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Accessing Spiropiperidines from Dihydropyridones through Tandem Triflation-Allylation and Ring-Closing Metathesis (RCM)

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A novel approach to build 2-spiropiperidine moieties starting from dihydropyridones was developed. The triflic anhydride-promoted conjugate addition of allyltributylstannane onto these dihydropyridones allowed for the formation of gem bis-alkenyl intermediates that were converted to the corresponding spirocarbocycles with excellent yields via ring closing metathesis. The vinyl triflate group generated onto these 2-spiro-dihydropyridine intermediates could be successfully used as a chemical expansion vector for further transformations namely Pd-catalyzed cross-coupling reactions.

Introduction

Drug discovery typically involves, once an original biological target was identified and validated, screening libraries of compounds or fragments in order to identify potentially active ones that will be further optimized to be drug candidates. The large synthetic libraries available today often suffer low hit rates in biological assays, in part because of their low degrees of structural complexity and diversity. The development of more complex molecules with increased shape diversity and « three-dimensionality » is therefore of great interest¹⁻⁹ and would allow for a larger chemical space exploration. Consequently, much effort is directed to optimizing fragment collections with, in particular the elaboration of original fragments bearing spirocycles, ubiquitous molecules with unique rigidity and three-dimensional geometry.¹⁰⁻¹²

medicinal chemists.¹³⁻²¹ (-)-Histrionicotoxin, a potent non-competitive antagonist of nicotinic acetylcholine receptors,²² (+)-nitramine²³ and ibutamoren, a potent agonist of the ghrelin receptor²⁴ are examples of synthetic or natural biologically active spiro-piperidines (Figure 1). Different synthetic approaches have been developed to generate these scaffolds, but their preparation remains challenging. In particular, there are limited methods for the synthesis of 2-spiropiperidines that offer chemical expansion vectors allowing for the generation of additional interactions with a biological target or to optimize an identified fragment.^{13,25-26}

The synthesis of dihydropyridones²⁷ and their use as intermediates for the synthesis of piperidine derivatives has been extensively developed over the last decades.²⁸⁻²⁹ In the past few years, we have developed a gold-catalyzed approach from the chiral pool of amino acids to build such dihydropyridones with an excellent stereochemical maintenance (Scheme 1a).³⁰ We also demonstrated that these dihydropyridones are valuable intermediates towards various piperidines.³¹⁻³²

At the same period, the group of Trauner et al. demonstrated in a seminal paper, that the triflic anhydride-promoted activation of enone allowed for the formation of an allylic trifloxy cation that can be trapped by the nucleophilic attack of allylstannane (Scheme 1b).³³ The scope of this reaction was limited to acyclic and carbocyclic enone and was not extended to heterocyclic enones as their reactivity may be quite challenging. This approach appeared interesting to us because, in a single step, it allows to introduce (i) an allyl side-chain that may be engaged in a ring-closing metathesis (RCM) reaction to build the spiro-cycle, and (ii) a vinyl triflate group that may be used as a chemical expansion vector for further transformations namely Pd-catalyzed cross-coupling reactions. We describe herein a new approach toward 4-substituted-2-spiropiperidines from dihydropyridones.

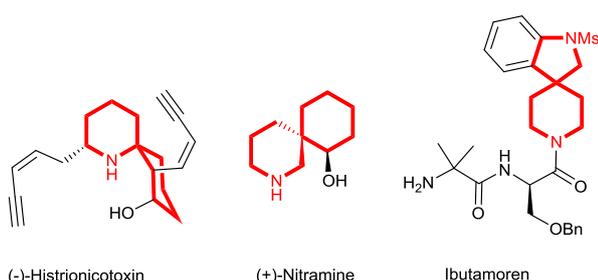
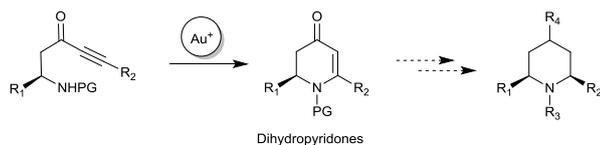


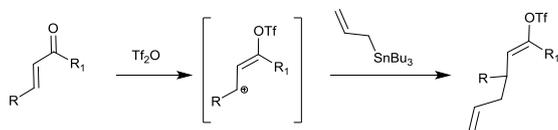
Figure 1 Representative bioactive compounds containing spiro-piperidine skeletons.

On the other hand, the piperidine ring is a common structural motif present in natural and/or synthetic products with pharmaceutical importance, and within this class of saturated nitrogen heterocycles, the spiro-piperidine moiety capable of exploring and spanning a large binding pocket due to its rigidly defined structure has been considered as « privileged structure » and thus have become sought-after motifs for

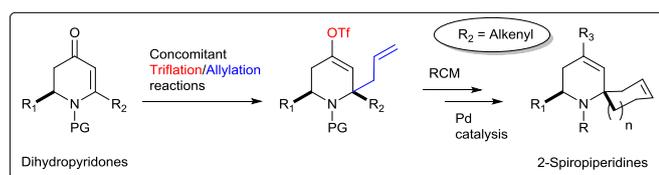
(a) Our gold-catalyzed approach towards dihydropyridones and piperidines



(b) Trauner's concomitant triflation/allylation of enone substrates

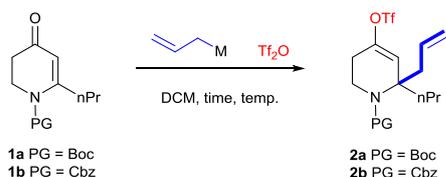


(c) This work

**Scheme 1** Our approach towards 2-spiropiperidines.

Results and discussion

To test the feasibility of the triflation/allylation of dihydropyridones, we initiated the exploration of reaction conditions by using *N*-Boc protected dihydropyridone **1a** as the typical substrate (Table 1).³⁴ Such starting material was selected for two main reasons. The Boc protecting group is probably the most common amine protecting group since it can be easily and quantitatively removed under relatively mild conditions. A dihydropyridone bearing a propyl side chain in position 6 instead of a phenyl ring was preferred since an aromatic in this position may undergo resonance stabilization of the carbenium intermediate, which may be an advantageous regarding the mode of activation.

Table 1 Screening of Optimal Reaction Conditions.^a

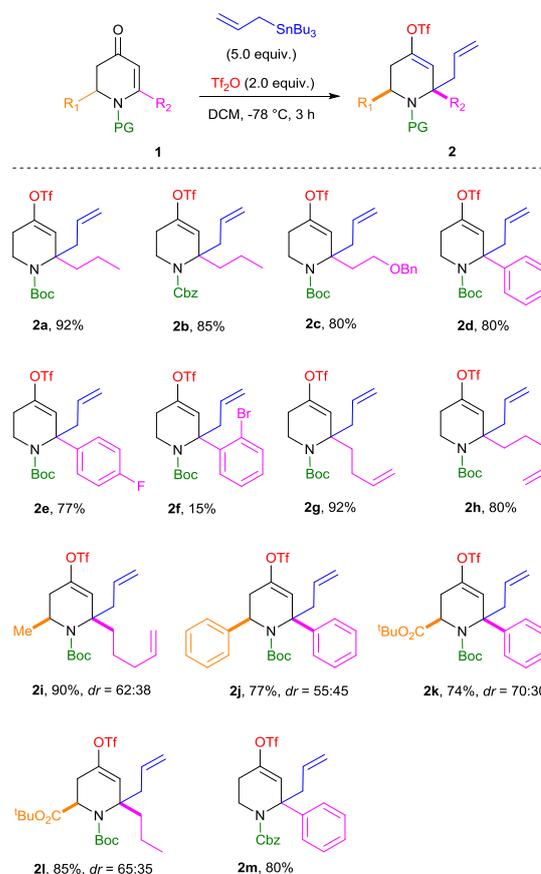
Entry	SM	M	Equiv.	Time (h)	Temp (°C)	Yield (%) ^b
1	1a	SiMe ₃	5.0	6	-78	< 5
2	1b	SiMe ₃	5.0	4	-78	40
3	1b	SnBu ₃	5.0	3	-78	85
4	1a	SnBu ₃	5.0	3	-78	92
5	1a	SnBu ₃	2.0	4	-78	25

^aReactions were carried out with **1** (0.10 mmol) and Tf₂O (2.0 equiv.) in 1.0 mL of DCM. ^bThe yields refer to the isolated yields.

The reaction of **1a** with allyltrimethylsilane (5.0 equiv.) in the presence of triflic anhydride (2.0 equiv.) in dichloromethane at

-78°C was initially examined. Despite a complete conversion was observed after 6h, most of the substrate underwent Boc deprotection in these conditions (Table 1, entry 1). As the Boc protecting group is prone to undergo TMS-mediated cleavage,³⁵ it was replaced with a Cbz moiety (**1b**). Using this new protecting group, we were able to obtain the desired compound (**2b**), however with a low yield (Table 1, entry 2). These first results led us to reconsider the nature of the nucleophile and to replace allyltrimethylsilane by allyltributyltin, that was demonstrated in Trauner's³³ and Comins³⁶⁻³⁷ studies to exhibit the appropriate properties. Notably, good conversion to the desired addition product **2b** was observed within 3 h under these novel conditions (Table 1, entry 3). This was also confirmed with *N*-Boc protected pyridone **1a** as starting material (Table 1, entry 4). Finally, attempt to decrease the nucleophile loading to 2 equivalents resulted in a significant loss of efficiency (Table 1, entry 5). With fewer equivalents of reagent, the reaction was slower and therefore required slightly longer reaction time to reach completion.

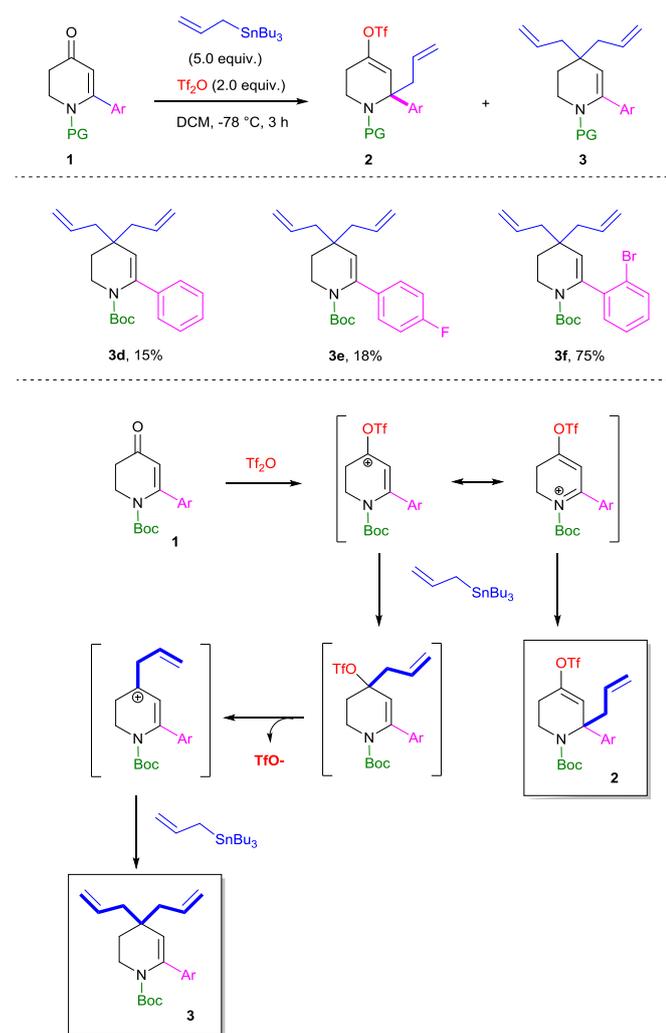
The substrate scope of the dihydropyridones **1** was next investigated with the optimized conditions (Table 1, entry 4) and the results are summarized in Table 2.

Table 2 Substrate scope for the triflic anhydride-promoted allylation reaction with different dihydropyridones.^a

^a Isolated yields are mentioned. The *dr* values were determined by ¹H NMR analysis of the crude material.

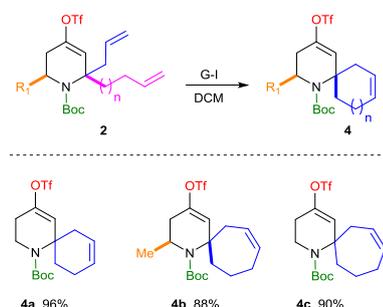
Several structural variations were tolerated, including alkyl and aryl substituents in position 6 (**1a-h**), methyl, phenyl and tert-butyl carboxylate in position 2 (**1i-l**), Cbz protecting group (**1b**, **1m**) and a series of 4-triflate-6-allyl-dihydropyridine derivatives **2a-m** could be successfully obtained with, in most of cases, good to excellent yields. In the cases of 2-substituted substrates, the desired compounds (**2i-l**) were obtained as a mixture of diastereoisomers that we could not separate. The low diastereoselectivities were evaluated by proton NMR analysis of the ethylenic signal near 5.6 ppm or CH-2 signal near 5.0 ppm and was confirmed by carbon NMR with a duplication of some signals in the same proportions.

It should be noted in the case of 6-aryldihydropyridones (**1d-f**) that, in addition to the expected 1,4-addition products (**2d-f**), compounds **3d-f** resulting from the 1,2-addition were also observed (Scheme 2). Such compounds **3** were not observed in the case of dihydropyridones substituted in position 6 with an alkyl side-chain, suggesting that steric hindrance brought about aryl substituent residing out of plane favored the observed competition. Moreover, this observation is reinforced when a bulky bromo-substituent is present in ortho-position on the aromatic ring (**3f**), as the 1,2-addition is strongly favored in this case. A plausible mechanism for the formation of **3** is proposed in scheme 2.



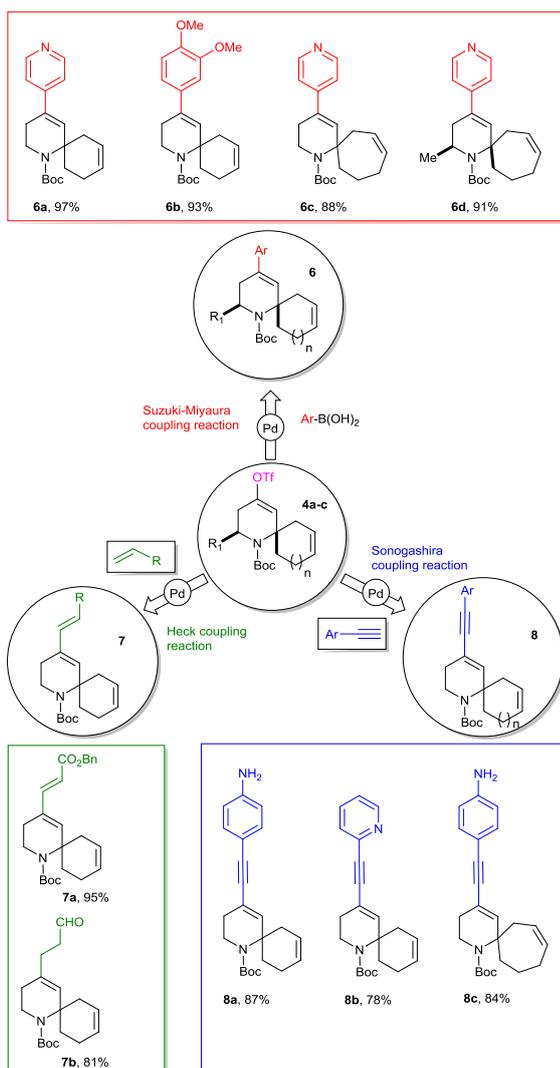
Scheme 2 Competition between the 1,2- and 1,4-addition for the triflic anhydride-promoted allylation reaction with 6-aryl-dihydropyridones and proposed mechanism explaining this competition.

Next, we turned our attention towards the synthesis of the targeted 2-spiropiperidines. To this end, ring-closing metathesis of these intermediates **2g-i** with Grubbs' first-generation catalyst furnished the desired spiro-compounds **4** in excellent yields (Scheme 3).³⁸



Scheme 3 Access to spiro-tetrahydropyridines via ring-closing metathesis.

The 2-spiranic 4-triflate-tetrahydropyridines **4a-c** were further functionalized by applying palladium-catalyzed processes such as Suzuki-Miyaura, Heck or Sonogashira cross-coupling reactions (Scheme 4).³⁹⁻⁴¹



Scheme 4 Pd-Catalyzed modifications of spiro-piperidines **4**.

For instance, compounds **6a-d** have been successfully obtained in 97%, 93%, 88% and 91% isolated yield respectively by the Suzuki cross-coupling reaction of **4a-c** with 4-pyridinylboronic acid or 3,4-dimethoxyphenylboronic acid. Concerning the Heck coupling reaction, two alkenes were chosen, benzyl acrylate and allyl alcohol respectively, and reactions were performed starting from vinyl triflate **4a**. Products **7a,b** were obtained in good to excellent yields, respectively 95% and 81%. Finally, compounds **8a-c** have been successfully obtained in 87%, 78% and 84% isolated yield respectively by the Sonogashira cross-coupling reaction of **4a,b** with 4-aminophenylacetylene or 2-pyridinylacetylene.

Conclusions

In conclusion, we described a novel approach for the construction of 2-spiropiperidine moieties from dihydropyridones. The gem bis-alkenyl intermediates generated from the triflic anhydride-promoted conjugate addition of allyltributylstannane onto these dihydropyridones were

successfully transformed to the corresponding spirocycles via ring-closing metathesis. The vinyl triflate group generated onto these 2-spiro-dihydropyridine intermediates could be successfully used as a chemical expansion vector for further transformations namely Pd-catalyzed cross-coupling reactions.

Experimental section

General information

Unless otherwise specified, all commercially available reagents were used as received. Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates with visualization by ultraviolet light or potassium permanganate dip. Column chromatography was carried out using silica gel 60 (70–200 μm). ^1H and ^{13}C NMR spectra were recorded on 300 or 500 MHz instruments. The chemical shifts are given in part per million (ppm) on the delta scale. The solvent peak was used as reference value: for ^1H NMR, $\text{CHCl}_3 = 7.26$ ppm; for ^{13}C NMR, $\text{CHCl}_3 = 77.16$ ppm. Infrared spectra were recorded neat. ESI-HRMS were carried out on an Agilent 6510 Q-TOF spectrometer at the CRMPO (Centre Regional de Mesures Physiques de l'Ouest), University of Rennes.

General procedure for synthesis of compounds **2** and **3**

To the dihydropyridone **1** (1.0 mmol) in dichloromethane (8.0 mL) cooled to -78°C was added under an argon atmosphere allyltributylstannane (5.0 mmol) followed by triflic anhydride (2.0 mmol) dropwise. The reaction mixture was stirred at -78°C for 3 h. Upon completion, the reaction was quenched by the addition of 1M NaOH. After stirring for 30 minutes, the layers were separated and the organic phase was washed successively with 1M NaOH, brine and then dried over sodium sulfate. Removal of the solvents gave a crude residue that was purified by column chromatography (silica gel, cyclohexane/DCM = 70/30 as eluent) to give the desired compounds **2a-2m** and **3d-f**.

tert-Butyl 6-allyl-6-propyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2a). Yield: 92%. Clear oil. ^1H NMR (300 MHz, CDCl_3) δ 5.77 – 5.59 (m, 1H), 5.42 (s, 1H), 5.07 (s, 1H), 5.03 (d, $J = 2.1$ Hz, 1H), 3.80 (d, $J = 12.6$ Hz, 1H), 3.60 – 3.47 (m, 1H), 3.03 (s, 1H), 2.57 – 2.39 (m, 1H), 2.40 – 2.25 (m, 2H), 2.20 (dd, $J = 13.7$, 6.5 Hz, 1H), 1.47 (s, 9H), 1.34 – 1.11 (m, 3H), 0.88 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.7, 147.5, 133.1, 124.8, 118.9, 118.6 (q, $J = 318.7$ Hz), 80.5, 61.9, 43.3, 42.6, 41.5, 28.5, 28.0, 17.2, 14.2. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{F}_3\text{NO}_5\text{SNa}$ 436.1376, found 436.1377.

Benzyl 6-allyl-6-propyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2b). Yield: 92%. Clear oil. ^1H NMR (300 MHz, CDCl_3) δ 7.45 – 7.28 (m, 5H), 5.66 (dddd, $J = 16.8$, 10.1, 8.5, 6.5 Hz, 1H), 5.45 (s, 1H), 5.14 (q, $J = 12.3$ Hz, 2H), 5.02 (dt, $J = 18.6$, 9.4 Hz, 2H), 3.93 – 3.80 (m, 1H), 3.71 – 3.60 (m, 1H), 3.09 (s, 1H), 2.64 – 2.43 (m, 1H), 2.43 – 2.28 (m, 2H), 2.22 (dd, $J = 13.7$, 6.4 Hz, 1H), 1.40 – 1.26 (m, 1H), 1.26 – 1.08 (m, 2H), 0.85 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.7, 147.3, 136.5, 132.8, 128.6, 128.2, 128.2, 124.5, 119.1,

118.6 (q, $J = 318.7$ Hz), 67.3, 62.4, 42.7, 40.9, 27.9, 17.2, 14.1. ; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{20}H_{24}NO_5F_3NaS$ 470.1220, found 470.1220.

tert-Butyl 6-allyl-6-(2-(benzyloxy)ethyl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2c). Yield: 80%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 5H), 5.75 – 5.59 (m, 1H), 5.53 (s, 1H), 5.10 (s, 1H), 5.06 (d, $J = 2.4$ Hz, 1H), 4.51 – 4.38 (m, 2H), 3.72 – 3.55 (m, 2H), 3.52 – 3.39 (m, 2H), 3.23 – 3.01 (m, 1H), 2.92 – 2.76 (m, 1H), 2.42 – 2.19 (m, 3H), 1.77 (dt, $J = 13.5, 6.6$ Hz, 1H), 1.46 (s, 9H). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 147.2, 138.3, 132.6, 128.4, 127.7, 127.7, 124.7, 119.2, 118.6 (q, $J = 318.75$ Hz), 80.8, 73.2, 66.4, 60.6, 43.3, 42.4, 38.3, 28.5, 28.0. ; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{23}H_{30}NO_6F_3NaS$ 528.1638, found 528.1637.

tert-Butyl 6-allyl-6-phenyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2d). Yield: 80%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.25 – 7.19 (m, 1H), 5.92 – 5.78 (m, 1H), 5.54 (s, 1H), 5.21 (d, $J = 4.0$ Hz, 1H), 5.16 (s, 1H), 4.10 (s, 1H), 3.70 (ddd, $J = 12.9, 8.0, 4.5$ Hz, 1H), 3.52 (dd, $J = 13.2, 8.0$ Hz, 1H), 2.82 (dd, $J = 13.5, 6.4$ Hz, 1H), 2.73 – 2.61 (m, 1H), 2.49 (dt, $J = 16.5, 4.7$ Hz, 1H), 1.17 (s, 9H). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 145.8, 145.3, 132.9, 128.6, 127.2, 125.5, 125.1, 119.7, 118.5 (q, $J = 318.75$ Hz), 80.8, 63.0, 42.2, 42.0, 28.2, 28.0. ; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{20}H_{24}NO_5F_3NaS$ 470.1219, found 470.1219.

tert-Butyl 6-allyl-6-(4-fluorophenyl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2e). Yield: 80%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 2H), 7.08 – 6.93 (m, 2H), 5.91 – 5.75 (m, 1H), 5.51 (s, 1H), 5.19 (dd, $J = 13.4, 1.8$ Hz, 1H), 4.12 (d, $J = 11.5$ Hz, 1H), 3.67 (ddd, $J = 13.0, 8.3, 4.4$ Hz, 1H), 3.58 – 3.45 (m, 1H), 2.79 (dd, $J = 13.5, 6.3$ Hz, 1H), 2.73 – 2.61 (m, 1H), 2.48 (dt, $J = 16.8, 4.7$ Hz, 1H), 1.21 (s, 9H). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 160.1, 154.4, 145.9, 141.1, 132.6, 126.9, 126.8, 125.3, 119.8, 118.4 (q, $J = 318.75$ Hz), 115.3, 115.0, 80.8, 62.4, 42.1, 41.9, 28.0, 27.8. ; HRMS (ESI) m/z $[M+K]^+$ calcd for $C_{20}H_{23}NO_5F_4KS$ 504.0865, found 504.0865.

tert-Butyl 6-allyl-6-(2-bromophenyl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2f). Yield: 75%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.47 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.34 – 7.27 (m, 1H), 7.09 (td, $J = 7.8, 1.6$ Hz, 1H), 5.99 – 5.83 (m, 1H), 5.45 (d, $J = 1.3$ Hz, 1H), 5.22 (d, $J = 5.2$ Hz, 1H), 5.18 (s, 1H), 4.45 (s, 1H), 3.59 – 3.44 (m, 1H), 3.33 (dd, $J = 13.0, 8.5$ Hz, 1H), 3.16 – 3.00 (m, 2H), 2.40 (ddd, $J = 16.9, 5.0, 2.6$ Hz, 1H), 1.12 (s, 9H). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 146.8, 141.7, 135.7, 132.8, 128.3, 127.8, 127.6, 121.6, 121.3, 120.3, 118.4 (q, $J = 318.75$ Hz), 80.6, 62.5, 43.0, 41.4, 28.0, 26.7. ; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{20}H_{23}NO_5F_3BrNaS$ 548.0325, found 548.0327.

tert-Butyl 6-allyl-6-(but-3-en-1-yl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2g). Yield: 92%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 5.85 – 5.63 (m, 2H), 5.44 (s, 1H), 5.11 (s, 1H), 5.09 – 5.04 (m, 1H), 5.04 – 4.90 (m, 2H), 3.99 – 3.81 (m, 1H), 3.54 – 3.43 (m, 1H), 3.15 – 2.93 (m, 1H), 2.75 – 2.54 (m, 1H), 2.51 – 2.16 (m, 4H), 2.01 – 1.87 (m, 2H), 1.49 (s, 9H). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 138.0, 133.0, 125.7, 122.3, 119.3, 118.6 (q, $J = 318$ Hz), 114.9, 80.8, 61.7, 42.6, 28.6, 28.4, 28.1, 27.0. ; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{18}H_{26}NO_5F_3NaS$ 448.1376, found 448.1382.

tert-Butyl 6-allyl-6-(pent-4-en-1-yl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2h). Yield: 80%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 5.83 – 5.62 (m, 2H), 5.42 (s, 1H), 5.10 (s, 1H), 5.07 – 5.03 (m, 1H), 5.03 – 4.92 (m, 2H), 3.92 – 3.75 (m, 1H), 3.60 – 3.47 (m, 1H), 3.06 (s, 1H), 2.51 (s, 1H), 2.47 – 2.36 (m, 1H), 2.31 (dt, $J = 16.4, 4.9$ Hz, 1H), 2.21 (dd, $J = 13.7, 6.5$ Hz, 1H), 2.03 (q, $J = 6.9$ Hz, 2H), 1.48 (s, 9H), 1.39 – 1.21 (m, 3H). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 138.5, 133.1, 124.7, 119.1, 118.6 (q, $J = 318$ Hz), 115.0, 80.7, 61.9, 42.7, 33.8, 28.6, 28.1, 23.3. ; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{19}H_{28}NO_5F_3NaS$ 462.1533, found 462.1534.

tert-Butyl 6-allyl-2-methyl-6-(pent-4-en-1-yl)-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2i). obtained as a complex mixture of diastereomers, Yield: 90%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 5.85 – 5.60 (m, 2H), 5.58 and 5.56 (2 x d, $J = 3.1$ Hz, peak height ratio: 0.38/0.62, total 1H), 5.14 – 4.91 (m, 4H), 4.76 – 4.58 (m, 1H), 3.23 and 2.16 (dd, $J = 13.8, 7.5$ Hz, peak height ratio: 0.6/0.4, total 1H), 2.80-2.49 (m, 2H), 2.29-1.93 (m, 4H), 1.65 – 1.31 (m, 3H), 1.48 (s, 9H), 1.20 (d, $J = 6.7$ Hz, 3H). ; ^{13}C NMR (75 MHz, $CDCl_3$) Dia 1 δ 154.0, 146.0, 138.4, 133.0, 123.1, 119.1, 118.6 (q, $J = 318$ Hz), 115.1, 80.4, 62.2, 48.3, 43.5, 38.7, 33.9, 33.6, 28.6, 24.4, 21.7; Dia 2 δ 154.0, 145.3, 138.7, 133.6, 122.7, 119.3, 118.6 (q, $J = 318$ Hz), 114.9, 80.6, 61.7, 48.1, 43.8, 38.5, 33.7, 33.5, 28.6, 23.0, 21.5 ; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{20}H_{30}NO_5F_3NaS$ 476.1689, found 476.1690.

tert-Butyl 6-allyl-2,6-diphenyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2j). obtained as a complex mixture of diastereomers and rotamers: Yield: 77%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 3H), 7.34 – 7.24 (m, 4H), 7.13 – 7.01 (m, 2H), 6.91 – 6.80 (m, 1H), 5.91 – 5.78 (m, 1H), 5.83 and 5.81 (2 x s, peak height ratio: 0.55/0.45, total 1H), 5.36 – 4.95 (m, 3H), 3.74 (dd, $J = 13.6, 8.0$ Hz, 1H), 3.21 (ddd, $J = 16.9, 6.9, 2.9$ Hz, 1H), 2.81 (dd, $J = 13.6, 6.7$ Hz, 1H), 2.66 (dd, $J = 16.9, 1.3$ Hz, 1H), 1.30 (s, 9H). ; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{26}H_{28}NO_5F_3NaS$ 546.1533, found 546.1536.

Di-tert-butyl 6-allyl-6-phenyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,2(2H)-dicarboxylate (2k). obtained as a complex mixture of diastereomers and rotamers: Yield: 74%. Clear oil. 1H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 1H),

7.39 – 7.27 (m, 3H), 7.26–7.18 (m, 1H), 6.10–5.95 (m, 1H), 5.66 and 5.63 (2 x d, $J = 1.5$ Hz, peak height ratio: 0.3/0.7, total 1H), 5.22–5.17 (m, 2.6H), 4.98 (dd, $J = 7.1, 3.1$ Hz, 0.4H), 3.36–3.31 (m, 1H), 3.02–2.80 (m, 3H), 1.48 and 1.42 (2 x s, peak height ratio: 6.0/3.0, total 9H), 1.27 and 1.15 (2 x s, peak height ratio: 3.2/5.8, total 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.3, 154.9, 145.7, 143.8, 132.5, 128.1, 127.2, 125.9, 124.8, 119.3, 118.6 (q, $J = 318$ Hz), 82.4, 81.7, 64.2, 56.1, 52.8, 42.9, 41.7, 28.2, 28.0. Dia 2 δ 169.7, 154.9, 145.7, 142.5, 134.0, 128.4, 127.3, 125.9, 124.4, 119.9, 118.6 (q, $J = 318$ Hz), 82.6, 81.4, 63.6, 56.0, 52.8, 43.8, 42.9, 28.8, 28.0; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{32}\text{NO}_7\text{F}_3\text{NaS}$ 570.1744, found 570.1749.

Di-tert-butyl 6-allyl-6-propyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,2(2H)-dicarboxylate (2l). Yield: 85%. Clear oil. obtained as a complex mixture of diastereomers and rotamers: ^1H NMR (300 MHz, CDCl_3) δ 5.85–5.52 (m, 1H), 5.66 and 5.61 (2 x bs, peak height ratio: 0.35/0.65, total 1H), 5.38–4.95 (m, 3H), 3.50–3.00 (m, 1H), 2.97–2.55 (m, 3H), 2.17–1.95 (m, 1H), 1.45 (bs, 18H), 1.35–1.25 (m, 2H), 1.12–1.00 (m, 1H), 0.92 and 0.88 (2 x t, $J = 7.1$ Hz, peak height ratio: 1.05/1.95, total 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.1, 155.5, 153.5, 144.9, 143.8, 133.4, 132.8, 122.8, 122.6, 119.6, 118.6 (q, $J = 318$ Hz), 119.0, 82.5, 82.4, 81.6, 80.7, 62.4, 61.8, 55.7, 43.5, 42.0, 40.8, 39.0, 28.9, 28.5, 28.0, 17.8, 16.7, 14.6, 14.1.; HRMS (ESI) m/z $[\text{M}+\text{K}]^+$ calcd for $\text{C}_{22}\text{H}_{34}\text{NO}_7\text{F}_3\text{KS}$ 552.1640, found 552.1638.

Benzyl 6-allyl-6-phenyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (2m). Yield: 80%. Clear oil. ^1H NMR (300 MHz, CDCl_3) δ 7.37 – 7.21 (m, 8H), 7.05 (s, 2H), 5.79 (dddd, $J = 16.6, 10.1, 8.5, 6.2$ Hz, 1H), 5.59 (s, 1H), 5.10 (dd, $J = 17.3, 9.7$ Hz, 2H), 5.01 – 4.90 (m, 2H), 4.02 (s, 1H), 3.92 – 3.79 (m, 1H), 3.59 (s, 1H), 2.79 (dd, $J = 13.7, 6.2$ Hz, 1H), 2.71 – 2.59 (m, 1H), 2.53 (dt, $J = 16.8, 5.2$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.1, 145.8, 143.9, 136.1, 132.5, 128.7, 128.4, 128.2, 128.1, 127.4, 125.4, 125.3, 119.9, 118.5 (q, $J = 318$ Hz), 67.4, 63.3, 42.5, 41.6, 27.9.; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{22}\text{NO}_5\text{F}_3\text{NaS}$ 504.1063, found 504.1064.

tert-Butyl 4,4-diallyl-6-phenyl-3,4-dihydropyridine-1(2H)-carboxylate (3d). Yield: 15%. ^1H NMR (300 MHz, CDCl_3) δ 7.33 – 7.20 (m, 5H), 5.81 (ddt, $J = 16.3, 10.8, 7.4$ Hz, 2H), 5.12 (s, 1H), 5.09 (d, $J = 0.7$ Hz, 2H), 5.05 (dd, $J = 8.7, 2.1$ Hz, 2H), 3.70 – 3.63 (m, 2H), 2.24 – 2.09 (m, 4H), 1.74 – 1.68 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.1, 140.7, 140.2, 134.5, 127.9, 127.1, 125.7, 122.1, 118.1, 80.3, 45.0, 42.7, 38.0, 33.6, 27.8.; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_2\text{Na}$ 362.2090, found 362.2095.

tert-Butyl 4,4-diallyl-6-(4-fluorophenyl)-3,4-dihydropyridine-1(2H)-carboxylate (3e). Yield: 18%. ^1H NMR (300 MHz, CDCl_3) δ 7.31 – 7.20 (m, 2H), 7.04 – 6.93 (m, 2H), 5.79 (ddt, $J = 16.6, 10.6, 7.4$ Hz, 2H), 5.11 – 5.06 (m, 4H), 5.03 (dt, $J = 2.4, 1.3$ Hz, 1H), 3.67 – 3.62 (m, 2H), 2.22 – 2.09 (m, 4H), 1.73 – 1.67 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 163.8, 160.6, 154.0, 139.3, 136.8, 134.4, 127.3, 127.2, 122.2, 118.2, 114.9,

114.6, 80.5, 45.0, 42.8, 38.0, 33.6, 27.9.; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_2\text{FNa}$ 380.1996, found 380.1998.

tert-Butyl 4,4-diallyl-6-(2-bromophenyl)-3,4-dihydropyridine-1(2H)-carboxylate (3f). Yield: 75%. ^1H NMR (300 MHz, CDCl_3) δ 7.49 (d, $J = 7.7$ Hz, 1H), 7.25 – 7.23 (m, 1H), 7.10 (ddd, $J = 7.9, 5.6, 3.6$ Hz, 1H), 5.84 (ddt, $J = 17.8, 10.6, 7.4$ Hz, 2H), 5.11 (d, $J = 1.4$ Hz, 2H), 5.09 – 5.02 (m, 2H), 4.87 (s, 1H), 3.77 – 3.66 (m, 2H), 2.20 (dd, $J = 6.7, 1.2$ Hz, 2H), 2.15 (dd, $J = 5.0, 3.8$ Hz, 2H), 1.77 – 1.72 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.0, 141.6, 138.1, 134.5, 132.4, 130.3, 128.4, 127.1, 123.5, 121.9, 118.2, 80.4, 44.7, 41.2, 37.6, 33.1, 27.9.; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_2\text{BrNa}$ 440.1196, found 440.1196.

General procedure for synthesis of compounds 4 and 5

Diene precursor **2** or **3** (0.25 mmol) was dissolved in freshly distilled and degassed dichloromethane (3 mL) under argon atmosphere. This solution was degassed again using argon gas for 10 minutes at room temperature, to the solution was added 1st Grubbs catalyst (3 mol%). After 10–14 hours at room temperature, the reaction was complete as indicated by TLC. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, cyclohexane/EtOAc = 70/30 as eluent) to give the desired compounds **4a–c** and **5d–f**.

tert-Butyl 4-(((trifluoromethyl)sulfonyl)oxy)-1-azaspiro[5.5]undeca-4,8-diene-1-carboxylate (4a). Yield: 96%. Clear oil. ^1H NMR (300 MHz, CDCl_3) δ 5.99 (s, 1H), 5.72 – 5.58 (m, 2H), 3.78 (ddd, $J = 13.1, 5.9, 4.8$ Hz, 1H), 3.64 (ddd, $J = 13.1, 6.7, 4.7$ Hz, 1H), 3.52 – 3.40 (m, 1H), 2.80 (td, $J = 12.2, 6.6$ Hz, 1H), 2.55 – 2.36 (m, 2H), 2.28 – 2.00 (m, 2H), 2.00 – 1.89 (m, 1H), 1.63 – 1.53 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.9, 146.8, 125.4, 124.8, 122.8, 118.6 (q, $J = 318.75$ Hz) 80.7, 57.6, 41.5, 33.6, 29.2, 28.7, 28.5, 24.0.; HRMS (ASAP) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_5\text{F}_3\text{S}$ 398.1243, found 398.1241.

tert-Butyl 2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)-1-azaspiro[5.6]dodeca-4,8-diene-1-carboxylate (4b). Yield: 88%. Clear oil. Mixture of diastereomers. ^1H NMR (300 MHz, CDCl_3) δ 6.34 and 6.24 (2 x d, $J = 2.9$ Hz, peak height ratio: 0.35/0.65, total 1H), 5.96 – 5.79 (m, 1H), 5.62 – 5.51 (m, 1H), 4.81 – 4.68 (m, 1H), 4.14 – 4.04 and 3.84 – 3.74 (m, peak height ratio: 0.7/0.3, total 1H), 3.26 – 3.14 (m, 0.3H), 2.90 – 2.73 (m, 1.7H), 2.33 – 1.40 (m, 7H), 1.50 (s, 9H), 1.21 and 1.19 (2 x d, $J = 6.9$ Hz, peak height ratio: 0.9/2.1, total 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.5, 154.4, 143.3, 143.0, 134.0, 133.0, 127.5, 126.4, 122.5, 118.7 (q, $J = 318.7$ Hz), 80.6, 59.9, 59.5, 48.7, 48.3, 43.0, 39.8, 39.4, 36.0, 33.4, 33.2, 28.7, 28.4, 23.3, 23.2, 20.4, 20.0.; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_5\text{F}_3\text{NaS}$ 448.1376, found 448.1373.

tert-Butyl 4-(((trifluoromethyl)sulfonyl)oxy)-1-azaspiro[5.6]dodeca-4,8-diene-1-carboxylate (4c). Yield: 90%. Clear oil. ^1H NMR (300 MHz, CDCl_3) δ 6.27 (s, 1H), 5.99 – 5.87

(m, 1H), 5.67 – 5.56 (m, 1H), 3.82 (ddd, $J = 10.3, 8.4, 5.0$ Hz, 2H), 3.54 (ddd, $J = 13.2, 7.4, 4.4$ Hz, 1H), 2.81 (td, $J = 13.1, 3.1$ Hz, 1H), 2.56 – 2.45 (m, 1H), 2.39 (dt, $J = 9.8, 4.7$ Hz, 1H), 2.27 – 2.13 (m, 2H), 2.04 (ddd, $J = 14.5, 8.8, 1.8$ Hz, 1H), 1.93 – 1.70 (m, 2H), 1.51 (s, 9H), 1.50 – 1.41 (m, 1H). ; ^{13}C NMR (75 MHz, CDCl_3) δ 155.0, 145.6, 133.5, 127.1, 123.7, 118.7 (q, $J = 318$ Hz), 80.7, 59.8, 41.4, 39.7, 37.0, 28.7, 28.6, 28.5, 22.9. ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_5\text{F}_3\text{NaS}$ 434.1220, found 434.1225.

tert-Butyl 7-phenyl-8-azaspiro[4.5]deca-2,6-diene-8-carboxylate (5d). Yield: 78%. Clear oil. ^1H NMR (300 MHz, CDCl_3) δ 7.33 – 7.18 (m, 5H), 5.76 – 5.58 (m, 2H), 5.25 (s, 1H), 3.78 – 3.72 (m, 2H), 2.55 – 2.45 (m, 2H), 2.30 – 2.19 (m, 2H), 1.85 – 1.79 (m, 2H), 1.08 (s, 9H). ; ^{13}C NMR (75 MHz, CDCl_3) δ 154.1, 141.0, 138.0, 129.1, 128.0, 126.9, 125.7, 124.1, 80.5, 47.3, 43.8, 43.0, 37.7, 27.8. ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_2\text{Na}$ 334.1777, found 334.1778.

tert-Butyl 7-(4-fluorophenyl)-8-azaspiro[4.5]deca-2,6-diene-8-carboxylate (5e). Yield: 83%. Clear oil. ^1H NMR (300 MHz, CDCl_3) δ 7.31 – 7.23 (m, 2H), 7.04 – 6.95 (m, 2H), 5.71 – 5.65 (m, 2H), 5.22 (s, 1H), 3.78 – 3.70 (m, 2H), 2.55 – 2.45 (m, 2H), 2.31 – 2.20 (m, 2H), 1.87 – 1.79 (m, 2H), 1.14 (s, 9H). ; ^{13}C NMR (75 MHz, CDCl_3) δ 163.7, 160.4, 154.0, 137.1, 137.1, 137.0, 129.1, 127.2, 127.1, 124.0, 114.9, 114.6, 80.7, 47.3, 43.9, 42.9, 37.6, 27.9. ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_2\text{FNa}$ 352.1683, found 352.1686.

tert-Butyl 7-(2-bromophenyl)-8-azaspiro[4.5]deca-2,6-diene-8-carboxylate (5f). Yield: 80%. Yellow oil. ^1H NMR (CDCl_3 , 300 MHz) : $\delta = 7.49$ (d, $J = 6.0$ Hz, 1H), 7.31-7.21 (m, 2H), 7.13-7.05 (m, 1H), 5.65 (s, 2H), 5.04 (s, 1H), 3.75 (s, 2H), 2.51 (AB syst., $J = 14.6$ Hz, 2H), 2.25 (AB syst., $J = 14.6$ Hz, 2H), 1.87 (t, $J = 6.0$ Hz, 2H), 1.06 (s, 9H Boc). ^{13}C NMR (CDCl_3 , 300 MHz) $\delta = 153.0$, 141.7, 136.4, 132.4, 130.3, 129.1, 128.3, 127.3, 125.3, 121.9, 80.4, 47.3, 42.5, 37.0, 27.9; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_2\text{BrNa}$ 412.0883, found 412.0884.

General Procedure for Suzuki-Miyaura coupling reaction. A 20 mL of dry Schlenk tube was charged with **4** (0.1 mmol) and 1,4-Dioxane/ H_2O (5/1, 2 mL) under an argon atmosphere. Argon was bubbled through the solution for 10 min. To the solution were added corresponding boronic acid (0.12 mmol), catalyst ($\text{Pd}(\text{PPh}_3)_4$ - 5 mol%), K_2CO_3 (0.25 mmol) and LiCl (0.25 mmol) with a gentle flow of argon. The reaction mixture was stirred at 90 °C for 4 h. The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with EtOAc (three times). The reaction mixture was diluted with brine then dried over sodium sulfate. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, cyclohexane/EtOAc = 70/30 as eluent) to give the desired compounds **6a-d**.

tert-Butyl 4-(pyridin-4-yl)-1-azaspiro[5.5]undeca-4,8-diene-1-carboxylate (6a). Yield: 97%. Pale yellow solid, m.p. = 124 °C. ^1H NMR (300 MHz, CDCl_3) δ 8.55 (s, 2H), 7.31 – 7.20 (m, 2H),

6.51 (s, 2H), 5.77 – 5.63 (m, 1H), 4.37 – 4.33 (m, 2H), 3.76 (ddd, $J = 13.0, 6.1, 4.6$ Hz, 1H), 3.64 (ddd, $J = 13.0, 6.8, 4.5$ Hz, 1H), 3.49 (d, $J = 17.1$ Hz, 1H), 2.91 – 2.79 (m, 1H), 2.59 – 2.40 (m, 2H), 2.27 – 2.14 (m, 2H), 1.95 (dd, $J = 17.9, 2.3$ Hz, 2H), 1.49 (s, 9H). ; ^{13}C NMR (75 MHz, CDCl_3) δ 155.3, 150.0, 147.9, 132.1, 132.1, 129.2, 127.1, 125.5, 125.4, 119.7, 80.2, 57.1, 41.1, 33.8, 29.4, 28.7, 26.9, 24.3. ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2\text{Na}$ 349.1887, found 349.1889.

tert-butyl 4-(3,4-dimethoxyphenyl)-1-azaspiro[5.5]undeca-4,8-diene-1-carboxylate (6b). Yield: 93%. Clear oil. ^1H NMR (300 MHz, CDCl_3) δ 6.96 – 6.87 (m, 2H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.18 (s, 1H), 5.75 – 5.61 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.78 – 3.60 (m, 2H), 3.45 (d, $J = 17.4$ Hz, 1H), 2.82 (dt, $J = 12.3, 9.4$ Hz, 1H), 2.58 – 2.40 (m, 2H), 2.26 – 2.15 (m, 2H), 2.04 – 1.91 (m, 1H), 1.63 – 1.58 (m, 1H), 1.49 (s, 9H). ; ^{13}C NMR (75 MHz, CDCl_3) δ 155.5, 148.9, 148.5, 134.0, 133.9, 127.1, 125.8, 125.3, 117.6, 111.1, 108.6, 79.9, 56.9, 56.1, 56.0, 41.5, 34.2, 29.7, 28.7, 27.9, 24.4. ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{31}\text{NO}_4\text{Na}$ 408.2145, found 408.2150.

tert-Butyl 4-(pyridin-4-yl)-1-azaspiro[5.6]dodeca-4,8-diene-1-carboxylate (6c). Yield: 88%. Pale yellow solid, m.p. = 120 °C. ^1H NMR (300 MHz, CDCl_3) δ 8.92-8.24 (m, 2H), 7.26 (s, 2H), 6.77 (s, 1H), 5.98 – 5.85 (m, 1H), 5.63 (dddd, $J = 11.0, 8.9, 4.5, 2.3$ Hz, 1H), 3.87 (d, $J = 14.6$ Hz, 1H), 3.78 – 3.67 (m, 1H), 3.56 (ddd, $J = 13.0, 6.4, 5.0$ Hz, 1H), 2.86 (dd, $J = 17.8, 7.6$ Hz, 1H), 2.46 (t, $J = 5.5$ Hz, 2H), 2.37 – 2.13 (m, 2H), 2.10 – 1.99 (m, 1H), 1.92 – 1.72 (m, 2H), 1.68 – 1.56 (m, 1H), 1.51 (s, 9H). ; ^{13}C NMR (75 MHz, CDCl_3) δ 155.5, 149.9, 148.0, 133.3, 133.1, 131.6, 127.5, 80.3, 59.6, 41.0, 40.1, 37.0, 28.9, 28.75, 26.8, 23.2. ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2\text{Na}$ 363.2043, found 363.2045.

tert-Butyl 2-methyl-4-(pyridin-4-yl)-1-azaspiro[5.6]dodeca-4,8-diene-1-carboxylate (6d). Yield: 91%. Mixture of diastereomers. ^1H NMR (300 MHz, CDCl_3) δ 8.56 (d, $J = 6.1$ Hz, 2H), 7.26 (d, $J = 5.1$ Hz, 2H), 6.84 and 6.78 (d, $J = 2.8$ Hz, 1H), 6.00 – 5.78 (m, 1H), 5.70-5.48 (m, 1H), 4.80 – 4.65 (m, 1H), 4.15 – 3.82 (m, 1H), 2.98 (tdd, $J = 16.3, 13.0, 6.4$ Hz, 1H), 2.73 (ddd, $J = 16.0, 5.5, 2.7$ Hz, 1H), 2.40 – 2.23 (m, 2H), 2.22 – 2.07 (m, 1H), 2.02 – 1.64 (m, 4H), 1.53 (d, $J = 0.9$ Hz, 9H), 1.13 (t, $J = 6.2$ Hz, 3H). ; ^{13}C NMR (75 MHz, CDCl_3) Dia 1 δ 154.9, 150.0, 148.6, 132.7, 132.5, 127.9, 127.6, 119.8, 80.0, 58.6, 46.9, 40.2, 38.7, 31.6, 28.8, 28.8, 23.4, 20.1; Dia 2 δ 154.8, 150.0, 148.6, 133.4, 132.4, 128.8, 127.2, 119.9, 80.0, 59.0, 47.5, 42.4, 36.7, 31.5, 28.9, 28.8, 23.7, 19.8 ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2\text{Na}$ 377.2199, found 377.2198.

General Procedure for Heck coupling reaction: A 20 mL of dry Sealed tube was charged with **4** (0.1 mmol) and DMF (1 mL) under an argon atmosphere. To the solution were added corresponding alkene (0.13 mmol), LiCl (0.15 mmol), triethylamine (0.2 mmol) with a gentle flow of argon. Then was added $\text{Pd}(\text{OAc})_2$ (5 mol%). The reaction mixture was stirred at 50 °C for 15 h. The resulting mixture was filtered through a pad of Celite. After addition of 5 mL satd aq NaHCO_3 and extraction

with EtOAc (three times), the combined organic phases were washed with brine then dried over sodium sulfate. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, cyclohexane/EtOAc = 70/30 as eluent) to give the desired compounds **7a-7b**.

tert-Butyl 4-(3-(benzyloxy)-3-oxoprop-1-en-1-yl)-1-azaspiro[5.5]undeca-4,8-diene-1-carboxylate (7a). Yield: 95%. White solid, m.p. = 74–76°C. ¹H NMR (300 MHz, CDCl₃) δ 7.41–7.29 (m, 6H), 6.27 (s, 1H), 5.88 (d, *J* = 15.5 Hz, 1H), 5.72–5.58 (m, 2H), 5.20 (s, 2H), 3.67 (dt, *J* = 13.0, 5.3 Hz, 1H), 3.57–3.38 (m, 2H), 2.80 (td, *J* = 11.9, 7.1 Hz, 1H), 2.23 (t, *J* = 6.0 Hz, 2H), 2.20–2.07 (m, 2H), 1.89 (dd, *J* = 18.3, 3.2 Hz, 1H), 1.56–1.48 (m, 1H), 1.47 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 167.1, 155.2, 146.7, 141.1, 136.2, 132.2, 128.7, 128.4, 128.3, 125.4, 125.2, 116.5, 80.2, 66.3, 57.3, 40.8, 33.6, 29.0, 28.6, 24.6, 24.2; HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₅H₃₁NO₄Na 432.2145, found 432.2147.

tert-Butyl 4-(3-oxopropyl)-1-azaspiro[5.5]undeca-4,8-diene-1-carboxylate (7b). Yield: 81%. Clear oil. ¹H NMR (300 MHz, CDCl₃) δ 9.76 (t, *J* = 1.7 Hz, 1H), 5.70–5.54 (m, 3H), 3.67–3.45 (m, 2H), 3.42–3.30 (m, 1H), 2.71 (td, *J* = 11.9, 7.1 Hz, 1H), 2.58–2.50 (m, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 2.15–2.06 (m, 2H), 2.02 (t, *J* = 5.6 Hz, 2H), 1.87–1.75 (m, 1H), 1.46 (s, 9H), 1.41–1.26 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 202.1, 155.5, 133.4, 126.7, 125.7, 125.3, 79.8, 56.6, 41.7, 41.2, 34.3, 29.6, 29.6, 28.8, 28.7, 24.3; HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₁₈H₂₇NO₃Na 328.1883, found 328.1885.

General Procedure for Sonogashira coupling reaction: A 20 mL of dry Schlenk tube was charged with **4** (0.1 mmol) and degassed anhydrous ACN (1.5 mL) under an argon atmosphere. To the solution were added corresponding alkyne (0.12 mmol), triethylamine (0.3 mL), TBAI (0.15 mmol), CuI (5 mol%) and Pd(PPh₃)₄ (2.5 mol%). The reaction mixture was stirred at room temperature for 10–14 h. The resulting mixture was filtered through a pad of Celite. The filtrate was extracted with EtOAc (three times). The reaction mixture was diluted with brine then dried over sodium sulfate. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, cyclohexane/EtOAc = 70/30 as eluent) to give the desired compounds **8a-8c**.

tert-Butyl 4-((4-aminophenyl)ethynyl)-1-azaspiro[5.5]undeca-4,8-diene-1-carboxylate (8a). Yield: 87%. Yellow solid, m.p. = 170°C. ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, *J* = 6.9 Hz, 2H), 6.64 (d, *J* = 6.7 Hz, 2H), 6.28 (s, 1H), 5.73–5.59 (m, 2H), 3.69–3.59 (m, 1H), 3.58–3.49 (m, 1H), 3.47–3.34 (m, 1H), 2.85–2.72 (m, 1H), 2.37–2.24 (m, 2H), 2.23–2.11 (m, 2H), 1.93 (dd, *J* = 17.2, 3.2 Hz, 1H), 1.59–1.51 (m, 1H), 1.47 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 146.6, 140.0, 132.9, 125.4, 125.3, 118.7, 114.8, 112.6, 89.5, 87.7, 80.0, 57.3, 41.2, 33.8, 30.0, 29.3, 28.7, 24.2; HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₃H₂₈N₂O₂Na 387.2043, found 387.2042.

tert-Butyl (S)-4-(pyridin-2-ylethynyl)-1-azaspiro[5.5]undeca-4,8-diene-1-carboxylate (8b). Yield: 78%. Clear oil. ¹H NMR (300 MHz, CDCl₃) δ 8.58 (s, 1H), 7.65 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.24–7.18 (m, 1H), 6.49 (s, 1H), 5.71–5.58 (m, 2H), 3.67 (dt, *J* = 13.0, 5.2 Hz, 1H), 3.58–3.48 (m, 1H), 3.43 (d, *J* = 17.0 Hz, 1H), 2.80 (dt, *J* = 12.6, 9.5 Hz, 1H), 2.44–2.29 (m, 2H), 2.18 (ddd, *J* = 6.0, 3.1, 1.4 Hz, 2H), 1.98–1.87 (m, 1H), 1.56–1.51 (m, 1H), 1.47 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 150.1, 143.5, 140.6, 136.3, 127.1, 125.4, 125.2, 122.8, 117.7, 89.9, 88.0, 80.2, 57.5, 41.1, 33.6, 29.5, 29.1, 28.7, 24.2; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₇N₂O₂ 351.2067, found 351.2061.

tert-Butyl 4-((4-aminophenyl)ethynyl)-1-azaspiro[5.6]dodeca-4,8-diene-1-carboxylate (8c). Yield: 84%. Clear oil. ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.61 (d, *J* = 8.3 Hz, 2H), 6.49 (s, 1H), 6.52–5.82 (m, 1H), 5.62 (dddd, *J* = 10.9, 8.9, 4.4, 2.2 Hz, 1H), 3.80 (d, *J* = 14.3 Hz, 1H), 3.67–3.54 (m, 1H), 3.47 (ddd, *J* = 13.0, 6.4, 4.8 Hz, 1H), 2.86–2.74 (m, 1H), 2.32–2.24 (m, 2H), 2.23–2.17 (m, 1H), 2.04–1.95 (m, 1H), 1.89–1.55 (m, 4H), 1.50 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.6, 146.6, 137.9, 132.9, 132.8, 127.6, 118.2, 114.8, 112.7, 89.4, 87.8, 80.1, 59.8, 41.1, 40.1, 36.8, 30.0, 28.8, 28.8, 23.1; HRMS (ESI) *m/z* [M+Na]⁺ calcd for C₂₄H₃₀N₂O₂Na 401.2200, found 401.2203.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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