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Synthesis of Polysubstituted Isoquinolines and Related Fused Pyridines from Alkenyl Boronic Esters via a Copper-Catalyzed Azidation/Aza-Wittig Condensation Sequence

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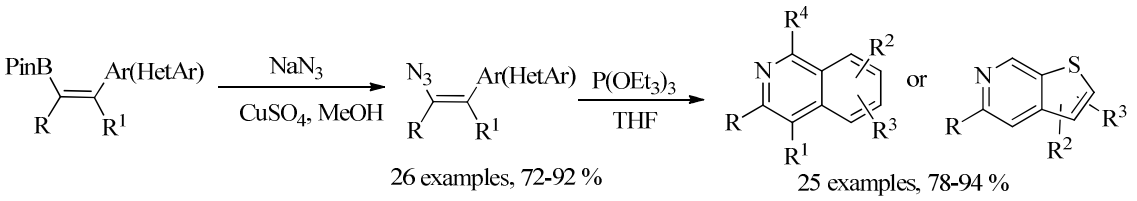
Abstract:

An efficient and straightforward synthesis of isoquinolines is reported from internal alkenyl boronic esters, easily prepared from the corresponding 1,2-bis(boronates), via a sequential copper-catalyzed azidation / aza-Wittig condensation. This synthetic method has been used to synthesize quinisocaine, a topical anesthetic used for the treatment of pain and pruritus, and further extended to thieno[2,3-*c*]pyridines by using 2-thiophenecarboxaldehyde as coupling partner in the first step.

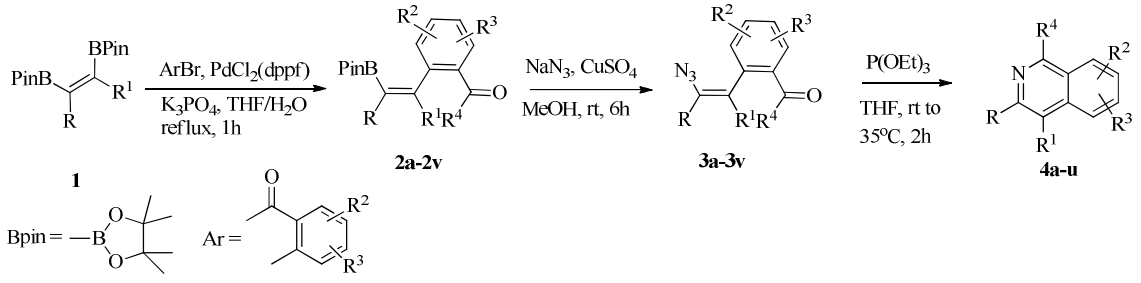


INTRODUCTION

The isoquinoline core, and the related heterocycle-fused pyridine motifs, can be found in many natural products.[1] These structural frameworks also constitute the common substructures of a large variety of biologically active substances and organic materials.[2,3] Due to such diverse properties, rapid and efficient routes to access isoquinolines are still attracting considerable attention from organic chemists over the past few years and a number of different synthetic strategies were devised for these nitrogen heterocycles. If the Bischler-Napieralski [4] and Pomerantz-Fritsch [5] reactions are classically used, alternative protocols, often possessing milder reaction conditions, wider substrate scope, and better functional compatibilities, are now available.[6] During the past decade, transition-metal-catalyzed annulation reactions have proven to be valuable key process for the synthesis of isoquinolines.[7] With respect to processes that do not use metal catalysts, intramolecular aza-Wittig reaction,[8] which occurs under mild and neutral conditions, has been also exploited to access isoquinolines and isoquinolones.[9] To the best of our knowledge, this approach was hitherto restricted to ester-substituted substrates resulting from the condensation reaction of an aldehyde with ethyl or methyl azidoacetate.

Organoboranes have recently emerged as valuable precursors of azido compounds via their copper(II)-catalyzed reaction with sodium or trimethylsilyl azide [10] that greatly increases the range of available vinyl azides. In this context, and on the basis of our previous works on alkenyl 1,2-bis(boronic esters),[11] herein we report a practical access to isoquinolines from these easily available starting material, based on a three steps sequence: regioselective Suzuki-Miyaura coupling with a 2-formyl aryl bromide / azidation / aza-Wittig condensation (Scheme 1).

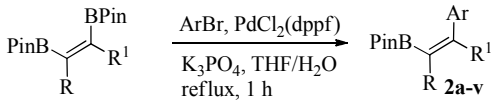
Scheme 1. Synthesis of isoquinolines **4** from alkenyl 1,2-bis(boronic esters) **1**



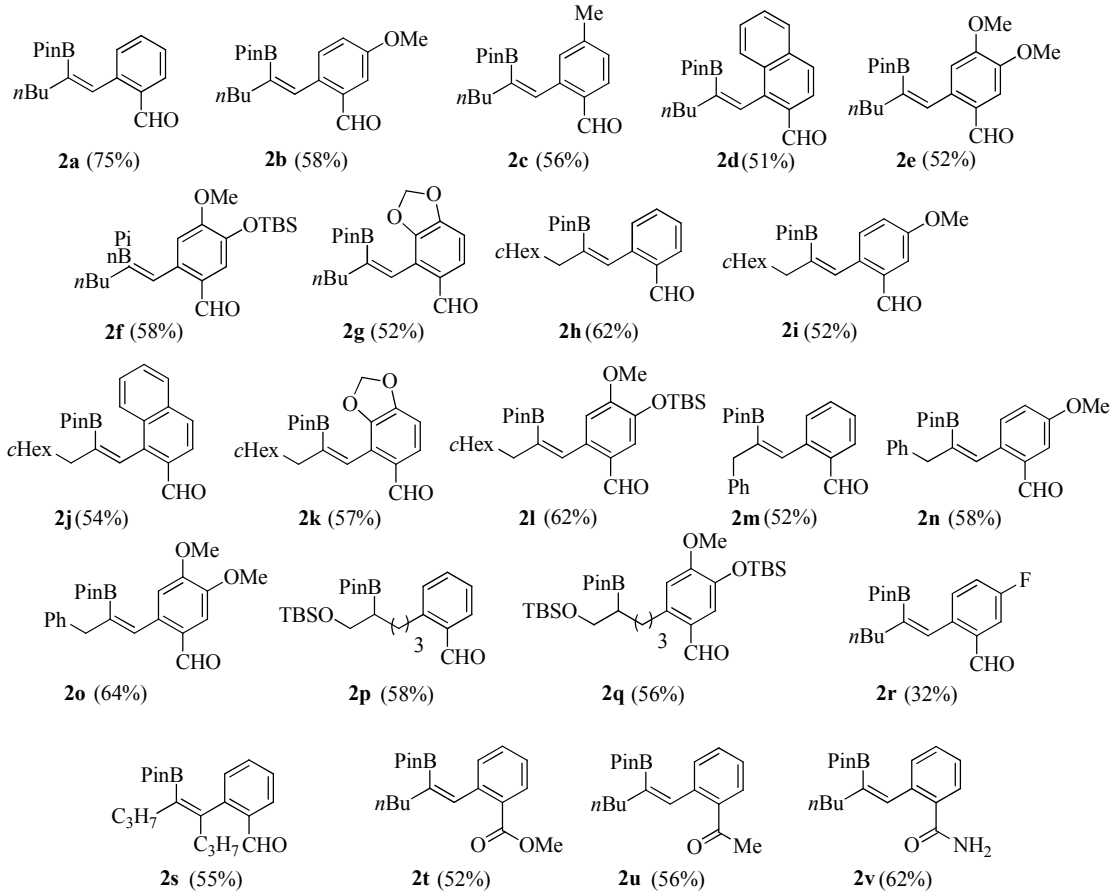
RESULTS AND DISCUSSION

(*E*)-Alkenyl 1,2-bis(boronates) **1a-e** were first prepared in good yields from the corresponding 1-alkynes and bis(pinacolato)diboron in the presence of tetrakis(triphenylphosphine)platinum as catalyst, according to reported procedures.[12] These compounds were then regioselectively converted to the internal boronic esters via Suzuki–Miyaura cross-couplings with 2-formyl aromatic halides in the presence of $Pd(dppf)Cl_2$ and K_3PO_4 in THF/H_2O at reflux as previously reported.[11] Yields are good to moderate with the formation of a single (*E*)-stereoisomer **2**, as ascertained by NMR spectroscopy (Scheme 2). Replacement of the aldehyde group by an ester, ketone or amide motif has no significant influence on the course of the coupling reaction.

Scheme 2. Suzuki–Miyaura cross-couplings with 1,2-bis(boronates) **1** [a,b]



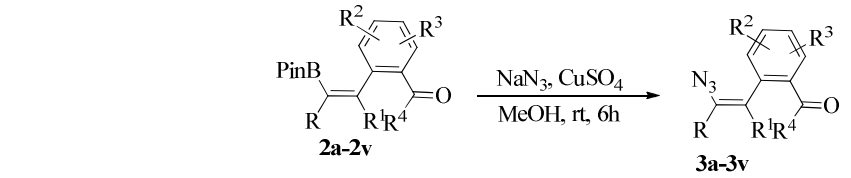
1a R = *n*-Bu, R^1 = H **1d** R = C_3H_6OTBS, R^1 = H
1b R = CH_2Ph, R^1 = H **1e** R = R^1 = C_3H_7
1c R = CH_2-*c*Hex, R^1 = H



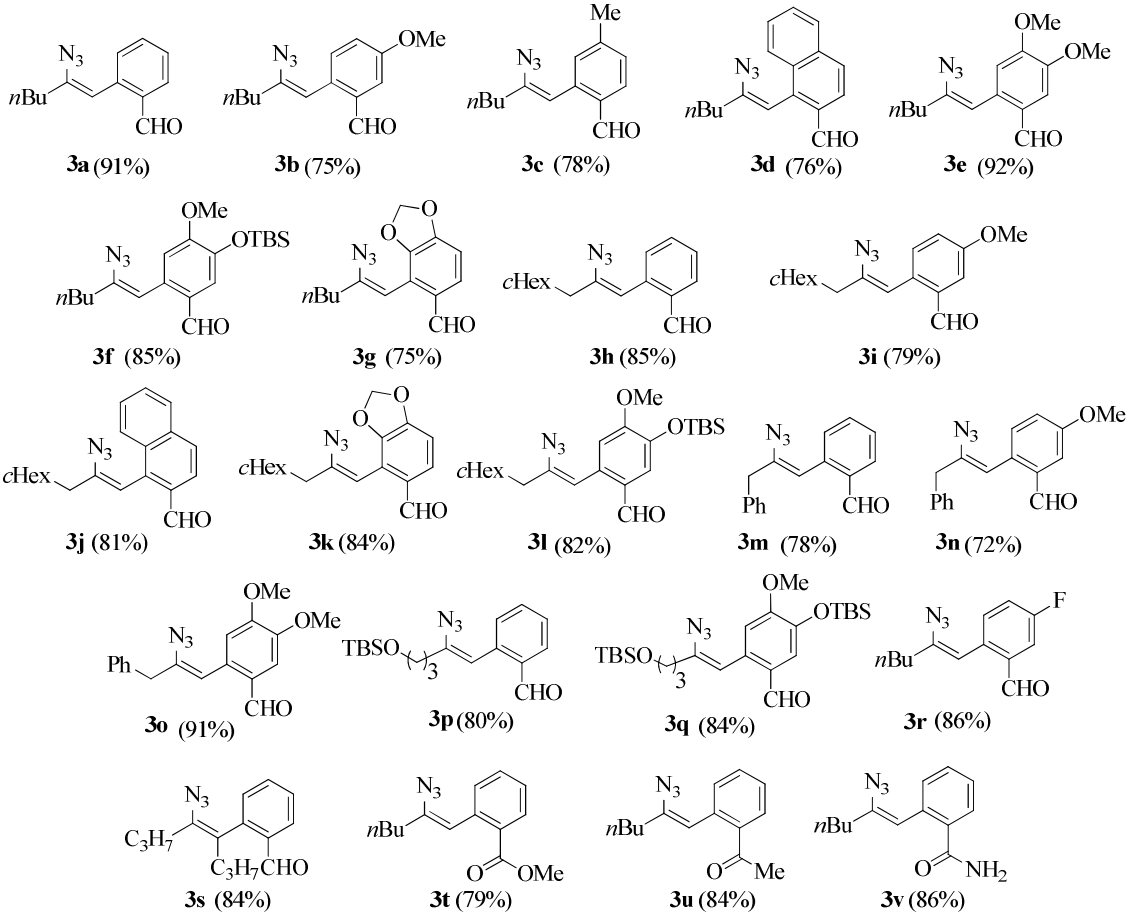
[a] General conditions: **1** (0.5 mmol), [1, 1'-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (0.01 mmol), potassium phosphate tribasic monohydrate (1.5 mmol) and arylbromide (0.5 mmol), THF (5 mL)/water (0.1 mL), reflux, 1 h. [b] Yields of isolated products.

We then studied the copper-catalyzed transformation of compounds **2** to the corresponding azides in methanol that took place at room temperature after 6 h, to give the azide in good yields (72 to 92%). The reaction was compatible with the presence of various functionalities, including carbonyl groups, alkyl and silyl ethers, fluorine, ester and amide (Scheme 3).

Scheme 3. Copper-catalyzed conversion of boronates **2** into azides **3**.[a,b]



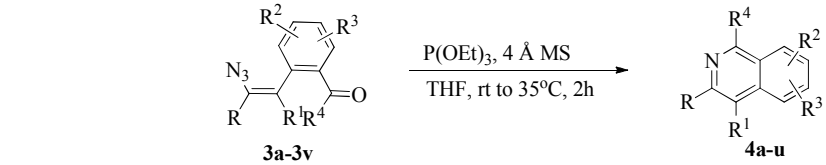
2a-2v **3a-3v**



[a] General conditions: **2** (0.5 mmol), sodium azide (0.6 mmol) and copper sulfate (0.3 mmol), MeOH (2 mL), rt, 6 h.
[b] Yields of isolated products.

We further investigated the substrate scope of the intramolecular aza-Wittig reaction of azidoaldehydes **3a-3v** in the presence of triethylphosphite. The desired quinolines **4a-4u** were isolated in yields ranging from 82% to 93% after 2 hours at 35 °C in THF (Scheme 4). This cyclization was not restricted to aldehyde derivatives and good yields were also observed with a ketone and an ester group. While, it failed with the amide **3v**.

Scheme 4. Synthesis of isoquinolines **4** from azides **3**.[a,b]



3a-3v **4a-u**

4a (93%) **4b** (85%) **4c** (85%) **4d** (83%) **4e** (84%)

4f (90%) **4g** (82%) **4h** (91%) **4i** (89%)

4j (92%) **4k** (88%) **4l** (90%) **4m** (89%) **4n** (87%)

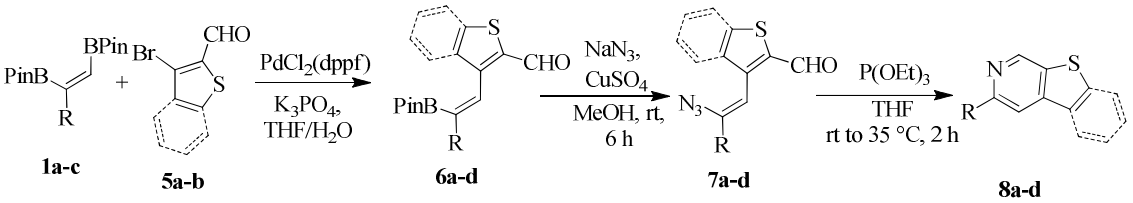
4o (86%) **4p** (85%) 3 **4q** (92%) **4r** (91%)

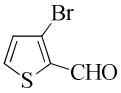
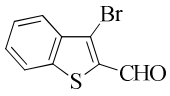
4s (91%) **4t** (87%) **4u** (88%) **4v** (0%)

[a] General conditions: **3** (0.5 mmol) THF (3 mL), 4 Å molecular sieves and triethylphosphite (0.5 mmol), THF (4 mL), rt, 30min.; triethoxyphosphite (1 mmol), 35 °C, 1.5 h. [b] Yields of isolated products.

Like isoquinolines, thieno[2,3-c]pyridines, which belong to the related fused pyridine family, are an important class of biologically active molecules.[13,14] Our above described approach was transposed to this class of heterocycles, to provide the starting Suzuki partner as a thiophene derivative. We thus succeeded to synthesize compounds **6a-6d** according to a three steps sequence in good overall yields from 3-bromothiophene-2-carboxaldehyde and 3-bromobenzothiophene-2-carboxaldehyde selected as model heteroaromatic halides (Table 1).

Table 1. Synthesis of thieno[2,3-c]pyridines **8** from bisboronates **1**.[a]

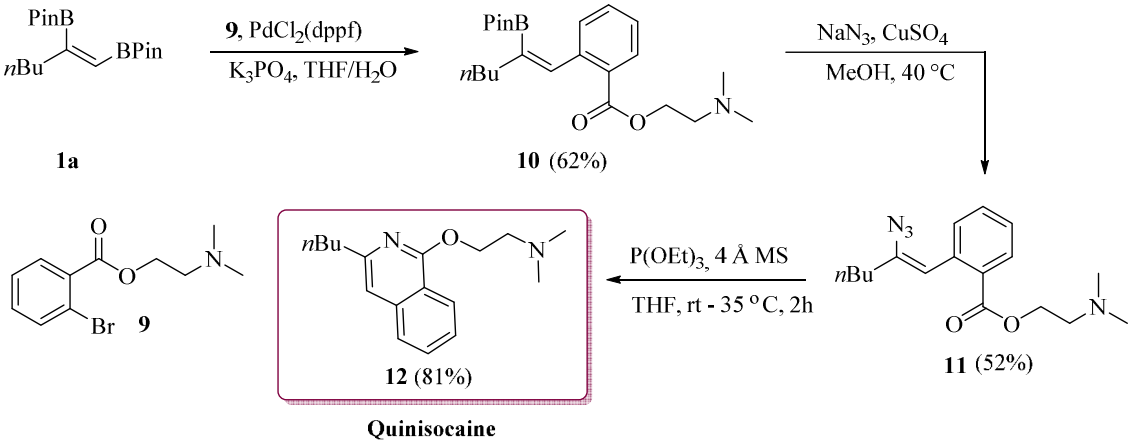


Entry	R	Heteroaromatic halide	Yield(%) 6	7	8
a	*n*-Bu		59	88	86
b	CH_2cHex	"	64	92	94
c	CH_2Ph	"	58	87	88
d	*n*-Bu		52	75	78

[a] Yields of isolated products

Finally, the utility of this sequence was demonstrated by the synthesis of quinisocaine, (dimethisoquin), a topical anesthetic used for the treatment of pain and pruritus.[15] The boronate **10** was first synthesized from **1a** and 2-(dimethylamino) ethyl 2-bromobenzoate **9** in a 62% yield. In presence of sodium azide and copper sulfate, it was readily converted to the corresponding azide **11**, which after an intramolecular aza-Wittig condensation, gave quinisocaine **12** in 81% yield (Scheme 5).

Scheme 5. Synthesis of Quinisocaine.



In conclusion, an efficient and widely applicable synthesis of isoquinolines from easily accessible or commercially available reactants was developed. The key features of this method are a regioselective Suzuki coupling at the terminal C-B bond of a (*E*)-1-alkene-1,2-

diboronic ester, the copper-catalyzed azidation and intramolecular Aza-Wittig reactions. This approach has been successfully extended to thieno[2,3-*c*]pyridines and exemplified by the synthesis of quinisocaine, a topical anesthetic.

EXPERIMENTAL SECTION

General Information and Materials. All commercially available chemicals were used without further purification. Tetrahydrofuran (THF) and diethylether were used as received. Analytical thin layer chromatography was performed on Silica Gel 60 F254 plates. The compounds were characterized by ^{1}H, ^{13}C NMR and ^{11}B NMR. Spectra were recorded in $CDCl_3$ (internal standard: 7.26 ppm for ^{1}H; 77.00 ppm for ^{13}C). ^{11}B NMR chemical shifts are related to external $BF_3 \cdot OEt_2$ (0.0 ppm). High-resolution mass spectra (HMRS) were recorded on a micro-TOF-Q II mass analyzer or Q-TOF 2 using positive ion electrospray. Compounds **1** were synthesized according to literature procedures.[12]

General Procedure for the Suzuki–Miyaura Cross-Couplings with 1, 2-Bis(boronates) (1a-1e). *Synthesis of compounds **2a-2v** and **6a-6d.*** A solution of bispinacolate ester **1** (0.89 mmol) in THF (8.9 mL) and water (0.18 mL) was degassed under argon atmosphere before the addition of [1, 1'-bis (diphenyl phosphino)ferrocene] dichloropalladium(II) (13.5 mg, 0.018 mmol), potassium phosphate tribasic monohydrate (616 mg, 2.66 mmol) and arylbromide (0.89 mmol). The reaction mixture was heated at reflux for 1 h, cooled to room temperature, diluted with water and extracted with Et_2O (2 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by column chromatography (230-400 mesh Silica gel, EtOAc in Hexane) to give the corresponding Suzuki products **2** or **6**.

The characterisation of compounds **2a, 2b, 2d, 2e, 2l, 2n** and **2o** was already reported in our previous paper.[11]

(E)-4-Methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)benzaldehyde (2c). 164 mg (56%). Colorless oil, R_f = 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.22 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.30 (s, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.11 (s, 1H), 2.37-2.34 (m, 5H), 1.58-1.45 (m, 2H), 1.39 (td, *J* = 14.6, 7.2 Hz, 2H), 1.12 (s, 12H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.0, 143.7,

142.9, 136.5, 131.5, 130.8, 128.5, 128.1, 83.4, 37.2, 31.8, 24.5, 22.4, 21.7, 14.0 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{20}H_{30}O_3B$ 329.2288, found 329.2289.

(E)-5-(tert-Butyldimethylsilyloxy)-4-methoxy-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)benzaldehyde (2f). 245 mg (58%). Colorless oil, R_f = 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.36 (s, 1H), 7.17 (s, 1H), 6.74 (s, 1H), 3.87 (s, 3H), 2.41-2.28 (m, 2H), 1.50 (ddd, *J* = 14.6, 9.4, 4.0 Hz, 2H), 1.44-1.35 (m, 2H), 1.09 (s, 12H), 0.99 (s, 9H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.15 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.9, 155.2, 144.3, 141.8 (br), 139.2, 135.9, 127.6, 118.9, 112.8, 83.4, 55.5, 37.1, 31.9, 25.7, 24.6, 22.4, 18.5, 14.0, -4. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{26}H_{44}O_5BSi$ 475.3051, found 475.3041.

(E)-4-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)benzo[d][1,3]dioxole-5-carbaldehyde (2g). 166 mg (52%). Colourless oil, R_f = 0.50 (EtOAc/Hexane 20:80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.19 (s, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.74 (dd, *J* = 8.0, 0.6 Hz, 1H), 6.12 (s, 2H), 2.38-2.28 (m, 2H), 1.52-1.45 (m, 2H), 1.42-1.33 (m, 2H), 1.15 (s, 12H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.5, 148.5, 147.7, 136.3, 135.6, 123.0, 117.5, 112.2, 102.5, 83.4, 37.0, 31.8, 24.7, 24.6, 22.4, 14.0 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{20}H_{28}O_5B$ 359.2030, found.359.2030.

(E)-2-(3-Cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyl)benzaldehyde (2h). 175 mg (62%). Colourless oil, R_f = 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.29 (d, *J* = 0.5 Hz, 1H), 7.86 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.26 (s, 1H), 2.27 (dd, *J* = 7.1, 1.0 Hz, 2H), 1.82-1.65 (m, 5H), 1.46 (dtd, *J* = 10.9, 7.2, 3.6 Hz, 1H), 1.28-1.18 (m, 3H), 1.09 (s, 12H), 0.96-.93 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.4, 143.0, 137.4, 133.7, 133.0, 130.4, 127.9, 127.2, 83.4, 45.6, 38.0, 33.3, 26.5, 26.4, 24.5 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{22}H_{31}O_3BNa$ 377.2264, found 377.2267.

(E)-2-(3-Cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyl)-5-methoxybenzaldehyde (2i). 159 mg (52%). Colourless oil, R_f = 0.30 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.36 (d, *J* = 2.8 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.18 (s, 1H), 7.04 (dd, *J* = 8.5, 2.8 Hz, 1H), 3.85 (s, 3H), 2.25 (dd, *J* = 7.1, 1.0 Hz, 2H), 1.78-1.70 (m, 5H), 1.53-1.38 (m, 1H), 1.29-1.17 (m, 3H), 1.11 (s, 12H), 1.01-0.87 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 192.0, 158.8, 140.1, 139.8 (br), 136.8, 136.3, 134.5, 131.7, 120.8, 109.7, 83.4, 55.5, 45.7, 38.0, 33.3, 26.5, 26.4, 24.5. HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{23}H_{33}BO_4Na$ 407.2369, found 407.2343.

(E)-1-(3-Cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyl)-2-naphthaldehyde (2j). 174 mg (54%). Colorless oil, R_f = 0.20 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (d, *J* = 0.8 Hz, 1H), 8.12 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.87-7.75 (m, 2H), 7.56 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 2H), 7.34 (s, 1H), 2.46 (dd, *J* = 22.9, 6.7 Hz, 2H), 1.91-1.65 (m, 5H), 1.58-1.50 (m, 1H), 1.33-1.17 (m, 3H), 1.05 (d, *J* = 10.6 Hz, 2H), 0.86 (s, 6H), 0.78 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 144.3, 135.7, 134.5, 132.5, 131.5, 128.4, 128.1, 127.3, 126.9, 126.4, 121.9, 83.2, 45.5, 38.1, 33.5, 26.5, 26.4, 24.2 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{26}H_{33}O_3BNa$ 427.2420, found 427.2424.

(E)-4-(3-Cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyl)benzo[d][1,3]dioxole-5-carbaldehyde (2k). 181 mg (57%). Yellow solid (m.p = 81-85 °C), R_f = 0.50 (EtOAc/Hexane 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.14 (s, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.74 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.12 (s, 2H), 2.22 (dd, *J* = 7.1, 0.9 Hz, 2H), 1.81-1.65 (m, 5H), 1.44 (ddd, *J* = 11.0, 7.4, 3.6 Hz, 1H), 1.25-1.15 (m, 3H), 1.14 (s, 12H), 0.99-0.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.6, 148.3, 147.7, 137.3, 135.6, 123.1, 117.5, 112.2, 102.5, 83.4, 45.5, 37.9, 33.3, 26.5, 26.4, 24.6 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{23}H_{31}O_5BNa$ 421.2162, found 421.2162.

(E)-2-(3-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyl)benzaldehyde (2m). 151 mg (52%). Colourless oil, R_f = 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.27 (s, 1H), 7.85 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.51-7.43 (m, 1H), 7.40-7.34 (m, 2H), 7.33-7.28 (m, 5H), 7.23-7.14 (m, 1H), 3.70 (d, *J* = 1.4 Hz, 2H), 0.96 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.2, 142.4, 139.9, 137.9, 133.7, 133.0, 130.42, 129.2, 128.6, 128.3, 127.4, 126.1, 83.5, 43.4, 24.4 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{22}H_{26}O_3B$ 349.1975, found 349.1970.

(E)-2-(5-(tert-Butyldimethylsilyloxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-enyl)benzaldehyde (2p). 154 mg (58%). Colorless oil, R_f = 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.27 (s, 1H), 7.86 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.47 (td, *J* = 7.5, 1.2 Hz, 1H), 7.40-7.27 (m, 3H), 3.68 (t, *J* = 6.5 Hz, 2H), 2.48-2.32 (m, 2H), 1.82-1.64 (m, 2H), 1.09 (s, 12H), 0.99-0.85 (m, 12H), 0.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$):

δ 192.2, 142.9, 136.8, 133.7, 133.0, 130.3, 128.0, 127.2, 83.5, 62.7, 33.8, 32.8, 26.0, 24.5, 18.3, -5.1 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+NH_4)^+$ calculated for $C_{24}H_{43}NO_4BSi$ 448.3054, found 448.3055.

(E)-5-(tert-Butyldimethylsilyloxy)-2-(5-(tert-butyldimethylsilyloxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-enyl)-4-methoxybenzaldehyde (2q). 219 mg (56%). Colorless oil, R_f = 0.30 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 7.36 (s, 1H), 7.20 (s, 1H), 6.74 (s, 1H), 3.87 (s, 3H), 3.68 (t, *J* = 6.5 Hz, 2H), 2.39 (dd, *J* = 8.0, 6.6 Hz, 2H), 1.79-1.70 (m, 2H), 1.08 (s, 12H), 0.99 (s, 9H), 0.91 (s, 9H), 0.15 (s, 6H), 0.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.8, 155.2, 144.3, 139.1, 136.4, 127.6, 118.9, 112.8, 83.4, 62.8, 55.5, 33.6, 32.9, 26.0, 25.7, 24.6, 18.5, 18.3, -4.6, -5.1 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{31}H_{55}O_6BNaSi_2$ 613.3528, found 613.3538.

(E)-5-Fluoro-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)benzaldehyde (2r). 95 mg (32%). Colourless oil, R_f = 0.10 (EtOAc/Hexane 5:95). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.22 (d, *J* = 3.0 Hz, 1H), 7.54 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.29-7.24 (m, 1H), 7.17 (dt, *J* = 8.3, 2.8 Hz, 2H), 2.36 (td, *J* = 7.7, 1.3 Hz, 2H), 1.55-1.44 (m, 2H), 1.41-1.34 (m, 2H), 1.09 (s, 12H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 191.0, 161.9 (d, *J* = 248 Hz), 139.3 (d, *J* = 2.6 Hz), 135.4 (d, *J* = 6 Hz), 135.2, 132.3 (d, *J* = 7 Hz), 120.1 (d, *J* = 22 Hz), 113.4 (d, *J* = 22 Hz), 83.5, 37.1, 31.8, 24.5, 22.4, 14.0 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{19}H_{26}O_3BFNa$ 355.1857, found 355.1856.

(E)-2-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)oct-4-en-4-yl)benzaldehyde (2s). 155 mg (55%). Yellow solid (m.p = 52-55 °C), R_f = 0.10 (EtOAc/Hexane 5:95). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (d, *J* = 0.6 Hz, 1H), 7.89 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 7.6, 0.7 Hz, 1H), 2.52-2.26 (m, 4H), 1.52-1.44 (m, 2H), 1.38-1.24 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.93-0.84 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.9, 149.2, 146.4, 134.3, 132.9, 130.2, 126.7, 126.3, 82.9, 37.3, 33.0, 24.3, 23.2, 20.7, 14.6, 14.3 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{21}H_{32}O_3B$ 343.2444, found 343.2444.

(E)-Methyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)benzoate (2t). 160 mg (52%). Colorless oil, R_f = 0.20 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.41 (s, 1H), 7.39-7.34 (m, 1H), 7.31 (ddd, *J* = 6.4, 3.5, 1.2 Hz, 1H), 7.28-7.25 (m, 1H), 3.86 (s, 3H), 2.33 (ddd, *J* = 7.7, 1.2, 1.2 Hz, 2H), 1.56-1.44 (m,

2H), 1.42-1.36 (m, 2H), 1.14 (s, 12H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.7, 141.4, 140.4, 131.3, 130.8, 130.2, 128.4, 126.7, 83.2, 51.8, 37.1, 31.9, 24.6, 22.4, 14.0 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{20}H_{29}O_4BNa$ 367.2057, found 367.2068.

(E)-1-(2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)phenyl)ethanone (2u). 164 mg (56%). Colorless oil, R_f = 0.30 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, J = 8.0, 1.3 Hz, 1H), 7.37-7.32 (m, 1H), 7.31-7.26 (m, 2H), 7.23 (s, 1H), 2.55 (s, 3H), 2.37-2.25 (m, 2H), 1.53-1.45 (m, 2H), 1.43-1.35 (m, 2H), 1.13 (s, 12H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.5, 140.4, 139.6, 137.6, 130.9, 130.9, 128.6, 126.9, 83.2, 37.1, 31.9, 30.1, 24.6, 22.5, 14.1 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{20}H_{29}O_3BNa$ 351.2107, found 351.2112.

(E)-2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)benzamide (2v). 183 mg (62%). Colorless oil, R_f = 0.40 (MeOH/$CHCl_3$ 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 6.9 Hz, 1H), 7.31 (t, J = 6.6 Hz, 2H), 7.20 (d, J = 6.8 Hz, 1H), 7.11 (s, 1H), 6.45 (br, 1H), 5.72 (br, 1H), 2.32 (t, J = 7.3 Hz, 2H), 1.50-1.44 (m, 2H), 1.39-1.33 (m, 2H), 1.10 (s, 12H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 138.9, 137.7, 133.8, 130.1, 130.0, 128.1, 127.3, 83.6, 36.6, 31.6, 29.7, 24.5, 22.4, 13.9 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{19}H_{28}O_3NBNa$ 352.2060, found 352.2086.

(E)-3-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)thiophene-2-carbaldehyde (6a). 168 mg (59%). Colorless oil, R_f = 0.20 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.95 (d, J = 1.2 Hz, 1H), 7.56 (dd, J = 5.0, 1.1 Hz, 1H), 7.19-7.11 (m, 1H), 7.06 (s, 1H), 2.36 (td, J = 7.7, 1.3 Hz, 2H), 1.52-1.46 (m, 2H), 1.41-1.35 (m, 2H), 1.18 (s, 12H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 183.4, 149.0, 138.8, 132.9, 130.6, 130.1, 83.8, 37.6, 31.7, 24.7, 22.4, 13.9 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{17}H_{25}O_3BNaS$ 343.1515, found 343.1513.

(E)-3-(3-Cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyl)thiophene-2-carbaldehyde (6b). 184 mg (64%). Yellow solid (m.p = 55-58 ^{o}C), R_f = 0.20 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.96 (d, J = 1.0 Hz, 1H), 7.56 (dd, J = 5.0, 0.6 Hz, 1H), 7.15 (d, J = 5.0 Hz, 1H), 7.01 (s, 1H), 2.25 (d, J = 7.1 Hz, 2H), 1.80-1.57 (m, 5H), 1.52-1.38 (m, 1H), 1.31-1.11 (m, 3H), 1.08 (s, 12H), 0.99-0.84 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.5, 148.9, 138.8, 132.9, 131.6, 130.2, 83.7, 46.0, 37.9,

33.3, 26.5, 26.3, 24.6 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{20}H_{29}O_3BNaS$ 383.1828, found 383.1831.

(E)-3-(3-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyl)thiophene-2-carbaldehyde (6c). 167 mg (58%).White solid (m.p = 95-98 ^oC), R_f = 0.30 (EtOAc/Hexane 10:90). ^1H NMR (400 MHz, $CDCl_3$): δ 9.95 (d, *J* = 1.1 Hz, 1H), 7.57 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.32-7.21 (m, 5H), 7.19 (d, *J* = 5.3 Hz, 1H), 7.11 (s, 1H), 3.69 (d, *J* = 1.1 Hz, 2H), 1.04 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.2, 148.3, 139.4, 139.1, 133.0, 131.9, 130.1, 129.2, 128.4, 126.3, 83.8, 43.8, 24.5 (the carbon α to boron was not found). HRMS (ESI+): *m/z* (M^+) calculated for $C_{20}H_{23}O_3BS$ 354.1461, found 354.1460.

(E)-3-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)benzo[b]thiophene-2-carbaldehyde (6d). 172 mg (52%). Colourless oil, R_f = 0.10 (EtOAc/Hexane 10:90). ^1H NMR (500 MHz, $CDCl_3$): δ 10.08 (s, 1H), 7.89-7.78 (m, 2H), 7.52-7.45 (m, 1H), 7.40 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.06 (s, 1H), 2.47 (td, *J* = 7.6, 1.3 Hz, 2H), 1.62-1.52 (m, 2H), 1.44-1.43 (m, 2H), 1.00 (s, 12H), 0.98 (t, *J* = 7.4 Hz, 3H). 13C NMR (101 MHz, $CDCl_3$): δ 185.9, 145.5, 141.3, 139.7, 139.1, 129.9, 127.9, 124.9, 124.7, 123.0, 83.6, 37.2, 31.8, 24.4, 22.4, 14.0 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{21}H_{28}O_3BS$ 371.1852, found 371.1851.

General Procedure for the Synthesis of vinyl Azides from Boronates 2 or 6a. *Synthesis of compounds **3a-3u** and **7a-7d**.* To a stirred solution of boronic ester **2** or **6** (0.477 mmol) in MeOH (2 mL), sodium azide (0.572 mmol) and copper sulfate (0.298 mmol) were added at room temperature and stirred for 6 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under vacuum. The resulting residue was purified by column chromatography (230-400 mesh Silica gel, EtOAc in Hexane) to give vinyl azide **3** or **7** in 69-92% yield.

(Z)-2-(2-Azidohex-1-enyl)benzaldehyde (3a). 99 mg (91%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^1H NMR (500 MHz, $CDCl_3$): δ 10.15 (s, 1H), 7.83 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.37 (td, *J* = 7.7, 0.9 Hz, 1H), 6.30 (s, 1H), 2.49 (dd, *J* = 11.5, 3.8 Hz, 2H), 1.70-1.63 (m, 2H), 1.51-148 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.4, 139.3, 137.7, 133.3, 133.0, 130.6, 130.4, 127.1, 111.1, 33.4, 30.0, 22.1, 13.8. IR (neat): 3056, 2957, 2930, 2865, 2110, 1695, 1630, 1591. HRMS (ESI+): *m/z* $(M-N_2+H)^+$ calculated for $C_{13}H_{16}ON$ 202.1232, found 202.1231.

(Z)-2-(2-Azidohex-1-enyl)-5-methoxybenzaldehyde (3b). 85 mg (75%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.53-7.46 (m, 1H), 7.35 (d, *J* = 2.9 Hz, 1H), 7.14-7.08 (m, 1H), 6.15 (s, 1H), 3.86 (s, 3H), 2.50-2.45 (m, 2H), 1.67-1.64 (m, 2H), 1.53-1.44 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 191.9, 158.6, 138.6, 134.0, 131.7, 130.9, 120.7, 112.4, 110.4, 55.5, 33.3, 30.0, 22.1, 13.8. IR (neat): 2956, 2864, 2108, 1717, 1595, 1494. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{14}H_{18}NO_2$ 232.1338, found 232.1345**.**

(Z)-2-(2-Azidohex-1-enyl)-5-methylbenzaldehyde (3c). 87 mg (78%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 5:95). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.42 (s, 1H), 7.18 (d, *J*= 7.9 Hz, 1H), 6.27 (s, 1H), 2.53-2.45 (m, 2H), 2.42 (s, 3H), 1.72-1.62 (m, 2H), 1.51-1.47 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.1, 144.2, 139.0, 137.6, 130.9, 130.90, 130.8, 128.0, 111.2, 33.4, 30.0, 22.1, 21.9, 13.8. IR (neat): 2958, 2929, 2865, 2113, 1692, 1634, 1601, 1563. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{14}H_{18}ON$ 216.1382, found 216.1396.

(Z)-1-(2-Azidohex-1-enyl)naphthalene (3d). 87 mg (76%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 5:95). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.31 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.86 (t, *J* = 9.3 Hz, 2H), 7.63 (dd, *J* = 10.2, 6.2 Hz, 1H), 7.59 (dd, *J* = 10.0, 6.3 Hz, 1H), 6.22 (s, 1H), 2.69-2.58 (m, 2H), 1.88-1.69 (m, 2H), 1.61-1.56 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.6, 142.5, 139.0, 136.0, 131.6, 131.0, 128.7, 128.6, 128.1, 126.8, 126.0, 122.4, 33.1, 30.1, 22.3, 13.8. IR (neat) : 2956, 2928, 2865, 2107, 1710, 1625, 1591. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{17}H_{18}NO$ 252.1388, found 252.1391.

(Z)-2-(2-Azidohex-1-enyl)-4,5-dimethoxybenzaldehyde (3e). 107 mg (92%). Colorless oil, R_f= 0.30 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.36 (s, 1H), 7.06 (s, 1H), 6.18 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 2.54-2.43 (m, 2H), 1.72-1.62 (m, 2H), 1.54-1.43 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.3, 153.3, 148.2, 139.1, 133.2, 126.5, 112.0, 110.18, 110.1, 56.1, 56.0, 33.4, 30.0, 22.1, 13.8. IR (neat): 3316, 2956, 2864, 2113, 1716, 1680, 1630, 1597. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{15}H_{20}NO_3$ 262.1443, found 262.1446.

(Z)-2-(2-Azidohex-1-enyl)-5-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (3f). 105 mg (85%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.29 (s, 1H), 7.14 (s, 1H), 6.29 (s, 1H), 3.90 (s, 1H), 2.54-2.41 (m, 2H), 1.68-1.64 (m, 2H), 1.51-1.47 (m, 2H), 1.03-0.95 (m, 12H), 0.19-0.14 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.7, 155.3, 144.1, 138.3, 133.1, 126.7, 121.7, 112.71, 110.7, 55.6, 55.5,

33.6, 30.1, 25.6, 22.1, 18.4, 13.8, -4.5. IR (neat):3303, 2956, 2931, 2858, 2112, 1682, 1601. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{20}H_{32}O_3NSi$ 362.2152, found 362.2171.

(Z)-4-(2-Azidohex-1-enyl)benzo[d][1,3]dioxole-5-carbaldehyde (3g). 86 mg (75%). Colorless oil, R_f= 0.20 (EtOAc/Hexane 10:90). ^1H NMR (500 MHz, $CDCl_3$): δ 10.19 (s, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.18 (s, 1H), 6.11 (s, 2H), 2.49-2.41 (m, 2H), 1.69-1.59 (m, 2H), 1.52-1.41 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.9, 149.9, 147.3, 138.1, 130.0, 123.4, 116.9, 111.2, 102.5, 33.3, 29.7, 22.1, 14.0, 13.8. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{14}H_{16}NO_3$ 246.1130, found 246.1132.

(Z)-2-(2-Azido-3-cyclohexylprop-1-enyl)benzaldehyde (3h). 97 mg (85%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^1H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 7.83 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.37 (td, *J* = 7.7, 1.1 Hz, 1H), 6.25 (s, 1H), 2.37 (d, *J* = 7.2 Hz, 2H), 1.89 (d, *J* = 1.8 Hz, 1H), 1.87 (d, *J* = 1.8 Hz, 1H), 1.82-1.73 (m, 3H), 1.61-1.57 (m, 1H), 1.34-1.18 (m, 3H), 1.05-1.02 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.4, 137.9, 137.6, 133.3, 132.9, 130.5, 130.4, 127.1, 112.4, 41.8, 36.5, 33.0, 26.3, 26.1. IR (neat) : 2924, 2850, 2112, 1696, 1630, 1594. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{16}H_{20}ON$ 242.1545, found 242.1554.

(Z)-2-(2-Azido-3-cyclohexylprop-1-enyl)-5-methoxybenzaldehyde (3i). 92 mg (79%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^1H NMR (400 MHz, $CDCl_3$): δ 10.14 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 2.9 Hz, 1H), 7.18-7.02 (m, 1H), 6.10 (s, 1H), 3.86 (s, 3H), 2.35 (d, *J* = 7.2 Hz, 2H), 1.92-1.65 (m, 5H), 1.60-1.58 (m, 1H), 1.38-1.14 (m, 3H), 1.04-1.01 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 191.8, 158.6, 137.1, 134.0, 131.7, 130.9, 120.7, 112.3, 111.8, 55.5, 41.6, 36.5, 33.0, 26.3, 26.1. IR (neat): 2924, 2849, 2113, 1690, 1635, 1599. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{17}H_{22}O_2N$ 272.1651, found 272.1662.

(Z)-1-(2-Azido-3-cyclohexylprop-1-enyl)-2-naphthaldehyde (3j). 96 mg (81%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 5:95). ^1H NMR (400 MHz, $CDCl_3$): δ 10.32 (d, *J* = 0.8 Hz, 1H), 8.08 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.89-7.81 (m, 2H), 7.65-7.54 (m, 2H), 6.19 (s, 1H), 2.52 (d, *J* = 7.1 Hz, 2H), 2.03-1.92 (m, 2H), 1.87-1.78 (m, 2H), 1.78-1.66 (m, 2H), 1.40-1.24 (m, 3H), 1.20-1.08 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.6, 141.1, 139.0, 136.0, 131.7, 131.0, 128.7, 128.63, 128.2, 126.8, 125.9, 122.4, 109.2, 41.6, 36.4, 33.2, 26.2, 26.1. IR (neat) : 2924, 2850, 2114, 1684, 1642, 1591. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$calculated for $C_{20}H_{22}ON$ 292.1701, found 292.1712.

(Z)-4-(2-Azido-3-cyclohexylprop-1-enyl)benzo[d][1,3]dioxole-5-carbaldehyde (3k). 99 mg (84%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^1H NMR (500 MHz, $CDCl_3$): δ

10.20 (s, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.13 (s, 1H), 6.11 (s, 2H), 2.33 (d, *J* = 7.2 Hz, 2H), 1.86 (d, *J* = 13.2 Hz, 2H), 1.81-1.68 (m, 3H), 1.63-1.58 (m, 1H), 1.35-1.26 (m, 3H), 1.09-0.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.9, 149.8, 147.3, 136.7, 130.0, 123.5, 116.9, 112.7, 112.6, 102.5, 41.7, 36.5, 32.9, 26.3, 26.1. IR (neat): 2923, 2853, 2115, 1688, 1630. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{17}H_{20}O_3N$ 286.1443, found 286.1454.

(Z)-2-(2-Azido-3-cyclohexylprop-1-enyl)-5-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (3l). 103 mg (82%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.29 (s, 1H), 7.15 (s, 1H), 6.25 (s, 1H), 3.90 (s, 3H), 2.35 (d, *J* = 7.1 Hz, 2H), 1.87 (d, *J* = 12.0, Hz, 2H), 1.77 (d, *J* = 12.9 Hz, 2H), 1.64-1.50 (m, 2H), 1.37-1.21 (m, 3H), 1.11-0.90 (m, 11H), 0.17 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 155.4, 144.0, 136.7, 133.1, 126.6, 121.5, 112.6, 112.0, 55.5, 41.9, 36.4, 32.9, 26.1, 26.2, 25.6, 18.5, -4.6. IR (neat) : 2928, 2854, 2116, 1685, 1629, 1595. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{23}H_{36}O_3NSi$ 402.2465, found 402.2482.

(Z)-2-(2-Azido-3-phenylprop-1-enyl)benzaldehyde(3m). 88 mg (78%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.39-7.37 (m, 5H), 7.32-7.29 (m, 1H), 6.36 (s, 1H), 3.84 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.4, 137.8, 137.2, 136.0, 133.3, 130.9, 130.5, 130.4, 128.9, 128.9, 113.3, 40.5. IR (neat): 2924, 2851, 2111, 1693, 1630, 1595. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{16}H_{14}ON$ 236.1075, found 236.1086.

(Z)-2-(2-Azido-3-phenylprop-1-enyl)-5-methoxybenzaldehyde (3n). 84 mg (72%). Colorless oil, R_f= 0.30 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.40-7.34 (m, 5H), 7.31 (d, *J* = 4.3 Hz, 1H), 7.11 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.21 (s, 1H), 3.86 (s, 3H), 3.83 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.8, 158.8, 137.0, 136.1, 134.1, 131.8, 130.4, 128.9, 128.8, 127.3, 120.6, 112.8, 112.6, 55.5, 40.3. IR (neat) : 2924, 2851, 2109, 1689, 1631, 1598. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{17}H_{16}O_2N$ 266.1181, found 266.1192.

(Z)-2-(2-Azido-3-phenylprop-1-enyl)-4,5-dimethoxybenzaldehyde (3o). 108 mg (91%). Colorless oil, R_f= 0.40 (EtOAc/Hexane 20:80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.06 (s, 1H), 7.42-7.35 (m, 5H), 7.34-7.31 (m, 1H), 7.11 (s, 1H), 6.22 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.83 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.2, 153.3, 148.3, 137.6, 135.9, 132.8, 129.0, 128.9, 127.4, 126.6, 112.2, 112.0, 110.4, 56.2, 56.0, 40.4. IR (neat): 2926, 2851, 2118, 2086,

1677, 1632, 1594. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{18}H_{18}O_3N$ 296.1287, found 296.1297.

(Z)-2-(2-Azido-5-(tert-butyldimethylsilyloxy)pent-1-enyl)benzaldehyde (3p). 97 mg (80%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.78 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.61-7.55 (m, 1H), 7.48 (dt, *J* = 13.4, 2.9 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.25 (s, 1H), 3.70 (t, *J* = 6.0 Hz, 2H), 2.70-2.32 (m, 2H), 1.92-1.71 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.3, 139.1, 137.6, 133.3, 133.0, 130.5, 130.3, 127.1, 111.1, 61.6, 31.0, 30.1, 26.0 25.9, -5.3. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{18}H_{28}NO_2Si$ 318.1889, found 318.1890.

(Z)-2-(2-Azido-5-(tert-butyldimethylsilyloxy)pent-1-enyl)-5-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (3q). 108 mg (84%). Colorless oil, R_f= 0.15 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.29 (s, 1H), 7.13 (s, 1H), 6.30 (s, 1H), 3.89 (s, 3H), 3.75 (t, *J* = 6.0 Hz, 2H), 2.62-2.50 (m, 2H),1.91-1.84 (m, 2H), 1.00 (s, 9H), 0.92 (s, 9H), 0.17 (s, 6H), 0.08 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$): δ 190.7, 155.3, 144.1, 138.1, 133.0, 126.7, 121.6, 112.6, 110.8, 61.7, 55.6, 31.0, 30.2, 25.9, 25.6, 18.4, 18.3, -4.5, -5.2. IR (neat): 2954, 2930, 2857, 2112, 1688, 1599. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{25}H_{44}O_4NSi_2$ 478.2809, found 478.2837.

(Z)-2-(2-Azidohex-1-enyl)-5-fluorobenzaldehyde (3r). 96 mg (86%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (d, *J* = 2.3 Hz, 1H), 7.57 (dd, *J* = 8.6, 5.3 Hz, 1H), 7.52 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.28-7.19 (m, 1H), 6.14 (s, 1H), 2.54-2.41 (m, 2H), 1.68-1.64 (m, 2H), 1.51-1.46 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.8, 162.7, 139.8, 134.6 (d, *J* = 5.7 Hz), 134.0 (d, *J* = 3.0 Hz), 132.4 (d, *J* = 7.0 Hz), 120.6 (d, *J* = 21. Hz), 115.61 (d, *J* = 22. Hz), 109.7, 33.3, 29.9, 22.1, 13.8. IR (neat): 2958, 2930, 2862, 2112, 1694, 1638, 1592. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{13}H_{15}ONF$ 220.1138, found 220.1147.

(Z)-2-(5-Azidooct-4-en-4-yl)benzaldehyde (3s). 99 mg (84%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.58 (dd, *J* = 10.8, 4.2 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 2.60-2.45 (m, 2H), 2.43-2.29 (m, 2H), 1.72-1.62 (m, 2H), 1.32-1.27 (m, 2H), 1.08 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.5, 159.2, 156.6, 133.6, 129.3, 127.4, 123.3, 122.1, 121.9, 36.5, 30.4, 21.8, 21.6, 14.1, 13.7. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{15}H_{20}ON$ 230.1545, found 230.1550.

(Z)-Methyl 2-(2-azidohex-1-enyl)benzoate (3t). 89 mg (79%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29-7.22 (m, 1H), 6.33 (s, 1H), 3.87 (s, 3H), 2.50-2.42 (m, 2H), 1.65 (ddd, *J* = 12.6, 8.5, 6.3 Hz, 2H), 1.48 (dd, *J* = 14.9, 7.4 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.8, 136.4, 136.3, 131.5, 130.7, 130.3, 128.7, 126.5, 114.0, 51.9, 33.5, 30.0, 22.0, 13.8. IR (neat): 2956, 2868, 2109, 1721, 1638, 1598, 1568. HRMS (ESI+): *m/z* $(M-N_2+H)^+$calculated for $C_{14}H_{18}NO_2$ 232.1338, found 232.1345.

(Z)-1-(2-(2-Azidohex-1-enyl)phenyl)ethanone(3u). 93 mg (84%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79-7.54 (m, 2H), 7.44 (td, *J* = 7.8, 1.2 Hz, 1H),7.28 (t, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 2.56 (s, 3H), 2.43 (dd, *J* = 9.9, 5.4 Hz, 2H), 1.71-1.55 (m, 2H), 1.52-1.42 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.8, 137.5, 136.6, 134.4, 131.0, 130.8, 128.7, 126.6, 114.0, 33.4, 29.9, 29.6, 22.1, 13.8. IR (neat): 2958, 2930, 2867, 2110, 1683, 1638, 1595, 1565. HRMS (ESI+): *m/z* $(M-N_2+H)^+$ calculated for $C_{14}H_{18}ON$ 216.1382, found 216.1396.

(Z)-2-(2-Azidohex-1-enyl)benzamide (3v). 96 mg (86%). Colorless oil, R_f= 0.30 (EtOAc/Hexane 30:70). ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.41 (td, *J* = 7.7, 1.3 Hz, 1H), 7.26-7.22 (m, 1H), 6.04 (s, 1H), 5.79 (br, 2H), 2.49-2.41 (m, 2H), 1.65-1.60 (m, 2H), 1.46-1.43 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 137.6, 133.2, 133.0, 130.1, 130.1, 127.5, 126.8, 112.4, 33.6, 30.0, 22.1, 13.8. IR (neat): 2956, 2864, 2108, 1717, 1595, 1494. IR (neat) : 3365, 3178, 2926, 2857, 2105, 1644, 1453. HRMS (ESI+): *m/z* $(M-N_2+H)^+$ calculated for $C_{13}H_{17}N_2O$ 217.1341, found 217.1328.

(Z)-3-(2-Azidohex-1-enyl)thiophene-2-carbaldehyde (7a). 97 mg (88%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.76 (d, *J* = 5.2 Hz, 1H), 7.63 (d, *J* = 5.2 Hz, 1H), 6.30 (s, 1H), 2.55-2.43 (m, 2H), 1.65 (dt, *J* = 12.7, 7.5 Hz, 2H), 1.52-1.43 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.1, 143.4, 140.1, 137.3, 133.7, 130.2, 106.4, 33.8, 30.1, 22.1, 13.8. IR (neat): 2958, 2930, 2867, 2112, 1655, 1627, 1522. HRMS (ESI+): *m/z* $(M-N_2+H)^+$ calculated for $C_{11}H_{14}NOS$ 208.0796, found 208.0807.

(Z)-3-(2-Azido-3-cyclohexylprop-1-enyl) thiophene-2-carbaldehyde (7b). 105 mg (92%). Colorless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (d, *J* = 0.8 Hz, 1H), 7.76 (d, *J* = 5.2 Hz, 1H), 7.63 (d, *J* = 5.2 Hz, 1H), 6.24 (s, 1H), 2.37 (d, *J* = 7.2

Hz, 2H), 1.91-1.71 (m, 5H), 1.62-1.59 (m, 1H), 1.37-1.14 (m, 3H), 1.03-1.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.1, 143.4, 138.7, 137.3, 133.7, 130.1, 107.7, 42.0, 36.7, 32.9, 26.2, 26.1. HRMS (ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{14}H_{18}NOS$ 248.1109, found 248.1130.

(Z)-3-(2-Azido-3-phenylprop-1-enyl) thiophene-2-carbaldehyde (7c). 99 mg (87%). Colorless oil, R_f= 0.20 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.97 (d, *J* = 0.6 Hz, 1H), 7.79 (d, *J* = 5.2 Hz, 1H), 7.64 (d, *J* = 5.1 Hz, 1H), 7.44-7.28 (m, 5H), 6.31 (s, 1H), 3.85 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.1, 143.0, 138.4, 137.7, 135.6, 133.8, 130.1, 129.0, 128.8, 127.5, 108.2, 40.7. IR (neat): 3448, 3086, 2923, 2127, 1651, 1622. HRMS (ESI+): *m/z* $(M+Na)^+$ calculated for $C_{14}H_{11}ON_3SNa$ 292.0520, found 292.0532.

(Z)-3-(2-Azidohex-1-enyl)benzo[b]thiophene-2-carbaldehyde (7d). 97 mg (75%). Colourless oil, R_f= 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 7.88-7.84 (m, 1H), 7.80-7.77 (m, 1H), 7.52-7.47 (m, 1H), 7.42 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 5.96 (t, *J* = 0.8 Hz, 1H), 2.64-2.54 (m, 2H), 1.80-1.67 (m, 2H), 1.60-1.48 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 184.5, 142.2, 140.6, 139.0, 137.7, 136.5, 127.1, 123.8, 123.4, 122.2, 104.1, 32.2, 28.9, 21.1, 12.8. HRMS(ESI+): *m/z* $(M\text{-}N_2+H)^+$ calculated for $C_{15}H_{16}ONS$ 258.0953, found 258.0973.

General Procedure for the Cyclisation of Vinyl Azides 3 and 7. *Synthesis of compounds* ***4a-4u*** and ***8a-8d***. A solution of triethylphosphite (58 mg, 0.349 mmol) in THF (3 mL) was added to a stirred solution of azide **3** or **7** (0.349 mmol) in THF (2 mL) with 4 Å molecular sieves at room temperature. Nitrogen evolved immediately. After 30 min, an additional triethylphosphite (116 mg, 0.698 mmol) was added and the mixture was heated at 35 ^{o}C for 1.5 h. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (230-400 mesh Silica gel, EtOAc in Hexane) to afford the isoquinoline **4** or thienopyridine **8**.

3-Butylisoquinoline (4a).[16] 60 mg (93%). Colorless oil, R_f = 0.40 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.93 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.64 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.47 (s, 1H), 2.97-2.92 (m, 2H), 1.86-1.74 (m, 2H), 1.49-1.38 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 152.0, 136.5, 130.2, 127.5, 127.0, 126.2, 126.1, 117.9, 37.8, 32.1, 22.5, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{13}H_{16}N$ 186.1283, found 186.1288.

3-Butyl-7-methoxyisoquinoline (4b). 56 mg (85%). Colorless oil, R_f = 0.70 (EtOAc/Hexane 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.40 (s, 1H), 7.32-7.27 (m, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 3.93 (s, 3H), 2.94-2.87 (m, 2H), 1.84-1.69 (m, 2H), 1.50-1.36 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 154.0, 150.5, 132.2, 128.0, 127.6, 123.4, 117.8, 104.5, 55.4, 37.6, 32.2, 22.5, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{14}H_{18}NO$ 216.1388, found 216.1389.

3-Butyl-7-methylisoquinoline (4c). 57 mg (85%). Yellow solid (m.p = 50-55 °C), R_f = 0.40 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.13 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.51 (s, 1H), 7.37 (s, 1H), 7.35 (dd, *J* = 8.3, 1.4 Hz, 1H), 2.95-2.88 (m, 2H), 2.53 (s, 1H), 1.85-1.72 (m, 2H), 1.47-1.36 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 151.6, 140.5, 136.9, 128.6, 127.3, 125.5, 125.0, 117.4, 37.8, 32.1, 22.5, 22.1, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{14}H_{18}N$ 200.1439, found 200.1447.

2-Butylbenzo[f]isoquinoline (4d). 56 mg (83%). Colorless oil, R_f = 0.40 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.17 (s, 1H), 8.68 (ddd, *J* = 7.0, 3.3, 3.2 Hz, 1H), 8.26 (s, 1H), 7.91 (dt, *J* = 5.7, 3.1 Hz, 1H), 7.77 (s, 2H), 7.74-7.64 (m, 2H), 3.11-2.99 (m, 2H), 1.94-1.81 (m, 2H), 1.54-1.42 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1, 151.2, 135.4, 133.6, 128.7, 128.5, 128.4, 127.3, 126.9, 125.0, 124.7, 123.1, 114.1, 38.4, 32.5, 22.6, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{18}N$ 236.1439, found 236.1441.

3-Butyl-6,7-dimethoxyisoquinoline (4e).[16] 57 mg (84%). Yellow solid (m.p = 160-162 °C), R_f = 0.50 (EtOAc/Hexane 40:60). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 7.68 (s, 1H), 7.51 (s, 1H), 7.19 (s, 1H), 4.13 (s, 3H), 4.10 (s, 3H), 3.22 (dd, *J* = 7.6, 7.6 Hz, 2H), 1.98-1.85 (m, 2H), 1.51-1.41 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.8, 152.4, 145.9, 142.0, 137.4, 122.6, 120.6, 106.6, 104.4, 56.8 (2C), 32.4, 31.4, 22.0, 13.7. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{15}H_{20}O_2N$ 246.1490, found 246.1504.

3-Butyl-6-(tertbutyldimethylsilyloxy)-7-methoxyisoquinoline (4f). 64 mg (90%). Yellow solid (m.p = 116-119 °C), R_f = 0.50 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 7.32 (s, 1H), 7.25 (s, 1H), 6.97 (s, 1H), 3.94 (s, 1H), 2.94-2.81 (m, 2H), 1.83-1.68 (m, 2H), 1.48-1.34 (m, 2H), 1.03 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.20 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.2, 154.3, 149.5, 145.8, 133.9, 123.0, 116.9, 115.4, 104.3, 55.4, 37.6, 32.3, 25.7, 22.5, 18.5, 14.0, -4.6. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{20}H_{32}O_2NSi$ 346.2202, found 346.2200.

8-Butyl-[1,3]dioxolo[4,5-f]isoquinoline (4g). 56 mg (82%). Colorless oil, R_f = 0.50 (EtOAc/Hexane 20:80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H), 7.39 (s, 1H), 7.35-7.31 (m, 2H), 6.21 (s, 2H), 3.10-2.72 (m, 2H), 1.87-1.71 (m, 2H), 1.47-1.35 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.6, 145.2, 143.8, 132.4, 119.5, 117.9, 114.8, 113.8, 102.2, 37.7, 32.1, 22.5, 14.0. HRMS (ESI *m/z* $(M+H)^+$ calculated for $C_{14}H_{16}O_2N$ 230,1181, found 230.1192.

3-(Cyclohexylmethyl)isoquinoline (4h). 61 mg (91%). Yellow solid (m.p = 45-48 ^oC), R_f = 0.40 (EtOAc/Hexane 10:90) .^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.62-7.54 (m, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.36 (s, 1H), 2.74 (d, *J* = 7.1 Hz, 2H), 1.89-1.73 (m, 1H), 1.66-1.57 (m, 5H), 1.28-1.05 (m, 4H), 1.03-0.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.5, 152.0, 136.3, 130.2, 127.5, 127.0, 126.3, 126.0, 119.0, 46.0, 38.5, 33.2, 26.6, 26.3. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{16}H_{20}N$ 226.1596, found 226.1595.

3-(Cyclohexylmethyl)-7-methoxyisoquinoline (4i). 61 mg (89%). Colorless oil, R_f = 0.35 (EtOAc/Hexane 20:80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.36 (s, 1H), 7.31 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 3.94 (s, 3H), 2.77 (d, *J* = 7.1 Hz, 2H), 1.87-1.82 (m, 1H), 1.73-1.63 (m, 5H), 1.29-1.14 (m, 3H), 1.07-0.96 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 152.6, 150.5, 132.0, 128.0, 127.6, 123.5, 118.9, 104.5, 55.4, 45.8, 38.6, 33.2, 26.6, 26.3. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{22}ON$ 256.1701, found 256.1704.

2-(Cyclohexylmethyl)benzo[f]isoquinoline (4j). 64 mg (92%). Colorless oil, R_f = 0.40 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 8.73-8.62 (m, 1H), 8.22 (s, 1H), 7.99-7.86 (m, 1H), 7.78 (s, 2H), 7.74-7.65 (m, 2H), 2.92 (d, *J* = 7.2 Hz, 2H), 1.97-1.87 (m, 1H), 1.80-1.63 (m, 5H), 1.35-1.18 (m, 3H), 1.14-1.02 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.9, 151.2, 135.2, 133.6, 128.7, 128.5, 128.4, 127.3, 126.9, 125.0, 124.7, 123.2, 115.1, 46.6, 38.9, 33.3, 26.6, 26.3. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{20}H_{22}N$ 276.1752, found 276.1752.

8-(Cyclohexylmethyl)-[1,3]dioxolo[4,5-f]isoquinoline (4k). 60.5 mg (88%). Colorless oil, R_f = 0.40 (EtOAc/Hexane 20:80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (s, 1H), 7.34 (s, 1H), 7.34-7.28 (m, 2H), 6.20 (s, 2H), 2.75 (d, *J* = 7.1 Hz, 2H), 1.91-1.80 (m, 1H), 1.75-1.64 (m, 5H), 1.22-1.15 (m, 3H), 1.05-0.98 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.2, 145.1, 143.8, 141.6, 132.2, 119.6, 119.0, 114.8, 113.8, 102.3, 46.0, 38.4, 33.2, 26.6, 26.3. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{20}ON_2$ 270.1494, found 270.1492.

6-(tertButyldimethylsilyloxy)-3-(cyclohexylmethyl)-7-methoxyisoquinoline (4l). 65 mg (90%). Colorless oil, R_f = 0.50 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 6.97 (s, 1H), 3.94 (s, 3H), 2.73 (d, *J* = 7.1 Hz, 2H), 1.90-1.77 (m, 1H), 1.71-1.63 (m, 5H), 1.28-1.14 (m, 3H), 1.07-0.96 (m, 2H), 1.04 (s, 9H), 0.20 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 153.0, 149.6, 145.8, 133.6, 123.05, 117.8, 115.4, 104.3, 55.4, 46.0, 38.5, 33.3, 26.6, 26.3, 25.7, 18.5, -4.6. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{23}H_{36}O_2NSi$ 386.2515, found 386.2536.

3-Benzylisoquinoline (4m).[17] 59 mg (89%). White solid (m.p = 56-58 °C), R_f = 0.30 (EtOAc/Hexane 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.63 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.53 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.42 (s, 1H), 7.36-7.29 (m, 4H), 7.27-7.19 (m, 1H), 4.32 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.4, 152.3, 139.8, 136.5, 130.4, 129.2, 128.6, 127.5, 127.1, 126.6, 126.3, 126.2, 118.7, 44.3. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{16}H_{14}N$ 220.1126, found 220.1133.

3-Benzyl-7-methoxyisoquinoline (4n). 59 mg (87%). White solid (m.p = 78-80 °C), R_f = 0.70 (EtOAc/Hexane 40:60). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.12 (s, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.36 (s, 1H), 7.33-7.28 (m, 4H), 7.28 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.22 (dt, *J* = 8.8, 4.5 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 4.29 (s, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0, 152.5, 150.8, 140.0, 132.2, 129.2, 128.5, 128.2, 127.83, 126.3, 123.6, 118.6, 104.6, 55.4, 44.1. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{16}NO$ 250.1232, found 250.1248.

3-Benzyl-6,7-dimethoxyisoquinoline (4o).[18] 59 mg (86%). Yellow solid (m.p = 182-185 °C), R_f = 0.50 (EtOAc/Hexane 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (br, 1H), 7.57 (br, 1H), 7.47 (s, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.10 (s, 1H), 4.62 (s, 2H), 4.09 (s, 3H), 4.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9, 152.5, 145.0, 141.7, 137.4, 135.9, 129.6, 129.21, 127.5, 122.7, 121.1, 106.7, 104.6, 56.91, 56.8, 38.5. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{18}H_{18}O_2N$ 280.1337, found 280.1347.

3-(3-(tertButyldimethylsilyloxy)propyl)isoquinoline (4p). 59 mg (85%). Colorless oil, R_f = 0.50 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.63-7.56 (m, 1H), 7.51-7.45 (m, 1H), 7.44 (s, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 2.99-2.92 (m, 2H), 2.01-1.97 (m, 4H), 0.86 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.2, 152.0, 136.5, 130.2, 127.5, 127.1, 126.3, 126.1, 118.1, 62.5, 34.4, 32.8, 26.1, 18.3, -5.2. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{18}H_{28}ONSi$ 302.1940, found 302.1943.

6-(tertButyldimethylsilyloxy)-3-(3-(tert-butyldimethylsilyloxy)propyl)-7-methoxyisoquinoline (4q). 67 mg (92%). Colorless oil, R_f = 0.60 (EtOAc/Hexane 20:80). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (s, 1H), 7.34 (s, 1H), 7.25 (s, 1H), 6.97 (s, 1H), 3.95 (s, 3H), 3.70 (t, *J* = 6.3 Hz, 2H), 3.04-2.82 (m, 2H), 2.10-1.94 (m, 2H), 1.04 (s, 9H), 0.91 (s, 9H), 0.20 (s, 6H), 0.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2, 153.8, 149.6, 145.8, 133.8, 123.1, 117.0, 115.4, 104.3, 62.7, 55.4, 34.3, 33.0, 26.0, 25.7, 18.5, 18.3, -4.6, -5.2. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{25}H_{44}O_3NSi_2$ 462.2860, found 462.2875.

3-Butyl-7-fluoroisoquinoline (4r). 60 mg (91%). Colorless oil, R_f = 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 7.76 (dd, *J* = 9.0, 5.2 Hz, 1H), 7.53 (dt, *J* = 14.9, 7.4 Hz, 1H), 7.47 (s, 1H), 7.43 (td, *J* = 8.8, 2.6 Hz, 1H), 3.00-2.87 (m, 2H), 1.88-1.71 (m, 2H), 1.49-1.33 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.8 (d, *J* = 248 Hz), 155.5 (d, *J* = 1.6 Hz), 151.2 (d, *J* = 5.3 Hz), 133.5, 128.7 (d, *J* = 8.3 Hz), 127.4 (d, *J* = 8.0 Hz), 120.9 (d, *J* = 25.6 Hz), 117.7, 110.4 (d, *J* = 20.5 Hz), 37.7, 32.1, 22.5, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{13}H_{15}FN$ 204.1188, found 204.1191.

3,4-Dipropylisoquinoline (4s).[19] 60 mg (91%). Colorless oil, R_f = 0.40 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (s, 1H), 7.97 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.70-7.63 (m, 1H), 7.51 (ddd, *J* = 8.0, 5.1, 1.0 Hz, 1H), 3.05-2.99 (m, 2H), 2.99-2.92 (m, 2H), 1.86-1.78 (m, 2H), 1.73-1.65 (m, 2H), 1.10 (t, *J* = 7.4 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.9, 150.1, 135.3, 129.9, 128.1, 128.0, 127.2, 125.6, 123.0, 37.3, 29.9, 224.1, 23.6, 14.6, 14.3. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{15}H_{20}N$ 214.1596, found 214.1601.

3-Butyl-1-methoxyisoquinoline (4t). 58 mg (87%). Colorless oil, R_f = 0.10 (EtOAc/Hexane 5:95). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.13 (m, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.58 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.00 (s, 1H), 4.11 (s, 3H), 2.82-2.73 (m, 2H), 1.83-1.71 (m, 2H), 1.46-1.36 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.2, 153.0, 138.6, 130.1, 125.6, 125.4, 124.0, 118.1, 111.7, 53.4, 37.6, 31.4, 22.4, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{14}H_{18}ON$ 216.1388, found 216.1398.

3-Butyl-1-methylisoquinoline (4u).[20] 58 mg (88%). Colorless oil, R_f = 0.10 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.62 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.51 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.32 (s, 1H), 2.95 (s, 3H), 2.92-2.86 (m, 2H), 1.82-1.74 (m, 2H), 1.48-1.39 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 154.5, 136.6, 129.8, 126.8, 126.0,

125.8, 125.5, 116.5, 37.9, 32.1, 22.6, 22.3, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{14}H_{18}N$ 200.1439, found 200.1445.

6-Butylthieno [3,4-c] pyridine (8a). 56 mg (86%). Colorless oil, R_f = 0.40 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.67 (d, *J* = 5.4 Hz, 1H), 7.55 (s, 1H), 7.30 (d, *J* = 5.3 Hz, 1H), 2.94-2.87 (m, 2H), 1.77 (tt, *J* = 7.7, 6.8 Hz, 2H), 1.47-1.35 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 145.7, 143.9, 133.8, 132.0, 122.7, 116.2, 37.7, 32.5, 22.5, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{11}H_{14}NS$ 192.0847, found 192.0856.

6-(Cyclohexylmethyl)thieno[3,4-c]pyridine (8b). 63 mg (94%). Colorless oil, R_f = 0.40 (EtOAc/Hexane 10:90). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (s, 1H), 7.66 (d, *J* = 5.4 Hz, 1H), 7.50 (d, *J* = 0.7 Hz, 1H), 7.29 (dd, *J* = 5.4, 0.7 Hz, 1H), 2.77 (d, *J* = 7.1 Hz, 2H), 1.85-1.76 (m, 1H), 1.70-1.62 (m, 5H), 1.28-1.13 (m, 3H), 1.09-0.95 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 145.4, 143.9, 133.8, 131.9, 122.7, 117.1, 46.0, 38.8, 33.2, 26.5, 26.3. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{14}H_{18}NS$ 232.1160, found 232.1163.

6-Benzylthieno[3,4-c]pyridine (8c). 59 mg (88%). Colorless oil, R_f = 0.30 (EtOAc/Hexane 20:80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.09 (s, 1H), 7.66 (d, *J* = 5.3 Hz, 1H), 7.49 (s, 1H), 7.31-7.29 (m, 4H), 7.25 (d, *J* = 2.8 Hz, 1H), 7.24-7.19 (m, 1H), 4.28 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 145.8, 144.1, 139.9, 134.2, 132.2, 129.1, 128.6, 126.3, 122.8, 116.8, 44.2. HRMS (ESI+): m/z $(M+H)^+$ calculated for $C_{14}H_{12}NS$ 226.0690, found 226.0686.

3-Butylbenzo[4,5]thieno[2,3-c]pyridine (8d). 53 mg (78%), colourless oil, R_f = 0.20 (EtOAc/Hexane 10:90). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.85 (s, 1H), 7.63-7.53 (m, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 3.07-2.86 (m, 2H), 1.92-1.73 (m, 2H), 1.52-1.39 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.1, 143.9, 142.5, 141.4, 133.8 , 133.2, 128.9, 124.7, 123.3, 122.8, 114.4, 38.0, 32.5, 22.5, 14.0. HRMS (ESI+): m/z $(M+H)^+$ calculated for $C_{15}H_{16}NS$ 242,1004, found 242.1015.

Synthesis of Quinisocaine 12: Compounds **10**, **11** and **12** were prepared according to the above procedures (for compound **11**: the reaction was performed at 40 °C for 18h).

(E)-2-(Dimethylamino)ethyl2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-1-enyl)benzoate (10). From 0.89 mmol of **9**,[21] 221 mg (62%). Colorless oil, R_f = 0.50 (MeOH/$CHCl_3$ 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.44 (s, 1H), 7.39-7.34 (m, 1H), 7.32 (dd, *J* = 9.6, 2.7 Hz, 1H), 7.29-7.25 (m, 1H), 4.38 (t, *J* = 6.0 Hz,

2H), 2.71 (dd, *J* = 11.1, 5.1 Hz, 2H), 2.35-2.29 (m, 8H), 1.53-1.46 (m, 2H), 1.43-1.35 (m, 2H), 1.14 (s, 12H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0, 140.4, 139.4, 130.3, 129.8, 129.2, 128.6, 127.4, 125.7, 82.1, 61.6, 56.7, 44.7, 36.2, 30.9, 23.6, 21.5, 13.0 (the carbon α to boron was not found). HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{23}H_{37}O_4BN$ 402.2816, found 402.2827.

(E) and (Z) 2-(Dimethylamino)ethyl 2-(2-azidohex-1-enyl)benzoate (11). From 0.5 mmol of **10**, 81 mg (52%). Colorless oil, R_f = 0.45 (MeOH/$CHCl_3$ 10:90) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.54-7.41 (m, 1H), 7.26-7.22 (m, 1H), 6.34 (s, 1H), 4.41 (t, *J* = 5.8 Hz, 2H), 2.75 (t, *J* = 4.9 Hz, 2H), 2.56-2.40 (m, 2H), 2.37 (s, 6H), 1.73-1.58 (m, 2H), 1.53-1.40 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.2, 136.5, 136.3, 131.5, 130.7, 130.3, 128.7, 126.5, 114.0, 62.5, 57.6, 45.6, 33.5, 30.0, 22.1, 13.8. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{25}O_2N_4$ 317.1977, found 317.1991.

Quinisocaine 12. From 0.16 mmol of **11**, 34 mg (81%). Colorless oil, R_f = 0.16 (MeOH/$CHCl_3$ 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.58 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.00 (s, 1H), 4.67 (t, *J* = 5.8 Hz, 2H), 2.87 (t, *J* = 5.8 Hz, 2H), 2.80-2.70 (m, 2H), 2.42 (s, 6H), 1.77-1.74 (m, 2H), 1.46-1.33 (m, 2H), 0.95 (, *J* = 7.4 Hz t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 152.9, 138.6, 130.1, 125.5, 125.3, 124.0, 118.0, 111.8, 63.7, 58.0, 45.8, 37.5, 31.4, 22.3, 14.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{25}ON_2$ 273.1966, found 273.1965.

Supporting Information. ^{1}H and ^{13}C spectra of compounds **1d, 2c, 2f-k, 2m, 2p-2v**, **3a-3v, 4a-4u, 6a-6d, 7a-7d, 8a-8d, 10, 11** and quinisocaine **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

The authors declare no competing financial interest.

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