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Synthesis of tetrafluorinated tetrahydroquinolines *via* photoredox catalysis

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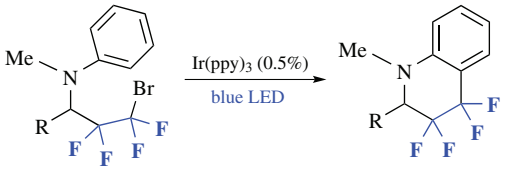
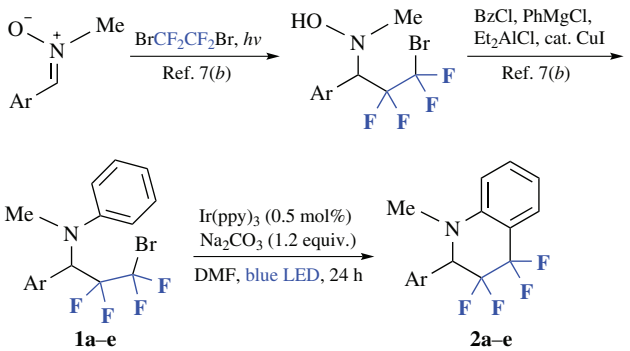
Blue light-promoted iridium photocatalytic cyclization of *N*-(3-bromo-2,2,3,3-tetrafluoropropyl)anilines affords 3,3,4,4-tetrafluoro-1,2,3,4-tetrahydroquinolines in good yields.



Increasing importance of organofluorine compounds in medicinal chemistry[1] has instigated the development of methods for their synthesis.[2] A significant attention has been devoted to the synthesis of fluorinated heterocyclic compounds.[3] On the other hand, photoredox catalysis has evolved as a powerful methodology for performing radical reactions,[4] and it has been frequently applied towards fluorinated molecules.[5,6] Recently, we found that fluorinated groups can be photocatalytically introduced at the C=N bond of nitrones with the use of polyfluoroalkyl halides.[7] In particular, with the application of readily available 1,2-dibromotetrafluoroethane this approach allows one to perform the facile synthesis of hydroxylamines bearing the bromotetrafluoroethyl fragment[7(b)] (Scheme 1). We also showed that N-positioned hydroxyl group in these products can be replaced by phenyl one to afford amines of type **1**.[7(b)] Herein, we report that compounds **1** can be converted into 3,3,4,4-tetrafluoro-1,2,3,4-tetrahydroquinolines **2** *via* a photoredox reaction. It should be pointed out that compounds containing tetrafluoroethylene fragment have attracted noticeable attention.[8] At the same time, quinolines having such structural motive have not been previously described.



	Ar	Yield (%)
a	Ph	73
b	4-Pr^{i}C$_6$H$_4$	67
c	4-MeOC$_6$H$_4$	47
d	4-MeO$_2$CC$_6$H$_4$	42
e	2,4-Cl$_2$C$_6$H$_3$	63

Scheme 1

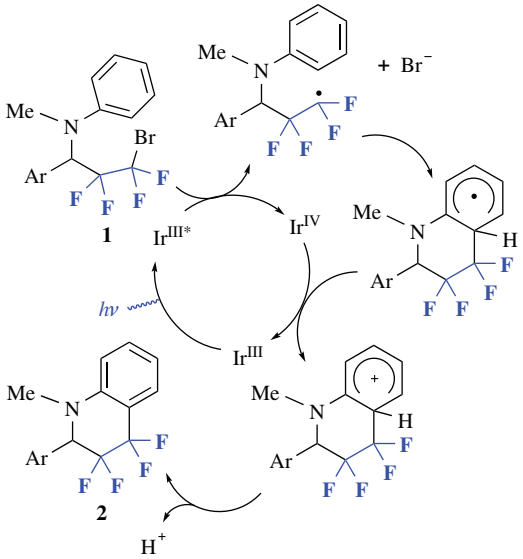
Compounds **1a–e** were irradiated employing blue light emitting diodes in the presence of 0.5 mol% of tris[2-phenylpyridinato-C^2,N]iridium(III) [Ir(ppy)$_3$]. Sodium carbonate was used as the base to scavenge evolving hydrogen bromide. Products **2a–e** were isolated in reasonable yields (see Scheme 1).[†]

As for the process mechanism, we believe that the reaction starts from the single electron reduction of the substrate **1** by photoexcited iridium catalyst leading to the dissociation of the C–Br bond (Scheme 2). The fluorinated radical undergoes intramolecular attack at the electron-rich aromatic ring to generate delocalized radical intermediate. Its subsequent oxidation with iridium(IV) leads to cationic intermediate stabilized by the nitrogen atom. At the final step, the elimination of proton regenerates aromaticity with the formation of product **2**.

In summary, an intramolecular reaction between the bromotetrafluoroalkyl and phenyl groups in amines of type **1** affording tetrafluorinated tetrahydroquinoline derivatives is described. The reaction proceeds under irradiation with visible light in the presence of the iridium photocatalyst.

[†] *General procedure for the photoredox reaction.* Substrate **1a–e** (0.30 mmol), *fac*-Ir(ppy)$_3$ (1.0 mg, 1.5 μmol) and sodium carbonate (38 mg, 0.37 mmol) were placed in a test tube. The tube was evacuated and filled with argon, DMF (1.5 ml) was added, and the tube was closed tightly with a screw-cap. The reaction mixture was irradiated for 24 h by a strip of light emitting diodes (2835-120LED 1M-Blue, 12V); during the irradiation the mixture was cooled with water to maintain temperature around 23–25 °C. The mixture was then poured into water (10 ml) and extracted with hexanes (5×4 ml). The combined organic phases were dried with Na_2SO_4, concentrated under reduced pressure, and the residue was purified by chromatography.

3,3,4,4-Tetrafluoro-1-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline **2a**. Yield 65 mg (73%). Colorless oil. Chromatography (EtOAc/hexanes 1/7, R_f 0.33). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (d, 1H, *J* 7.8 Hz), 7.50–7.36 (m, 6H), 6.93 (t, 1H, *J* 7.5 Hz), 6.87 (d, 1H, *J* 8.4 Hz), 4.72 (dt, 1H, *J* 19.2, 8.3 Hz), 2.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.8 (dd, *J* 5.8, 4.3 Hz), 133.1, 132.1, 129.5, 129.3, 128.7, 126.2 (dd, *J* 5.1, 2.5 Hz), 118.2 (d, *J* 1.8 Hz), 116.2–115.2 (m), 114.4 (td, *J* 23.5, 1.4 Hz), 113.0, 112.8–111.9 (m), 109.1 (ddd, *J* 31.6, 22.7, 6.8 Hz), 66.5 (dd, *J* 26.8, 22.1 Hz), 37.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –96.7 (dm, 1F, *J* 265.1 Hz), –120.9 (dm, 1F, *J* 265.1 Hz), –124.1 (dm, *J* 253.7 Hz), –128.8 (d, 1F, *J* 253.7 Hz). HRMS (ESI), *m/z*: (M + H) 296.1052 (calc. for $C_{16}H_{14}F_4N$, *m/z*: 296.1057).



Scheme 2

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.09.012.

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