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Synthesis of 3-Fluoropyrrolidines and 4-Fluoropyrrolidin-2-ones from Allylic Fluorides

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Abstract: Various 3-fluoropyrrolidines and 4-fluoropyrrolidin-2-ones were prepared by 5-*exo*-*trig* iodocyclisation from allylic fluorides bearing a pending nitrogen nucleophile. These bench-stable precursors were made accessible upon electrophilic fluorination of the corresponding allylsilanes. The presence of the allylic fluorine substituent induces *syn*-stereocontrol upon iodocyclisation with diastereomeric ratios ranging from 10:1 to > 20:1 for all *N*-tosyl-3-fluoropent-4-en-1-amines and amides. The sense and level of stereocontrol is strikingly similar to the corresponding iodocyclisation of structurally related allylic fluorides bearing pending oxygen nucleophiles. These results suggest that the *syn* selectivity observed upon ring closure involves I_2–π complexes with the fluorine positioned *inside*.

Keywords: diastereoselectivity · fluorine · iodocyclization · lactams · nitrogen heterocycles

Introduction

The majority of the drugs produced in the pharmaceutical industry have structural features inspired by natural products. Among them, pyrrolidines hold a prominent position as key motifs or sub-motifs of many alkaloids such as pyrrolizidines and indolizidines.[1] Since fluorine substitution is a well-established strategy to improve the efficacy of lead compounds,[2] fluorinated pyrrolidines have become privileged targets for drug-discovery and in medicinal chemistry research.[3] For example, a recent study of O'Hagan and coworkers revealed that C–F bond incorporation into a peripheral pyrrolidine of a G-quadruplex DNA ligand imposes a distinct pyrrolidine ring conformation with respect to the non-fluorinated analogue and changes the mode of binding.[4] Perhaps, one of the most striking illustrations of the impact of fluorine substitution on N-heterocycles is in the use of diastereomeric fluoroprolines towards the development of hyperstable collagen materials.[5] The preferential C^{γ}-*exo* puckering and C^{γ}-*endo* puckering of (4*R*-F)Pro and (4*S*-F)Pro respectively, was documented 40 years ago[6] and the increased stability of synthetic collagen triple helix bearing (4*R*-F)Pro was reported in 1998.[7] More recently, the use of fluorinated pyrrolidines (and structural derivatives) has been extended to organocatalysis based on the observation that stereoelectronic and electrostatic effects resulting from fluorine substitution can dramatically improve catalyst performance for a range of important transformations.[8] In this general context, our aim was to prepare variously substituted fluorinated pyrrolidines for conformational analysis in solution using a combination of ^{19}F–^{1}H scalar couplings and a ^{19}F–^{1}H 1D HOESY sequence optimised for small molecules, from which ^{1}H–^{19}F internuclear separation estimates could be extracted.[9] Known syntheses of 3-fluoropyrrolidines include the nucleophilic fluorination of hydroxylated precursors,[10] the ring opening of suitably functionalised 3,4-epoxypyrrolidines with fluoride sources,[11] 1,3-dipolar cycloadditions of 3-fluoroacrylates,[12] and the rearrangement of 2-hydroxyalkylazetidines.[13] We opted for the development of a new synthetic route using allylic fluorides as starting materials. In 2008, our group reported that fluorinated tetrahydrofurans and γ-lactones are accessible upon iodocyclisation of allylic fluorides bearing a pending oxygen nucleophile.[14] In these reactions, the fluorine substituent is an effective *syn*-directing group, a stereochemical preference dictated by an *"inside* fluoro effect*"*. Building on these results, we questioned whether this effect would operate with similar efficiency for amino-functionalised allylic fluorides undergoing iodoaminations. An electrophilic fluorination of allylsilanes was envisaged to prepare the necessary allylic fluorides (Figure 1).[15]

This study therefore started with the synthesis of allylsilanes bearing a nitrogen nucleophile suitably protected to undergo both electrophilic fluorination and the programmed cyclisation. The feasibility and the stereochemical aspects of the halocyclisation were examined on a range of precursors leading to fluorinated pyrrolidines and lactams; further functionalisation of a selected ring-closed product is also presented leading to a fluoroindolizidine.

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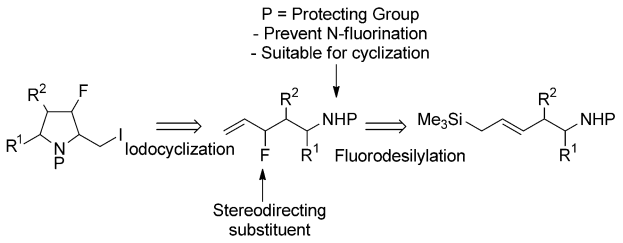
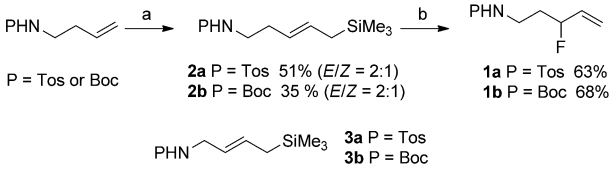


Figure 1. Synthesis of fluoropyrrolidines from allylsilanes.



Scheme 1. Synthesis of **1a** and **1b**: a) allyltrimethylsilane, Grubbs second-generation catalyst (5 mol%), 1,4-benzoquinone, CH_2Cl_2, reflux, 3 days; b) Selectfluor, $NaHCO_3$, MeCN, 48 h.

Results and Discussion

Preliminary validation: The model N-tosylated allylic fluoride **1a** was synthesised to study the feasibility of the halocyclisation.[16] Cross metathesis of *N*-3-butenyl-4-methylbenzenesulfonamide with allyltrimethylsilane under Ru catalysis (second-generation Grubbs catalyst) afforded **2a** as a mixture of *E/Z* isomers (2:1). It was necessary to conduct this reaction in the presence of benzoquinone to minimise olefin migration, a process leading to the truncated side product **3a**.[17] Compound **2a** was subjected to fluorination in acetonitrile upon treatment with 1-chloromethyl-4-fluoro-1,2-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor) in the presence of $NaHCO_3$ leading to compound **1a** in 63% yield. A similar protocol delivered the *N*-Boc-protected allylic fluoride **1b** with comparable yields (Scheme 1).

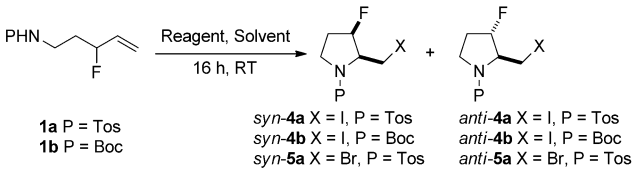
The iodoamination of **1a** was conducted at room temperature with I_2 in various solvents (Table 1, entries 1–4). The use of CH_2Cl_2 and aqueous $NaHCO_3$ was optimal leading to the 3-fluoro-2-iodomethyl pyrrolidine **4a** in 88%. The diastereomeric ratio (d.r.) was 14:1 in favour of the *syn* isomer (Table 1, entry 1). This reaction was superior to the ones performed in CH_3CN, Et_2O, or acetone both in terms of yield and diastereocontrol (Table 1, entries 2–4).

As an alternative to I_2, *N*-iodosuccinimide (NIS) was a suitable I^+ source affording **4a** in 82% yield with a d.r. of 12:1 when the reaction was performed in $CH_2Cl_2/NaHCO_3$ (Table 1, entry 5). *N*-Bromosuccinimide (NBS) was slightly less efficient. Under the best reaction conditions, the brominated fluoropyrrolidine **5a** was formed in 71% conversion as a mixture of diastereomers (8:1; Table 1, entries 7 and 8). The nature of the N-protection had a clear influence on the reaction efficiency, the more acidic NHTos nucleophile being more reactive than NHBoc (NHTos, pK_a (DMSO) $\approx$ 16; NHBoc, pK_a (DMSO) $\approx$ 25).[18,19] Under the best reaction conditions, the cyclisation of the *N*-Boc-protected allylic fluoride **1b** did occur but was significantly less efficient as reflected by the yield (42%) and d.r. (4:1; Table 1, entry 9). The lower level of stereocontrol for **1a** versus **1b** is likely to be due to the different rotational barrier of the carbamate versus the arylsufonamide group.[20] This result prompted us to focus our scope and limitation study on *N*-tosyl-protected allylic fluorides. The stereochemistry of the major diastereomer was assigned based on NOE/HOESY experiments indicating a *syn* relationship between the fluorine and the iodomethyl substituents.[9] X-ray analysis provided unequivocal evidence of the *syn* pyrrolidine being formed preferentially.[9,16]

Scope and limitation: Having established that the iodocyclisations of allylic fluorides **1a** and **1b** are feasible and superior for **1a**, we examined next the scope of this reaction with a series of racemic compounds **1c–i** selected based on diversity in terms of substitution patterns. Compounds **1h** and **1i** serve to probe the reactivity of substrates featuring the N-nucleophile one methylene group closer or further apart from the double bond. Compound **1g** is a potential precursor of 4-fluoropyrrolidin-2-one (Figure 2).

Several synthetic routes were applied to synthesise **1c–i**. A metathesis reaction was the key assembling step to access most silylated precursors. The ring-closing metathesis of readily accessible alkenyloxysilanes followed by ring opening with MeLi at −78 °C in THF led to the formation of the homoallylic alcohols **6** and **7**. Mesylation followed by nucleophilic substitution with tosylamine afforded **2c** and **2d**. The electrophilic fluorination was performed in acetonitrile at room temperature in the presence of $NaHCO_3$. This reac-

Table 1. Iodo- and bromoamination of allylic fluorides **1a** and **1b**.



Entry	1	Reagent	Solvent	Product	Yield [%][a]	d.r. (*syn*/*anti*)[b]
1	**1a**	I_2	$CH_2Cl_2/NaHCO_3$ (1:1)	**4a**	88	14:1
2	**1a**	I_2	CH_3CN	**4a**	50	10:1
3	**1a**	I_2	Et_2O	**4a**	51	10:1
4	**1a**	I_2	acetone	**4a**	39	8:1
5	**1a**	NIS	$CH_2Cl_2/NaHCO_3$ (1:1)	**4a**	82	12:1
6	**1a**	NIS	CH_3CN	**4a**	56	12:1
7	**1a**	NBS	$CH_2Cl_2/NaHCO_3$ (1:1)	**5a**	71[c]	8:1
8	**1a**	NBS	CH_3CN	**5a**	61	11:1
9	**1b**	I_2	$CH_2Cl_2/NaHCO_3$ (1:1)	**4b**	42	4:1

[a] Isolated yields. [b] Determined by ^{19}F NMR analysis of the crude product. [c] Conversion.

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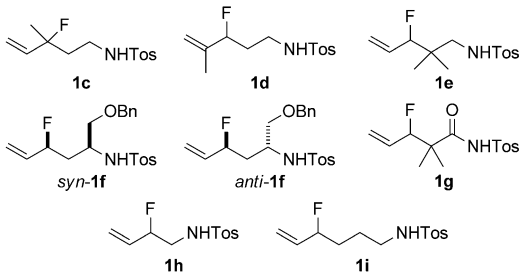
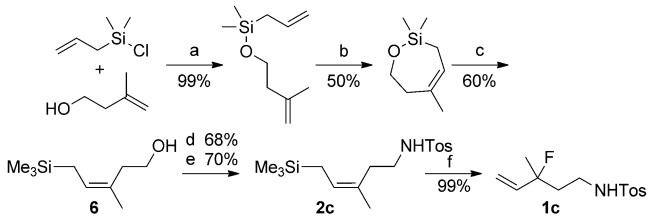
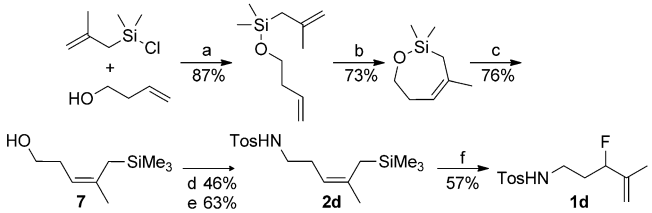


Figure 2. Selection of allylic fluorides for iodo-N-cyclisation.



Scheme 2. Synthesis of **1c** by ring-closing metathesis (RCM) and electrophilic fluorination: a) NEt_3, CH_2Cl_2, 0 °C, 15 h; b) Hoveyda–Grubbs second-generation catalyst (2 mol %), CH_2Cl_2, reflux, 1.5 h; c) MeLi, THF, −78 °C, 4 h; d) MsCl, NEt_3, CH_2Cl_2, 0 °C, 2.5 h; e) NH_2Ts, KOH, DMF, 120 °C, 3 h; f) Selectfluor, CH_3CN, $NaHCO_3$, RT, 24 h.

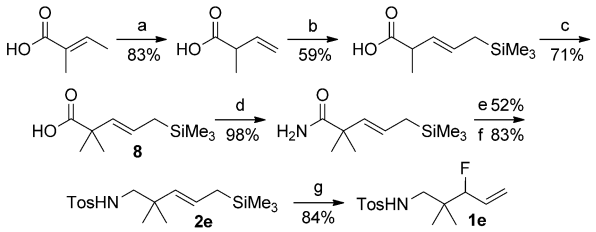


Scheme 3. Synthesis of **1d** by RCM and electrophilic fluorination: a) NEt_3, CH_2Cl_2, 0 °C, 15 h; b) Hoveyda–Grubbs second-generation catalyst (2 mol %), CH_2Cl_2, reflux, 1.5 h; c) MeLi, THF, −78 °C, 4 h; d) MsCl, NEt_3, CH_2Cl_2, 0 °C, 2 h 30 min; e) NH_2Ts, KOH, DMF, 120 °C, 3 h; f) Selectfluor, CH_3CN, $NaHCO_3$, RT, 24 h.

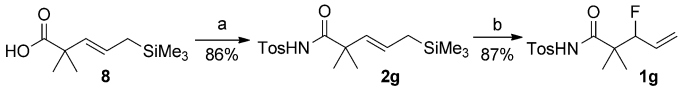
tion was quantitative for **2c** giving **1c** in 99% yield; **1d** was isolated in 57% yield (Scheme 2 and Scheme 3).

Compounds **1e-i** were prepared by using a cross metathesis and an electrophilic fluorination as key steps. The synthesis of the *gem*-dimethylated trimethylallylsilane **8** commenced with the deconjugative isomerisation of tiglic acid. Cross metathesis of the resulting β,γ-unsaturated carboxylic acid with allyltrimethylsilane followed by methylation led to the desired 2,3-dimethyl-5-trimethylsilylpent-3-enoic acid **8**. The conversion of **8** into **2e** required amide formation, reduction and tosylation. The electrophilic fluorination of **2e**, carried out under standard conditions, was high yielding (84%, Scheme 4).

The fluorination of amide **2g** (prepared in one step upon treatment of carboxylic acid **8** with tosylisocyanate) is also



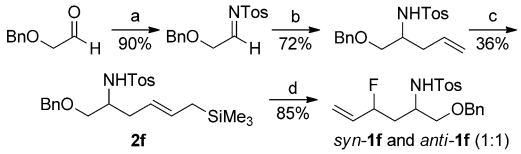
Scheme 4. Synthesis of **1e** by cross metathesis and electrophilic fluorination: a) lithium diisopropylamide (LDA), THF, −78 °C, 1 h; b) allyltrimethylsilane, Hoveyda–Grubbs second-generation catalyst (3 mol %), CH_2Cl_2, reflux, 24 h; c) LDA, MeI, THF, −78 °C, 1 h; d) 1,1′-carbonyldiimidazole (1,1′-CDI), NH_4OH, DMF, 80 °C, 1 h; e) $LiAlH_4$, THF, RT, 16 h; f) TsCl, NEt_3, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, RT, 3 h; g) Selectfluor, $NaHCO_3$, RT, 48 h.



Scheme 5. Synthesis of **1g** by cross metathesis and electrophilic fluorination: a) *p*-tosyl isocyanate, NEt_3, THF, 1 h; b) Selectfluor, $NaHCO_3$, CH_3CN, 48 h.

an efficient transformation delivering **1g** in 87% yield (Scheme 5).

The synthesis of *syn*-**1f** and *anti*-**1f** began with the allylation of *N*-(2-benzyloxy)ethylidene)tosylamine. Cross metathesis of the resulting homoallylic *N*-tosylamine with allyltrimethylsilane gave access to **2f** as a mixture of *E*/*Z* geometrical isomers (≈1:1). Fluorodesilylation led to the desired allylic fluoride **1f** in 85% yield (Scheme 6).



Scheme 6. Synthesis of *syn*-**1f** and *anti*-**1f** by cross metathesis and electrophilic fluorination: a) $TosNH_2$, sodium toluene sulfimide, HCO_2H, H_2O, 24 h; b) allylmagnesium bromide (1 M in Et_2O), CH_2Cl_2, −78 °C, 5 h; c) allyltrimethylsilane, Grubbs second-generation catalyst (5 mol %), 1,4-benzoquinone, CH_2Cl_2, reflux, 3 days; d) Selectfluor, $NaHCO_3$, CH_3CN, 48 h.

As expected,[21] the presence of the remote stereogenic centre in **2f** did not induce stereocontrol upon fluorination and two diastereomers (1:1) were formed; these could be separated by silica gel chromatography.

The synthesis of allylic fluorides **1h–i** is straightforward applying the standard cross metathesis/fluorination sequence (Scheme 7).

Notably, all allylic fluorides **1a–i** were found to be bench stable and could be kept without decomposition at room temperature for an extended period of time.

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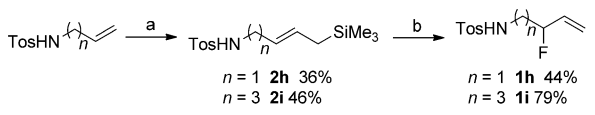
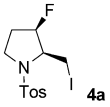
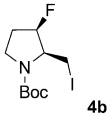
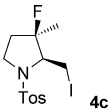
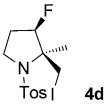
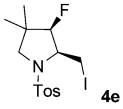
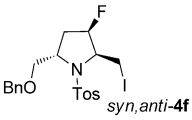
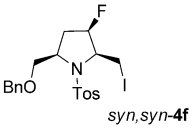
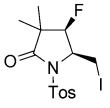
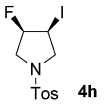
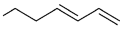


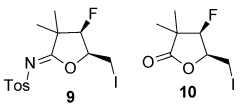
Scheme 7. Synthesis of **1h** and **1i** via cross-metathesis and electrophilic fluorination: a) allyltrimethylsilane, Hoveyda–Grubbs second-generation catalyst (5 mol%), 1,4-benzoquinone, CH_2Cl_2, reflux, 3 days; b) Selectfluor, $NaHCO_3$, CH_3CN, 48 h.

Allylic fluorides **1c–i** were subjected to iodocyclisation at room temperature with I_2 either in acetonitrile in the absence of base (conditions **A**) or in CH_2Cl_2/aqueous $NaHCO_3$ (conditions **B**) (Table 2).[16] The reaction tolerates *gem*-disubstituted alkenes as well as quaternary fluorinated allylic carbon atoms. The iodocyclisation of allylic fluorides **1c** and **1d** led to the fluoropyrrolidines **4c** and **4d** in 85% and 65% yield respectively (Table 2, entries 3 and 4). The diastereomeric ratio was found to be >8:1 consistently in favour of the *syn* isomer. For **1c**, the level of diastereocontrol was dependent on the solvent, better results being obtained in CH_3CN (d.r. = 12:1 versus 8:1), but at the expense of reduced chemical yield (from 85 to 42%) (Table 2, entry 3). Using acetonitrile, compound **4d** was formed in 65% yield as a 10:1 mixture of diastereomers (Table 2, entry 4). The cyclisation of compound **1e** featuring a *gem*-dimethyl group was quantitative and proceeded with complete stereocontrol (d.r. > 20:1; Table 1, entry 5).[22] The structurally related *gem*-disubstituted amide **1g** cyclised successfully under conditions A or B (Table 2, entry 8). In CH_2Cl_2/$NaHCO_3$, two separable products **4g** and **9** (overall yield 86%) resulting from both N- and O-cyclisation were formed.[23] Structural assignment was consistent with IR data (N-cyclisation: 1738 cm^{-1}; O-cyclisation: 1650 cm^{-1}) and unambiguously confirmed based on single-crystal X-ray analysis secured for both structural isomers **4g**[9] and **9**.[16] In the ^{13}C NMR spectra, the chemical shift for the carbon bearing the iodomethyl group was very distinctive (N-cyclisation: $\delta = 61.9$ ppm; O-cyclisation: $\delta = 85.2$ ppm). Both cyclisations products led to a single *syn* isomer. In acetonitrile, the lactone *syn*-**10** (d.r. > 20:1) was isolated in 84% yield with no evidence for the lactam product in the crude mixture. The cyclisation of *syn*-**1f** and *anti*-**1f** led to the fluoropyrrolidines *syn,anti*-**4f** and *syn,syn*-**4f**, respectively in good yields and with comparable control over selectivity (>13:1) (Table 2, entries 6 and 7). The observed sense of diastereocontrol is therefore imposed by the allylic fluorine substituent, not the stereogenic centre proximal to the N-nucleophile. The homoallylic amine **1h** underwent 5-*endo-trig* cyclisation under more forceful conditions (conditions **C**: CH_3CN, 75°C). The yield of **4h** remained low, just under 30%, and the selectivity in favour of the *syn*-fluoropyrrolidine was moderate (10:1; Table 2, entry 9).[24] Finally, compound **1i** could not be cyclised. Under mild conditions (**A** or **B**), the starting material remained intact with no evidence of 6-*exo-trig* ring closure. The diene **11** resulting from elimination was observed under conditions **B** (Table 2, entry 10). This result is consistent with the observation that the structurally

Table 2. Iodocyclisation of allylic fluorides **1a–i**.

Entry	1	Product	Conditions[a]	Yield [%][b]	d.r. (*syn*/*anti*)[c]
1	**1a**	 **4a**	**A**	50	10:1
			B	88	14:1
2	**1b**	 **4b**	**B**	42	4:1
3	**1c**	 **4c**	**A**	42	12:1
			B	85	8:1
4	**1d**	 **4d**	**A**	65	10:1 (>20:1)[d]
5	**1e**	 **4e**	**B**	97	>20:1
6	*syn*-**1f**	 *syn,anti*-**4f**	**B**	78	17:1 (>20:1)[d]
7	*anti*-**1f**	 *syn,syn*-**4f**	**B**	95	13:1
8	**1g**	 **4g**	**A**	–[e]	–
			B	62[f]	>20:1
9	**1h**	 **4h**	**C**	29	10:1 (>20:1)[d]
10	**1i**	TosHN  **11**	**B**	0	–

[a] Conditions **A**: I_2, CH_3CN, 16 h, RT; Conditions **B**: I_2, CH_2Cl_2/$NaHCO_3$ (aq) (1:1), 16 h, RT; Conditions **C**: CH_3CN, 75°C. [b] Isolated yields. [c] Determined by ^{19}F NMR analysis of the crude product. [d] d.r. after purification. [e] The reaction yielded the lactone **10** in 84% yield (d.r. > 20:1); no trace of **4g** in the reaction mixture. [f] This reaction also gave 24% yield of **9** (d.r. > 20:1).



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related *N*-tosyl-4-hydroxy-5-hexenylamine did not undergo cyclisation with various halogen electrophiles.[18] The relative stereochemistry of compound **4a–h** was unambiguously assigned by a combination of NOE/HOESY experiments and X-ray diffraction analysis when possible.[9]

The preferential *syn* selectivity observed for all *5-exo-trig* cyclisations is in accordance with the fluorine-directed diastereoselective iodocyclisation of structurally related allylic fluorides bearing a pending oxygen nucleophile (alcohol or carboxylic acid) (Figure 3).[14] The diastereoselectivities observed are strikingly similar between these two series of compounds, a safe indicator that the same effects are responsible for the observed sense of stereocontrol.

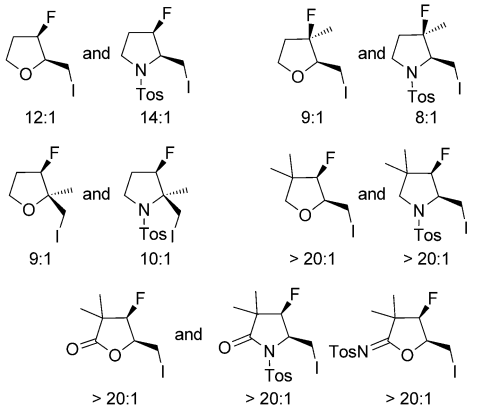


Figure 3. Iodocyclisation of allylic fluoride with O- versus N-nucleophile.

The reaction appears to be under kinetic control, since additional experiments indicate that prolonging the reaction time or heating the reaction mixture did not alter the d.r. When **1a** (d.r. 14:1) was subjected to the reaction conditions, this material was recovered intact after 16 h. It is therefore reasonable to advance that, by analogy with the fluorine-directed diastereoselective iodoetherification and iodolactonisation of allylic fluorides, the preferential *syn* selectivity of the cyclisations shown in Table 2 arises from the formation of a loosely associated I_2–π complex adopting the preferential *inside* fluoro conformation. The proximally oriented tosylated amino group is ideally positioned for backside attack on the iodonium ion (Figure 4).

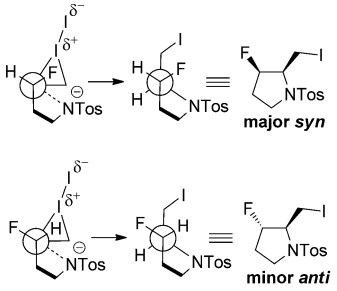
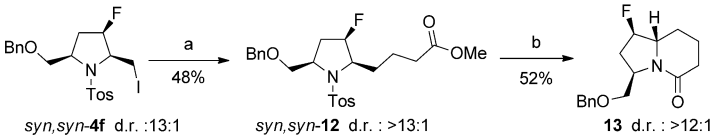


Figure 4. Rationale for *syn*-preference.

To demonstrate that further functionalisation of 3-fluoro-2-iodomethyl-*N*-tosyl-pyrrolidines is possible, we transformed the representative fluoropyrrolidine *syn,syn*-**4f** (d.r. = 13:1) into the corresponding indolizidine **13** (Scheme 8). The union of methyl acrylate with **4f** upon treatment with CuI and zinc in methanol/water led to compound **12** with no erosion of d.r.[25] The reaction of **12** with Na/Hg (5%) and Na_2HPO_4 in MeOH allowed for reductive deprotection of the amine and its subsequent cyclisation. The desired indolizidine **13** was isolated in 52% (d.r. > 12:1).



Scheme 8. Synthesis of indolizidine **13**: a) CuI, Zn, methyl acrylate, H_2O/MeOH, sonicated, 45 min; b) Na/Hg (5%), Na_2HPO_4, MeOH, 3 h.

Conclusion

This study presents the first examples of iodocyclisation with functionalised allylic fluorides bearing nitrogen nucleophiles. The *5-exo-trig* cyclisation of variously substituted *N*-tosylated 3-fluoro-4-pentenylamines is a suitable transformation to prepare 3-fluoropyrrolidines in high yields (up to 97%) and with good to excellent level of diastereocontrol (up to d.r. > 20:1). The method can be extended to the preparation of 4-fluoropyrrolidinones. The sense and level of diastereocontrol observed upon iodoamination is imposed by the fluorine substituent and influenced by the N-protecting group. The more acidic *N*-tosylamine nucleophiles were found to be superior nucleophiles (yield and d.r.) in comparison with the corresponding *N*-Boc carbamates. The striking similarities observed for allylic fluorides bearing *O*- and *N*-tosyl nucleophiles with respect to stereocontrol, suggest that the cyclisations studied herein are likely to involve I_2–π complexes with the fluorine adopting the *inside* position. The *5-endo-trig* cyclisation of *N*-(*p*-tolylsulfonyl)-3-fluoro-4-butenylamine was found to be successful but low yielding. In contrast, 3-fluoropiperidines could not be accessed using this methodology. The necessary allylic fluorides were prepared reliably by electrophilic fluorination of the corresponding allylsilanes. As presented, the synthesis of the starting allylsilanes requires multiple steps and this will need optimisation for large-scale operation. However, with the appearance of new transition-metal catalysed (asymmetric) allylic fluorinations, one can now envisage accessing (enantiopure) aminated allylic fluorides from the corresponding allylic alcohols or chlorides with fluoride.[26] These new routes could potentially speed up the access to this important class of compounds that are 3-fluoropyrrolidines.

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Experimental Section

Representative synthetic procedure—preparation of (±)-3-fluoro-2-(iodomethyl)-1-[(4-methylphenyl)sulfonyl] pyrrolidine (4a): To a solution of allylic fluoride **1a** (100 mg, 0.39 mmol, 1 equiv) in saturated $NaHCO_3$ solution/CH_2Cl_2 (1:1; 0.13 M) in a darkened vessel, was added iodine (218 mg, 0.86 mmol, 2.2 equiv). The reaction mixture was then stirred overnight before being quenched by the addition of saturated NaS_2O_3 solution/saturated $NaHCO_3$ solution (1:1). The aqueous layer was extracted three times with Et_2O, the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel (hexane/Et_2O 8:2) to yield **4a** (131 mg, 88%, d.r. 14:1) as a white solid. *Data for the major syn diastereoisomer*: R_f = 0.4 (hexane/EtOAc 7:3); m.p. = 72 °C; ^{1}H NMR (500 MHz, C_6D_6) δ = 0.52 (ddddd, 1H, ^3J(H,F) = 42.2 Hz, ^2J(H,H) = 14.0 Hz, ^3J(H,H) = 12.2, 8.7, 3.4 Hz), 1.21 (ddd, 1H, ^3J(H,F) = 16.0 Hz, ^2J(H,H) = 14.0 Hz, ^3J(H,H) = 5.4 Hz), 1.86 (s, 3H), 3.22 (ddd, 1H, ^2J(H,H) = 11.7 Hz, ^3J(H,H) = 12.2 Hz, 5.4 Hz), 3.28 (dd, 1H, ^3J(H,H) = 11.6 Hz, ^2J(H,H) = 9.3 Hz), 3.40 (dd,1H, ^2J(H,H) = 11.7 Hz, ^3J(H,H) = 8.7 Hz), 3.67 (dddd, 1H, ^3J(H,F) = 23.8 Hz, ^3J(H,H) = 11.6, 3.9, 3.7 Hz), 3.93 (ddd,1H, ^2J(H,H) = 9.3 Hz, ^4J(H,F) = 3.9 Hz, ^3J(H,H) = 3.9 Hz), 4.63 (ddd, 1H, ^2J(H,F) = 52.2 Hz, ^3J(H,H) = 3.7, 3.4 Hz), 6.68 (d, 2H, ^3J(H,H) = 7.9 Hz), 7.54 ppm (d, 2H, ^3J(H,H) = 8.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 1.1 (d, ^3J(C,F) = 12.8 Hz), 21.6, 31.5 (d, ^2J(C,F) = 21.6 Hz), 48.6, 65.9 (d, ^2J(C,F) = 19.2 Hz), 93.5 (d, ^1J(C,F) = 184.5 Hz), 127.4, 130.1, 133.9, 144.3 ppm; ^{19}F{^{1}H} NMR (377 MHz, C_6D_6) δ = −196.48 ppm; IR (KBr): $\tilde{\nu}$ = 1685, 1330, 1160, 982, 772 cm^{-1}; HRMS (CI$^+$): *m/z* calcd for $C_{12}H_{16}FINO_2S$ ($[M+H]^+$): 383.9931; found: 383.9947. *Characteristic data for the minor anti diastereoisomer*: ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ = −176.26 ppm.

X-ray crystallographic analysis: Samples of **4c** and **9** were quench cooled to 150 K using an Oxford Cryosystems Cryostream 600 series open flow N_2 cooling device.[27] Data were collected using a Nonius Kappa-CCD and intensity data were processed using the DENZO-SMN package.[28] The structures were solved by direct methods[29] and refined by full-matrix least squares on F^2 using the CRYSTALS suite;[30] hydrogen atoms were treated in the usual manner.[31] CCDC-896062 (**4c**) and CCDC-896063 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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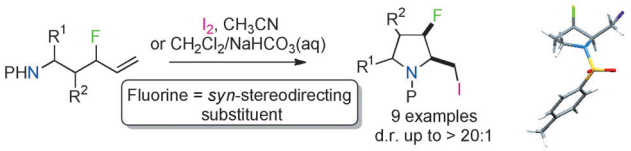
Synthetic Methods



The 5-*exo*-*trig* cyclisation of N-protected allylic fluorides leads to fluoropyrrolidin(on)es in yields up to 97%. The fluorine substituent is an efficient stereodirecting group imposing a *syn* relationship with the newly formed iodomethylated stereogenic centre (see scheme). The striking similarities, with respect to stereocontrol, observed for allylic fluorides bearing *O*- and *N*-tosyl nucleophiles indicate that the cyclisations studied herein involve I_2–π complexes with the fluorine adopting the *inside* position.

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