Electronic Supplementary Information

Safe generation and use of bromine azide under continuous flow conditions – selective 1,2-bromoazidation of olefins

David Cantillo, Bernhard Gutmann, and C. Oliver Kappe*

Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010 Graz (Austria)

E-mail: oliver.kappe@uni-graz.at

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**General remarks.** $^1$H-NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 $\times$ 4.6 mm, particle size 5 mm) at 25 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.0 mL min$^{-1}$. The following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. GC/MS (FOCUS-GC/DSQ II MS, ThermoFisher) monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m $\times$ 0.250 mm $\times$ 0.025 μm). After 1 min at 50 °C the temperature was increased in 25 °C min$^{-1}$ steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL min$^{-1}$ in constant-flow mode. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Proof of purity and identity was obtained by $^1$H NMR, $^{13}$C NMR and MS spectroscopy.

**General procedure for the preparation of 1,2-bromine azides from alkenes under continuous flow conditions (Scheme 1).**

**CAUTION:** Bromine azide (BrN$_3$) is a highly poisonous and explosive compound. Proper protective measures (proper shielding and an additional safety screen in the fume hood, safety glasses or a face shield, leather coat, leather or Kevlar gloves) should be used when undertaking work involving BrN$_3$.

The flow setup (cf. Figure 1) consisted of three separate feeds (Feed A, Feed B, and Feed C). The reagents were introduced in the flow reactor using sample loops. Feed A contained 4 mL of a 0.5 M solution of the alkene in DCM. Feed B contained 1.2 equiv (260 mg) of NaN$_3$ and 1.2 equiv (411 mg) of NaBr in water (total volume 4 mL). Feed C contained 2 equiv (1475 mg) of Oxone in water (total volume 6 mL). The solutions A and B were pumped to the system using syringe pumps (Syrris) and solution C was pumped using a HPLC pump. The following flow rates were used: Feed A 600 μL min$^{-1}$, Feed B 600 μL min$^{-1}$, and Feed C 900 μL min$^{-1}$. The three solutions were mixed using a PEEK cross-assembly (0.5 mm i.d.) before entering the photoreactor (FEP tubing, 0.8 mm id, 18 mL volume) (see Figure S2 for details). The crude reaction mixture was immediately quenched in the reactor output with a solution of Na$_2$S$_2$O$_3$ in water after a residence time of ca. 10 min. The organic phase mixture was separated in a separatory funnel, washed three times with water, dried over MgSO$_4$, and evaporated under reduced pressure to yield the desired 1,2-bromine azide adducts.
1-Bromo-1-phenyl-2-ethylazide (2a). (405 mg, 90%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.50 – 7.31 (m, 5H), 5.04 (t, $J$ = 7.3 Hz, 1H), 3.90 (dd, $J$ = 7.3, 3.5 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 138.5, 129.2, 129.0, 127.7, 57.6, 51.1; HRMS (ESI): m/z calcd for C$_8$H$_9$BrN$^+$ [M + H – N$_2$]$^+$ 197.991289, found 197.991567.

Ethyl 2-azido-3-bromo-3-phenylpropionate (2b). (507 mg, 85%); 1:1.4 Mixture of two diastereomers; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (mayor diastereomer) 7.50-7.28 (m, 5H), 5.23 (d, $J$ = 9.6 Hz, 1H), 4.42 (d, $J$ = 9.6 Hz, 1H), 4.30-4.38 (m, 2H), 1.36 (t, $J$ = 7.1 Hz, 1H); (minor diastereomer) 7.50-7.28 (m, 5H), 5.32 (d, $J$ = 7.1 Hz, 1H), 4.30-3.38 (m, 1H) 4.15 (t, $J$ = 7.1 Hz, 1H), 1.16 (t, $J$ = 7.1 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (mayor diastereomer) 167.6, 136.8, 129.5, 128.9, 128.3, 67.3, 62.5, 49.4, 14.1; (minor diastereomer) 167.1, 137.2, 129.3, 128.8, 128.2, 68.1, 62.4, 52.5, 13.9. HRMS (ESI): m/z calcd for C$_{11}$H$_{13}$BrNO$_2$$^+$ [M + H – N$_2$]$^+$ 270.012418, found 270.012781.

1-Bromo-1-(4-chlorophenyl)-2-ethylazide (2c). (448 mg, 86%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38 (s, 5H), 4.99 (t, $J$ = 7.2 Hz, 1H), 3.87 (qd, $J$ = 13.0, 7.3 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 137.1, 135.1, 129.2, 129.1, 57.4, 49.9; HRMS (ESI): m/z calcd for C$_8$H$_8$BrClN$^+$ [M + H – N$_2$]$^+$ 231.952316, found 231.952463.

1-Bromo-1-(3-nitrophenyl)-2-ethylazide (2d). (428 mg, 79%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.32 (t, $J$ = 2.0 Hz, 1H), 8.23 (dd, $J$ = 8.2, 2.2 Hz, 1H), 7.84 – 7.74 (m, 1H), 7.60 (t, $J$ = 8.0 Hz, 1H), 5.08 (t, $J$ = 6.0 Hz, 1H), 3.95 (qd, $J$ = 13.0, 7.1 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 148.4, 140.6, 133.9, 130.1, 124.0, 122.9, 57.2, 48.5; HRMS (ESI): m/z calcd for C$_8$H$_9$BrN$_2$O$_2$$^+$ [M + H – N$_2$]$^+$ 242.976367, found 242.976396.

1-Bromo-1-(4-methoxyphenyl)-2-ethylazide (2e). (443 mg, 86%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.28 (d, $J$ = 8.7 Hz, 1H), 6.95 (d, $J$ = 8.8 Hz, 1H), 4.75 (dd, $J$ = 7.7, 6.1 Hz, 1H), 3.55 (dd, $J$ = 6.9, 1.8 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 160.1, 129.0, 128.2, 114.4, 66.4, 55.4, 55.2; HRMS (ESI): m/z calcd for C$_9$H$_{11}$BrNO$^+$ [M + H – N$_2$]$^+$ 228.001853, found 228.001980.

Ethyl 2-azido-3-bromo-3-(4-nitrophenyl)propionate (2f). (624 mg, 91%); 1:1.1 Mixture of two diastereomers; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.33 – 8.19 (m, 4H), 7.66 (dt, $J$ = 19.4, 8.8 Hz, 4H), 5.41 (dd, $J$ = 8.8, 2.8 Hz, 1H), 5.30 (d, $J$ = 7.8 Hz, 1H), 4.34 (m, 6H), 1.49 – 1.20 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.9, 166.7, 148.2, 144.5, 144.2, 143.7, 129.6, 129.5, 129.2, 124.2, 124.0, 123.9, 67.1, 67.0, 62.9, 62.9, 50.3, 48.1, 47.2, 46.1, 14.1, 14.0; HRMS (ESI): m/z calcd for C$_{11}$H$_{12}$BrN$_2$O$_4$$^+$ [M + H – N$_2$]$^+$ 314.997496, found 314.997908.

1-Bromo-1,2-diphenyl-2-ethylazide (2g). (507 mg, 84%); 1:3:1 mixture of diastereomers; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.48 – 7.02 (m, 10H), 5.07 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 140.0, 138.1, 138.0, 136.8, 136.3, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 127.9, 127.8, 127.5, 72.2, 71.2, 57.9, 55.7; HRMS (ESI): m/z calcd for C$_{14}$H$_{13}$BrN$^+$ [M + H – N$_2$]$^+$ 274.022804, found 274.022804.

1-Bromo-1,2-bis(4-cyanophenyl)-2-ethylazide (2h). (535 mg, 76%); 1:1:1 mixture of diastereomers; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.69 (dd, $J$ = 11.5, 8.4 Hz, 4H), 7.57 (t, $J$ = 8.2 Hz, 4H), 7.51 (d, $J$ = 8.4 Hz, 2H), 7.41 (d, $J$ = 8.3 Hz, 2H), 7.33 (d, $J$ = 8.4 Hz, 2H), 7.24 (d, $J$ = 8.4 Hz, 2H), 5.11 (d, $J$ = 8.0 Hz, 2H), 5.07 (d, $J$ = 8.2 Hz, 1H), 4.98 (t, $J$ = 7.3 Hz, 1H), 3.87 (dd, $J$ = 7.3, 3.5 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 148.1, 144.2, 144.5, 143.7, 129.6, 129.5, 129.2, 124.2, 124.0, 123.9, 67.1, 67.0, 62.9, 62.9, 50.3, 48.1, 47.2, 46.1, 14.1, 14.0; HRMS (ESI): m/z calcd for C$_{11}$H$_{12}$BrN$_2$O$_4$$^+$ [M + H – N$_2$]$^+$ 314.997496, found 314.997908.
Hz, 1H), 5.02 (s, 2H), 4.98 (d, J = 8.0 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 142.2, 142.1, 141.3, 140.7, 132.6, 132.5, 132.4, 129.5, 129.2, 128.4, 128.3, 118.0, 117.9, 113.3, 113.2, 113.1, 112.9, 70.8, 70.2, 55.2, 53.2; HRMS (ESI): m/z calcd for C$_{16}$H$_{11}$BrN$_3$ $^+$ [M + H – N$_2$]$^+$ 324.013118, found 324.013087.

1-Bromo-1,2-bis(4-methoxyphenyl)-2-ethylazide (2i). (580 mg, 80%); 1:1.1 Mixture of diastereomers; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.51 – 6.69 (m, 16H), 5.12 – 5.00 (m, 3H), 4.96 (d, J = 9.4 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.9, 159.9, 159.6, 159.5, 159.3, 159.2, 129.8, 129.5, 129.1, 129.0, 128.9, 128.8, 128.3, 127.4, 126.2, 114.1, 113.9, 113.9, 113.8, 71.8, 70.8, 58.1, 56.1, 55.3; HRMS (ESI): m/z calcd for C$_{16}$H$_{17}$BrNO$_2$ $^+$ [M + H – N$_2$]$^+$ 334.043718, found 334.04363.

Synthesis of 2-phenyl aziridine (3). 2 mmol of styrene were processed using the continuous flow 1,2-bromoazidation protocol described above. The crude material obtained was dissolved in dry Et$_2$O (4 mL) and added dropwise to a stirred suspension of LiAlH$_4$ (6 mmol, 228 mg) in dry Et$_2$O (10 mL). The mixture was further stirred for 15 min and then quenched with an excess of sat. NaHCO$_3$. The organic phase was evaporated, and the crude product purified by flash chromatography using petroleum ether/ethyl acetate as eluent. (148 mg, 62%); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.42 – 7.15 (m, 5H), 3.04 (dd, J = 6.0, 3.4 Hz, 1H), 2.23 (d, J = 6.0 Hz, 1H), 1.82 (d, J = 3.4 Hz, 1H), 1.16 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.4, 128.5, 127.1, 125.7, 32.1, 29.3; MS-EI: m/z 119 (15%), 118 (100%), 117 (20%), 91 (25%).

Synthesis of 2,3-diphenyl-2H-azirine (4a). 2 mmol of stilbene were processed using the continuous flow 1,2-bromoazidation protocol described above. The crude material obtained was dissolved in dry THF (5 mL), and then 1.5 equiv (336 mg) of KOTBu were added under stirring. After 15 min at room temperature the reaction mixture was quenched with water (5 mL) and diluted with Et$_2$O (5 mL). The organic phase was washed with water, dried over MgSO$_4$, and evaporated under reduced pressure. The crude oil was dissolved in toluene (4 mL) and heated at 150 °C for 15 min. Then, the solvent was removed and the residue purified by column chromatography using petroleum ether/ethyl acetate as eluent (202 mg, 52%); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.97 – 7.91 (m, 2H), 7.60 (ddd, J = 7.2, 6.3, 3.3 Hz, 3H), 7.38 – 7.24 (m, 3H), 7.21 – 7.16 (m, 2H), 3.36 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.5, 140.9, 133.2, 129.9, 129.3, 128.3, 127.1, 126.1, 124.1, 34.5; MS-EI: m/z 194 (15%), 193 (100%), 192 (45%), 165 (40%).

Synthesis of 2,3-bis(4-cyanophenyl)-2H-azirine (4b). 2 mmol of 4,4’-dicyanostilbene were processed using the continuous flow 1,2-bromoazidation protocol described above. The crude DCM solution obtained from the reactor was treated with a 1 M solution of KOH in ethanol (1.5 equiv, 3 mL). After 15 min at room temperature the solution was washed with water, dried over MgSO$_4$, and evaporated under reduced pressure. The crude oil was dissolved in toluene (4 mL) and heated at 150 °C for 15 min.
Then, the solvent was removed and the residue purified by column chromatography using petroleum ether/ethyl acetate as eluent (370 mg, 76%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.07 – 7.98 (m, 2H), 7.89 (d, $J$ = 8.6 Hz, 2H), 7.60 (d, $J$ = 8.4 Hz, 2H), 7.24 (d, $J$ = 8.5 Hz, 2H), 3.45 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 162.4, 145.4, 133.2, 132.3, 130.3, 127.1, 126.6, 118.7, 117.5, 117.1, 111.2, 34.8, 34.8; MS-EI: m/z 244 (15%), 243 (100%), 215 (15%).

**Synthesis of ethyl 1Indole-2-carboxylate (5).** 2 mmol of ethyl cinnamate were processed using the continuous flow 1,2-bromoazidation protocol described above. The crude DCM solution obtained from the reactor was treated with a 1 M solution of KOH in ethanol (1.5 equiv, 3 mL). After 15 min at room temperature the solution was washed with water, dried over MgSO$_4$, and evaporated under reduced pressure. The crude oil was dissolved in toluene (4 mL) and heated at 160 °C for 15 min. Then, the solvent was removed and the residue crystallized from cyclohexane (284 mg, 75%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.23 (s, 1H), 7.72 (d, $J$ = 8.9 Hz, 1H), 7.46 (d, $J$ = 8.3 Hz, 1H), 7.35 (t, $J$ = 7.6 Hz, 1H), 7.27 (d, $J$ = 2.9 Hz, 1H), 7.18 (t, $J$ = 7.5 Hz, 1H), 4.46 (q, $J$ = 7.1 Hz, 1H), 1.46 (t, $J$ = 7.1 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 162.2, 136.9, 127.5, 125.3, 122.6, 120.8, 111.9, 108.7, 61.1, 14.4; MS-EI: m/z 244 (15%), 243 (100%), 215 (15%). MS-EI: m/z 189 (50%), 143 (100%), 115 (40%), 89(45%).
Figure S1. Continuous flow setup utilized for the 1,2-bromoazidation of alkenes. Pump A: DCM or EtOAc, 600 μL/min; Pump B: water, 600 μL/min; Pump C: water, 900 μL/min; Loop A: 4 mL, 0.5 M substrate in DCM or EtOAc; Loop B: 4 mL, 1.2 equiv NaBr + 1.2 equiv NaN₃; Loop C: 6 mL, 2 equiv Oxone; Photoreactor: for details see Figure S2.
Figure S2. Schematic view of the continuous flow photochemical reactor utilized for the 1,2-bromo azidation of alkenes.
Figure S3. (a) GC-MS chromatogram of the crude reaction mixture for the 1,2-bromoazidation of styrene under optimal conditions (cf Table 1, entry 3). (b) a) HPLC chromatogram of the crude reaction mixture for the 1,2-bromoazidation of ethyl cinnamate under optimal conditions (cf Table 1, entry 7).
Mechanism of the Hemetsberger-Knittel indolization

The mechanism of the Hemetsberger-Knittel indolization reaction is believed to proceed in two steps via the aziridine intermediate $4c$ (Scheme S1). Our procedure to generate the vinyl azide from HBr elimination gives a mixture (80:20) of the two possible E/Z isomers ($VA + VA'$). Upon heating at 160 °C for 15 min, pure indole $5$ was observed by HPLC analysis.

![Scheme S1. Accepted mechanism for the Hemetsberger-Knittel indolization.](image)

To shed light into the mechanism we performed the reaction at lower temperature (120 °C) and carefully monitored the reaction progress by HPLC. Notably, we were able to detect the aziridine intermediate (Figure S3), which is rapidly formed upon heating. A fraction of the reaction mixture was cooled at this point and the solvent evaporated under reduced pressure. NMR analysis of the crude product confirmed the structure of the aziridine intermediate. After further heating at 120 °C during 150 min the aziridine $4c$ was slowly transformed into the indole $5$ (Figure S4).

![Figure S4. HPLC monitoring of the thermolysis of $VA + VA'$ in toluene at 120 °C.](image)
A preliminary DFT evaluation of the reaction pathway at the M06-2X/6-311G(d,p) level\textsuperscript{[S2]} was also performed using the Gaussian09 software package.\textsuperscript{[S3]} All stationary points located for the reaction pathway are depicted in Figure S5. Notably, the process proceeds via two transition states. In a first transition structure the extrusion of nitrogen takes places resulting in a stable aziridine intermediate. This transformation is exothermic and 34.7 kcal/mol are released (from the most stable vinyl azide isomer VA). In the second transition structure the aziridine nitrogen approach the aromatic carbon to form a non-aromatic intermediate, which rapidly rearranges to the aromatic indole 5. The energy barrier for the second step (+43.9 kcal/mol) is significantly higher as compared to the barrier for the first step (+32.9 and +28.9 kcal/mol). This explains that the formation of the aziridine is much faster, and this intermediate stable enough to be isolated.

Interestingly, no nitrene intermediates could be located for the indolization pathway in this case. IRC calculation from the transition state VA→4c (Figure S6) confirmed that the transition state directly connects the vinyl azide with the aziridine. Yet, the shape of the energy profile suggests that for other substrates, possibly with electron-withdrawing groups attached to the aromatic ring, the nitrene intermediate could be stabilized and be located.
Figure S6. IRC calculation for the extrusion of N₂ from VA.


