Rhodium-Mediated Electrophilic ^{18}F -Oxyfluorination of Diazoketones

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Fluorine in Nature

- 13th most abundant element in Earth's crust
- Low bioavailability
 - Solubility
 - Reactivity
- Only 5 fluorinated natural products unequivocally identified

out of *ca* 130 000!

a) David, D. B. Harper, *J. Fluorine Chem.* **1999**, 100, 127-133; b) C. D. Murphy, C. Schaffrath, D. O'Hagan, *Chemosphere* **2003**, 52, 455-461; c) D. O'Hagan, H. Deng, *Chem. Rev.* **2015**, 115, 634-649.

Fluorine in Drugs and Pharmaceuticals

- >20% of pharmaceuticals contain (at least) one fluorine atom
- Small ionic radius and high electronegativity
- Modulation of physicochemical and biological properties
 - pKa
 - Conformation
 - Lipophilicity
 - Metabolic stability

Fluorine is essential to ensure therapeutical properties

Atorvastatin
Cholesterol

Capecitabine
Chemotherapy

Aprepitant
Antihemetic

Fluoxetine
Antidepressant

Celecoxib
Arthritis

Efavirenz
Antiretroviral

a) B. E. Smart, *J. Fluorine Chem.* **2001**, 109, 3-11; b) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, 5, 637-643; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, 317, 1881-1886; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, 37, 320-330; e) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, 167, 16-29; f) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, 114, 2432-2506; g) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, 116, 422-518.

Positron Emission Tomography

- Non-invasive imaging technique
- Positron-emitting nuclide containing molecules

○ ^{15}O

○ ^{13}N

○ ^{11}C

○ ^{18}F

Bombardment

Labelling

Formulation/Analysis

Scan

PET Image

Privileged isotope: ^{18}F

- Half-life (109.7 min)
- Positron-energy (0.64 MeV)

[^{18}F]FDG
(metabolism)

[^{18}F]fluoro-L-DOPA
(protein metabolism)

[^{18}F]fluorothymidine
(oncology)

[^{18}F]fallylpride
(dopamine receptor)

[^{18}F]Celecoxib
(COX-2 expression)

a) P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem. Int. Ed.* **2008**, 47, 8998-9033; b) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* **2016**, 116, 719-766; c) M. G. Campbell, J. Mercier, C. Genicot, V. Gouverneur, J. M. Hooker, T. Ritter, *Nat Chem* **2017**, 9, 1-3; d) D. van der Born, A. Pees, A. J. Poot, R. V. A. Orru, A. D. Windhorst, D. J. Vugts, *Chem. Soc. Rev.* **2017**.

Nucleophilic ^{18}F -Fluorination

Nucleophilic Fluorination

- High solvation energy
- Low reactivity
- High basicity when dry

Method of choice for synthesis of $[^{18}\text{F}]\text{FDG}$: nucleophilic ^{18}F -fluorination

Electrophilic ^{18}F -Fluorination

Electrophilic Fluorination

- Reagents derived from $[^{18}\text{F}]\text{F}_2$
- Hazardous and unselective
- Inherent limitation: low molar activity

Electrophilic synthesis of $[^{18}\text{F}]\text{FDG}$

¹⁸F-Labeling - Challenges

The principles of fluorine-19 chemistry must not be assumed

- Extreme scale difference (mmol vs pmol)
- Effect of impurities
- Time constraint
- Ionizing radiation

The reactions need to be robust and simple

Fluorine-19 conditions are rarely applicable to fluorine-18. They need to be *translated* into fluorine-18 chemistry

a) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science* **2011**, 334, 639-642; b) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci.* **2014**, 5, 4545-4553.

[¹⁸F]Fluoro-Benziodoxole

- The product cannot be analyzed by common methods (radio-HPLC, radio-TLC)
- Extraction in hexane provides the reagent free of precursor and [¹⁸F]Bu₄NF
- Reagent identity confirmed by ¹⁹F-NMR and HRMS of decayed sample

Decayed sample

Reference

Bu₄NF

¹⁸F-Oxyfluorination of Diazoketones

Previous report of our group:

W. Yuan, L. Eriksson and K. J. Szabó, *Angew. Chem. Int. Ed.*, 2016, **55**, 8410-8415.

Very good labelling candidate:

- Short reaction time
- Mild reaction conditions
- Interesting α-fluoroethers

¹⁸F-Oxyfluorination of Diazoketones

Translation of diazocompound fluorofunctionalization:

The desired product was not obtained

The alcohol is not a good option as reaction partner due to its nucleophilicity

Trimethylorthoformate: a non nucleophilic –OMe surrogate:

TMOF gives excellent result

¹⁸F-Oxyfluorination of Diazoketones - Optimization

A more soluble Rh-complex was tested: Rh₂(OPiv)₄:

Deviation from conditions	RCY (n = 2)
No Rh	0%
MeOH instead of TMOF	0%
DCM/TMOF 1:1	0%
Rh ₂ (OAc) ₄ instead of Rh ₂ (OPiv) ₄	90 ± 2%
Rh ₂ (esp) ₂ instead of Rh ₂ (OPiv) ₄	21 ± 1%
Rh ₂ (TPA) ₄ instead of Rh ₂ (OPiv) ₄	26 ± 9%
0.1 mg Rh ₂ (OPiv) ₄ instead of 0.5 mg Rh ₂ (OPiv) ₄	28 ± 3%
[¹⁸ F]Bu ₄ NF instead of [¹⁸ F]Fluoro-benziodoxole	0%

Rh₂(OPiv)₄ has higher solubility and provides better RCY

Diazoketone Scope

RCY $98 \pm 1\%$
(n = 2)

RCY: $94 \pm 5\%$
(n = 2)

RCY: $91 \pm 2\%$
(n = 2)

RCY: $96 \pm 1\%$
(n = 2)

RCY: $26 \pm 6\%$
(n = 2)

RCY: $98 \pm 1\%$
(n = 2)

RCY: $67 \pm 8\%$
(n = 2)

RCY: $79\% \pm 9\%$
(n = 2)

RCY: $95 \pm 4\%$
(n = 2)

RCY: $49 \pm 4\%$
(n = 2)

RCY: $16 \pm 3\%$
(90 °C, n = 2)

RCY: 0%
(n = 2)

High RCY was obtained in most of cases
Aliphatic diazoketone could not be labelled

Isolation and Molar Activity measurement

Product isolated by semi-preparative HPLC

- Activity Yield (AY): amount of labelled product obtained from a known amount of activity
- Molar Activity (A_m): measured radioactivity per molar amount of final product (GBq/ μ mol) - Important parameter for quantitative PET studies

- Moderate activity yield: 9%
- Moderate radiochemical purity (RCP): >89%
- Excellent molar activity: 216 GBq/ μ mol

Very good molar activity two hours after production of fluorine-18

Suggested Mechanism

Based on our previous experimental and DFT studies¹

[1] a) W. Yuan, L. Eriksson, K. J. Szabó, *Angew. Chem. Int. Ed.* **2016**, 55, 8410-8415. b) B. K. Mai, K. J. Szabó, F. Himo, *ACS Catal.* **2018**, 8, 4483-4492

Key mechanistic features:

- Rhodium carbene
- Rhodium ylide
- Rhodium enolate
- I–F bond isomerization

Conclusions

- A rhodium-mediated oxyfluorination of diazoketones has been translated into a labelling procedure
- The products were obtained in high radiochemical yield in short reaction time and generally mild conditions
- High molar activity was obtained

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