Solution-Phase Parallel Synthesis of Novel Spirooxazolinoisoxazolines

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A practical and efficient solution-phase parallel synthesis of spirooxazolinoisoxazolines has been developed. Starting from methyl serine ester, the key steps are (1) acylation with concomitant β-elimination to form an α,β-unsaturated ester, (2) 1,3-dipolar cycloaddition with an oxime to form an isoxazoline ring, (3) reduction with $NaBH_4$, and (4) mesylation and in situ cyclization to form an oxazoline ring. All reaction steps and workup procedures were modified to allow the use of automated equipment including a synthesizer, a multifunctional liquid handler, and a vacuum centrifuge. Using this equipment, we synthesized a 100-membered library of spirooxazolinoisoxazoline in high yield, high purity, and excellent regioselectivity.

Introduction

Small molecule combinatorial chemistry has dramatically accelerated the development of biologically interesting molecules in chemical biology and drug discovery.[1] To allow the efficient preparation of small molecule libraries, solid- or solution-phase organic synthesis[1] has been developed for use with a variety of automated equipment such as liquid handlers, and techniques, such as the fluorous-tag approach[2a] and solid-phase extraction,[2b] have been devised.

Solution-phase organic synthesis is often more suitable than solid-phase organic synthesis for the preparation of relatively small and focused libraries because (1) analysis or monitoring of reaction progress is easier, (2) reaction kinetics are more favorable under homogeneous conditions, and (3) synthetic routes can be developed more quickly. The main disadvantage of this approach is the likelihood that the products may require time-consuming purification, but fortunately several strategies have been developed to overcome this, such as "smart design" based on chemical efficiency[3] and automatic extraction and purification.[4]

The natural products and synthetic molecules that include the spirocyclic skeleton in their structures show a wide range of biological properties.[1a,5] For example, spiroisoxazoline natural products exhibiting diverse antimicrobial, cytotoxic, and anti-inflammatory activities have been identified as a new class of novel alkaloids from marine sponge (Figure 1).[6] In addition, spirooxazoline-containing molecules have been reported as potent 5-HT_3 antagonists and antimicrobial agents (Figure 1).[7]

Because of their broad-spectrum biological activities, the spirocyclic cores have been considered privileged scaffolds for drug design.[1a] Not surprisingly, many spirooxazolines or spiroisoxazolines synthesis have been extensively studied.[8] Our research interests include the design and synthesis of heterocyclic small molecule libraries via a solid- or solution-phase combinatorial approach,[9,10] and in a previous paper, we reported the development of a novel solution-phase synthetic route for the preparation of spiroisoxazolinohydantions **3**, by construction of a hydantoin ring, followed by formation of an isoxazoline ring (Scheme 1).[9a]

To the best of our knowledge, however, direct combination of the oxazoline and isoxazoline moieties to efficiently generate a spirocyclic skeleton has not been reported. Herein, we report an efficient solution-phase parallel synthetic method (steps i−iv) under mild reaction conditions for

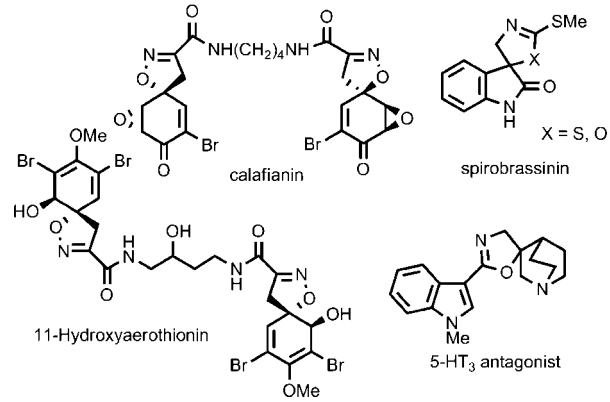
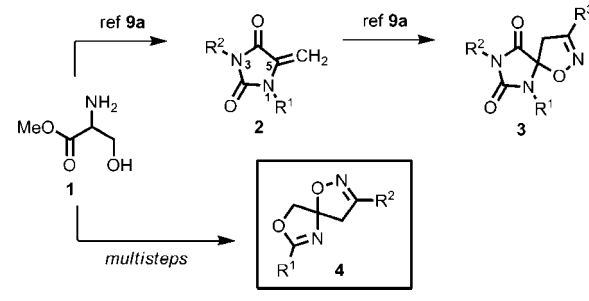


Figure 1. Examples of bioactive molecules containing spirooxazoline or spiroisoxazoline scaffolds.

Scheme 1. General Synthetic Route for the Preparation Spiromolecules **3** and **4**



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Scheme 2. Acylation and Elimination to Prepare Alkene **8**{4}

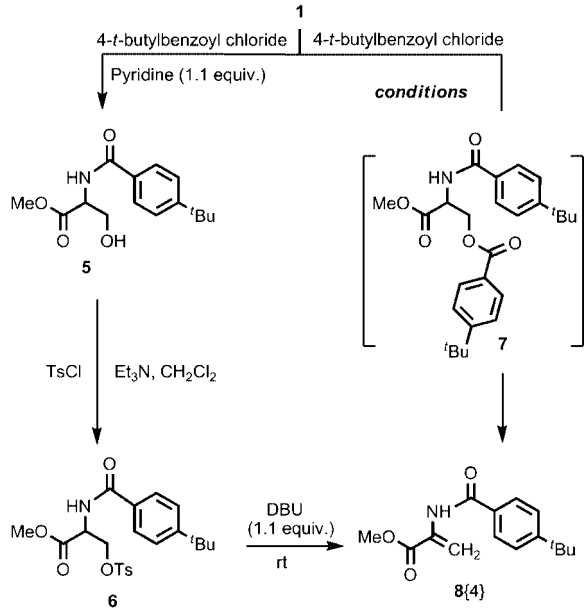


Table 1. Optimization of Conditions for the Preparation of α,β-Unsaturated Ester **8**{*4*}

entry	conditions (base/solvent/temp/time)	yield (%) of **8**{*4*}[a]
1	Et_3N (10 equiv)/CH_2Cl_2/rt/6 h	72
2	imidazole (10 equiv)/CH_2Cl_2/rt/ 3 h	21
3	imidazole (10 equiv)/CH_2Cl_2/reflux/ 3 h	65
4	Et_3N (10 equiv)/CH_2Cl_2/reflux/ 6 h	89
5	imidazole (2.2 equiv)/CH_2Cl_2/rt/3 h then DBU (1.1 equiv)/CH_2Cl_2/50 °C/1 h	93[b]

[a] Isolated yield by silica-gel column chromatography. [b] Removal of CH_2Cl_2 and then extraction with EtOAc, HCl (1 N), H_2O, saturated $NaHCO_3$ solution, saturated NaCl solution.

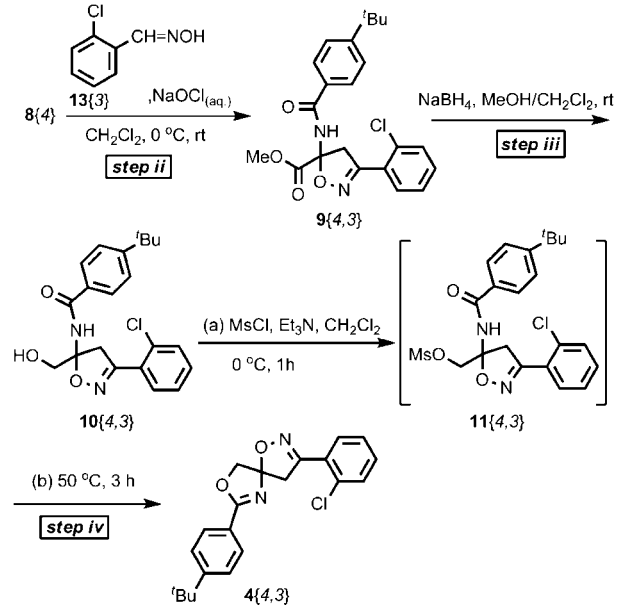
combining these two interesting structural features within a single framework to form spirooxazolinoisoxazolines **4**{*1*−*10*,*1*−*10*} with two points of substitution diversity (R^1 and R^2 in **4**, see in Scheme 1). Judicious use of an automated liquid handler, solution-phase synthesizer, and evaporator accelerated the preparation process of our small molecule library.[11,12]

Results and Discussion

Preliminary Model Studies. Treatment of commercially available DL-serine methyl ester **1** with 4-*t*-butylbenzoyl chloride (1.1 equiv) in the presence of pyridine gave **5** in an 80% yield (Scheme 2). Subsequent tosylation (TsCl) of alcohol **5** using Et_3N as the base gave **6** (81%) without observation of the elimination product **8**{*4*}. Treatment of **6** with DBU at room temperature smoothly delivered the elimination product **8**{*4*} (79%).

Various reaction conditions were examined (Table 1) in the hope that a one-pot preparation of **8**{*4*} from **1** could be accomplished by treatment of **1** with 4-*t*-butylbenzoyl chloride (2.2 equiv) under basic conditions to give the diacylated intermediate **7**, followed by β-elimination to afford α,β-unsaturated ester **8**{*4*}.[9a,13] Using imidazole as the base and maintaining the reaction mixture at room temperature, we could obtain the major product **7** and only small amount of **8** (21%) (entry 2). Increasing the reaction temperature from 25 to 50 °C improved the yield of **8**{*4*} to 65%. However, by stirring the reaction with two bases, first imidazole (2.2 equiv) at room temperature for 3 h, followed by DBU (1.1 equiv) at 50 °C for 1 h, we obtained α,β-unsaturated **8**{*4*} in good yield (93%). This procedure also simplified extraction of the product because the imidazole could be easily removed in an aqueous wash. In contrast, use of Et_3N resulted in serious emulsification during the phase separation, which was thought likely to cause problems during automatic liquid−liquid extraction and phase separation.

Scheme 3. Model Studies for the Preparation of Spirooxazolinoisoxazoline **4**{*4*,*3*}



Direct reduction of **8**{*4*} with $NaBH_4$ resulted in polymerization, hence the 1,3-dipolar cycloaddition[14] was performed first. Treatment of the alkene **8**{*4*} with 2-chlorobenzaldehyde oxime **12**{*3*} in the presence of NaOCl gave isoxazoline **9**{*4*,*3*} as a single diasteroisomer in excellent yield (98%) (Scheme 3).[15] Reduction of **9**{*4*,*3*} using $NaBH_4$ in a mixture of CH_2Cl_2 and MeOH gave the primary alcohol **10**{*4*,*3*} in 92% yield. Mesylation of **10**{*4*,*3*} to give **11**{*4*,*3*} followed by in situ intramolecular cyclization (oxazoline ring formation)[16] delivered the first model product, spirooxazolinoisoxazoline **4**{*4*,*3*}, in a yield of 88% over two steps. In ^1H NMR spectrum of **4**{*4*,*3*}, the chemical shifts of the methylene protons in the ozaxoline ring were 3.72 and 3.81 ppm, and the geminal coupling constant was 10 Hz. For the corresponding protons in the isoxazoline ring, the chemical shifts were 4.50 and 4.82 ppm and the coupling constant was 17 Hz.

Library Synthesis. With the successful model studies and reaction conditions in hand, a solution-based methodology to efficiently generate our spirooxazolinoisoxazoline library was pursued. Ten acyl chlorides **12**{*1*−*10*} (Figure 2) and ten oximes **13**{*1*−*10*} (Figure 3) were chosen for substituent diversity (Scheme 4).

The reaction vessel chosen was a 16 × 150 mm test tube because of its compatibility with our synthesizer, liquid-handler (dispensation, retraction, and aspiration), and evapo-

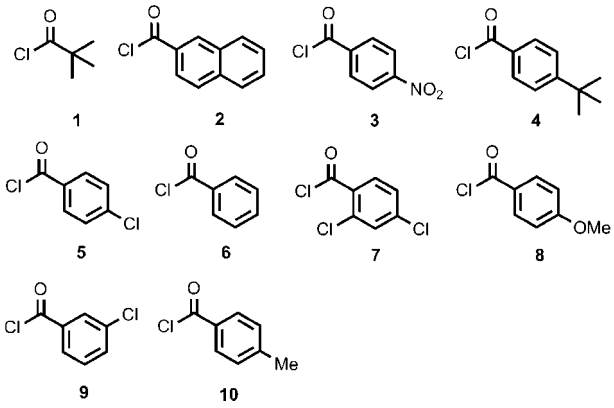


Figure 2. Set of acyl chlorides **12**{*1*−*10*} for the library.

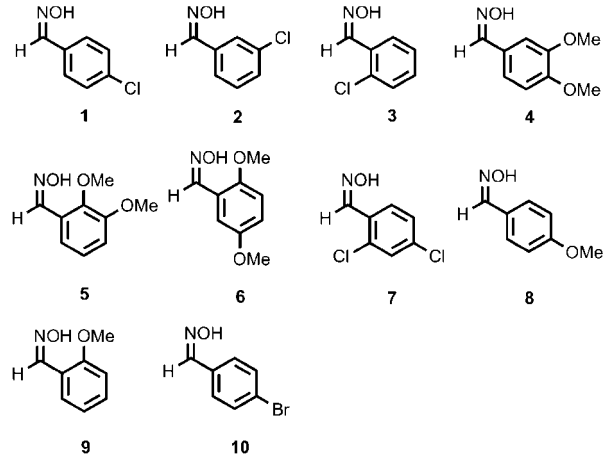
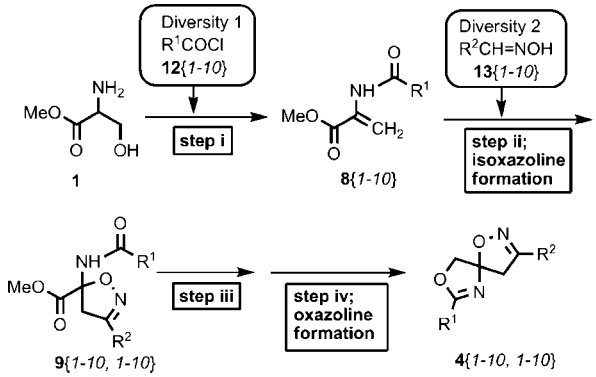


Figure 3. Set of oximes **13**{*1*−*10*} for the library.

Scheme 4. Solution-Phase Combinatorial Synthesis of Spirooxazolinoisoxazoline **4**{*1*−*10*,*1*−*10*}



rator.[17] It was recognized that optimization of the liquid−liquid extraction processes was crucial to the formation of high-purity products without the need for tedious chromatography[18] because addition of appropriate organic extraction solvents and aqueous washing solutions could remove impurities or water soluble reagents and therefore improve product purities. Modern automated liquid handlers[12,19] are able to detect the phase boundary of solutions by virtue of their different electric conductivities, and therefore, selective transfer or aspiration of most an organic or aqueous phase is straightforward.

Ethyl acetate (EtOAc) was chosen as our organic extracting solvent for all steps because of its capacity to dissolve all the reaction intermediates without resulting in emulsification. Reaction solvents such as CH_2Cl_2 (step i and iv) or

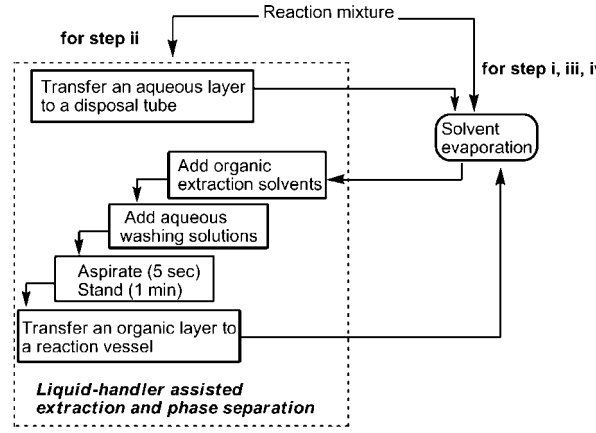


Figure 4. General workup procedure for the synthesis of spirooxazolinoisoxazolines.

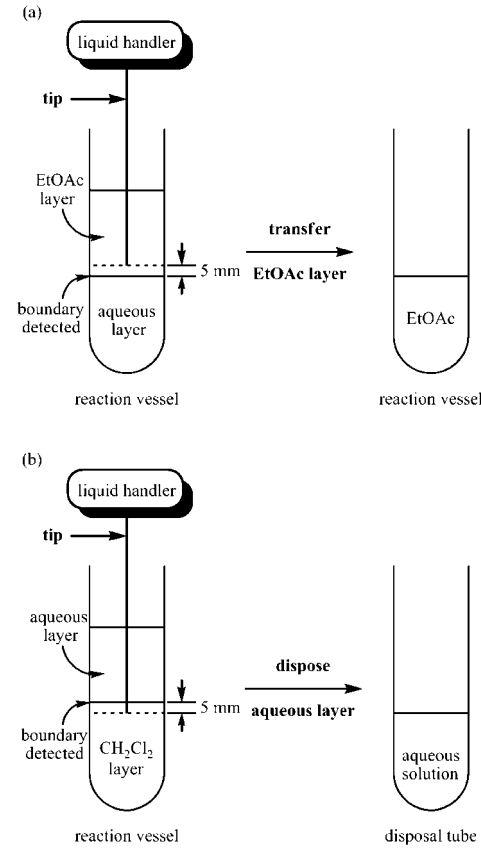


Figure 5. Operation principles for our liquid−liquid extraction.

MeOH (step iii) were removed before extraction (Figure 4). In step i, repeated extraction with ethyl acetate and aqueous $NaHCO_3$ was carried out to remove excess acids, derived from acyl chloride **12**{*1*−*10*}. After phase separation, the conductive tip could recognize the boundary of the conductive liquid (H_2O) and then retract 5 mm from the surface of aqueous phase, aspirate the organic layer, and transfer it to a clean vessel for further evaporation (Figure 5). In step ii, a biphasic reaction mixture comprising a mixture of CH_2Cl_2 and H_2O were used, and so after the reaction was complete and the layers were allowed to separate, the needle tip of the liquid handler was allowed to dip 5 mm below the boundary phase, and the aqueous solution was aspirated and transferred into another fresh reaction vessel (Figure 5). After parallel liquid−liquid extraction, products were obtained

Table 2. Yields and Purities of the Spirooxazolinoisoxazoline Library[a,b]

	$R^1 = 1$	2	3	4	5	6	7	8	9	10
$R^2 = 1$	80 (90)[c]	78 (80)	67 (99)	82 (79)	73 (79)	80 (80)	80 (79)	82 (99)	79 (99)	79 (89)
2	75 (93)	69 (95)	71 (99)	76 (94)	81 (99)	81 (82)	76 (99)	82 (80)	82 (93)	80 (80)
3	81 (80)	69 (99)	82 (82)	77 (99)	84 (99)	77 (93)	73 (99)	81 (99)	77 (99)	81 (80)
4	83 (82)	77 (89)	85 (99)	82 (99)	78 (82)	68 (84)	82 (82)	75 (99)	75 (80)	79 (81)
5	82 (93)	85 (89)	82 (99)	80 (88)	74 (99)	77 (99)	79 (99)	77 (93)	77 (99)	76 (92)
6	81 (89)	69 (92)	80 (88)	75 (81)	86 (99)	80 (99)	77 (99)	70 (99)	76 (99)	84 (94)
7	78 (99)	65 (91)	80 (99)	77 (99)	77 (88)	87 (99)	78 (89)	83 (99)	74 (92)	76 (92)
8	79 (99)	75 (79)	87 (92)	83 (80)	76 (91)	85 (86)	72 (90)	80 (87)	82 (85)	90 (73)
9	84 (99)	65 (95)	78 (82)	69 (99)	81 (92)	84 (79)	72 (92)	80 (81)	74 (93)	83 (88)
10	73 (87)	81 (88)	66 (87)	75 (95)	80 (80)	77 (95)	85 (84)	85 (94)	85 (91)	79 (81)

[a] Crude yields after overall synthesis. [b] Average purity determined by HPLC and mass (ESI) analysis of the crude material at 220 nm. [c] Purities shown in parentheses.

without further purification and directly submitted to the next chemical transformation.

The final library was characterized by HPLC and mass (ESI) analysis, and the purity of the crude products was found to range from 70 to 99% (see in Table 2). The average purity was 83%, and more than 80% of compounds had a purity of more than 80%.

Conclusion

A general, chromatography-free, highly automated solution-based methodology for the preparation of novel spirooxazolinoisoxazolines with two diversity positions was explored and optimized and was used to synthesize a 100-membered library. The key chemical transformations in the synthesis were a one-pot preparation of α,β-unsaturated ester **8** via diacylation and concomitant with β-elimination, 1,3-dipolar cycloaddition of isoxazoline formation, and intramolecular oxazoline formation. Equipment such as a synthesizer, multichannel liquid handler, and vacuum centrifuge allowed the automation of solution-phase chemistry and assisted in the preparation of high quality products.

Experimental Section

General Information. All the solvents and reagents were obtained commercially and used without further purification. NMR spectra (^{1}H at 400 or 600 MHz; ^{13}C at 100 or 150 MHz) were recorded on a spectrometer in $CDCl_3$ solvent at ambient temperature. ^{1}H and ^{13}C chemical shifts are given in ppm (δ) relative to tetramethylsilane ($\delta = 0.00$). Analytical HPLC spectra were recorded at 220 nm on a HITACHI L-2450 equipped with photodiode array detector and a Mightysil column (C-18, GP 150−4.6, 5 μm) gradient eluted with 95% H_2O (0.1% TFA)/5% CH_3CN (0.1% TFA) to 5% H_2O (0.1% TFA)/95% CH_3CN (0.1% TFA) over 50 min, flow rate = 1 mL/min. Mass spectra were obtained by Bruker Daltonics BioTOF III. Parallel synthesis was performed on Buchi SynCore 96-well synthesizer and the reaction vessels (16 × 150 mm). Multiple-functional liquid handler (Freedom EVO, TECAN) was utilized for extraction and separation. Solvent evaporation was performed on Thermo Scientific Savant Explorer SpeedVac Concentrator Explorer-220. CC refers to column chromatography.

Model Study for the Synthesis of Spirooxazolinoisoxazoline 4{*4,3*}: Methyl 2-(4-tert-butylbenzamido)acrylate 8{*4*}. A mixture of DL-serine methylester (0.25 g, 1.6 mmol), 4-*t*-butylbenzoyl chloride (0.69 g, 3.5 mmol, 2.2 equiv.), and imidazole (0.24 g, 3.5 mmol, 2.2 equiv) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 30 min and then allowed to slowly warm to rt. After 3 h, DBU (0.26 g, 1.7 mmol, 1.1 equiv) was added, and the reaction was stirred at 50 °C for 1 h. The reaction was concentrated, extracted with EtOAc (10 mL), and washed successively with 1 N $HCl_{(aq)}$, water, and saturated $NaHCO_{3(aq)}$. The organic layer was dried with $MgSO_4$ and concentrated. The residue was purified by CC (25% EtOAc in hexanes) to give a white solid **8**{*4*} in 93% yield: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 9H), 3.85 (s, 3H), 5.95 (s, 1H), 6.76 (s, 1H), 7.46 (d, 2H, $J = 8.5$ Hz), 7.75 (d, 2H, $J = 8.5$ Hz), 8.50 (br, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 164.7, 155.6, 131.3, 131.0, 126.7 (×2), 125.6 (×2), 108.6, 53.0, 34.9, 31.0 (×3); HRMS calcd for $[C_{15}H_{19}NO_3 + H]^+$ 262.1438, found 262.1431.

Methyl 5-(4-*tert*-Butylbenzamido)-3-(2-chlorophenyl)-4,5-dihydro-isoxazole-5-carboxylate 9{*4,3*}. A mixture of **8**{*4*} (0.39 g, 1.5 mmol) and 2-chlorobenzaldehyde oxime (0.23 g, 1.5 mmol) was dissolved in CH_2Cl_2 (2 mL). Bleach (6% NaOCl, 10 mL) was added dropwise at 0 °C. The reaction was stirred for 2 h at 0 °C and for further 3 h at rt. After removal of the aqueous layer, the organic phase was washed with saturated $NaCl_{(aq)}$ (10 mL × 2), dried with $MgSO_4$, and concentrated. The residue was purified by CC (20% EtOAc in hexanes) to give **9**{*4,3*} (0.61 g, 1.47 mmol, 98%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 9H), 3.92 (s, 3H), 4.01 (d, 1H, $J = 17.8$ Hz), 4.34 (d, 2H, $J = 17.8$ Hz), 7.30 (t, 1H, $J = 7.6$ Hz), 7.34 (t, 1H, $J = 7.6$ Hz), 7.40 (d, 1H, $J = 8.0$ Hz), 7.43 (d, 2H, $J = 8.4$ Hz), 7.65 (s, 1H), 7.74 (d, 2H, $J = 8.4$ Hz), 7.79 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 166.7, 156.5, 155.9, 132.9, 131.2, 131.1 (×2), 130.4, 130.1, 127.8, 127.1 (×2), 125.6 (×2), 92.5, 54.0, 45.7, 34.9, 31.0 (×3); HRMS calcd for $[C_{22}H_{23}ClN_2O_4 + H]^+$ 415.1419, found 415.1425.

4-*tert*-Butyl-*N*-(3-(2-chlorophenyl)-5-(hydroxymethyl)-4,5-dihydroisoxazol-5-yl) Benzamide 10{*4,3*}. A mixture of **9**{*4,3*} (1.5 mmol) and $NaBH_4$ (0.06 g, 1.5 mmol) in the cosolvent of CH_2Cl_2 (2 mL) and MeOH (2 mL) was stirred at rt for 3 h. The mixture was concentrated, extracted with EtOAc (10 mL), and washed successively with 1N $HCl_{(aq)}$, water, and saturated $NaCl_{(aq)}$. The organic layer was concentrated to give **10**{*4,3*}(92%) as a white solid, which was used in the next step without further purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.91 (br, 1H), 3.39 (br, 1H), 3.70 (d, 1H, $J = 17.9$ Hz), 3.93 (d, 1H, $J = 11.3$ Hz), 3.99 (d, 1H, $J = 17.9$ Hz), 4.10 (d, 1H, $J = 11.3$ Hz), 7.16 (s, 1H), 7.26 (t, 1H, $J = 7.5$ Hz), 7.31 (t, 1H, $J = 7.5$ Hz), 7.37−7.70 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3,

157.8, 155.7, 132.8, 131.0 (×2), 130.8, 130.6, 130.4, 128.4, 127.0 (×2), 125.5 (×2), 96.2, 65.8, 43.5, 34.9, 31.0 (×3); HRMS calcd for $[C_{21}H_{23}ClN_2O_3 + H]^+$ 387.1470, found 387.1466.

7-(4-*tert*-Butylphenyl)-3-(2-chlorophenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*4,3*}. A mixture of **10**{*4*,*3*} (1.4 mmol) and Et_3N (0.28 g, 2.8 mmol, 2 equiv) was dissolved in CH_2Cl_2 (5 mL) at 0 °C, and methanesulfonyl chloride (0.18 g, 1.54 mmol, 1.1 equiv) was added. The reaction was stirred for 1 h (0 °C→ rt) and for a further 3 h at 50 °C. After concentration, the residue was extracted with EtOAc (10 mL), washed successively with 10% aqueous HCl, water, saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$), and concentrated. The residue was purified by CC (20% EtOAc in hexanes) to give **4**{*4*,*3*} as white solid in 96% yield: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 9H), 3.72 (d, 1H, J = 17.8 Hz), 3.80 (d, 1H, J = 17.8 Hz), 4.49 (d, 1H, J = 10.6 Hz), 4.82 (d, 1H, J = 10.6 Hz), 7.29−7.44 (m, 5H), 7.78−7.93 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 156.6, 156.1, 132.7, 131.0, 130.8, 130.6, 128.8 (×2), 128.7, 127.0, 125.4 (×2), 123.8, 109.9, 75.2, 47.8, 35.1, 31.1(×3); HRMS calcd for $[C_{21}H_{21}ClN_2O_2 + H]^+$ 369.1364, found 369.1359; purity (>99%); t_R = 25 min.

Synthesis of a Spirooxazolinoisoxazoline Library. General Procedure for the Diacylation, Followed by β-elimination (step i). Each reaction vessel in the synthesizer was charged with serine methylester (0.25 g, 1.6 mmol), imidazole (3.5 mmol, 2.2 equiv), and CH_2Cl_2 (2 mL). Acyl chloride **12** (3.5 mmol, 2.2 equiv) was added slowly at 0 °C under nitrogen. After the reaction mixture was shaken vigorously for 4 h (0 °C → rt), DBU (1.7 mmol, 1.1 equiv) was added slowly, and then the reaction was shaken at 50 °C for 1 h. After removal of the solvent using the evaporator, workup of the reaction mixture was carried out in the automated liquid−liquid extraction module. The residue was dissolved in EtOAc (10 mL), washed successively with 1 N $HCl_{(aq)}$ (10 mL × 2), water (10 mL × 2), saturated $NaHCO_{3(aq)}$ (10 mL × 3), and saturated $NaCl_{(aq)}$ (10 mL), and evaporated to give **8**, which was used in the next step without further purification.

General Procedure for the 1, 3-Dipolar Cycloaddition (step ii). A mixture of **8** and the corresponding oxime **13** (1.5 mmol) was dissolved in CH_2Cl_2 (2 mL). The reaction solution was cooled to 0 °C, and bleach (6% NaOCl, 10 mL) was added dropwise over 30 min. The resulting mixture was shaken at 0 °C for 2 h and then for a further 8 h (0 °C → rt). Workup of the reaction mixture was carried out in the automated liquid−liquid extraction module. After the aqueous phase was removed by using the liquid handler and the organic layer was concentrated by the evaporator, the reaction mixture was added with EtOAc (10 mL) as an organic solvent and washed with water (10 mL × 2), followed by evaporation to give **9**, which was used in the next step without further purification.

General Procedure for the Reduction of Methyl Ester (step iii). A mixture of **9** and $NaBH_4$ (1.5 mmol) was dissolved in the cosolvent of CH_2Cl_2 (2 mL) and MeOH (2 mL) at 0 °C. The reaction mixture was shaken for 3 h (0 °C → rt), and the solvent was removed by the evaporator. Workup of the reaction mixture was carried out in the automated liquid−liquid extraction module. The residue was dissolved in EtOAc (10 mL), washed successively with 1 N $HCl_{(aq)}$ (10 mL × 2), water (10 mL × 2), saturated $NaHCO_{3(aq)}$ (10 mL × 3), and saturated $NaCl_{(aq)}$ (10 mL), and evaporated to give **10**, which was used in the next step without further purification.

General Procedure for the Mesylation and In Situ Cyclization (step iv). A mixture of **10** and Et_3N (2 mmol) was dissolved in CH_2Cl_2 (2 mL) and methanesulfonyl chloride (1.7 mmol) was added slowly at 0 °C. The reaction mixture was shaken for 1 h (0 °C → rt) and for further 3 h at 50 °C. After removal of the solvent using the evaporator, workup of the reaction mixture was carried out in the automated liquid−liquid extraction module. The residue was dissolved in EtOAc (10 mL), washed successively with 1N $HCl_{(aq)}$ (10 mL × 2), water (10 mL × 2), saturated $NaHCO_{3(aq)}$ (10 mL × 3), and saturated $NaCl_{(aq)}$ (10 mL), and evaporated to give **4**.

3-(4-Chlorophenyl)-7-(naphthalen-1-yl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*2,1*}: yield = 77.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (d, 1H, J = 17 Hz), 3.78 (d, 1H, J = 17 Hz), 4.53 (d, 1H, J = 10 Hz), 4.85 (d, 1H, J = 10 Hz), 7.24−8.18 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 136.3, 133.6, 133.1 (×2), 131.1 130.0, 129.0 (×2), 128.5, 127.9, 127.7 (×2), 126.3 (×2), 124.5, 123.1 (×2), 109.8, 73.95, 45.46; HRMS calcd for $[C_{21}H_{15}ClN_2O_2 + H]^+$ 363.0900, found 363.0906; purity 79.8%, t_R = 31 min.

3-(3-Chlorophenyl)-7-(naphthalen-1-yl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*2,2*}: yield = 69.4%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.16 (d, 1H, J = 18 Hz), 3.49 (d, 1H, J = 18 Hz), 4.58 (d, 1H, J = 11 Hz), 4.65 (d, 1H, J = 11 Hz), 7.29−8.87 (m, 11H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 155.0, 134.8, 133.8, 131.4, 131.3, 130.5, 130.1, 130.0, 128.5, 127.9, 126.4, 126.3 (× 2), 126.2 (× 2), 125.6, 124.4, 97.4, 67.0, 42.2; HRMS calcd for $[C_{21}H_{15}ClN_2O_2 + H]^+$ 363.0900, found 363.0915; purity 94.5%, t_R = 25 min.

3-(3,4-Dimethoxyphenyl)-7-(4-nitrophenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*3,4*}: yield = 84.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (d, 1H, J = 17 Hz), 3.70 (d, 1H, J = 17 Hz), 3.90 (s, 6H), 4.57 (d, 1H, J = 10 Hz), 4.86 (d, 1H, J = 10 Hz), 6.83−8.27 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 157.7, 151.9, 150.3, 149.1, 132.5, 129.9 (×2), 123.5 (×2), 121.5, 120.5, 110.5, 108.8 (×2), 75.2, 56.0, 55.9, 45.7; HRMS calcd for $[C_{19}H_{17}N_3O_6 + H]^+$ 384.1196, found 384.1198; purity >99%, t_R = 25 min.

7-(4-*tert*-Butylphenyl)-3-(2-chlorophenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*4,3*}: yield = 76.5%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 9H), 3.72 (d, 1H, J = 18 Hz), 3.80 (d, 1H, J = 18 Hz), 4.49 (d, 1H, J = 11 Hz), 4.82 (d, 1H, J = 11 Hz), 7.29−7.44 (m, 5H), 7.78−7.93 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 156.6, 156.1, 132.7, 131.0, 130.8, 130.6, 128.8 (×2), 128.7, 127.0, 125.4 (×2), 123.8, 109.9, 75.2, 47.8, 35.1, 31.1 (×3); HRMS calcd for $[C_{21}H_{21}ClN_2O_2 + H]^+$ 369.1364, found 369.1359; purity >99%, t_R = 25 min.

3-(3-Chlorophenyl)-7-(4-chlorophenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*5,2*}: yield = 81.4%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43 (d, 1H, J = 18 Hz), 3.67 (d, 1H, J = 18 Hz), 4.51 (d, 1H, J = 12 Hz), 4.82 (d, 1H, J = 12 Hz), 7.24−7.93 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 155.8, 138.9, 134.8, 130.9, 130.4 (× 2), 130.3, 130.1, 128.9 (× 2), 126.8, 125.1, 124.8, 109.4, 75.1, 45.2; HRMS calcd for $[C_{17}H_{12}Cl_2N_2O_2 + H]^+$ 347.0354, found 347.0377; purity >99%, t_R = 30 min.

3-(2-Chlorophenyl)-7-(4-chlorophenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*5,3*}: Yield = 83.6%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.73 (d, 1H, J = 18 Hz), 3.80 (d, 1H, J = 18 Hz), 4.51 (d, 1H, J = 11 Hz), 4.83 (d, 1H, J = 11 Hz), 7.29−7.95 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 157.7, 138.7, 132.7, 131.1, 130.7, 130.6, 130.3 (×2), 128.8 (×2), 128.5, 127.1, 125.1, 109.7, 75.1, 47.7; HRMS calcd for $[C_{17}H_{12}Cl_2N_2O_2 + H]^+$ 347.0349, found 347.0378; purity >99%, t_R = 29 min.

7-(4-Chlorophenyl)-3-(2,5-dimethoxyphenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*5,6*}: yield = 85.7%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.60 (d, 1H, J = 18 Hz), 3.75−3.80 (m, 7H), 4.48 (d, 1H, J = 12 Hz), 4.78 (d, 1H, J = 12 Hz), 6.83−7.93 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 165.2, 153.4, 151.8, 138.5, 131.1, 130.2, 128.7 (×2), 125.3, 118.6, 118.2, 112.8, 112.8, 109.0, 75.1, 56.0, 55.7, 48.0; HRMS calcd for $[C_{19}H_{17}ClN_2O_4 + H]^+$ 373.0955, found 373.0943; purity >99%, t_R = 30 min.

7-(4-Chlorophenyl)-3-(2,4-dichlorophenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*5,7*}: yield = 77.1%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.70 (d, 1H, J = 18 Hz), 3.77 (d, 1H, J = 18 Hz), 4.51 (d, 1H, J = 12 Hz), 4.82 (d, 1H, J = 12 Hz), 7.24−7.96 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 155.7, 138.8, 136.5, 133.2, 131.4, 131.1, 130.4, 130.2, 128.8 (×2), 127.5, 127.0, 125.0, 109.8, 74.9, 47.4; HRMS calcd for $[C_{17}H_{11}Cl_3N_2O_2 + H]^+$ 380.9964, found 380.9973; purity 88.1%, t_R = 31 min.

3-(2,4-Dichlorophenyl)-7-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*6,7*}: yield = 86.7%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.68 (d, 1H, J = 18 Hz), 3.73 (d, 1H, J = 18 Hz), 4.50 (d, 1H, J = 12 Hz), 4.82 (d, 1H, J = 12 Hz), 7.24−7.99 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 155.7, 136.5, 133.3, 132.4, 131.5, 130.4, 128.9 (×2), 128.4 (×2), 127.5, 127.1, 126.5, 109.9. 74.9, 47.4; HRMS calcd for $[C_{17}H_{12}Cl_2N_2O_2 + H]^+$ 347.0349, found 347.0332; purity >99%, t_R = 33 min.

3-(2-Methoxyphenyl)-7-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*6,9*}: yield = 83.6%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.85 (d, 1H, J = 18 Hz), 4.07 (d, 1H, J = 18 Hz), 4.11 (d, 1H, J = 12 Hz), 4.20 (d, 1H, J = 12 Hz), 6.88−7.77 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 157.5, 133.3, 132.5, 132.0, 131.9, 131.5, 129.3, 128.5, 128.4, 127.0, 120.7, 117.4, 111.3, 94.9, 55.4, 46.2, 46.0; HRMS calcd for $[C_{18}H_{16}N_2O_3 + Na]^+$ 331.1053, found 331.1061; purity 79.4%, t_R = 31 min.

7-(2,4-Dichlorophenyl)-3-(2-methoxyphenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*7,8*}: yield = 71.5%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.45 (d, 1H, J = 18 Hz), 3.70 (d, 1H, J = 18 Hz), 3.82 (s, 3H), 4.51 (d, 1H, J = 12 Hz), 4.80 (d, 1H, J = 12 Hz), 6.89−7.83 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 161.2, 156.4, 138.0, 134.7, 132.8, 130.7, 128.2, 127.9, 127.0, 124.8, 121.5, 114.1 (×2), 108.4, 74.9, 55.3, 45.8; HRMS calcd for $[C_{18}H_{14}Cl_2N_2O_3 + H]^+$ 378.0381, found 378.0350; purity 90.1%, t_R = 24 min.

7-(2,4-Dichlorophenyl)-3-(4-methoxyphenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*7,9*}: yield = 72.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.67 (d, 1H, J = 18 Hz), 3.77 (d, 1H, J = 18 Hz), 3.82 (s, 3H), 4.47 (d, 1H, J = 12 Hz), 4.79 (d, 1H, J = 12 Hz), 6.88−7.94 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 162.9, 155.5, 136.3, 133.2, 131.3 (×2), 130.7 (×2), 130.2, 127.3, 127.1, 118.6, 113.7, 109.8, 74.9, 55.3, 47.2; HRMS calcd for $[C_{18}H_{14}Cl_2N_2O_3 + H]^+$ 377.0454, found 377.0421; purity 92.3%, t_R = 28 min.

3,7-Bis(4-methoxyphenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*8,8*}: yield = 79.8%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.58 (d, 1H, J = 18 Hz), 3.80 (d, 1H, J = 18 Hz), 3.81 (s, 3H), 3.87 (s, 3H), 4.54 (d, 1H, J = 12 Hz), 4.76 (d, 1H, J = 12 Hz), 6.88−7.95 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 162.9, 157.4, 156.2, 131.5, 130.9 (×4), 129.4 (×2), 120.9, 118.4, 113.8, 111.3, 108.8, 75.4, 55.4, 48.1; HRMS calcd for $[C_{19}H_{18}N_2O_4 + Na]^+$ 361.1159, found 361.1173; purity 86.8%, t_R = 26 min.

3-(2-Methoxyphenyl)-7-(4-methoxyphenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*8,9*}: yield = 80.4%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.59 (d, 1H, J = 18 Hz), 3.79−3.87 (m, 7H), 4.44 (d, 1H, J = 12 Hz), 4.76 (d, 1H, J = 12 Hz), 6.88−7.95 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 162.9, 157.4, 156.1, 131.4, 130.8 (×2), 129.3, 120.8, 118.4, 113.7 (×2), 111.3, 108.8, 75.4, 55.4, 55.3, 48.0, 36.5; HRMS calcd for $[C_{19}H_{18}N_2O_4 + H]^+$ 339.1345, found 339.1369; purity 80.9%, t_R = 31 min.

3,7-Bis(3-chlorophenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*9,2*}: yield = 82.1%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.86 (d, 1H, J = 18 Hz), 4.05 (d, 1H, J = 12 Hz), 4.10 (d, 1H, J = 18 Hz), 4.16 (d, 1H, J = 12 Hz), 6.82−7.76 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 156.9, 136.8, 133.6, 133.2, 132.4, 131.5, 130.4, 128.9, 128.7 (×2), 127.5, 127.0 (×2), 95.5, 46.5, 45.2; HRMS calcd for $[C_{17}H_{12}Cl_2N_2O_2 + H]^+$ 347.0349, found 347.0354; purity 93.3%, t_R = 28 min.

7-(3-Chlorophenyl)-3-(3,4-dimethoxyphenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*9,4*}: yield = 74.9%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.60 (d, 1H, J = 18 Hz), 3.78 (d, 1H, J = 18 Hz), 3.84 (s, 3H), 3.86 (s, 3H), 4.50 (d, 1H, J = 12 Hz), 4.80 (d, 1H, J = 12 Hz), 6.95−8.00 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 155.9, 153.0, 147.6, 134.5, 132.3, 129.7, 129.0, 128.5, 127.0, 124.3, 123.5, 120.7, 114.1, 108.9, 75.3,61.1, 55.8, 47.7; HRMS calcd for $[C_{19}H_{17}ClN_2O_4 + H]^+$ 373.0955, found 373.0981; purity 80.2%, t_R = 34 min.

7-(3-Chlorophenyl)-3-(4-methoxyphenyl)-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*9,8*}: yield = 81.8%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.44 (d, 1H, J = 18 Hz), 3.68 (d, 1H, J = 18 Hz), 3.83 (s, 3H), 4.51 (d, 1H, J = 12 Hz), 4.81 (d, 1H, J = 12 Hz), 6.89−8.00 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 161.2, 156.4, 134.5, 132.3, 129.7, 129.3, 128.9, 128.3, 128.2, 126.9, 121.5, 114.1, 111.2, 108.6, 75.2, 55.4, 45.7; HRMS calcd for $[C_{18}H_{15}ClN_2O_3 + H]^+$ 343.0844, found 343.0858; purity 84.9%, t_R = 30 min.

3-(2,3-Dimethoxyphenyl)-7-*p*-tolyl-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*10*,*5*}: yield = 75.6%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.60 (d, 1H, J = 18 Hz), 3.80 (d, 1H, J = 18 Hz), 3.78−3.88 (m, 6H), 4.47 (d, 1H, J = 12 Hz), 4.79 (d, 1H, J = 12 Hz), 6.94−7.91 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 155.7, 152.9, 147.5, 142.9, 129.0 (×2), 128.8 (×2), 124.1, 123.8, 123.6, 120.6, 113.9, 109.0, 75.2, 61.0, 55.7, 47.6, 21.5; HRMS calcd for $[C_{20}H_{20}N_2O_4 + H]^+$ 353.1496, found 353.1484; purity 92.4%, t_R = 27 min.

3-(2,5-Dimethoxyphenyl)-7-*p*-tolyl-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*10*,*6*}: yield = 84.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.59 (d, 1H, J = 18 Hz), 3.74−3.81 (m, 7H), 4.45 (d, 1H, J = 12 Hz), 4.77 (d, 1H, J = 12 Hz), 6.82−7.89 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 156.1, 153.4, 151.8, 142.8, 129.0 (×2), 128.8 (×2), 123.8, 118.6, 118.0, 112.8, 112.8, 109.0, 75.1, 55.9, 55.7, 48.0, 21.5; HRMS calcd for $[C_{20}H_{20}N_2O_4 + H]^+$ 353.1496, found 353.1480; purity 93.6%, t_R = 28 min.

3-(2,4-Dichlorophenyl)-7-*p*-tolyl-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*10*,*7*}: yield = 76.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.53 (d, 1H, J = 18 Hz), 3.63 (d, 1H, J = 18 Hz), 4.34 (d, 1H, J = 12 Hz), 4.65 (d, 1H, J = 12 Hz). 7.06−7.73 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 155.6, 143.1, 136.3, 133.2, 131.4, 130.3, 129.2 (×2), 129.1, 128.8, 127.4, 127.1, 123.5, 109.7, 74.8, 47.3, 21.6; HRMS calcd for $[C_{18}H_{14}Cl_2N_2O_2 + H]^+$ 361.0505, found 361.0481; purity 91.7%, t_R = 25 min.

3-(2-Methoxyphenyl)-7-*p*-tolyl-1,8-dioxa-2,6-diazaspiro[4.4]nona-2,6-diene 4{*10*,*9*}: yield = 82.7%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.59 (d, 1H, J = 18 Hz), 3.78−3.81 (m, 4H), 4.44 (d, 1H, J = 12 Hz), 4.75 (d, 1H, J = 12 Hz), 6.88−7.89 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 157.3, 156.0, 142.7, 131.3, 129.1 (×2), 128.9, 128.7 (×2), 123.8, 120.6, 118.2, 111.2, 108.8, 75.0, 55.2, 48.0, 21.4; HRMS calcd for $[C_{19}H_{18}N_2O_3 + H]^+$ 323.1390, found 323.1349; purity 88.4%, t_R = 24 min.

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Supporting Information Available. Copies of ^{1}H and ^{13}C NMR spectra for 20 representative library members and characterization for this library. This material is available free of charge via the Internet at http://pubs.acs.org.

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