17; F, 47.33.

3-Benzoyl-6-heptafluoroisopropylpyridine (5g). Purified by chromatography on neutral aluminum oxide using 5:1 hexanes/Et_2O as the eluent; colorless oil: IR (film, ν_{max}/cm^{-1}) 3067, 1668, 1592, 1318, 1281, 1234, 1216, 1169, 1116, 983, 966, 924, 738, 716; ^{1}H NMR (400 MHz) δ 7.55 (2H, t, $^3J_{HH}$ = 8.1 Hz, Ph), 7.68 (1H, tt, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.8 Hz, Ph), 7.84 (2H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.3 Hz, Ph), 7.87 (1H, ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 2.6 Hz,

$^5J_{HH}$ = 0.7 Hz, CHC═N), 8.30 (1H, dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.2 Hz, C*H*═CHC═N), 9.08 (1H, dm, $^4J_{HH}$ = 2.0 Hz, C*H*═CCOPh); ^{13}C NMR (100 MHz) δ 90.8 (dm, $^1J_{CF}$ = 203.5 Hz, $^2J_{CF}$ = 32.8 Hz), 120.0 (qd, $^1J_{CF}$ = 287.9 Hz, $^2J_{CF}$ = 26.7 Hz), 121.6 (d, $^3J_{CF}$ = 9.5 Hz), 128.8, 130.0, 133.7, 134.6, 135.9, 138.5 (d, $^4J_{CF}$ = 2.6 Hz), 150.2 (d, $^2J_{CF}$ = 25.9 Hz), 150.3 (d, $^4J_{CF}$ = 3.4 Hz), 193.6; ^{19}F NMR (376 MHz) δ −182.81 (1F, sept. of d, $^3J_{FF}$ = 6.9 Hz, $^4J_{FH}$ = 2.8 Hz, C*F*(CF$_3$)$_2$), −74.85 (6F, d, $^3J_{FF}$ = 6.9 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 351 (M$^+$, 61), 332 (16), 282 (5), 274 (8), 246 (11), 182 (61), 105 (100), 77 (48); HRMS (EI) calcd for $C_{15}H_8NOF_7$ (M$^+$), 351.0494; found, 351.0487. Anal. Calcd for $C_{15}H_8NOF_7$: C, 51.30; H, 2.30; N, 3.99; F, 37.86. Found: C, 51.43; H, 2.04; N, 3.92; F, 36.57.

4-Ethoxy-2-heptafluoroisopropyl-5-nitropyridine (5i). Purified by chromatography on silica gel using 10:1 hexanes/EtOAc; pale yellow oil, solidified on standing at rt: mp 50−51 °C; IR (film, ν_{max}/cm^{-1}) 2995, 1608, 1570, 1535, 1308, 1278, 1234, 1203, 1170, 1128, 1030, 984, 925, 856, 756, 742; ^{1}H NMR (400 MHz) δ = 1.56 (3H, t, $^3J_{HH}$ = 7.2 Hz, OCH$_2$C*H*$_3$), 4.37 (2H, q, $^3J_{HH}$ = 7.2 Hz, OC*H*$_2$CH$_3$), 7.41 (1H, d, $^4J_{HF}$ = 2.4 Hz, CHC═N), 9.01 (1H, d, $^5J_{HF}$ = 0.6 Hz, CH═CNO$_2$); ^{13}C NMR (100 MHz) δ 14.0, 66.7, 90.6 (dm, $^1J_{CF}$ = 204.3 Hz, $^2J_{CF}$ = 32.8 Hz), 107.9 (d, $^3J_{CF}$ = 11.2 Hz), 119.8 (qd, $^1J_{CF}$ = 287.9 Hz, $^2J_{CF}$ = 26.7 Hz), 137.4, 146.5 (d, $^4J_{CF}$ = 2.6 Hz), 152.2 (d, $^2J_{CF}$ = 25.0 Hz), 159.1 (d, $^4J_{CF}$ = 1.7 Hz); ^{19}F NMR (376 MHz) δ −181.50 (1F, sept. of d, $^3J_{FF}$ = 6.6 Hz, $^4J_{FH}$ = 2.6 Hz, C*F*(CF$_3$)$_2$), −74.81 (6F, d, $^3J_{FF}$ = 6.6 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 336 (M$^+$, 6), 308 (33), 292 (74), 262 (100); HRMS (EI) calcd for $C_{10}H_7N_2O_3F_7$ (M$^+$), 336.0345; found, 336.0350. Anal. Calcd for $C_{10}H_7N_2O_3F_7$: C, 35.73; H, 2.10; N, 8.33; F, 39.56. Found: C, 35.97; H, 2.04; N, 8.15; F, 37.52.

4-Cyano-2-heptafluoroisopropylpyridine (5j). Pale yellow oil: IR (film, ν_{max}/cm^{-1}) 3076, 2992, 2937, 2840, 2243, 1613, 1601, 1514, 1467, 1311, 1284, 1231, 1171, 1136, 1098, 1036, 1012, 986, 814, 752, 716; ^{1}H NMR (400 MHz) δ 7.74 (1H, dd, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.3 Hz, CH═C*H*CN), 7.94 (1H, m, CHC═N), 8.94 (1H, dm, $^3J_{HH}$ = 5.0 Hz, C*H*═CHCN); ^{13}C NMR (100 MHz) δ 90.5 (dm, $^1J_{CF}$ = 204.3 Hz, $^2J_{CF}$ = 32.8 Hz), 115.3, 119.8 (qd, $^1J_{CF}$ = 287.9 Hz, $^2J_{CF}$ = 26.7 Hz), 122.4 (d, $^4J_{CF}$ = 2.6 Hz), 123.5 (d, $^3J_{CF}$ = 10.4 Hz), 127.2, 149.3 (d, $^2J_{CF}$ = 15.9 Hz), 150.7 (d, $^4J_{CF}$ = 2.6 Hz); ^{19}F NMR (376 MHz) δ −183.02 (1F, sept. of d, $^3J_{FF}$ = 6.3 Hz, $^4J_{FH}$ = 2.8 Hz, C*F*(CF$_3$)$_2$), −74.55 (6F, d, $^3J_{FF}$ = 7.0 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 272 (M$^+$, 69), 253 (26), 203 (100), 153 (100), 103 (57); HRMS (EI) calcd for $C_9H_3N_2F_7$ (M$^+$), 272.0184; found, 272.0179. Anal. Calcd for $C_9H_3N_2F_7$: C, 39.72; H, 1.11; N, 10.29; F, 48.88. Found: C, 39.52; H, 1.13; N, 10.42; F, 48.79.

2-Heptafluoroisopropyl-5-methoxyquinoline (5k). Purified by chromatography on silica gel using 10:1 hexanes/Et$_2$O; white solid: mp 80−81 °C; IR (KBr, ν_{max}/cm^{-1}) 2955, 2925, 2856, 1622, 1591, 1476, 1410, 1295, 1275, 1252, 1225, 1169, 1138, 1090, 978, 810, 754; ^{1}H NMR (400 MHz) δ 4.02 (3H, s, OCH$_3$), 6.93 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.8 Hz, H$_{arom}$), 7.66−7.77 (3H, m, H$_{arom}$), 8.74 (1H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 0.8 Hz, H$_{arom}$); ^{13}C NMR (100 MHz) δ 55.9, 91.1 (dm, $^1J_{CF}$ = 203.5 Hz, $^2J_{CF}$ = 32.8 Hz), 105.6, 116.8 (d, $^3J_{CF}$ = 8.6 Hz), 120.3 (qd, $^1J_{CF}$ = 288.0 Hz, $^2J_{CF}$ = 27.6 Hz), 120.9, 122.1, 130.6, 132.7 (d, $^4J_{CF}$ = 1.7 Hz), 147.5 (d, $^2J_{CF}$ = 25.0 Hz), 147.9 (d, $^4J_{CF}$ = 2.6 Hz), 155.0; ^{19}F NMR (376 MHz) δ −182.61 (1F, sept. of d, $^3J_{FF}$ = 6.4 Hz, $^4J_{FH}$ = 2.8 Hz, C*F*(CF$_3$)$_2$), −74.65 (6F, d, $^3J_{FF}$ = 7.0 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 327 (M$^+$, 100), 312 (10), 308 (8), 284 (27), 258 (11), 215 (18); HRMS (EI) calcd for $C_{13}H_8NOF_7$ (M$^+$), 327.0494; found, 327.0496. Anal. Calcd for $C_{13}H_8NOF_7$: C, 47.72; H, 2.46; N, 4.28; F, 40.64. Found: C, 47.90; H, 2.21; N, 4.17; F, 40.59.

3-Heptafluoroisopropylphenanthroline (5l). Yellow solid: mp 126−128 °C; IR (KBr, ν_{max}/cm^{-1}) 1590, 1509, 1494, 1313, 1280, 1242, 1211, 1162, 1132, 980, 970, 848, 718; ^{1}H NMR (400 MHz) δ 7.68 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 4.3 Hz, H$_{arom}$), 7.87 (2H, AB, $^3J_{HH}$ = 8.9 Hz, H$_{arom}$), 7.99 (1H, dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.2 Hz, H$_{arom}$), 8.27 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.8 Hz, H$_{arom}$), 8.43 (1H, d, $^3J_{HH}$ = 8.5 Hz, H$_{arom}$), 9.29 (1H, dd, $^3J_{HH}$ = 4.4 Hz, $^4J_{HH}$ = 1.8 Hz, H$_{arom}$); ^{13}C NMR (100 MHz) δ 91.1 (dm, $^1J_{CF}$ = 203.5 Hz, $^2J_{CF}$ = 31.9 Hz), 120.0 (d, $^3J_{CF}$ = 7.8 Hz), 120.4 (qd, $^1J_{CF}$ = 287.1 Hz, $^2J_{CF}$ = 26.7 Hz), 123.5, 125.8, 128.8, 129.2, 129.3, 136.1, 137.5 (d, $^4J_{CF}$ = 2.2 Hz), 145.7 (d, $^4J_{CF}$ = 2.6 Hz), 145.9, 146.6 (d, $^2J_{CF}$ = 24.1 Hz), 151.3; ^{19}F NMR (376 MHz) δ −182.25 (1F, m, C*F*(CF$_3$)$_2$), −74.55 (6F, d, $^3J_{FF}$ = 7.6 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 348 (M$^+$, 100), 329 (10), 279 (68), 229 (28), 179 (29); HRMS (EI) calcd for $C_{15}H_7N_2F_7$ (M$^+$), 348.0498; found, 348.0505. Anal. Calcd for $C_{15}H_7N_2F_7$: C, 51.74; H, 2.03; N, 8.04; F, 38.19. Found: C, 51.52; H, 1.91; N, 7.76; F, 37.96.

2-Heptafluoroisopropyl-3,6-bis(methoxycarbonyl)pyridine (5o). Purified by chromatography on silica gel using 5:1 hexanes/AcOEt; yellow solid: mp 60−61 °C; IR (KBr, ν_{max}/cm^{-1}) 2968, 1761, 1736, 1429, 1312, 1268, 1246, 1214, 1163, 1092, 1002, 977, 960, 710; ^{1}H NMR (400 MHz) δ 3.97 (3H, s, OCH$_3$), 4.01 (3H, s, OCH$_3$), 8.00 (1H, d, $^3J_{HH}$ = 8.0 Hz, H$_{arom}$), 8.28 (1H, d, $^3J_{HH}$ = 8.0 Hz, H$_{arom}$); ^{13}C NMR (100 MHz) δ 53.2, 53.4, 91.9 (dm, $^1J_{CF}$ = 206.0 Hz, $^2J_{CF}$ = 32.8 Hz), 119.9 (qd, $^1J_{CF}$ = 288.8 Hz, $^2J_{CF}$ = 26.7 Hz), 125.9, 132.7, 138.4, 143.4 (d, $^2J_{CF}$ = 25.9 Hz), 148.2 (d, $^3J_{CF}$ = 3.4 Hz), 163.9, 166.3; ^{19}F NMR (376 MHz) δ −181.64 (1F, sept., $^3J_{FF}$ = 5.4 Hz, C*F*(CF$_3$)$_2$), −74.19 (6F, d, $^3J_{FF}$ = 5.4 Hz, CF(C*F*$_3$)$_2$); MS (EI 70 eV, *m*/*z*, %) 363 (M$^+$, <1), 344 (10), 332 (24), 305 (100), 273 (12); HRMS (EI) calcd for $C_{12}H_8NO_4F_7$ (M$^+$), 363.0342; found, 363.0348. Anal. Calcd for $C_{12}H_8NO_4F_7$: C, 39.69; H, 2.22; N, 3.86; F, 36.62. Found: C, 40.36; H, 2.39; N, 3.94; F, 35.44.

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Supporting Information Available: Analytical data for compounds **2c′**, **3c′**, **2d′**, **2e′**, **3e′**, **2f′**, **3f′**, **2g′**, **3g′**, **3h′**, **2i′**, **2j′**, **2k′**, **3k′**, **2l′**, **3l′**, **2m′**, **2n′**, **2o′**, and **3o′**, procedure of one-pot synthesis of dihydroazines **2** and **3**, procedure of synthesis of compounds **2n′**, **2o′**, and **3o′** (Scheme 9), and copies of NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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