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Diastereoselective synthesis of fluorinated piperidine quinazoline spirocycles as iNOS selective inhibitors

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ABSTRACT

A diastereoselective synthesis of fluoropiperidine quinazoline spirocycles has been developed through a silyl triflate mediated intermolecular coupling of difluorobenzamidine and racemic N-protected 3-fluoropiperidine dimethyl ketals or piperidones. Combination of the silyl reagents together with Lewis acids (such as $BF_3{\cdot}OEt_2$, $ZnCl_2$, $InCl_3$, etc.) accelerated the coupling reaction to afford the desired fluorospirocycles in good yields (40–83%) and high diastereoselectivity. A ratio of the two diastereoisomers of up to 10:1 in favor of the desired isomer can be achieved.

The fluorine atom has been routinely utilized in medicinal chemistry programs in order to fine-tune the physicochemical, pharmacological, and drug metabolism and pharmacokinetic (DMPK) properties of drug-like molecules. The unique properties of the fluorine atom, such as small size and strong electron-withdrawing ability, frequently make fluorinated compounds more metabolically stable, yet often with minimum impact on pharmacology.[1] On the other hand, the C–F bond may change the physicochemical features of a molecule markedly (e.g., amine pK_a and hence lipophilicity at physiological pH, Log$D$) and so may have a significant impact on the biological properties.[2] As a result, the regioselective and stereoselective introduction of a fluorine atom into drug candidates is a fairly common strategy in modern medicinal chemistry.[3]

We have previously reported the identification of iNOS selective inhibitors based on fluoropiperidine spirocyclo-3,4-dihydroquinazolines. Inducible nitric oxide synthase (iNOS) is an isoform of NOS that catalyzes the formation of NO from arginine.[4] Inhibitors of iNOS have been proposed as treatments for a variety of conditions involving the immune response and inflammation, including rheumatoid arthritis and neuropathic pain. In order to improve the metabolic stability of the lead compound AR-C 102222 **1**,[5] and to improve the cell permeability by reducing amidine basicity, we introduced a fluorine atom at the 3-position of the piperidine ring of **1** (Fig. 1). Our goal was, (i) to reduce the basicity and increase the lipophilicity of the amidine moiety at physiological pH (Log$D$) in order to improve cellular membrane permeability and CNS exposure and (ii) to stabilize the aminal moiety. Two promising

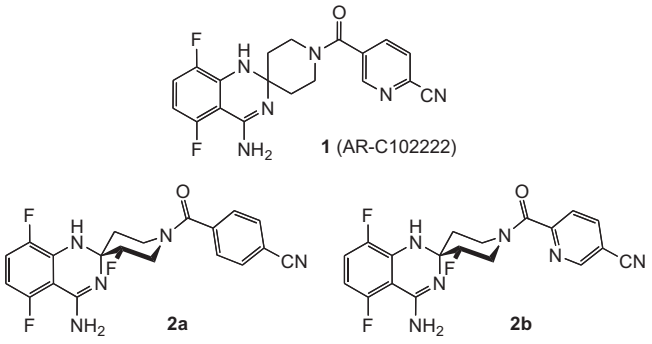

Figure 1. Spirocyclic fluoropiperidine quinazoline selective iNOS inhibitors: **1** (AR-C102222) and the F-Piperidine Spirocyclic iNOS inhibitors **2a** and **2b**.

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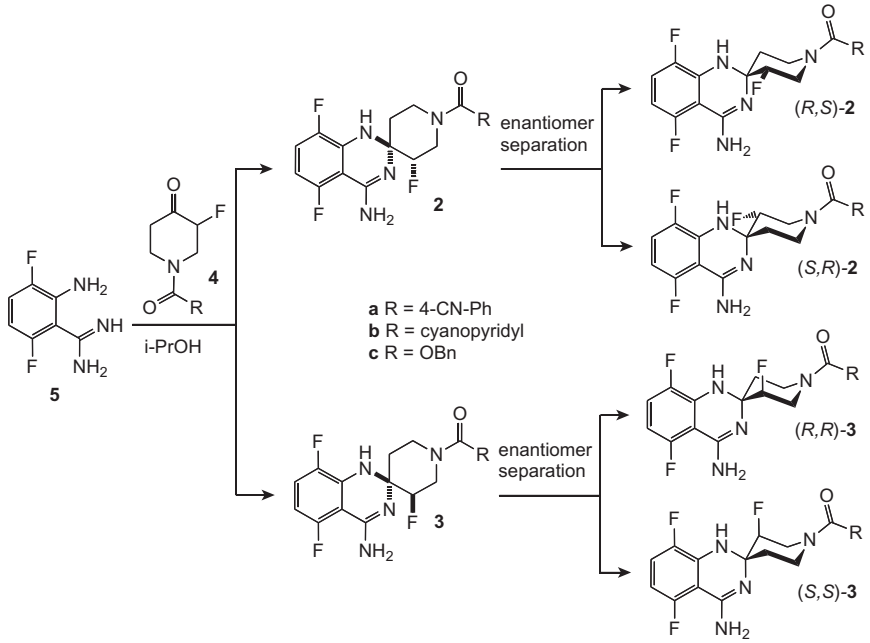


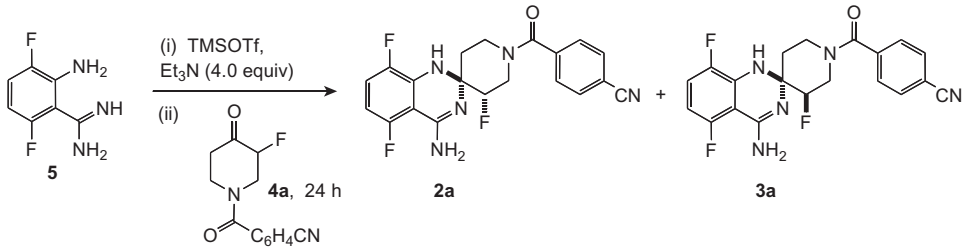
Scheme 1. A synthetic route to fluoropiperidine spirocycles **2** and **3**.

compounds **2a** and **2b** have been identified, which retain iNOS inhibitory potency and selectivity over other NOS isoforms and have excellent oral efficacy in rodent models of neuropathic pain. The potential of **2a** and **2b** as novel analgesics and the details of the fluorine atom's effects on the physicochemical and pharmacological properties of the iNOS selective inhibitors will be reported elsewhere.[6]

As the introduction of a fluorine atom generates two stereogenic centers in the final fluorinated iNOS inhibitors **2a** and **2b**, a simple and practical method for the synthesis of these compounds as single stereoisomers was required. Of the four possible stereoisomers, the desired stereoisomer is the one in which the fluorine atom resides in an equatorial position on the piperidine ring and has a *cis*-relationship to the amidine group of the quinazoline ring. The formation of **2a** and **2b** would thus need to be accomplished with both diastereo- and enantiocontrol. In recent years, various enantioselective fluorination methods have been achieved utilizing a variety of conditions, including the use of organic chiral sulfonamide-type fluorination reagents, Cinchona alkaloid/Selectfluor® or NFSI combinations, and by using organometallic catalysis, for example, chiral palladium or chiral titanium complexes.[7] There is however no precedence for achieving a diastereocontrolled synthesis of compounds such as **2a** and **2b**. In this Letter, we disclose a synthesis of fluoropiperidine spirocycles **2** as iNOS selective inhibitors by the diastereocontrolled coupling of a difluorobenzeneamidine[5] with a racemic fluoropiperidinone[8,9] mediated by Lewis acid agents.[10]

Initially, we examined the direct fluorination of AR-C102222 using Selectfluor™, but this led to the formation of complex mixtures. Therefore an approach in which fluorinated piperidinones

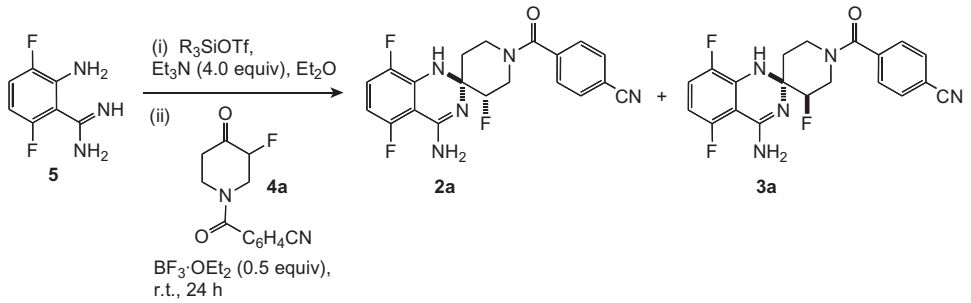
Table 1
TMSOTf mediated coupling of amidine **5** with 3-fluoropiperidinone **4a**



Entry	TMSOTf (equiv)	Solvent	Temp (°C)	**2a**:**3a** ratio[a]	Yield[b] (%) (isomer **2a**)
1	1.0	THF	50	1:1.6	19
2	2.0	THF	50	1.1:1	34
3	3.0	THF	50	2.4:1	28
4	4.0	THF	50	2.8:1	22
5	5.0	THF	50	3.4:1	30
6	5.0	THF	Reflux	3.4:1	30
7	3.0	Toluene	50	1.6:1	39
8	4.0	Toluene	50	2.3:1	32

[a] Determined by HPLC.
[b] Isolated yield by MPLC on silica gel.

Table 2
Trialkylsilyl triflate and $BF_3{\cdot}OEt_2$ mediated coupling of amidine **5** with 3-fluoropiperidinone **4a**



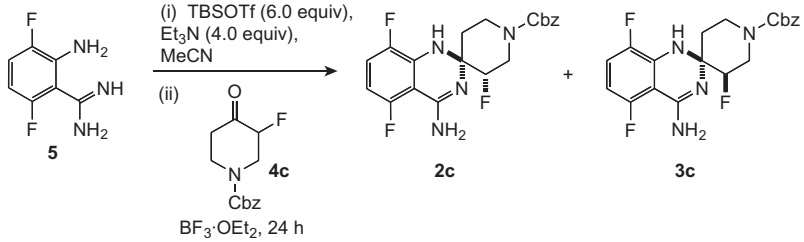
Entry	R_3SiOTf (equiv)	**2a**:**3a** ratio[a]	Yield[b] (%) (isomer **2a**)
1	TMSOTf (4.0)	3.6:1	33
2	TMSOTf (5.0)	3.1:1	48
3	TBSOTf (4.0)	4.2:1	50
4	TBSOTf (5.0)	3.8:1	38

[a] Determined by HPLC.
[b] Isolated by MPLC on silica gel.

4 are coupled with the *ortho*-aminobenzeneamidine **5** was envisaged. The precursor fluorinated piperidinones **4** can be readily generated by electrophilic fluorination of N-acylpiperidinones using Selectfluor™ under acidic catalysis.[9] The coupling reaction of **5** with racemic piperidinones **4** in refluxing ethanol[5] afforded the four stereoisomers (*R*,*S*)-**2** (desired stereoisomer), (*S*,*R*)-**2**, (*R*,*R*)-**3,** and (*R*,*R*)-**3** in a non-stereoselective manner (Scheme 1). Although the racemic diastereomers **2** and **3** could be simply separated by flash column chromatography and the enantiomers of both diasteroisomers **2** and **3** were separable by OD or AD chiral column chromatography with a high recovery rate, the overall yield was limited to about 12% of the desired enantiomer.

An improved and diastereocontrolled formation of the products using the coupling of **4** and **5** was therefore desired. The use of a silylating reagent (e.g., TMSOTf) was found to facilitate the coupling reaction of **4a** and **5** at lower reaction temperatures, in favor of diastereoisomer **2a**, which has the amidine functionality of the quinazoline ring axially oriented and the fluorine substituent equatorially oriented on the piperidine ring.[11–13] The selectivity achieved was found to be dependent upon the quantity of TMSOTf used (Table 1). When the amidine **5** was pre-treated with 1.0 equiv of TMSOTf in THF in the presence of excess triethylamine, followed by reaction with the 3-fluoropiperidinone **4a** at 50 °C for 24 h, the undesired diastereoisomer **3a** was isolated as the major compound (Table 1, entry 1). By increasing the amount of TMSOTf used, the diastereoselectivity was reversed in favor of the desired isomer **2a**. The ratio of **2a**:**3a** was found to increase with increasing TMSOTf stoichiometry (Table 1, entries 1–5). When 5.0 equiv of TMSOTf was used, the ratio of the two diastereomers **2a**:**3a** reached 3.4:1, with a 30% isolated yield of diastereoisomer **2a** (Table 1, entry 5). The spirocyclization reaction became impractically slow at temperatures below 50 °C. In addition, the diastereoselectivity and yield remained unchanged on increasing the reaction temperature from 50 °C to reflux (Table 1, entry 6). Replacing the THF by toluene as a solvent resulted in slightly lower diastereoselectivity but higher isolated product yields were obtained under otherwise identical conditions (Table 1, entry 3 versus 7, and entry 4 versus 8).

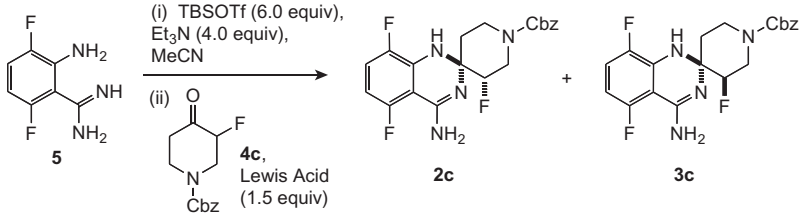
Table 3
tert-Butyldimethylsilyltriflate and boron trifluoride etherate Lewis acid mediated coupling of amidine **5** and 3-fluoropiperidinone **4c**



Entry	TBSOTf (equiv)	$BF_3{\cdot}OEt_2$ (equiv)	Temp (°C)	Solvent	**2c**:**3c** ratio[a]	Yield[b] (%) (**2c** + **3c**)
1	5.0	0.1	4	THF[c]	4.5:1	70
2	4.0	0.5	rt	Et_2O	3.0:1	80
3	4.0	0.5	4	Et_2O	4.6:1	71
4	5.0	0.1	4	Et_2O	4.6:1	57
5	4.0	0.5	40	CH_2Cl_2	1:1.1	48
6	6.0	1.6	rt	CH_2Cl_2	4.0:1	—
7	6.0	1.6	rt	MeCN	4.3:1	65

[a] Determined by ^{19}F NMR.
[b] Isolated by MPLC on silica gel.
[c] THF polymerization occurred at 40 °C or room temperature.

Table 4
tert-Butyldimethylsilyltriflate mediated coupling of amidine **5** and 3-fluoropiperidinone **4c** using various Lewis acids



Entry	Lewis acid	Time (h)	**2c**:**3c** ratio[a]	Yield[b,c] (%)·(**2c** + **3c**)
1	$BF_3{\cdot}OEt_2$	96	4.3:1	65
2	$LiClO_4$	24	5.4:1	46
3	$MgBr_2$	48	4.4:1	19
4	$ZnCl_2$	48	4.8:1	69
5	$Mg(ClO_4)_2$	48	5.0:1	60
6	$Yb(OTf)_3$	36	5.3:1	33
7	$Dy(OTf)_3$	72	6.4:1	16
8	$Sc(OTf)_3$	24	6.2:1	46
9	$InCl_3$	48	10:1	40

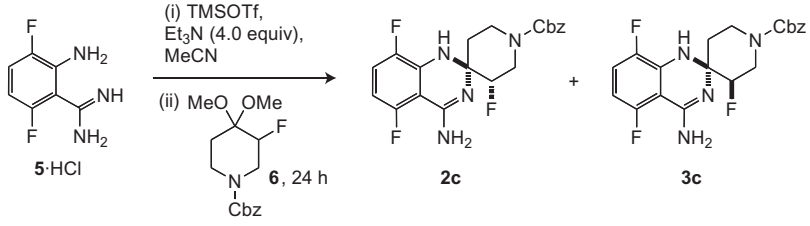
[a] Determined by ^{19}F NMR.
[b] Isolated yield by MPLC on silica gel.
[c] The reactions were performed at room temperature.

The use of 4 equiv of TMSOTf together with $BF_3{\cdot}OEt_2$ in diethyl ether improved both the diastereomeric ratio of **2a**:**3a** and the product yield, and could be achieved at room temperature (Table 2, entry 1). The isolated yield of diastereomer **2a** could be increased further to 48% using 5.0 equiv of TMSOTf. The best diastereoselectivity was achieved using 4.0 equiv of TBSOTf and 0.5 equiv of $BF_3{\cdot}OEt_2$, resulting in a ratio of 4.2:1 in favor of the desired diastereomer **2a** and a 50% isolated yield of pure **2a** (Table 2, entry 3).

The optimization of the coupling of benzamidine **5** with *N*-Cbz-3-fluoropiperidinone **4c** was also investigated in order to make the two desired products **2a** and **2b** by parallel synthesis. Both solvent and temperature played important roles in the trialkylsilyl triflate mediated coupling reaction in combination with a Lewis acid. Using 5.0 equiv of TBSOTf and 0.1 equiv of $BF_3{\cdot}OEt_2$ at 4 °C in THF, led to an improvement of the ratio of the two diastereoisomers **2c**/**3c** to 4.5:1 and the combined yield to 70% (Table 3, entry 1).[14,15] When the solvent was changed to diethyl ether, using 4.0 equiv of TBSOTf and 0.5 equiv of $BF_3{\cdot}OEt_2$ at room temperature, the ratio dropped slightly to 3.0:1 with a combined yield of 80% (Table 3, entry 2). At lower temperature, the selectivity could be improved (Table 3, Entry 3). The use of additional TBSOTf did not improve the diastereoselectivity (Table 3, entry 4). When the reaction was performed in dichloromethane at an elevated temperature (40 °C) in the presence of 4.0 equiv of TBSOTf and 0.5 equiv of $BF_3{\cdot}OEt_2$, the reaction was not diastereoselective (Table 3, entry 5). Although the diastereoselectivity in favor of **2a** was restored by employing 6.0 equiv of TBDMSOTf and 1.6 equiv of $BF_3{\cdot}OEt_2$ at room temperature, the yield was very poor (Table 3, entry 6). The use of acetonitrile as a solvent led to comparable diastereoselectivity to that observed for the reaction run in THF (Table 3, entry 7).

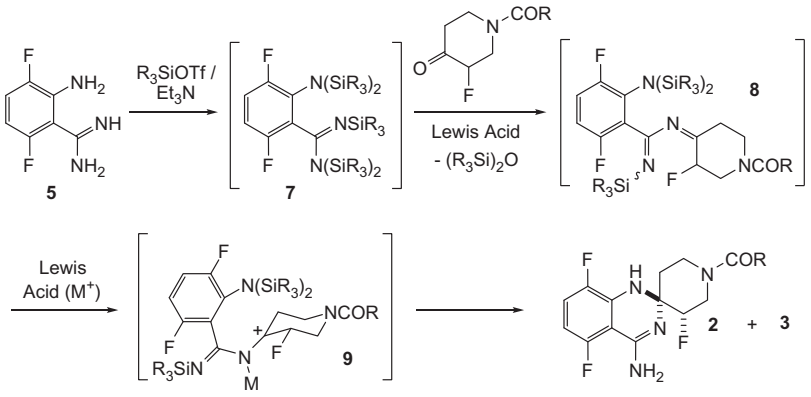
A range of other Lewis acids were also tested for the coupling of **4c** and **5** to evaluate their effects on diastereoselectivity and chemical yield (Table 4). Lithium perchlorate, magnesium bromide, zinc chloride, ytterbium triflate, dysprosium triflate, or scandium triflate mediated cyclization gave modestly improved diastereoselectivity compared to $BF_3{\cdot}OEt_2$. The diastereoselectivity ranged from 4.4:1

Table 5
Trimethylsilyltriflate and boron trifluoride etherate mediated coupling of amidine **5** and fluoroketal **6**



Entry	TMSOTf (equiv)	Lewis acid (equiv)	Temp (°C)	**2c**:**3c** ratio[a]	Yield[b] (%) (**2c** + **3c**)
1	4.0	—	rt	—	0
2	8.0	—	rt	6.3:1	55
3	8.0	—	0	6.3:1	83
4	16.0	—	0	6.1:1	71
5	16.0	—	−25	4.9:1	53
6	8.0	$InCl_3$ (1.5)	0	6.3:1	50
7	8.0	$ZnCl_2$ (1.5)	0	5.9:1	43
8	8.0	$Sc(OTf)_3$ (1.5)	0	—	Trace

[a] Determined by ^{19}F NMR.
[b] Isolated by MPLC on silica gel.



Scheme 2. Possible mechanism for formation of fluoropiperidine spirocycles **2** and **3**.

to 6.4:1 in favor of isomer **2c**, with the combined yield of **2c** and **3c** varying from 16% to 69% (Table 4, entries 2–8). Interestingly, the use of indium chloride together with TBSOTf, led to the highest diastereoisomeric ratio of 10:1, although in only 40% overall yield.

Finally, a similar approach could be employed for coupling ketal **6** with the hydrochloride salt of amidine **5** (Table 5). Formation of **2c** over **3c** was favored, with similar levels of diastereoselectivity to that obtained from the ketone **4c**. Optimal conditions were found to use TMSOTf (8.0 equiv) and triethylamine (4.0 equiv) at 0 °C for 24 h, giving **2c** and **3c** in combined 83% yield, in a 6.3:1 ratio (Table 5, entry 3). Reaction at higher or lower temperatures led to lower product ratios or yields.

The origins of the diastereoselectivity differences obtained under the various conditions are not clear. The major product **2** is likely the thermodynamically more stable diastereomer,[11] but it is unlikely that the reaction is occurring under the conditions of thermodynamic control, since a control reaction showed that isomerization of either **2a** or **3a** did not occur under the reaction conditions. A plausible mechanism for the formation of **2** and **3** involves initial formation of the persilylated amidine **7**, followed by reaction with the fluoropiperidone **4** (or corresponding ketal **6**) to give **8**. Subsequent Lewis acid promoted cyclization via **9** or a similar intermediate and subsequent hydrolysis would then afford **2** and **3** (Scheme 2).

In summary, a practical and efficient route for the diastereoselective synthesis of novel spirocyclic fluoropiperidine quinazoline selective iNOS inhibitors has been established. Initial attempts at coupling the amidine and ketone partners by analogy with non-fluorinated substituted piperidones led to unselective reaction and poor reaction yields. However, unexpectedly we demonstrate that the presence of silylation reagents and Lewis acids can significantly alter product selectivities and yields. Thus, the use of TMSOTf or TBSOTf in excess, along with added triethylamine and Lewis acids, was found to facilitate the coupling reaction of fluorinated piperidinones with *ortho*-aminobenzeneamidine. The spirocyclic core generated in this manner was formed with improved yields and diastereoselectivity favoring the desired diastereoisomer **2**. Similar conditions could also be employed using ketals rather than the fluorinated piperidinone.

Acknowledgments

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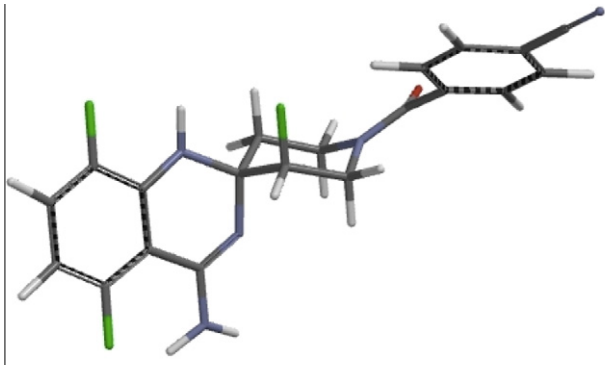
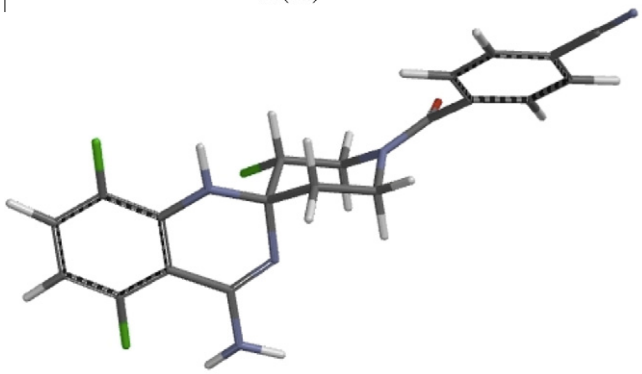
10. The coupling of the benzamidine **5** and the optically pure 3-fluoropiperidine ketones **4a** and **4c** in the presence of TMSOTf and triethylamine retained the chirality of the fluorine-attached stereogenic centre. However, the fluorine-attached stereogenic centre racemized during the cyclization reaction in the presence of protic acid or Lewis acid.
11. DFT calculations (B3LYP/6-31G*, THF/ZPVE corrected) on the diastereoisomers **2a** and **3a**, reveal that the lowest energy conformations are **A** (**2a**) and **B** (**3a**) respectively. Diastereoisomer **A** (**2a**) was found to be 3.3 kcal/mol lower in energy than **B** (**3a**). In both cases the lowest energy conformations **A** and **B** have the amidine group of the quinazoline ring adopting an axial orientation on the piperidine ring. The conformation **A** (**2a**) is also the biologically relevant conformation found in co-crystal structures of the inhibitor with the iNOS enzyme (Ref.[6a]). The conformations (not shown) corresponding to the amidine group of the quinazoline ring in an equatorial orientation were both found to be 4.6 kcal/mol higher in energy than **A** (**2a**). This compares to a 1.3 kcal/mol energy difference (B3LYP/6-31G*, THF/ZPVE corrected) between the corresponding conformations of the unfluorinated analog of **2a**:**3a**, the lowest energy conformation also favoring an axially oriented amidine. The lower energy of **A** (**2a**) compared to **B** (**3a**) may be due to electronic effects, since there is a known preference of fluorine to adopt an axial orientation in 3-fluoropiperidinium ring systems (5.4 kcal/mol), see: (a) Sum, A. M.; Lankin, D. C.; Hardcastle, K.; Snyder, J. P. *Chem. Eur. J.* **2005**, *11*, 1579.; (b) Lankin, D. C.; Chandrakumar, N. S.; Shashidhar, N. R.; Spangler, D. P.; Snyder, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 3356.



A (2a)



B (3a)

12. A referee suggests that the preferred conformation **A** (**2a**) is due to the greater opposition of dipoles from the fluorine lone pairs and the amidine imino-type nitrogen lone pairs that occurs when these groups adopt a *trans*-diaxial orientation.
13. *Cis*-1-(4-cyanobenzoyl)-3,5′,8′-trifluorospiro[piperidine-4,2′(1′H)-quinazoline]-4′-amine trifluoroacetate (**2a**). IR (free amine, NaCl disc): υ 3400, 2229, 1624 cm^{-1}; ^1H NMR (amine, $CDCl_3$/TMS): δ 1.70–2.03 (m, 2H), 3.27–3.46 (m, 2H), 3.51–3.80 (m, 2H), 4.30–5.00 (m, 1H), 4.71 (s, 1H), 5.18 (s, 2H), 6.34 (m, 1H), 7.01 (m, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 7.2 Hz, 2H); MS (m/z): 399.89 (M + H); Analysis for $C_{20}H_{16}F_3N_5O{\cdot}CF_3COOH{\cdot}0.3H_2O$: calcd C 50.93, H 3.42, N 13.5: obtained: C 50.90, H 3.37, N 13.26.
Trans-1-(4-cyanobenzoyl)-3,5′,8′-trifluorospiro[piperidine-4,2′(1′H)-quinazoline]-4′-amine trifluoroacetate (**3a**). IR (amine, NaCl disc): υ 3322 (br), 2229, 1623 cm^{-1}; ^1H NMR (amine, $CDCl_3$/TMS): δ 1.50–2.23 (m, 2H), 3.35–3.80 (m, 4H), 4.20–4.62 (m, 1H), 4.28 (s, 1H), 5.30 (br s, 2H), 6.30 (m, 1H), 6.97 (m, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H); MS (m/z): 400.14 (M + H); Analysis for $C_{20}H_{16}F_3N_5O{\cdot}1.10CF_3CO_2H$: calcd C 50.81, H 3.28, N 13.34; obtained C 50.90, H 3.37, N 13.26.
14. *Representative coupling protocol*: To a stirred solution of amidine **4c** (1.0 equiv), in dry, freshly distilled THF under an atmosphere of N_2 at 0 °C, TBSOTf (5.0 equiv) and NEt_3 (6.0 equiv) were added. A 5% by volume solution of BF3·OEt_2 (0.1 equiv) in THF was then added. After stirring the solution at 0 °C for 45 min, a solution of CBz protected piperidone **4c** (1.0 equiv) in THF (2 mL) was added. The reaction mixture was then warmed to 4 °C, sealed, and stirred for 24 h. The reaction was then quenched with sat. $NaHCO_3$, extracted with Et_2O (3×), and the combined organic phases washed with brine and dried over $MgSO_4$. After filtration and concentration, the ratio of the diastereoisomers was determined by ^{19}F NMR (or HPLC). Flash chromatography (5% MeOH in CH_2Cl_2) yielded a mixture of diastereoisomers **2c** and **3c**. Purification by MPLC (CH_2Cl_2/MeOH 20:1–10:1) gave the spirocycles as two separated diastereoisomers.
15. Benzyl *cis*-4′-amino- 3,5′,8′-trifluorospiro[piperidine-4,2′(1′H)-quinazoline]-1-carboxylate (Diastereoisomer **2c**): IR (amine, NaCl disc): υ 3322 (br), 2229, 1623 cm^{-1}; ^1H NMR (amine, $CDCl_3$/TMS): δ 1.61 (br, 3H), 2.01 (br, 1H), 3.50 (br, 2H), 3.91 (br, 1H), 4.01–4.40 (m, 2H), 5.14 (s, 2H), 5.21 (br, 1H), 6.31 (m, 1H), 6.90 (m, 1H), 7.40 (m, 5H); MS (m/z): 405 (M + H); ^{19}F NMR ($CDCl_3$) δ −119.4 (m, 1F, aromatic F), −143.3 (m, 1F, aromatic F), −196.9 (dm, 1F, J = 53.0 Hz, piperidine F). Benzyl *trans*-4′-amino-3,5′,8′-trifluorospiro[piperidine-4,2′(1′H)-quinazoline]-1-carboxylate (Diastereoisomer **3c**): MS (m/z): 405 (M + H); ^{19}F NMR ($CDCl_3$) δ −119.5 (m, 1F, aromatic F), −142.1 (m, 1F, aromatic F), −194.4 (m, 1F, piperidine F).