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The Catalytic Enantioselective Synthesis of β-Lactams: The First Intramolecular Kinugasa Reactions and the Interception of an Intermediate in the Reaction Cascade

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I. General

CH_2Cl_2, Et_2O, and THF were purified by passing through a neutral alumina column under argon. MeCN (anhydrous; Aldrich) was used as received.

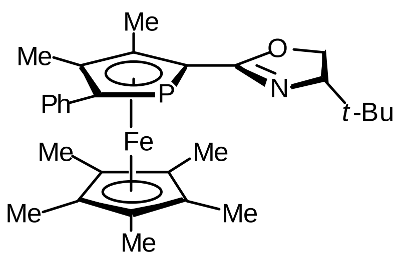
Cy_2NMe (Aldrich) was distilled over KOH under vacuum. Allyl iodide (Avocado) was distilled under vacuum prior to use. CuBr (Strem), 1-phenyl-1-(trimethylsilyloxy)ethylene (Aldrich), and KOAc (Mallinckrodt) were used as received. Ligands **6**,[1] **5a**,[1] and **4**[2] were prepared as previously described.

All the other chemicals and solvents were purchased from Aldrich, Mallinckrodt, EM Science, or J. T. Baker and used as received.

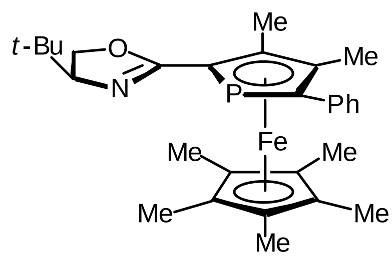
All air- and moisture-sensitive manipulations were carried out under argon with standard Schlenk techniques or under nitrogen in a glove box.

II. Synthesis of Ligands and Substrates

The yields have not been optimized.



5b



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Ligands 5b and 8. These ligands were synthesized from (±)-1',2',3,3',4,4',5'-heptamethyl-5-phenyl-2-trifluoroacetylphosphaferrocene and (*S*)-*tert*-leucinol following the reported procedure.[1] Ligand **5b** (*S*,*R*): Orange solid, 21% overall yield. Ligand **8** (*S*,*S*): Orange solid, 19% overall yield. The relative and absolute configurations were assigned by analogy with **5a** and **6**.[1]

Ligand **5b** (*S*,*R*): ^{1}H NMR (CD_2Cl_2): δ 7.43-7.39 (m, 2H), 7.29-7.24 (m, 2H), 7.19-7.16 (m, 1H), 4.14-4.09 (m, 1H), 3.99-3.86 (m, 2H), 2.46 (s, 3H), 2.20 (s, 3H), 1.65 (s, 15H), 0.91 (s, 9H). ^{13}C NMR (CD_2Cl_2): δ 165.9 (d, $^2J_{CP}$ = 17.9 Hz), 139.9 (d, $^2J_{CP}$ = 18.0 Hz), 129.8 (d, $^3J_{CP}$ = 9.2 Hz), 128.1 (s), 125.8 (s), 101.0 (d, $^1J_{CP}$ = 52.8 Hz), 95.8 (d, $^2J_{CP}$ = 5.0 Hz), 92.5 (d, $^2J_{CP}$ = 5.2 Hz), 83.8 (s), 78.9 (d, $^1J_{CP}$ = 54.6 Hz), 77.4 (d, $^4J_{CP}$ = 1.7 Hz), 67.2 (s), 34.3 (s), 26.3 (s), 14.2 (s), 13.5 (s), 10.1 (s). ^{31}P{^{1}H} NMR (CD_2Cl_2): δ –44.6 (s). FTIR (neat) 3055, 2953, 2901, 2867, 1635, 1597, 1479, 1446, 1377, 1295, 1259, 1208, 1124, 1069, 1027, 965, 757, 700 cm^{-1}. M.p. 136-138 C (dec). $[\alpha]^{20}_D$ +142.7 (*c* 0.54, THF). HRMS (ESI) calcd for $C_{29}H_{39}FeNOP$ ($M+H^+$) 504.2113, found 504.2106.

Ligand **8** (*S*,*S*): ^{1}H NMR (CD_2Cl_2): δ 7.30-7.39 (m, 2H), 7.29-7.23 (m, 2H), 7.18-7.13 (m, 1H), 4.24-4.18 (m, 1H), 3.94-3.79 (m, 2H), 2.38 (s, 3H), 2.20 (s, 3H), 1.66 (s, 15H), 0.97 (s, 9H). ^{13}C NMR (CD_2Cl_2): δ 166.7 (d, $^2J_{CP}$ = 17.9 Hz), 140.0 (d, $^2J_{CP}$ = 18.0 Hz), 129.7 (d, $^3J_{CP}$ = 9.2 Hz), 128.1 (s), 125.8 (s), 100.6 (d, $^1J_{CP}$ = 53.1 Hz), 94.7 (d, $^2J_{CP}$ = 5.0 Hz), 92.1 (d, $^2J_{CP}$ = 5.4

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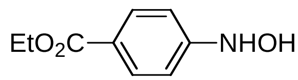
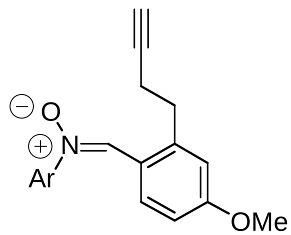
Hz), 83.8 (s), 80.6 (d, ${}^{1}J_{CP}$ = 54.3 Hz), 77.4 (d, ${}^{4}J_{CP}$ = 1.4 Hz), 67.6 (s), 33.9 (s), 26.8 (s), 14.3 (s), 13.7 (s), 10.3 (s). ${}^{31}P\{{}^{1}H\}$ NMR (CD_2Cl_2): δ –41.4 (s). FTIR (neat) 3055, 2954, 2902, 2866, 2720, 1630, 1597, 1478, 1414, 1377, 1363, 1299, 1264, 1299, 1264, 1195, 1123, 1071, 1026, 1009, 803, 758, 738, 700 cm^{-1}. M.p. 98-99 C. $[\alpha]^{20}_{D}$ –172.8 (*c* 0.72, THF). HRMS (ESI) calcd for $C_{29}H_{39}FeNOP$ (M^+) 504.2113, found 504.2106.



Ethyl 4-hydroxyaminobenzoate. (CAS 24171-85-5) Zn powder (13.1 g, 0.200 mol) was added over 20 minutes to a stirring mixture of ethyl 4-nitrobenzoate (19.5 g, 0.100 mol) and NH_4Cl (6.42 g, 0.120 mol) in ethanol (65 mL) / H_2O (65 mL). The reaction mixture was stirred for 1.5 h at 60 °C and 14 h at room temperature. The precipitate was then removed by filtration, and the ethanol was removed under vacuum. The aqueous layer was extracted with CH_2Cl_2, and the CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O / CH_2Cl_2 = 1 / 9 ∅ 1 / 7, affording the hydroxylamine as a pale-yellow solid (5.29 g, 29.2 mmol; 29%).

${}^{1}H$ NMR ($CDCl_3$): δ 7.92 (d, ${}^{3}J_{HH}$ = 8.5 Hz, 2H), 7.12 (br s, 1H), 6.93 (d, ${}^{3}J_{HH}$ = 8.5 Hz, 2H), 6.68 (br s, 1H), 4.32 (q, ${}^{3}J_{HH}$ = 7.2 Hz, 2H), 1.35 (t, ${}^{3}J_{HH}$ = 7.2 Hz, 3H). ${}^{13}C$ NMR ($CDCl_3$): δ 167.2, 154.3, 131.1, 123.3, 113.1, 61.0, 14.4.



Ar = *p*-carboethoxyphenyl

Table 2, entry 2. $HgCl_2$ (150 mg, 0.55 mmol) was added to a stirring suspension of Mg (1.60 g, 65.8 mmol) in Et_2O (15 mL). The mixture was stirred for 30 min at room temperature and then cooled to 0 °C. Propargyl bromide (80 wt% in toluene; 8.92 g, 60.0 mmol) was added dropwise to this mixture over 40 min, and the resulting mixture was stirred for 1 h at 0 °C, yielding a solution of allenylmagnesium bromide. This solution was added, with the aid of additional THF (10 mL), to a solution of 2-bromo-5-methoxybenzyl bromide (11.2 g, 40.0 mmol) in THF (40 mL) at 0 °C. The mixture was stirred for 24 h at room temperature, and then the reaction was quenched with dilute HCl (aqueous). The resulting mixture was extracted with Et_2O, and the organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 10.2 g of an orange oil. A solution of this oil in THF (40 mL) was treated with LDA [generated from diisopropylamine (6.73 mL, 48.0 mmol) and *n*-BuLi (2.87 M in hexane; 16.7 mL, 47.9 mmol) in THF (50 mL)] at 0 °C, and the resulting mixture was stirred for 2 h at 0 °C. TMSCl (8.6 mL, 67.8 mmol) was added, and the reaction mixture was stirred for 11 h at room temperature. It was then quenched with dilute HCl (aqueous) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O/hexane=1/20 to afford 3-(4'-trimethylsilyl-3'-butynyl)-4-bromoanisole as pale-yellow liquid (9.80 g, 31.5 mmol; 79%).

^{1}H NMR ($CDCl_3$): δ 7.41 (d, $^3J_{HH}$ = 8.7 Hz, 1H), 6.86 (d, $^4J_{HH}$ = 3.0 Hz, 1H), 6.67 (dd, $^3J_{HH}$ = 8.4 Hz and $^4J_{HH}$ = 3.0 Hz, 1H), 3.80 (s, 3H), 2.94 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 2.56 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 0.18 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 158.8, 140.6, 133.2, 116.6, 114.8, 113.8, 106.2, 85.7, 55.6, 35.7, 20.6, 0.5. FTIR (neat) 3002, 2959, 2904, 2835, 2176, 1596, 1573, 1475, 1416, 1305,

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1279, 1249, 1161, 1057, 1043, 1021, 843, 760, 699, 600 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{19}BrOSiNa$ ($M+Na^+$) 333.0281, found 333.0285.

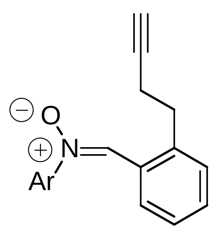
1,2-Dibromoethane (100 μL, 1.16 mmol) was added to a stirring suspension of Mg (842 mg, 34.6 mmol) in THF (2 mL). The resulting mixture was stirred for 5 min (bubbles observed), and then a solution of 3-(4'-trimethylsilyl-3'-butynyl)-4-bromoanisole (9.80 g, 31.5 mmol) in THF (25 mL) was added over 30 minutes. The reaction mixture was stirred for 1.5 h at room temperature. DMF (4.9 mL, 63 mmol) was then added, and the mixture was stirred for 9.5 h at room temperature. The reaction was then quenched with NH_4Cl (aqueous, saturated), and the solution was acidified with HCl (aqueous, 1 N). The reaction mixture was extracted with Et_2O, and the organic layer was dried over Na_2SO_4, filtered, and concentrated to afford a brown oil. The oil was dissolved in methanol (60 mL), and then NaOH (20 mL; aqueous, 6 N) was added. The mixture was stirred for 1 h at room temperature, and then it was neutralized with HCl (aqueous, 6 N). The resulting mixture was concentrated under vacuum and then extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O/hexane=1/4 to 1/2, affording 2-(3'-butynyl)-4-anisaldehyde as pale-yellow oil (4.80 g, 25.5 mmol; 81%).

^{1}H NMR ($CDCl_3$): δ 10.06 (s, 1H), 7.78 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 6.91 (dd, $^3J_{HH}$ = 8.4 Hz and $^4J_{HH}$ = 2.4 Hz, 1H), 6.85 (d, $^4J_{HH}$ = 2.4 Hz, 1H), 3.90 (s, 3H), 3.26 (t, $^3J_{HH}$ = 7.2 Hz, 2H), 2.56 (td, $^3J_{HH}$ = 7.2 Hz and $^4J_{HH}$ = 2.7 Hz, 2H), 2.00 (t, $^4J_{HH}$ = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 191.1, 163.6, 145.1, 136.2, 127.5, 117.2, 112.1, 83.5, 69.8, 55.8, 32.1, 20.4. FTIR (neat) 3292, 2942, 2841, 2740, 2116, 1686, 1600, 1567, 1497, 1464, 1429, 1290, 1252, 1208, 1164, 1119, 1102, 1041, 873, 813 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{12}O_2Na$ ($M+Na^+$) 211.0730, found 211.0737.

A solution of 2-(3'-butynyl)-4-anisaldehyde (1.00 g, 5.31 mmol) and ethyl 4-hydroxyaminobenzoate (962 mg, 5.31 mmol) in ethanol (10 mL) was stirred for 22 h at room temperature. The solvent was then removed under vacuum, and the residue was crystallized from Et_2O to afford the alkyne-nitrone as a pale-yellow solid (707 mg, 2.01

mmol; 38%).

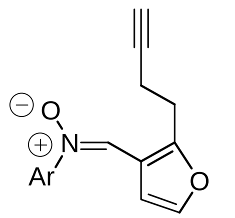
^1H NMR (benzene-d_6): δ 10.19 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 8.03-7.98 (m, 2H), 7.87 (s, 1H), 7.71-7.67 (m, 2H), 6.72-6.66 (m, 2H), 4.11 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 3.29 (s, 3H), 2.54 (t, $^3J_{HH}$ = 7.2 Hz, 2H), 2.13 (td, $^3J_{HH}$ = 7.2 Hz and $^4J_{HH}$ = 2.7 Hz, 2H), 1.76 (t, $^4J_{HH}$ = 2.7 Hz, 1H), 1.04 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR (benzene-d_6): δ 165.5, 161.8, 153.5, 142.0, 132.0, 131.3, 131.1, 130.5, 122.9, 122.3, 117.0, 111.6, 83.4, 71.0, 61.7, 55.3, 32.6, 20.9, 14.8. FTIR (neat) 3291, 3083, 2980, 2939, 2839, 2117, 1716, 1602, 1568, 1499, 1480, 1423, 1367, 1276, 1197, 1170, 1104, 1075, 1041, 1017, 865, 832, 771, 698, 635 cm^{-1}. M.p. 95-97 °C. HRMS (ESI) calcd for $C_{21}H_{22}NO_4$ (M+H$^+$) 352.1543, found 352.1537.



Ar = *p*-carboethoxyphenyl

Table 1; Table 2, entry 1. Alkyne-nitrone **2** was synthesized from 2-bromobenzyl bromide by the procedure described above for Table 2, entry 2. White solid, 11% overall yield.

^1H NMR (CD_2Cl_2): δ 9.35-9.32 (m, 1H), 8.19 (s, 1H), 8.17-8.13 (m, 2H), 7.86-7.83 (m, 2H), 7.46-7.32 (m, 3H), 4.39 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 3.01 (t, $^3J_{HH}$ = 7.5 Hz, 2H), 2.55 (td, $^3J_{HH}$ = 7.5 Hz and $^4J_{HH}$ = 2.7 Hz, 2H), 2.05 (t, $^4J_{HH}$ = 2.7 Hz, 1H), 1.42 (t, $^3J_{HH}$ = 6.9 Hz, 3H). ^{13}C NMR (CD_2Cl_2): δ 165.5, 152.8, 140.0 132.2, 131.9, 131.2, 130.8, 130.2, 129.0, 128.3, 127.2, 122.3, 83.4, 70.2, 61.9, 32.4, 21.1, 14.7. FTIR (neat) 3291, 3104, 3065, 2982, 2906, 2117, 1716, 1604, 1543, 1498, 1466, 1425, 1396, 1367, 1277, 1203, 1172, 1105, 1076, 1017, 868, 772, 697 cm^{-1}. M.p. 92-94 °C. HRMS (ESI) calcd for $C_{20}H_{19}NO_3Na$ (M+Na$^+$) 344.1257, found 344.1258.



Ar = *p*-carboethoxyphenyl

Table 2, entry 3. 3-Bromofuran (3.06 mL, 34.0 mmol) was added to a solution of LDA [generated from diisopropylamine (5.00 mL, 35.7 mmol) and *n*-BuLi (2.87 M in hexane; 12.4 mL, 35.6 mmol) in THF (50 mL)] at 0 °C, and the resulting mixture was stirred for 40 min at 0 °C. DMF (3.2 mL, 41 mmol) was added, and the mixture was stirred for 5.5 h at room temperature. The reaction was quenched with NH_4Cl (aqueous, saturated), and the mixture was diluted with HCl (aqueous, 1N) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was passed through silica gel with Et_2O / hexane=1 / 2 to afford 3.43 g of a yellow oil. This oil was treated with $NaBH_4$ (741 mg, 19.6 mmol) in methanol (50 mL) for 50 min at room temperature. Water was then added, and the mixture was concentrated under vacuum and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 3.56 g of a yellow oil. This oil was dissolved in Et_2O (45 mL), and then PBr_3 (1.96 mL, 20.6 mmol) was added over 5 minutes at 0 °C. The mixture was stirred for 10 h at room temperature, and then the reaction was quenched with ice. After neutralization with $NaHCO_3$, the mixture was extracted with Et_2O, and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O / hexane=1 / 7 to afford 3-bromo-2-bromomethylfuran (CAS 164513-47-7) as colorless oil (3.24 g, 13.5 mmol; 40%).

^{1}H NMR ($CDCl_3$): δ 7.41 (d, $^3J_{HH}$ = 1.9 Hz, 1H), 6.45 (d, $^3J_{HH}$ = 1.9 Hz, 1H), 4.54 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 147.5, 143.6, 114.7, 100.8, 21.4.

$HgCl_2$ (50 mg, 0.18 mmol) was added to a stirring suspension of Mg (542 mg, 22.3 mmol) in Et_2O (5 mL). The resulting mixture was stirred for 30 min at room temperature and then cooled to 0 °C. Propargyl bromide (80 wt% in toluene; 3.01 g, 20.2 mmol) was added dropwise to this solution over 20 min, and the resulting mixture was stirred for 2.5 h at 0 °C to obtain a solution of allenylmagnesium bromide. This solution was added, with the aid of additional THF (3 mL), to a solution of 3-bromo-2-bromomethylfuran (3.24 g, 13.5 mmol) in THF (15 mL) at 0 °C. The mixture was stirred for 18 h at room temperature, and then the reaction was quenched with dilute HCl (aqueous). The mixture was extracted with Et_2O, and the organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 2.78 g of a yellow liquid. A solution of this liquid in THF (15 mL) was treated with LDA [generated from diisopropylamine (2.27 mL, 16.2 mmol) and *n*-BuLi (2.87 M in hexane; 5.64 mL, 16.2 mmol) in THF (18 mL)] at 0 °C. After 1 h of stirring at 0 °C, TMSCl (3.30 mL, 26.0 mmol) was added, and the resulting mixture was stirred for 6.5 h at room temperature. The reaction was then quenched with dilute HCl (aqueous), and the mixture was extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O/hexane=1/30 to afford 3-bromo-2-(4'-trimethylsilyl-3'-butynyl)furan as yellow oil (3.02 g, 11.1 mmol; 82%).

^{1}H NMR ($CDCl_3$): δ 7.28 (d, $^3J_{HH}$ = 2.2 Hz, 1H), 6.36 (d, $^3J_{HH}$ = 1.9 Hz, 1H), 2.90 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 2.55 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 0.17 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 151.1, 141.6, 113.7, 105.4, 97.0, 85.8, 26.0, 19.1, 0.4. FTIR (neat) 3127, 2960, 2919, 2845, 2179, 1600, 1508, 1430, 1379, 1336, 1250, 1190, 1139, 1067, 1042, 1006, 956, 842, 760, 729, 638 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{15}BrOSiNa$ ($M+Na^+$) 292.9968, found 292.9977.

n-BuLi (2.87 M in hexane; 4.27 mL, 12.3 mmol) was added to a solution of 3-bromo-2-(4'-trimethylsilyl-3'-butynyl)furan (3.02 g, 11.1 mmol) in Et_2O (20 mL) at –78 °C. After 50 min of stirring at –78 ° C, DMF (1.73 mL, 22.3 mmol) was added, and the mixture was allowed to warm to room temperature (total time: 14 h). The reaction was quenched with water, and the mixture was acidified through the addition of HCl (aqueous, 1 N) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 3.00 g of orange oil. This oil was dissolved in methanol (20 mL), and NaOH (aqueous, 6 N; 6.5 mL) was added. The mixture was stirred for 1 h at room temperature, neutralized with HCl (aqueous, 6 N), concentrated under vacuum, and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O/hexane=1/5 ∅ 2/5, which afforded 2-(3'-butynyl)-3-furaldehyde as a pale-yellow solid (772 mg, 5.21 mmol; 47%).

^{1}H NMR ($CDCl_3$): δ 9.92 (s, 1H), 7.32 (d, $^3J_{HH}$ = 2.2 Hz, 1H), 6.68 (d, $^3J_{HH}$ = 1.9 Hz, 1H), 3.16 (t, $^3J_{HH}$ = 7.2 Hz, 2H), 2.59 (td, $^3J_{HH}$ = 7.2 Hz and $^4J_{HH}$ = 2.5 Hz, 2H), 2.00 (t, $^4J_{HH}$ = 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 184.7, 162.6, 142.5, 123.4, 108.1, 81.9, 70.4, 26.3, 18.0. FTIR (neat) 3295, 3153, 3127, 2923, 2846, 2749, 2120, 1679, 1584, 1522, 1424, 1399, 1247, 1171, 1125, 1075, 891, 777, 755 cm^{-1}. M.p. 42-44 °C. HRMS (ESI) calcd for $C_9H_8O_2Na$ ($M+Na^+$) 171.0417, found 171.0418.

A solution of 2-(3'-butynyl)-3-furaldehyde (350 mg, 2.36 mmol) and ethyl 4-hydroxyaminobenzoate (428 mg, 2.36 mmol) in ethanol (6 mL) was stirred for 26 h at room temperature. After removing the solvent under vacuum, the residue was crystallized from Et_2O to afford the desired alkyne-nitrone as a white solid (467 mg, 1.50 mmol; 64%).

^{1}H NMR (benzene-d_6): δ 8.12 (d, $^3J_{HH}$ = 2.1 Hz, 1H), 8.03-7.98 (m, 2H), 7.65-7.60 (m, 2H), 7.52 (s, 1H), 6.98-6.97 (m, 1H), 4.11 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 2.54 (t, $^3J_{HH}$ = 7.2 Hz, 2H), 2.20 (td, $^3J_{HH}$ = 7.2 Hz and $^4J_{HH}$ = 2.4 Hz, 2H), 1.74 (t, $^4J_{HH}$ = 2.7 Hz, 1H), 1.03 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR (benzene-d_6): δ 165.5, 156.5, 152.2, 141.8, 132.1, 130.9, 126.3, 122.1, 116.4, 111.8, 83.0, 70.9, 61.7, 26.9, 18.5, 14.8. FTIR (neat) 3296, 3138, 2982, 2935, 2119, 1716, 1597, 1589, 1537, 1516, 1498, 1429, 1388, 1368, 1278, 1208, 1163, 1109, 1082, 1071, 1022, 881, 865, 771, 696 cm^{-1}. M.p. 82-84 °C. HRMS (ESI) calcd for $C_{18}H_{18}NO_4$ ($M+H^+$) 312.1230, found 312.1232.

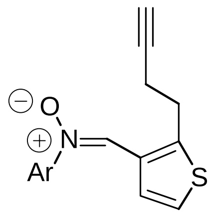


Table 2, entry 4. The alkyne-nitrone was synthesized from 3-bromothiophene by the procedure described above for Table 2, entry 3. Pale-yellow solid, 26% overall yield.

^{1}H NMR (CD_2Cl_2): δ 8.58 (d, $^3J_{HH}$ = 5.4 Hz, 1H), 8.15-8.11 (m, 2H), 8.05 (s, 1H), 7.87-7.83 (m, 2H), 7.27 (d, $^3J_{HH}$ = 5.7 Hz, 1H), 4.39 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 3.21 (t, $^3J_{HH}$ = 7.2 Hz, 2H), 2.60 (td, $^3J_{HH}$ = 7.2 Hz and $^4J_{HH}$ = 2.7 Hz, 2H), 2.10 (t, $^4J_{HH}$ = 2.7 Hz, 1H), 1.41 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR (CD_2Cl_2): δ 165.5, 152.0, 147.4, 132.0, 130.7, 129.7, 128.8, 128.3, 123.0, 122.1, 83.0, 70.6, 61.9, 27.9, 21.9, 14.7. FTIR (neat) 3291, 3100, 2981, 2936, 2907, 2117, 1714, 1605, 1558, 1491, 1436, 1420, 1391, 1367, 1278, 1244, 1212, 1172, 1109, 1084, 1017, 890, 864, 773, 696, 635 cm^{-1}. M.p. 104-106 °C. HRMS (ESI) calcd for $C_{18}H_{17}NO_3SNa$ (M+Na$^+$) 350.0821, found 350.0818.

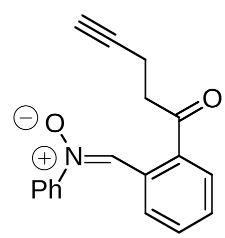
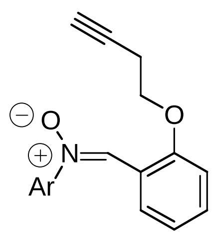


Table 2, entry 5. 1,2-Dibromoethane (0.400 mL, 4.64 mmol) was added to a stirring suspension of Mg (2.07 g, 85.2 mmol) in THF (5 mL). The resulting mixture was stirred for 5 min (bubbles observed), and then 2-bromobenzaldehyde ethylene glycol acetal (17.7 g, 77.3 mmol) in THF (45 mL) was added over 25 minutes. The reaction mixture was stirred for 50 min at room temperature and then cooled to 0 °C. 4-Pentynal (2.53 g, 30.8 mmol) was added, and the mixture was stirred for 12 h at room temperature. Then, the reaction was quenched with NH_4Cl (aqueous, saturated), and the mixture was acidified with HCl (aqueous, 1 N) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O / hexane=1 / 1 to afford 3.83 g of the alkyne-alcohol as a yellow oil. DMSO (2.58 mL, 36.4 mmol) was added to a solution of oxalyl chloride (1.58 mL, 18.1 mmol) in CH_2Cl_2 (45 mL) at –78 °C, and the mixture was stirred for 15 min. A solution of the alkyne-alcohol (3.83 g) in CH_2Cl_2 (15 mL) was added, and the mixture was stirred for 1 h at –78 °C. Triethylamine (11.5 mL, 82.5 mmol) was added, and the mixture was stirred for 3.5 h at room temperature. The reaction was then quenched with water, and the mixture was acidified with HCl (aqueous, 1 N) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 3.75 g of an orange oil. This oil was dissolved in acetone (30 mL) / water (25 mL), and *p*-toluenesulfonic acid (monohydrate; 100 mg, 0.53 mmol) was added. The mixture was refluxed for 4 h, and then $NaHCO_3$ (aqueous, saturated) was added. The reaction mixture was extracted with Et_2O, and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O / hexane=1 / 1 to afford 2-(1'-oxo-4'-pentynyl)benzaldehyde as a yellow oil (2.50 g, 13.4 mmol; 44%).

^{1}H NMR ($CDCl_3$): δ 10.14 (s, 1H), 7.90-7.87 (m, 1H), 7.67-7.61 (m, 3H), 3.17 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 2.67 (td, $^3J_{HH}$ = 7.1 Hz and $^4J_{HH}$ = 2.4 Hz, 2H), 1.99 (t, $^4J_{HH}$ = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 201.6, 191.8, 140.4, 135.6, 133.3, 131.6, 130.3, 127.7, 82.9, 69.3, 40.4, 13.7. FTIR (neat) 3289, 3069, 2918, 2855, 2751, 2120, 1694, 1594, 1573, 1484, 1431, 1407, 1361, 1276, 1244, 1207, 1112, 1053, 987, 827, 761, 641 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{10}O_2Na$ (M+Na^+) 209.0573, found 209.0579.

A solution of 2-(1'-oxo-4'-pentynyl)benzaldehyde (1.00 g, 5.37 mmol) and phenylhydroxyamine (590 mg, 5.41 mmol) in ethanol (10 mL) was stirred for 19 h at room temperature. After removing the solvent under vacuum, the residue was crystallized from Et_2O to afford the alkyne-nitrone as a pale-pink solid (649 mg, 2.34 mmol; 44%).

^{1}H NMR (CD_2Cl_2): δ 8.91-8.89 (m, 1H), 8.55 (s, 1H), 7.78-7.74 (m, 3H), 7.65-7.59 (m, 1H), 7.55-7.46 (m, 4H), 3.25 (t, $^3J_{HH}$ = 7.5 Hz, 2H), 2.64 (td, $^3J_{HH}$ = 7.5 Hz and $^4J_{HH}$ = 2.7 Hz, 2H), 2.05 (t, $^4J_{HH}$ = 2.7 Hz, 1H). ^{13}C NMR (CD_2Cl_2): δ 200.8, 149.4, 137.9 132.2, 131.8, 130.3, 130.1, 129.5, 129.4, 128.9, 128.4, 122.0, 83.8, 69.1, 40.2, 14.1. FTIR (neat) 3294, 3062, 2920, 2118, 1683, 1591, 1567, 1540, 1486, 1458, 1407, 1359, 1297, 1189, 1118, 1073, 982, 765, 689 cm^{-1}. M.p. 84-86 °C. HRMS (ESI) calcd for $C_{18}H_{15}NO_2Na$ (M+Na$^+$) 300.0995, found 300.0995.



Ar = *p*-carboethoxyphenyl

Table 2, entry 6. 2-Bromophenol (2.55 mL, 22.0 mmol) was added to a solution of 4-trimethylsilyl-3-butyn-1-ol (2.85 g, 20.0 mmol) and triphenylphosphine (5.77 g, 22.0 mmol) in CH_2Cl_2 (60 mL). The mixture was cooled to 0 °C, and diethyl azodicarboxylate (3.46 mL, 22.0 mmol) was slowly added over 10 minutes. The reaction mixture was stirred for 12 h at room temperature, and then the solvent was removed under vacuum. The residue was chromatographed on silica gel with Et_2O/hexane=1/3 to afford *o*-bromophenyl 4-trimethylsilyl-3-butynyl ether as a colorless liquid (2.01 g, 6.77 mmol; 34%).

^{1}H NMR ($CDCl_3$): δ 7.56-7.53 (m, 1H), 7.29-7.23 (m, 1H), 6.95-6.83 (m, 2H), 4.16 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 2.80 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 0.21 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 154.9, 133.5, 128.5, 122.4, 114.0, 112.6, 102.3, 86.9, 67.5, 21.1, 0.4. FTIR (neat) 3066, 2959, 2899, 2180, 1587, 1575, 1478, 1470, 1443, 1386, 1278, 1250, 1162, 1127, 1054, 1032, 1022, 920, 844, 747, 699, 667, 643 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{17}BrOSiNa$ (M+Na$^+$) 319.0124, found 319.0121.

n-BuLi (2.87 M in hexane; 2.47 mL, 7.09 mmol) was added to a solution of *o*-bromophenyl 4-trimethylsilyl-3-butynyl ether (2.01 g, 6.77 mmol) in Et_2O (15 mL) at –78 °C. The mixture was stirred for 1 h at –78 °C, and then DMF (1.05 mL, 13.6 mmol) was added. The reaction mixture was stirred for 6.5 h at room temperature, and then it was

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quenched with HCl (aqueous, 1 N) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford a yellow oil. This oil was dissolved in methanol (12 mL), and then NaOH (aqueous, 6 N; 4 mL) was added. The reaction mixture was stirred for 1 h at room temperature and then neutralized with HCl (aqueous, 6 N). After removing the methanol, the mixture was extracted with Et_2O, and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel with Et_2O/hexane=1/5 to afford 2-(3'-butynoxy)benzaldehyde as a pale-yellow oil (405 mg, 2.33 mmol; 34%).

^{1}H NMR ($CDCl_3$): δ 10.51 (s, 1H), 7.84-7.81 (m, 1H), 7.56-7.50 (m, 1H), 7.06-6.96 (m, 2H), 4.21 (t, $^3J_{HH}$ = 6.6 Hz, 2H), 2.75 (td, $^3J_{HH}$ = 6.6 Hz and $^4J_{HH}$ = 3.0 Hz, 2H), 2.08 (t, $^3J_{HH}$ = 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 189.6, 160.7, 135.9, 128.3, 125.1, 121.2, 112.7, 80.0, 70.5, 66.6, 19.7. FTIR (neat) 3294, 3077, 2951, 2886, 2762, 2123, 1688, 1600, 1487, 1458, 1388, 1289, 1243, 1190, 1162, 1104, 1043, 1028, 899, 830, 759, 653 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{10}O_2Na$ ($M+Na^+$) 197.0573, found 197.0574.

A solution of 2-(3'-butynoxy)benzaldehyde (330 mg, 1.89 mmol) and ethyl 4-hydroxyaminobenzoate (342 mg, 1.89 mmol) in ethanol (3 mL) was stirred for 17 h at room temperature. After removing the solvent under vacuum, the residue was crystallized from Et_2O to afford the alkyne-nitrone as a pale-yellow solid (463 mg, 1.37 mmol; 73%).

^{1}H NMR (CD_2Cl_2): δ 9.44-9.41 (m, 1H), 8.54 (s, 1H), 8.16-8.11 (m, 2H), 7.90-7.86 (m, 2H), 7.47-7.41 (m, 1H), 7.13-6.95 (m, 2H), 4.39 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 4.19 (t, $^3J_{HH}$ = 6.6 Hz, 2H), 2.74 (td, $^3J_{HH}$ = 6.6 Hz and $^4J_{HH}$ = 2.7 Hz, 2H), 2.10 (t, $^4J_{HH}$ = 2.7 Hz, 1H), 1.41 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR (CD_2Cl_2): δ 165.5, 156.8, 152.7, 132.6, 131.9, 130.7, 129.4, 128.8, 122.0, 121.5, 120.6, 111.8, 81.0, 70.1, 67.1, 61.9, 20.1, 14.7. FTIR (neat) 3291, 3071, 2982, 2938, 2886, 2120, 1717, 1604, 1595, 1548, 1498, 1466, 1456, 1422, 1393, 1367, 1278, 1249, 1181, 1172, 1109, 1076, 1047, 1017, 954, 894, 867, 828, 771, 756, 694 cm^{-1}. M.p. 113-114 °C. HRMS (ESI) calcd for $C_{20}H_{19}NO_4Na$ ($M+Na^+$) 360.1206, found 360.1207.

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III. Intramolecular Kinugasa Reactions

Because the yields that are reported in the paper are the average of two runs, the yields that are given below for a specific experiment may differ from the values in the paper.

General procedure for Table 1. In a glove box, a solution of CuBr (2.2 mg, 15 μmol) and ligand (17 μmol) in MeCN (0.8 mL) was stirred for 30 min at room temperature. In a separate vessel, Cy_2NMe (32.1 μL, 0.150 mmol) was added to a solution of alkyne-nitrone **2** (0.300 mmol) in MeCN (6.0 mL) at –30 °C. The pre-mixed solution of the Cu(I)/ligand complex, along with additional MeCN (0.7 mL), was added to this –30 °C solution of alkyne-nitrone. The reaction mixture was stirred for 20 h at 0 °C, and then it was passed through a plug of silica gel (washing with EtOAc). The residue was chromatographed on silica gel with Et_2O/hexane = 2/3 to afford β-lactam product **3**.

The ee was determined on a Daicel Chiralpak AD column with hexanes : isopropanol = 90 : 10, flow = 1 mL/min. Retention times: 14.1 min [(3*R*,4*R*)-enantiomer], 21.0 min [(3*S*,4*S*)-enantiomer].

^1H NMR ($CDCl_3$): δ 7.97-7.92 (m, 2H), 7.58-7.50 (m, 3H), 7.34-7.19 (m, 3H), 5.19 (d, $^3J_{HH}$ = 5.2 Hz, 1H), 4.33 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 3.89-3.86 (m, 1H), 2.86-2.77 (m, 2H), 2.53-2.45 (m, 1H), 1.72-1.60 (m, 1H), 1.37 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 168.2, 166.0, 141.5, 140.3, 131.34, 131.28, 130.8, 129.4, 129.0, 126.6, 125.6, 116.6, 61.0, 55.1, 50.7, 27.4, 23.5, 14.6. FTIR (neat) 3370, 2980, 2938, 2851, 1751, 1710, 1605, 1513, 1458, 1424, 1367, 1274, 1174, 1106, 1027, 853, 769, 753 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{19}NO_3Na$ ($M+Na^+$) 344.1257, found 344.1254.

General procedure for Table 2. In a glove box, a solution of CuBr (2.5 mg, 17 μmol) and the ligand (19 μmol) in MeCN (1.0 mL) was stirred for 30 min at room temperature. In a separate vessel, Cy_2NMe (37.5 μL, 0.175 mmol) was added to a solution of the alkyne-nitrone (0.350 mmol) in MeCN (7.0 mL) at –30 °C. The pre-mixed solution of the

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Cu(I)/ligand complex, along with additional MeCN (0.75 mL), was added to the solution of alkyne-nitrone. The resulting mixture was stirred for 20 h at 0 °C, and then it was passed through a plug of silica gel (washing with EtOAc). The residue was chromatographed on silica gel with Et_2O/hexane to afford the desired β-lactam.

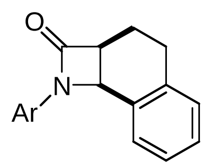

Table 2, entry 1. Pale-yellow solid. 72% yield. 87% ee. $[\alpha]^{20}_{D}$ +43.0 (*c* 0.63, $CHCl_3$). M.p. 104-106 °C.

The absolute configuration of the product was determined through X-ray crystallographic analysis of the bis(amide) that is produced upon the reaction of β-lactam **3** with excess 2-bromobenzylamine (see Section IV).

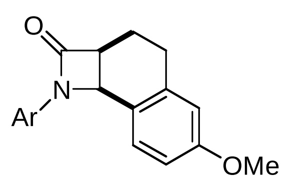

Table 2, entry 2. Pale-yellow solid. 57% yield. The ee was determined on a Daicel Chiralpak AD column with hexanes : isopropanol = 90 : 10, flow = 1 mL/min. Retention times: 22.0 min [(3*R*,4*R*)-enantiomer], 28.1 min [(3*S*,4*S*)-enantiomer]. 84% ee. $[\alpha]^{20}_{D}$ +39.5 (*c* 1.46, $CHCl_3$). The absolute configuration was assigned by analogy with entry 1.

^{1}H NMR ($CDCl_3$): δ 7.96-7.92 (m, 2H), 7.53-7.45 (m, 3H), 6.84-6.73 (m, 2H), 5.15 (d, $^{3}J_{HH}$ = 5.5 Hz, 1H), 4.33 (q, $^{3}J_{HH}$ = 6.9 Hz, 2H), 3.86-3.81 (m, 1H), 3.80 (s, 3H), 2.88-2.70 (m, 2H), 2.48-2.44 (m, 1H), 1.70-1.57 (m, 1H), 1.37 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 168.3,

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165.9, 159.8, 141.7, 141.4, 132.4, 130.7, 125.5, 123.3, 116.5, 114.8, 111.8, 61.0, 55.5, 54.7, 50.6, 27.7, 23.3, 14.6. FTIR (neat) 3369, 2980, 2938, 2850, 1754, 1711, 1606, 1513, 1425, 1368, 1308, 1275, 1174, 1108, 1040, 1025, 853, 769 cm^{-1}. M.p. 85-87 °C. HRMS (ESI) calcd for $C_{21}H_{21}NO_4Na$ ($M+Na^+$) 374.1363, found 374.1359.

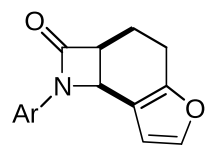

Table 2, entry 3. The reaction was conducted at room temperature. White solid. 45% yield. The ee was determined on a Daicel Chiralpak AD column with hexanes : isopropanol = 90 : 10, flow = 1 mL / min. Retention times: 15.9 min [(3*R*,4*R*)-enantiomer], 23.5 min [(3*S*,4*S*)-enantiomer]. 91% ee. $[\alpha]^{20}_{D}$ –96.9 (*c* 1.75, $CHCl_3$). The absolute configuration was assigned by analogy with entry 1.

^{1}H NMR ($CDCl_3$): δ 8.03-7.98 (m, 2H), 7.50-7.45 (m, 2H), 7.28 (d, $^3J_{HH}$ = 1.9 Hz, 1H), 6.56 (d, $^3J_{HH}$ = 1.9 Hz, 1H), 5.12 (d, $^3J_{HH}$ = 5.5 Hz, 1H), 4.35 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 3.91-3.86 (m, 1H), 2.90-2.83 (m, 1H), 2.75-2.63 (m, 1H), 2.57-2.49 (m, 1H), 1.91-1.78 (m, 1H), 1.39 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 167.7, 166.0, 153.7, 141.1, 140.9, 130.9, 125.6, 116.1, 114.0, 110.9, 61.1, 49.6, 49.3, 22.2, 21.1, 14.6. FTIR (neat) 3370, 3149, 2981, 2940, 2853, 1751, 1711, 1605, 1515, 1425, 1374, 1310, 1277, 1173, 1106, 1022, 887, 853, 769 cm^{-1}. M.p. 129-131 °C. HRMS (ESI) calcd for $C_{18}H_{17}NO_4Na$ ($M+Na^+$) 334.1050, found 334.1052.

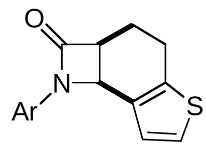

Table 2, entry 4. The reaction was conducted at room temperature. White solid. 67% yield. The ee was determined on a Daicel Chiralpak AD column with hexanes : isopropanol = 90 : 10, flow = 1 mL / min. Retention times: 17.5 min [(3*R*,4*R*)-enantiomer], 27.3 min [(3*S*,4*S*)-enantiomer]. 91% ee. $[\alpha]^{20}_{D}$ –46.5 (*c* 1.25, $CHCl_3$). The absolute configuration was assigned by analogy with entry 1.

^{1}H NMR ($CDCl_3$): δ 8.00-7.96 (m, 2H), 7.53-7.49 (m, 2H), 7.21 (d, $^3J_{HH}$ = 5.0 Hz, 1H), 7.12 (d, $^3J_{HH}$ = 5.2 Hz, 1H), 5.24 (d, $^3J_{HH}$ = 5.5 Hz, 1H), 4.34 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 3.91-3.87 (m, 1H), 3.03-2.98 (m, 1H), 2.86-2.75 (m, 1H), 2.59-2.51 (m, 1H), 1.81-1.69 (m, 1H), 1.38 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 167.9, 165.9, 141.3, 141.2, 131.0, 130.9, 128.3, 125.6, 122.4, 116.2, 61.0, 50.2, 49.8, 23.6, 22.7, 14.6. FTIR (neat) 3370, 3106, 2980, 2938, 2851, 1750, 1711, 1606, 1514, 1425, 1372, 1309, 1276, 1174, 1107, 1018, 852, 769, 722 cm^{-1}. M.p. 111-113 °C. HRMS (ESI) calcd for $C_{18}H_{17}NO_3SNa$ ($M+Na^+$) 350.0821, found 350.0821.

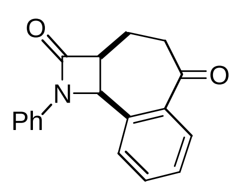

Table 2, entry 5. The reaction was conducted at room temperature. Pale-orange solid. 53% yield. The ee was determined on a Daicel Chiralpak AD column with hexanes : isopropanol = 85 : 15, flow = 1 mL / min. Retention times: 14.4 min [(3*S*,4*S*)-enantiomer], 18.1 min [(3*R*,4*R*)-enantiomer]. 85% ee. $[\alpha]^{20}_{D}$ –50.2 (*c* 1.04, $CHCl_3$). The absolute configuration was assigned by analogy with entry 1.

^{1}H NMR ($CDCl_3$): δ 7.60-7.45 (m, 4H), 7.22-7.15 (m, 4H), 7.04-6.98 (m, 1H), 5.15 (d, $^3J_{HH}$

= 5.8 Hz, 1H), 3.92-3.88 (m, 1H), 3.12-3.00 (m, 1H), 2.79-2.70 (m, 1H), 2.35-2.25 (m, 1H), 2.12-2.01 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 205.4, 166.5, 139.1, 137.4, 133.6, 132.0, 130.5, 129.9, 129.3, 129.1, 124.5, 117.0, 59.6, 52.9, 39.4, 19.9. FTIR (neat) 3351, 3065, 2925, 1753, 1683, 1599, 1499, 1374, 1278, 1228, 1140, 1106, 1086, 951, 867, 749, 692 cm^{-1}. M.p. 109-111 °C. HRMS (ESI) calcd for $C_{18}H_{15}NO_2Na$ (M+Na$^+$) 300.0995, found 300.0988.

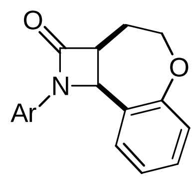

Table 2, entry 6. White solid. 70% yield. The ee was determined on a Daicel Chiralpak AD column with hexanes : isopropanol = 85 : 15, flow = 1 mL / min. Retention times: 16.2 min [(3*R*,4*R*)-enantiomer], 35.0 min [(3*S*,4*S*)-enantiomer]. 89% ee. $[\alpha]^{20}_D$ –45.2 (*c* 1.07, $CHCl_3$). The absolute configuration was assigned by analogy with entry 1.

^{1}H NMR ($CDCl_3$): δ 7.96-7.91 (m, 2H), 7.42-7.31 (m, 4H), 7.21-7.15 (m, 1H), 7.04-7.01 (m, 1H), 5.15 (d, $^3J_{HH}$ = 6.1 Hz, 1H), 4.41-4.30 (m, 1H), 4.32 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 4.08-4.01 (m, 1H), 3.91-3.86 (m, 1H), 2.12-1.95 (m, 2H), 1.37 (t, $^3J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 166.8, 166.0, 154.9, 141.9, 130.90, 130.87, 130.1, 129.2, 125.4, 125.2, 123.5, 116.3, 68.6, 61.0, 58.0, 49.7, 23.2, 14.6. FTIR (neat) 3070, 2989, 2932, 2872, 1755, 1705, 1606, 1515, 1491, 1426, 1374, 1308, 1282, 1258, 1175, 1125, 1102, 1024, 854, 807, 770, 748 cm^{-1}. M.p. 182-184 °C. HRMS (ESI) calcd for $C_{20}H_{19}NO_4Na$ (M+Na$^+$) 360.1206, found 360.1194.

General Procedure for Equations 3 and 4. In a glove box, a solution of CuBr (2.2 mg, 15 μmol) and ligand **5a** (8.1 mg, 17 μmol) in MeCN (0.8 mL) was stirred for 30 min at room temperature. In a separate vessel, allyl iodide (82.3 μL, 0.900 mmol), 1-phenyl-1-(trimethylsilyloxy)ethylene (123 μL, 0.600 mmol), and KOAc (29.4 mg, 0.300 mmol) were

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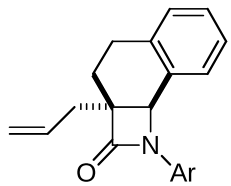
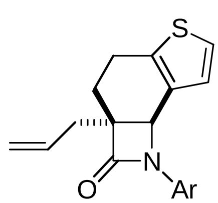
added to a solution of the alkyne-nitrone (0.300 mmol) in MeCN (6.0 mL) at –30 °C. The pre-mixed solution of Cu(I)/**5a**, along with additional MeCN (0.7 mL), was added to the solution of alkyne-nitrone. The resulting mixture was stirred for 21 h at room temperature, and then it was passed through a plug of silica gel (washing with EtOAc). The residue was chromatographed on silica gel with Et_2O/hexane = 1/4 to afford the desired β-lactam.



Equation 3. Yellow oil. 79% yield. The ee was determined on a Daicel Chiralpak AD column with hexanes : isopropanol = 93 : 7, flow = 1 mL/min. Retention times: 14.6 min [(3*R*,4*R*)-enantiomer], 17.8 min [(3*S*,4*S*)-enantiomer]. 84% ee. $[\alpha]^{20}_{D}$ +57.2 (*c* 1.07, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 1.

^{1}H NMR ($CDCl_3$): δ 7.98-7.91 (m, 2H), 7.57-7.47 (m, 3H), 7.31-7.26 (m, 2H), 7.22-7.19 (m, 1H), 5.94-5.82 (m, 1H), 5.26-5.16 (m, 2H), 4.93 (s, 1H), 4.33 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H), 2.91-2.69 (m, 2H), 2.72 (dd, $^{2}J_{HH}$ = 14.0 Hz and $^{3}J_{HH}$ = 6.3 Hz, 1H), 2.54 (dd, $^{2}J_{HH}$ = 14.3 Hz and $^{3}J_{HH}$ = 8.0 Hz, 1H), 2.39-2.33 (m, 1H), 1.59-1.48 (m, 1H), 1.37 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 170.4, 165.9, 141.2, 140.4, 132.6, 131.5, 131.3, 130.8, 129.11, 129.09, 126.6, 125.6, 119.5, 116.7, 61.0, 60.1, 60.0, 38.2, 29.5, 28.0, 14.6. FTIR (neat) 3397, 3076, 2980, 2935, 2850, 1754, 1712, 1606, 1513, 1424, 1368, 1310, 1274, 1174, 1106, 1019, 853, 770 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{24}NO_3$ $(M+H^+)$ 362.1751, found 362.1753.



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Equation 4. Pale-yellow oil. 71% yield. The ee was determined on a Daicel Chiralpak AD column with hexanes : isopropanol = 96 : 4, flow = 1 mL / min. Retention times: 30.3 min [(3*R*,4*R*)-enantiomer], 33.4 min [(3*S*,4*S*)-enantiomer]. 90% ee. $[\alpha]^{20}_{D}$ –14.2 (*c* 1.35, $CHCl_3$). The absolute configuration was assigned by analogy with Table 2, entry 1.

^{1}H NMR ($CDCl_3$): δ 7.99-7.94 (m, 2H), 7.51-7.47 (m, 2H), 7.20-7.10 (m, 2H), 5.94-5.80 (m, 1H), 5.24-5.14 (m, 2H), 4.94 (s, 1H), 4.33 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H), 3.01-2.93 (m, 1H), 2.86-2.66 (m, 2H), 2.53 (dd, $^{2}J_{HH}$ = 14.2 Hz and $^{3}J_{HH}$ = 7.9 Hz, 1H), 2.44-2.37 (m, 1H), 1.67-1.56 (m, 1H), 1.35 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 170.1, 165.9, 141.5, 141.0, 132.5, 131.6, 130.8, 128.3, 125.6, 122.5, 119.6, 116.4, 61.0, 59.5, 54.9, 39.0, 30.0, 23.1, 14.6. FTIR (neat) 3283, 3077, 2980, 2935, 2850, 1750, 1712, 1606, 1514, 1443, 1425, 1372, 1309, 1276, 1174, 1105, 1022, 924, 856, 770, 696 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{22}NO_3S$ $(M+H^+)$ 368.1315, found 368.1307.

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IV. X-ray Crystal Structure of 03108rsm

[the bis(amide) that is produced upon reaction of β-lactam **3** with excess 2-bromobenzylamine]

A colorless MeOH / CH_2Cl_2 solution of the compound was prepared. Crystals suitable for X-ray structural analysis were obtained by solvent evaporation at room temperature.

A colorless needle of dimensions 0.45 x 0.05 x 0.05 mm^3 was mounted under STP and transferred to a Bruker AXS / CCD three-circle diffractometer (χ fixed at 54.78°) equipped with a cold stream of N_2 gas. An initial unit cell was determined by harvesting reflections I > 20 σ(I) from 45 x 10-s frames of 0.30° ω scan data with monochromated Mo K_α radiation (λ = 0.71073 Å). The cell thus determined was orthorhombic.

A hemisphere of data was then collected using ω scans of 0.30° and 25-s frames. The raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. An initial background was determined from the first 12° of data. Backgrounds were then calculated as a continuing average over 8 frames of data. The data that were collected (10850 total reflections, 4004 unique, R_{int} = 0.1567) had the following Miller index ranges: -9 to 10 in h, -9 to 11 in k, and -30 to 29 in l. The data were corrected for Lorentz and polarization effects. No absorption correction was performed.

All aspects of the solution and refinement were handled by SHELXTL NT version 5.10. The structure was solved by direct methods in the chiral orthorhombic space group $P2_12_12_1$, a = 9.829(2) Å; b = 10.462(2) Å; c = 27.135(6) Å; α = 90°; β = 90°; γ = 90°, and refined using standard difference Fourier techniques. Final, full-matrix least-squares refinement (4004 data for 157 parameters) on F^2 yielded residuals of R_1 and wR_2 of 0.1381 and 0.2582 for data I > 2σ(I), and 0.1744 and 0.2767, respectively, for all data. During the final refinement, all non-hydrogen atoms were treated *isotropically*. Hydrogen atoms were included in calculated positions and refined isotropically on a riding model. Residual electron density amounted to a maximum of 2.507 e / $Å^3$ and a minimum of –2.818 e / $Å^3$.

The absolute structure (Flack) parameter for the correct enantiomer is 0.06(4). The structure was also inverted and refined in order to confirm the initial assignment of absolute stereochemistry.

Tables 1-5 provide the full crystallographic data for the X-ray structure.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC–212727. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).

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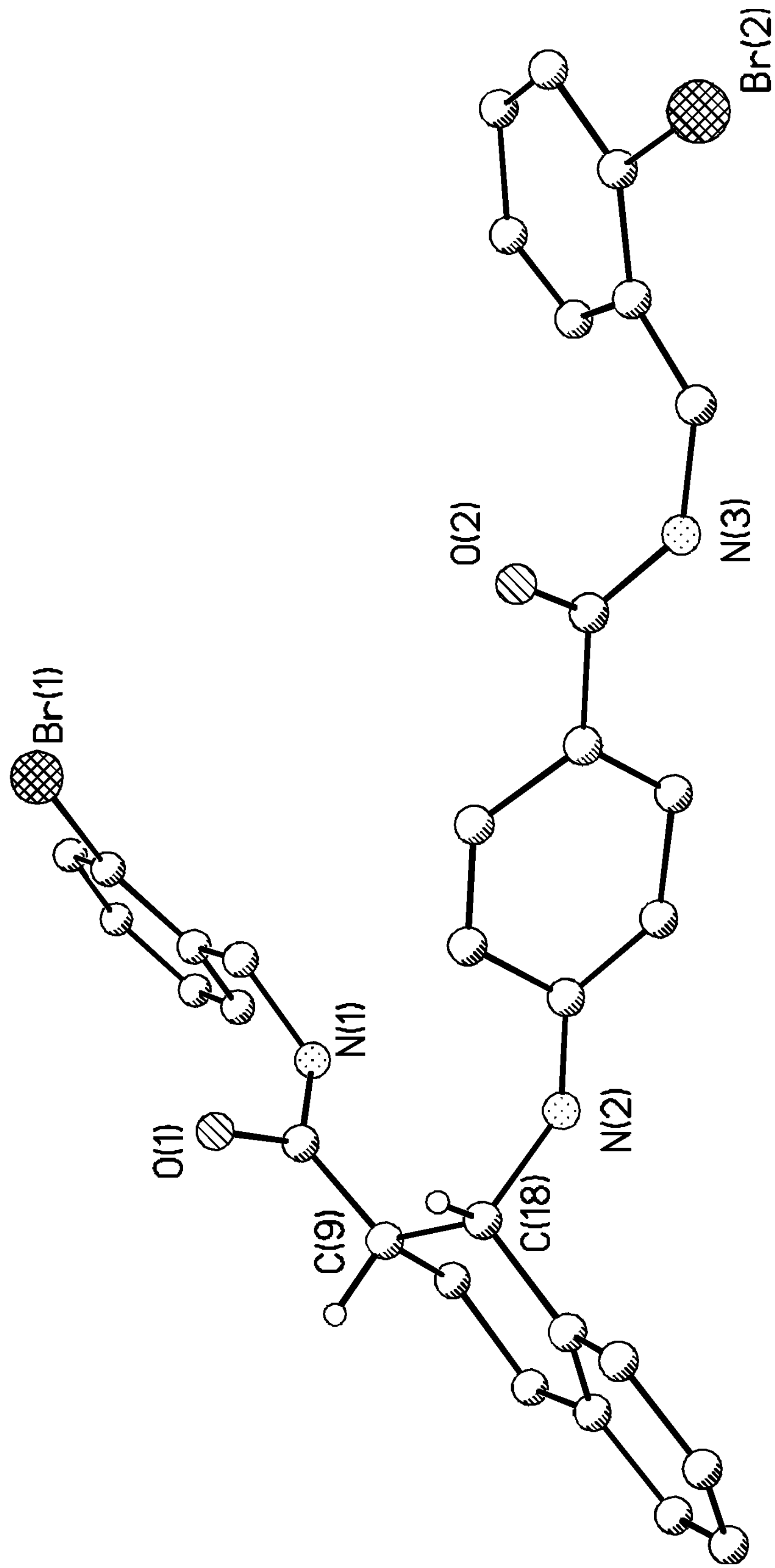

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Table 1. Crystal data and structure refinement for 03108rsm.

Identification code	03108rsm	
Empirical formula	C32 H29 Br2 N3 O2	
Formula weight	647.40	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhomic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.829(2) Å	a= 90°.
	b = 10.462(2) Å	b= 90°.
	c = 27.135(6) Å	g = 90°.
Volume	2790.6(10) Å^3	
Z	4	
Density (calculated)	1.541 Mg/m^3	
Absorption coefficient	2.940 mm^{-1}	
F(000)	1312	
Crystal size	0.45 x 0.05 x 0.05 mm^3	
Theta range for data collection	2.20 to 23.35°.	
Index ranges	-9<=h<=10, -9<=k<=11, -30<=l<=29	
Reflections collected	10850	
Independent reflections	4004 [R(int) = 0.1567]	
Completeness to theta = 23.35°	99.1 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4004 / 0 / 157	
Goodness-of-fit on F^2	1.113	
Final R indices [I>2sigma(I)]	R1 = 0.1381, wR2 = 0.2582	
R indices (all data)	R1 = 0.1744, wR2 = 0.2767	
Absolute structure parameter	0.06(4)	
Largest diff. peak and hole	2.507 and -2.818 e.Å^{-3}	

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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03108rsm. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	-1575(2)	4699(2)	1633(1)	29(1)
Br(2)	-1475(3)	3177(2)	-2561(1)	37(1)
O(1)	-1972(13)	9300(14)	1203(5)	27(4)
O(2)	-1963(12)	6197(13)	-1176(5)	19(3)
N(1)	167(15)	8596(15)	1284(5)	11(4)
N(2)	558(14)	10339(16)	247(5)	10(3)
N(3)	181(14)	5941(14)	-1411(5)	5(3)
C(1)	-46(18)	5480(20)	1962(7)	16(5)
C(2)	510(20)	4850(20)	2354(8)	32(6)
C(3)	1590(20)	5450(20)	2599(8)	37(5)
C(4)	2050(18)	6580(20)	2439(7)	20(5)
C(5)	1500(20)	7219(19)	2035(7)	23(5)
C(6)	422(18)	6668(19)	1795(6)	13(4)
C(7)	-210(20)	7305(19)	1347(7)	19(5)
C(8)	-721(16)	9554(17)	1208(6)	1(4)
C(9)	-296(18)	10821(18)	1098(6)	10(4)
C(10)	1127(18)	11270(20)	1286(7)	20(5)
C(11)	1380(20)	12638(19)	1166(7)	23(5)
C(12)	768(17)	13240(20)	713(6)	11(4)
C(13)	1061(19)	14500(20)	597(7)	21(5)
C(14)	400(20)	15040(20)	199(7)	30(6)
C(15)	-520(20)	14340(20)	-83(8)	29(6)
C(16)	-743(19)	13080(20)	44(7)	17(5)
C(17)	-100(18)	12511(18)	424(6)	6(4)
C(18)	-442(18)	11151(18)	526(6)	10(4)
C(19)	264(17)	9391(18)	-62(6)	9(4)
C(20)	-1016(16)	8742(17)	-68(6)	4(4)
C(21)	-1300(20)	7793(18)	-394(6)	15(5)
C(22)	-358(17)	7408(17)	-758(6)	5(4)
C(23)	911(16)	7957(17)	-742(6)	4(4)
C(24)	1179(16)	8938(16)	-382(6)	4(4)

C(25)	-766(19)	6422(19)	-1123(7)	14(5)
C(26)	-140(15)	5031(15)	-1769(6)	1(4)
C(27)	-39(18)	3667(19)	-1663(7)	18(5)
C(28)	587(19)	3180(20)	-1231(7)	19(5)
C(29)	620(20)	1950(20)	-1085(8)	29(6)
C(30)	55(19)	1020(20)	-1410(7)	20(5)
C(31)	-596(18)	1376(19)	-1842(7)	14(5)
C(32)	-602(19)	2713(19)	-1957(7)	17(5)

Table 3. Bond lengths [Å] and angles [°] for 03108rsm.

Br(1)-C(1)	1.930(19)
Br(2)-C(32)	1.912(19)
O(1)-C(8)	1.258(19)
O(2)-C(25)	1.21(2)
N(1)-C(8)	1.35(2)
N(1)-C(7)	1.41(2)
N(2)-C(19)	1.33(2)
N(2)-C(18)	1.50(2)
N(3)-C(25)	1.31(2)
N(3)-C(26)	1.40(2)
C(1)-C(2)	1.36(3)
C(1)-C(6)	1.40(3)
C(2)-C(3)	1.40(3)
C(3)-C(4)	1.35(3)
C(4)-C(5)	1.39(3)
C(5)-C(6)	1.37(3)
C(6)-C(7)	1.52(3)
C(8)-C(9)	1.42(2)
C(9)-C(10)	1.56(2)
C(9)-C(18)	1.60(2)
C(10)-C(11)	1.49(3)
C(11)-C(12)	1.51(3)
C(12)-C(17)	1.39(2)
C(12)-C(13)	1.39(3)
C(13)-C(14)	1.38(3)
C(14)-C(15)	1.39(3)
C(15)-C(16)	1.38(3)
C(16)-C(17)	1.35(3)
C(17)-C(18)	1.49(3)
C(19)-C(24)	1.34(2)
C(19)-C(20)	1.43(2)
C(20)-C(21)	1.36(2)
C(21)-C(22)	1.41(2)
C(22)-C(23)	1.37(2)

C(22)-C(25)	1.49(3)
C(23)-C(24)	1.44(2)
C(26)-C(27)	1.46(3)
C(27)-C(32)	1.39(3)
C(27)-C(28)	1.42(3)
C(28)-C(29)	1.35(3)
C(29)-C(30)	1.43(3)
C(30)-C(31)	1.39(3)
C(31)-C(32)	1.43(3)
C(8)-N(1)-C(7)	124.0(16)
C(19)-N(2)-C(18)	126.6(15)
C(25)-N(3)-C(26)	121.0(15)
C(2)-C(1)-C(6)	123.1(19)
C(2)-C(1)-Br(1)	118.2(16)
C(6)-C(1)-Br(1)	118.7(14)
C(1)-C(2)-C(3)	118(2)
C(4)-C(3)-C(2)	119(2)
C(3)-C(4)-C(5)	123(2)
C(6)-C(5)-C(4)	118.3(19)
C(5)-C(6)-C(1)	118.2(17)
C(5)-C(6)-C(7)	120.9(18)
C(1)-C(6)-C(7)	120.9(17)
N(1)-C(7)-C(6)	114.1(16)
O(1)-C(8)-N(1)	118.6(17)
O(1)-C(8)-C(9)	118.8(17)
N(1)-C(8)-C(9)	122.4(15)
C(8)-C(9)-C(10)	118.2(16)
C(8)-C(9)-C(18)	112.3(15)
C(10)-C(9)-C(18)	109.5(15)
C(11)-C(10)-C(9)	111.3(17)
C(10)-C(11)-C(12)	120.9(18)
C(17)-C(12)-C(13)	121.5(17)
C(17)-C(12)-C(11)	118.5(17)
C(13)-C(12)-C(11)	120.0(17)
C(14)-C(13)-C(12)	118(2)

C(13)-C(14)-C(15)	122(2)
C(16)-C(15)-C(14)	118(2)
C(17)-C(16)-C(15)	123(2)
C(16)-C(17)-C(12)	118.6(18)
C(16)-C(17)-C(18)	117.3(17)
C(12)-C(17)-C(18)	124.0(16)
C(17)-C(18)-N(2)	107.4(15)
C(17)-C(18)-C(9)	111.5(15)
N(2)-C(18)-C(9)	107.9(14)
N(2)-C(19)-C(24)	121.9(16)
N(2)-C(19)-C(20)	123.5(16)
C(24)-C(19)-C(20)	114.6(16)
C(21)-C(20)-C(19)	122.3(17)
C(20)-C(21)-C(22)	122.0(18)
C(23)-C(22)-C(21)	117.0(16)
C(23)-C(22)-C(25)	123.7(16)
C(21)-C(22)-C(25)	119.2(16)
C(22)-C(23)-C(24)	118.9(16)
C(19)-C(24)-C(23)	124.8(16)
O(2)-C(25)-N(3)	122.9(18)
O(2)-C(25)-C(22)	118.5(18)
N(3)-C(25)-C(22)	118.1(16)
N(3)-C(26)-C(27)	121.0(15)
C(32)-C(27)-C(28)	113.0(18)
C(32)-C(27)-C(26)	124.2(17)
C(28)-C(27)-C(26)	122.7(18)
C(29)-C(28)-C(27)	127(2)
C(28)-C(29)-C(30)	117(2)
C(31)-C(30)-C(29)	121(2)
C(30)-C(31)-C(32)	116.6(18)
C(27)-C(32)-C(31)	125.0(18)
C(27)-C(32)-Br(2)	119.2(15)
C(31)-C(32)-Br(2)	115.9(14)

Symmetry transformations used to generate equivalent atoms:

Table 4.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{3}) for 03108rsm.

	x	y	z	U(eq)
H(1)	1039	8786	1295	14
H(2A)	1086	10901	70	12
H(2B)	1120	9988	482	12
H(3A)	1029	6197	-1377	6
H(2)	184	4043	2456	38
H(3)	2000	5049	2877	45
H(4)	2784	6975	2610	24
H(5)	1862	8014	1928	27
H(7A)	52	6821	1049	23
H(7B)	-1215	7258	1377	23
H(9)	-966	11389	1268	12
H(10A)	1180	11142	1647	24
H(10B)	1843	10734	1131	24
H(11A)	2374	12755	1145	28
H(11B)	1062	13145	1453	28
H(13)	1695	14984	786	26
H(14)	580	15904	114	36
H(15)	-979	14718	-355	35
H(16)	-1375	12594	-143	20
H(18)	-1389	10962	412	12
H(20)	-1692	8983	164	5
H(21)	-2155	7375	-376	17
H(23)	1601	7694	-966	5
H(24)	2070	9288	-372	5
H(26)	-429	5304	-2086	1
H(28)	1027	3788	-1024	23
H(29)	1008	1710	-777	35
H(30)	125	139	-1329	24
H(31)	-1016	764	-2051	17

Table 5. Torsion angles [°] for 03108rsm.

C(6)-C(1)-C(2)-C(3)	1(3)
Br(1)-C(1)-C(2)-C(3)	-178.0(15)
C(1)-C(2)-C(3)-C(4)	-1(3)
C(2)-C(3)-C(4)-C(5)	0(3)
C(3)-C(4)-C(5)-C(6)	1(3)
C(4)-C(5)-C(6)-C(1)	-2(3)
C(4)-C(5)-C(6)-C(7)	-179.3(18)
C(2)-C(1)-C(6)-C(5)	0(3)
Br(1)-C(1)-C(6)-C(5)	179.3(14)
C(2)-C(1)-C(6)-C(7)	178.2(19)
Br(1)-C(1)-C(6)-C(7)	-3(2)
C(8)-N(1)-C(7)-C(6)	-130.2(18)
C(5)-C(6)-C(7)-N(1)	-15(3)
C(1)-C(6)-C(7)-N(1)	167.7(17)
C(7)-N(1)-C(8)-O(1)	2(3)
C(7)-N(1)-C(8)-C(9)	-173.7(17)
O(1)-C(8)-C(9)-C(10)	157.8(17)
N(1)-C(8)-C(9)-C(10)	-27(3)
O(1)-C(8)-C(9)-C(18)	-73(2)
N(1)-C(8)-C(9)-C(18)	102.3(19)
C(8)-C(9)-C(10)-C(11)	-176.4(17)
C(18)-C(9)-C(10)-C(11)	53(2)
C(9)-C(10)-C(11)-C(12)	-31(3)
C(10)-C(11)-C(12)-C(17)	4(3)
C(10)-C(11)-C(12)-C(13)	-177.2(18)
C(17)-C(12)-C(13)-C(14)	3(3)
C(11)-C(12)-C(13)-C(14)	-175.3(18)
C(12)-C(13)-C(14)-C(15)	-1(3)
C(13)-C(14)-C(15)-C(16)	-1(3)
C(14)-C(15)-C(16)-C(17)	-1(3)
C(15)-C(16)-C(17)-C(12)	3(3)
C(15)-C(16)-C(17)-C(18)	179.4(18)
C(13)-C(12)-C(17)-C(16)	-5(3)
C(11)-C(12)-C(17)-C(16)	173.9(17)

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C(13)-C(12)-C(17)-C(18)	179.4(17)
C(11)-C(12)-C(17)-C(18)	-2(3)
C(16)-C(17)-C(18)-N(2)	92.4(19)
C(12)-C(17)-C(18)-N(2)	-91.9(19)
C(16)-C(17)-C(18)-C(9)	-149.6(16)
C(12)-C(17)-C(18)-C(9)	26(2)
C(19)-N(2)-C(18)-C(17)	-127.5(19)
C(19)-N(2)-C(18)-C(9)	112.2(19)
C(8)-C(9)-C(18)-C(17)	175.4(15)
C(10)-C(9)-C(18)-C(17)	-51(2)
C(8)-C(9)-C(18)-N(2)	-66.9(19)
C(10)-C(9)-C(18)-N(2)	66.6(19)
C(18)-N(2)-C(19)-C(24)	163.0(17)
C(18)-N(2)-C(19)-C(20)	-20(3)
N(2)-C(19)-C(20)-C(21)	178.8(17)
C(24)-C(19)-C(20)-C(21)	-4(3)
C(19)-C(20)-C(21)-C(22)	-2(3)
C(20)-C(21)-C(22)-C(23)	6(3)
C(20)-C(21)-C(22)-C(25)	-176.1(17)
C(21)-C(22)-C(23)-C(24)	-4(2)
C(25)-C(22)-C(23)-C(24)	177.9(16)
N(2)-C(19)-C(24)-C(23)	-177.0(16)
C(20)-C(19)-C(24)-C(23)	5(3)
C(22)-C(23)-C(24)-C(19)	-2(3)
C(26)-N(3)-C(25)-O(2)	-6(3)
C(26)-N(3)-C(25)-C(22)	-178.6(15)
C(23)-C(22)-C(25)-O(2)	-164.4(19)
C(21)-C(22)-C(25)-O(2)	17(3)
C(23)-C(22)-C(25)-N(3)	8(3)
C(21)-C(22)-C(25)-N(3)	-170.0(17)
C(25)-N(3)-C(26)-C(27)	-93(2)
N(3)-C(26)-C(27)-C(32)	165.9(17)
N(3)-C(26)-C(27)-C(28)	-10(3)
C(32)-C(27)-C(28)-C(29)	-3(3)
C(26)-C(27)-C(28)-C(29)	173.9(19)
C(27)-C(28)-C(29)-C(30)	5(3)

C(28)-C(29)-C(30)-C(31)	-5(3)
C(29)-C(30)-C(31)-C(32)	3(3)
C(28)-C(27)-C(32)-C(31)	1(3)
C(26)-C(27)-C(32)-C(31)	-175.4(18)
C(28)-C(27)-C(32)-Br(2)	-179.3(13)
C(26)-C(27)-C(32)-Br(2)	4(3)
C(30)-C(31)-C(32)-C(27)	-2(3)
C(30)-C(31)-C(32)-Br(2)	178.8(13)

Symmetry transformations used to generate equivalent atoms:

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References

[1]

R. Shintani, G. C. Fu, *Org. Lett.* **2002**, *4*, 3699–3702.

[2]

D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726–728.