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Synthesis of nitrogen and oxygen containing heterocycles by Prins cyclization in continuous flow

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Abstract Aza-silyl-Prins and oxa-Prins cyclization reactions in continuous flow chemistry are described for the synthesis of the corresponding tetrahydropyridines and pyran derivatives, respectively. In particular, the use of pyridine-carboxaldehydes for aza-silyl-Prins reaction led to a symmetrical triarylmethane or two new bicyclic compounds. 4-fluorinated-2-substituted tetrahydropyran derivatives were also obtained in the oxa-Prins cyclization with good selectivity in favor of the *anti* isomer

Key words Aza-silyl-Prins • Oxa-Prins • Continuous flow chemistry • Tetrahydropyridine • dihydropyran

Six-membered heterocycles containing oxygen, nitrogen or sulfur atoms represent an important moiety in natural products or biologically active compounds. Prins-type cyclization is an interesting approach for carbon-heteroatom and carbon-carbon bonds formation in the way to synthesize these structures.¹ This reaction involves the condensation between an aldehyde and a homoallylic alcohol, amine, or thiol, mediated by a Lewis² or Brønsted³ acid, which can also act as reactant providing a nucleophile. The choice of the homoallylic partner is determinant for the structure of product obtained: for example, a non-substituted homoallylic derivative, gives a saturated six-membered heterocycle with a substituent at C-4 (Scheme 1a)^{1a,4} while a silyl-substituted homoallylic derivative leads to a heterocycle with a double bond in position C-3/C-4 (Scheme 1b).⁵ Different methodologies, such as the use of ionic liquids,⁶ microwave assistance⁷ and more recently Vibrational Strong Coupling (VSC),⁸ have been applied in the study of Prins-type cyclization reactions.

In this context, continuous flow chemistry has become an important technique in organic synthesis due to many advantages. Indeed, the high surface-to-volume ratio enables an optimal control of heating. Mixing is also improved compared to batch conditions, which leads to cleaner and

faster reactions. In addition, a better control of the key reaction parameters enables good reproducibility as well as easy scale-up of the reactions. Finally, the high surface area allows for a good control of exotherms, and potential hazardous intermediates are only formed in small amounts, which improves the process safety compared to classical batch reactors.⁹ Continuous flow chemistry has been used in the synthesis of N-containing heterocycles, such as pyridine,¹⁰ quinoline,¹¹ pyrrolidine and pyrrole derivatives,¹² as well as oxygen-containing ones, like pyran¹³ and furan derivatives.¹⁴ Despite the large number of studies about the Prins cyclization, there are no reports on the continuous flow conditions to synthesize six-membered heterocycles by this reaction. We proposed that flow chemistry could overcome some problems classically encountered with Prins reaction in batch, namely the presence of undesirable byproducts, and the sometimes moderate yields. Additionally, we aimed to study the stereochemistry of the reaction under flow conditions. We report herein the synthesis of tetrahydropyridine and pyran derivatives by Prins cyclization under flow conditions.

Scheme 1 a) Prins cyclization; b) silyl-Prins cyclization.

The aza-Prins cyclization has become an important tool for the synthesis of tetrahydropyridine cores, important intermediates in the synthesis of piperidine-type alkaloids.¹⁵ We started the study of this reaction under continuous flow conditions,

between (*Z*)-*N*-(4-(trimethylsilyl)but-3-en-1-yl)aniline (**1a**)^{5c} and 3-phenylpropanal (**2a**) in order to form the desired tetrahydropyridine **3a** (Table 1). To our delight, the use of 1.5 equivalents of FeCl₃ as Lewis acid and the same quantity of aldehyde **2a** at room temperature with a flow rate of 200 μL·min⁻¹ gave 33% of conversion rate (entry 1). By increasing the temperature to 50 °C, an increment of the conversion was observed to 60%, and it does not matter if the injection was made by one or two pumps (entries 2 and 3). Increasing the amount of the acid led to an insoluble reaction mixture. The use of boron trifluoride diethyl etherate (BF₃·Et₂O) under the

same conditions led to the product with a lower yield, but with improvement of the solubility, allowing us to test other conditions (entry 4). When the pressure was increased to 5 bar, a good increment in the conversion rate (75%) was observed (entry 5), and the conversion was improved to 80% with two equivalents of acid and aldehyde (entry 6). Injecting the mixture of all the reactants with one pump gave a slightly better conversion rate (90%, entry 7). The best result was observed when the solvent was changed for 1,4-dioxane and when the temperature was increased to 70 °C, in which case a complete transformation was observed (entry 8).

Table 1 Optimization conditions for aza-silyl-Prins cyclization

	1a , 1 equiv	2a , X equiv				
Entry	Equiv. of aldehyde	Acid, (equiv)	Temperature °C	Solvent	Injection mode ^[b]	Conversion rate to 3a (%) ^[a]
1	1.5	FeCl ₃ , 1.5	rt	MeCN	One pump	33
2	1.5	FeCl ₃ , 1.5	50	MeCN	One pump	60
3	1.5	FeCl ₃ , 1.5	50	MeCN	Two pumps	60
4	1.5	BF ₃ ·OEt ₂ , 1.5	50	MeCN	Two pumps	40
5 ^[c]	1.5	BF ₃ ·OEt ₂ , 1.5	50	MeCN	Two pumps	75
6 ^[c]	2	BF ₃ ·OEt ₂ , 2	50	MeCN	Two pumps	80
7 ^[c]	2	BF ₃ ·OEt ₂ , 2	50	MeCN	One pump	90
8 ^[c]	2	BF ₃ ·OEt ₂ , 2	70	1,4-Dioxane	One pump	100

^a Measured by ¹H NMR of the crude. ^b One pump: all reagents in one pump, with a flow rate of 200 μL min⁻¹. Two pumps: mixture of amine and aldehyde in the first pump, Lewis acid in the second pump (flow rate of 100 μL min⁻¹ for each pump). ^c With a pressure of 5 bar.

With the optimized reaction conditions in hand, we investigated the scope of the method (Scheme 2). Different aldehydes (**2a-d**) were first tried in the presence of (*Z*)-*N*-(4-(trimethylsilyl)but-3-en-1-yl)aniline (**1a**). When the reaction was performed with aldehydes bearing an aliphatic chain, the desired tetrahydropyridines **3a** and **3b** were isolated in very good yields (up to 90%). The use of phenylacetaldehyde (**2c**) or 2-methylpentanal (**2d**) led to the products **3c** and **3d** respectively with lower yields, probably due to the steric hindrance. It is important to note that the reaction performed with **2d** bearing a stereogenic center afforded tetrahydropyridine **3d** as a 1:1 mixture of diastereomers. The reaction with an aromatic aldehyde or an enal did not work. Then, amine **1b** bearing a non electronwithdrawing group, namely a benzyl group was studied, as we expected that the use of flow conditions could led to better yields than known in batch conditions. The tetrahydropyridines **3e-f** were obtained with very low yields in the case of aliphatic aldehydes **2a-b**, and the reaction with the 2-methylpentanal (**2d**) did not proceed.

The reactivity of several pyridinecarboxaldehydes with (*Z*)-*N*-(4-(trimethylsilyl)but-3-en-1-yl)aniline (**1a**) was also tested under the same conditions, and resulted in unexpected products **4-6** (Scheme 3). On the one hand, the reaction with 4-pyridinecarboxaldehyde **2g** produced only the symmetrical triarylmethane (**4**) in a yield of 36%, obtained by the double addition of the phenyl group of **1a** to the aldehyde (Scheme 3a). Analogs of this product were reported by the reaction of pyridine carboxaldehydes and aniline derivatives,¹⁶ or by the reaction of aromatic aldehydes with different phenyl derivatives.¹⁷

On the other hand, the reaction of the silylated amine **1a** with pyridine-2-carboxaldehyde derivatives gave polycyclic compounds as main products.

The reaction with pyridine-2-carboxaldehyde **2h** gave the Prins derivative **3h** in 14%, and as main product the new tetracyclic derivative **5**, which was isolated as its tetrafluoroborate salt in 51% (Scheme 3b). Based on its NMR, we proposed that this compound presents a bridged diazepine, which is formed by the addition of the pyridinic nitrogen to the carbocation in an intramolecular cyclization. The confirmation of this interesting core was done by the use of 6-methoxy-pyridine-2-carboxaldehyde **2i**, obtaining the tetrahydropyridine **3i** in 18% and corresponding bridged diazepine **6** in 70 % yield (Scheme 3c). The complete structure and relative stereochemistry of **6** were established by NMR as well as X-ray diffraction (Figure 1).

Scheme 3 Isolated products of the reaction of silylated amine **1a** with pyridine-carboxaldehyde derivatives

We propose a mechanism starting with the condensation of the amino group to the aldehyde, to obtain the corresponding iminium **A** (Scheme 4). Then, the diastereoselective attack of the π electrons of the double bond to the iminium **A** could give the β -silylated cationic intermediate **B**, in which structure, the silyl group is *anti* to the pyridine core. Then, the *syn* attack of the nitrogen of pyridine to the carbocation **B** could form a new carbon-nitrogen bond to give the five-membered heterocycle, pyridinium **C**. When $\text{R} = \text{OMe}$, a final deprotection of the methoxy group leads to the corresponding pyridone **6**. The stereochemistry proposed in the mechanism was in concordance with the X-ray diffraction of compound **6** (Figure 1).

Figure 1 Ortep diagram of compound **6**.

Scheme 4 Putative mechanism for reaction between (Z)-N-(4-(trimethylsilyl)but-3-en-1-yl)aniline **1a** and 2-pyridinecarboxaldehyde derivatives.

The oxa-Prins cyclization is known to give a mixture of dihydropyran or 4-substituted tetrahydropyran derivatives. Under batch conditions, the reaction between but-3-en-1-ol **7** and phenylacetaldehyde **2c** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ in 1,4-dioxane at reflux temperature (115 °C), gave the mixture of dihydropyrans **8c** and **9c** as products in 70% overall yield (Scheme 5), whose NMR data were consistent with the ones reported in the literature.^{2d} The reaction under flow conditions was then studied, starting with similar conditions than the ones described above for the aza-Prins reaction (Scheme 2). A mixture of dihydropyrans **8c** and **9c** (19%) together with a mixture of fluorinated products **10c** and **11c** (43%, 1:4.5 *syn:anti*) were obtained (entry 1, Table 2). An unexpected selectivity for the *anti* isomer **11c** over the *syn* **10c** was observed. It is important to note that the *syn* isomer has been reported as the main product in the synthesis of 4-fluorotetrahydropyrans by Prins cyclization under batch conditions.^{2b,6a,6b,7a,18} The reaction carried out at room temperature, gave the isomer **11c** in better proportion, but the general yield was lower (entry 2). With DCM as solvent, and only the mixture of 4-fluorinated products **10c** and **11c** was obtained in 59% yield, but the *syn:anti* ratio was inversed (2.3:1), in agreement with the results reported for the reaction under batch conditions^{2b,7a,18b} (entry 3). The reaction was then tested with a 1:1 mixture of dioxane-DCM as a solvent at 40 °C, and the mixture of dihydropyrans **8c** and **9c** was obtained in low yield (10%), and the yield of fluorinated products (58%; 1:4 **10c:11c**) was increased (entry 4). Changes in solvent (DCE instead of DCM), equivalents of the acid (1 eq), residence time (flow decreased to 150 $\mu\text{L min}^{-1}$) or acid (HBF_4), did not improve the result obtained (entries 5-8).

Scheme 5 Oxa-Prins cyclization in batch conditions.

Table 2 Optimization conditions of oxa-Prins cyclization under flow conditions.

Entry	Conditions ^[a]	Yield (%) ^[b] 8c + 9c	Yield (%) ^[b] 10c + 11c	Ratio ^[c] (10c:11c)
1	Dioxane, 70 °C	19	43	1:4.5
2	Dioxane, rt	18	29	1:6.9
3	DCM, rt	0	59	2.3:1
4	Dioxane-DCM (1:1), 40 °C	10	58	1:4
5	Dioxane-DCE (1:1), 40 °C	19	39	1:4
6	Dioxane-DCM (1:1), 40 °C, BF ₃ ·OEt ₂ (1 eq; 0.5 mmol)	8	22	1:4
7	Dioxane-DCM (1:1), 40 °C, 150 µL min ⁻¹	19	53	1:3.8
8	Dioxane-DCM (1:1), 40 °C, HBF ₄	18	30	1:2.6

^a General conditions: buten-1-ol (**7**) (0.5 mmol), BF₃·OEt₂ (1 mmol) (except for entries 6 and 8), aldehyde **2c** (1 mmol), in solvent (q. s. 5 mL), all reagents in one pump, with a flow rate of 200 µL min⁻¹. ^b Isolated yields. ^[c] Measured by ¹⁹F NMR in the crude reaction.

With the optimal conditions for this reaction being established, different aldehydes **2j-p** were studied (Table 3). In all cases, fluorinated compounds (**10** and **11**) were obtained as the major products, with a diastereomeric ratio in favor of the *anti* isomer **11**. The reaction with an aliphatic aldehyde such as octanal **2j** gave a good overall yield of 80%; in favor to the fluorinated products (50%) but with a lower *syn:anti* ratio (1:1.7; **10j:11j**). In the case of a branched aldehyde **2k**, the overall yield and the ratio **10k:11k** slightly decreased. The reaction with 4-nitrobenzaldehyde **2l** gave the mixture of 4-fluorinated products **10l** and **11l** in 42%, with the best selectivity for the *anti* isomer **11l** (*syn:anti* 1:6). Its stereochemistry was confirmed by X-ray diffraction analysis (Figure 2). The reaction with other aromatic aldehydes such as 2-nitrobenzaldehyde **2m**, 3-trifluoromethylbenzaldehyde **2n** and 4-chlorobenzaldehyde **2o** gave poor yields. We can notice that with an electron donating group like in the 4-acetamidobenzaldehyde **2p**, the reaction did not work.

Figure 2 Ortep diagram of compound **11l**.

Table 3 Scope of the oxa-Prins cyclization

Entry	Yield ^[a] 8 + 9	Yield ^[a] 10 + 11	Ratio 10:11
Octanal 2j	30 ^[c]	50 ^[c]	1:1.7
Cyclohexanal 2k	19 ^[c]	44 ^[c]	1:1.3
4-nitrobenzaldehyde 2l ^[b]	18 ^[c]	42 ^[c]	1:6
2-nitrobenzaldehyde 2m ^[b]	17	23	1:3
3-(trifluoromethyl)benzaldehyde 2n ^[b]	6	23	1:3.2
4-chlorobenzaldehyde 2o ^[b]	Traces	14	1:2
4-acetamidobenzaldehyde 2p ^[b]	0	0	

General conditions: buten-1-ol (**7**) (0.5 mmol), BF₃·OEt₂ (1 mmol), aldehyde (1 mmol), in 1,4-dioxane-DCM (1:1) (q. s. 5 mL), with a flow rate of 200 µL min⁻¹, at 70 °C and 5 bar. ^a Isolated yields. ^b Reaction with a flow rate of 150 µL min⁻¹. ^[c] NMR data consistent with literature.

In conclusion, conditions for two Prins-type cyclizations were studied using flow chemistry. In the case of the aza-silyl-Prins reaction, the best results were observed with *N*-phenyl protected amines in the presence of aliphatic, non-branched aldehydes. When using pyridinecarbaldehydes, unexpected products were obtained. On the other hand, the oxa-Prins reaction gave as main product the *anti*-4-fluorotetrahydropyran derivative, which is always reported as minor product under batch conditions.

General Methods: DCM was distilled over calcium hydride and stored with calcium chloride under Ar. Acetonitrile and 1,4-dioxane were used as purchased. ¹H NMR spectra were recorded in a Bruker AV-I 300 MHz spectrometer at 298 K, and were calibrated using residual CHCl₃ (δ = 7.26 ppm) or MeOH (δ = 4.87). ¹³C NMR spectra were recorded with a Bruker Avance 300 spectrometer at 75 MHz and 298 K, and were calibrated using CDCl₃ (δ = 77.16 ppm) or MeOH (δ = 49.00). ¹⁹F NMR were recorded with a Bruker Avance 300 spectrometer at 282 MHz and CFCl₃ (δ = 0.00 ppm) was used as reference. ¹H NMR spectroscopic data

are reported as follows: chemical shift δ [ppm] (multiplicity, coupling constant [Hz], integration). Multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, m = multiplet. High-resolution mass spectra (HRMS) were obtained with a Waters Xevo QTOF instrument with an electrospray ionisation source (ESI+), using enkephaline leucine as internal calibrant. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or Fluorochem and were used as received unless otherwise stated. (Z)-4-trimethylsilyl-3-but-*N*-protected amines were synthesized as reported.^{5c}

General procedure for Aza-Silyl Prins cyclization

Stock solutions were prepared by adding BF₃·OEt₂ (0.68 mmol, 2 eq) to a mixture of amine (0.34 mmol, 1 eq) and aldehyde (0.68 mmol, 2 eq) in 1,4-dioxane, q.s. 3.4 mL. Then 3 mL of solution was pumped through an easy Photochem E-series system from Vapourtec with a 10 mL reactor, at a flow rate of 200 μ L min⁻¹ at 70 °C, and 5 bar of pressure. After collecting the reaction, an aqueous solution of NaOH 1 M was added, and the mixture was extracted with DCM (10 mL X3). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography.

General procedure for Oxa-Prins cyclization in batch conditions

BF₃·OEt₂ (0.6 mmol, 2 eq) was added to a mixture of but-3-en-1-ol (0.3 mmol, 1 eq) and phenylacetaldehyde (0.6 mmol, 2 eq) in 3 mL of 1,4-dioxane, then the mixture was stirred at reflux temperature (115 °C) for 3 h. Then, water was added and the reaction was extracted with DCM (10 mL X 3); the combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography.

General Procedure for Oxa-Prins cyclization

Stock solutions were prepared by adding BF₃·OEt₂ (1.0 mmol, 2 eq) to a mixture of the alcohol (0.5 mmol, 1 eq) the aldehyde (1.0 mmol, 2 eq) in 1,4-dioxane-DCM (1:1), q.s. 5.4 mL. Then 5 mL of each solution was pumped through an easy Photochem E-series system from Vapourtec with a 10 mL reactor, at a flow rate of 200 μ L min⁻¹ or 150 μ L min⁻¹ at 40 °C, and 5 bar of pressure. After collecting the reaction, water was added, and the mixture was extracted with DCM (10 mL X3). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography.

6-phenethyl-1-phenyl-1,2,3,6-tetrahydropyridine (3a)

Prepared by the general procedure for Aza-Silyl Prins cyclization. Isolated by flash column chromatography with a mixture of pentane-DCM (9:1) as yellow pale oil, (71 mg, 90%).

IR ATR: = 3052, 3024, 2956, 2924, 2858, 1598, 1502, 1318, 1245, 745, 688 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.29-7.15 (m, 7H), 6.82 (d, *J* = 8.1 Hz, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), 5.88 (s, 2H), 4.1 (t, *J* = 6.8 Hz, 1H), 3.64 (dd, *J* = 13.4, 4.9 Hz, 1H), 3.33-3.18 (m, 1H), 2.79-2.64 (m, 2H), 2.39-2.28 (m, 1H), 2.01 (brd, *J* = 16.9 Hz, 1H), 1.92 (q, *J* = 7.4 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃) δ = 150.3 (C_q), 142.3 (C_q), 129.6 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH), 126.0 (CH), 125.9 (CH), 118.0 (CH), 115.6 (CH), 56.6 (CH), 41.0 (CH₂), 34.7 (CH₂), 32.7 (CH₂), 24.3 (CH₂)..

HRMS TOF ES⁺ calcd. for C₁₉H₂₂N [M+H]⁺ 264.1752; found 264.1744.

6-butyl-1-phenyl-1,2,3,6-tetrahydropyridine (3b)

Prepared by the general procedure for Aza-Silyl Prins cyclization. Isolated by flash column chromatography with a mixture of pentane-DCM (9:1) as colorless oil, (58 mg, 89%).

IR ATR = 3059, 3025, 2955, 2926, 2857, 1596, 1500, 1386, 1240, 1033, 745, 689 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.26 (dd, *J* = 8.8, 7.2 Hz, 2 H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.76 (t, *J* = 7.2 Hz, 1H), 5.87 (s, 2H), 4.06 (m, 1H), 3.66 (dd, *J* = 13.4, 3.7 Hz, 1H), 3.25 (ddd, *J* = 13.2, 10.9, 4.0 Hz, 1H), 2.44-2.28 (m, 1H), 2.02 (d, *J* = 17.9 Hz, 1H), 1.67-1.57 (m, 2H), 1.48-1.31 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 150.3 (C_q), 130.0 (CH), 129.3 (CH), 125.5 (CH), 117.5 (CH), 115.1 (CH), 56.2 (CH), 40.5 (CH₂), 32.7 (CH₂), 28.7 (CH₂), 24.3 (CH₂), 23.0 (CH₂), 14.2 (CH₃).

HRMS TOF ES⁺ calcd. for C₁₅H₂₂N [M + H]⁺ 216.1752; found 216.1742.

6-(pentan-2-yl)-1-phenyl-1,2,3,6-tetrahydropyridine (3d)

Prepared by the general procedure for Aza-Silyl Prins cyclization. Isolated by flash column chromatography with a mixture of pentane-DCM (20:1) as (mixture of isomers a and b): colorless oil, (21 mg, 30%).

IR ATR = 3060, 2956, 2926, 2870, 1596, 1499, 1378, 1235, 984, 745, 689 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.25-7.19 (m, 4H), 6.87 (d, *J* = 8.1 Hz, 4H), 6.74-6.70 (m, 2H), 5.93-5.83 (m, 4H), 3.87 (brs, 1H, Ha), 3.79 (d, *J* = 7.0 Hz, 1H, Hb), 3.70-3.62 (m, 2H), 3.39-3.28 (m, 2H), 2.38-2.27 (m, 2H), 2.01-1.92 (m, 4H), 1.61-1.40 (m, 4H), 1.33-1.10 (m, 4H), 1.00 (d, *J* = 6.8 Hz, 3Ha), 0.92-0.87 (m, 9H).

¹³C NMR (75 MHz, CDCl₃) δ = 150.8 (C_q), 150.5 (C_q), 129.2 (CH), 128.4 (CH), 127.8 (CH), 126.6 (CH), 126.4 (CH), 125.7 (CH), 117.4 (CH), 117.3 (CH), 115.2 (CH), 115.1 (CH), 61.4 (CH), 60.6 (CH), 42.0 (CH₂), 41.8 (CH₂), 37.1 (CH), 36.6 (CH₂), 36.5 (CH), 35.3 (CH₂), 23.8 (CH₂), 23.4 (CH₂), 20.7 (CH₂), 20.5 (CH₂), 17.1 (CH₃), 16.1 (CH₃), 14.6 (CH₃), 14.5 (CH₃).

HRMS TOF ES⁺ calcd. for C₁₆H₂₄N [M + H]⁺ 230.1909; found 230.1909.

1-benzyl-6-phenethyl-1,2,3,6-tetrahydropyridine (3e)

Prepared by the general procedure for Aza-Silyl Prins cyclization. Isolated by flash column chromatography with a mixture of pentane-diethylether-triethylamine (100:2:1) as yellow oil, (9 mg, 11%).

IR ATR= 3084, 3060, 3024, 2930, 2796, 1602, 1494, 1452, 1361, 1104, 1072, 727, 695 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.38-7.08 (m, 10H), 5.82-5.76 (m, 1H), 5.59 (dd, *J* = 10.1, 2.4 Hz, 1H), 3.88 (d, *J* = 13.6 Hz, 1H), 3.38 (d, *J* = 13.6 Hz, 1H), 2.96 (brs, 1H), 2.86 (dt, *J* = 11.7, 5.6 Hz, 1H), 2.77-2.54 (m, 2H), 2.37 (dt, *J* = 11.7, 5.6 Hz, 1H), 1.99 (brs, 2H), 1.97-1.72 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ = 143.1 (C_q), 139.8 (C_q), 129.8 (CH), 1289.0 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 126.9 (CH), 125.8 (CH), 125.7 (CH), 58.6 (CH), 58.2 (CH₂), 46.1 (CH₂), 35.3 (CH₂), 31.6 (CH₂), 23.9 (CH₂).

HRMS TOF ES⁺ calcd. for C₂₀H₂₄N [M + H]⁺ 278.1909; found 278.1906.

1-benzyl-6-butyl-1,2,3,6-tetrahydropyridine (3f)

Prepared by the general procedure for Aza-Silyl Prins cyclization. Isolated by flash column chromatography with a mixture of pentane-diethylether-triethylamine (100:2:1) as yellow oil, (10 mg, 15%).

IR ATR = 3062, 3026, 2954, 2929, 2860, 1731, 1629, 1453, 1429, 1360, 1072, 1028, 727, 696 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.42-7.20 (m, 5H), 5.84-5.74 (m, 1H), 5.66 (dd, *J* = 10.1, 2.4 Hz, 1H), 3.94 (d, *J* = 13.6 Hz, 1H), 3.40 (d, *J* = 13.6 Hz, 1H), 2.94-2.85 (m, 2H), 2.39 (dt, *J* = 12.0, 6.0 Hz, 1H), 2.02 (brs, 2H), 1.66-1.55 (m, 2H), 1.52-1.19 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 139.7 (C_q), 130.2 (CH), 128.9 (CH), 128.2 (CH), 126.8 (CH), 125.1 (CH), 59.0 (CH), 58.1 (CH₂), 46.2 (CH₂), 33.1 (CH₂), 27.6 (CH₂), 24.0 (CH₂), 23.0 (CH₂), 14.2 (CH₃).

HRMS TOF ES⁺ calcd. for C₁₆H₂₄N [M + H]⁺ 230.1909; found 230.1901.

4,4'-(pyridin-4-ylmethylene)bis(N-((Z)-4-(trimethylsilyl)but-3-en-1-yl)aniline) (4)

Prepared by the general procedure for Aza-Silyl Prins cyclization. Isolated by flash column chromatography with a mixture of DCM-MeOH (20:1) as yellow oil, (29 mg, 36%).

IR ATR = 3020, 2952, 2895, 2851, 1610, 1515, 1411, 1321, 1246, 1178, 833, 761 cm⁻¹.

¹H NMR (300 MHz, MeOD) δ = 8.35 (d, *J* = 5.5 Hz, 2H), 7.13 (d, *J* = 5.5 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 4H), 6.57 (d, *J* = 8.6 Hz, 4H), 6.35 (dt, *J* = 14.1, 7.2

Hz, 2H), 5.59 (dt, J = 14.1, 1.3 Hz, 2H), 5.30 (s, 1H), 3.12 (t, J = 7.2 Hz, 4H), 2.42 (q, J = 7.2 Hz, 4H), 0.09 (s, 18H).

^{13}C NMR (75 MHz, MeOD) δ = 157.8 (C_q), 149.6 (CH), 148.3 (C_q), 147.0 (CH), 132.5 (C_q), 132.0 (CH), 131.0 (CH), 126.3 (CH), 114.2 (CH), 56.0 (CH), 44.7 (CH₂), 34.3 (CH₂), 0.3 (CH₃).

HRMS TOF ES⁺ calcd. for C₃₂H₄₆N₃Si₂ [M + H]⁺ 528.3230; found 528.3225.

1-phenyl-1,2,5,6-tetrahydro-2,2'-bipyridine (3h)

Prepared by the general procedure for Aza-Silyl Prins cyclization, using a mixture 1,4-dioxane-MeCN (9:1) as solvent. Isolated by flash column chromatography with DCM as yellow oil, (10 mg, 14%).

IR: $\tilde{\nu}$ = 3037, 3005, 2916, 2833, 1596, 1587, 1501, 1465, 1432, 848, 745, 689 cm⁻¹.

^1H NMR (300 MHz, CDCl₃) δ = 8.59 (d, J = 4.8 Hz, 1H), 7.58 (td, J = 7.8, 1.6 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.23-7.07 (m, 3H), 6.85 (d, J = 8.1 Hz, 2H), 6.72 (t, J = 7.2 Hz, 1H), 6.16-6.05 (m, 1H), 6.04-5.96 (m, 1H), 5.23 (s, 1H), 3.73 (dt, J = 12.8, 4.8 Hz, 1H), 3.56 (ddd, J = 12.8, 8.4, 4.4 Hz, 1H), 2.48-2.35 (m, 1H), 2.34-2.18 (m, 1H).

^{13}C NMR (75 MHz, CDCl₃) δ = 162.2 (C_q), 149.8 (C_q), 149.4 (CH), 137.2 (CH), 129.2 (CH), 128.8 (CH), 125.9 (CH), 121.9 (CH), 120.9 (CH), 118.2 (CH), 115.2 (CH), 62.0 (CH₂), 43.1 (CH), 24.8 (CH).

HRMS TOF ES⁺ calcd. for C₁₆H₁₇N₂ [M + H]⁺ 237.1392; found 237.1388.

2-phenyl-11-(trimethylsilyl)-2,3,4,5-tetrahydro-1H-1,5-methanopyrido[1,2-a][1,4]diazepin-6-ium tetrafluoroborate (5)

Prepared by the general procedure for Aza-Silyl Prins cyclization, using a mixture 1,4-dioxane-MeCN (9:1) as solvent. Isolated by flash column chromatography with a mixture of DCM-MeOH (9:1) as brown oil, (48 mg, 51%).

IR ATR = 3051, 2952, 2853, 1710, 1624, 1596, 1579, 1492, 1475, 1250, 1056, 1030, 894, 837, 756, 726, 693 cm⁻¹.

^1H NMR (300 MHz, CDCl₃) δ = 9.11 (d, J = 5.9 Hz, 1H), 8.27 (t, J = 7.8 Hz, 1H), 7.89 (t, J = 6.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 8.0 Hz, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.1 Hz, 2H), 5.69 (brs, 1H), 5.55 (d, J = 3.7 Hz, 1H), 3.32 (dd, J = 12.4, 6.0 Hz, 1H), 2.47-2.32 (m, 2H), 2.24 (brs, 1H), 2.20-2.10 (m, 1H), 0.29 (s, 9H).

^{13}C NMR (75 MHz, CDCl₃) δ = 154.6 (C_q), 148.1 (C_q), 146.0 (CH), 141.1 (CH), 129.8 (CH), 127.1 (CH), 122.1 (CH), 121.4 (CH), 116.7 (CH), 72.2 (CH), 64.7 (CH), 41.2 (CH₂), 40.7 (CH), 27.4 (CH₂), -1.1 (CH₃). ^{19}F NMR (282 MHz, CDCl₃) δ = -152.0 (s), -152.1 (s).

HRMS TOF ES⁺ calcd. for C₁₉H₂₅N₂Si [M]⁺ 309.1787; found 309.1782.

6'-methoxy-1-phenyl-1,2,5,6-tetrahydro-2,2'-bipyridine (3i)

Prepared by the general procedure for Aza-Silyl Prins cyclization. Isolated by flash column chromatography with DCM as yellow oil, (14 mg, 18% yield).

IR ATR = 3036, 2947, 2916, 2851, 1594, 1575, 1502, 1463, 1428, 1412, 1308, 1256, 1030, 987, 823, 785, 746, 689 cm⁻¹.

^1H NMR (300 MHz, CDCl₃) δ = 7.46 (t, J = 7.8 Hz, 1H), 7.19 (t, J = 8.0 Hz, 2H), 6.89-6.83 (m, 3H), 6.71 (t, J = 7.3 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.15 (brd, J = 10.0 Hz, 1H), 6.07-5.94 (m, 1H), 5.15 (s, 1H), 3.93 (s, 3H), 3.79 (dt, J = 13.1, 4.4 Hz, 1H), 3.59-3.50 (m, 1H), 2.54-2.35 (m, 1H), 2.24 (m, 1H).

^{13}C NMR (75 MHz, CDCl₃) δ 164.0 (C_q), 159.3 (C_q), 149.8 (C_q), 139.2 (CH), 129.2 (CH), 128.9 (CH), 125.8 (CH), 117.5 (CH), 114.5 (CH), 113.2 (CH), 108.6 (CH), 61.5 (CH), 53.5 (CH₃), 41.9 (CH₂), 24.8 (CH₂).

HRMS TOF ES⁺ calcd. for C₁₇H₁₉N₂O [M + H]⁺ 267.1497; found 267.1484.

2-phenyl-11-(trimethylsilyl)-2,3,4,5-tetrahydro-1,5-methanopyrido[1,2-a][1,4]diazepin-7(1H)-one (6)

Prepared by the general procedure for Aza-Silyl Prins cyclization. Isolated by flash column chromatography with a mixture of DCM-MeOH (19:1) as white crystals, mp = 162-165 °C, (68 mg, 70%).

IR ATR = 3061, 3038, 3001, 2951, 2859, 2839, 1650, 1581, 1539, 1504, 1494, 1468, 1242, 1210, 1183, 979, 878, 833, 794, 753, 737 cm⁻¹.

^1H NMR (300 MHz, CDCl₃) δ = 7.29 (t, 8.0 Hz, 2H), 7.20 (dd, J = 9.1, 6.6 Hz, 1H), 6.95-6.81 (m, 3H), 6.43 (d, J = 9.1, Hz, 1H), 5.86 (d, J = 6.6 Hz, 1H), 5.21 (t, J = 4.4 Hz, 1H), 5.09 (d, J = 3.8 Hz, 1H), 3.25 (dd, J = 12.1, 6.4 Hz, 1H), 2.55 (td, J = 11.5, 5.9 Hz, 1H), 2.29-2.06 (m, 2H), 1.65 (brs, 1H), 0.24 (s, 9H).

^{13}C NMR (75 MHz, CDCl₃) δ = 160.8 (C_q), 149.3 (C_q), 148.4 (C_q), 139.8 (CH), 129.3 (CH), 120.1 (CH), 119.4 (CH), 116.6 (CH), 99.9 (CH), 64.6 (CH), 58.5 (CH), 41.6 (CH₂), 39.9 (CH), 25.7 (CH₂), -0.9 (CH₃).

HRMS TOF ES⁺ calcd. for C₁₉H₂₅N₂OSi [M + H]⁺ 325.1736; found 325.1742.

Cis-2-benzyl-4-fluorotetrahydro-2H-pyran (10c)

Prepared according to the general procedure for Oxa-Prins cyclization. Purified by flash column chromatography with a mixture of pentane-diethylether (30:1) as colorless oil, (11 mg, 11%).

IR ATR = 3062, 3028, 2954, 2925, 2849, 1495, 1454, 1369, 1157, 1116, 1081, 1031, 996, 983, 750, 697 cm⁻¹.

^1H NMR (300 MHz, CDCl₃) δ = 7.40-7.20 (m, 5H), 4.65 (dtt, J = 49.2, 10.8, 5.0 Hz, 1H), 4.09 (dt, J = 11.9, 5.6 Hz, 1H), 3.61-3.45 (m, 1H), 3.39 (t, J = 11.9 Hz, 1H), 3.00 (dd, J = 13.7, 6.7 Hz, 1H), 2.77 (dd, J = 13.7, 6.3 Hz, 1H), 2.19-1.97 (m, 2H), 1.85-1.68 (m, 1H), 1.49 (p, J = 11.0 Hz, 1H).

^{13}C NMR (75 MHz, CDCl₃) δ = 138.0 (C_q), 129.5 (CH), 128.5 (CH), 126.6 (CH), 89.4 (d, $J_{\text{C-F}}$ = 176.2 Hz, CH), 76.7 (d, J = 10.6 Hz, CH), 65.2 (d, J = 11.6 Hz, CH₂), 42.6 (d, J = 1.6 Hz, CH₂), 38.4 (d, J = 17.1 Hz, CH₂), 33.1 (d, J = 17.5 Hz, CH₂).

^{19}F NMR (282 MHz, CDCl₃) δ -169.45 to -169.82 (m).

HRMS ASAP⁺ calcd. for C₁₂H₁₆OF [M+H]⁺ 195.1185; found 195.1177.

Trans-2-benzyl-4-fluorotetrahydro-2H-pyran (11c)

Prepared according to the general procedure for Oxa-Prins cyclization. Purified by flash column chromatography with a mixture of pentane-diethylether (30:1) as colorless oil, (46 mg, 47%).

IR ATR = 3062, 3028, 2949, 2861, 1496, 1454, 1365, 1337, 1258, 1068, 955, 748, 697 cm⁻¹.

^1H NMR (300 MHz, CDCl₃) δ = 7.41-7.16 (m, 5H), 5.00 (d, J = 48.1 Hz, 1H), 4.05-3.90 (m, 1H), 3.91-3.78 (m, 2H), 2.91 (dd, J = 13.8, 7.0 Hz, 1H), 2.71 (dd, J = 13.8, 6.0 Hz, 1H), 2.02-1.72 (m, 3H), 1.70-1.40 (m, 1H).

^{13}C NMR (75 MHz, CDCl₃) δ 138.2 (C_q), 129.4 (CH), 128.4 (CH), 126.4 (CH), 86.8 (d, J = 168.2, CH), 72.8 (CH), 62.7 (CH₂), 42.7 (CH₂), 36.4 (d, J = 20.4 Hz, CH₂), 30.9 (d, J = 20.7 Hz, CH₂).

^{19}F NMR (282 MHz, CDCl₃) δ -184.9 to -185.5 (m).

HRMS ASAP⁺ calcd. for C₁₂H₁₆OF [M+H]⁺ 195.1185; found 195.1183.

Trans-4-fluoro-2-(4-nitrophenyl)tetrahydro-2H-pyran (11l)

Prepared according to the general procedure for Oxa-Prins cyclization, with a flow rate of 150 $\mu\text{L min}^{-1}$. Purified by flash column chromatography with a mixture of pentane-acetone (20:1) as colorless crystals, mp = 102-105 °C, (41 mg, 36%).^{7a}

2-(2-nitrophenyl)-3,6-dihydro-2H-pyran (8m)

Prepared according to the general procedure for Oxa-Prins cyclization, with a flow rate of 150 $\mu\text{L min}^{-1}$. Purified by flash column chromatography with a mixture of pentane-acetone (49:1) as colorless oil, (18 mg, 17%).

IR ATR = 3080, 3040, 2948, 2918, 2839, 1610, 1580, 1512, 1346, 1335, 1176, 1078, 1025, 897, 860, 790, 742, 656 cm⁻¹.

^1H NMR (300 MHz, CDCl₃) δ = 7.89 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 5.98-5.87 (m, 1H), 5.86-5.83 (dd, J = 10.2, 1.4 Hz, 1H), 5.10 (dd, J = 10.2, 3.2 Hz, 1H), 4.42-4.30 (m, 2H), 2.53 (brd, J = 17.0 Hz, 1H), 2.43-2.16 (m, 1H).

^{13}C NMR (75 MHz, CDCl₃) δ 147.9 (C_q), 138.0 (C_q), 133.6 (CH), 128.2 (CH), 128.1 (CH) 126.2 (CH), 124.4 (CH), 124.2 (CH), 71.5 (CH), 66.9 (CH₂), 32.5 (CH₂).

HRMS ASAP⁺ calcd. for C₁₁H₁₂NO₃ [M+H]⁺ 206.0817; found 206.0823.

Trans-4-fluoro-2-(2-nitrophenyl)tetrahydro-2H-pyran (11m)

Prepared according to the general procedure for Oxa-Prins cyclization, with a flow rate of 150 $\mu\text{L min}^{-1}$. Purified by flash column chromatography with a mixture of pentane-acetone (97:3) as colorless oil, (19 mg, 17%).

IR ATR = 2945, 2920, 2867, 1611, 1579, 1515, 1439, 1342, 1332, 1254, 1064, 1034, 945, 863, 792, 739, 702 cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ = 7.89 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 5.32 (d, J = 11.4 Hz, 1H), 5.09 (d, J = 47.7 Hz, 1H), 4.05-3.97 (m, 2H), 2.46 (brt, J = 12.5 Hz, 1H), 2.10-1.88 (m, 2H), 1.83-1.59 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ = 147.9 (C_q), 137.6 (C_q), 133.5 (CH), 128.3 (CH), 128.1 (CH), 124.3 (CH), 86.4 (d, J = 170.2 Hz, CH), 70.4 (CH), 63.4 (CH_2), 38.1 (d, J = 20.6 Hz, CH_2), 30.7 (d, J = 20.8 Hz, CH_2).

^{19}F NMR (282 MHz, CDCl_3) δ = -186.2 to -186.7 (m).

HRMS TOF ES^+ calcd. for $\text{C}_{11}\text{H}_{13}\text{NO}_3\text{F}$ [$\text{M} + \text{H}$] $^+$ 226.0879; found 226.0870.

2-(3-(trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran (8n)

Prepared according to the general procedure for Oxa-Prins cyclization, with a flow rate of 150 $\mu\text{L min}^{-1}$. Purified by flash column chromatography with a mixture of pentane-ethyl acetate (99:1) as yellow oil, (7 mg, 6%).

IR ATR = 3040, 2929, 2896, 2831, 1450, 1339, 1325, 1160, 1118, 1089, 1070, 799, 701, 655 cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ = 7.66 (s, 1H), 7.55 (m, 2H), 7.47 (m, 1H), 5.93 (m, 1H), 5.76 (brd, J = 10.4, Hz, 1H), 4.62 (t, J = 6.9 Hz, 1H), 4.39 (s, 2H), 2.31 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ = 143.8 (C_q), 130.8 (q, J = 32.2 Hz, C_q), 129.3 (CH), 128.9 (CH), 126.6 (CH), 124.4 (q, J = 3.8 Hz, CH), 124.3 (q, J = 272.2 Hz, C_q), 124.2 (CH), 122.8 (q, J = 3.9 Hz, CH), 75.0 (CH), 66.7 (CH_2), 33.0 (CH_2).

^{19}F NMR (282 MHz, CDCl_3) δ = -63.1 (s).

HRMS ASAP^+ calcd. for $\text{C}_{12}\text{H}_{12}\text{OF}_3$ [$\text{M} + \text{H}$] $^+$ 229.0840; found 229.0829.

Cis-4-fluoro-2-(3-(trifluoromethyl)phenyl)tetrahydro-2H-pyran (10n)

Prepared according to the general procedure for Oxa-Prins cyclization, with a flow rate of 150 $\mu\text{L min}^{-1}$. Purified by flash column chromatography with a mixture of pentane-ethyl acetate (49:1) as colorless oil, (7 mg, 6%).

IR ATR = 2959, 2938, 2855, 1451, 1365, 1325, 1204, 1158, 1120, 1071, 1040, 983, 962, 801, 701, 669 cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ = 7.64 (s, 1H), 7.59-7.44 (m, 3H), 4.84 (dtt, J = 49.0, 10.7, 4.9 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 4.31-4.17 (m, 1H), 3.58 (t, J = 12.3 Hz, 1H), 2.41-2.36 (m, 1H), 2.22-2.07 (m, 1H), 1.97-1.79 (m, 1H), 1.79-1.65 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ = 142.5 (d, J = 1.9 Hz, C_q), 131.0 (q, J = 32.4 Hz, C_q), 129.2 (d, J = 1.5 Hz, CH), 129.1 (CH), 124.8 (q, J = 3.8 Hz, CH), 124.2 (q, J = 272.4 Hz, C_q), 122.8 (q, J = 3.9 Hz, CH), 89.2 (d, J = 177.4 Hz, CH), 77.2 (d, J = 11.6 Hz, CH), 65.6 (d, J = 11.8 Hz, CH_2), 40.7 (d, J = 17.4 Hz, CH_2), 33.0 (d, J = 17.7 Hz, CH_2).

^{19}F NMR (282 MHz, CDCl_3) δ = -63.1 (s), -170.5 to -170.8 (m).

HRMS ASAP^+ calcd. for $\text{C}_{12}\text{H}_{13}\text{OF}_4$ [$\text{M} + \text{H}$] $^+$ 249.0903; found 249.0896.

Trans-4-fluoro-2-(3-(trifluoromethyl)phenyl)tetrahydro-2H-pyran (11n)

Prepared according to the general procedure for Oxa-Prins cyclization, with a flow rate of 150 $\mu\text{L min}^{-1}$. Purified by flash column chromatography with a mixture of pentane-acetone (49:1) as colorless oil, (21 mg, 17%).

IR ATR = 2956, 2867, 1450, 1431, 1370, 1326, 1256, 1205, 1161, 1116, 1069, 874, 799, 700, 659 cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ = 7.65 (s, 1H), 7.55-7.43 (m, 3H), 5.10 (d, J = 47.8 Hz, 1H), 4.81 (dd, J = 11.8, 2.3 Hz, 1H), 4.03 (dd, J = 9.6, 3.1 Hz, 2H),

2.28-2.12 (m, 1H), 2.11-1.80 (m, 3H), 1.72 (ddd, J = 14.3, 11.8, 2.2 Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ = 143.4 (C_q), 10.9 (q, J = 32.0 Hz, C_q), 129.2 (CH), 129.0 (CH), 124.5 (q, J = 3.7 Hz, CH), 124.3 (q, J = 272.2 Hz, C_q), 122.7 (q, J = 3.8 Hz, CH), 86.7 (d, J = 169.3 Hz, CH), 73.6 (CH), 63.2 (CH_2), 38.8 (d, J = 20.2 Hz, CH_2), 30.6 (d, J = 20.7 Hz, CH_2).

^{19}F NMR (282 MHz, CDCl_3) δ = -63.1 (s), -186.2 to -186.7 (m).

HRMS ASAP^+ calcd. for $\text{C}_{12}\text{H}_{12}\text{OF}_4$ [M] $^+$ 248.0824; found 248.0834.

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