Fluorocyclisation via I(I)/I(III) catalysis: a concise route to fluorinated oxazolines

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Abstract
Herein, we describe a catalytic fluorooxygenation of readily accessible N-allylcarboxamides via an I(I)/I(III) manifold to generate 2-oxazolines containing a fluoromethyl group. Catalysis is conditional on the oxidation competence of Selectfluor®, whilst HF serves as both a fluoride source and Brønsted acid activator. The C(sp³)–F bond of the mono-fluoromethyl unit and the C(sp³)–O bond of the ring are aligned in a synclinal relationship thereby engaging in stabilising hyperconjugative interactions with vicinal, electron-rich σ-bonds (σ_C–C→σ*C–F and σ_C–H→σ*C–O). This manifestation of the stereoelectronic gauche effect was established by X-ray crystallographic analysis of a representative example. Given the importance of fluorine in drug discovery, its ability to modulate conformation, and the prevalence of the 2-oxazoline scaffold in Nature, this strategy provides a rapid entry into an important bioisostere class.

Introduction
Marine and terrestrial natural product bioprospecting has established a broad spectrum of structurally complex, bioactive metabolites containing the venerable 2-oxazoline unit [1,2]. This diversity is exemplified by the siderophore antibiotic D-fluviabactin, the cytotoxic agent westiellamide, the antifungal macrolide leupyrrin A₁ and the antitumour compound BE-70016 (Figure 1). In addition, synthetic polymers based on the 2-oxazoline building block constitute versatile platforms for a range of biomedical applications ranging from drug delivery through to tissue engineering [3,4]. Collectively, the importance of the 2-oxazoline scaffold for translational research, together with its strategic value in the design of chiral ligands and auxiliaries [5-7], has culminated in a rich and innovative arsenal of synthetic methods.
To contribute to the current catalysis ordnance for the preparation of 2-oxazolines, and provide a direct route to 5-fluoromethyl derivatives from simple unactivated alkenes, the fluorocyclisation of N-allylcarboxamides facilitated by the in situ generation of p-TolIF₂ was envisaged [8-11]. Since hydrogen and hydroxy groups are often substituted by fluorine in molecular editing processes [12], this transformation would provide facile access to a bioisostere of the parent scaffold (Figure 1, right).

In recent years, I(I)/I(III) catalysis has emerged as a powerful and expansive platform for the generation of structural complexity [13-24]. Motivated by the noticeable absence of mild, catalysis-based strategies to generate the vicinal difluoroethylene motif directly from simple alkenes [25-27], we recently exploited I(I)/I(III) catalysis to enable this transformation [28,29]. Employing Selectfluor® as the terminal oxidant, it was possible to generate p-TolIF₂ in situ from p-iodotoluene and an inexpensive HF source [30-35]. This strategy proved to be mild and general, smoothly converting terminal olefins to the corresponding 1,2-difluoroethylene unit; a substructure that may be considered a chiral, hybrid bioisostere of the Et and CF₃ groups (Figure 2, top) [36].

Since the success of this process is contingent on the efficient generation of p-TolIF₂ in situ, the platform lends itself to related oxidative transformations. To that end, it was envisaged that the protocol could be effectively translated to the fluorocyclisation of readily accessible N-allylcarboxamides (Figure 2, bottom). Whilst the initial phase of catalysis would resemble that of the catalytic difluorination, the presence of the amide would allow the original reaction path to be intercepted to generate a 2-oxazoline with an exocyclic fluoromethyl unit.

Results and Discussion

Optimisation: As a starting point, the conversion of N-allylbenzamide (1) to the corresponding 2-phenyloxazoline 2 was investigated (Table 1). Reactions were performed in DCE (0.2 mol·L⁻¹) with 20 mol % catalyst loading, and using Selectfluor® as the oxidant. An initial reaction screen, based on the conditions reported for our vicinal difluorination study [9].

Figure 1: Selected examples of bioactive compounds containing the 2-oxazoline motif.

Figure 2: The catalytic difluorination of alkenes (top) and the proposed fluorocyclisation via the same I(I)/I(III) manifold (bottom).
began with an exploration of the effect of amine/HF ratio. This was deemed prudent due to the perceived likelihood that HF also functions as a Brønsted acid activator in catalysis. Employing an amine/HF ratio of 1:4.5, product formation was observed (Table 1, entry 1, 46%). Reducing this ratio to 1:3 had a detrimental effect on catalysis efficiency, generating the product in <5% yield (Table 1, entry 2). Increasing the ratio to 1:7.5 and 1:9.23 (Olah’s reagent) restored catalysis efficiency but did not surpass previous observations (44 and 46% yields, Table 1, entries 3 and 4, respectively). For comparison, the reaction was attempted using Pyr-HF (6 equiv) but this alteration had an adverse effect on yield (27%, Table 1, entry 5). Based on these findings, the remainder of the study was performed with an amine/HF ratio of 1:4.5. Reducing the concentration from 0.2 mol·L\(^{-1}\) to 0.1 mol·L\(^{-1}\) led to a large increase in yield (81%, Table 1, entry 6).

| Entry | Concentration [mol·L\(^{-1}\)] | Solvent | Catalyst loading [mol %] | Amine/HF ratio | Conversion\(^b\) [%] | Yield [%]e |
|-------|---------------------------------|---------|--------------------------|----------------|----------------------|------------|
| 1     | 0.2                             | DCE     | 20                       | 1:4.5          | >95                  | 46         |
| 2     | 0.2                             | DCE     | 20                       | 1:3            | 50                   | <5         |
| 3     | 0.2                             | DCE     | 20                       | 1:7.5          | >95                  | 44         |
| 4     | 0.2                             | DCE     | 20                       | 1:9.23         | >95                  | 46         |
| 5     | 0.2                             | DCE     | 20                       | Pyr-HF (6 equiv) | >95                  | 27         |
| 6     | 0.1                             | DCE     | 20                       | 1:4.5          | >95                  | 81         |
| 7     | 0.1                             | toluene | 20                       | 1:4.5          | >95                  | 72         |
| 8     | 0.1                             | MeCN    | 20                       | 1:4.5          | 78                   | 47         |
| 9     | 0.1                             | THF     | 20                       | 1:4.5          | 34                   | <5         |
| 10    | 0.1                             | DCM     | 20                       | 1:4.5          | >95                  | >95        |
| 11    | 0.1                             | DCM     | 10                       | 1:4.5          | >95                  | >95 (67)   |
| 12    | 0.1                             | DCM     | 2.5                      | 1:4.5          | 40                   | 30         |
| 13    | 0.1                             | DCM     | 0                        | 1:4.5          | <5                   | <5         |

\(^a\)Standard reaction conditions: N-allylbenzamide (200 µmol), catalyst p-iodotoluene, solvent, amine/HF source 1:1 (v/v), Selectfluor® (1.5 equiv), ambient temperature, 24 h; \(^b\)Determined from the \(^1\)H NMR spectrum using ethyl fluoroacetate (1.0 equiv) as internal standard; \(^c\)Determined from the \(^19\)F NMR spectrum using ethyl fluoroacetate (1.0 equiv) as an internal standard; \(^d\)Reaction conducted with 1 mL of solvent; \(^e\)Yield after column chromatography on silica gel. Reduction in yield is due to hydrolysis. DCE: 1,2-dichloroethane.

Establishing scope: With a general procedure having been developed, attention was then focused on establishing the scope of the transformation (Figure 3). To explore the effect of changes to the aryl ring, compared to the parent scaffold 2a, representative N-allylcarboxamides containing the p-OCH\(_3\), p-NO\(_2\) and p-CF\(_3\) substituents were exposed to the general conditions (to generate 2b, 2c and 2d, respectively). These transformations proceeded smoothly to deliver the target 2-oxazolines in good yields (up to 69%) and in the case of compound 2c, the fluorocyclisation was performed on a 1 mmol scale with no impact on the yield. However, the aldehyde derivative 2e proved to be more challenging and was isolated in a modest 31% yield. Systems containing ortho-substituents (2f and 2g) were also well tolerated but in the case of 2f it was necessary to extend the reaction time to 40 h. Disubstitution patterns such as in 2h and 2i, the latter of which contains a free phenol moiety, were also tolerated (69% and 65% yield, respectively), as was the highly deactivated pentafluorophenyl analogue 2j (48%). To
briefly explore the effect of chain length on efficiency, the cyclisation of \( N \)-(but-3-en-1-yl)benzamide and \( N \)-(pent-4-en-1-yl)benzamide was explored (to generate 2k and 2l, respectively). Unsurprisingly, whilst the 6-membered ring formed in 42% yield, cyclisation to form the analogous 7-membered ring failed. It was, however, possible to generate heterocyclic species such as the 9-fluorenonyl-substituted oxazoline 2m (48%) and the furan 2n (59%). Whilst it was not possible to generate the bisoxazoline 2o (\( X = N \)), the analogous carbogenic scaffold 2p (\( X = CH \)) formed in 46% yield. Finally, although more challenging, it was also possible to generate an aliphatic 2-oxazoline (2q) in a modest 44% yield.

Finally, to explore possible diastereoselectivity in the cyclisation event, oxazoline 2r was generated from the corresponding \( \alpha \)-chiral amide under standard conditions. Analysis of the crude reaction mixture by \(^{19}\)F NMR allowed a yield of >95% to be determined and a 1:1 dr. This is to be expected given the remote nature of the stereocentre. It is important to note that attempts to separate this compound by column chromatography resulted in significant hydrolysis. Consequently, the oxazoline was exposed to acidic media and quantitatively hydrolysed to the fluorohydrin 3 in 61% yield (Scheme 1). In contrast, the cyclisation to form 2s was highly diastereoselective on account of the proximal nature of the stereocentre (65%, dr >95:5).
Scheme 1: Exploring diastereoccontrol and the synthesis of the fluorohydrin 3. Yields in parentheses were determined by $^{19}$F NMR using ethyl fluoroacetate as an internal standard. Unless otherwise stated, yields refer to isolated values.

Table 2: Crystallographic data for compound 2c.

| Entry                  | Data                        |
|------------------------|-----------------------------|
| formula                | C$_{10}$H$_9$FN$_2$O$_3$     |
| $M_r$                  | 224.19                      |
| crystal size, mm$^3$   | 0.032 × 0.162 × 0.247       |
| crystal system         | orthorhombic                |
| space group            | Pna2$_1$                    |
| cell constants         |                             |
| a, Å                   | 10.0315(3)                  |
| b, Å                   | 15.4164(5)                  |
| c, Å                   | 6.5161(2)                   |
| $V$, Å$^3$             | 1007.71(5)                  |
| Z                      | 4                           |
| $D_m$, Mg m$^{-3}$     | 1.48                        |
| $\mu$, mm$^{-1}$       | 1.06                        |
| F(000), e              | 464                         |
| $T$, K                 | 100(2)                      |
| $\lambda$, Å           | 1.54178                     |
| 2$\theta_{\text{max}}$, deg | 137                      |
| transmissions          | 0.78–0.97                   |
| refl. meas./indep./R$_{int}$ | 10003/1813/0.034 |
| ref. parameters        | 182                         |
| restraints             | 118                         |
| $R$ [F ≥ 4 σ(F)]       | 0.032                       |
| wR (F$^2$, all refl.)  | 0.086                       |
| S                      | 1.05                        |
| $\Delta \rho_{\text{max}}$, e Å$^{-3}$ | 0.145/0.194 |

Conclusion

An operationally simple route to 5-fluoromethyl-2-oxazolines from readily accessible N-allylcarboxamides is disclosed based
on an I(II)/I(III) catalysis manifold. This metal-free fluorocyclisation employs p-iodotoluene (10 mol %) as an inexpensive organocatalyst and Selectfluor® as oxidant. The optimal amine/HF ratio (1:4.5) is easily obtained by combining commercially available triethylamine tris(hydrogenfluoride) (Et₃N·3HF) and Olah’s reagent (Pyr·HF). Broad functional group tolerance is observed in the products, the structures of which display the stereoelectronic fluorine gauche effect.

Supporting Information
Supporting Information File 1
Experimental part.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-88-S1.pdf]

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