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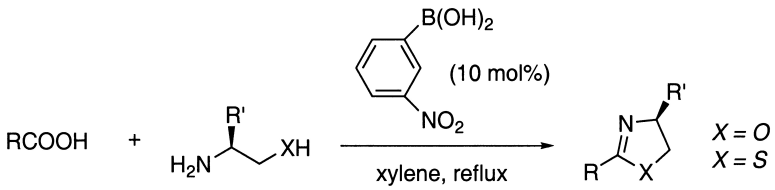

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Parallel Synthesis of Oxazolines and Thiazolines by Tandem Condensation−Cyclodehydration of Carboxylic Acids with Amino Alcohols and Aminothiols

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A combinatorial library of oxazolines and thiazolines was synthesized in moderate to excellent yields using a newly developed methodology. Free carboxylic acids were directly condensed with amino alcohols and aminothiols in the presence of 3-nitrophenylboronic acid as a dehydration catalyst. The library synthesis illustrates the scope of this process: After traditional reaction optimization, a total of 17 oxazolines and 6 thiazolines were successfully prepared in a 24-reaction setup in a Radleys GreenHouse parallel synthesizer. The yields of the parallel reactions ranged from moderate to excellent, depending largely on carboxylate reactivity and functionalization, and generally exceeded those of the traditional reaction setup. The target compounds were isolated in high purities (average purity is 96% according to GC analysis) after passing reaction mixtures through short PrepSep SPE Florisil cartridges.

Introduction

The use of oxazoline and thiazoline building blocks in pharmaceutical drug discovery is continually increasing.[1] Enantiomerically pure 2-oxazolines are also extensively used as chiral auxiliaries and as ligands in asymmetric synthesis.[2] Thiazolines are found in numerous interesting biologically active natural products such as curacin A, thiangazole, mirabazole B, and lissoclinamides.[3] In addition to the popular cyclodehydration of amido alcohols,[4] a variety of methods have been reported for the synthesis of oxazolines including condensation of imidate hydrochlorides,[5] carboxylic acids,[6] ortho esters,[7] imino ether hydrochlorides,[8] and nitriles[9] with amino alcohols. General methodologies available for synthesis of thiazolines include coupling of imidates and esters with aminothiols,[10] cyclodehydration of hydroxy thioamides,[11] and heterocycle interconversions from oxazolines[12] or oxazolidines.[13] While a method for the accelerated synthesis of oxazolines from hydroxyamides by resin capture and ring-forming release has recently been reported,[14] a rapid one-step solution-phase parallel synthesis of oxazolines and thiazolines from commercially readily available precursors has been lacking. Herein, we report a new protocol for tandem condensation−cyclodehydration of carboxylic acids and amino alcohols or aminothiols. The enabling technology for this method is the use of catalytic amounts of commercially available 3-nitrophenylboronic acid as a water carrier. Oxazolines and thiazolines were obtained in moderate to excellent yields. The utility and general scope of this convenient method for combinatorial solution-phase synthesis was demonstrated by a 6×4 library synthesis of oxazolines and thiazolines in a Radleys GreenHouse parallel synthesizer. A total of 17 oxazolines and 6 thiazolines were synthesized in moderate to excellent yields and high purities from 24 attempted reactions without the need for time-consuming chromatographic purification. Since oxidation of oxazolines and thiazolines to the corresponding oxazoles and thiazoles is readily accomplished by inorganic reagents that can be simply filtered off,[1e,15,16] a further extension of our strategy toward the parallel solution synthesis of the corresponding aromatic heterocycles would be straightforward.

Results and Discussion

In 1996, Yamamoto's group reported that arylboronic acids with electron-withdrawing substituents could act as highly efficient dehydration catalysts in the condensation of carboxylic acids and amines.[17] The catalytic effect could be explained by the formation of (acyloxy)boronic acid intermediates from carboxylates followed by trapping with amines. We expected that the formation of oxazolines and thiazolines was possible if, after N-acylation of 2-amino alcohols and 2-aminothiols, cyclodehydration was facilitated thermally and by removing water from the equilibrium. While 3,4,5-trifluorobenzeneboronic acid was found be a slightly more active catalyst,[17] we decided to use the commercially available 3-nitrophenylboronic acid instead.

In the presence of 10 mol % of 3-nitrophenylboronic acid in toluene at reflux, an equimolar amount of hydrocinnamic acid and (L)-valinol provided the corresponding ester as the major product in 16% yield (Scheme 1; Table 1, entry 1). Upon increasing the relative amount of (L)-valinol, the desired oxazoline became the major product (entry 2). However, the yield was only moderate. Even under Dean−Stark conditions that facilitate the irreversible removal of water from the reaction system (entry 4), or upon extension of the reaction time (entry 3), the reaction yield was still not as high as desired. In contrast, in refluxing xylene the yield of the reaction was improved considerably from 58% to 84% (entry 5). An excess of 1 equiv of (L)-valinol was

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Scheme 1. Synthesis of Oxazoline **1a** from Acid and Amino Alcohol Building Blocks

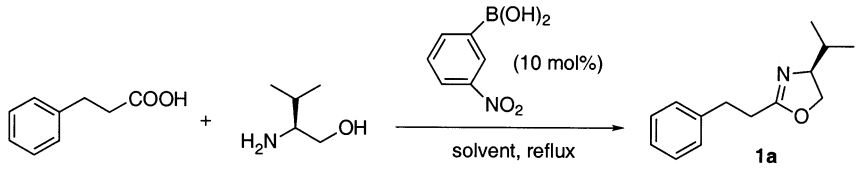


Table 1. Reaction Optimization for Tandem Condensation−Cyclodehydration of Hydrocinnamic Acid and (L)-Valinol[a]

entry	hydrocinnamic acid [mmol]	(L)-valinol [mmol]	solvent	time [h]	yield[b] [%]
1	0.30	0.30	toluene	30	15
2	0.30	0.60	toluene	30	39
3	0.30	0.60	toluene	69	53
4[c]	0.30	0.60	toluene	30	58
5[c]	0.30	0.60	xylene	27	84
6[c]	0.30	0.45	xylene	28	72

[a] The reaction mixture was heated under reflux in the presence of 10 mol % of 3-nitrophenylboronic acid. [b] Isolated yield after chromatographic purification. [c] Under Dean−Stark conditions.

still necessary to suppress formation of the ester side product (entry 6).

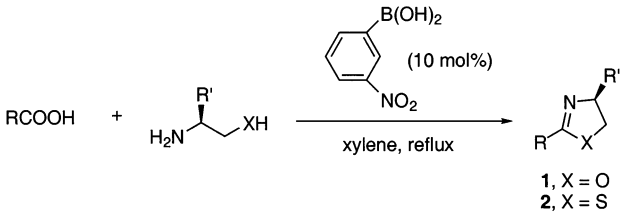
Table 2 shows the application of our optimized reaction conditions to a small series of acids, amino alcohols, and aminothiols. Hydrocinnamic acid reacted cleanly and in excellent yields with amino alcohols such as *tert*-leucinol and phenylglycinol as well as with aminoethanethiol (entries 1−3). Related aliphatic acids were converted in good yields to the corresponding oxazolines (entries 10 and 11). Entry 11 also demonstrates that an ester is compatible with this process. For the α,β-unsaturated cinnamic acid, yields of isolated heterocycles dropped, in particular with aminoethanethiol (entries 4−6). Quite likely, the C(2)-α,β-unsaturated 1,3-azoles will react further or decompose under the reaction conditions. In addition, the conjugation decreases the electrophilicity of the carboxylate. With aromatic acid substrates (entries 7−9), the combined steric and electronic effects of the phenyl ring also reduced the yield of the reaction.

Since we envisioned that the major use of this methodology lies in the parallel synthesis of combinatorial libraries of oxazolines and thiazolines, we further explored the scope of the tandem condensation−cyclodehydration process with a 6 × 4 reaction array of 6 carboxylic acids, 3 amino alcohols, and 1 aminothiol (Table 3). The reactions were performed in a Radleys GreenHouse parallel synthesizer. A total of 17 oxazolines and 6 thiazolines were successfully obtained from the attempted 24 reactions. The reaction of 3,5-dinitrobenzoic acid with phenylglycinol failed. It is noteworthy that the yields of these reactions are comparable to or better than what was found in the traditional reaction setup. A rapid PrepSep Florisil cartridge filtration of the crude reaction mixtures was sufficient to remove most impurities. For oxazolines, an additional 4 mL of a mixture of EtOAc and hexanes (3:7) was used to rinse the cartridge; for thiazolines, a 1:1 mixture of EtOAc and hexanes was utilized. The solvents were subsequently evaporated in a Savant SpeedVac SC110, and product yields were determined by NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard. In addition, the purities of all products were determined by GC−MS analysis.

Conclusions

An efficient new methodology for the synthesis of oxazolines and thiazolines by tandem condensation−cyclodehydration of carboxylates and amino alcohols or aminothiols

Table 2. Expansion of Reaction Scope to Substituted Oxazolines and Thiazolines[a]



entry	carboxylic acid	amino alcohol or aminothiol	product	time [h]	yield[c] [%]
1	hydrocinnamic acid	(L)-*tert*-leucinol	**1b**	30	80
2	hydrocinnamic acid	(*S*)-phenylglycinol	**1c**	32	68
3[b]	hydrocinnamic acid	2-aminoethanethiol·HCl	**2a**	30	100
4	cinnamic acid	(L)-valinol	**1d**	49	46
5	cinnamic acid	(L)-*tert*-leucinol	**1e**	48	54
6[b]	cinnamic acid	2-aminoethanethiol·HCl	**2b**	30	15
7	benzoic acid	(L)-valinol	**1f**	28	33
8	*p*-*tert*-butylbenzoic acid	(L)-valinol	**1g**	45	41
9	3,5-dinitrobenzoic acid	(L)-valinol	**1h**	29	36
10	cyclohexanecarboxylic acid	(L)-valinol	**1s**	28	75
11	*N*-Cbz-L-glutamic acid 1-methyl ester	(L)-valinol	**1t**	28	62

[a] Carboxylic acid (0.30 mmol) and amino alcohol or aminothiol (0.60 mmol) were heated under reflux in a nitrogen atmosphere in the presence of 0.030 mmol of 3-nitrophenylboronic acid. [b] 2.0 equiv of $(i\text{-Pr})_2$NEt was added. [c] Isolated yield after chromatographic separation.

Table 3. Parallel Combinatorial Synthesis of Oxazolines and Thiazolines[a]

azole	R	R′	yield[b] [%]	purity[c] [%]
1a	$PhCH_2CH_2$	*i*-Pr	92	97
1b	$PhCH_2CH_2$	*t*-Bu	92	100
1c	$PhCH_2CH_2$	Ph	79	100
1d	PhCH═CH	*i*-Pr	52	98
1e	PhCH═CH	*t*-Bu	46	100
1f	Ph	*i*-Pr	38	96
1g	4-(*t*-Bu)Ph	*i*-Pr	41	96
1h	3,5-$(NO_2)_2$Ph	*i*-Pr	50	97
1i	4-(NO_2)Ph	*i*-Pr	66	96
1j	4-(*t*-Bu)Ph	*t*-Bu	28	100
1k	4-(NO_2)Ph	*t*-Bu	68	97
1l	3,5-$(NO_2)_2$Ph	*t*-Bu	11	100
1m	Ph	*t*-Bu	40	100
1n	PhCH═CH	Ph	36	97
1o	Ph	Ph	31	100
1p	4-(*t*-Bu)Ph	Ph	25	100
1q	4-(NO_2)Ph	Ph	23	93
1r	3,5-$(NO_2)_2$Ph	Ph	0	
2a	$PhCH_2CH_2$	H	100	100
2b	PhCH═CH	H	17	82
2c	Ph	H	46	91
2d	4-(*t*-Bu)Ph	H	50	82
2e	4-(NO_2)Ph	H	9	100
2f	3,5-$(NO_2)_2$Ph	H	3	

[a] Acid (0.10 mmol), amino alcohol or aminothiol (0.20 mmol), and 3-nitrophenylboronic acid (0.010 mmol) were heated at reflux in 2 mL of xylenes. [b] Yields were determined by NMR spectroscopy using 1,4-dimethoxybenzene (0.030 M solution in $CDCl_3$) as internal standard. [c] Product purities were determined by GC−MS analysis.

in the presence of catalytic amounts of an arylboronic acid was developed. This reaction is well suited for the parallel solution synthesis of combinatorial libraries of oxazolines and thiazolines because the starting materials are readily available. A test 6 × 4 reaction setup provided 17 oxazolines and 6 thiazolines, and only one reaction between a very reactive carboxylic acid and phenylglycinol failed. The average yield in our library synthesis was 45% and the average purity of samples was >96%. Significantly, in many cases the results of the combinatorial synthesis were improved over the traditional single reaction setup followed by chromatographic purification of the reaction mixture. In particular, the ease of reaction setup and product isolation distinguishes this protocol from more traditional consecutive condensation−cyclodehydration processes.[6]

Experimental Section

General Information. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[a]_D$ (*c* g/(100 mL)). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker Avance-300 (75 MHz) spectrometer with complete proton decoupling. Mass spectra were obtained on a VG-7070 or Fisons Autospec high-resolution magnetic sector mass spectrometer. PrepSep Florisil cartridges (1 g/(6 mL)) were purchased from Fisher Scientific Co. GC−MS analyses were performed on a Hewlett-Packard 5871A mass spectrometer with a 5890 series II gas chromatograph (HP-1 Agilent Technology column, 12 m × 0.2 mm, 0.33 μm thick film).

General Procedure A for the Preparation of Oxazolines and Thiazolines (Single Reaction Setup). A solution of carboxylic acid (0.30 mmol) and amino alcohol or aminothiol (0.60 mmol), $(i\text{-Pr})_2$NEt (0.60 mmol; only for thiazoline synthesis), and 3-nitrophenylboronic acid (0.030 mmol) in xylene (6 mL) was heated under reflux with a Dean−Stark trap containing 4 Å molecular sieves under nitrogen for 22−48 h. The solvent was removed in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc/*n*-hexanes).

(*S*)-4-Isopropyl-2-phenethyl-4,5-dihydrooxazole (1a). According to general procedure A, a mixture of hydrocinnamic acid (45 mg, 0.30 mmol), (L)-valinol (62 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) provided **1a** (54.8 mg, 84%): $[\alpha]_D$ −44.1 (*c* 1.1, $CHCl_3$); IR (neat) 3028, 2958, 1671, 1604, 1497, 1454, 1384, 1365, 1164, 985, 698 cm^{-1}; ^{1}H NMR δ 7.32−7.18 (m, 5 H), 4.26−4.21 (m, 1 H), 3.98−3.88 (m, 2 H), 2.97 (t, 2 H, J = 8.0 Hz), 2.62 (t, 2 H, J = 8.1 Hz), 1.73 (dq, 1 H, J = 6.5, 6.5 Hz), 0.94 (d, 3 H, J = 6.8 Hz), 0.86 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 166.8, 140.7, 128.5, 128.4, 126.3, 72.0, 70.1, 32.6, 32.4, 30.0, 18.8, 18.1; MS (EI) *m*/*z* (relative intensity) 217 ([M]$^+$, 93), 174 (100), 140 (38), 117 (25), 104 (39); HRMS (EI) *m*/*z* calculated for $C_{14}H_{19}NO$ 217.1467, found 217.1469.

(*S*)-4-*tert*-Butyl-2-phenethyl-4,5-dihydrooxazole (1b). According to general procedure A, a mixture of hydrocinnamic acid (45 mg, 0.30 mmol), (L)-*tert*-leucinol (70 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **1b** (55.8 mg, 80%): $[\alpha]_D$ −56.8 (*c* 1.3, $CHCl_3$); IR (neat) 3063, 3028, 2954, 2904, 2868, 1673, 1604, 1496, 1479, 1454, 1363, 1230, 1209, 1170, 983, 914, 749, 698 cm^{-1}; ^{1}H NMR δ 7.29−7.15 (m, 5 H), 4.13 (dd, 1 H, J = 10.1, 8.6 Hz), 3.99 (t, 1 H, J = 8.2 Hz), 3.84−3.77 (m, 1 H), 2.94 (t, 2 H, J = 8.0 Hz), 2.65−2.56 (m, 2 H), 0.83 (s, 9 H); ^{13}C NMR δ 166.5, 140.6, 128.4, 128.3, 126.1, 75.6, 68.4, 33.4, 32.3, 29.8, 25.7; MS (EI) *m*/*z* (relative intensity) 231 ([M]$^+$, 55), 216 (7), 174 (91), 154 (9), 132 (14), 117 (17), 105 (35); HRMS (EI) *m*/*z* calculated for $C_{15}H_{21}NO$ 231.1623, found 231.1624.

(*S*)-2-Phenethyl-4-phenyl-4,5-dihydrooxazole (1c). According to general procedure A, a mixture of hydrocinnamic acid (45 mg, 0.30 mmol), (*S*)-phenylglycinol (82 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **1c** (50.9 mg, 68%): $[\alpha]_D$ −52.5 (*c* 1.2, $CHCl_3$); IR (neat) 3061, 3027, 2928, 1739, 1665, 1603, 1494, 1453, 1161, 986, 751, 698 cm^{-1}; ^{1}H NMR δ 7.44−7.20 (m, 10 H), 5.26 (t, 1 H, J = 9.1 Hz), 4.70 (dd, 1 H, J = 10.2, 8.4 Hz), 4.15 (t, 1 H, J = 8.2 Hz), 3.21−3.13 (m, 2 H), 2.90−2.81 (m, 2 H); ^{13}C NMR δ 168.0, 142.2, 140.4, 128.6, 128.5, 128.4, 127.4, 126.5, 126.2, 74.6, 69.5, 32.1, 29.7; MS (EI) *m*/*z* (relative intensity) 251 ([M]$^+$, 92), 220 (17), 174 (24), 131 (22), 117 (66), 104 (100); HRMS (EI) *m*/*z* calculated for $C_{17}H_{17}NO$ 251.1310, found 251.1307.

2-Phenethyl-4,5-dihydrothiazole (2a). According to general procedure A, a mixture of hydrocinnamic acid (45 mg, 0.30 mmol), 2-aminoethanethiol hydrochloride (68 mg, 0.60 mmol), $(i\text{-Pr})_2$NEt (78 mg, 0.60 mmol), and 3-nitrophenyl-

boronic acid (5.0 mg, 0.030 mmol) afforded **2a** (57.5 mg, 100%): IR (neat) 3084, 3061, 3026, 2955, 2854, 1629, 1603, 1496, 1453, 1260, 1181, 1096, 1029, 974, 920, 798, 750, 698 cm^{-1}; ^1H NMR δ 7.30−7.16 (m, 5 H), 4.20 (tt, 2 H, J = 8.3, 1.4 Hz), 3.27 (t, 2 H, J = 8.4 Hz), 3.00−2.95 (m, 2 H), 2.82−2.77 (m, 2 H); ^{13}C NMR δ 170.7, 140.5, 128.4, 128.2, 126.1, 64.4, 35.9, 33.8, 33.4; MS (EI) *m*/*z* (relative intensity) 191 ($[M]^+$, 41), 114 (11); HRMS (EI) *m*/*z* calculated for $C_{11}H_{13}NS$ 191.0769, found 191.0767.

(*S*)-4-Isopropyl-2-styryl-4,5-dihydrooxazole (1d). According to general procedure A, a mixture of cinnamic acid (44 mg, 0.30 mmol), (L)-valinol (62 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **1d** (30.0 mg, 46%): $[\alpha]_D$ −104 (*c* 0.97, $CHCl_3$); IR (neat) 3060, 3026, 2959, 2898, 2872, 1655, 1610, 1449, 1360, 1250, 991, 972, 917, 759, 693 cm^{-1}; ^1H NMR δ 7.47−7.30 (m, 6 H), 6.65 (d, 1 H, J = 16.3 Hz), 4.37−4.30 (m, 1 H), 4.05−3.96 (m, 2 H), 1.79 (dq, 1 H, J = 6.6, 6.6 Hz), 1.00 (d, 3 H, J = 6.7 Hz), 0.90 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 163.3, 139.9, 135.2, 129.4, 128.8, 127.4, 115.1, 72.4, 70.0, 32.8, 18.9, 18.3; MS (EI) *m*/*z* (relative intensity) 215 ($[M]^+$, 65), 172 (100), 144 (48), 130 (20), 115 (67), 103 (27); HRMS (EI) *m*/*z* calculated for $C_{14}H_{17}NO$ 215.1310, found 215.1314.

(*S*)-4-*tert*-Butyl-2-styryl-4,5-dihydrooxazole (1e). According to general procedure A, a mixture of cinnamic acid (44 mg, 0.30 mmol), (L)-*tert*-leucinol (70 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **1e** (36.9 mg, 54%): mp 94.0−94.8 °C; $[\alpha]_D$ −92.3 (*c* 0.65, $CHCl_3$); IR (neat) 2971, 2957, 2894, 2863, 1656, 1610, 1448, 1363, 1352, 1271, 1198, 975, 758, 688 cm^{-1}; ^1H NMR δ 7.49−7.44 (m, 2 H), 7.37−7.31 (m, 4 H), 6.71 (d, 1 H, J = 16.3 Hz), 4.30 (dd, 1 H, J = 10.0, 8.6 Hz), 4.15 (t, 1 H, J = 8.3 Hz), 3.98 (dd, 1 H, J = 10.0, 8.0 Hz), 0.93 (s, 9 H); ^{13}C NMR δ 163.5, 140.2, 135.2, 129.5, 128.8, 127.5, 114.9, 75.8, 68.6, 33.9, 25.9; MS (EI) *m*/*z* (relative intensity) 229 ($[M]^+$, 2), 214 (3), 172 (100), 144 (23), 131 (16), 115 (43); HRMS (EI) *m*/*z* calculated for $C_{15}H_{19}NO$ ($M - C_4H_9$) 172.0762, found 172.0760.

2-Styryl-4,5-dihydrothiazole (2b). According to general procedure A, a mixture of cinnamic acid (44 mg, 0.30 mmol), 2-aminoethanethiol hydrochloride (68 mg, 0.60 mmol), $(i\text{-Pr})_2NEt$ (78 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **2b** (8.3 mg, 15%): mp 94.5−95.5 °C; IR (neat) 3037, 3002, 2945, 2850, 1633, 1583, 1450, 1187, 1001, 958, 755, 691 cm^{-1}; ^1H NMR δ 7.50−7.47 (m, 2 H), 7.38−7.32 (m, 3 H), 7.16 (AB, 1 H, J = 16.2 Hz), 7.07 (AB, 1 H, J = 16.2 Hz), 4.37 (t, 2 H, J = 8.2 Hz), 3.34 (t, 2 H, J = 8.2 Hz); ^{13}C NMR δ 168.6, 141.7, 135.3, 129.6, 128.9, 127.6, 122.3, 64.2, 32.9; MS (EI) *m*/*z* (relative intensity) 188 ($[M - H]^+$, 10), 141 (7), 131 (15), 129 (18), 103 (17); HRMS (EI) *m*/*z* calculated for $C_{11}H_{11}NS$ 189.0612, found 189.0604.

(*S*)-4-Isopropyl-2-phenyl-4,5-dihydrooxazole (1f). According to general procedure A, a mixture of benzoic acid (37 mg, 0.30 mmol), (L)-valinol (62 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **1f** (18.6 mg, 33%): $[\alpha]_D$ −86.1 (*c* 1.8, $CHCl_3$); IR (neat) 3062, 2959, 2898, 2873, 1652, 1604, 1580, 1495, 1450, 1354, 1253, 1081, 1065, 1026, 968, 904, 779, 694 cm^{-1}; ^1H NMR δ 7.96−7.92 (m, 2 H), 7.45−7.24 (m, 3 H), 4.42−4.35 (m, 1 H), 4.15−4.08 (m, 2 H), 1.85 (dq, 1 H, J = 6.7, 6.7 Hz), 1.01 (d, 3 H, J = 6.8 Hz), 0.91 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 163.4, 131.2, 128.3, 127.8, 72.4, 70.1, 32.8, 18.9, 18.0.

(*S*)-2-(4-*tert*-Butylphenyl)-4-isopropyl-4,5-dihydrooxazole (1g). According to general procedure A, a mixture of *p*-*tert*-butylbenzoic acid (54 mg, 0.30 mmol), (L)-valinol (62 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) provided **1g** (30.3 mg, 41%): $[\alpha]_D$ −56.9 (*c* 0.74, $CHCl_3$); IR (neat) 2961, 2905, 2871, 1650, 1609, 1465, 1409, 1352, 1265, 1112, 1073, 1020, 963, 846 cm^{-1}; ^1H NMR δ 7.87 (dd, 2 H, J = 6.7, 1.9 Hz), 7.40 (dd, 2 H, J = 6.7, 2.0 Hz), 4.40−4.33 (m, 1 H), 4.15−4.05 (m, 2 H), 1.86 (dq, 1 H, J = 6.7, 6.7 Hz), 1.31 (s, 9 H), 1.00 (d, 3 H, J = 6.8 Hz), 0.90 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 163.5, 154.8, 128.1, 125.2, 124.9, 72.2, 70.0, 34.9, 32.7, 31.2, 18.9, 17.9; MS (EI) *m*/*z* (relative intensity) 245 ($[M]^+$, 2), 228 (4), 202 (100), 131 (11), 118 (25), 103 (12); HRMS (EI) *m*/*z* calculated for $C_{16}H_{23}NO$ 245.1780, found 245.1794.

(*S*)-2-(3,5-Dinitrophenyl)-4-isopropyl-4,5-dihydrooxazole (1h). According to general procedure A, a mixture of 3,5-dinitrobenzoic acid (64 mg, 0.30 mmol), (L)-valinol (62 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **1h** (29.7 mg, 36%): mp 102.2−103.0 °C; $[\alpha]_D$ −52.5 (*c* 0.08, $CHCl_3$); IR (neat) 3108, 2961, 2921, 2874, 1657, 1631, 1543, 1466, 1344, 1147, 1072, 961, 933, 730, 697 cm^{-1}; ^1H NMR δ 9.10−9.06 (m, 3 H), 4.54 (t, 1 H, J = 8.3 Hz), 4.26−4.13 (m, 2 H), 1.90 (dq, 1 H, J = 6.6, 6.6 Hz), 1.03 (d, 3 H, J = 6.7 Hz), 0.94 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 159.6, 148.5, 131.7, 128.1, 120.6, 73.2, 71.5, 32.8, 18.8, 18.3; MS (EI) *m*/*z* (relative intensity) 280 ($[M + H]^+$, 1), 236 (100), 220 (25), 208 (28), 162 (13), 116 (11); HRMS (EI) *m*/*z* calculated for $C_{12}H_{13}N_3O_5$ 279.0855, found 279.0855.

(*S*)-2-Cyclohexyl-4-isopropyl-4,5-dihydrooxazole (1s). According to general procedure A, a mixture of cyclohexanecarboxylic acid (39 mg, 0.30 mmol), (L)-valinol (62 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **1s** (43.7 mg, 75%): $[\alpha]_D$ −47.4 (*c* 1.2, $CHCl_3$); IR (neat) 2932, 2855, 1666, 1467, 1450, 1385, 1344, 1265, 1244, 1194, 1171, 1037, 981, 892, 852 cm^{-1}; ^1H NMR δ 4.16−4.08 (m, 1 H), 3.91−3.81 (m, 2 H), 2.27 (tt, 1 H, J = 3.5, 11.3 Hz), 1.89−1.85 (m, 2 H), 1.77−1.61 (m, 4 H), 1.47−1.15 (m, 5 H), 0.89 (d, 3 H, J = 6.8 Hz), 0.82 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 170.5, 71.6, 69.3, 37.5, 32.4, 30.0, 25.8, 25.7, 18.6, 17.6; MS (EI) *m*/*z* (relative intensity) 195 ($[M]^+$, 13), 152 (100), 140 (24), 128 (14); HRMS (EI) *m*/*z* calculated for $C_{12}H_{21}NO$ 195.1623, found 195.1624.

(2*S*,4′*S*)-2-Benzyloxycarbonylamino-4-(4′-isopropyl-4′,5′-dihydrooxazol-2-yl)butyric Acid Methyl Ester (1t). According to general procedure A, a mixture of *N*-carbobenzyloxy-L-glutamic acid 1-methyl ester (89 mg, 0.30 mmol), (L)-valinol (62 mg, 0.60 mmol), and 3-nitrophenylboronic acid (5.0 mg, 0.030 mmol) afforded **1t** (67.2 mg, 62%): $[\alpha]_D$ −31.5 (*c* 0.6, $CHCl_3$); IR (neat) 3334 (br), 3033, 2958, 1747, 1731, 1668, 1531, 1454, 1347, 1214, 1175, 1057, 983, 778, 740, 699 cm^{-1}; ^1H NMR δ 7.33−7.27 (m, 5 H), 6.23 (d, 1 H, J = 7.5 Hz), 5.07 (s, 2 H), 4.42−4.37 (m, 1 H), 4.17 (dd,

1 H, $J = 9.2$, 7.9 Hz), 3.91−3.80 (m, 2 H), 3.71 (s, 3 H), 2.32 (t, 2 H, $J = 7.2$ Hz), 2.20−2.16 (m, 1 H), 2.05−1.98 (m, 1 H), 1.75−1.60 (m, 1 H), 0.91 (d, 3 H, $J = 6.7$ Hz), 0.82 (d, 3 H, $J = 6.7$ Hz); ^{13}C NMR δ 172.4, 166.6, 156.0, 136.3, 128.4, 128.0, 72.0, 70.2, 66.9, 53.6, 52.4, 32.5, 28.2, 24.2, 18.7, 18.1; MS (EI) *m*/*z* (relative intensity) 362 ($[M]^+$, 8), 319 (6), 303 (22), 169 (10), 140 (18), 127 (46), 91 (100); HRMS (EI) *m*/*z* calculated for $C_{19}H_{26}N_2O_5$ 362.1842, found 362.1836.

General Procedure for the Parallel Synthesis of Oxazolines and Thiazolines in a 6 × 4 Reaction Setup. A solution or suspension of acid (0.10 mmol), amino alcohol or aminothiol (0.20 mmol), and 3-nitrophenylboronic acid (0.010 mmol) in 2 mL of xylenes was added to reaction tubes in a Radleys GreenHouse parallel synthesizer. For aminothiols, $(i\text{-Pr})_2$NEt (0.20 mmol) was also added to the reaction mixtures. After connection of the synthesizer to a nitrogen line, the 24 tubes were heated at 160 °C for 42 h. Subsequently, the reaction mixtures were passed through a PrepSep Florisil cartridge (1 g/(6 mL)). For oxazolines, the cartridge was rinsed with 4 mL of a 3:7 mixture of EtOAc and hexanes; for thiazolines, 4 mL of a 1:1 solvent mixture was utilized. The volatiles were evaporated in a Savant SpeedVac SC110. Yields were determined by NMR using 1,4-dimethoxybenzene (0.030 M solution in $CDCl_3$) as an internal standard. Product purities were determined by GC−MS analysis.

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Supporting Information Available. NMR spectra with internal standard and GC−MS traces for the 6 × 4 parallel reaction setup. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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