CHEMTRIX
Scalable Flow Chemistry

Application Note 24

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Chemtrix BV

'Fluoroalkynylations of Aryl Halides under Continuous Flow Homogeneous Catalysis' [1]

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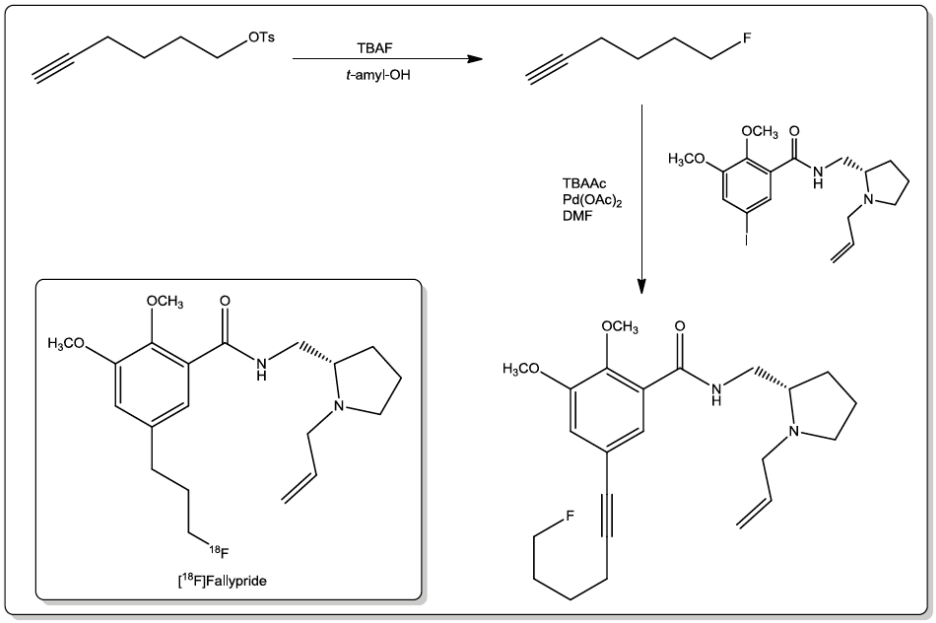


Introduction: Organo-fluorine compounds are increasing in their synthetic importance not only due to their significance in the preparation of pharmaceutical agents but also due to their emerging application as radiopharmaceuticals – which has led to a surge in demand. Consequently, numerous research groups are focusing their activities on the development of facile and selective methods for the efficient incorporation of fluorine into organic molecules. In the case of radiopharmaceuticals, the short half life of ^{18}F ($t_{1/2}$ = 109 min) further increases the importance of reducing the time taken for execution of synthetic, and subsequent purification, steps.

With this in mind, Jones *et al*. [1] recently reported the application of continuous flow techniques for the synthesis of fluorinated alkynyl arenes and heteroarenes utilising a Labtrix®-S1 micro reaction system – with a view to improving reaction time and substrate specificity when compared to conventional synthetic techniques that are based on Sonogashira coupling methodology.

Materials: Dimethylformamide, 2-methyl-2-butanol (*tert*-amyl alcohol), tetrabutylammonium fluoride (trihydrate), tetrabutylammonium acetate and palladium acetate were used as received, without additional purification. Solutions were degassed *via* sparging with argon prior to drawing into the 1 ml glass, gas-tight syringes used for dosing of reagents into the glass micro reactors employed herein.

Figure 1. Illustration of Labtrix®-S1, the automated micro reaction development apparatus developed by Chemtrix.

Reaction Conditions: Reactions were performed using the Labtrix®-S1 system illustrated in Figure 1, suitable for the execution of flow reactions at temperatures ranging from -20 to 195 ºC at pressures up to 20bar. The experiments described herein employed a glass micro reactor with a T-mixer (Device 3023) and a reaction volume of 10 µl. Reagents were dosed *via* 1 ml glass, gas-tight syringes (SGE, UK) and the system maintained at 3 bar. Reaction products were collected automatically into HPLC sample vials containing MeCN (0.1 % formic acid) prior to offline analysis by HPLC.

Analytical Methodology: The flow reaction products were analysed using reversed phase HPLC with detection performed at 254 nm (Waters 2690 solvent delivery system coupled to a Waters 996 PDA detector) and product yield determined utilising 4-bromoaniline as the internal standard.

Nucleophilic Fluorination: The first step in achieving the tandem reaction was to assess the nucleophilic fluorination reaction. Utilising TBAF.3H_2O in *t*-amyl alcohol, the effect of reactor temperature on the S_N2 fluoride displacement of a tosylate was initially investigated under flow conditions (Residence time = 2.5 min), using the reaction manifold and model reaction illustrated in Figure 2.

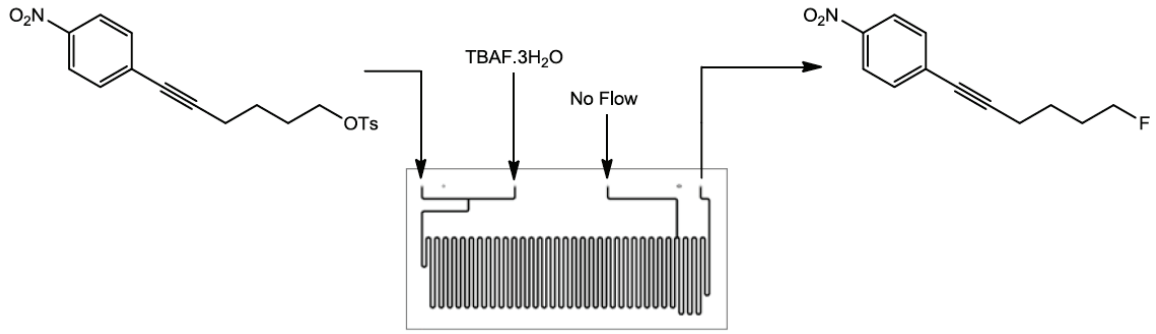


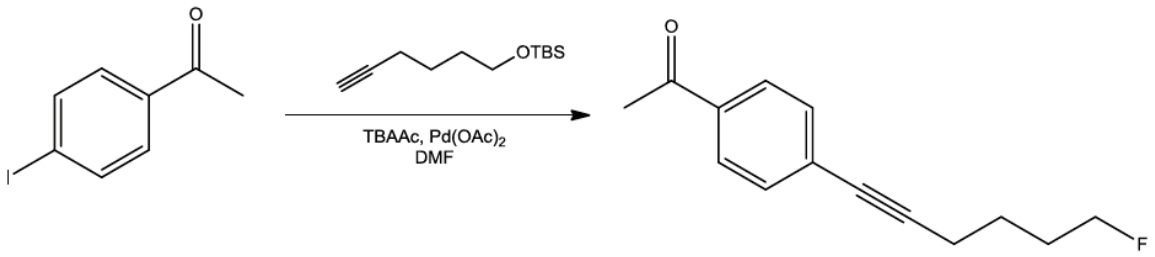
Figure 2. Schematic illustrating the Labtrix® reaction manifold used for the assessment of nucleophilic fluorination under flow conditions.

Whilst 15 h reaction times were required in batch to obtain the target fluoro-compound in 95 % yield, employing a reaction temperature of 100 ºC and 1.5 eq. of TBAF.3H_2O under flow conditions afforded the target fluoroalkyne in quantitative yield – as determined by HPLC analysis. Table 1 illustrates a selection of the reaction conditions assessed prior to identifying the optimal conditions for this particular transformation.

Residence Time (min)	R-OTs Conc. (M)	TBAF.3H$_2$O (Eq.)	Set Temperature (°C)	Yield (%)
2.5	0.3	1	60	29
2.5	0.3	1	70	47
2.5	0.3	1	80	60
2.5	0.3	1	90	87
2.5	0.3	1	100	83
2.5	0.3	1.5	90	95
2.5	0.3	1.5	100	100

Table 1. A selection of the process conditions examined for the nucleophilic fluorination under flow conditions [1].

Cross-coupling Reaction: With literature precedent for the performance of cross coupling reactions utilising alcohols as co-solvents, Jones *et al*. rationalised a strategy whereby the ^{18}F fluorination could be followed in series by an alkynylation reaction to afford the target fluoroalkynes in less than 15 min. With this in mind, the authors initially optimised the reaction conditions using the model system depicted in Scheme 1; between 4-iodoacetophenone and 5-hexyn-1-OTBS.



Scheme 1. Illustration of the model reaction used to optimise the Pd-catalysed coupling reaction.

Imposing an upper temperature limit of 80 ºC to avoid the formation of Pd^0 – commonly associated with temperatures ≥ 90 ºC [2] and which could lead to clogging of the flow reactor, the authors assessed the use of a capillary reactor for the coupling reaction. Assessing the effect of reaction time (1 to 6 min), the authors observed an increase in conversion from 59 to 98 % with increasing reaction time. Gratified with this result, the authors expanded their investigation to demonstrate the *in-situ* fluorination and subsequent coupling reaction [3]. Employing 1.5 eq. of TBAF.3H$_2$O, 1.0 eq. of arene, 1.5 eq. of TBAAc and 5 mol % of Pd(OAc)$_2$ at a substrate concentration of 0.1 M, the scope of the reaction was assessed and the results are summarised in Table 2.

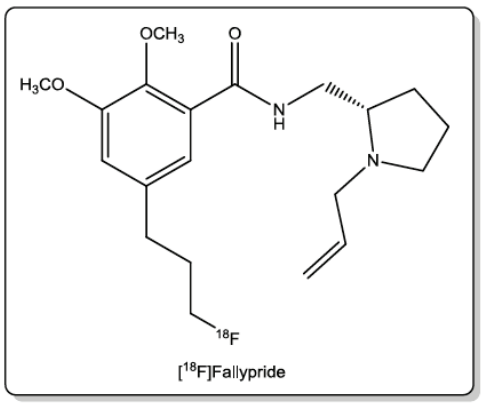
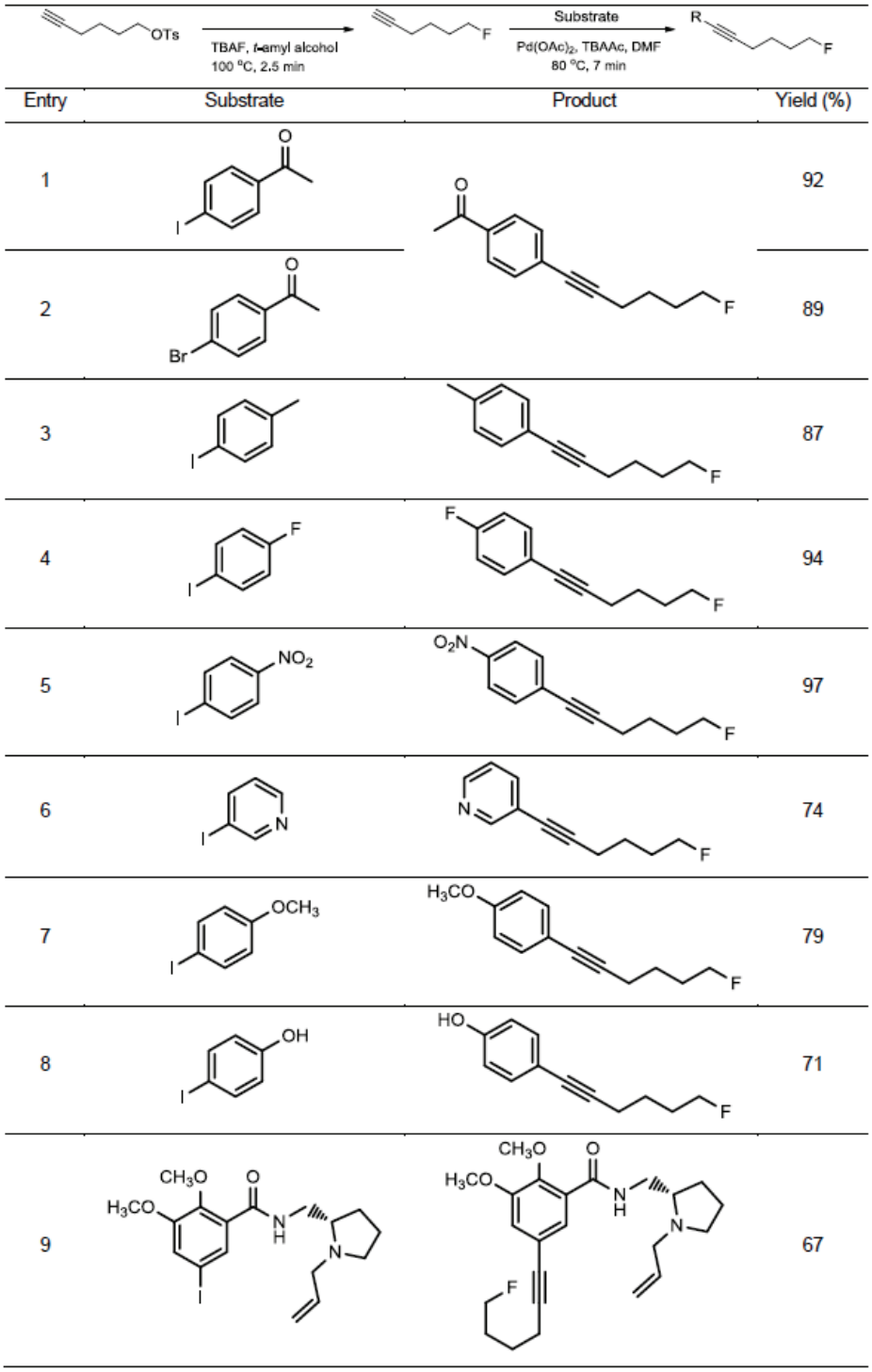


Figure 3. [^{18}F]Fallypride.

Together with evaluating the effect of various aromatic substituents, Entry 9 (Table 2) represents an analogue of Fallypride® (Figure 3), the dopamine D2/3 receptor imaging agent used for assessment of CNS disease including Parkinson's Alzheimer's and Huntington's, together with the disorder Schizophrenia, demonstrating the applicability of the developed methodology towards the on demand synthesis of radiopharmaceuticals.



Entry	Substrate	Product	Yield (%)
1			92
2			89
3			87
4			94
5			97
6			74
7			79
8			71
9			67

Table 2. A selection of fluoroalkynyl derivatives synthesised using the tandem approach described under flow conditions [1].

Conclusion: Applying continuous flow techniques to the synthesis of fluorinated alkynyl arenes and heteroarenes, Jones *et al*. utilised Labtrix®-S1 to demonstrate the ability to improve reaction time and substrate specificity when compared to conventional synthetic techniques. Showing an immediate applicability towards the production of ^{18}F labelled materials for use in Positron Emission Tomography (PET) imaging, the synthesis of an analogue of the Alzheimer's disease imaging agent Fallypride® was reported with a yield of 67 %.

References:

[1]. M. S. Placzek, J. M. Chmielecki, C. Houghton, A. Calder, C. Wiles and G. B. Jones, *J. Flow Chem*., 2013, **3**(2), 46-50.
[2]. R. L. Hartman, *Org. Proc. Res. Dev*., 2012, **16**, 870-887.
[3]. S. Urgaonkar and J. Verkade, *J. Org. Chem*., 2004, **69**, 5752-5755.