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A Convenient Access to Variously Substituted Spiro[cyclopropane-1,4′-oxazoline]s[‡]

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Michael additions of carboxamides **2a**–**d** under basic conditions onto methyl 2-chloro-2-cyclopropylideneacetate (**1**) with subsequent ring closure furnished the 4-spirocyclopropanated methyl oxazolinecarboxylates **3a**–**d** (51–81 % yields), from which the corresponding free carboxylic acids **4a**–**d** were obtained by hydrolysis in excellent yield (89–93 %). Coupling reactions of **4a**–**d** with different *o*-hydroxyaniline derivatives in the presence of HOAt/EDC and 2,4,6-collidine gave the anilides **5** in good to very good yields (55–92 %). The latter under Mitsunobu reaction conditions (Ph_3P/DEAD) furnished the benzoxazole derivatives **6** (81–88 %). The bromine substituent in the *N*-methylated 4-spirocyclopropanated 2-(bromophenyl)oxazoline-5-carboxanilides **8c**,**d** were aminated with various secondary amines under Buchwald–Hartwig reaction conditions to give the 2-(aminophenyl)-oxazolinecarboxanilides **9** (12–90 %). Suzuki cross-couplings of **8c** with arene- and hetareneboronic acids provided the oxazolines with 2-biaryl substituents **10**–**13** (65–90 %).

Introduction

As has recently been demonstrated, the highly electrophilic Michael acceptor methyl 2-chloro-2-cyclopropylideneacetate (**1**)[1–3] in the presence of sodium hydride undergoes addition of arenecarboxamides with subsequent intramolecular nucleophilic substitution of the chlorine atom to yield methyl 2′-arylspiro[cyclopropane-1,4′-oxazoline]-5′-carboxylates **3**.[4] The latter essentially are protected cyclic derivatives of β-(*N*-acylamino)-α-hydroxycarboxylic acids and have been employed as such to prepare various analogues of Taxol (**4**);[5,6] yet in more general terms they can be regarded as mimics of aryl-substituted hetarenes. Since a large number of biologically active compounds are composites of heterocycles including oxazolines[7] and heterosubstitued arenes, we set out to develop a set of methods to further diversify the 4-spirocyclopropanated 2-aryloxazolinecarboxylates **3** in order to make a library of potentially biologically active derivatives accessible, since one such compound had previously exhibited an interesting insecticidal activity. The fact that a spirocyclopropanated analogue of Imidacloprid® is virtually as potent an insecticide as the commercial Imidacloprid itself,[8] made this a reasonable endeavor.

Results and Discussion

By employing the previously published procedure,[4] methyl 2-chloro-2-cyclopropylideneacetate (**1**)[1,2] in acetonitrile upon reaction with benzamide (**2a**) in the presence of sodium hydride gave methyl 2′-phenylspiro[cyclopropane-1,4′-oxazoline]-5-carboxylate (**3a**) in 54% isolated yield after column chromatography. Analogously, 4-(trifluoromethyl)- as well as 4-bromo- and 3-bromobenzamide (**2b**–**d**) furnished the corresponding oxazolinecarboxylates **3b**–**d** in yields ranging from 51 to 81% (Scheme 1 and Table 1). The bromobenzamides **2c**,**d** were specifically chosen in order to provide an opportunity for further derivatization of the products **3c** and **3d** by cross-coupling reactions. The hydrolyses of the esters **3a**–**d** to the corresponding oxazolinecarboxylic acids **4a**–**d** were brought about more efficiently than previously reported by treatment with 1 N aqueous sodium hydroxide in methanol/tetrahydrofuran (4:1). Thus, the free carboxylic acids were isolated after purification by column chromatography in 89–93% yield.

With the 5-(benzoxazolyl)oxazoline derivatives as targets in mind, conversion of the oxazolinecarboxylic acids to the corresponding amides with substituted *o*-hydroxyanilines were intended. First attempts were made with the 3′-phenylspiro[cyclopropane-1,4′-oxazoline]-5′-carboxylic acid (**4a**) and 5-chloro-2-hydroxyaniline by employing dicyclohexyl-

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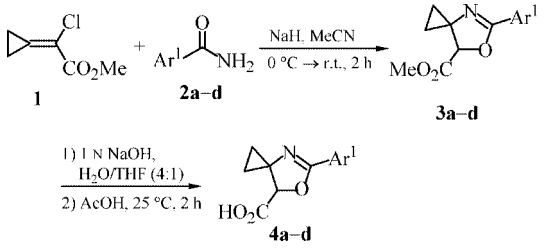
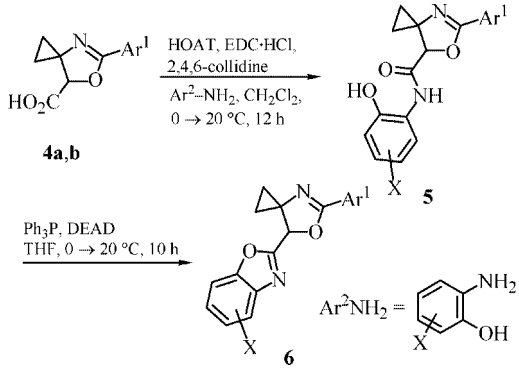


Scheme 1. 2′-Arylspiro[cyclopropane-1,4′-oxazoline]carboxylic acids **4a–d** from arenecarboxamides and methyl 2-chloro-2-cyclopropylideneacetate (**1**). For details see Table 1.

Table 1. Methyl 2′-arylspiro[cyclopropane-1,4′-oxazoline]-5′-carboxylates **3a–d** and the corresponding oxazolinecarboxylic acids **4a–d** from **1** (see Scheme 1).

Amide	Ar^1	Product	Yield (%)	Product	Yield (%)
2a	Ph	**3a**	54	**4a**	89
2b	4-$F_3CC_6H_4$	**3b**	81	**4b**	93
2c	4-BrC_6H_4	**3c**	51	**4c**	91
2d	3-BrC_6H_4	**3d**	64	**4d**	90

carbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in dichloromethane. However, after 18 h at 20 °C, the unchanged starting materials were completely recovered, and the same result was achieved with DCC and 1-hydroxybenzotriazole (HOBT) in dichloromethane.[9] An attempted conversion of the carboxylic acid **4a** to the acyl chloride by treatment with thionyl chloride and subsequent reaction with the aniline led to complete decomposition of the starting material **4a**. Eventually, the amide coupling succeeded in the presence of 1-hydroxy-7-azabenzotriazole (HOAt), *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC) and 2,4,6-collidine to furnish the oxazolinecarboxanilide **5aa** in 92% yield. Under these conditions, the reactions of the 2-[4-(trifluoromethyl)phenyl]oxazolinecarboxylic acid **4b** with different mono- and disubstituted *o*-hydroxyanilines gave the corresponding anilides **5ba**, **5bb**, **5bc**, **5bd** in 55–85% yield (Scheme 2, Table 2).



Scheme 2. Amide coupling of oxazolinecarboxylic acids **4a**,**b** with *o*-hydroxyanilines followed by dehydrative cyclization to yield 5-(benzoxazolyl)oxazoline derivatives **6**. For details see Table 2.

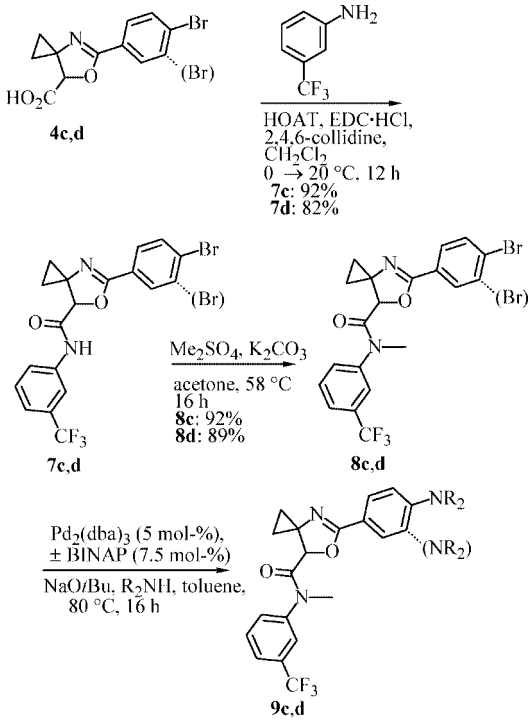
Table 2. Amide coupling of oxazolinecarboxylic acids **4a**,**b** with *o*-hydroxyanilines and dehydrative cyclization of the products to 5-(benzoxazolyl)oxazoline derivatives **6** (see Scheme 2).

4	Ar^1	X in Ar^2NH_2	Product	Yield (%)	Product	Yield (%)
4a	Ph	5-Cl	**5aa**	92	**6aa**	83
4b	4-$F_3CC_6H_4$	5-Cl	**5ba**	85	**6ba**	85
4b	4-$F_3CC_6H_4$	5-F_3CO	**5bb**	55	**6bb**	81
4b	4-$F_3CC_6H_4$	3,5-Cl_2	**5bc**	79	**6bc**	88
4b	4-$F_3CC_6H_4$	5-F_3C	**5bd**	78	**6bd**	81

An attempted dehydrative cyclization of **5aa** with phosphorus pentoxide in carbon tetrachloride at 80 °C also left the starting material unchanged, and with pyridinium *p*-toluenesulfonate (PPTs) in dichloroethane after 12 h at 85 °C only a small amount (12%) of the product **6aa** was isolated. The desired product **6aa** was also not observed when the same reaction was carried out in toluene by employing a Dean–Stark trap. Finally, under Mitsunobu conditions[10] (Ph_3P, DEAD), the product **6aa** was formed from **5aa** in 83% isolable yield. Analogously, the other anilides **5** were converted into the corresponding (benzoxazolyl)-oxazolines **6ba**, **6bb**, **6bc**, **6bd** in 81–88% yield (Scheme 2, Table 2).

The spiro[cyclopropane-1,4′-oxazoline]-5′-carboxylic acids **4c**,**d** were further diversified with heteroatom-containing substituents by conversion to 3-(trifluoromethyl)anilides **7c**,**d** under the same conditions as employed for **4a**,**b**, subsequent *N*-methylation with dimethyl sulfate and final Buchwald–Hartwig amination[11,12] of the *N*-methylanilides **8c**,**d** with various secondary amines. An attempted amide coupling of the 4-bromophenyl derivative **4c** with *N*-methyl-3-(trifluoromethyl)aniline in the presence of HOAt, EDC·HCl and 2,4,6-collidine did not give any of the desired product, but with 3-(trifluoromethyl)aniline under the same reaction conditions the anilide **7c** was obtained in 92% yield, and methylation with dimethyl sulfate in the presence of potassium carbonate furnished the desired *N*-methyl derivative **8c** as the precursor for the envisioned Pd-catalyzed aminations. Analogously, the (3-bromophenyl)oxazolinecarboxanilide **8d** was prepared in 73% overall yield. By employing well-established conditions [$Pd_2(dba)_3$, BINAP, Na*t*OBu], the cross coupling of **8c** with morpholine in toluene furnished the product **9ca** in 71% yield within 16 h. The conditions as optimized with respect to the amount of catalyst called for 2 mol-% of $Pd_2(dba)_3$ and 3 mol-% of (±)-BINAP to give best yields. The same oxazoline **9c** with pyrrolidine under these conditions gave the product **9cb** in 90% yield, but the *N*-methyl- and *N*-benzylpiperazine derivatives **9cc** and **9cd** were obtained in only 59 and 62%, respectively (Scheme 3 and Table 3).

The cross coupling of **8c** with the bicyclic secondary amine 3,3-dibenzyl-3-azabicyclo[3.1.0]hexane[13] also proceeded smoothly to afford the product **9ce** in 67% yield. The same five amines were also coupled with the 3-bromophenyl derivative **8d** to give the corresponding 2-(3-aminophenyl)oxazolinecarboxamides **9da–9de**; however, 5 mol-% of $Pd_2(dba)_3$ and 7.5 mol-% of (±)-BINAP had to be



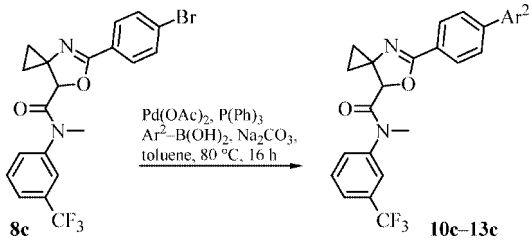
Scheme 3. *N*-Methyl-*N*-[3-(trifluoromethyl)phenyl]anilides **7c**,**d** from 2′-(bromophenyl)spiro[cyclopropane-1,4′-oxazoline]-5′-carboxylic acids **4c**,**d** and subsequent Buchwald–Hartwig amination of the bromophenyl groups in the *N*-methylanilides **8c**,**d** with various secondary amines. For details see Table 3.

Table 3. Buchwald–Hartwig aminations of the bromophenyl substituents in the *N*-methyl-*N*-[3-(trifluoromethyl)phenyl]spiro[cyclopropane-1,4′-oxazoline]-5′-carboxamides **8c**,**d** (see Scheme 3).

Starting material **8**	R_2NH	Product **9**	Yield (%)
8c	morpholine	**9ca**	71
8c	pyrrolidine	**9cb**	90
8c	*N*-methylpiperazine	**9cc**	59
8c	*N*-benzylpiperazine	**9cd**	62
8c	3,3-dibenzyl-3-azabicyclo[3.1.0]hexane	**9ce**	67
8d	morpholine	**9da**	82
8d	pyrrolidine	**9db**	73
8d	*N*-methylpiperazine	**9dc**	13
8d	*N*-benzylpiperazine	**9dd**	12
8d	3,3-dibenzyl-3-azabicyclo[3.1.0]hexane	**9de**	81

used in these cases. In spite of that, the yields of the *N*-benzyl-*N*-methylpiperazines were rather poor (13 and 12%, respectively), and the reactions did not go to completion even after 40 h (Scheme 3 and Table 3).

The possibility to further diversify the library of 2′-arylspiro[cyclopropane-1,4′-oxazoline]-5′-carboxanilides **7** by palladium-catalyzed cross coupling with areneboronic acids (Suzuki–Miyaura coupling)[14] was also tested. After several conditions had been tried, it was found that the coupling of **8c** with benzeneboronic acid required 10 mol-% of $Pd(OAc)_2$ and 40 mol-% of Ph_3P to go to completion within 16 h, and the product **10c** could be isolated in 90% yield. [*p*-(Trifluoromethoxy)phenyl]boronic acid under the same reaction conditions gave the product **11c** in 84% yield. 3-Thienyl- and 2-naphthylboronic acid also formed the products **12c** and **13c** in 65 and 85% yield, respectively (Scheme 4 and Table 4).



Scheme 4. Suzuki–Miyaura coupling of (bromophenyl)oxazolinecarboxanilide **8c**. For details see Table 4.

Table 4. 2′-Biarylspiro[cyclopropane-1,4′-oxazoline]-5′-carboxanilides **10c**–**13c** by Suzuki–Miyaura coupling of the 2-(bromophenyl)-oxazolinecarboxyamide derivative **8c** (see Scheme 4).

Starting material	Ar^2 in $Ar^2B(OH)_2$	Product	Yield (%)
8c	Ph	**10c**	90
8c	4-$F_3COC_6H_4$	**11c**	80
8c	3-thienyl	**12c**	65
8c	2-naphthyl	**13c**	85

Experimental Section

General Remarks: All reagents were used as purchased without further purification. All reactions in organic solvents were carried out by using standard Schlenk techniques under dry nitrogen. The solvents were purified and dried prior to use according to conventional methods; tetrahydrofuran (THF) and toluene were freshly distilled from sodium/benzophenone. Solvents and reagents are abbreviated as follows: CH_2Cl_2 = dichloromethane, EtOAc = ethyl acetate, MeOH = methanol, C_5H_{12} = pentane, Et_2O = diethyl ether, DEAD = diethyl azodicarboxylate, DCC = *N*,*N*′-dicyclohexylcarbodiimide, EDC = *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide, HOBt = 1-hydroxybenzotriazole, HOAt = 1-hydroxy-7-azabenzotriazole. ^1H and ^{13}C NMR spectra were recorded at ambient temperature with either Bruker AM 250 or Varian 200 or 300 MHz instruments. Chemical shifts (δ) are given in ppm relative to residual resonances of solvents (^1H: δ = 7.26 ppm for $CDCl_3$ and δ = 3.31 ppm for CD_3OD; ^{13}C: δ = 77.0 ppm for $CDCl_3$, and δ = 49.0 ppm for CD_3OD). Coupling constants (*J*) are given in Hz. Multiplicities of signals are described as follows: br. = broad, s = singlet, d = doublet, t = triplet, m = multiplet, dt = doublet of triplets. The multiplicities of signals were determined by the DEPT technique: DEPT: + = primary (CH_3) or tertiary (CH) (positive DEPT signal), – = secondary (CH_2) (negative DEPT signal), $C_{quat.}$ = quaternary C atoms. *J* values in ^{13}C NMR spectra refer to ^{13}C,^{19}F couplings. "cPr" refers to cyclopropyl. IR: Bruker IFS 66. MS: Finnigan MAT 95, 70 eV. Chromatographic separations were carried out on Merck silica gel 60 (0.063–0.200 mm, 70–230 mesh ASTM). The dimensions of the columns are given in cm as "diameter × height of the silica gel column". TLC: Macherey–Nagel, ready-to-use TLC plates Alugram® Sil G/UV_{254}. Detection under UV light at 254 nm. Melting points (uncorrected) were determind in capillaries with a Büchi 510 apparatus. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen.

General Procedure for the Preparation of Methyl 2′-Arylspiro[cyclopropane-1,4′-oxazoline]-5′-carboxylates 3 (GP1): A solution of methyl 2-chloro-2-cyclopropylideneacetate (**1**)[1,2] and the respective carboxamide (1 equiv.) in anhydrous acetonitrile was treated with 1 equiv. of NaH (60% dispersion in mineral oil) at 0 °C. The resulting suspension was subsequently stirred at this temperature for 1 h and at 20 °C for an additional 1 h. After removal of the solvent, the pale yellow residue was taken up with diethyl ether (300 mL) and the solution washed with water (100 mL). The aq. layer was extracted with diethyl ether (2 × 100 mL), and the combined organic phases were dried with $MgSO_4$. The solvents were evaporated under reduced pressure, and the crude product was purified by column chromatography.

Methyl 5-Phenyl-6-oxa-4-azaspiro[2.4]hept-4-ene-7-carboxylate (3a): The crude product obtained from **1** (2.50 g, 17.0 mmol), benzamide (**2a**, 5.20 g, 17.0 mmol) and NaH (595 mg, 17.0 mmol) in anhydrous acetonitrile (50 mL) according to GP1 was purified by column chromatography (R_f = 0.38; pentane/Et_2O, 4:1; 3 × 10 cm) to yield 2.2 g (54%) of **3a** as a colorless solid, m.p. 48 °C. IR (KBr): $\tilde{\nu}$ = 2948, 1732, 1449, 1284, 1057, 694 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.91–1.08 (m, 2 H, cPr-H), 1.18–1.27 (m, 1 H, cPr-H), 1.32–1.42 (m, 1 H, cPr-H), 3.80 (s, 3 H, CH_3), 4.93 (s, 1 H, CH), 7.39–7.54 (m, 3 H, aryl-H), 7.91–7.99 (m, 2 H, aryl-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 10.4 (–, cPr-C), 14.7 (–, cPr-C), 52.3 (+, CH_3), 53.3 (–, cPr-C), 79.7 (+, CH-C), 127.0 (–, aryl-C), 128.0 (+, 2 C, aryl-C), 128.4 (+, 2 C, aryl-C), 131.5 (+, aryl-C), 163.5 (–, CN-C), 169.5 (–, CO-C) ppm. MS (70 eV): *m*/*z* (%) = 231 (35) [M^+], 172 (100) [$M^+ - CO_2Me$], 144 (60), 105 (26).

General Procedure for the Hydrolysis of Methyl Spiro[cyclopropane-1,4′-oxazoline]carboxylates 3 (GP2): Aq. NaOH (1 N, 5 equiv.) was added to a solution of the respective methyl oxazolinecarboxylate **3** (1 equiv.) in MeOH/THF (4:1) at room temperature. The resulting solution was stirred for 30 min, then glacial AcOH (10 equiv.) was added, the mixture stirred for an additional 15 min, and the solvent evaporated in vacuo. The residue was filtered through a pad of SiO_2 gel (Et_2O/AcOH, 50:1) and the product crystallized from ether/hexane.

5-Phenyl-6-oxa-4-azaspiro[2.4]hept-4-ene-7-carboxylic Acid (4a): From **3a** (3.40 g, 14.7 mmol), NaOH (2.96 g, 74 mmol) and AcOH (8.80 g, 147 mmol) in MeOH/THF (200 mL) according to GP2 (R_f = 0.40; Et_2O/AcOH, 50:1), 5.10 g (93%) of **4a** was obtained as a colorless solid, m.p 182 °C. IR (KBr): $\tilde{\nu}$ = 3061 , 3009, 1717, 1638, 1457, 1364, 1211, 1069, 735 cm^{-1}. ^1H NMR (250 MHz, CD_3OD): δ = 0.95–1.03 (m, 1 H, cPr-H), 1.05–1.34 (m, 3 H, cPr-H), 4.99 (s, 1 H, CH), 7.40–7.59 (m, 3 H, aryl-H), 7.86–7.98 (m, 2 H, aryl-H) ppm. ^{13}C NMR (62.9 MHz, CD_3OD, DEPT): δ = 11.0 (–, cPr-C), 15.3 (–, cPr-C), 54.0 ($C_{quat.}$, cPr-C), 81.3 (+, CH-C), 128.3 ($C_{quat.}$, aryl-C), 129.3 (+, 2 C, aryl-C), 129.9 (+, 2 C, aryl-C), 133.3 (+, aryl-C), 166.2 (–, CN-C), 172.4 (–, CO-C) ppm. MS (70 eV): *m*/*z* (%) = 217 (48) [M^+], 172 (100) [$M^+ - CO_2H$], 144 (57), 104 (28).

General Procedure for the Preparation of Oxazolinecarboxanilides 5 and 7 (GP3): To an ice-cold solution of the respective oxazolinecarboxylic acid **4** (1 equiv.) and HOAt (1.2 equiv.) in anhydrous CH_2Cl_2 was added EDC·HCl (1.5 equiv.) in one portion, the mixture was stirred for 15 min, then 2,4,6-collidine (2.0 equiv.) and the respective aniline (1.3 equiv.) were added. The cooling bath was removed, and the resulting pale yellow reaction mixture was stirred at 20 °C for 12 h and filtered through a pad of silica gel. The crude product was purified by column chromatography.

***N*-(5-Chloro-2-hydroxyphenyl)-5-phenyl-6-oxa-4-azaspiro[2.4]hept-4-ene-7-carboxamide (5aa):** The crude product obtained from **4a** (185 mg, 0.85 mmol), HOAt (139 mg, 1.02 mmol), EDC·HCl (244 mg, 1.27 mmol), 2,4,6-collidine (206 mg, 1.70 mmol) and 5-chloro-2-hydroxyaniline (146 mg, 1.1 mmol) in CH_2Cl_2 (15 mL) according to GP3 was purified by column chromatography (R_f = 0.25; pentane/Et_2O, 1:1) to yield 268 mg (92%) of **5aa** as a colorless solid, m.p. 211 °C. IR (KBr): $\tilde{\nu}$ = 3381 , 3052, 1668, 1558, 1431, 1339, 1195, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.96–1.18 (m, 2 H, cPr-H), 1.34–1.50 (m, 2 H, cPr-H), 5.01 (s, 1 H, CH), 6.87–6.92 (m, 1 H, Ar-H), 7.05 (dd, ^3J = 8.2, ^4J = 2.5 Hz, 1 H, aryl-H) 7.42–7.58 (m, 3 H, aryl-H), 7.77 (s, 1 H, aryl-H), 7.96–8.00 (m, 2 H, aryl-H), 8.27 (br. s, 1 H, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.6 (–, cPr-C), 14.5 (–, cPr-C), 53.7 (–, cPr-C), 80.2 (+, CH-C), 120.1 (+, aryl-C), 121.9 (+, aryl-C), 125.5 (–, aryl-C), 126.6 (–, aryl-C), 127.0 (+, aryl-C), 127.9 (+, 2 C, aryl-C), 128.7 (+, 2 C, aryl-C), 131.9 (+, aryl-C), 146.8 (–, aryl-C), 161.5 (–, CN-C), 168.2 (–, CO-C) ppm. MS (70 eV): *m*/*z* (%) = 344/342 (6/20) [M^+], 200 (55), 173 (100), 172 (58), 105 (54). $C_{18}H_{15}ClN_2O_3$ (342.8): calcd. C 63.07, H 4.41, N 8.17; found C 63.32, H 4.18, N 8.02.

General Procedure (GP4) for the Preparation of (Benzoxazolyl)-oxazolines 6: A solution of DEAD (2.2 equiv.) was added dropwise to a solution of the respective anilide **5** (1 equiv.) and Ph_3P (2.2 equiv.) in anhydrous THF (10 mL) in an ice bath, and the mixture was stirred at 20 °C for 10 h. To the reaction mixture were added Et_2O (25 mL) and H_2O (80 mL), and the organic layer was separated. The aq. layer was extracted with Et_2O (2 × 25 mL), the combined ethereal layers were dried with $MgSO_4$ and concentrated, and the residue was purified by column chromatography to yield the corresponding benzoxazoles.

5-Chloro-2-(5-phenyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-yl)benzoxazole (6aa): The crude product obtained from **5aa** (103 mg, 0.3 mmol), Ph_3P (173 mg, 0.66 mmol) and DEAD (115 mg, 0.66 mmol) according to GP4 was purified by column chromatography (R_f = 0.35; pentane/Et_2O, 5:1) to yield 83 mg (85%) of **6aa** as a colorless solid, m.p. 129 °C. IR (KBr): $\tilde{\nu}$ = 3077 , 2971, 1653, 1569, 1427, 1335, 1293, 1078, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.54–0.63 (m, 1 H, cPr-H), 0.98–1.06 (m, 1 H, cPr-H), 1.18–1.28 (m, 1 H, cPr-H), 1.36–1.45 (m, 1 H, cPr-H), 5.70 (s, 1 H, CH), 7.28–7.39 (m, 1 H, aryl-H), 7.40–7.57 (m, 4 H, aryl-H), 7.69 (s, 1 H, aryl-H), 7.95–8.02 (m, 2 H, aryl-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.1 (–, cPr-C), 14.7 (–, cPr-C), 54.2 (–, cPr-C), 77.8 (+, CH-C), 111.9 (+, aryl-C), 120.4 (+, aryl-C), 126.1 (+, aryl-C), 126.8 (–, aryl-C), 128.1 (+, 2 C, aryl-C), 128.5 (+, 2 C, aryl-C), 130.2 (–, aryl-C), 131.6 (+, aryl-C), 141.5 (–, aryl-C), 149.5 (–, aryl-C), 163.2 (–, CN-C), 163.7 (–, CN-C) ppm. MS (70 eV): *m*/*z* (%) = 325/323 (2/8) [M^+], 172 (16), 155 (100), 105 (18), 91 (82). $C_{18}H_{13}ClN_2O_2$ (324.8): calcd. C 66.57, H 4.03, N 8.63; found C 66.58, H 3.84, N 8.55.

General Procedure (GP5) for the Buchwald–Hartwig Amination of (Bromophenyl)oxazolinecarboxanilides 8: An oven-dried Schlenk flask purged with nitrogen, was charged with $Pd_2(dba)_3$ and (±)-BINAP in toluene (5 mL). The mixture was heated at 80 °C with stirring for 5 min to dissolve the BINAP. After cooling, the respective (bromophenyl)oxazolinecarboxanilide **8** (1 equiv.), the respective secondary amine (1.5 equiv.), and NaO*t*Bu (1.5 equiv.) were added, and the mixture was heated at 80 °C for 16 h. After cooling to room temperature, it was diluted with Et_2O (25 mL), filtered, and concentrated in vacuo. The crude product was purified by column chromatography.

***N*-Methyl-5-[4-(morpholin-4-yl)phenyl]-*N*-[3-(trifluoromethyl)-phenyl]-6-oxa-4-azaspiro[2.4]hept-4-ene-7-carboxamide (9ca):** The crude product obtained from **8c** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (3.65 mg), (±)-BINAP (3.74 mg), morpholine (26.0 mg,

0.30 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) according to GP5 was purified by column chromatography (R_f = 0.25; Et_2O) to yield 65 mg (71%) of **9ca** which crystallized from Et_2O at 0 °C as a colorless solid, m.p. 159–160 °C. IR (KBr): $\tilde{\nu}$ = 3084 , 2969, 2864, 1655, 1607, 1521, 1335, 1228, 1119 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.62–0.83 (m, 1 H, cPr-H), 0.98–1.33 (m, 3 H, cPr-H), 3.02–3.20 (m, 2 H), 3.28 (s, 3 H, CH_3), 3.66–3.91 (m, 2 H), 4.97 (s, 1 H, CH), 6.62 (d, ^3J = 8.2 Hz, 2 H, aryl-H) 7.03–7.50 (m, 6 H, aryl-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.8 (–, cPr-C), 14.4 (–, cPr-C), 39.0 (+, CH_3), 48.1 (–, 2 C, CH_2-C), 53.4 (–, cPr-C), 66.6 (–, 2 C, CH_2-C), 80.8 (+, CH-C), 113.6 (+, 2 C, aryl-C), 117.0 (–, aryl-C), 123.3 (–, q, $^1J_{C–F}$ = 264 Hz, CF_3), 124.2 (+, q, $^3J_{C–F}$ = 4.3 Hz, aryl-C), 124.3 (+, q, $^3J_{C–F}$ = 3.2 Hz, aryl-C), 129.0 (+, 2 C, aryl-C), 130.1 (+, aryl-C), 131.8 (–, q, $^2J_{C–F}$ = 32.5 Hz, aryl-C), 143.2 (–, aryl-C), 153.1 (–, aryl-C), 162.4 (–, CN-C), 168.2 (–, CO-C) ppm. MS (70 eV): *m*/*z* (%) = 459 (22) [M^+], 285 (16), 257 (20), 190 (100).

General Procedure (GP6) for the Suzuki–Miyaura Coupling of (Bromophenyl)oxazolinecarboxanilide 8c: A 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (4.5 mg, 10 mol-%) and $P(Ph)_3$ (21 mg, 40 mol-%) in toluene (5 mL). The mixture was deoxygenated for 5 min by bubbling nitrogen through it. To this solution was added **8c** (90.6 mg, 0.2 mmol), the respective boronic acid (0.30 mmol) and aq. Na_2CO_3 (0.40 mmol, 2 N), and the mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature, taken up in Et_2O (25 mL), washed with water (10 mL), and the aq. layer was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography.

5-(Biphenyl-4-yl)-*N*-methyl-[3-(trifluoromethyl)phenyl]-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxamide (10c): The crude product obtained from **8c** and phenylboronic acid (36.5 mg) according to the GP6 was purified by column chromatography (R_f = 0.30; pentane/Et_2O, 1:2), to yield 81 mg (90%) of **10c** as a colorless solid, m.p. 136–137 °C. IR (KBr): $\tilde{\nu}$ = 3081 , 1660, 1643, 1334, 1128, 1067, 705 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.74–0.83 (m, 1 H, cPr-H), 1.03–1.38 (m, 3 H, cPr-H), 3.25 (s, 3 H, CH_3), 5.02 (s, 1 H, CH-H), 7.09–7.59 (m, 13 H, aryl-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.7 (–, cPr-C), 39.1 (+, CH_3), 53.7 (–, cPr-C), 81.0 (+, CH-C), 123.2 (–, q, $^1J_{C–F}$ = 262 Hz, CF_3), 124.1 (+, q, $^3J_{C–F}$ = 3.8 Hz, aryl-C), 124.4 (+, q, $^3J_{C–F}$ = 3.8 Hz, aryl-C), 125.2 (–, aryl-C), 126.6 (+, 2 C, aryl-C), 127.1 (+, 2 C, aryl-C), 127.9 (+, aryl-C), 128.1 (+, 2 C, aryl-C), 128.9 (+, 2 C, aryl-C), 130.2 (+, aryl-C), 132.0 (–, q, $^2J_{C–F}$ = 33.2 Hz, aryl-C), 140.1 (–, aryl-C), 143.2 (–, aryl-C), 143.9 (–, aryl-C), 162.2 (–, CN-C), 168.0 (–, CO-C) ppm. MS (70 eV): *m*/z (%) = 450 (92) [M^+], 276 (91), 248 (61), 181 (100). $C_{26}H_{21}F_3N_2O_2$ (450.5): calcd. C 69.33, H 4.70, N 6.22; found C 69.26, H 4.48, N 6.18.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures for and full characterization of all the new compounds **3b**–**3d**, **4b**–**4d**, **5ba**–**5bd**, **6ba**–**6bd**, **7c**, **7d**, **8d**, **9cb**–**9ce**, **9da**–**9de**, **11c**, **12c**, **13c**.

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