Studies of a Diastereoselective Electrophilic Fluorination Reaction Employing a Cryo-Flow Reactor

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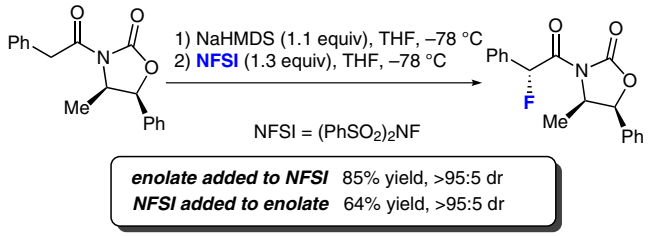
Abstract: The application of meso-scale flow chemistry in research laboratories continues to increase. Here, we report on the use of a modular cryo-flow device as applied to a diastereoselective fluorination process. The reactor can be incorporated into existing flow chemistry setups to permit continuous processing at low temperatures without recourse to cryogenic consumables.

Key words: diastereoselective fluorination, flow chemistry, cryo-flow reactor, polymer-supported reagents, chiral auxiliary

Enantioenriched molecular scaffolds containing fluorine are an interesting class of building blocks for the preparation of new functional compounds.[2] Whilst there are many methods available for the preparation of these types of materials,[3] one approach was particularly noteworthy in the context of an ongoing research project. Specifically, Davis and Kasu reported that the asymmetric auxiliary controlled addition of an enolate to a fluorine electrophile provides the corresponding α-fluorocarbonyl derivatives in both good yields and high diastereoselectivities (Scheme 1).[4]



Scheme 1 Observations made by Davis and Kasu

On scaling the process in batch several observations were made:

Firstly, slow addition of a room temperature solution of *N*-fluorobenzenesulfonimide (NFSI) to a –78 °C solution of a lithium enolate resulted in less than 50% conversion.

Under the same conditions, fast addition of NFSI resulted in much greater conversion (>80%), however, an exotherm of up to 50 °C occurred in the reactor.

Only when both reagents were cooled and the enolate metered into the vessel containing NFSI was high conversion obtained, within the range of 85–90% (HPLC assay).

The reduced conversion obtained upon slow addition of a room temperature solution of NFSI to the enolate can be explained by a propensity for the unreacted parent enolate to protonate by quenching with the more acidic fluorinated product. Presumably the high diastereomeric ratio obtained under these conditions therefore results from asymmetric protonation of the fluorous enolate, although some induction from the direct fluorination cannot be ruled out. The low conversion can be overcome to some extent by fast addition of the NFSI, whereby any pseudo first order concentration effects are minimised and thus the rate of the desired reaction is competitive with that of the unwanted reaction.

Overall, the scaled batch process used to obtain these materials is costly and inefficient, requiring liquid nitrogen based temperature regulation for two large cryogenic reactors. Additionally, the length of time required to cool and later warm the reactors as well as the necessity for the slow dosing of one reagent into the other is a concern. The ΔT values observed for the scaled batch processes without careful control of these addition rates were typically between 20–50 °C. With these clear drawbacks for the batch process, we opted to investigate a flow route, starting at the meso-scale with the eventual vision of moving to a larger, more commercially viable continuous reactor; our findings are summarized herein.

We began by constructing a simple modular apparatus consisting of the recently developed cryo-flow reactor[5] with a Vapourtec R2 unit.[6] Our initial investigations towards a flow method for the diastereoselective fluorination utilized approaches developed in our previous low-temperature borylation work.[7] Specifically, one stream containing both the electrophilic species and the latent organolithium was combined with another stream containing the base. Our reactor comprised two 5 mL reagent loading loops, the stream-one loop was charged with a 5 mL segment of a 0.1 M solution of LiHMDS in tetrahydrofuran and the stream-two loop was charged with a mixture of NFSI and the carbonyl auxiliary, also at 0.1 M in tetrahydrofuran. The two streams were each pumped at 0.5 mL/min passing through a 1 mL pre-cooling coil before combining at a T-piece connector and entering the

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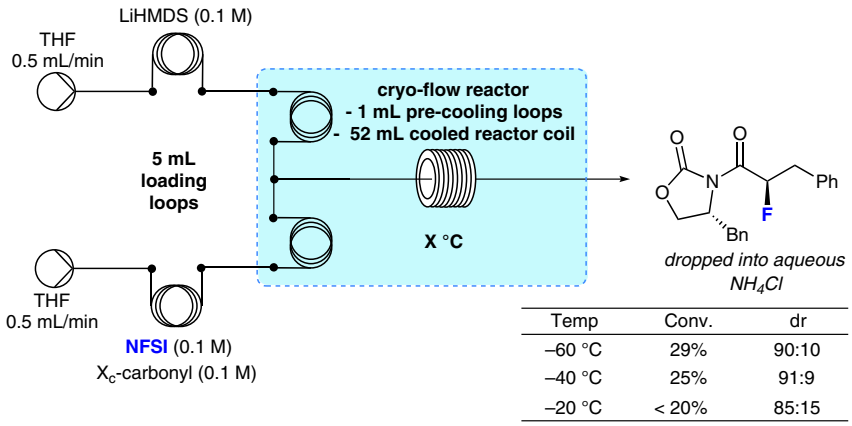


Temp	Conv.	dr
–60 °C	29%	90:10
–40 °C	25%	91:9
–20 °C	< 20%	85:15

Scheme 2 Schematic of the flow apparatus for the in situ quench studies

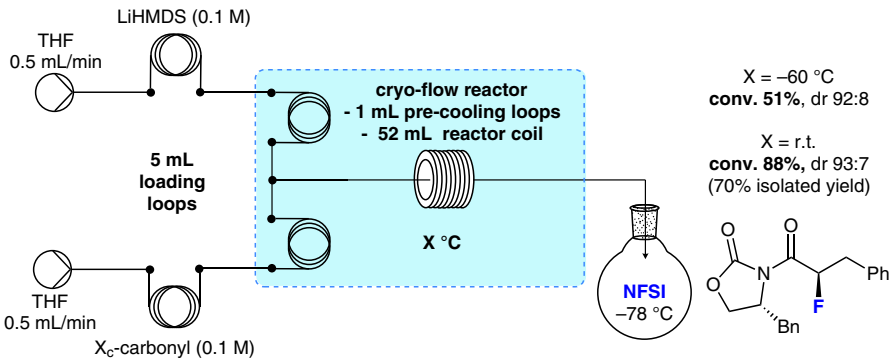
main cooled reactor coil. The reactor output was collected directly in a flask containing a saturated aqueous solution of ammonium chloride (Scheme 2). The temperature of the cryo-flow reactor was varied and the output analyzed. Through the use of this in situ quenching (NFSI present during deprotonation), only low conversion into the desired fluorinated product was observed at –60, –40 and –20 °C.

The setup was modified to provide a sequential addition of the electrophile; the key results are outlined in Scheme 3. It was found that, at these concentrations and flow rates, active cooling was actually detrimental to the lithiation step. However, when the post-reactor NFSI quench-pot was not cooled, the resulting isolated yield was poor. Pleasingly, the percentage conversion could be translated into isolated yield following extraction and flash column chromatography. Although it was noted that the extraction part of this purification process was found to lead to some observed variability, attributable to losses of the corresponding α-fluoro carboxylic acid to the aqueous phase, the ease of hydrolysis of α-substituted amides of this type has previously been documented.[3] However, such cleavage is typically accompanied by an erosion of the enantiomeric excess in the product and so a reductive or peroxy-mediated release protocol is often preferred.[2f]

Having established that a sequence of room temperature deprotonation and subsequent addition of the fluorine electrophile at low temperatures gave the best results, we constructed the corresponding flow setup to reflect this, including a third stream (Table 1). The depicted apparatus allowed us to assess a number of additional parameters. As expected, and inline with the batch and flow observations, performing the quench part of the reaction over a range of low temperatures did not affect the diastereoselectivity of the process (Table 1, entries 1, 2 and 3). However, the conversion into the desired fluorinated product was markedly better when the quench temperature was lowest (c.f. Table 1, entries 1, 2 and 3). It was found that the setup depicted could be reliably used for reaction concentrations up to 0.2 M in oxazolidinone (entry 4), at 0.4 M the system was prone to occasional and unpredictable blockages due to the small tube diameters involved (0.8 mm i.d.).

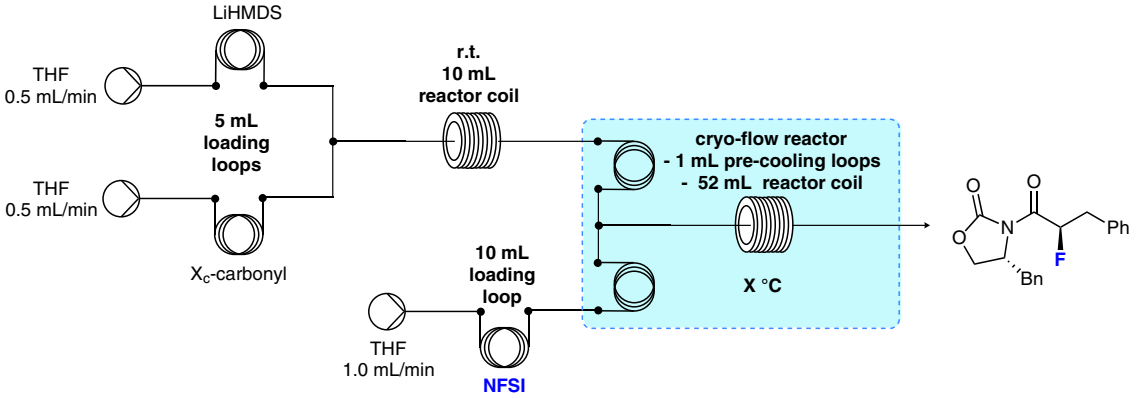
We employed this same experimental setup to provide a further three diastereoenriched fluorinated building blocks, all of which were produced in good selectivity without modification of the protocol (Figure 1).[8] However, hydrolysis during the aqueous extraction of the α-fluoro products remained an issue, as seen by comparison of conversion values with those of the isolated yields.

To some extent this issue can be dealt with by simply recovering the lost material from the aqueous layer. However, when employing meso-scale flow systems a better solution is often to use polymer-supported reagents, to



Scheme 3 Schematic of the flow apparatus for the preliminary assessment of a sequential addition quench protocol

Table 1 Assessment of the Flow Apparatus for the Two-Part Diastereoselective Fluorination Protocol



Entry	[LiHMDS] (M)	[X_c-Carbonyl] (M)	[NFSI] (M)	Temp (°C)	Conv. (%)[a]	dr
1	0.11	0.1 M	0.055 M	–60	84 (60)	92:8
2	0.11	0.1 M	0.055 M	–40	66	91:9
3	0.11	0.1 M	0.055 M	–20	31	93:7
4	0.22	0.2 M	0.2 M	–60	88 (62)	96:4

[a] Numbers in parentheses represent the isolated yield.

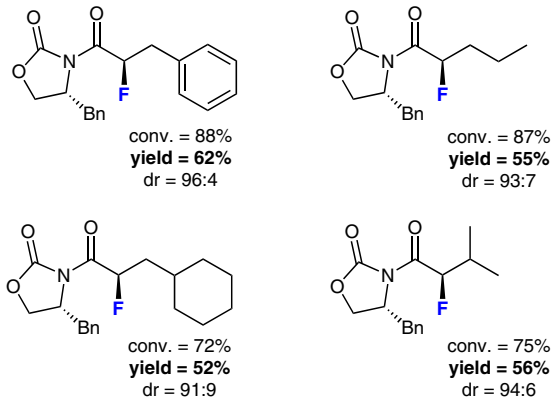
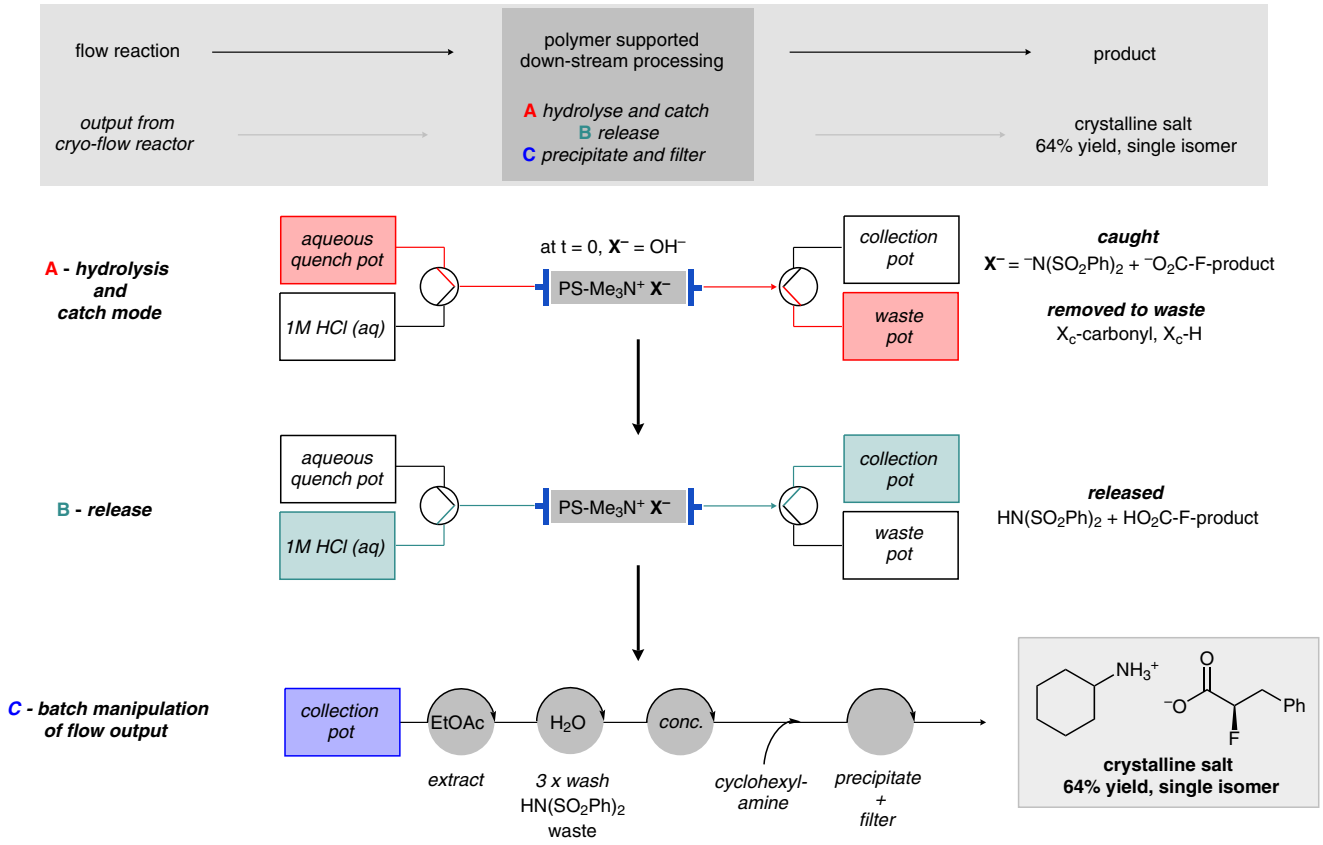


Figure 1 Examples run in this process

avoid any losses and, in this case promote the saponification in-line through downstream processing. We therefore investigated this idea by passing the output stream from the first reaction in the cryo reactor into an aqueous quench pot and then re-pumping this mixture through a column pre-loaded with an ammonium hydroxide resin. Pleasingly, the resin did serve to hydrolyse, deprotonate and catch the resulting α-fluoro carboxylate material on the solid support (see operation A: hydrolysis and catch; Scheme 4). The liquid output from this initial pass of the crude material through the hydroxide cartridge was found to contain both unreacted starting carbonyl-auxiliary and the cleaved auxiliary fragment. We presume, based on these observations, that only the fluorinated product was saponified under these conditions and subsequently bound to the polymeric ammonium resin as the carboxylate ion. In addition to the sequestering of the fluorous carboxylate, the anion of the sulfonimide byproduct derived from NFSI was also caught. At this point the input feed was switched to an aqueous acid reservoir to release the product (see operation B: release; Scheme 4).

Pleasingly, with a greatly simplified product mixture, we were able to perform a series of traditional batch processes (C; Scheme 4) in order to provide a crystalline salt of the product, as a single enantiomer.[9] Importantly for the prospect of scale-up, the method did not require column chromatography. The off-line workup consisted of an organic extraction and aqueous wash to remove the amine byproduct, concentration of the organics, and addition of cyclohexylamine, which permitted crystallization and precipitation of the product in salt form. For longer runs, many of these batch manipulations could be translated into their flow equivalents to further reduce the manual intervention required.[10]

In conclusion, we have reported studies toward the development of a diastereoselective fluorination process under meso-scale flow conditions. These studies include preliminary findings on the configuration of equipment that may be required and the development of a streamlined workup that leads to the isolation of the product in a convenient salt form. Whereas in batch mode the reaction necessitates two cooled reactors and slow reagent addition to ensure good conversion into product, the findings in meso-flow suggest that cooling of the lithiation is not necessary because of the surface area to volume ratios and mixing dynamics involved. Furthermore, the work has highlighted the necessity to ensure that the electrophilic quench is kept cold in order to deliver good conversion into the



Scheme 4 Assisted workup by downstream processing with polymer support

fluorinated product and prevent unwanted side reactions. We believe that further studies on scaling this continuous approach will provide a favourable alternative to the inconsistent batch pilot runs.

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(8) **Typical procedure for the flow synthesis of α-fluoroamides [collection inclusive of slug diffusion (Table 1 and Figure 1)]:** The cryo-flow reactor was set at –60 °C, which took approximately 45 minutes to reach this target from ambient temperature (ca. 22 °C). This process was only

required for the first use, the reactor could then be left at the desired temperature for subsequent processes. The loops were loaded with the corresponding starting materials, at the depicted concentrations, and pumping was initiated at 0.5 mL/min for channels A and B before switching the loaded loops in-line. After 10.5 min, the pump for channel C was turned on and the loaded loop was switched in line. The collected material was quenched directly into a saturated aqueous solution of NH_4Cl, following the end of the run (typically around 45 min) and extracted with EtOAc (3 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient mixture of hexane–EtOAc) to provide the desired products. Complete hydrolysis of these amides can be achieved by using LiOH.

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