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Iodine(III)-precursors for n.c.a. Radiofluorination of Electron Rich Arenes

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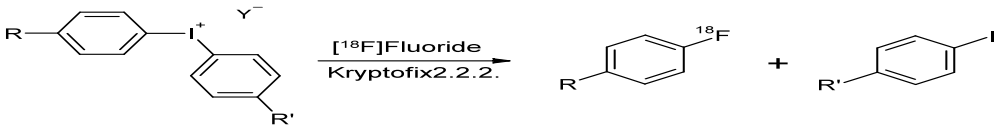
7th International Symposium on Radiohalogens, September 15-19, 2012, Whistler, BC

Nucleophilic ^{18}F-substitution via iodonium salts



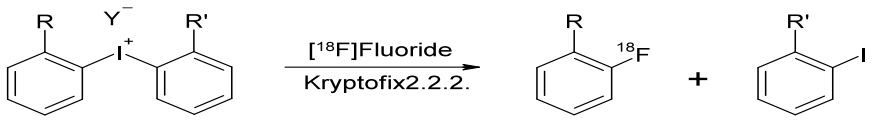
R = OMe, OBn, Alkyl, H, Cl, Br, I
R' = OMe, OBn, Alkyl, H, Cl, Br, I
Y = Br, I, OTs, OTf

Pike et al., Chem. Comm. 2215 (1995)

Hocke et al. . J. Label. Compds Radiopharm. **40**, 50 (1997)

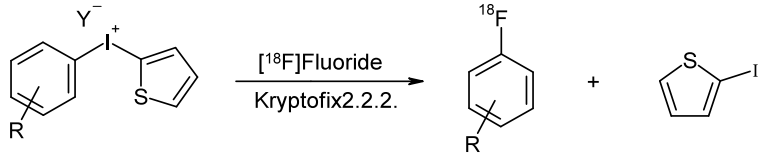
Wüst et al., J. Label. Compds Radiopharm. **46**, 699 (2003)

Ermert et al., J. Label. Compds Radiopharm. **47**, 429 (2004)



R = OMe, Alkyl, H, Br
R' = OMe, Alkyl, H
Y = Cl

Chun et al., J. Org. Chem. **75**, 3332 (2010) (Microwave)



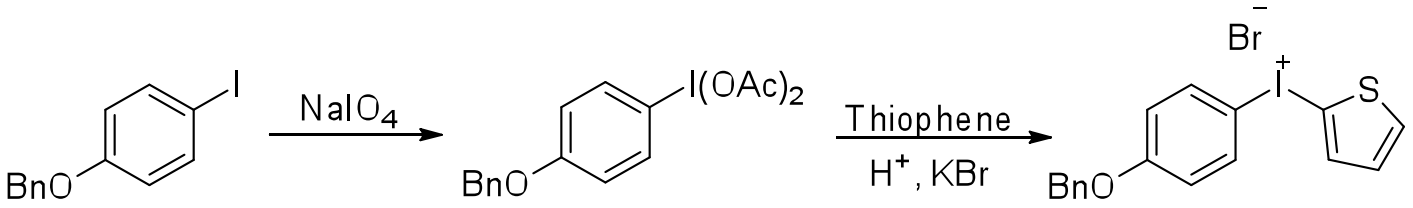
R = *o*-, *m*-, *p*-OMe, OBn, Me, H, Cl, Br, I

Y = Br, I, OTs, OTf

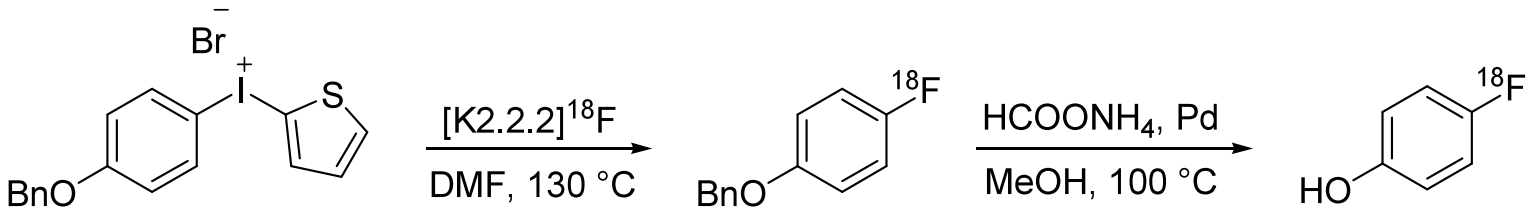
Ross et al., J. Am. Chem. Soc. **129**, 8018 (2007)

Synthesis of no-carrier-added 4-[^{18}F]fluorophenol

Synthesis of 4-benzyloxyphenyl-(2-thienyl)iodonium bromide



Synthetic sequence of the two step radiosynthesis of n.c.a 4-[^{18}F]fluorophenol



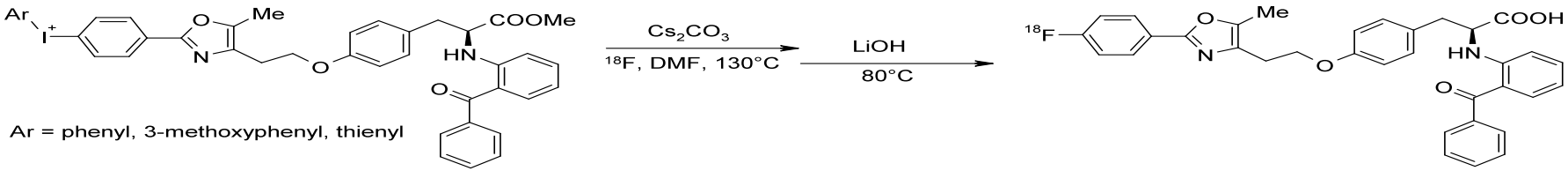
RCY = 34 – 36 %

Ross, T. L., et al., Molecules 2011, 16, 7621.

Recent examples of a direct ^{18}F-labelling of complex molecules via iodonium salts

RCY = 75 %

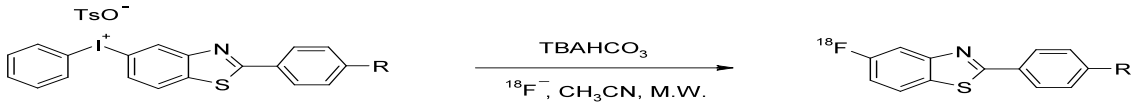
Zhang et al., Tetrahedron Lett. **48**, 8632 (2007)



Ar = phenyl, 3-methoxyphenyl, thienyl

RCY = 35 %

Lee et al., Nucl. Med. Biol., **36**, 147 (2009)



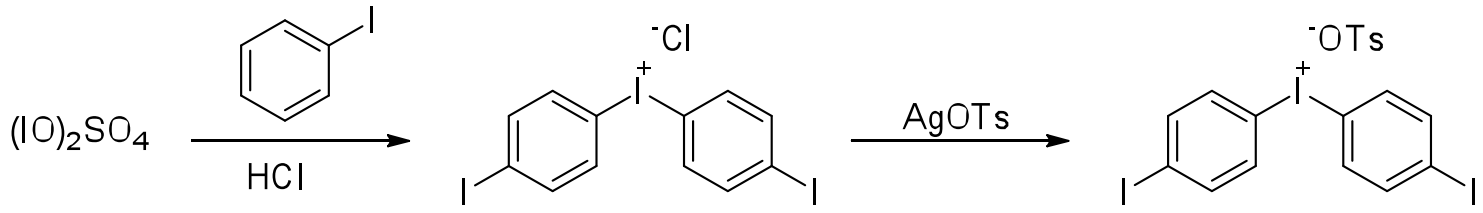
R = NO_2, NCH_3Boc, $N(CH_3)_2$

RCY = 60 %

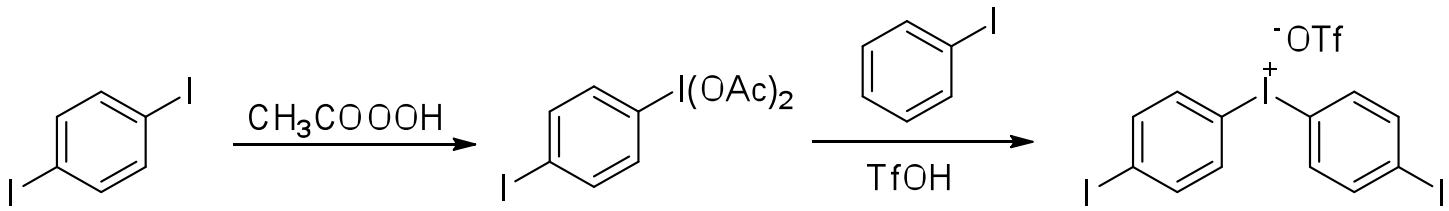
Lee et al., Bioorg. Med. Chem., **19**, 2980 (2011)

Preparation of (4-iodophenyl)-(aryl)iodonium salts

Synthesis of 4,4-diiododiphenyliodonium salts



27% 25%

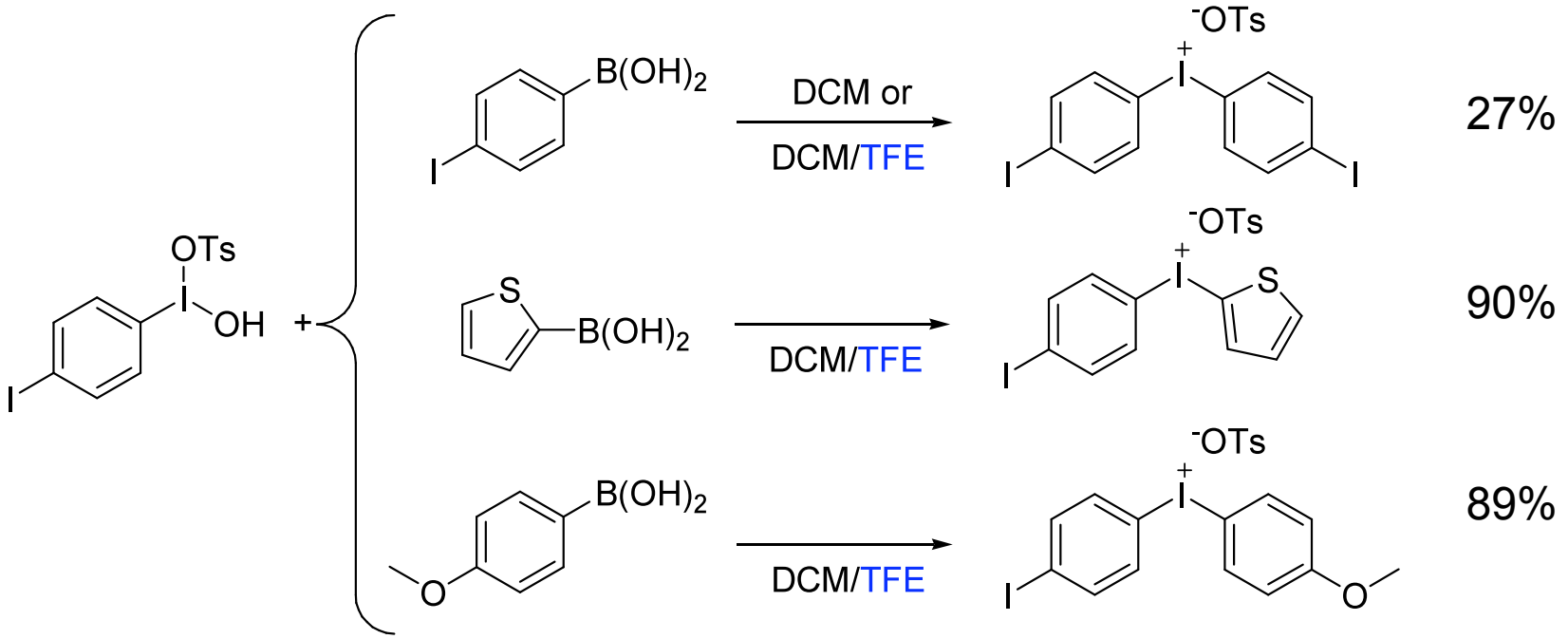


32%

Wüst, F. R.; Kniess, T. J. Label. Compd. Radiopharm. 2003, **46**, 699.

Convenient preparation of (4-iodophenyl)-aryliodonium salts

Reaction of *p*I-HTIB with boronic acids in trifluoroethanol

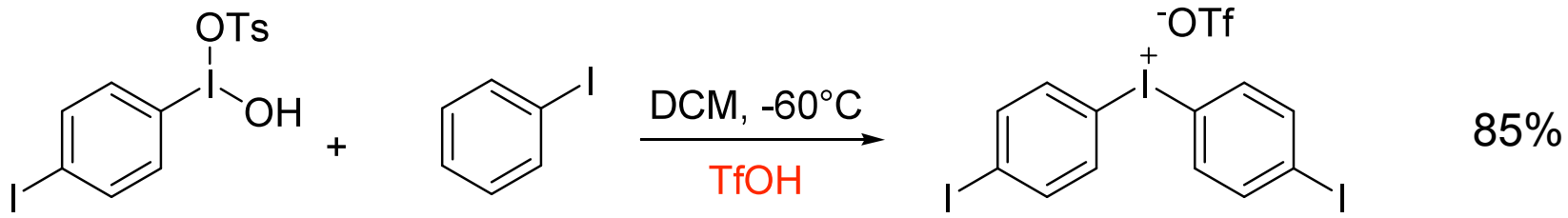


Carroll et al., Tetrahedron Lett. 2000, **41**, 5393.
Dohi et al. Chem. Commun. **2007**, 4152. (TFE)

Cardinale, J., *et al*., Tetrahedron 2012, **68**, 4112.

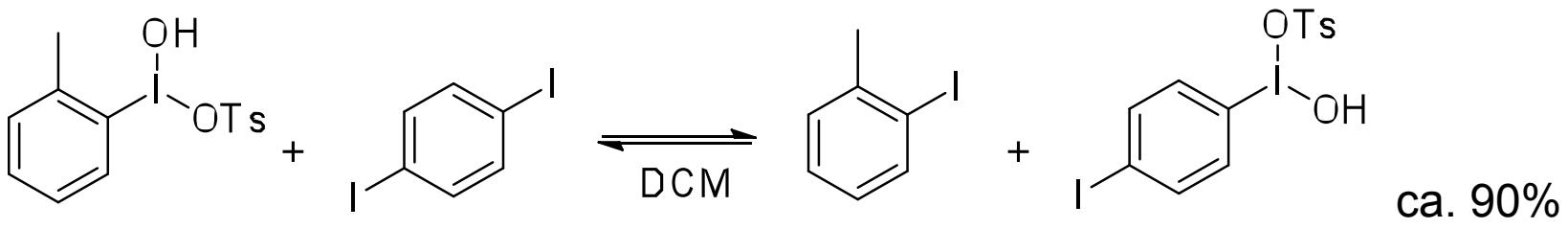
Preparation of 4,4´-di(iodophenyl)-iodonium tosylate

Direct reaction of *p*I-HTIB with triflic acid and iodobenzene in DCM



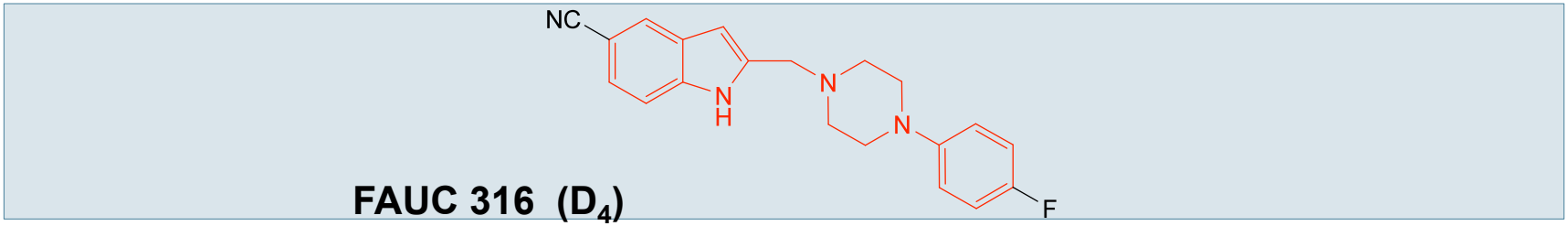
Cardinale, J., *et al*., Tetrahedron 2012, **68**, 4112.

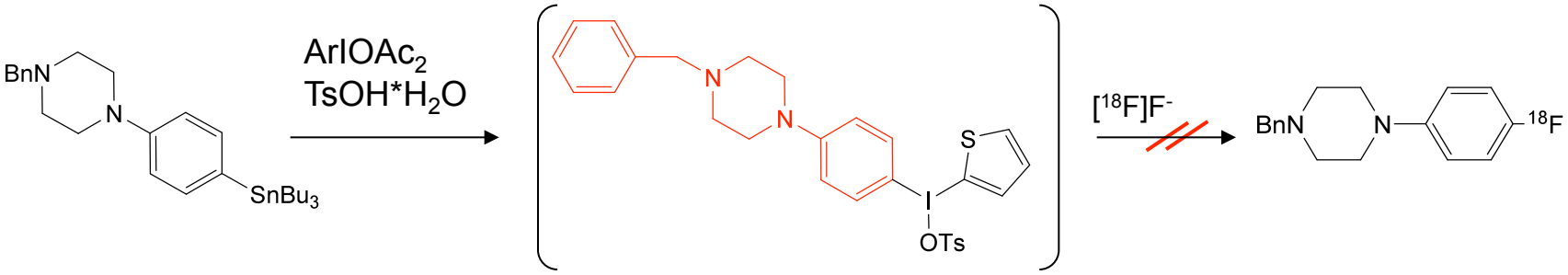
Preparation of *p*I-HTIB by ligand exchange



Toluene derivative soluble in DCM: Carman and Koser, J Org Chem 1983, **48**, 2534.

[^{18}F]FAUC 316 – via iodonium precursor ?

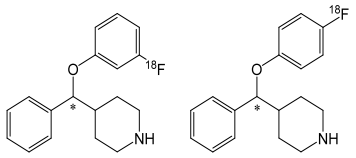




precursor of "FAUC test system"

- **no "defined" product isolated**

Radiosynthesis of the SERT and NET ligands *rac*-4-{(3- und 4-[^{18}F]fluorophenoxy)phenylmethyl}piperidine



3-[^{18}F]FPPMP
SERT/NET

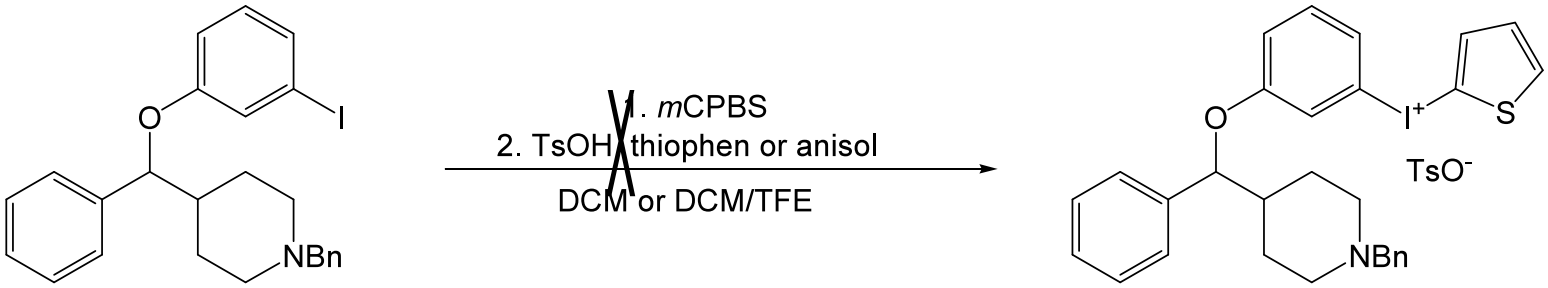
4-[^{18}F]FPPMP
SERT

	K_i [nM]	
	(-) 3-FPPMP	(+) 4-FPPMP
5-HT1A	> 1000	> 1000
5HT2A	> 1000	> 1000
SERT	1.9	0.4
NET	13.5	111.4
DAT	461.3	821.0

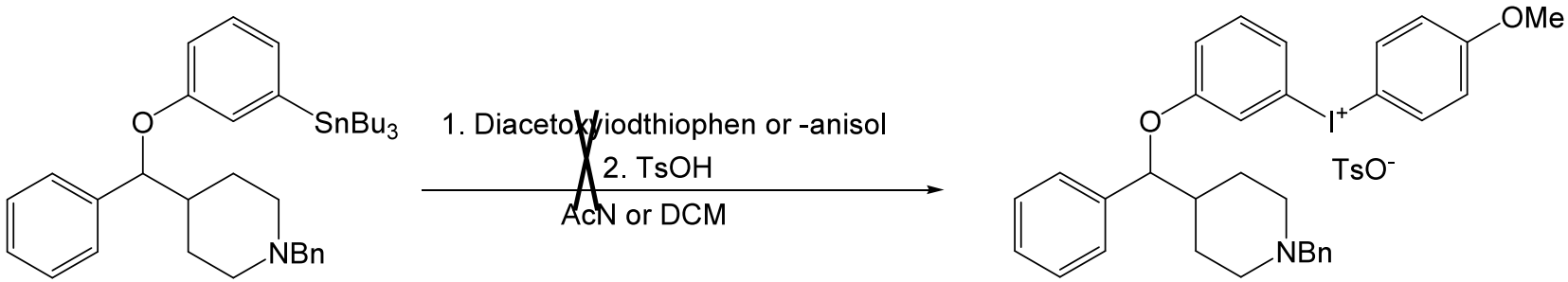
Orjales et al., *J. Med. Chem.* 2003, **46**, 5512-5532.

Goal: Preparation of compounds 3- and 4-[^{18}F]FPPMP via direct labelling of suitable precursors with no-carrier-added [^{18}F]fluoride.

Synthesis of precursors



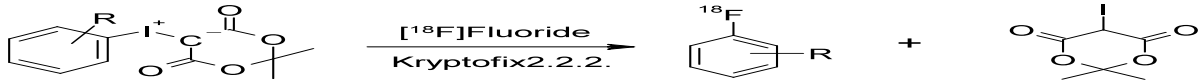
M. Bielawski et al., *Chem. Commun.* **2007**, 2521-2523.



M.-R. Zhang et al., *Tetrahedron Letters* 2007, **48**, 8632–8635.

Nucleophilic ^{18}F-substitution via iodonium compounds: recent developments

Phenyliodoniumylides



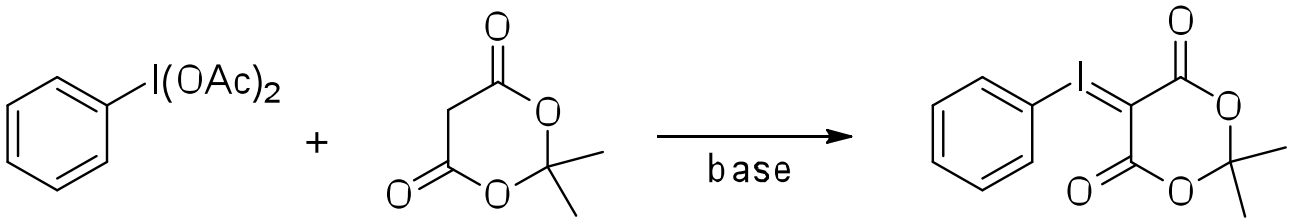
R	H	CH_3	1,3,5-CH_3	2-OCH_3	3-OCH_3	4-OCH_3	Cl	Br	NO_2
RCY (%)	61.6	58.5	62.7	75.6	19.0	32.3	72.9	73.0	87.3

Iodyl as leaving group

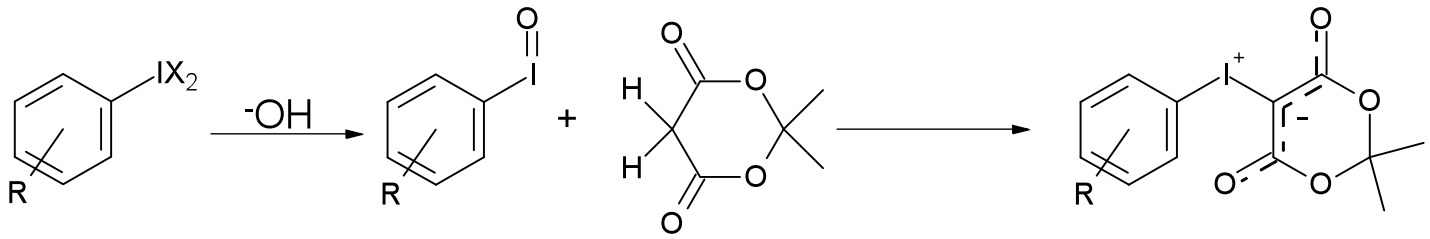
R	H	4-CH_3	4-$COCH_3$	4-CHO	4-CN	4-$COOCH_2CH_3$	4-NO_2
RCY (%)	6.6	2.4	46.2	76.7	86.2	86.0	82.7

Satyamurthy and Barrio, US Patent WO2010008522 A2 (2010)

Synthesis of aryliodonium ylides



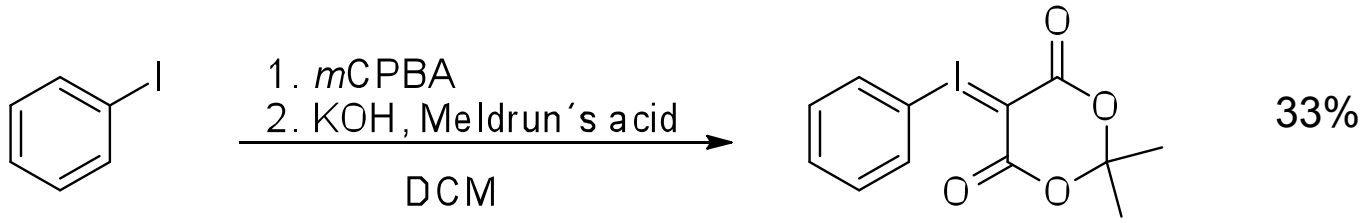
V. V. Zhdankin and P. J. Stang; *Chem. Rev.* 2008, **108**, 5299–5358.



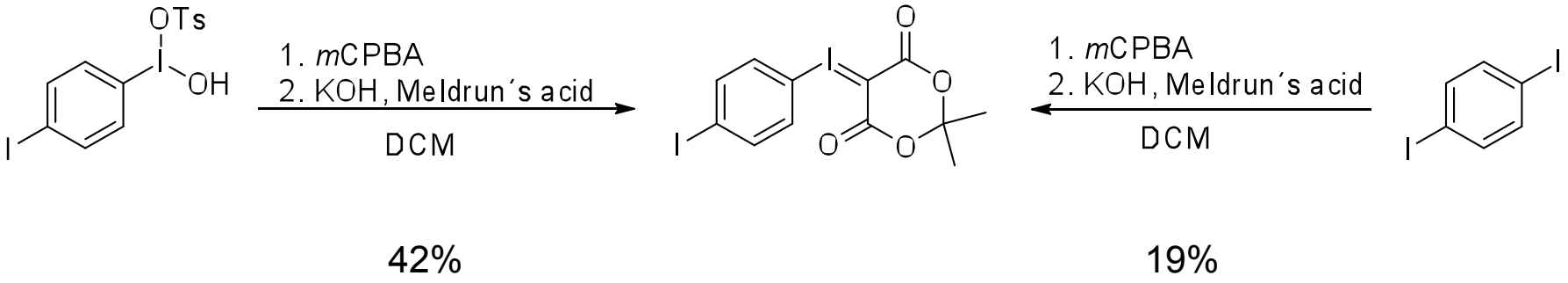
O. Neilands et al., Zhurnal Organicheskoi Khimii 1971, **7**, 1611-1615.

S. R. Goudreau et al., *J. Org. Chem.* 2009, **74**, 470-473.

New one-pot synthesis of iodonium ylides

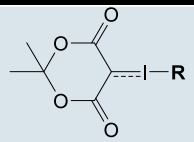
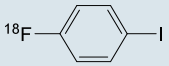
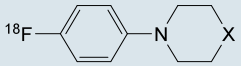
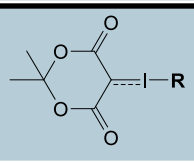
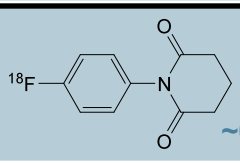
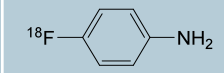


Synthesis of 2-(4-iodophenyl)iodonio-5,5-dimethyl-4,6-dioxa-1,3-dioxocyclohexane ylide:

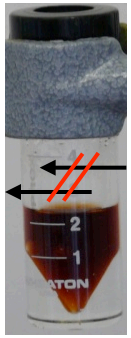


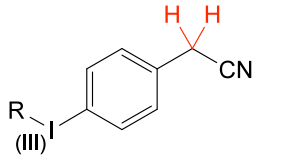
Cardinale, J., *et al*., Tetrahedron Letters, to be submitted

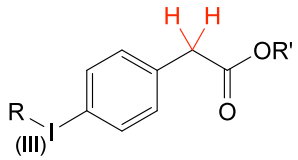
Various [^{18}F]fluoro-amines in two steps from iodonium

Main Precursor	Intermediate ^{18}F-R RCY	Amine RCY$_{overall}$
Ylide 	 70±10 %	 50±10 %
Ylide 	 ~60 %	 ~47 %

base sensitive
but also no neutral
radiofluorination

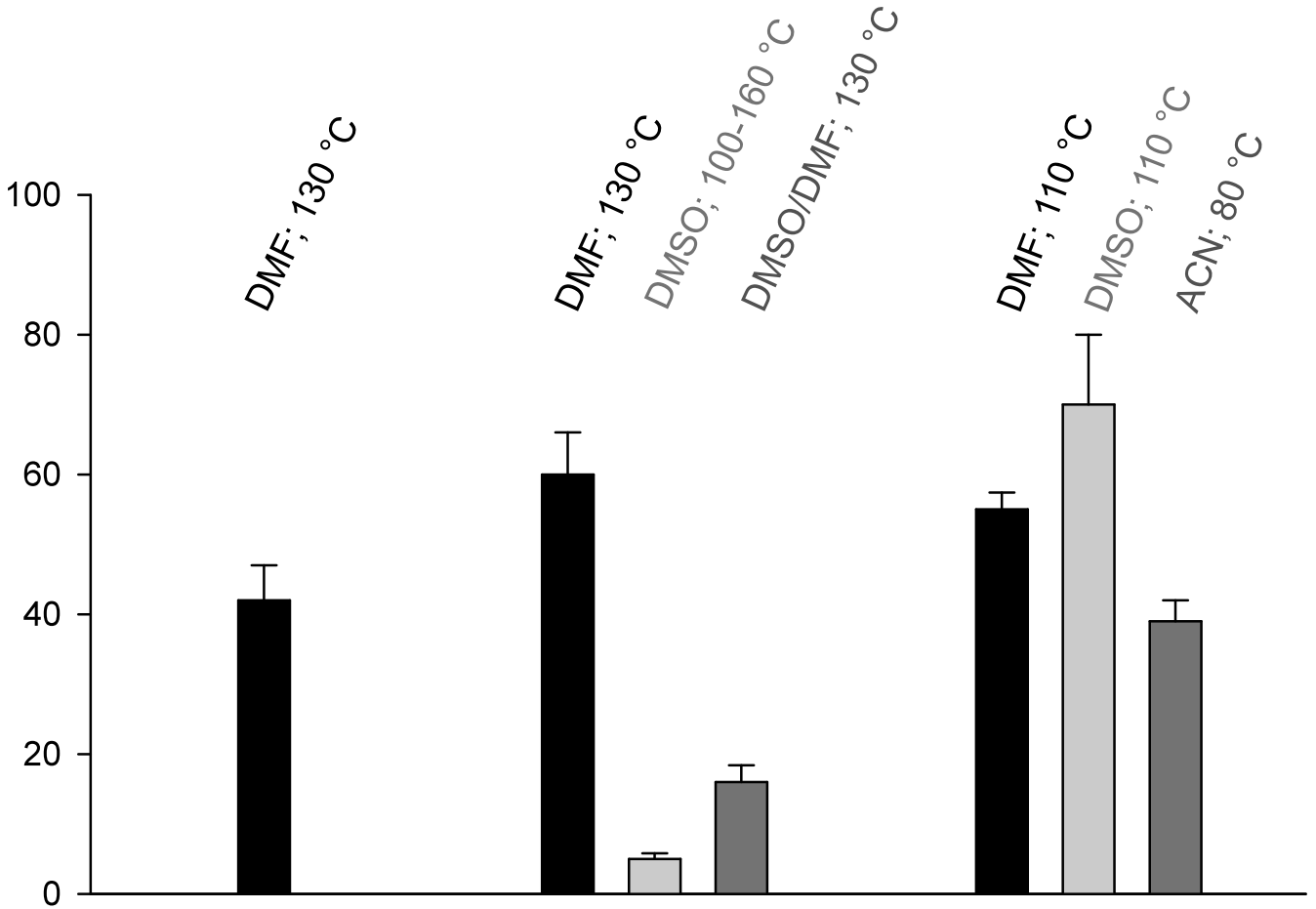


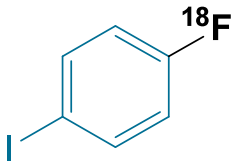




degradation

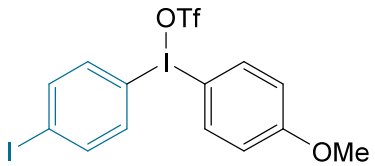
N.c.a 4-[^{18}F]fluoroiodobenzene via iodo(III)-precursors

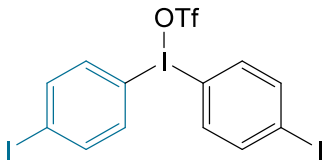


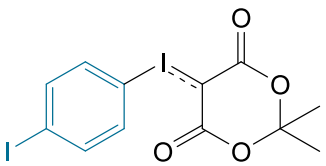


[^{18}F]F$^-$
K<2.2.2./CO_3
or
TBAHCO_3

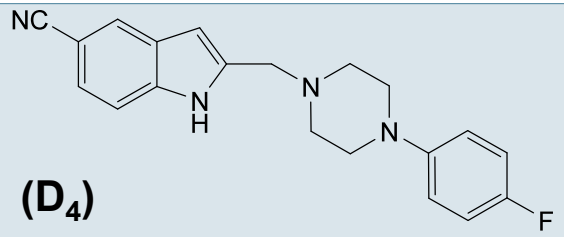
Precursors:



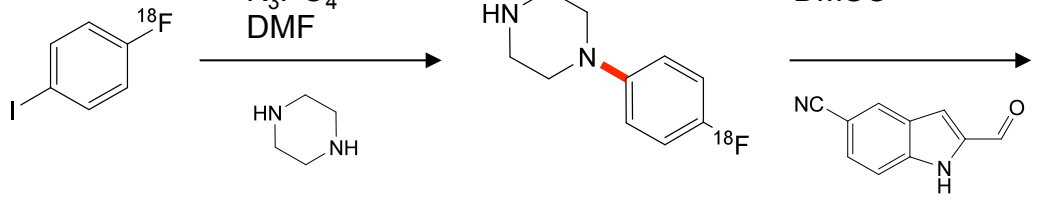




[^{18}F]FAUC 316 by *N*-cross-coupling



FAUC 316 (D_4)

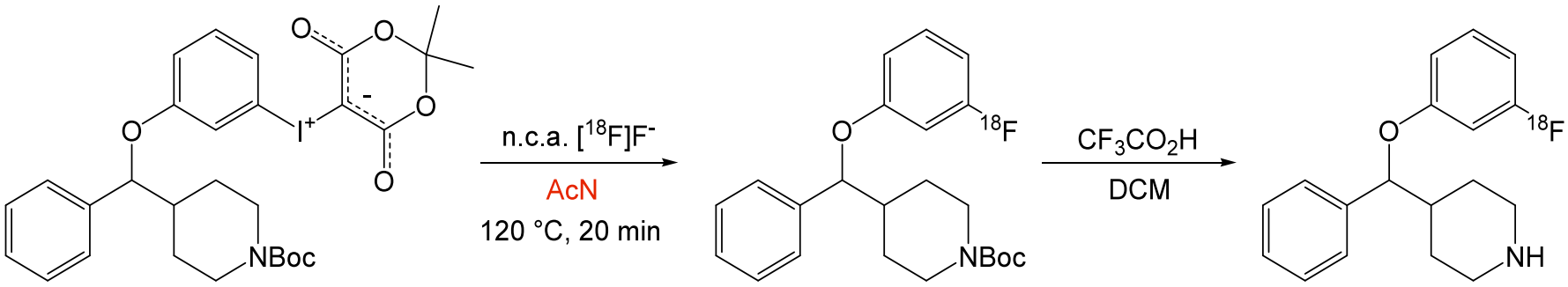


non-specific binding ≥90 %

n.c.a. [^{18}F]FAUC 316

- **$RCY_{(overall)}$ = 15 ± 3 %**
- **RCP > 99 %**
- **A_m = 90 GBq/µmol**

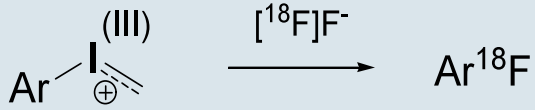
Radiosynthesis of 3-and 4-[^{18}F]FPPMP



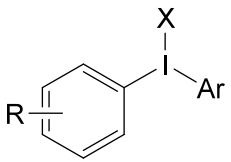
Compound	Time of synthesis	RCY	Molar Activity
3-[^{18}F]FPPMP	ca. 110 min	ca. 20 %	> 50 GBq/µmol
4-[^{18}F]FPPMP	ca. 145 min	ca. 10 %	> 50 GBq/µmol

λ³-Iodane, i.e. “iodonium“, precursors

General formula



Iodonium **salts**:



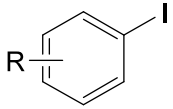
X = OTs, OTf, Br...

Ar = Ph, PhOMe, thiophene, Ar-R

R = "individual"

TsOH / TfOH /…
mCPBA

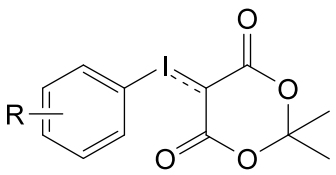
strongly acidic / oxidative



KOH
mCPBA

strongly basic / oxidative

Iodonium **ylides**:



R = "individual"

- **rather independent from e⁻-effects of substituents**
- **high flexibility / variability**

Summary

- The preparation of iodonium salts as precursors too ineffective in various cases.
- Features of iodonium precursors are far from exhausted.
- Suitable iodonium ylides could be prepared with good yields as alternative precursors.
- Target compounds were obtained with satisfying yields by direct labelling of iodonium ylides with n.c.a. [^{18}F]fluoride.

→ **Iodonium ylides offer themselves as promising alternative to iodonium salts.**