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Quinazolines and Azaspirocycles

Lewis-Acid-Catalysed Activation of Nitriles: A Microwave-Assisted Solvent-Free Synthesis of 2,4-Disubstituted Quinazolines and 1,3-Diazaspiro[5.5]undec-1-enes

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Abstract: Two different modes of cyclization take place to synthesize quinazoline, quinazolinone, and 1,3-diazaspiro[5.5]undec-1-ene derivatives through the Lewis-acid-catalysed activation of both aliphatic and aromatic nitriles in a single-step, solvent-free, and transition-metal-free reaction. An amidine is expected to form as an intermediate; this then undergoes intramolecular cyclization in a one-pot reaction sequence. The reaction is carried out under microwave irradiation using trimethylsilyltrifluoromethane sulfonate (TMSOTf) as a catalyst and nitriles as a nitrogen source with the respective reaction partners.

Introduction

N-Heterocycles are powerful pharmacophores that are found in a large number of promising biologically active natural products as well as synthetic compounds.[1] Among the various N-heterocycles, quinazolines[2] and 1-azaspirocycles[3] are privileged classes of compounds that show a wide range of biological activities with therapeutic potential, such as antibacterial,[4] antiviral,[5] antifungal,[6] anti-inflammatory,[7] antihypertensive,[8] antimalarial,[9] antitubercular,[10] anticonvulsant,[11] and anticancer activities.[12] There are various positions on the ring systems of these skeletons where substitutions can occur, resulting in a diaspora of compounds that occur naturally and synthetically. In addition, the presence of heteroatoms constrained by quaternary carbon centres gives well-defined benefits, for instance in enhancing selectivity in drug binding.[13] The growing importance of quinazoline and azaspiro derivatives is also highlighted by the presence of these structural motifs in either market-available drugs or promising drug candidates, such as erysotramidine, lepadiformine, gefitinib, metolazone, and erlotinib (Figure 1). Consequently, in recent decades, enormous progress has been made in developing efficient and versatile methods for the rapid synthesis and transformation of these significant heterocyclic scaffolds.[14–21]

The first synthesis of quinazoline was by Griess in 1869;[15a] he used cyanogen as a nitrogen source in a reaction with anthranilic acid. Von Niementowski optimized the reaction using amides as a nitrogen source.[15b] Later, many different nitrogen

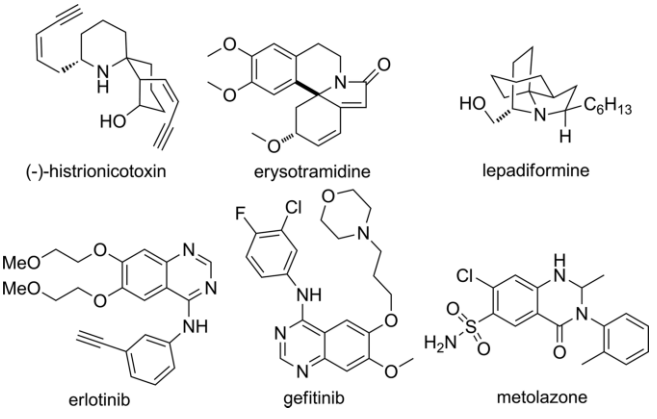

Figure 1. A few examples of biologically active quinazolines and spirocyclic compounds.

sources and starting materials were studied. These reactions include a three component reaction of ammonia with different carbon sources and 2-aminocarbonyl compounds or 2-halocarbonyl compounds,[16] the reaction of 2-aminobenzylamine with benzyl aldehydes or 2-aminocarbonyl compounds,[17] the reaction of 2-amino-substituted aryl oximes with aldehydes,[18] the reaction of amidines with 2-halocarbonyl compounds or benzylamines,[19] the intramolecular cyclization of amidines,[19g] and the reaction of nitriles with 2-aminobenzyl alcohols or ketones (Scheme 1).[20]

Amidines have been found to be an efficient nitrogen source for the synthesis of quinazolines; however, they must be synthesized from the corresponding acetanilides using a two-step reaction sequence.[19] An alternative approach involves the in-situ generation of amidines from nitriles. Cook and Moffat reported the synthesis of 3-phenyl-2,4-diazafluoranthene by the reaction of 1-aminofluorenone with an in-situ-generated amidine prepared from benzonitrile.[20a] The synthesis required HCl gas to be passed through the reaction mixture for 11 h at a tempera-

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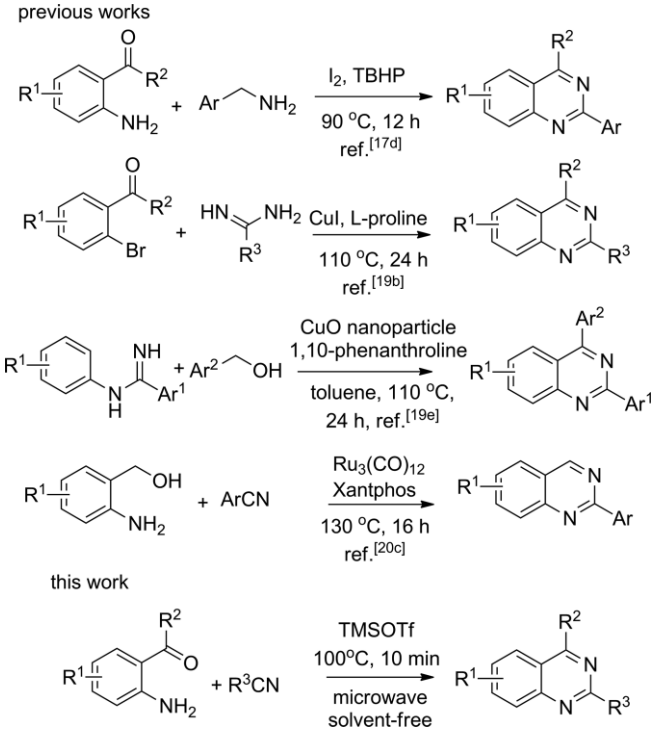


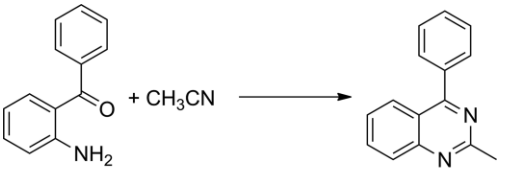
Scheme 1. Different strategies for the synthesis of quinazolines. TBHP = *tert*-butyl hydroperoxide; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

ture of 180–185 °C. Similar reaction conditions were used by Dave et al. for the synthesis of 4-phenyl quinazoline derivatives.[20b] Chen et al. reported the synthesis of quinazolines using amidines generated in situ from benzonitriles;[20c] an expensive ruthenium carbonyl complex was used as a catalyst, and also the reaction was limited to 2-aryl quinazolines only (Scheme 1). Adib and coworkers used a one-pot but two-step method for the synthesis of quinazolinones from anthranilic acid and nitriles; a separate step was needed for the preparation of amidines from nitriles and hydroxylamine.[20d] More recently, Abe et al. produced quinazolinones from anthranilic acid and nitriles; $POCl_3$ (5 equiv.) was needed for this reaction.[20e] Although the reported methods are efficient and high yielding, most of them are not free from drawbacks such as the requirement of harsh reaction conditions,[20a,20e] the use of expensive catalysts and ligands,[20c] multistep synthesis of starting materials,[19,20d] selectivity towards aromatic or aliphatic substrates, and prolonged reaction times.[20a] Thus, it is highly desirable to search for a more convenient and efficient approach to the synthesis of these skeletons. Recent reports from our lab have shown that the treatment of amines with nitriles in the presence of Lewis acids such as trimethylsilyl iodide (TMSI) led to the in-situ generation of amidines, which, upon hydrolysis, were converted into acetamides.[22]In this communication, we report a single-step, mild, solvent-free, and transition-metal-free reaction for the synthesis of quinazolines from aminobenzophenones/acetophenones and of quinazolinones from 2-aminobenzoic acids through the trapping of in-situ-generated amidines by intramolecular cyclization. Homoallylic amines like 2-cyclohexylethylamines were also used as substrates in the same reaction to produce a series of 1,3-diazaspiro[5.5]undec-1-enes.

Results and Discussion

To start with, acetonitrile was selected as the nitrile source; it was heated at reflux with 2-aminobenzophenone (**1a**) in the presence of trimethylsilyl iodide as a catalyst. After 10 h at reflux under a nitrogen atmosphere, 2-methyl-2-phenylquinazoline (**2a**) was obtained in a moderate yield. When the reaction was carried out under microwave heating conditions (MW) for 10 min, a better yield of the product was obtained (Table 1, entry 1). To optimize the reaction conditions, a number of different Lewis acids were tested (Table 1, entries 1–8). Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was identified as the most effective catalyst (Table 1, entry 6). This reaction gave the best yield of the product when a slight excess of the nitrile was used as both reactant and solvent. Other solvents, like DMSO, DMF, toluene, and THF, were not suitable for this purpose (Table 1, entries 9–12).

Table 1. Optimization of the reaction conditions for the synthesis of quinazolines.[a]



1a **2a**

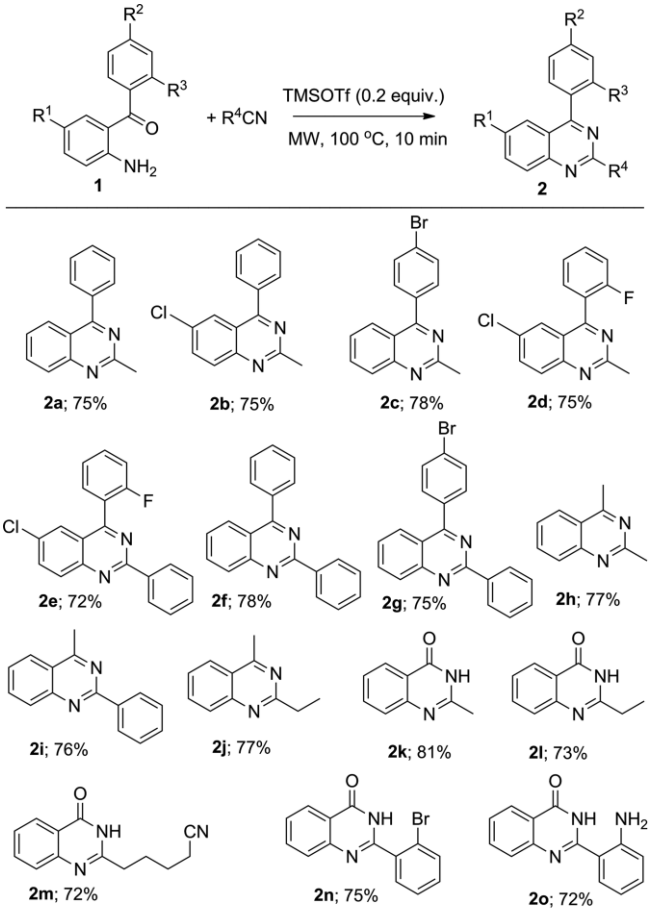
Entry	Catalyst	Solvent	Temp [°C]	Time [min]	Yield [%]
1	TMSI	none	120	15	56
2	TMSCl	none	120	15	10
3	$InCl_3$	none	120	15	0
4	$AlCl_3$	none	120	15	0
5	$CuBr_2$	none	120	15	5
6	TMSOTf	none	120	15	75
7	TMSOTf	none	100	10	75
8	H_3PO_3	none	120	15	0
9	TMSOTf	DMF	120	15	20
10	TMSOTf	DMSO	120	15	10
11	TMSOTf	THF	90	15	0
12	TMSOTf	toluene	120	15	0

[a] Reaction conditions: 2-aminobenzophenone (**1a**; 1 equiv.), acetonitrile (3 equiv.), catalyst (0.2 equiv.), solvent (2 mL), heated in a microwave reaction vial (10 mL).

Having standardized the conditions, the reaction was carried out with a few different benzophenone and nitrile substrates (Table 2). We observed that benzophenones with substituents on both the phenyl rings were almost equally reactive, and gave the corresponding quinazolines **2a**–**2d** in good yields. To vary the nitrogen source, benzonitrile was used, and 2-phenyl quinazolines **2e**–**2g** were produced. 2-Aminoacetophenones gave 4-methyl quinazolines **2h**–**2j** upon reaction with acetonitrile, benzonitrile, and propionitrile. The reaction was also found to be equally applicable to the synthesis of quinazolinones. Using anthranilic acid as a substrate, 2-substituted quin-

azolinones **2k**–**2o** were prepared. Different nitriles, like acetonitrile, propionitrile, adiponitrile, 2-bromobenzonitrile, and 2-aminobenzonitrile, showed almost the same reactivity. Interestingly, in the case of adiponitrile, only one of the two nitrile groups took part in the reaction. All the products were characterized using IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and HRMS. The structures were unequivocally assigned by comparison of their spectroscopic data with those of reported compounds. Also, the melting points of the products matched the reported melting points.

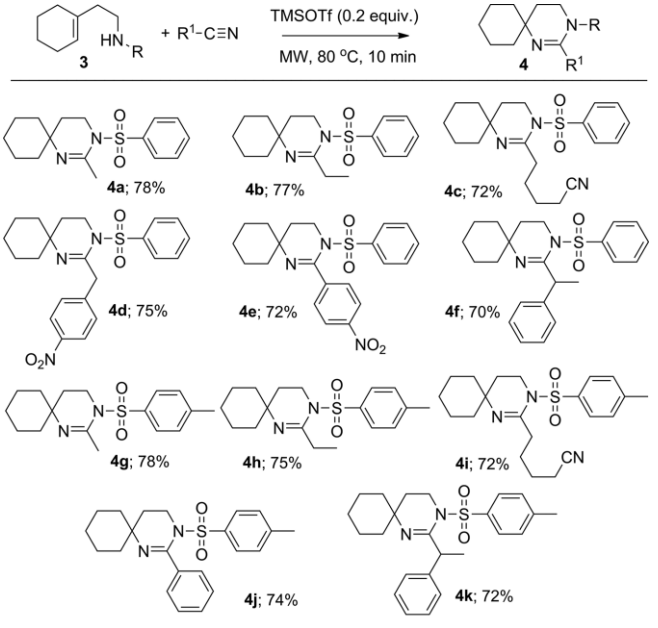
Table 2. Synthesis of quinazolines by the reaction of 2-aminobenzophenones/acetophenones and anthranilic acids with nitriles.



Encouraged by the above results, we decided to further explore the scope of the reaction. Earlier results from our lab showed that in the presence of a Lewis acid, *N*-acyl-2-(cyclohex-1-en-1-yl)ethylamines undergo an intramolecular cyclization to give 1,3-spirooxazine derivatives.[23] We envisaged that the amidine formed by the reaction of 2-(cyclohex-1-en-1-yl)ethylamine and a nitrile might undergo a similar intramolecular cyclization, with a single Lewis acid acting as catalyst for both reactions. Accordingly, an experiment was carried out by heating a mixture of 2-(cyclohex-1-en-1-yl)ethylamine and acetonitrile under microwave irradiation in the presence of a catalytic amount of TMSOTf. The reaction failed to produce any isolable product. We carried out a series of experiments, and observed that arylsulfonyl protection of the primary amine was necessary for the reaction to occur. Thus the reaction of mesyl-protected 2-(cyclohex-1-en-1-yl)ethylamine **3a**, prepared by treatment of the amine with benzenesulfonyl chloride, with acetonitrile produced 2-methyl-3-(phenylsulfonyl)-1,3-diazaspiro[5.5]undec-1-ene (**4a**). The structure of compound **4a** was determined by complete spectroscopic analysis. The ^{1}H and ^{13}C NMR spectra confirmed the number and nature of the protons and carbons, respectively. The crucial spiro and cyclic amidine carbons appeared at δ = 53.1 and 145.3 ppm, respectively. The quaternary nature of these two carbons was confirmed by their absence in DEPT-135 and HMQC spectra (see Supporting Information). A HMBC experiment also confirmed the presence of CH_2 groups adjacent to the spiro carbon, and a CH_3 group adjacent to the amidine carbon (see Supporting Information). The mass of the compound was confirmed by HRMS.

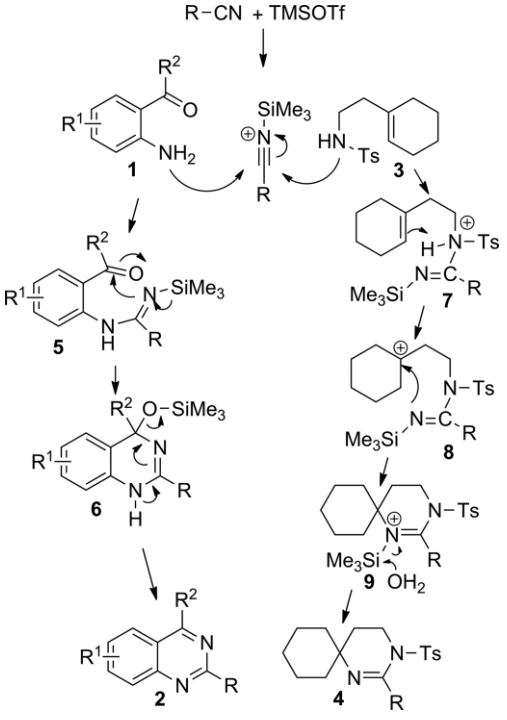
Optimization of the reaction conditions revealed that the best yield was obtained by treatment of **3** (1 equiv.), nitrile (1 equiv.), and TMSOTf (0.2 equiv.) at 80 °C under microwave irradiation for 10 min. Under these optimal reaction conditions, a number of different mesyl-protected **3a**–**3f** and tosyl-protected **3g**–**3k** 2-(cyclohex-1-en-1-yl)ethylamines were subjected to the spirocyclization reaction (Table 3). Aliphatic and aromatic nitriles with electron-donating and electron-withdrawing groups were equally reactive, and 1,3-diazaspiro[5.5]undec-1-enes **4a**–**4k** were obtained. The structures of all the compounds were determined by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and HRMS. For further confirmation of the identities of the spiro and cyclic amidine carbons, DEPT-135 analysis was carried out for **4g**, **4i**, **4j**, and **4k** (see Supporting Information). 2D HMQC and HMBC experiments for **4g** gave results similar to those obtained for **4a** (see Supporting Information). Unfortunately, a crystal structure could not be obtained.

Table 3. Preparation of 1,3-diazaspiro[5.5]undec-1-enes.[a]



[a] Reaction conditions: amine (1 equiv.), nitrile (3 equiv.), catalyst (0.2 equiv.), heated in a microwave reaction vial (10 mL) at 80 °C for 10 min.

Mechanistically, it may be proposed that electron-rich nitriles are activated by coordination with TMSOTf. Nucleophilic attack of the amine onto the activated nitrile produces an amidine **5** or **7**. In **5**, the amidine nitrogen attacks the carbonyl to produce **6**, which undergoes aromatization to give quinazoline derivatives **2** (Scheme 2). In the case of **7**, the amidine nitrogen attacks the activated double bond to produce spirocyclic intermediate **9** via intermediate **8**. Finally, 1,3-diazaspiroundecene **4** is obtained by removal of the TMS group by hydrolysis.



Scheme 2. Plausible mechanism of quinazoline and diazaspirocycle formation.

Conclusions

We have developed a rapid and efficient, transition-metal-free, solvent-free, single-step reaction in which a variety of 2,4-disubstituted quinazolines, 2-substituted quinazolinones, and 1,3-diazaspiro[5.5]undec-1-enes are synthesized, starting from 2-aminophenyl carbonyl compounds and *N*-tosyl-2-(cyclohexenyl)ethylamines. Nitriles activated by TMSOTf were used as the nitrogen source, and the reaction was carried out under solvent-free conditions. The reaction was equally applicable to both aliphatic and aromatic nitriles. Very short reaction times, a broad substrate scope, clean reactions, and mild conditions are significant features of this process. Research into applications of this method for the synthesis of more complex and biologically important quinazolines and azaspirocyclic derivatives is ongoing.

Experimental Section

General Procedure for the Synthesis of Quinazolines: TMSOTf (0.2 equiv.) was added to a solution of 2-aminobenzophenone/2-aminoacetophenone/anthranilic acid (1 mmol) in the appropriate nitrile (3 mmol) in a microwave reaction vessel (10 mL). The vial was sealed with a Teflon septum, and the mixture was heated under microwave irradiation at 100 °C for 10 min. The mixture was cooled, and the reaction was quenched by the addition of ammonia (1 mL). Low-boiling nitriles were removed under vacuum. The remaining solution was extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with water (2 × 10 mL), sodium thiosulfate (10 mL), sodium hydrogen carbonate (10 mL), and brine (10 mL). The mixture was dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give the corresponding quinazolines **2a**–**2j** and quinazolinones **2k**–**2o**.

2-Methyl-4-phenylquinazoline (2a):[24] Low-melting solid. IR (KBr): $\tilde{\nu}$ = 2922, 1614, 1550, 1447, 1377, 1263 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.0 Hz, 1 H), 7.99 (d, J = 8.0 Hz, 1 H), 7.83 (t, J = 8.5 Hz, 1 H), 7.74–7.71 (m, 2 H), 7.54–7.51 (m, 3 H), 7.49 (t, J = 8.0 Hz, 1 H), 2.93 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8 (C), 164.0 (C), 151.6 (C), 137.5 (C), 133.8 (CH), 130.0 (CH), 128.8 (CH), 128.8 (CH), 128.3 (CH), 127.2 (CH), 126.9 (CH), 121.2 (C), 26.5 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{13}N_2$ $[M + H]^+$ 221.1079; found 221.1076.

6-Chloro-2-methyl-4-phenylquinazoline (2b): Yellow solid. M.p. 105–107 °C (lit.[25] 107–109 °C). IR (KBr): $\tilde{\nu}$ = 3059, 1548, 1478, 1386, 1296, 1145, 1072 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, J = 2.0 Hz, 1 H), 7.97 (d, J = 9.0 Hz, 1 H), 7.80 (dd, J = 9.0, 2.0 Hz, 1 H), 7.77–7.71 (m, 2 H), 7.63–7.57 (m, 3 H), 2.94 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0 (C), 164.4 (C), 150.1 (C), 136.9 (C), 134.8 (CH), 132.6 (C), 130.4 (CH), 130.1 (CH), 129.9 (CH), 129.0 (CH), 126.0 (CH), 121.8 (C), 26.8 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{12}N_2Cl$ $[M + H]^+$ 255.0689; found 255.0687.

4-(4-Bromophenyl)-2-methylquinazoline (2c): Pale yellow solid. M.p. 160–162 °C. IR (KBr): $\tilde{\nu}$ = 3051, 1588, 1549, 1483, 1398, 1332, 1215 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.5 Hz, 1 H), 7.97 (d, J = 7.5 Hz, 1 H), 7.84 (t, J = 7.5 Hz, 1 H), 7.67 (d, J = 8.0 Hz, 2 H), 7.61 (d, J = 8.0 Hz, 2 H), 7.50 (t, J = 7.5 Hz, 1 H), 2.91 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.5 (C), 164.0 (C), 151.7 (C), 136.3 (C), 134.0 (CH), 132.1 (CH), 131.6 (CH), 128.5 (CH), 127.3 (CH), 126.7 (CH), 124.7 (C), 120.9 (C), 26.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{12}N_2Br$ $[M + H]^+$ 299.0184; found 299.0181.

6-Chloro-4-(2-fluorophenyl)-2-methylquinazoline (2d): White solid. M.p. 138–140 °C (lit.[26] 139–141 °C). IR (KBr): $\tilde{\nu}$ = 3064, 1608, 1556, 1492, 1380, 1215 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, J = 9.0 Hz, 1 H), 7.79 (dd, J = 9.0, 2.0 Hz, 1 H), 7.70 (t, J = 2.0 Hz, 1 H), 7.58–7.52 (m, 2 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.29–7.24 (m, 1 H), 2.93 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5 (C), 164.1 (C), 159.9 (d, J = 250.0 Hz, C), 149.6 (C), 135.2 (CH), 132.8 (C), 132.2 (d, J = 9.0 Hz, CH); 131.6 (d, J = 3.0 Hz, CH), 130.0 (CH), 125.7 (d, J = 3.0 Hz, CH), 125.1 (d, J = 3.5 Hz, CH), 124.8 (d, J = 15.0 Hz, C), 122.6 (C), 116.5 (d, J = 21.0 Hz, CH), 26.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{11}N_2FCl$ $[M + H]^+$ 273.0595; found 273.0590.

6-Chloro-4-(2-fluorophenyl)-2-phenylquinazoline (2e): Pale yellow solid. M.p. 178–180 °C (lit.[27] 180–181 °C). IR (KBr): $\tilde{\nu}$ = 3072, 1616, 1560, 1532, 1392 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.65–8.60 (m, 2 H), 8.08 (d, J = 9.0 Hz, 1 H), 7.81 (dd, J = 9.0, 2.0 Hz, 1 H), 7.76 (t, J = 2.0 Hz, 1 H), 7.67 (t, J = 7.5 Hz, 1 H), 7.61–7.47 (m, 4 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.30 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.0 (C), 160.9 (C), 160.1 (d, J = 250 Hz, C), 150.1 (C), 137.8 (C), 135.1 (CH), 133.0 (C), 132.2 (d, J = 7.5 Hz, CH), 132.0 (d, J = 3.0 Hz, CH), 131.1 (CH), 130.9 (CH), 128.9 (CH), 128.8 (CH), 125.8 (d, J = 3.0 Hz, CH), 125.2 (d, J = 15.0 Hz, C), 124.9 (d, J =

2.5 Hz, CH), 123.2 (C), 116.5 (d, J = 21 Hz, CH) ppm. HRMS (ESI): calcd. for $C_{20}H_{13}N_2FCl$ $[M + H]^+$ 335.0751; found 335.0758.

2,4-Diphenylquinazoline (2f): White solid. M.p. 119–121 °C (lit.[26] 117–119 °C). IR (KBr): $\tilde{\nu}$ = 3058, 1610, 1556, 1545, 1331 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.68 (dd, J = 8.0, 1.5 Hz, 2 H), 8.15 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 8.0 Hz, 1 H), 7.90–7.84 (m, 3 H), 7.61–7.45 (m, 7 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5 (C), 160.4 (C), 152.2 (C), 138.4 (C), 137.8 (C), 133.8 (CH), 130.7 (CH), 130.4 (CH), 130.1 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 127.2 (CH), 121.9 (C) ppm. HRMS (ESI): calcd. for $C_{20}H_{15}N_2$ $[M + H]^+$ 283.1235; found 283.1236.

4-(4-Bromophenyl)-2-phenylquinazoline (2g): Pale yellow solid. M.p. 152–154 °C (lit.[17d] 154–156 °C). IR (KBr): $\tilde{\nu}$ = 3063, 1535, 1484, 1340, 1011 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.66 (d, J = 7.0 Hz, 2 H), 8.14 (d, J = 8.5 Hz, 1 H), 8.04 (d, J = 8.5 Hz, 1 H), 7.87 (t, J = 8.5 Hz, 1 H), 7.78–7.84 (m, 4 H), 7.57–7.47 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.3 (C), 160.4 (C), 152.2 (C), 138.2 (C), 136.7 (C), 133.9 (CH), 132.0 (CH), 131.9 (CH), 130.8 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 127.4 (CH), 126.7 (CH), 124.8 (C), 121.6 (C) ppm. HRMS (ESI): calcd. for $C_{20}H_{14}N_2Br$ $[M + H]^+$ 361.0340; found 361.0334.

2,4-Dimethylquinazoline (2h): Yellow solid. M.p. 287–289 °C (lit.[19a] 288–290 °C). IR (KBr): $\tilde{\nu}$ = 2990, 1625, 1410, 1395, 1280, 1075 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.0 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.83 (t, J = 8.0 Hz, 1 H), 7.56 (t, J = 8.0 Hz, 1 H), 2.90 (s, 3 H), 2.83 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4 (C), 163.7 (C), 150.1 (C), 133.9 (CH), 128.4 (CH), 126.9 (CH), 125.1 (CH), 122.4 (C), 26.6 (CH_3), 21.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{10}H_{11}N_2$ $[M + H]^+$ 159.0922; found 159.0918.

4-Methyl-2-phenylquinazoline (2i): Yellow solid. M.p. 69–70 °C (lit.[26] 71–74 °C). IR (KBr): $\tilde{\nu}$ = 3059, 1614, 1581, 1546, 1256, 1160 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.0 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 1 H), 7.68–7.63 (m, 3 H), 7.51 (t, J = 8.0 Hz, 1 H), 7.21 (t, J = 8.0 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 2.71 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0 (C), 147.5 (C), 144.8 (C), 130.2 (CH), 129.9 (CH), 129.4 (CH), 126.5 (C), 126.0 (CH), 123.7 (CH), 121.8 (C), 121.2 (CH), 117.4 (CH), 19.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{13}N_2$ $[M + H]^+$ 221.1079; found 221.1076.

2-Ethyl-4-methylquinazoline (2j):[16d] Yellow oil. IR (KBr): $\tilde{\nu}$ = 2971, 1616, 1561, 1495, 1390, 1287, 1195 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.5 Hz, 1 H), 7.91 (d, J = 8.5 Hz, 1 H), 7.79 (t, J = 8.5 Hz, 1 H), 7.51 (t, J = 8.5 Hz, 1 H), 3.05 (q, J = 7.5 Hz, 2 H), 2.88 (s, 3 H), 1.41 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3 (C), 167.9 (C), 150.1 (C), 133.6 (CH), 128.6 (CH), 126.7 (CH), 125.1 (CH), 122.6 (C), 33.3 (CH_2), 21.9 (CH_3), 13.3 (CH_3) ppm. HRMS (ESI): calcd. for $C_{11}H_{13}N_2$ $[M + H]^+$ 173.1079; found 173.1073.

2-Methylquinazolin-4(3*H*)-one (2k): Yellow solid. M.p. 228–229 °C (lit.[28] 229–230 °C). IR (KBr): $\tilde{\nu}$ = 3013, 2912, 1730, 1442, 1273, 1120 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 12.07 (s, 1 H), 8.26 (dd, J = 8.0, 1.5 Hz, 1 H), 7.76 (dt, J = 8.0, 1.5 Hz, 1 H), 7.66 (d, J = 8.0 Hz, 1 H), 7.46 (t, J = 8.0 Hz, 1 H), 2.59 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.2 (C), 153.3 (C), 149.2 (C), 134.9 (CH), 126.9 (CH), 126.4 (CH), 126.1 (CH), 120.1 (C), 22.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_9H_9N_2O$ $[M + H]^+$ 161.0715; found 161.0716.

2-Ethylquinazolin-4(3*H*)-one (2l): Yellow solid. M.p. 228–230 °C (lit.[29] 229–231 °C). IR (KBr): $\tilde{\nu}$ = 3037, 1680, 1605, 1462, 1120 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 12.04 (s, 1 H), 8.27 (dd, J = 8.0, 1.0 Hz, 1 H), 7.76 (dt, J = 8.0, 1.5 Hz, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.46 (t, J = 8.0 Hz, 1 H), 2.83 (q, J = 7.5 Hz, 2 H), 1.43 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.6 (C), 157.9 (C), 149.5 (C), 135.1 (CH), 127.3 (CH), 126.6 (CH), 126.4 (CH), 120.6 (C), 29.4 (CH_2), 11.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{10}H_{11}N_2O$ $[M + H]^+$ 175.0871; found 175.0874.

5-(4-Oxo-3,4-dihydroquinazolin-2-yl)pentane Nitrile (2m): Yellow solid. M.p. 180–182 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 12.22 (s, 1 H), 8.27 (dd, J = 8.0, 1.5 Hz, 1 H), 7.77 (dt, J = 7.5, 1.5 Hz, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 1 H), 2.85 (t, J = 7.5 Hz, 2 H), 2.45 (t, J = 7.5 Hz, 2 H), 2.12–2.02 (m, 2 H), 1.90–1.80 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.7 (C), 155.6 (C), 149.5 (C), 135.2 (CH), 127.5 (CH), 126.9 (CH), 126.4 (CH), 120.6 (C), 119.6 (C), 34.7 (CH_2), 26.3 (CH_2), 25.0 (CH_2), 17.2 (CH_2) ppm. HRMS (ESI): calcd. for $C_{13}H_{14}N_3O$ $[M + H]^+$ 228.1137; found 228.1135.

2-(2-Bromophenyl)quinazolin-4(3*H*)-one (2n): Pale brown solid. M.p. 173–175 °C (lit.[30] 175–177 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 8.29 (d, J = 8.0 Hz, 1 H), 7.82–7.66 (m, 4 H), 7.55–7.45 (m, 2 H), 7.39 (dt, J = 7.5, 1.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.5 (C), 152.2 (C), 149.0 (C), 135.1 (CH), 133.9 (CH), 132.2 (CH), 131.4 (CH), 130.1 (C), 128.2 (CH), 128.2 (CH), 127.6 (CH), 126.7 (CH), 121.3 (C), 121.1 (C) ppm. HRMS (ESI): calcd. for $C_{14}H_{10}N_2OBr$ $[M + H]^+$ 300.9977; found 300.9980.

2-(2-Aminophenyl)quinazolin-4(3*H*)-one (2o): Colourless solid. M.p. 153–155 °C (lit.[31] 155–156 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.39 (d, J = 8.0 Hz, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.68–7.58 (m, 2 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.21–7.15 (m, 1 H), 6.80–6.70 (m, 2 H), 5.89 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3 (C), 161.0 (C), 150.0 (C), 148.8 (C), 133.2 (CH), 131.3 (CH), 131.2 (CH), 128.1 (CH), 125.6 (CH), 121.9 (CH), 120.0 (C), 117.2 (CH), 117.0 (CH), 112.6 (C) ppm. HRMS (ESI): calcd. for $C_{14}H_{12}N_3O$ $[M + H]^+$ 238.0980; found 238.0974.

General Procedure for Synthesis of 1,3-Diazaspiro[5.5]undec-1-ene Derivatives: TMSOTf (0.2 equiv.) was added to a solution of tosyl protected 2-(cyclohex-1-en-1-yl)ethan-1-amine (1 mmol) in the appropriate nitrile (3 mmol) in a microwave reaction vessel (10 mL). The vial was sealed with a Teflon septum, and the mixture was heated under microwave irradiation at 80 °C for 10 min. The mixture was cooled, and the reaction was quenched by the addition of ammonia (1 mL). Low-boiling nitriles were removed under vacuum. The remaining solution was extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with water (2 × 10 mL), sodium thiosulfate (10 mL), sodium hydrogen carbonate (10 mL), and brine (10 mL). The organic phase was dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give 1,3-diazaspiro[5.5]undec-1-ene derivatives **4a**–**4k**.

2-Methyl-3-(phenylsulfonyl)-1,3-diazaspiro[5.5]undec-1-ene (4a): Pale brown solid. M.p. 105–107 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.0 Hz, 2 H), 7.57 (t, J = 8.0 Hz, 1 H), 7.49 (t, J = 8.0 Hz, 2 H), 3.64 (t, J = 6.0 Hz, 2 H), 2.21 (s, 3 H), 1.62–1.15 (m, 12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.3 (C), 140.3 (C), 133.3 (CH), 129.5 (CH), 126.8 (CH), 53.1 (C), 42.2 (CH_2), 38.0 (CH_2), 30.6 (CH_2), 25.9 (CH_2), 25.6 (CH_3), 21.9 (CH_2) ppm. HRMS (ESI): calcd. for $C_{16}H_{23}N_2O_2S$ $[M + H]^+$ 307.1480; found 307.1485.

2-Ethyl-3-(phenylsulfonyl)-1,3-diazaspiro[5.5]undec-1-ene (4b): Yellow solid. M.p. 115–117 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.5 Hz, 2 H), 7.56 (t, J = 7.5 Hz, 1 H), 7.49 (dd, J = 8.5, 7.5 Hz, 2 H), 3.59 (t, J = 6.0 Hz, 2 H), 2.58 (q, J = 6.0 Hz, 2 H), 1.65–1.09 (m, 12 H), 1.03 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.2 (C), 140.4 (C), 133.2 (CH), 129.4 (CH), 126.9 (CH), 52.9 (C), 42.3 (CH_2), 38.4 (CH_2), 32.0 (CH_2), 30.5 (CH_2), 26.1 (CH_2), 21.9 (CH_2), 12.2 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{27}N_2O_3S$ $[M + H]^+$ 339.1742; found 339.1747.

5-[3-(Phenylsulfonyl)-1,3-diazaspiro[5.5]undec-1-en-2-yl]-pentanenitrile (4c): Yellow semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78–7.74 (m, 2 H), 7.63–7.49 (m, 3 H), 3.58 (t, *J* = 6.0 Hz, 2 H), 2.62 (t, *J* = 7.0 Hz, 2 H), 2.28 (t, *J* = 7.0 Hz, 2 H), 1.75–1.08 (m, 16 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9 (C), 140.1 (C), 133.4 (CH), 129.5 (CH), 126.8 (CH), 118.9 (C), 53.1 (C), 42.3 (CH_2), 38.5 (CH_2), 36.0 (CH_2), 32.1 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 24.4 (CH_2), 21.8 (CH_2), 16.8 (CH_2) ppm. HRMS (ESI): calcd. for $C_{20}H_{28}N_3O_2S$ $[M + H]^+$ 374.1902; found 374.1908.

2-(4-Nitrobenzyl)-3-(phenylsulfonyl)-1,3-diazaspiro[5.5]undec-1-ene (4d): Yellow solid. M.p. 153–155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.5 Hz, 2 H), 7.64 (d, *J* = 8.5 Hz, 2 H), 7.57 (t, *J* = 8.5 Hz, 1 H), 7.46 7.57 (t, *J* = 7.5 Hz, 2 H), 7.38 7.57 (t, *J* = 7.5 Hz, 2 H), 4.14 (s, 2 H), 3.52 (t, *J* = 6.0 Hz, 2 H), 1.60–1.15 (m, 12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.8 (C), 146.1 (C), 145.7 (C), 139.5 (C), 133.6 (CH), 130.0 (CH), 129.5 (CH), 127.0 (CH), 123.4 (CH), 53.9 (C), 43.4 (CH_2), 42.5 (CH_2), 38.5 (CH_2), 31.9 (CH_2), 26.0 (CH_2), 21.8 (CH_2) ppm. HRMS (ESI): calcd. for $C_{22}H_{26}N_3O_4S$ $[M + H]^+$ 428.1644; found 428.1648.

2-(4-Nitrophenyl)-3-(phenylsulfonyl)-1,3-diazaspiro[5.5]undec-1-ene (4e): Yellow solid. M.p. 149–151 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.5 Hz, 2 H), 7.68 (d, *J* = 8.5 Hz, 2 H), 7.65–7.46 (m, 5 H), 3.69 (t, *J* = 6.0 Hz, 2 H), 1.47 (t, *J* = 6.0 Hz, 2 H), 1.44–1.10 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.5 (C), 147.9 (C), 144.7 (C), 138.7 (C), 133.9 (CH), 129.7 (CH), 129.5 (CH), 127.7 (CH), 123.2 (CH), 55.5 (C), 42.5 (CH_2), 38.3 (CH_2), 31.9 (CH_2), 25.9 (CH_2), 21.9 (CH_2) ppm. HRMS (ESI): calcd. for $C_{21}H_{24}N_3O_4S$ $[M + H]^+$ 414.1488; found 414.1484.

2-(1-Phenylethyl)-3-(phenylsulfonyl)-1,3-diazaspiro[5.5]undec-1-ene (4f): Pale brown semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.46 (m, 3 H), 7.38 (t, *J* = 7.5 Hz, 2 H), 7.20–7.11 (m, 5 H), 4.54 (q, *J* = 7.0 Hz, 1 H), 3.75–3.65 (m, 1 H), 3.19–3.11 (m, 1 H), 1.85–1.42 (m, 6 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.37–1.15 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.9 (C), 144.3 (C), 140.4 (C), 133.0 (CH), 129.2 (CH), 128.3 (CH), 127.9 (CH), 127.0 (CH), 126.4 (CH), 53.5 (C), 45.1 (CH), 42.8 (CH_2), 39.1 (CH_2), 39.0 (CH_2), 33.8 (CH_2), 26.3 (CH_2), 22.2 (CH_2), 22.1 (CH_2), 21.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{23}H_{29}N_2O_2S$ $[M + H]^+$ 397.1950; found 397.1945.

2-Methyl-3-tosyl-1,3-diazaspiro[5.5]undec-1-ene (4g): Pale brown solid. M.p. 208–210 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.5 Hz, 2 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 3.67 (t, *J* = 6.0 Hz, 2 H), 2.42 (s, 3 H), 2.25 (s, 3 H), 1.69–1.61 (m, 4 H), 1.50–1.20 (m, 8 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.7 (C), 144.4 (C), 137.4 (C), 130.1 (CH), 127.0 (CH), 53.2 (C), 42.2 (CH_2), 38.1 (CH_2), 30.5 (CH_2), 26.0 (CH_2), 25.6 (CH_3), 22.0 (CH_2), 21.8 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{27}N_2O_3S$ $[M + H]^+$ 339.1742; found 339.1747.

2-Ethyl-3-tosyl-1,3-diazaspiro[5.5]undec-1-ene (4h): Pale brown solid. M.p. 178–180 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 7.5 Hz, 2 H), 3.59 (t, *J* = 5.5 Hz, 2 H), 2.58 (q, *J* = 7.0 Hz, 2 H), 2.39 (s, 3 H), 1.65–1.55 (m, 2 H), 1.51 (t, *J* = 5.5 Hz, 2 H), 1.42–1.10 (m, 8 H), 1.03 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.7 (C), 144.2 (C), 137.3 (C), 130.0 (CH), 126.9 (CH), 52.9 (C), 42.3 (CH_2), 38.3 (CH_2), 31.7 (CH_2), 30.5 (CH_2), 26.0 (CH_2), 21.9 (CH_2), 21.7 (CH_3), 12.4 (CH_3) ppm. HRMS (ESI): calcd. for $C_{18}H_{29}N_2O_3S$ $[M + H]^+$ 353.1899; found 353.1905.

5-(3-Tosyl-1,3-diazaspiro[5.5]undec-1-en-2-yl)pentanenitrile (4i): Yellow semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 3.58 (t, *J* = 7.0 Hz, 2 H), 2.62 (t, *J* = 7.0 Hz, 2 H), 2.41 (s, 3 H), 2.29 (t, *J* = 7.0 Hz, 2 H), 1.80–1.10 (m, 16 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.2 (C), 144.4 (C), 137.3 (C), 130.1 (CH), 126.9 (CH), 120.0 (C), 53.1 (C), 42.2 (CH_2), 38.5 (CH_2), 36.0 (CH_2), 32.1 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 24.9 (CH_2), 21.9 (CH_2), 21.7 (CH_3), 17.1 (CH_2) ppm. HRMS (ESI): calcd. for $C_{21}H_{30}N_3O_2S$ $[M + H]^+$ 388.2059; found 388.2051.

2-Phenyl-3-tosyl-1,3-diazaspiro[5.5]undec-1-ene (4j): Yellow semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 4 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 3.79 (t, *J* = 6.5 Hz, 2 H), 2.49 (s, 3 H), 1.85–1.20 (m, 12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.3 (C), 144.3 (C), 138.5 (C), 136.6 (C), 129.7 (CH), 129.6 (CH), 128.9 (CH), 127.7 (CH), 127.7 (CH), 54.8 (C), 42.5 (CH_2), 38.3 (CH_2), 32.1 (CH_2), 25.9 (CH_2), 22.0 (CH_2), 21.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{22}H_{27}N_2O_2S$ $[M + H]^+$ 383.1793; found 383.1790.

2-(1-Phenylethyl)-3-tosyl-1,3-diazaspiro[5.5]undec-1-ene (4k): Yellow semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.0 Hz, 2 H), 7.21–7.12 (m, 7 H), 4.56 (q, *J* = 7.0 Hz, 1 H), 3.72–3.64 (m, 1 H), 3.18–3.10 (m, 1 H), 2.37 (s, 3 H), 1.85–1.70 (m, 2 H), 1.58–1.42 (m, 4 H), 1.38 (d, *J* = 7.0 Hz, 3 H), 1.40–1.17 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.0 (C), 144.4 (C), 143.8 (C), 137.5 (C), 129.7 (CH), 128.3 (CH), 127.9 (CH), 127.0 (CH), 126.3 (CH), 53.4 (C), 45.0 (CH), 42.6 (CH_2), 39.1 (CH_2), 39.0 (CH_2), 33.8 (CH_2), 26.4 (CH_2), 22.2 (CH_3), 22.1 (CH_2), 21.7 (CH_2), 21.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{24}H_{31}N_2O_2S$ $[M + H]^+$ 411.2106; found 411.2099.

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