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Synthesis of Ugi-4CR boronate analogues via microwave irradiation

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Abstract The synthetic condition for the synthesis of boronate ester Ugi-4CR analogs under mild conditions was developed. The reported reactions were carried out in methanol and promoted by microwave heating. This synthetic strategy could provide unique access to a broad range of boron-containing chemical libraries.

Keywords Boron · Multicomponent reaction · Ugi reaction · Suzuki–Miyaura cross-coupling

Introduction

Compounds that contain a boron functional group have been broadly used as the key building blocks in a wide range of organic reactions [1, 2]. In 2003, bortezomib (Velcade^{TM}) became the first FDA-approved boron-containing agent to treat multiple myeloma [3, 4] (Fig. 1). Since then, significant research efforts have been focused on finding the next organoboron molecules to be used in medicinal applications [5–8] (Fig. 1). Despite their structural differences, the current strategy for the synthesis of organoboron compounds is mainly dependent on multi-step operations. This strategy often requires extensive reaction time, as well as time-consuming purification efforts. One alternative solution that could resolve this hurdle is to utilize a multi-component reaction (MCR) [9–11], where three or more reagents are put in one pot to yield the desired products. Although widely used in many medicinal programs, it is underutilized in the making of organoboron compounds. Westcott and co-workers reported one of the earliest examples of using

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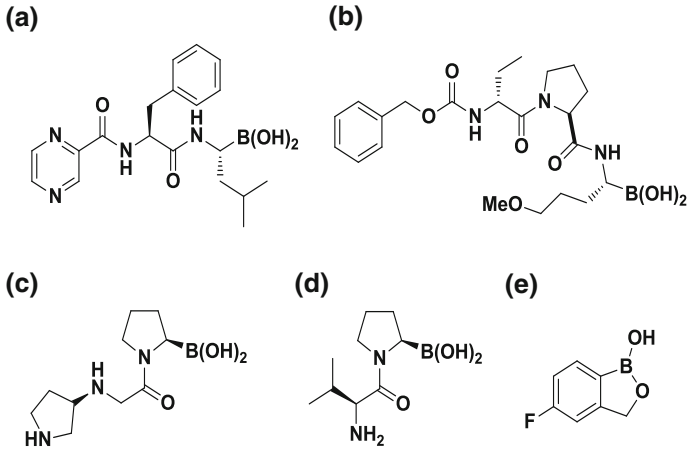
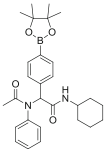


Fig. 1 **a** Velcade; **b** TR150c; **c** PHX1149; **d** PT100; **e** Kerydin

Ugi-4CR to synthesize boronate esters [12]. Although, the desired compounds were retrieved in good yields, it required 4–10 days to complete the reactions. Herein, we report a microwave-assisted synthetic condition that could synthesize boron-containing Ugi-4CR derivatives in 30 min.

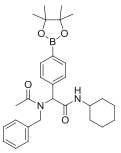
Experimental section

General procedure for the synthesis of boronic ester-containing Ugi analogues B1–B10

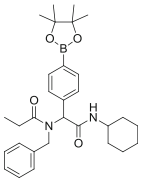


N-cyclohexyl-2-(N-phenylacetamido)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**1**) A 10-mL glass tube containing aniline (0.10 mL; 0.55 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (116 mg; 0.50 mmol), and 0.5 mL of methanol was first stirred for 5 min at room temperature. Then, acetic acid (0.03 mL; 0.55 mmol) and cyclohexylisocyanide (0.07 mL; 0.55 mmol) were added to the reaction mixture. Microwave irradiation was applied for 30 min (45 °C, 150 W) under medium-speed magnetic stirring, and the reaction mixture was concentrated and re-dissolved in dichloromethane. The crude solution was then washed with 1 M $HCl_{(aq)}$ and $NaHCO_{3(aq)}$, respectively. The organic solution was collected and dried over $MgSO_4$ and concentrated in vacuo. The concentrated material was placed under vacuum at 40 °C for 8 h to afford the desired product in a 93 % yield (221.94 mg) mp = 265 °C. ^{1}H NMR

(300 MHz, $CDCl_3$) δ: 7.62 (d, 2H), 7.19–7.12(m, 7H), 5.99 (s, 1H), 5.49 (br, 1H), 3.79–3.90 (m, 1H), 1.60–2.00 (m, 6H), 1.25–1.40 (m, 15H), 0.80–1.09 (m, 4H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 175.85, 168.82, 138.49, 137.85, 135.04, 128.89, 128.35, 126.81, 126.08, 83.87, 63.00, 50.07, 48.51, 32.67, 27.32, 25.46, 24.84, 24.81, 24.73, 9.34. ^{11}B NMR (192.5 MHz, $CDCl_3$) δ: 30.65. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, found 477.2937. $C_{28}H_{37}BN_2O_4$ requires 477.2923.

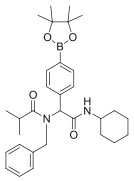


2-(N-benzylacetamido)-N-cyclohexyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**2**) The desired compound was prepared using benzylamine (0.06 mL; 0.55 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (116 mg; 0.50 mmol), acetic acid (0.03 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (398.73 mg, 81 % yield). mp = 183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (d, 2H), 7.37 (d, 2H), 7.13–7.16 (m, 3H), 7.02–7.04 (m, 2H), 5.87 (s, 1H), 5.62 (br, 1H), 4.60 (dd, J = 42.0, 18.0, 2H), 3.77–3.79 (m, 1H), 2.04 (s, 3H), 1.82–1.92 (m, 2H), 1.59–1.65 (m, 3H), 1.23–1.32 (m, 15H), 1.01–1.07 (m, 2H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 172.55, 168.44, 138.22, 137.44, 135.01, 128.80, 128.31, 126.80, 83.81, 62.90, 50.48, 48.44, 32.62, 25.36, 24.70, 22.40. ^{11}B NMR (192.5 MHz, $CDCl_3$) δ: 30.88. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, 491.3079. $C_{29}H_{39}BN_2O_4$ requires 491.3079.

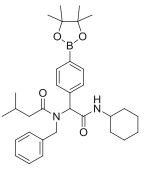


N-benzyl-N-(2-(cyclohexylamino)-2-oxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)propionamide (**3**) The desired compound was prepared using benzylamine (0.06 mL; 0.55 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (116 mg; 0.50 mmol), propanoic acid (0.05 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (401.56 mg, 80 % yield). mp = 210 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 (br, 2H), 7.35 (br, 2H), 7.24–7.11 (m, 3H), 7.03 (br, 2H), 5.89 (s, 1H), 5.64 (br. 1H), 4.64 (dd, J = 43.2, 17.3, 2H), 3.87–3.71 (m, 1H), 2.48–2.15 (m, 2H), 1.96–1.74 (m, 2H), 1.70–1.48 (m, 3H), 1.46–1.20 (m, 15H), 1.21–0.94 (m, 5H). ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ: 171.43, 168.77, 140.83, 137.86, 134.84, 130.47, 129.66, 129.05, 128.17, 113.90, 84.03, 65.43, 48.86, 32.87, 25.74, 25.57, 24.96, 24.83, 23.27. ^{11}B NMR (193 MHz, $CDCl_3$) δ: 30.79. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, found 505.3232. $C_{30}H_{41}BN_2O_4$ requires 505.3236.

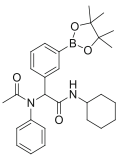


N-benzyl-N-(2-(cyclohexylamino)-2-oxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)isobutyramide (**4**) The desired compound was prepared using benzylamine (0.06 mL; 0.55 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (116 mg; 0.50 mmol), isobutric acid (0.05 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (286.21 mg, 55 % yield). mp = 78 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.71 (d, 2 H), 7.36 (d, 2 H), 7.21–7.02 (m, 5H), 5.86 (s, 1H), 5.63 (br, 1H), 4.61 (dd, J = 56.6, 17.6, 2H), 3.88–3.69 (m, 1H), 2.75–2.60 (m, 1H), 1.96–1.80 (m, 2H), 1.74–1.48 (m, 3H), 1.32 (s, 15H), 1.21–1.15 (m, 2H), 1.11 (d, 3H), 1.05 (d, 3H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 179.28, 168.53, 138.42, 137.90, 135.04, 128.77, 128.39, 126.92, 126.0183.91, 63.20, 50.03, 48.50, 32.76, 32.71, 31.46, 25.49, 24.84, 24.71, 19.63, 19.28. ^{11}B NMR (193 MHz, $CDCl_3$) δ: 30.68. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, found 519.3388. $C_{31}H_{43}BN_2O_4$ requires 519.3392.

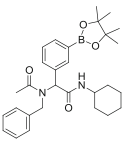


N-benzyl-N-(2-(cyclohexylamino)-2-oxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-3-methylbutanamide (**5**) The desired compound was prepared using benzylamine (0.06 mL; 0.55 mmol), 4-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)benzaldehyde (116 mg; 0.50 mmol), isovalic acid (0.07 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (433.59 mg, 83 % yield). mp = 169 °C. ^1H NMR (300 MHz, CD_3OD-d_4) δ: 7.67 (d, 2H), 7.33 (d, 2H), 7.18–7.02 (m, 5H), 5.90–5.75 (m, 1H), 4.60 (dd, J = 55.0, 17.6, 2H), 3.87–3.70 (m, 1H), 2.24–2.08 (m, 3H), 1.96–1.82 (m, 2H), 1.71–1.52 (m, 3H), 1.38–1.17 (m, 15H), 1.12–1.05 (m, 2H), 0.99–0.81 (m, 6H). ^{13}C NMR

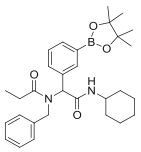
(150.9 MHz, $CDCl_3$) δ: 174.62, 168.60, 138.37, 137.58, 135.06, 128.88, 128.39, 126.96, 126.26, 83.92, 63.59, 50.45, 48.56, 42.79, 32.71, 25.85, 25.48, 24.85, 22.62, 22.54. ^{11}B NMR (193 MHz, $CDCl_3$) δ: 30.99. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, found 533.3532. $C_{32}H_{45}BN_2O_4$ requires 533.3549.



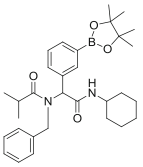
2-(N-phenylacetamido)-N-cyclohexyl-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**6**) The desired compound was prepared using aniline (0.10 mL; 0.55 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (116 mg; 0.50 mmol), acetic acid (0.03 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (371.13 mg, 78 % yield). mp = 152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61(s, 2H), 7.16(s, 4H), 7.09(s, 3H), 6.07(s, 1H), 5.58(br, 1H), 3.91–3.75(m, 1H), 1.95–1.79(m, 3H), 1.63–1.52(m, 4H), 1.38–1.23(m, 15H), 1.15–0.97(m, 3H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 167.34, 164.93, 136.60, 133.17, 130.75, 130.12, 129.02, 126.50, 124.89, 124.02, 123.71, 79.98, 60.91, 44.75, 28.78, 21.55, 20.95, 19.25. ^{11}B NMR (192.5 MHz, $CDCl_3$) δ: 30.30. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, found 477.2899. $C_{28}H_{37}BN_2O_4$ requires 477.2923.



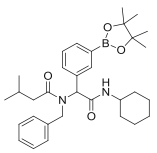
2-(N-benzylacetamido)-N-cyclohexyl-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**7**) The desired compound was prepared using benzylamine (0.06 mL; 0.55 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (116 mg; 0.50 mmol), acetic acid (0.03 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (355.08 mg, 72 % yield). mp = 139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.62 (d, 1H), 7.48 (d, 1H), 7.25–6.96 (m, 6H), 5.98 (s, 1H), 5.48 (br, 1H), 4.58 (dd, J = 39.0, 17.8, 2H), 3.90–3.75 (m, 1H), 2.06 (s, 3H), 1.95–1.84 (m, 2H), 1.71–1.51 (m, 3H), 1.42–1.29 (m, 15H), 1.21–0.98 (m, 2H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 172.63, 168.80, 137.63, 136.73, 134.80, 134.42, 132.24, 128.27, 128.09, 126.75, 126.11. 83.89, 62.66, 50.68, 48.53, 32.74, 25.49, 24.90, 22.27. ^{11}B NMR (192.5 MHz, $CDCl_3$) δ: 30.65. HRMS (ESI, positive ion): $[M + H]^+$, found 491.3077. $C_{29}H_{39}BN_2O_4$ requires 491.3079.



N-benzyl-N-(2-(cyclohexylamino)-2-oxo-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)propionamide (***8***) The desired compound was prepared using benzylamine (0.06 mL; 0.55 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (116 mg; 0.50 mmol), propanoic acid (0.04 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (430.82 mg, 85 % yield). mp = 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 (s, 1H), 7.62 (d, 1H), 7.49 (d, 1H), 7.23–6.95 (m, 6H), 6.00 (s, 1H), 5.62 (br, 1H), 4.60 (dd, J = 43.4, 17.9, 2H), 3.98–3.78 (m, 1H), 2.61–2.27 (m, 2H), 2.12–1.86 (m, 2H), 1.86–1.59 (m, 3H), 1.59–1.31 (m, 15H), 1.31–1.07 (m, 5H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 175.80, 168.96, 137.85, 136.74, 134.73, 132.24, 128.63, 128.05, 126.69, 126.0583.87, 62.83, 49.88, 48.51, 32.73, 27.30, 25.49, 24.90, 9.38. ^{11}B NMR (193 MHz, $CDCl_3$) δ: 30.79. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, found 505.3243. $C_{30}H_{41}BN_2O_4$ requires 505.3236.

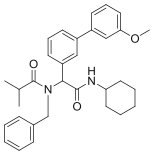


N-benzyl-N-(2-(cyclohexylamino)-2-oxo-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)isobutyramide (**9**) The desired compound was prepared using benzylamine (0.06 mL; 0.55 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde (116 mg; 0.50 mmol), isobutric acid (0.05 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (443.32 mg, 86 % yield). mp = 79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.60 (d, 1H), 7.45 (d, 1H), 7.31–6.95 (m, 6H), 5.97 (s, 1H), 5.76 (br, 1H), 4.62 (dd, J = 58.2, 17.9, 2H), 3.77–3.84 (m, 1H), 2.67–2.77 (m, 1H), 1.82–1.97 (m, 2H), 1.58–1.72 (m, 3H), 1.31–1.43 (m, 15H), 1.21–1.12 (m 8H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 179.19, 168.79, 138.05, 136.54, 134.57, 132.13, 128.21, 127.96, 126.70, 125.91. ^{11}B NMR (193 MHz, $CDCl_3$) δ: 30.60. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, found 518.3320. $C_{31}H_{43}BN_2O_4$ requires 518.3313.



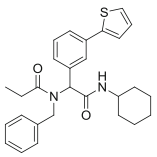
N-benzyl-N-(2-(cyclohexylamino)-2-oxo-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-3-methylbutanamide (**10**) The desired compound was prepared using benzylamine (0.06 mL; 0.55 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (116 mg; 0.50 mmol), isovalic acid (0.07 mL; 0.55 mmol), and cyclohexylisocyanide (0.07 mL; 0.55 mmol) by general procedure (411.02 mg, 77 % yield). mp = 78 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.61 (d, 1H), 7.66 (d, 1H), 7.24–6.97 (m, 6H), 5.91 (s, 1H), 5.64 (br, 1H), 4.61 (dd, J = 62.0, 17.8, 2H), 3.79–3.73 (m, 1H), 2.29–2.13 (m, 3H), 1.97–1.89 (m, 2H), 1.69–1.56 (m, 3H), 1.37–1.26 (m, 15H), 1.16–1.04 (m, 2H), 1.04–0.97 (m, 6H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 174.50, 168.85, 137.78, 136.59, 134.61, 132.22, 128.19, 126.72, 126.15, 83.83, 63.05, 50.07, 48.49, 42.77, 32.70, 25.88, 25.51, 24.89, 24.77, 24.70, 22.65, 22.60. ^{11}B NMR (193 MHz, $CDCl_3$) δ: 30.46. *m/z* HRMS (ESI, positive ion): $[M + H]^+$, found 533.3566. $C_{32}H_{45}BN_2O_4$ requires 533.3549.

General procedure F for the synthesis 11–14

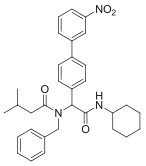


N-benzyl-N-(2-(cyclohexylamino)-1-(3′-methoxy-[1,1′-biphenyl]-3-yl)-2-oxoethyl)isobutyramide (**11**) Compound **9** (100.5 mg, 0.194 mmol), 1-bromo-3-methoxybenzene (0.031 mL, 0.25 mmol), and $Pd(PPh_3)_2Cl_2$ (5.09 mg, 0.0194 mmol) were added to a flask containing a magnetic stir with EtOH (1.90 mL). Triethylamine (0.06 mL, 0.426 mmol) was then added to the reaction mixture and this mixture was stirred under reflux conditions for 10 h under a N_2 atmosphere. After cooling the mixture to room temperature, solvent was removed in vacuo. The crude material was diluted with ethyl acetate (5.00 mL) and water (5.00 mL). The aqueous layer was separated from the organic layer, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). Organic layers were then combined, washed with brine solution, and dried with $MgSO_4$, and solvent was removed in vacuo. The crude material was then purified by flash column chromatography on silica gel using n-hexane/ethyl acetate = 1:1 as the eluent to give the desired product **11** as an oil (m.p. 180 °C) in 61 % yield (59 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.47–6.85 (m, 13H), 6.01 (s, 1H), 5.73 (br, 1H), 4.67 (dd, J = 18, 103.2, 2H), 3.82 (s, 3H), 3.79–3.76 (m, 1H),

2.70 (quint, $J = 6.6$, 1H), 1.92–1.86(m, 2H), 1.66–1.54 (m, 2H), 1.35–1.22 (m, 4H), 1.12 (dd, $J = 6.6$, 30, 8H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 179.42, 168.83, 160.10, 142.23, 141.62, 138.13, 135.88, 129.92, 129.16, 128.88, 128.70, 128.47, 127.35, 127.05, 126.06, 119.81, 113.10, 112.99, 62.73, 55.49, 49.88, 48.73, 33.05, 32.95, 31.65, 25.67, 24.99, 24.91, 19.96, 19.52.

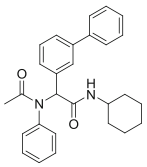


N-benzyl-N-(2-(cyclohexylamino)-2-oxo-1-(3-(thiophen-2-yl)phenyl)ethyl)propionamide (**12**) Following general procedure F, the desired compound was synthesized utilizing **8** (98.1 mg, 0.193 mmol), 2-bromothiophene (0.023 ml, 0.251 mmol), $Pd(PPh_3)_2Cl_2$ (5.05 mg, 0.019 mmol), and triethylamine (0.059 ml, 0.424 mmol), giving compound **12** as a white solid (m.p. 177 °C) in 78 % yield (69.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.53–6.98 (m, 12H), 6.01 (s, 1H), 5.79 (br, 1H), 4.65 (dd, $J = 18$, 81.6, 2H), 3.79 (s, 1H), 2.39–2.23(m, 2H), 1.91–1.85(m, 2H), 1.63–1.53(m, 4H), 1.40–1.08(m, 7H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 176.03, 168.82, 143.77, 137.88, 136.21, 134.96, 129.35, 128.73, 128.51, 128.20, 127.62, 127.04, 126.21, 126.11, 125.34, 123.61, 62.78, 50.17, 48.77, 32.98, 32.93, 27.49, 25.65, 24.98, 24.91, 9.61.



N-benzyl-N-(2-(cyclohexylamino)-1-(3′-nitro-[1,1′-biphenyl]-4-yl)-2-oxoethyl)-3-methylbutanamide (**13**) Following general procedure F, the desired compound was synthesized utilizing **5** (133 mg, 0.25 mmol), 1-bromo-3-nitrobenzene (0.065 mg, 0.325 mmol), $Pd(PPh_3)_2Cl_2$ (6.557 mg, 0.025 mmol), and triethylamine (0.08 mL, 0.55 mmol), giving compound **13** as an oil in 42 % yield (55.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.96 (d,1H), 7.59 (d, 1H), 7.36 (t, 2H), 7.04 (s, 1H), 6.95 (quint, $J = 6.6$, 7.8, 5.4, 6.6, 4H), 6.80 (d, 3H), 5.71 (s, 1H), 5.66 (br, 1H), 4.47 (dd, $J = 7.2$, 126, 2H), 3.57 (s, 1H), 2.09–1.71(m, 4H), 1.69–0.66(m, 15H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 174.79, 168.68, 148.93, 142.28, 138.76, 137.69, 135.95, 133.11, 130.60, 129.97, 128.57, 127.41, 127.21, 126.43, 122.45,

122.09, 62.85, 50.56, 48.82, 42.97, 33.04, 32.96, 26.12, 25.69, 25.08, 24.98, 24.93, 22.85, 22.78.



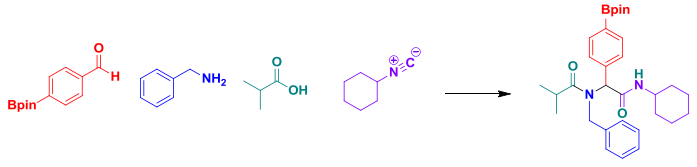
2-([1,1′-biphenyl]-3-yl)-N-cyclohexyl-2-(N-phenylacetamido)acetamide (**14**) Following general procedure F, the desired compound was synthesized utilizing **6** (119.1 mg, 0.25 mmol), bromobenzene (0.034 ml, 0.325 mmol), $Pd(PPh_3)_2Cl_2$ (6.55 mg, 0.025 mmol), and triethylamine (0.076 mL, 0.55 mmol), giving compound **14** as a white solid (mp = 79 °C) in 60 % yield (64 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.61 (s, 1H), 7.41–7.06 (m, 13H), 6.10 (s, 1H), 5.66 (br, 1H), 3.81–3.80 (m, 1H), 1.93–1.53 (m, 7H), 1.34–0.99 (m, 6H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 171.51, 168.95, 141.44, 140.83, 140.59, 135.44, 133.19, 130.65, 129.44, 129.40, 129.13, 128.95, 128.31, 127.68, 127.33, 127.20, 65.07, 49.01, 33.08, 33.01, 25.69, 25.03, 24.95, 23.49.

Results and discussion

Experiments were performed to find the optimum synthetic conditions. The results are shown in Table 1. It should be noted that all boronic acid building blocks (R-$B(OH)_2$) used in the synthesis were protected by pinacol as the boronate ester analogues (R-Bpin). First, ranges of solvents were selected (entry 1–4), and it was found that methanol provided the best result (entry 4, 62 %). Second, when the reaction was carried out with an elevated temperature (45 °C), the yields improved from 62 % (entry 4) to 68 % (entry 5). In addition, it was found that the reaction could finish earlier if microwave irradiation was applied (entry 6). It is important to note that further reducing the reaction period from 0.5 h (entry 6) to 0.25 h (entry 7) significantly lowered the overall yield from 78 to 42 %. After the optimal condition was determined, ranges of building blocks were used to synthesize boron-containing Ugi derivatives (Table 2). In all cases, the desired products **1**–**10** were synthesized in good to excellent yields (55–93 %).

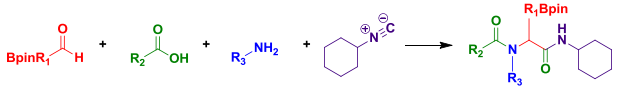
One of the advantages of synthesizing boron-containing Ugi analogs was that post-Ugi modification could be accomplished via a palladium-catalyzed Suzuki–Miyaura reaction. Four examples were included in this report where aryl/heteroaryl halides were successfully coupled to the boronate esters to yield the desired products **11**–**14** in moderate to good yields (Scheme 1).

Table 1 Optimization of Ugi-4CR



Entry	Solvent	Temp.	Time (h)	Conc. (M)	Yield (%)
1	H_2O	r.t.	1	0.25	13
2	Ether	r.t.	1	0.25	2
3	DCM	r.t.	1	0.25	0
4	MeOH	r.t.	1	0.25	62
5	MeOH	45 °C	1	0.25	68
6	MeOH	μw, 45 °C	0.5	1.0	78
7	MeOH	μw, 45 °C	0.25	1.0	42

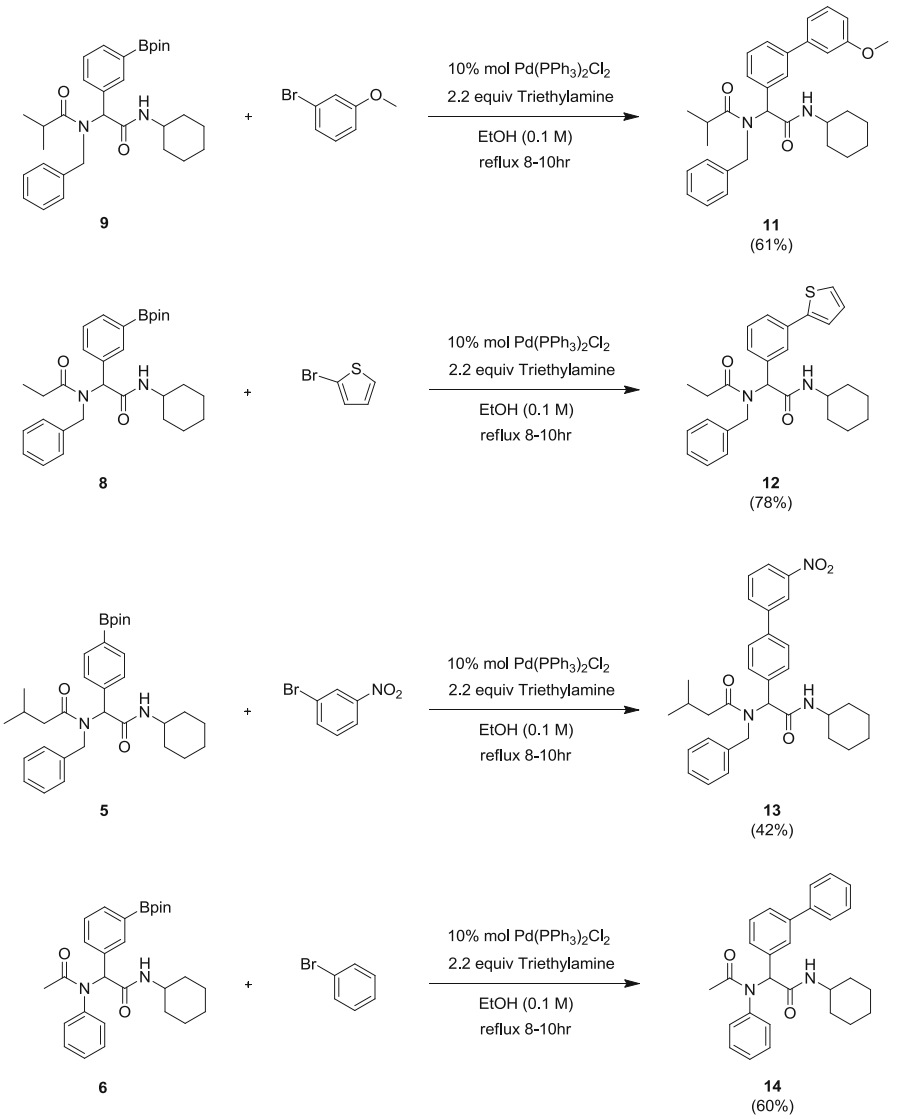
Table 2 Synthesizing Ugi-4CR Products with Optimized Condition



Entry	R_1	R_2	R_3	Product	Yield (%)
1	4-Bpin-Ph	Me	Ph	**1**	93
2	3-Bpin-Ph	Me	Ph	**2**	78
3	4-Bpin-Ph	Me	Bn	**3**	81
4	3-Bpin-Ph	Me	Bn	**4**	72
5	4-Bpin-Ph	Et	Bn	**5**	80
6	3-Bpin-Ph	Et	Bn	**6**	85
7	4-Bpin-Ph	i-Pr	Bn	**7**	55
8	3-Bpin-Ph	i-Pr	Bn	**8**	77
9	4-Bpin-Ph	i-Bu	Bn	**9**	83
10	3-Bpin-Ph	i-Bu	Bn	**10**	86

Conclusions

In summary, a microwave-assisted Ugi-4CR reaction that could synthesize boron-containing compounds was developed. Further, post-Ugi modification was also successfully demonstrated, making this strategy suitable for chemical library synthesis. More boron-containing analogs are being synthesized and their biological activity will be tested and reported in due course.



Scheme 1 Pd-mediated Suzuki–Miyaura cross-coupling of boron containing Ugi-4CR substrates

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