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General Synthesis of Substituted 1,2-Dihydropyridines

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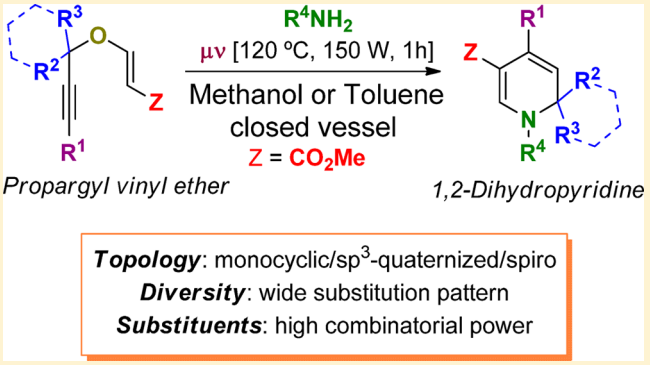
Supporting Information

ABSTRACT: A general and practical metal-free protocol for the synthesis of 1,2-dihydropyridines with wide structural/functional diversity at the ring and featuring mono, double, or spiro substitution at the sp^3 position is described. The protocol entails a microwave-assisted domino reaction of a propargyl vinyl ether (secondary or tertiary) and a primary amine (aliphatic or aromatic) in toluene or methanol.

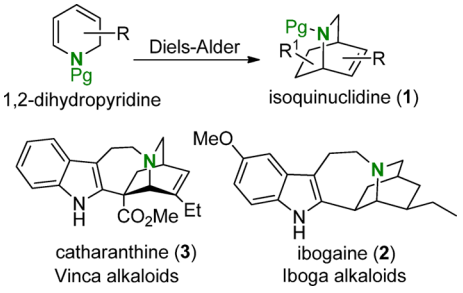


Dihydropyridines (DHPs) represent a group of organic scaffolds based on the pyridine ring.[1] Among the five possible isomeric structures containing this motif, 1,2- and 1,4-dihydro constitute the most populated group. Although 1,4-DHPs have received much attention due to their wide variety of biological and pharmacological actions,[2] the biological annotation of 1,2-DHPs remains relatively unexplored,[3] which makes them valuable as candidate structures for the design of heterocyclic-focused libraries. On the other hand, 1,2-DHPs have found important synthetic applications as cyclic aza-dienes in the Diels–Alder-mediated preparation of isoquinuclidines,[4] an important structural motif present in many pharmacologically relevant natural products,[5] such as the alkaloids ibogaine (**2**)[6] and catharanthine (**3**),[7] a chemical and biological precursor of the potent antitumor alkaloids vinblastine and vincrastin[8] (Scheme 1).

The synthesis of the 1,2-DHPs has been recently reviewed.[9] Currently, these heterocyclic scaffolds are synthesized from activated pyridines (reduction, condensation)[10] or from the corresponding 1-azatrienes by a 6π-aza-electrocyclization process.[11,12] Although less general, azadienes have also been used as convenient precursors.[13,14] Moreover, the first approach suffers from a reliance on the pyridine inputs, which translates into a limited degree of substitution at the DHP's ring. The second approach allows for wider degrees of substitution at the ring, and it is better suited for diversity-oriented library construction. However, the key to this approach resides on the efficient access to highly functionalized 1-azatriene platforms. Currently, these platforms are formed in situ by coupling of vinylogous amides and α,β-unsaturated iminium salts or by direct condensation of primary amines with 2,4-dienals.[12] We[12b] and others[12a,c] have developed a direct protocol toward 1,2-DHPs **8** from propargyl vinyl ethers (PVEs) **4** using the propargyl Claisen rearrangement[15] to directly deliver the 2,4-dienals **6**. In the presence of a primary amine, these units condense to generate the corresponding 1-azatrienes **7**, which, by a 6π-aza-electrocyclization process, construct the corresponding 1,2-DHPs **8**.

In spite of these advances, the domino synthesis of 1,2-DHPs from propargyl vinyl ethers still possesses a number of experimental limitations toward becoming a robust, general, and practical methodology with direct application in diversity-oriented synthetic programs. The main limitation is related to the grade of substitution at the sp^3 position (for clarity, we will refer to this position as the C-2 position regardless of the other substituents on the ring). The current methodology synthesizes 1,2-DHPs bearing only one substituent at this position. The introduction of a second substituent should allow access to quaternary or spiro motifs, which should not only increase the degree of structural diversity but also provide new chemotypes with unpredictable biological (pharmaceutical) properties. The establishment of a method for the simple and efficient access to

Scheme 1. Isoquinuclidinic Alkaloids



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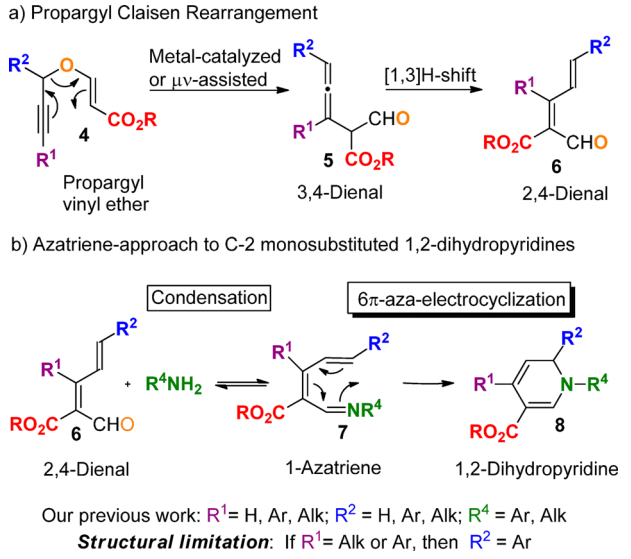
spiro 1,2-DHPs should pave the way for the construction of chemical libraries that will have high value in medicinal chemistry.[16] The number of reported methodologies to access quaternary/spiro 1,2-DHPs is quite scarce.[17] In addition to this general limitation, our own approach to these scaffolds[12b] showed a particular structural restraint regarding internal alkynes ($R^1 \neq H$, Scheme 2a). In these cases, the reaction

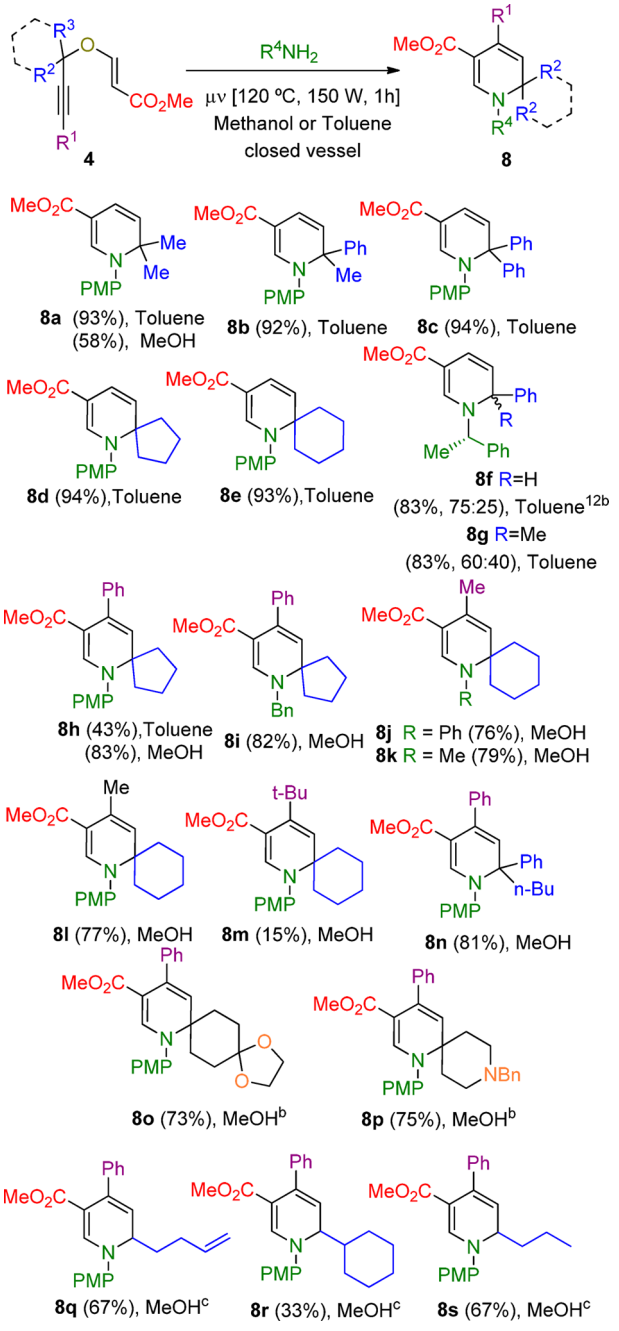
Scheme 2. 1-Azatriene Approach to 1,2-Dihydropyridines



did not tolerate an alkyl substituent at the propargylic position ($R^2 \neq$ Alk). This restriction has also been reported by Xu and colleagues[12c] in their Au/Ag-catalyzed domino protocol. Interestingly, Kirsch and colleagues[12a] have described an Au-catalyzed one-pot protocol that overrides this substituents restraint but poses a new structural limitation on the use of terminal alkynes. In this note, we describe our advances in the development of a metal-free protocol to deliver these important heterocyclic scaffolds with wide structural/functional diversity at the ring and featuring mono, double, or spiro substitution at the sp^3 position. The protocol entails a microwave-assisted domino reaction involving a propargyl vinyl ether (secondary or tertiary)[18] and a primary amine. The manifold constructs 1,2-DHPs featuring a wide array of topologies spanning simple monocyclic scaffolds to spiro derivatives. The protocol tolerates a topologically diverse substitution pattern at the triene terminus of the 1-azatriene intermediate **7**, which is directly delivered to the C-2 position of the final 1,2-DHP (Table 1).

We undertook this work studying the reaction of the tertiary PVE **4a**[19] (R^1 = H, R^2 = R^3 = Me; Table 1) and *p*-methoxyaniline (1.1 equiv) under the microwave conditions established in our previous protocol [toluene, *μν* (120 °C, 150 W, 1 h, closed vessel)].[12b] Under these conditions, the quaternary 1,2-DHP **8a** was cleanly obtained in an excellent 93% yield. Other tertiary PVEs also delivered the corresponding quaternary 1,2-DHPs in excellent yields. Thus, for example, PVEs **4b** and **4c** were cleanly transformed into the corresponding products **8b** and **8c** in 92 and 94% yields, respectively. The manifold was able to transform the monocyclic tertiary PVEs **4d** and **4e** into the spiro derivatives **8d** and **8e** with high efficiency (94 and 93%, respectively). In our previous work,[12b] we performed the reaction of secondary PVE **4f** with (*S*)-1-phenylethanamine, obtaining the chiral 1,2-

Table 1. Microwave-Assisted Domino Synthesis of 1,2-Dihydropyridines 8 from Propargyl Vinyl Ethers 4[a]



[a]PVE (1 equiv), amine (1.1 equiv), toluene (methanol) (5 mL). [b]3 h. [c]3 h, 150 °C. PMP = *p*-methoxyphenyl.

DHP **8f** in excellent yield (83%) but modest diastereoselectivity (75:25). However, when the tertiary PVE **4g** was submitted to the same set of reaction conditions, the chiral quaternary 1,2-DHP **8g** was obtained with the same high efficiency (83%) but with practically null diastereoselectivity (60:40). This decrease in diastereoselectivity was, in some sense, predictable due to the marked steric difference between a methyl group and hydrogen.[20] Nevertheless, the two isomers could be separated by simple flash chromatography. When we attempted to perform the reaction using tertiary PVEs armed with internal alkynes ($R^1 \neq$ H), the yields dropped considerably. This was the case for spiro 1,2-DHP **8h**, which was obtained with a

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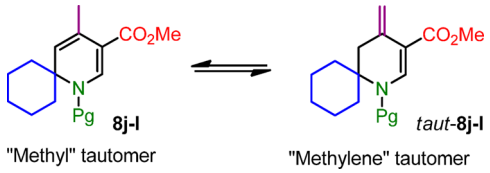
modest 43% yield. Fortunately, the use of methanol as the reaction solvent[21] reverted the reaction's efficiency back to its previous high levels, rendering the spiro derivative in 83% yield. Interestingly, the quaternary 1,2-DHP **8a** could be also obtained under these new conditions ($\mu\nu$, methanol) but with a significant reduction in the yield (58%). These new conditions proved to be highly tolerant of the structure of the PVE (secondary or tertiary, internal alkyne) and the electronic nature of the primary amine (aliphatic or aromatic). The power of this reaction to generate diversity on the nitrogen atom regardless of the structure of the PVE is remarkable: quite different primary amines (aliphatic, aromatic) are able to react with tertiary PVEs armed with electronically different alkyne moieties to afford the corresponding heterocyclic core with similar overall yields. This is the case of the spiro derivatives **8h** (*p*-anisidine, 83%) and **8i** (benzylamine, 82%) or **8j** (aniline, 76%), **8k** (methylamine, 79%), and **8l** (*p*-anisidine, 77%). The reaction showed high tolerance for the electronic nature of the internal alkyne moiety of the PVE. The generation of the spiro 1,2-DHP **8m** is remarkable. In spite of the steric congestion that a *tert*-butyl group should introduce into the 1-azatriene intermediate **7m** (Scheme 2b), this is formed and cyclized to generate **8m**, although in a 15% yield. The reduction of the steric demand from a *tert*-butyl to a methyl substituent was mirrored in a net increase of the reaction efficiency (compare **8m** with **8j–l**). The reaction manifold also accepted acyclic tertiary PVEs to generate the corresponding quaternary derivatives (e.g., **8n**, 81%). Cyclic tertiary PVEs **4o** and **4p** afforded the functionalized spiro 1,2-DHPs **8o** and **8p** in very good yields, although they need more time to be fully transformed into the final products. The extra functionalization incorporated at the spiro cycle (protected amine, masked ketone) constitutes a convenient chemical handle for further chemical access to this ring or for the generation of molecular complexity. Finally, the reaction was also able to override the structural limitation found in our previous model: the use of secondary PVEs armed with internal alkynes and alkyl substituents at the propargylic position. The 1,2-DHPs **8q–s** are nice examples of this structural breakthrough. In these cases, the reaction needs more energy and more time (3 h under 150 °C and irradiation) to be accomplished.

It is interesting to note that 1,2-DHPs **8j–l** exist in equilibrium as mixtures of the methyl and methylene tautomers (endocyclic or exocyclic double bond, respectively; Scheme 3) (see Supporting Information for details).

Scheme 3. Tautomeric Equilibrium in 1,2-Dihydropyridines



In summary, we have enhanced the practicality and generality of our previous metal-free synthetic protocol for access to 1,2-DHPs from propargyl vinyl ethers and primary amines. This improved version delivers these important heterocyclic scaffolds with a wider diversity at the ring and mono, double, or spiro substitution at the sp^3 position. The protocol accepts secondary and tertiary propargyl vinyl ethers bearing internal or terminal alkyne moieties and aromatic and aliphatic primary amines.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz, respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor equipped with a surface sensor to measure the temperature of the reaction mixture. FT-IR spectra were measured in chloroform solutions using a FT-IR spectrophotometer. Mass spectra (low resolution) (EI/CI) and HRMS (EI/TOF) were obtained with a gas chromatograph/mass spectrometer. Analytical thin-layer chromatography plates used UV-active silica on aluminum. Flash column chromatography was carried out with silica gel (particle size less than 0.020 mm), using appropriate mixtures of ethyl acetate and hexanes as eluents. All reactions were performed in oven-dried glassware. All materials were obtained from commercial suppliers and used as received unless otherwise noted. When necessary, the propargyl alcohols were prepared by addition of the lithium acetylides onto the appropriate aldehydes or ketones following the standard procedures (see below for a general procedure). Products **4a**,[19] **4b**,[19] **4e**,[19] **4n**,[19] and **4s**[22] have been previously prepared.

General Procedure for the Synthesis of Propargyl Alcohols. A terminal alkyne (13 mmol) was dissolved in 25 mL of dry THF in a round-bottomed flask. After the mixture was cooled to −40 °C, a 1.6 M solution of BuLi in hexanes (13 mmol) was added dropwise. The temperature was maintained for 1 h with stirring. The ketone was then added slowly (if solid, then it was dissolved in THF), and stirring was continued overnight, allowing the reaction mixture to warm to room temperature slowly without additional cooling. After completion, the reaction was quenched with a saturated NH_4Cl solution and extracted with CH_2Cl_2. This was followed by isolation of the corresponding product by flash column chromatography (silica gel; appropriate mixtures of *n*-hexane/EtOAc).

Representative Procedure for the Synthesis of Propargyl Vinyl Ethers 4 from Secondary or Tertiary Alcohols. Methyl propiolate (2.6 mmol) was added dropwise (time of addition 10 min) to a solution of 1-(phenylethynyl)cyclopentanol (2.0 mmol) and DABCO (0.20 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred for 5 min (TLC control). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel; *n*-hexane/EtOAc, 90:10) to give **4h** (512 mg, 90%). Less reactive alcohols were synthesized in *n*-hexanes to control the competitive dimerization of methyl propiolate.[19]

(*E*)-Methyl 3-(1,1-Diphenylprop-2-ynyloxy)acrylate (4c). This product partially rearranges (around 15%) during isolation by column chromatography. The rearranged product has a similar R_f, so the mixture can be used for the synthesis of the corresponding dihydropyridine. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.79 (s, 1H), 3.64 (s, 3H), 5.57 (d, $^3J_{(H,H)}$ = 12.1, 1H), 7.28–7.36 (m, 6H), 7.50–7.52 (m, 4H), 7.74 (d, $^3J_{(H,H)}$ = 12.1, 1H).

(*E*)-Methyl 3-(1-Ethynylcyclopentyloxy)acrylate (4d). Yield: 361 mg, 93%; colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.71–1.78 (m, 4H), 1.95–2.03 (m, 2H), 2.09–2.15 (m, 2H), 2.64 (s, 1H), 3.67 (s, 3H), 5.37 (d, $^3J_{(H,H)}$ = 12.1 Hz, 1H), 7.76 (d, $^3J_{(H,H)}$ = 12.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.3 (2C), 40.4 (2C), 51.0, 75.4, 83.0, 84.2, 100.0, 158.6, 168.1. IR ($CHCl_3$, cm^{-1}) 3305.5, 2954.0, 2118.6, 1702.3, 1641.0, 1438.3, 1333.5, 1294.9, 1169.8. MS (70 eV): *m*/*z* (%): 194 (2.0) [M$^+$], 135 (11), 103 (14), 93 (81), 92 (37), 91 (100), 77 (89), 65 (28). HRMS calcd for $C_{11}H_{14}O_3$, 194.0943; found, 194.0945.

(*E*)-Methyl 3-(1-(Phenylethynyl)cyclopentyloxy)acrylate (4h). Yield: 512 mg, 90%; colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.80–1.84 (m, 4H), 2.05–2.12 (m, 2H), 2.19–2.23 (m, 2H), 3.69 (s, 3H), 5.41 (d, $^3J_{(H,H)}$ = 12.1, 1H), 7.28–7.32 (m, 3H), 7.42–7.45 (m, 2H), 7.89 (d, $^3J_{(H,H)}$ = 12.1, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.5 (2C), 40.6 (2C), 51.0, 85.1, 87.2, 88.1, 99.8, 122.0, 128.3 (2C), 128.7, 131.8 (2C), 159.0, 158.2. IR ($CHCl_3$, cm^{-1}) 3015.49, 2953.95, 2878.33, 2230.20, 1701.20, 1638.73, 1558.93, 1540.42, 1490.37, 1438.07, 1334.77, 1294.38, 1222.25, 1209.89, 1166.91, 1135.38, 1050.74. MS (70 eV): *m*/*z* (%): 270 (1.7) [M$^+$], 211 (11), 169 (100), 154 (29), 141 (75), 128 (37), 115 (77), 91 (80),

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77 (13), 67 (11). HRMS calcd for $C_{17}H_{18}O_3$, 270.1256; found, 270.1259.

(*E*)-Methyl 3-(1-(Prop-1-ynyl)cyclohexyloxy)acrylate (4j). Yield: 435 mg, 98%; colorless oil. Repeated on 20 mmol scale and obtained the same yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23−1.33 (m, 1H), 1.44−1.57 (m, 3H), 1.59−1.70 (m, 4H), 1.83−1.87 (m, 2H), 1.87 (s, 3H), 3.67 (s, 3H), 5.35 (d, $^3J_{(H,H)}$ = 12.1 Hz, 1H), 7.92 (d, $^3J_{(H,H)}$ = 12.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 3.6, 22.5 (2C), 24.8, 37.9 (2C), 50.9, 78.5, 79.0, 84.6, 98.7, 158.8, 168.5. IR ($CHCl_3$, cm^{-1}) 2942.6, 2860.5, 2241.6, 1701.5, 1636.9, 1438.3, 1334.4, 1305.5, 1231.5, 1133.1. MS (70 eV): *m*/*z* (%): 222 (2.6) [M$^+$], 179 (3.8), 163 (5.6), 121 (100), 105 (12), 93 (29), 91 (14), 79 (14). HRMS calcd for $C_{13}H_{18}O_3$, 222.1256; found, 222.1250.

(*E*)-methyl 3-(1-(3,3-Dimethylbut-1-ynyl)cyclohexyloxy)-acrylate (4m). Yield: 486 mg, 92%; colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21−1.34 (m, 1H), 1.26 (s, 9H), 1.51−1.60 (m, 3H), 1.65−1.70 (m, 4H), 1.88−1.92 (m, 2H), 3.71 (s, 3H), 5.38 (d, $^3J_{(H,H)}$ = 12.1 Hz, 1H), 8.00 (d, $^3J_{(H,H)}$ = 12.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.8 (2C), 24.9, 27.5, 30.9 (3C), 38.1 (2C), 50.8, 77.7, 79.3, 98.3, 98.5, 158.9, 168.5. IR ($CHCl_3$, cm^{-1}) 2971.8, 2942.2, 2863.6, 2231.0, 1702.1, 1636.3, 1438.4, 1334.4, 1191.6. MS (70 eV): *m*/*z* (%): 264 (0.9) [M$^+$], 163 (100), 121 (30), 107 (46), 95 (37), 93 (29), 91 (24), 81 (25). HRMS calcd for $C_{16}H_{24}O_3$, 264.1725; found, 264.1729.

(*E*)-Methyl 3-(8-(Phenylethynyl)-1,4-dioxaspiro[4.5]decan-8-yloxy)acrylate (4o). Yield: 671 mg, 98%; colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.77−1.83(m,4H), 2.13 (pseudo t, $^3J_{(H,H)}$ = 6.3, 4H), 3.67 (s, 3H), 3.93 (s, 4H), 5.44 (d, $^3J_{(H,H)}$ = 12.1, 1H), 7.27−7.35 (m, 3H), 7.42−7.44 (m, 2H), 7.97 (d, $^3J_{(H,H)}$ = 12.1, 1H) . ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.8 (2C), 35.2 (2C), 50.9, 64.4 (2C), 77.4, 87.2, 88.2, 99.8, 107.3, 121.7, 128.3 (2C), 128.9, 131.8 (2C), 158.1, 168.1. IR ($CHCl_3$, cm^{-1}) 2955.69, 2887.50, 2226.76, 1703.49, 1639.32, 1490.25, 1438.38, 1374.26, 1335.76, 1293.65. MS (70 eV): *m*/*z* (%): 342 (1.1) [M$^+$], 241 (100), 197 (23), 179 (34), 141 (11), 127 (12), 115 (12), 99 (21), 86 (13). HRMS calcd for $C_{20}H_{22}O_5$, 342.1467; found, 342.1469.

(*E*)-Methyl 3-(1-Benzyl-4-(phenylethynyl)piperidin-4-yloxy)-acrylate (4p). Yield: 735 mg, 98%; colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.01−2.13 (m, 4H), 2.48−2.52 (m, 2H), 2.63−2.67 (m, 2H), 3.53 (s, 2H), 3.69 (s, 3H), 5.47 (d, $^3J_{(H,H)}$ = 12.1, 1H), 7.25−7.27 (m, 1H), 7.25−7.27 (m, 1H), 7.31−7.33 (m, 7H), 7.44−7.46 (m, 2H), 7.99 (d, $^3J_{(H,H)}$ = 12.1, 1H) . ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.3 (2C), 49.5 (2C), 50.9, 62.6, 77.1, 87.3, 89.0, 99.8, 121.7, 127.1, 128.2 (2C), 128.3 (2C), 128.91, 128.93 (2C), 131.8 (2C), 138.4, 158.1, 168.1. IR ($CHCl_3$, cm^{-1}) 3028.72, 2952.64, 2814.99, 2226.76, 1705.38, 1639.61, 1490.58, 1438.29. MS (70 eV): *m*/*z* (%): 375 (4.9) [M$^+$], 347 (10), 274 (75), 182 (8.2), 146 (6.7), 155 (6.4), 91 (100). HRMS calcd for $C_{24}H_{25}NO_3$, 375.1834; found, 375.1848.

(*E*)-Methyl 3-((1-Phenylhept-6-en-1-yn-3-yl)oxy)acrylate (4q). Yield: 569 mg, 97%; colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.87−2.02 (m, 2H), 2.19−2.25 (m, 2H), 3.62 (s, 3H), 4.71 (t, $^3J_{(H,H)}$ = 6.6, 1H), 4.95−5.03 (m, 2H), 5.35 (d, $^3J_{(H,H)}$ = 12.6, 1H), 5.70−5.80 (m, 1H), 7.21−7.27 (m, 3H), 7.35−7.37 (m, 2H), 7.60 (d, $^3J_{(H,H)}$ = 12.6, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.1, 34.5, 51.1, 71.4, 85.1, 88.1, 98.6, 115.9, 121.8, 128.3, 128.9, 131.8, 136.7, 160.6, 168.1. IR ($CHCl_3$, cm^{-1}) 3082.8, 3063.5, 3026.7, 3013.5, 2953.7, 2850.1, 2229.4, 2205.1, 1706.1, 1642.8, 1624.2, 1491.2, 1438.6, 1416.9, 1333.8, 1292.9, 1222.7, 1209.5, 1191.8, 1141.8, 1070.6, 1050.0. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{18}O_3Na$ [M + Na]$^+$, 293.1154; found, 293.1158.

(*E*)-Methyl 3-(1-Cyclohexyl-3-phenylprop-2-ynyloxy)-acrylate (4r). Yield: 584 mg, 98%; yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10−1.34 (m, 5H), 1.68−1.70 (m, 1H), 1.73−1.84 (m, 3H), 1.88−1.93 (m, 2H), 3.69 (s, 3H), 4.55 (d, $^3J_{(H,H)}$ = 6.1, 1H), 5.42 (d, $^3J_{(H,H)}$ = 12.5, 1H), 7.28−7.33 (m, 3H), 7.41−7.46 (m, 2H), 7.69 (d, $^3J_{(H,H)}$ = 12.6, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.69, 25.70, 26.2, 28.2, 28.6, 42.6, 51.0, 76.9, 84.5, 88.6, 98.2, 122.0, 128.3 (2C), 128.8, 131.8 (2C), 161.0, 168.2. IR ($CHCl_3$, cm^{-1}) 3025.7, 2933.3, 2856.9, 2227.4, 1704.3, 1641.6, 1623.4, 1490.8, 1438.5, 1322.2, 1294.3, 1231.6, 1136.1. ES (70 eV): *m*/*z* (%): 298 (0.9) [M$^+$], 197 (86), 155 (30), 141 (29), 129 (29), 117 (46), 115 (100), 91(40). HRMS calcd for $C_{19}H_{22}O_3$, 298.1569; found, 298.1575.

Representative Procedure for the Microwave-Assisted Reaction of Propargyl Vinyl Ethers 4 with Primary Amines. Propargyl vinyl ether **4a** (1.0 mmol) and *p*-anisidine (1.10 mmol) in toluene (1 mL) were placed in a microwave-specific closed vial, and the solution was irradiated for 1 h in a single-mode microwave oven (150 W, 120 °C). After removing the solvent at reduced pressure, the products were purified by flash column chromatography (silica gel; *n*-hexane/EtOAc 85:15) to yield **8a**. Yield: 254 mg, 93%.

Methyl 1-(4-Methoxyphenyl)-6,6-dimethyl-1,6-dihydropyridine-3-carboxylate (8a). Yield: 254 mg, 93%; yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 6H), 3.64 (s, 3H), 3.78 (s, 3H), 4.88 (d, $^3J_{(H,H)}$ = 9.9 Hz, 1H), 6.34 (d, $^3J_{(H,H)}$ = 9.9 Hz, 1H), 6.84 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.12 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.1 (2C), 50.6, 55.4, 58.4, 98.4, 114.0 (2C), 199.9, 120.6, 130.2 (2C), 136.1, 146.7, 158.9, 167.0. IR ($CHCl_3$, cm^{-1}) 2964.1, 2842.0, 1683.0, 1640.6, 1557.4, 1507.7, 1437.9, 1264.2, 1219.0, 1096.0. MS (70 eV): *m*/*z* (%): 273 (3.5) [M$^+$], 259 (17), 258 (100), 242 (3.6), 214 (3.5), 188 (2.7), 134 (4.7), 77 (7.1). HRMS calcd for $C_{16}H_{19}NO_3$, 273.1365; found, 273.1369.

Methyl 1-(4-Methoxyphenyl)-6-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (8b). Yield: 308 mg, 92%; amorpous pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.65 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 4.99 (d, $^3J_{(H,H)}$ = 9.9 Hz, 1H), 6.44 (dd, $^3J_{(H,H)}$ = 9.9 and 1.5 Hz, 1H), 6.64−6.70 (m, 4H), 7.24−7.28 (m, 1H), 7.29−7.31 (m, 2H), 7.35 (s, 1H), 7.41−7.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.8, 50.7, 55.4, 63.9, 97.4, 113.7 (2C), 118.1, 121.4, 126.7 (2C), 127.6, 128.3 (2C), 128.9 (2C), 136.6, 146.0, 146.8, 158.5, 167.1. IR ($CHCl_3$, cm^{-1}) 2975.6, 2947.2, 1678.9, 1645.5, 1547.4, 1509.1, 1440.7, 1288.0, 1250.9, 1185.9, 1099.3. MS (70 eV): *m*/*z* (%): 335 (7.8) [M$^+$], 321 (25), 320 (100), 276 (16), 258 (59), 149 (11), 115 (11), 77 (25). HRMS calcd for $C_{21}H_{21}NO_3$, 335.1521; found, 335.1519.

Methyl 1-(4-Methoxyphenyl)-6,6-diphenyl-1,6-dihydropyridine-3-carboxylate (8c). Yield: 373 mg, 94%; amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.62 (s, 3H), 3.67 (s, 3H), 5.34 (d, $^3J_{(H,H)}$ = 9.6 Hz, 1H), 6.45−6.49 (m, 3H), 6.76 (d, $^3J_{(H,H)}$ = 9.1 Hz, 2H), 7.15−7.18 (m, 2H), 7.21−7.24 (m, 4H), 7.31−7.33 (m, 4H), 7.61 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.8, 55.3, 72.5, 100.3, 113.4 (2C), 118.0, 121.5, 127.2 (2C), 127.8 (4C), 128.1 (2C), 128.7 (4C), 137.9, 143.6 (2C), 144.1, 157.7, 167.0. IR ($CHCl_3$, cm^{-1}) 3009.8, 2952.8, 1683.8, 1635.7, 1560.2, 1509.2, 1441.7, 1266.2, 1233.3, 1109.2. MS (70 eV): *m*/*z* (%): 397 (36) [M$^+$], 339 (23), 338 (100), 320 (62), 203 (13), 202 (23), 165 (23), 77 (24). HRMS calcd for $C_{26}H_{23}NO_3$, 397.1678; found, 397.1667.

Methyl 6-(4-Methoxyphenyl)-6-azaspiro[4.5]deca-7,9-diene-8-carboxylate (8d). Yield: 281 mg, 94%; amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36−1.45 (m, 2H), 1.53−1.63 (m, 2H), 1.70−1.76 (m, 2H), 1.79−1.86 (m, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 5.06 (d, $^3J_{(H,H)}$ = 9.9 Hz, 1H), 6.36 (dd, $^3J_{(H,H)}$ = 9.9 and 1.5 Hz, 1H), 6.85 (d, $^3J_{(H,H)}$ = 9.1 Hz, 2H), 7.14 (d, $^3J_{(H,H)}$ = 9.1 Hz, 2H), 7.32 (d, $^3J_{(H,H)}$ = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3 (2C), 40.0 (2C), 50.6, 55.4, 68.5, 98.5, 114.1 (2C), 119.0, 119.9, 130.5 (2C), 136.3, 147.6, 158.9, 167.0. IR ($CHCl_3$, cm^{-1}) 3010.4, 2953.0, 1675.7, 1635.5, 1560.9, 1510.0, 1441.7, 1278.8, 1212.2. MS (70 eV): *m*/*z* (%): 299 (34) [M$^+$], 271 (27), 270 (100), 207 (32), 175 (32), 160 (19), 121 (39). HRMS calcd for $C_{18}H_{21}NO_3$, 299.1521; found, 299.1513.

Methyl 1-(4-Methoxyphenyl)-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (8e). Yield: 291 mg, 93%; dark red oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89−0.99 (m, 1H), 1.28−1.35 (m, 2H), 1.49−1.58 (m, 5H), 1.98−2.01 (m, 2H), 3.66 (s, 3H), 3.80 (s, 3H), 5.35 (d, $^3J_{(H,H)}$ = 9.9 Hz, 1H), 6.48 (d, $^3J_{(H,H)}$ = 9.9 Hz, 1H), 6.85 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.11 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.32 (d, $^3J_{(H,H)}$ = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3 (2C), 25.3, 36.0 (2C), 50.6, 55.5, 60.8, 99.1, 114.0 (2C), 115.7, 121.0, 130.9 (2C), 135.7, 147.3, 159.0, 167.1. IR ($CHCl_3$, cm^{-1}) 2937.9, 2854.3, 1683.3, 1627.2, 1554.4, 1508.0, 1440.7, 1222.2. MS (70 eV): *m*/*z* (%): 313 (31) [M$^+$], 271 (28), 270 (100), 257 (22), 256 (39), 242 (10), 134

(10), 123 (16), 121 (19). HRMS calcd for $C_{19}H_{23}NO_3$, 313.1678; found, 313.1683.

Methyl 6-Methyl-6-phenyl-1-((*S*)-1-phenylethyl)-1,6-dihydropyridine-3-carboxylate (8g). Yield: 277 mg, 83%; orange oil. Two diastereomers separated by flash chromatography (60:40 of less polar/more polar). Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (d, $^3J_{(H,H)}$ = 7.1 Hz, 3H), 1.56 (s, 3H), 3.72 (s, 3H), 4.23 (q, $^3J_{(H,H)}$ = 7.1 Hz, 1H), 4.81 (d, $^3J_{(H,H)}$ = 10.1 Hz, 1H), 6.38 (dd, $^3J_{(H,H)}$ = 10.1 and 1.5 Hz, 1H), 7.24−7.27 (m, 3H), 7.30−7.35 (m, 3H), 7.39−7.42 (m, 2H), 7.54−7.56 (m, 2H), 7.74 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4, 27.1, 50.6, 56.9, 64.7, 95.1, 117.7, 121.0, 125.8 (2C), 127.0 (2C), 127.2, 127.7, 128.4 (2C), 128.8 (2C), 143.2, 144.1, 146.4, 167.1. Minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.65 (d, $^3J_{(H,H)}$ = 7.1 Hz, 3H), 1.83 (s, 3H), 3.68 (s, 3H), 4.28 (q, $^3J_{(H,H)}$ = 7.1 Hz, 1H), 4.81 (d, $^3J_{(H,H)}$ = 10.1 Hz, 1H), 6.41 (dd, $^3J_{(H,H)}$ = 10.1 and 1.5 Hz, 1H), 6.61 (dd, $^3J_{(H,H)}$ = 7.3 and 1.5 Hz, 2H), 7.06−7.10 (m, 3H), 7.22−7.27 (m, 3H), 7.44−7.46 (m, 2H), 7.58 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4, 25.5, 50.6, 56.1, 64.2, 95.5, 118.3, 120.1, 126.5 (2C), 127.2, 127.7, 128.0 (2C), 128.2 (2C), 128.3 (2C), 141.4, 142.4, 145.3, 167.0. IR (major isomer) ($CHCl_3$, cm^{-1}) 3009.9, 2950.4, 1671.6, 1638.3, 1563.0, 1434.7, 1321.2, 1254.3, 1128.2. MS (70 eV): *m*/*z* (%): 333 (65) [M$^+$], 318 (77), 302 (15), 274 (32), 256 (23), 215 (17), 214 (100), 105 (76). HRMS calcd for $C_{22}H_{23}NO_2$, 333.1729; found, 333.1740.

Methyl 6-(4-Methoxyphenyl)-9-phenyl-6-azaspiro[4.5]deca-7,9-diene-8-carboxylate (8h). Yield: 311 mg, 83%; amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.47−1.55 (m, 2H), 1.62−1.71 (m, 2H), 1.80−1.90 (m, 4H), 3.49 (s, 3H), 3.83 (s, 3H), 4.99 (s, 1H), 6.90 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.20 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.24−7.32 (m, 5H), 7.61 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0 (2C), 38.6 (2C), 50.3, 55.5, 68.8, 100.0, 114.2 (2C), 120.9, 126.6, 127.4 (2C), 127.6 (2C), 130.2 (2C), 134.6, 136.0, 141.3, 149.4, 158.9, 166.6. IR ($CHCl_3$, cm^{-1}) 3011.1, 2953.0, 1683.1, 1618.3, 1554.3, 1509.5, 1438.5, 1283.6, 1240.4. MS (70 eV): *m*/*z* (%): 375 (59) [M$^+$], 374 (19), 347 (40), 346 (100), 332 (19), 123 (45), 121 (44). HRMS calcd for $C_{24}H_{25}NO_3$, 375.1834; found, 375.1836.

Methyl 6-Benzyl-9-phenyl-6-azaspiro[4.5]deca-7,9-diene-8-carboxylate (8i). Yield: 295 mg, 82%; reddish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.61−1.70 (m, 4H), 1.76−1.82 (m, 2H), 1.85−1.92 (m, 2H), 3.46 (s, 3H), 4.49 (s, 2H), 4.90 (s, 1H), 7.21−7.30 (m, 8H), 7.32−7.50 (m, 2H), 7.55 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.1 (2C), 39.3 (2C), 50.2, 53.7, 68.1, 98.9, 121.0, 126.3 (2C), 126.5, 127.3 (2C), 127.5, 127.6 (2C), 128.8 (2C), 134.2, 138.6, 141.3, 149.9, 166.4. IR ($CHCl_3$, cm^{-1}) 3011.6, 2957.3, 2873.7, 1678.5, 1623.7, 1562.4, 1495.7, 1438.2, 1395.7, 1354.8, 1324.1, 1298.8, 1225.2, 1188.7, 1148.4, 1091.3. MS (70 eV): *m*/*z* (%): 359 (33) [M$^+$], 331 (26), 330 (64), 317 (35), 316 (18), 240 (20), 91 (100). HRMS calcd for $C_{24}H_{25}NO_2$, 359.1885; found, 359.1875.

Methyl 4-Methyl-1-phenyl-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (8j). Yield: 226 mg, 76%; amorphous pale solid. Major tautomer (4-methyl group): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88−1.01 (m, 1H), 1.26−1.40 (m, 2H), 1.49−1.67 (m, 5H), 1.99 (d, $^3J_{(H,H)}$ = 11.1 Hz, 2H), 2.13 (s, 3H), 3.63 (s, 3H), 5.09 (s, 1H), 7.18−7.22 (m, 2H), 7.30−7.38 (m, 3H), 7.45 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 21.5 (2C), 25.3, 35.7 (2C), 50.3, 60.9, 100.7, 114.6, 127.6, 128.9 (2C), 129.8 (2C), 130.3, 142.9, 148.1, 167.2. Minor tautomer (4-methylene group): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88−1.01 (m, 1H), 1.26−1.40 (m, 2H), 1.49−1.67 (m, 5H), 1.74 (d, $^3J_{(H,H)}$ = 11.1 Hz, 2H), 2.59 (s, 2H), 3.66 (s, 3H), 4.79 (d, $^3J_{(H,H)}$ = 2.5 Hz, 1H), 5.73 (d, $^3J_{(H,H)}$ = 2.5 Hz, 1H), 7.12−7.15 (m, 2H), 7.30−7.38 (m, 3H), 7.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7 (2C), 25.3, 33.6 (2C), 40.1, 50.5, 60.0, 98.3, 108.8, 127.7, 128.9 (2C), 129.4 (2C), 133.7, 143.1, 147.3, 167.4. IR ($CHCl_3$, cm^{-1}) 3011.9, 2943.2, 2860.0, 1733.1, 1678.3, 1625.6, 1573.7, 1494.0, 1438.1, 1292.2, 1232.0, 1093.1. MS (70 eV): *m*/*z* (%): 297 (30) [M$^+$], 255 (20), 254 (100), 241 (11), 240 (30), 93 (16), 77 (13). HRMS calcd for $C_{19}H_{23}NO_2$, 297.1729; found, 297.1726.

Methyl 1,4-Dimethyl-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (8k). Yield: 186 mg, 79%; yellowish oil. Major tautomer (4-methyl group): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03−1.25 (m, 1H), 1.44−1.70 (m, 7H), 1.78−1.88 (m, 2H), 2.04 (s, 3H), 2.96 (s, 3H), 3.63 (s, 3H), 4.89 (s, 1H), 7.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3 (2C), 21.4, 25.5, 33.4, 37.3 (2C), 50.1, 59.2, 98.4, 112.4, 130.5, 150.0, 167.2. Minor tautomer (4-methylene group): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03−1.25 (m, 1H), 1.44−1.70 (m, 7H), 1.78−1.88 (m, 2H), 2.42 (s, 2H), 2.95 (s, 3H), 3.67 (s, 3H), 4.65 (d, $^3J_{(H,H)}$ = 2.5 Hz, 1H), 5.57 (d, $^3J_{(H,H)}$ = 2.5 Hz, 1H), 7.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5 (2C), 25.5, 31.3, 37.2 (2C), 39.6, 50.3, 58.0, 107.2, 133.8, 149.1, 167.5. IR ($CHCl_3$, cm^{-1}) 3010.0, 2941.1, 2858.6, 1670.4, 1623.9, 1588.3, 1572.0, 1439.3, 1298.1, 1154.2, 1068.7. MS (70 eV): *m*/*z* (%): 235 (21) [M$^+$], 206 (8.7), 204 (7.3), 193 (18), 192 (100), 179 (37). HRMS calcd for $C_{14}H_{21}NO_2$, 235.1572; found, 235.1567.

Methyl 1-(4-Methoxyphenyl)-4-methyl-1-azaspiro[5.5]-undeca-2,4-diene-3-carboxylate (8l). Yield: 252 mg, 77%; amorphous pale brown solid. Major tautomer (4-methyl group): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90−0.98 (m, 1H), 1.23−1.36 (m, 2H), 1.45−1.60 (m, 5H), 1.96 (d, $^3J_{(H,H)}$ = 11.1 Hz, 2H), 2.13 (s, 3H), 3.63 (s, 3H), 3.81 (s, 3H), 5.06 (s, 1H), 6.86 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.12 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.42 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 21.5 (2C), 25.3, 35.7 (2C), 50.2, 55.4, 60.8, 100.2, 113.95 (2C), 114.0, 130.3, 130.8 (2C), 135.6, 145.6, 158.9, 167.2. Minor tautomer (4-methylene group): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90−0.98 (m, 1H), 1.23−1.36 (m, 2H), 1.45−1.60 (m, 5H), 1.71 (d, $^3J_{(H,H)}$ = 11.6 Hz, 2H), 2.58 (s, 2H), 3.66 (s, 3H), 3.81 (s, 3H), 4.78 (d, $^3J_{(H,H)}$ = 2.5 Hz, 1H), 5.71 (d, $^3J_{(H,H)}$ = 2.5 Hz, 1H), 6.86 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.05 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.43 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7 (2C), 25.3, 33.5 (2C), 40.1, 50.4, 55.4, 59.9, 97.8, 108.5, 114.4 (2C), 130.5 (2C), 130.8, 135.8, 147.8, 158.9, 167.4. IR ($CHCl_3$, cm^{-1}) 3011.7, 2941.8, 2859.8, 1677.8, 1625.2, 1573.9, 1509.5, 1438.4, 1292.3, 1249.2, 1170.2, 1093.3. MS (70 eV): *m*/*z* (%): 327 (32) [M$^+$], 285 (21), 284 (100), 271 (13), 270 (24), 123 (15). HRMS calcd for $C_{20}H_{25}NO_3$, 327.1834; found, 327.1828.

Methyl 4-*tert*-Butyl-1-(4-methoxyphenyl)-1-azaspiro[5.5]-undeca-2,4-diene-3-carboxylate (8m). Yield: 56 mg, 15%; amorphous pale brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20−1.27 (m, 2H), 1.29 (s, 9H), 1.45−1.58 (m, 6H), 1.96−1.99 (m, 2H), 3.63 (s, 3H), 3.81 (s, 3H), 5.22 (s, 1H), 6.85 (d, $^3J_{(H,H)}$ = 9.1 Hz, 2H), 7.11 (d, $^3J_{(H,H)}$ = 9.1 Hz, 2H), 7.44 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.9 (2C), 25.5, 30.6 (3C), 34.7 (2C), 34.9, 50.5, 55.5, 59.9, 101.9, 113.3, 113.9 (2C), 130.6 (2C), 135.8, 142.5, 149.1, 158.8, 167.9. IR ($CHCl_3$, cm^{-1}) 2940.6, 1686.4, 1618.6, 1508.9, 1435.9, 1362.4, 1289.6, 1247.9. MS (70 eV): *m*/*z* (%): 369 (16) [M$^+$], 327 (24), 326 (100), 313 (16), 312 (24), 296 (7.4), 282 (6.3). HRMS calcd for $C_{23}H_{31}NO_3$, 369.2304; found, 369.2298.

Methyl 6-Butyl-1-(4-methoxyphenyl)-4,6-diphenyl-1,6-dihydropyridine-3-carboxylate (8n). Yield: 367 mg, 81%; reddish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (t, $^3J_{(H,H)}$ = 7.3 Hz, 3H), 1.21−1.34 (m, 2H), 1.48−1.67 (m, 2H), 1.75−1.82 (m, 1H), 2.08−2.16 (m, 1H), 3.50 (s, 3H), 3.74 (s, 3H), 4.80 (s, 1H), 6.68 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 6.74 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.24−7.30 (m, 6H), 7.34 (t, $^3J_{(H,H)}$ = 7.3 Hz, 2H), 7.51 (d, $^3J_{(H,H)}$ = 7.3 Hz, 2H), 7.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0, 22.9, 26.6, 36.9, 50.4, 55.4, 67.8, 98.1, 113.7 (2C), 121.5, 126.5, 126.9 (2C), 127.3 (2C), 127.6 (2C), 127.7, 128.2 (2C), 128.4 (2C), 133.9, 136.4, 141.4, 146.7, 148.4, 158.3, 166.6. IR ($CHCl_3$, cm^{-1}) 2958.8, 1681.9, 1630.7, 1560.5, 1509.4, 1438.2, 1280.9, 1237.0, 1182.3, 1099.8. MS (70 eV): *m*/*z* (%): 453 (12) [M$^+$], 397 (37), 396 (100), 394 (31), 320 (36), 123 (23). HRMS calcd for $C_{30}H_{31}NO_3$, 453.2304; found, 453.2292.

Methyl 1-(4-Methoxyphenyl)-9-oxo-4-phenyl-1-azaspiro-[5.5]undeca-2,4-diene-3-carboxylate ethylene ketal (8o). Yield: 327 mg, 73%; amorphous brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.58−1.64 (m, 2H), 1.71−1.78 (m, 2H), 1.89−1.97 (m, 2H), 2.04−2.07 (m, 2H), 3.50 (s, 3H), 3.82 (s, 3H), 3.84−3.93 (m, 4H), 5.22 (s, 1H), 6.89 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.18 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.26−7.33 (m, 5H), 7.61 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.4 (2C), 31.9 (2C), 50.4, 55.5, 60.2, 64.2, 64.3, 100.8, 107.7, 114.2 (2C), 115.4, 126.9, 127.5 (2C), 127.7 (2C), 130.3 (2C), 135.3, 136.9, 141.2, 148.8, 159.0, 166.6. IR ($CHCl_3$, cm^{-1}) 3011.7, 2952.6, 1682.7, 1548.8, 1509.6, 1438.5, 1368.7, 1281.2, 1236.2, 1172.3,

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1105.7. MS (70 eV): *m/z* (%): 447 (8.9) [M$^+$], 404 (10), 388 (9.1), 347 (32), 346 (100), 332 (21), 123 (21). HRMS calcd for $C_{27}H_{29}NO_5$, 447.2046; found, 447.2037.

Methyl 9-Benzyl-1-(4-methoxyphenyl)-4-phenyl-1,9-diazaspiro[5.5]undeca-2,4-diene-3-carboxylate (8p). Yield: 360 mg, 75%; amorphous pale orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73−1.78 (m, 2H), 1.98−2.04 (m, 2H), 2.32−2.37 (m, 2H), 2.70−2.72 (m, 2H), 3.50 (s, 3H), 3.50 (s, 2H), 3.83 (s, 3H), 5.19 (s, 1H), 6.88−6.90 (m, 2H), 7.16−7.18 (m, 2H), 7.25−7.32 (m, 10H), 7.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.7 (2C), 49.1 (2C), 50.4, 55.5, 59.5, 62.9, 100.8, 114.2 (2C), 116.2, 126.8, 127.0, 127.5 (2C), 127.7 (2C), 128.2 (2C), 129.0 (2C), 130.6 (2C), 135.1, 136.3, 138.4, 141.3, 148.9, 159.1, 166.6. IR ($CHCl_3$, cm^{-1}) 2927.7, 1683.9, 1616.7, 1549.8, 1509.0, 1438.4, 1364.3, 1294.0, 1222.0, 1105.0. MS (70 eV): *m/z* (%): 480 (10) [M$^+$], 451 (9.0), 389 (15), 347 (34), 346 (65), 332 (34), 91 (100). HRMS calcd for $C_{31}H_{32}N_2O_3$, 480.2413; found, 480.2418.

Methyl 6-(But-3-en-1-yl)-1-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyridine-3-carboxylate (8q). Yield: 252 mg, 67%; dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62−1.71 (m, 1H), 2.00−2.08 (m, 1H), 2.16−2.30 (m, 2H), 3.53 (s, 3H), 3.80 (s, 3H), 4.59−4.64 (m, 1H), 4.99−5.08 (m, 2H), 5.19 (d, $^3J_{(H,H)}$ = 6.3 Hz, 1H), 5.78−5.90 (m, 1H), 6.90−6.92 (m, 2H), 7.12−7.14 (m, 2H), 7.22−7.31 (m, 5H), 7.80 (d, $^3J_{(H,H)}$ = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 32.6, 50.9, 56.0, 58.2, 104.4, 114.2, 115.2 (2C), 115.8, 121.4 (2C), 127.2, 127.9 (2C), 128.0 (2C), 137.0, 138.1, 138.3, 141.4, 143.2, 157.3, 167.0. IR ($CHCl_3$, cm^{-1}) 3009.0, 2950.2, 2840.0, 2360.3, 1684.5, 1618.3, 1557.7, 1511.0, 1437.6, 1231.3, 1037.0. MS (70 eV): *m/z* (%): 375 (1.3) [M$^+$], 321 (22), 320 (100), 277 (9.2), 217 (4.2), 154 (2.7), 128 (4.1), 115 (4.9), 92 (4.1). HRMS calcd for $C_{24}H_{25}NO_3$, 375.1834; found, 375.1832.

Methyl 6-Cyclohexyl-1-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyridine-3-carboxylate (8r). Yield: 133 mg, 33%; dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99−1.13 (m, 5H), 1.40−1.49 (m, 3H), 1.50−1.59 (m, 2H), 1.76−1.79 (m, 1H), 3.37 (s, 3H), 3.67 (s, 3H), 4.40−4.43 (m, 1H), 4.95 (d, $^3J_{(H,H)}$ = 6.1 Hz, 1H), 6.74−6.78 (m, 2H), 7.02−7.04 (m, 2H), 7.08−7.17 (m, 5H), 7.70 (d, $^3J_{(H,H)}$ = 1.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 26.3, 26.4, 27.2, 28.5, 43.3, 50.5, 55.6, 63.8, 106.3, 113.1, 114.8 (2C), 122.0 (2C), 126.7, 127.4 (2C), 127.5 (2C), 137.0, 138.7, 141.4, 144.3, 156.9, 166.6. IR ($CHCl_3$, cm^{-1}) 3005.6, 2931.0, 2855.1, 2360.4, 1684.2, 1617.3, 1559.8, 1511.1, 1438.1, 1231.7. MS (70 eV): *m/z* (%): 403 (1.0) [M$^+$], 332 (3.8), 321 (28), 320 (100), 277 (8.5), 217 (3.0), 123 (2.6), 115 (3.8), 92 (3.6). HRMS calcd for $C_{26}H_{29}NO_3$, 403.2147; found, 403.2133.

Methyl 1-(4-Methoxyphenyl)-4-phenyl-6-propyl-1,6-dihydropyridine-3-carboxylate (8s). Yield: 244 mg, 67%; dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, $^3J_{(H,H)}$ = 6.9 Hz, 3H), 1.52−1.55 (m, 4H), 3.53 (s, 3H), 3.81 (s, 3H), 4.57−4.61 (m, 1H), 5.20 (d, $^3J_{(H,H)}$ = 6.3 Hz, 1H), 6.90−6.92 (m, 2H), 7.13−7.15 (m, 2H), 7.27−7.31 (m, 5H), 7.80 (d, $^3J_{(H,H)}$ = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 17.6, 35.5, 50.5, 55.6, 58.3, 106.3, 114.4, 114.8 (2C), 121.0 (2C), 126.8, 127.5 (2C), 127.6 (2C), 136.3, 138.0, 141.1, 142.8, 156.8, 166.6. IR ($CHCl_3$, cm^{-1}) 3009.0, 2960.3, 2839.8, 2360.5, 1684.4, 1621.8, 1557.8, 1511.0, 1437.5, 1230.9, 1036.2. MS (70 eV): *m/z* (%): 363 (1.3) [M$^+$], 321 (25), 320 (100), 277 (8.1), 217 (3.1), 131 (4.0), 115 (3.0). HRMS calcd for $C_{23}H_{25}NO_3$, 363.1834; found, 363.1836.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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