



HAL
open science

Scalable 9-Step Synthesis of the Splicing Modulator NVS-SM2

Hussein Abou-Hamdan, Laurent Désaubry

► **To cite this version:**

Hussein Abou-Hamdan, Laurent Désaubry. Scalable 9-Step Synthesis of the Splicing Modulator NVS-SM2. *Journal of Organic Chemistry*, 2018, 83 (5), pp.2954-2958. 10.1021/acs.joc.7b03009 . hal-01830554

HAL Id: hal-01830554

<https://hal.sorbonne-universite.fr/hal-01830554>

Submitted on 5 Jul 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Scalable 9-Step Synthesis of the Splicing Modulator NVS-SM2

Hussein Abou-Hamdan,^{†‡} Laurent Désaubry^{†‡*}

[†] Laboratory of Therapeutic Innovation (UMR 7200), University of Strasbourg–CNRS, Faculty of Pharmacy, 67401, Illkirch, France

[‡] Laboratory of Biomolecules (UMR7203), Sorbonne University–CNRS, 4 place Jussieu, 75005 Paris, France

Supporting Information



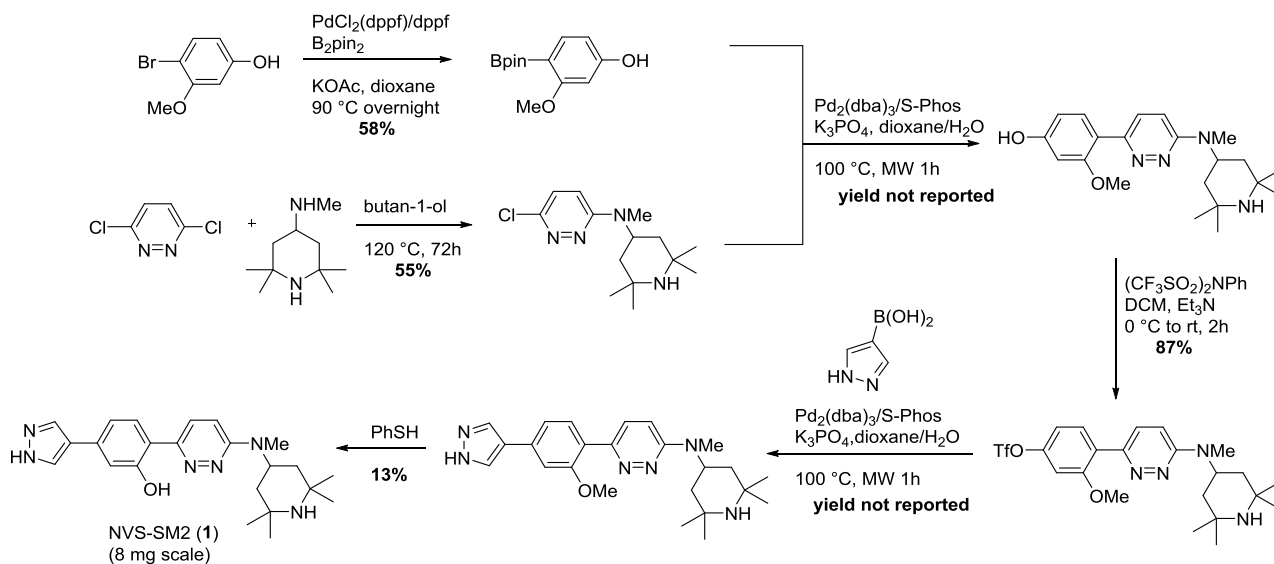
ABSTRACT: NVS-SM2, the first activator of pre-mRNA splicing, displays remarkable pharmacological *in vivo* activities in models of spinal muscular atrophy. Herein we describe an improved approach to the synthesis of this compound, which features a convenient introduction of sterically encumbered amine moiety onto a fluoropyridazine intermediate.

In 2015, Novartis scientists reported the discovery of NVS-SM2 (**1**, Scheme 1), the first activator of pre-mRNA splicing.¹ This orally active small molecule doubled life-span in a majority of treated mice in a model of spinal muscular atrophy (SMA). SMA is a major genetic cause of infant mortality caused by a mutation of the gene SMN that is essential to pre-mRNA splicing. The pharmacological investigation of **1** in SMA and other diseases is highly hindered by the availability of this compound. Indeed its preparation on an 8 mg scale has only been reported in one patent by Novartis' scientists.² The caveat in this synthesis lies in the deprotection of the phenol and the introduction of sterically hindered amine that respec-

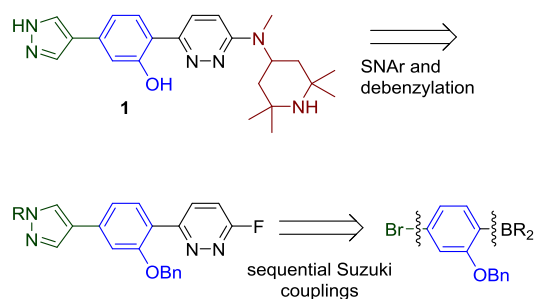
tively occurred with a 13 and 55% yield, and also with the Suzuki-Miyaura coupling of highly functionalized aryl and heteroaryl moieties, the yield of which was not reported (Scheme 1). In this communication, the execution of a 9-step, scalable synthesis of **1** is presented.

To overcome the limitation of the original synthesis of NVS-SM2, we explored several routes and we finally envisioned to protect the phenol as a benzyloxy and to introduce the congested amine onto a reactive fluoropyridazine. We considered also to assemble the aryl and heterocyclic moieties Suzuki coupling under optimized reactions (Scheme 2).

Scheme 1. Novartis Synthesis of NVS-SM2



Scheme 2. Synthesis Plan for NVS-SM2 (1)



Our synthesis commenced with a palladium-catalyzed borylation³ of iodide **2** that afforded a mixture (90:10) of boronates **3** and **3'**, which was directly used in a Suzuki-Miyaura coupling with iodopyridazine **4** to furnish adduct **5** (Scheme 3).⁴ Initial attempts to perform this reaction using Fu's condition^{5,6} did not yield the expected adduct **5** (entry 1, Table 1). Switching to other catalytic systems using S-Phos, X-Phos or PPh₃ as ligands provided the desired adduct with a conversion of 20-32% (entries 2-4). Ultimately, the air and moisture stable PdCl₂(dppf) proved to be particularly effective (entry 5). Finally, several other combinations of solvent and base were examined, and when the reaction was carried out in dioxane/H₂O with the use of K₃PO₄ as a base, a 70% yield could be achieved (entry 8). This preference for K⁺ as a counteraction of the base suggests that this Suzuki coupling involves a fast oxidation step and a rate-determining transmetalation.⁷

Further continuation of the synthesis required the replacement of the methoxy by a benzyloxy that can be efficiently deprotected in the final step. Indeed, Novartis scientists reported in their patent that the demethylation at a latter step is performed with a 13% yield only.² Thus, demethylation with boron trichloride of **5**, followed by benzylation, gave the requisite intermediate **7** in a 98% yield.

Scheme 3. Synthesis of Intermediate 7

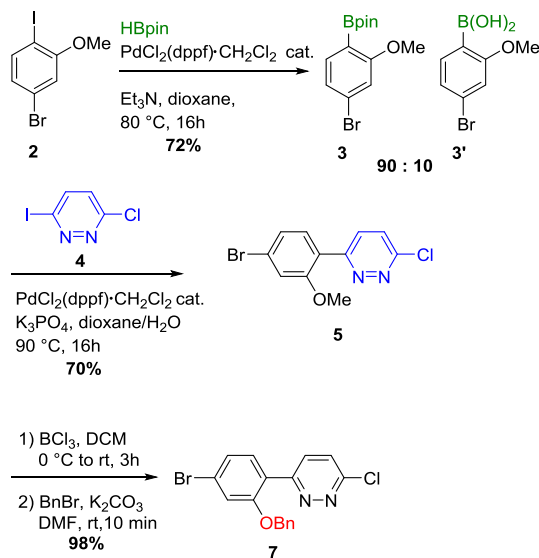
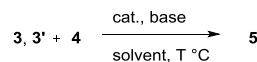


Table 1. Optimization of the First Suzuki-Miyaura Coupling



entry	cat.	base (eq)	solvent	T °C	yield (%)
1	Pd ₂ (dba) ₃ (2 mol%) P(<i>t</i> Bu) ₃ (3 mol%)	KF (3)	THF	80	trace
2	Pd(OAc) ₂ (10 mol%) S-Phos (20 mol%) (2.2)	K ₂ CO ₃	ACN/H ₂ O	110	20
3	Pd(OAc) ₂ (10 mol%) X-Phos (12 mol%) (2)	K ₃ PO ₄	<i>n</i> -BuOH/H ₂ O	110	21
4	Pd(PPh ₃) ₄ (5 mol%)	Na ₂ CO ₃ (2)	EtOH/toluene/ H ₂ O	reflux	32
5	PdCl ₂ (dppf)·CH ₂ Cl ₂ (10 mol%)	Na ₂ CO ₃ (2)	DMF/H ₂ O	100	40
6	PdCl ₂ (dppf)·CH ₂ Cl ₂ (10 mol%)	CsF (0.5)	DMF/H ₂ O	100	17
7	PdCl ₂ (dppf)·CH ₂ Cl ₂ (10 mol%)	Na ₂ CO ₃ (2)	THF/ACN/H ₂ O	100	12
8	PdCl ₂ (dppf)·CH ₂ Cl ₂ (10 mol%)	K ₃ PO ₄ (3)	dioxane/H ₂ O	90	70

With the intermediate **7** in hand, we proceeded to its coupling with the pyrazolylboronate moiety. Original attempts to perform this reaction using a pyrazolylboronate protected with a Boc were not satisfactory, due to the lability of the Boc in the examined conditions. To circumvent this issue, we incorporated a Trityl protecting group onto the pyrazolylboronate. This reagent was conveniently prepared in 3 steps from pyrazole **8** (Scheme 4).

Scheme 4. Preparation of Tritylpyrazolylboronate 11

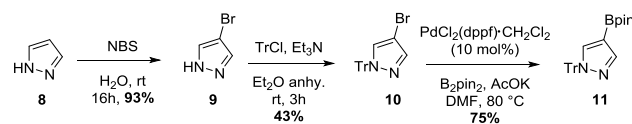
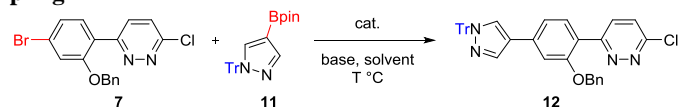
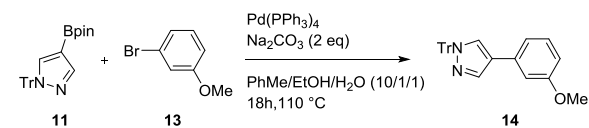


Table 2. Optimization of the Second Suzuki-Miyaura Coupling



entry	cat.	base (eq)	solvent	T °C	yield (%)
1	Pd ₂ (dba) ₃ (3 mol%) P(<i>t</i> Bu) ₃ (7 mol%)	KF (3.3)	THF	70	0
2	Pd ₂ (dba) ₃ (1 mol%) PCy ₃ (2.4 mol%)	K ₃ PO ₄ (1.7)	dioxane/H ₂ O	100	0
3	Pd(PPh ₃) ₄ (10 mol%)	Na ₂ CO ₃ (2)	DME/H ₂ O (6/3)	MW 150	28
4	Pd(PPh ₃) ₄ (10 mol%)	Na ₂ CO ₃ (2)	PhMe/EtOH/H ₂ O (10/1/1)	110	30

Table 3. Optimization of second Suzuki-Miyaura using 3-bromoanisole **13 as a substrate**



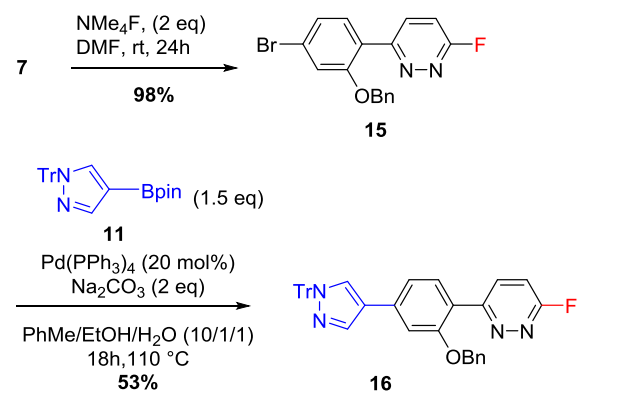
entry	11 (eq)	Pd(PPh ₃) ₄ (mol%)	yield (%)
1	1.5	10	33
2	3	10	28
3	1.5	20	70

After extensive studies, we found that arylbromide **7** can be coupled in the presence of Pd(PPh₃)₄ with boronate **11** to prepare adduct **12** in a 30% yield (entries 3-4, Table 2). Initial attempts to use unprotected pyrazole-4-boronic acid did not deliver the expected adducts. When we examined this reaction with the reactant protected as a Boc, the yield was not reproducible and lied between 0 and 20%.

To improve this reaction condition, we examined the coupling of **11** with 3-bromoanisole **13** using Pd(PPh₃)₄, Na₂CO₃ in PhMe/EtOH/H₂O.⁸ Our initial assay afforded the expected adduct in a 33% yield (entry 1, Table 3). Increasing the amount of boronate **11** did not modify the yield (entry 2). Gratefully, doubling the amount of catalyst improved the yield up to 70% (entry 3), suggesting that the catalyst is unstable in this condition.

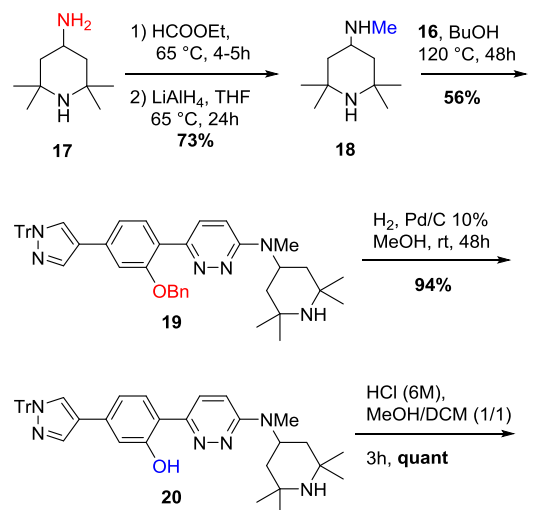
With an optimized Suzuki-Miyaura coupling of boronate **11** in hand, an efficient route to synthesize advanced intermediate **16** was developed (Scheme 5). First, the iminochloride **7** was treated with anhydrous tetramethylammonium fluoride under Sanford's condition⁹ to smoothly furnish fluoropyridazine **15**, in 98% yield. The latter has two main advantages compared to the cognate chloropyridazine **7**: the imino fluoride moiety is resistant to Suzuki coupling, and importantly, it is much more reactive in S_NAr reactions. The coupling of boronate **11** with **15** delivered adduct **16** in 53% yield.

Scheme 5. Synthesis of advanced intermediate



The synthesis of diamine **18** was conveniently achieved by formylation of **17** with ethyl formate and reduction of the obtained formamide with LiAlH₄. Its condensation with fluoropyridazine **16** gave aminopyridazine **19** in a satisfactory yield (56%) (Scheme 6). We originally considered performing this reaction with a chloropyridazine, but all of our attempts failed to deliver the expected adduct. Completion of the synthesis was accomplished by a double deprotection of the phenol and pyrazole moieties with a 94% yield for both steps.

Scheme 6. Endgame of the Synthesis



In conclusion, the synthesis of NVS-SM2 has been accomplished in 9 linear steps with an overall yield of 14% (average yield: 82%). It involves few more steps than the original one, however we optimized all the steps and some of them can be carried a very convenient manner with a near quantitative yield. For example, the conversion of **5** into **7** was performed in 2 steps with an overall yield of 98% and the intermediate of this sequence was directly used in the second step without purification. Actually, this sequence can be easily achieved in half a day. The fluoridation (**7** → **15**) and deprotection (**19** → **20** → **1**) steps are also performed in high yield in a very expedient manner.

Thus, this route can satisfy the global demand for NVS-SM2 to examine in detail its therapeutic potential to treat SMA and other diseases associated with alterations in RNA splicing. In addition, the efficacy of the synthesis reported herein offers an opportunity to explore further the pharmacological effects of chemical modifications in the structure of NVS-SM2.

EXPERIMENTAL SECTION

All commercial reagents were used without purification. All the anhydrous solvents used are commercial or are conserved on molecular sieves. All reactions sensitive to moisture or oxygen were carried out under argon atmosphere and in flasks dried at 110 °C. Reactions were stirred with a magnetic stirrer. Temperatures for the reactions refer to bath temperatures. Reactions were monitored by TLC (0.2 mm, Merck DC Platten Kieselgel 60 F₂₅₄) with detection by UV light (λ = 254 nm) and treatment with anisaldehyde and potassium permanganate-stain. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected.

NMR spectras were acquired on a Bruker DRX-400 spectrometer in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.0 ppm for ¹³C), (CD₃)₂SO (referenced to 2.50 ppm for ¹H and 39.5 ppm for ¹³C) or CD₃OD (referenced to 3.31 ppm for ¹H and 49 ppm for ¹³C) as solvents. Coupling constants (J) are in Hz. Chemical shifts are reported in parts per million (ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet. High resolution mass spectra were recorded on a Bruker MicroTOF-Q (ESI Q-TOF) spectrometer.

3-(4-Bromo-2-methoxyphenyl)-6-chloropyridazine (5)

1,1'-Bis(diphenylphosphinoferrocene)-palladium (II) dichloride CH₂Cl₂ complex (574 mg, 0.70 mmol) was added to a dioxane (19 mL) / H₂O (1 mL) solution of iodopyridazine **4** (1.86 g, 7.73 mmol), boronates (**3**, **3'**) (2.2 g, 7.03 mmol) and potassium phosphate (4.48 g, 21.08 mmol) at room temperature under argon atmosphere (the flask was evacuated and refilled with argon five times before adding of Pd complex). The reaction was heated at 90 °C for 16h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (50 mL), filtered through celite with copious washings, and then concentrated. The organic layer was washed with water, brine, dried over anhydrous MgSO₄, filtered, concentrated and purified by column chromatography on silica gel using DCM (100%) as eluent to give **5** (1.63 g, 70%) as a white solid ; mp = 133-136 °C ; ¹H NMR (400 MHz, CDCl₃) δ 3.87 (3H, s), 7.16 (1H, d, *J* = 1.4 Hz), 7.26 (1H, dd, *J* = 1.4, 8.3 Hz), 7.49 (1H, d, *J* = 9 Hz), 7.84 (1H, d, *J* = 8.3 Hz), 7.98 (1H, d, *J* = 9 Hz) ; ¹³C NMR (100 MHz, CDCl₃) δ 56.0, 115.0, 123.6, 124.6, 125.4, 127.2, 130.3, 132.2, 155.1, 157.1, 157.6 ; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₁H₉BrClN₂O 298.9581 ; found 298.9571.

5-Bromo-2-(6-chloropyridazin-3-yl)phenol (6)

To a stirred solution of **5** (500 mg, 1.67 mmol) in dry DCM (50 mL), BCl₃ (5 mL, 5 mmol, 1M in DCM) was added dropwise at 0 °C under argon atmosphere. The resulting reaction mixture was stirred over 3h at room temperature then quenched with water. The aqueous layer was extracted with DCM (2 × 50 mL). Combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated to give **6** (470 mg, 99%) as a pale-yellow solid which was used without further purification ; mp = 161-164 °C ; ¹H NMR (400 MHz, CDCl₃) : δ 7.10 (1H, dd, *J* = 1.5, 8.5 Hz), 7.29 (1H, d, *J* = 1.5 Hz), 7.52 (1H, d, *J* = 8.5 Hz), 7.67 (1H, d, *J* = 9.3 Hz), 8.01 (1H, d, *J* = 9.3 Hz) ; ¹³C NMR (100 MHz, CDCl₃) : δ 114.9, 122.4, 122.9, 125.7, 127.1, 127.5, 130.1, 155.0, 159.5, 160.5 ; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₀H₇BrClN₂O 284.9425 ; found 284.9420.

3-[2-(Benzyloxy)-4-bromophenyl]-6-chloropyridazine (7)

To a stirred solution of phenol **6** (130 mg, 0.45 mmol) in dry DMF (1.5 mL), was added potassium carbonate (126 mg, 0.9 mmol) and then benzyl bromide (86 mg, 0.5 mmol) at room temperature under argon atmosphere. The resulting reaction mixture was stirred over 10 min at the same temperature and then diluted with DCM (15 mL). The organic layer was washed with water, dried over anhydrous MgSO₄, filtered and concentrated to give chloropyridazine **7** (167 mg, 98%) as a white solid which was used without further purification ; mp =

177-180 °C ; ¹H NMR (400 MHz, CDCl₃) : δ 5.12 (2H, s), 7.27-7.41 (8H, m), 7.89 (1H, d, *J* = 8.3 Hz), 7.98 (1H, d, *J* = 9 Hz) ; ¹³C NMR (100 MHz, CDCl₃) : δ 71.4, 116.6, 124.1, 125.1, 125.4, 127.2, 127.5, 128.6, 128.9, 130.4, 132.5, 135.6, 155.2, 156.9, 157.1 ; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₇H₁₃BrClN₂O 374.9894 ; found 374.9883.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-trityl-1H-pyrazole (11)

To a stirred solution of 4-bromo-tritylpyrazole **10** (2 g, 5.14 mmol) and bis(pinacolato)diboron (1.44 g, 5.65 mmol) in DMF (14 mL), was added 1,1'-bis(diphenylphosphinoferrocene)-palladium (II) dichloride CH₂Cl₂ complex (420 mg, 0.51 mmol) and potassium acetate (1.51g, 15.42 mmol) at room temperature under argon atmosphere. The resulting mixture was heated at 80 °C for 16h. After cooling to room temperature, the reaction mixture was diluted with DCM (50 mL). The organic layer was washed with water, brine, dried over anhydrous MgSO₄, filtered, concentrated and purified by column chromatography on silica gel using pentane / Et₂O (10/0 to 8/2) as eluent to give boronate **11** (1.8 g, 75%) as a white solid ; mp = 190-193 °C ; ¹H NMR (400 MHz, CDCl₃) : δ 1.33 (12H, s), 7.13-7.20 (6H, d, m), 7.28-7.34 (9H, d, m), 7.79 (1H, s), 7.98 (1H, s) ; ¹³C NMR (100 MHz, CDCl₃) : δ 24.9, 78.8, 83.4, 127.7, 127.8, 130.2, 138.8, 143.2, 145.9 ; HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₈H₂₉BN₂NaO₂ 459.2214 ; found 459.2210.

3-(2-(Benzyloxy)-4-(1-trityl-1H-pyrazol-4-yl)phenyl)-6-chloropyridazine (12)

Pd(PPh₃)₄ (31 mg, 0.027 mmol) was added to a stirred solution of chloropyridazine **7** (100 mg, 0.27 mmol), boronate **11** (174 mg, 0.40 mmol) and Na₂CO₃ (117 mg, 0.53 mmol) in PhMe (3 ml) / EtOH (0.3 ml) / H₂O (0.3 ml) at room temperature under argon atmosphere (the flask was purged five times with argon before adding the Pd complex). The resultant mixture was stirred at the same temperature for 5 min and then at 110 °C for 18h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (25 mL). The organic layer was washed with water, brine, dried over MgSO₄, concentrated and purified by column chromatography on silica gel using pentane / Et₂O (8/2 to 5/5) as eluent to give chloropyridazine **12** (50 mg, 30%) as a white solid ; mp = 216-219 °C ; ¹H NMR (400 MHz, CDCl₃) : δ 5.07 (2H, s), 7.05 (1H, d, *J* = 0.9 Hz), 7.07-7.20 (8H, m), 7.21-7.35 (14H, m), 7.60 (1H, s), 7.88 (1H, s), 7.90 (1H, d, *J* = 8 Hz), 7.96 (1H, d, *J* = 9 Hz) ; ¹³C NMR (100 MHz, CDCl₃) : δ 71.1, 79.1, 110.2, 119.1, 121.0, 123.0, 127.0, 127.5, 127.9, 128.0, 128.3, 128.8, 129.6, 130.2, 130.5, 131.7, 136.3, 137.4, 143.0, 154.7, 156.9, 157.6 ; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₃₉H₃₀ClN₄O 605.2103 ; found 605.2108.

4-(3-Methoxyphenyl)-1-trityl-1H-pyrazole (14)

The title compound was prepared similarly to the synthesis of chloropyridazine **12** starting from 3-bromoanisole **13** (80 mg, 0.054 mmol), boronate **11** (281 mg, 0.64 mmol), sodium carbonate (91 mg, 0.86 mmol), Pd(PPh₃)₄ (100 mg, 0.086 mmol) and PhMe (3 ml) / EtOH (0.3 ml) / H₂O (0.3 ml). The crude product was purified by chromatography on silica gel using pentane / Et₂O (10/0 to 80/20) as eluent to give pyridazine **14** (126 mg, 70%) as a white solid ; mp = 120-123 °C ; ¹H NMR

(400 MHz, CDCl₃): δ 3.82 (3H, s), 6.75 (1H, ddd, J = 1.0, 2.6, 8.4 Hz), 7.96 (1H, dd, J = 1.4, 2.6 Hz), 7.03 (1H, ddd, J = 1, 1.4, 7.7 Hz), 7.20-7.25 (7H, m), 7.30-7.35 (9H, m), 7.61 (1H, d, J = 0.8 Hz), 7.93 (1H, d, J = 0.8 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 55.3, 78.9, 111.4, 111.6, 118.2, 121.5, 127.8, 127.9, 129.3, 129.8, 130.2, 134.0, 137.3, 143.1, 160.0; HRMS (ESI-TOF) m/z : [M+Na]⁺ calcd for C₂₉H₂₄N₂NaO 439,1786; found 439,1768.

3-[2-(Benzyloxy)-4-bromophenyl]-6-fluoropyridazine (15)

To a stirred solution of chloropyridazine **7** (750 mg, 1.99 mmol) in dry DMF (12 mL), anhydrous NMe₄F (375 mg, 3.98 mmol) was added at room temperature under argon atmosphere. The resulting reaction mixture was stirred at the same temperature for 24h before it was diluted with DCM (70 mL). The organic layer was washed with water (3 \times 120 mL), brine (1 \times 100 mL), dried over anhydrous MgSO₄, filtered and concentrated to give fluoropyridazine **15** (700 mg, 98%) as a white solid which was used without further purification; mp = 167-170 °C; ¹H NMR (400 MHz, CDCl₃): δ 5.12 (2H, s), 7.13 (1H, dd, J = 1.5, 9.2 Hz), 7.27-7.40 (7H, m), 7.8 (1H, d, J = 8.2 Hz), 8.12 (1H, dd, J = 7.5, 8.2 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 71.3, 114.7 (d, J = 33 Hz), 116.5, 124.2, 125.1, 125.2, 127.5, 128.6, 128.9, 132.5, 133.7 (d, J = 7 Hz), 135.6, 156.7, 157.6 (d, J = 2.7 Hz), 165.7 (d, J = 245 Hz); ¹⁹F NMR decoupled ¹H (376 MHz, CDCl₃): -81.27 (1F, s); ¹⁹F NMR coupled ¹H (376 MHz, CDCl₃): -81.27 (1F, d, J = 7.5 Hz); HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₇H₁₃BrFN₂O 359.0190; found 359.0192.

3-[2-(Benzyloxy)-4-(1-trityl-1H-pyrazol-4-yl)phenyl]-6-fluoropyridazine (16)

The title compound was prepared similarly to the synthesis of chloropyridazine **12** starting from fluoropyridazine **15** (200 mg, 0.55 mmol), boronate **11** (364 mg, 0.83 mmol), sodium carbonate (117 mg, 1.1 mmol), Pd(PPh₃)₄ (129 mg, 0.11 mmol) and PhMe (5 ml) / EtOH (0.5 ml) / H₂O (0.5 ml). The crude product was purified by chromatography on silica gel using pentane / Et₂O (8/2 to 5/5) as eluent to give fluoropyridazine **16** (172 mg, 53%) as a white solid; mp = 203-206 °C; ¹H NMR (400 MHz, CDCl₃): δ 5.19 (2H, s), 7.13 (1H, dd, J = 1.5, 9.2 Hz), 7.18 (7H, d, J = 1.5 Hz), 7.22 (1H, d, J = 8.3 Hz), 7.24-7.3 (6H, m), 7.32-7.43 (14H, m), 7.73 (1H, s), 7.99 (1H, dd, J = 1.4, 8.2 Hz), 8.00 (1H, s), 8.21 (1H, dd, J = 7.5, 8.3 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 71.1, 79.1, 110.2, 114.5 (d, J = 33 Hz), 119.1, 121.0, 123.1, 127.4, 127.9, 128.0, 128.3, 128.7, 129.5, 130.2, 131.8, 133.6 (d, J = 6.8 Hz), 136.1, 132.3, 137.5, 143.0, 156.6, 158.1 (d, J = 2.5 Hz), 165 (d, J = 244 Hz); ¹⁹F NMR decoupled ¹H (376 MHz, CDCl₃): -81.99; ¹⁹F NMR coupled ¹H (376 MHz, CDCl₃): -81.99 (dd, J = 1.4, 7.5 Hz); HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₃₉H₂₉FN₄O 589.2398; found 589.2395.

N,2,2,6,6-pentamethylpiperidin-4-amine (18)

A solution of **17** (4.4 mL, 0.026 mmol) in ethyl formate (6.5 mL, 0.078 mmol) was heated at 65 °C for 4-5 h. The resulting thick, white suspension was cooled to room temperature and filtered. After the filter cake was washed with EtOAc (20 mL), the solid was dried under vacuum to give 3.8 g (79 % yield) of *N*-(2,2,6,6-tetramethylpiperidin-4-yl)formamide, which was used directly in the next step. A 250 mL round bottom flask

equipped with a large Teflon-coated stir bar was charged with LiAlH₄ (1.17 g, 31 mmol), fitted with a reflux condenser, and purged with argon. THF (40 mL) was added and the resulting suspension was cooled to 0 °C. A *N*-(2,2,6,6-tetramethylpiperidin-4-yl)formamide (3.8 g, 20.6 mmol) was added in portion over 10 min (CAUTION: hydrogen gas evolution!). The cooling bath was replaced with an oil bath and the colorless solution was heated at 65 °C for 24h under a slow stream of argon. The resulting white suspension was cooled to 0 °C and then carefully quenched by dropwise addition of water (10 mL; CAUTION: violently exothermic reaction, evolution of hydrogen gas!) followed by a 20% aq NaOH solution (20 mL). The resulting suspension was stirred at room temperature for 15 min. MeOH (40 mL) was added then the mixture was filtered on celite. The filtrate was concentrated and then the residue was dissolved with EtOAc (50 mL). The organic layer was washed with water, brine, dried over anhydrous MgSO₄, filtered and concentrated to give diamine **18** (3.25 g, 93%) as a yellow liquid which was used without further purification; ¹H NMR (400 MHz, (CD₃)₂SO): δ 0.72 (2H, t, J = 11.8 Hz), 1.00 (6H, s), 1.09 (6H, s), 1.68 (2H, dd, J = 3.4, 12.3 Hz), 2.26 (3H, s), 2.6 (1H, tdd, J = 3.5, 11.5, 11.5 Hz); ¹³C NMR (100 MHz, (CD₃)₂SO): δ 28.5, 32.5, 34.3, 44.5, 49.7, 50.6; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₀H₂₃N₂ 171.1856; found 171.1853.

6-[2-(Benzyloxy)-4-(1-trityl-1H-pyrazol-4-yl)phenyl]-*N*-methyl-*N*-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (19)

To a stirred solution of **16** (230 mg, 0.39 mmol) in butan-1-ol (4 ml), diamine **18** (133 mg, 0.78 mmol) was added at room temperature under argon atmosphere. The mixture was heated at 120 °C for 48h. After cooling to room temperature, butan-1-ol was removed using rotary evaporator, then the residue was diluted with DCM (50 mL). The organic layer was washed with water, dried over anhydrous MgSO₄, filtered, concentrated and purified by flash chromatography on silica gel using DCM / MeOH (10/0 to 8/2) as eluent to give **19** (160 mg, 56%) as a yellow solid; mp = 105-108 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.18 (6H, s), 1.35 (6H, s), 1.38 (2H, m), 1.70 (2H, dd, J = 2.1, 12 Hz), 2.96 (3H, s), 5.13 (2H, s), 5.15 (1H, m), 6.72 (1H, d, J = 9.7 Hz), 7.07 (1H, d, J = 1.3 Hz), 7.14 (1H, dd, J = 1.3, 8 Hz), 7.17-7.25 (6H, m), 7.28-7.4 (14H, m), 7.63 (1H, s), 7.84 (1H, d, J = 9.5 Hz), 7.92 (1H, s), 7.98 (1H, d, J = 8 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 28.8, 29.2, 35.3, 41.9, 47.5, 51.5, 71.0, 79.0, 110.4, 119.0, 121.4, 125.3, 127.3, 127.8, 127.9, 128.6, 129.2, 129.4, 130.2, 130.9, 134.1, 137.0, 137.4, 143.1, 149.1, 156.3, 158.2; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd for C₄₉H₅₁N₆O 739.4119; found 739.4138.

2-[6-[Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino]pyridazin-3-yl]-5-(1-trityl-1H-pyrazol-4-yl)phenol (20)

To a stirred solution of **19** (110 mg, 0.15 mmol) in MeOH (7 ml), catalytic amount of 10% palladium on carbon was added under H₂ atmosphere. The mixture was stirred for 48h at room temperature and then filtered on celite. The filtrate was concentrated and purified by flash chromatography on silica gel using DCM / MeOH (10/0 to 8/2) as eluent to give phenol **20** (90 mg, 94%) as a yellow solid; mp = 132-135 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.18 (6H, s), 1.35 (6H, s), 1.40 (2H, t, J = 12.3 Hz), 1.69 (2H, dd, J = 2, 12 Hz), 3.00 (3H, s), 4.88 (1H,

m), 6.98 (1H, d, $J = 9.8$ Hz), 7.01 (1H, d, $J = 8.1$ Hz), 7.11 (1H, s), 7.16-7.23 (6H, m), 7.29-7.37 (9H, m), 7.52 (1H, d, $J = 8.3$ Hz), 7.66 (1H, s), 7.92 (1H, s), 7.79 (1H, d, $J = 9.8$ Hz), 7.98 (1H, s); ^{13}C NMR (100 MHz, CDCl_3): δ 28.9, 29.4, 35.3, 42.0, 48.4, 51.5, 79.1, 113.9, 114.8, 116.0, 116.8, 121.2, 124.5, 125.4, 128.0, 129.7, 130.3, 134.8, 137.5, 143.2, 151.6, 157.9, 159.4; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{42}\text{H}_{45}\text{N}_6\text{O}$ 649.3649; found 649.3634.

2-[6-[Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino]pyridazin-3-yl]-5-(1H-pyrazol-4-yl)phenol (1)

To a stirred solution of **20** (80 mg, 0.12 mmol) in THF (2 ml) / MeOH (2 ml), 2 ml of HCl (6M) was added at room temperature. The mixture was stirred at the same temperature. After 3h, solvents were removed using rotary evaporator. The yellow product obtained in salt form was dissolved in DCM / MeOH (50/50) and neutralized with addition of solid NaHCO_3 . Then the mixture was filtered through celite. The filtrate was concentrated and purified by flash chromatography using DCM / MeOH (10/0 to 8/2) as eluent to give NVS-SM2 (**1**) (48 mg, quant.) as a yellow solid; mp = 146-149 °C; ^1H NMR (400 MHz, MeOD): δ 1.22 (6H, s), 1.35 (6H, s), 1.48-1.65 (4H, m), 2.87 (3H, s), 4.98 (1H, m), 7.04-7.17 (3H, m), 7.59 (1H, d, $J = 7.4$ Hz), 7.89 (1H, d, $J = 9.4$ Hz), 7.97 (2H, s); ^{13}C NMR (100 MHz, MeOD): δ 27.5, 29.8, 33.6, 41.3, 54, 115, 116.3, 117.2, 117.6, 123, 126.4, 127.3, 136.2, 152.8, 159.2, 159.9; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{31}\text{N}_6\text{O}$ 407.2554; found 407.2550.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Spectral data for compounds described herein (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: desaubry@unistra.fr

Present Address

Laboratory of Therapeutic Innovation (UMR 7200), Faculty of Pharmacy, University of Strasbourg-CNRS, 67401, Illkirch, France

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the “Ministère de l'Enseignement Supérieur et de l'Innovation” for a fellowship to H. A-H.

■ REFERENCES

- (1) Palacino, J.; Swalley, S. E.; Song, C.; Cheung, A. K.; Shu, L.; Zhang, X.; Van Hoosear, M.; Shin, Y.; Chin, D. N.; Keller, C. G.; Beibel, M.; Renaud, N. A.; Smith, T. M.; Salcius, M.; Shi, X.; Hild, M.; Servais, R.; Jain, M.; Deng, L.; Bullock, C.; McLellan, M.; Schuierer, S.; Murphy, L.; Blommers, M. J.; Blaustein, C.; Berenshteyn, F.; Lacoste, A.; Thomas, J. R.; Roma, G.; Michaud, G. A.; Tseng, B. S.; Porter, J. A.; Myer, V. E.; Tallarico, J. A.; Hamann, L. G.; Curtis, D.; Fishman, M. C.; Dietrich, W. F.; Dales, N. A.; Sivasankaran, R. *Nat. Chem. Biol.* **2015**, *11*, 511-517.
- (2) Cheung, A.; Chin, D. N.; Dales, N.; Fazal, A.; Hurley, T. B.; Kerrigan, J.; O'Brien, G.; Shu, L.; Sun, R.; Sung, M., WO2014028459A1.
- (3) Murata, M.; Watanabe, S.; Masuda, Y., *J. Org. Chem.* **1997**, *62*, 6458-6459.
- (4) We considered starting our synthesis with a reagent protected by a benzyl, but the borylation step (similar to **2** \rightarrow **3** + **3'**) did not afford the expected compound.
- (5) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 1282-1284.
- (6) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.
- (7) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. - Eur. J.* **2012**, *18*, 6616-6625.
- (8) Aryl bromides have been shown to afford higher yield than the cognate triflates on this type of substrates: Yang, Y.; Oldenhuis N. J.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **2013**, *52*, 615-619.
- (9) Schimler, S. D.; Ryan, S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S., *J. Org. Chem.* **2015**, *80*, 12137-121.