Synthesis S. Deng et al. Paper

Synthesis of Multibromo-Substituted Quinolines by NBS-Mediated Cascade Electrophilic Bromination/Cyclization of *N*-(3-Phenylprop-2-ynyl)anilines

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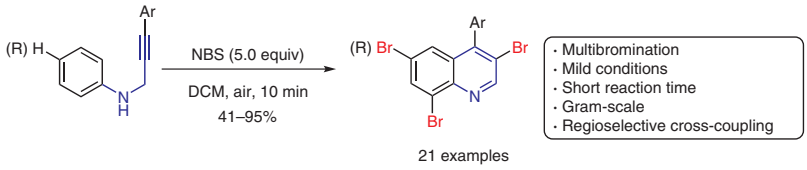

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Abstract A new and convenient protocol is presented here for the synthesis of 3,6,8-tribromoquinolines via cascade cyclization of *N*-(3-phenylprop-2-ynyl)anilines employing *N*-bromosuccinimide as an electrophile. The metal-free process is carried out under mild conditions and is compatible with a variety of substituents. The Sonogashira coupling reaction regioselectively occurs at position C-6 of the obtained products.

Key words tribromoquinolines, electrophilic cyclization, *N*-bromosuccinimide, propargylanilines

Quinolines represent the privileged skeletons of a large number of naturally occurring and pharmacologically active compounds which display a broad spectrum of biological activities.[1–3] A series of methodologies have been developed for their synthesis.[4–8] The most prevalent strategies for constructing quinoline rings are the classic annulation reactions, including the Skraup–Doebner–Von Miller synthesis,[8a,b] Combes synthesis,[8c,d] Pfitzinger reaction,[8e] Camps synthesis[8f] and Friedländer synthesis,[8g] among others. Although the synthesis of quinolines has been fully developed, the great need for further development, such as milder reaction conditions, broad functional group compatibility and higher yield, is still of great urgency.

In recent years, the intramolecular cyclization of alkynes has proven to be an efficient method for the construction of heterocycles. Our works[9] and that of others[10–12] on the electrophilic cyclization of functionally substituted alkynes showed that it is a powerful strategy to construct heterocycles. The alkyne bond is easily activated by electrophiles such as I_2, ICl, NIS, Br_2 or NBS to undergo halogenation/cyclization sequences. As shown in Scheme 1, 3-haloquinolines can be obtained via electrophilic cyclization of 1-azido-2-alkynylbenzenes with various halogen electrophiles (Scheme 1a).[10d] This reaction provided a useful method for the synthesis of multisubstituted quinolines in good to high yields. Subsequently, Likhar's group reported the synthesis of 2-perfluoroalkyl-3-iodoquinolines employing an I_2/$NaHCO_3$ system, in which a diverse range of quinolines were generated from substrates bearing various perfluoroalkyl groups (Scheme 1b).[10e] Meanwhile, Pan's group reported a novel diiodination of *N*-(1,3-diarylprop-2-yn-1-yl)anilines in the presence of NIS, giving the diiodinated quinolines in moderate to excellent yields. In this reaction, the electrophilic substitution reaction occurs first, and then radical cyclization to form the desired products (Scheme 1c).[10f] Another elegant work was developed by Larock's group using more readily prepared arylpropargylanilines as the substrate. A wide variety of monoiodo-substituted quinolines have been readily synthesized through 6-*endo*-*dig* electrophilic cyclization of arylpropargylanilines in the presence of an electrophile (ICl, I_2 or NIS) and 2 equivalents of $NaHCO_3$ as base. New 3,6-dibromoquinoline derivatives could be obtained when bromine was used as electrophilic reagent. However, no cyclization product was obtained using NBS (2.0 equiv) as electrophile for this reaction, and only 4-bromo-*N*-(3-phenylprop-2-yn-1-yl)aniline was obtained (Scheme 1d).[11a]

Quinoline compounds multisubstituted with halogen atoms, especially bromine atoms, can provide multiple sites for further coupling reactions. If regioselective coupling is possible, it will be easy to establish a library of quinoline compounds. NBS, as an environmentally friendly bromine source and a metal-free system, proved to be a vital strategy in a series of transformations.[13] Encouraged by Larock's work, we envisioned that multibromo-substituted quinolines might be obtained through cascade electrophilic bromination and cyclization when excess NBS was applied because the *ortho*- and *para*-positions of aromatic amines

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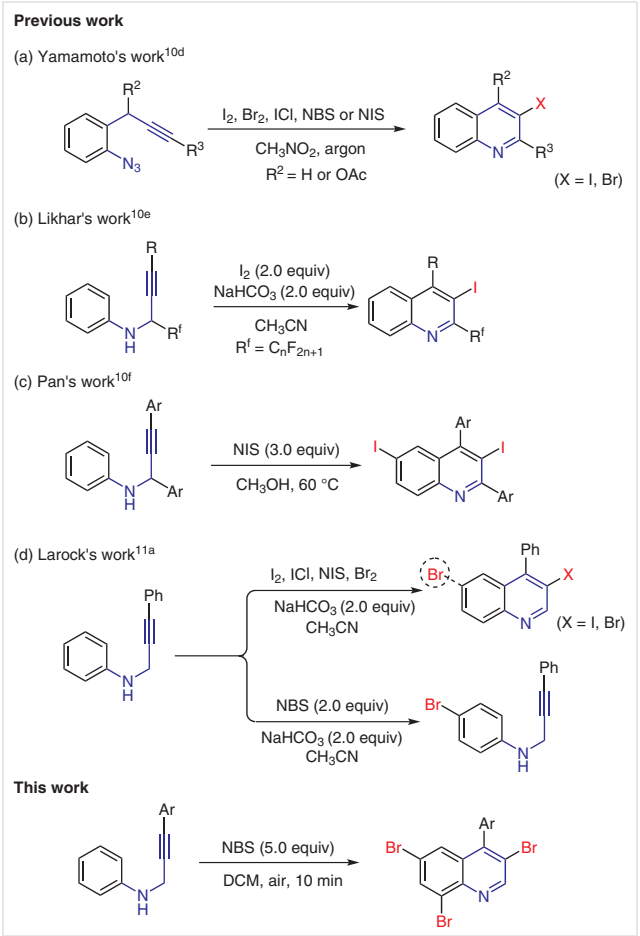
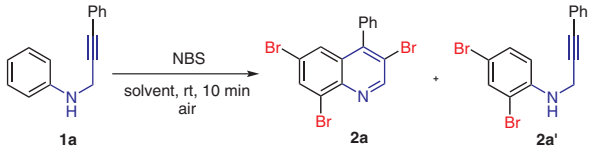


Scheme 1 Synthesis of haloquinolines

easily undergo electrophilic substitution reactions in the presence of NBS. Herein, we report an NBS-mediated cascade electrophilic bromination/cyclization of arylpropargylanilines to form 3,6,8-tribromoquinolines, which can further undergo the Sonogashira coupling reaction at position C-6 regioselectively. Compared with Larock's method, our developed strategy has the merit of multibromination, simple operation and no additional base.

Initially, *N*-(3-phenylprop-2-ynyl)aniline (**1a**) was chosen as the model substrate (Table 1). The desired product **2a** was obtained in 32% yield in the presence of NBS (3.0 equiv) in DCM (Table 1, entry 1). The structure of **2a** was unambiguously confirmed by X-ray crystallography.[14] Moreover, another compound, 2,4-dibromo-*N*-(3-phenylprop-2-ynyl)-aniline (**2a′**), was also isolated in 46% yield, which indicated that electrophilic bromination of the aromatic ring is preferred to cyclization. Compound **2a′** disappeared when the amount of NBS was increased to 5.0 equivalents, and the desired product **2a** was obtained in 84% yield (entry 2). Next, some representative solvents, such as $CHCl_3$, CH_3CN, EtOAc, THF, CH_3OH, DMF and toluene, were screened. Only a trace amount of product was detected using CH_3OH as the solvent (entry 3). There was a decrease in the yield when CH_3CN or DMF was used as the solvent (56% and 68%, respectively; entries 4 and 9), while other solvents (EtOAc, THF, $CHCl_3$, toluene) all gave good yields (entries 5–8). Considering the easy operation, DCM was selected as the solvent for subsequent transformations. Furthermore, adding NBS in batches was also investigated for this transformation and we found that the yield showed no obvious change (entry 10). After screening the conditions carefully, the use of 5.0 equivalents of NBS in DCM under air was selected as the optimal conditions for this novel transformation (Table 1, entry 2).

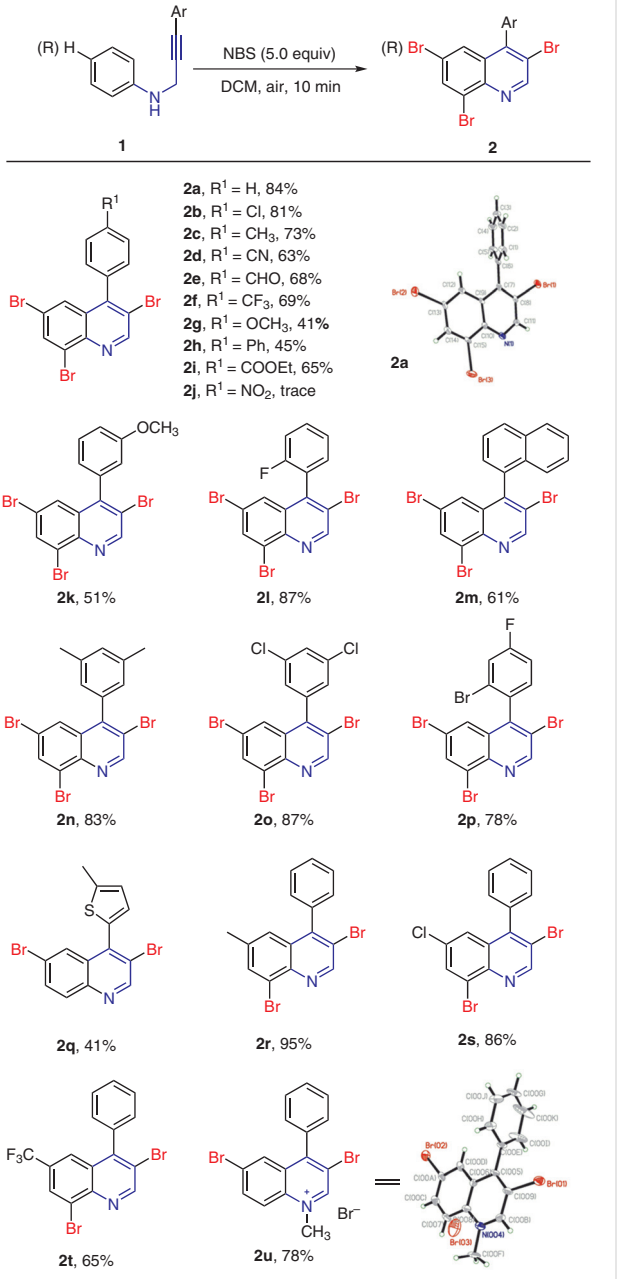
Table 1 Optimization of the Reaction Conditions[a]



Entry	Halo source (equiv)	Solvent	Yield (%)[b] of **2a**
1[c]	NBS (3.0)	DCM	32
2	NBS (5.0)	DCM	84
3	NBS (5.0)	CH_3OH	13
4	NBS (5.0)	CH_3CN	56
5	NBS (5.0)	THF	83
6	NBS (5.0)	EtOAc	81
7[d]	NBS (5.0)	toluene	83
8	NBS (5.0)	$CHCl_3$	83
9	NBS (5.0)	DMF	68
10[e]	NBS (5.0)	DCM	82
11	NCS (5.0)	DCM	n.r.
12[f]	NIS (5.0)	DCM	81[f]

[a] Reaction conditions: **1a** (0.2 mmol), solvent (2.0 mL), rt, air atmosphere.
[b] Isolated yields.
[c] **2a′** was obtained in 46% yield.
[d] 15 min.
[e] NBS was added in batches.
[f] 3-Iodo-4-phenylquinoline was obtained.

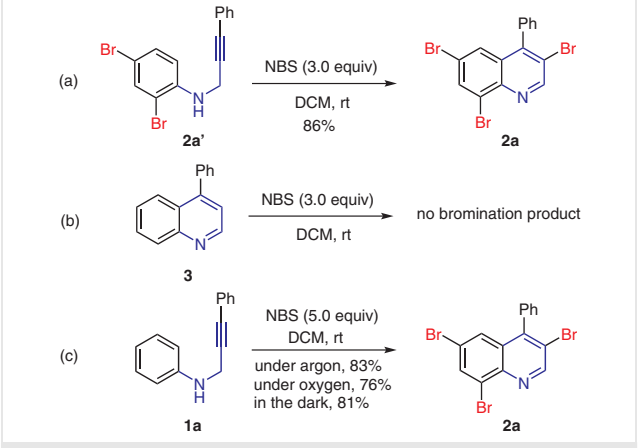
With the optimal reaction conditions in hand, we next carried out the reactions of a variety of *N*-(3-phenylprop-2-ynyl)anilines **1** to investigate the substrate scope (Scheme 2). The corresponding products **2** were obtained in moderate to good yields within 10 minutes despite **1** bearing electron-rich, electron-neutral or electron-poor substituents (CH_3, OCH_3, Cl, F, Br, CF_3, CHO, COOEt, CN, phenyl) on the benzene ring. For substrates having a substituent at the *para*-position of the benzene ring, the corresponding products **2b–2i** were obtained in 41–81% yield. Unfortunately, the desired product **2j** could not be observed, only an unknown complex mixture, when using nitro-substituted **1j**



Scheme 2 NBS-mediated bromination and cascade cyclization to 3,6,8-tribromo-4-phenylquinolines **2**. *Reagents and conditions*: **1** (0.2 mmol), DCM (2.0 mL), rt, air atmosphere; isolated yields.

as the substrate. For substrates with *ortho*-, *meta*- or disubstitution (3,5-dimethyl, 3,5-dichloro, 2-bromo-4-fluoro; **1n–1p**) on the aromatic ring, the corresponding products **2k–2p** were obtained in 51–87% yield. When compound **1q** was used as the substrate, 3,6-dibromo-4-(5-methylthiophen-2-yl)quinoline (**2q**) was afforded in 41% yield, suggesting that the alkyne was more likely to be attacked due to the electron-donating effect of the thiophene group. Furthermore, substrates containing substituents on the aniline (CH_3, Cl, CF_3; **1r–1t**) were also employed and provided the corresponding products **2r–2t** in 65–95% yield. When *N*-methyl-substituted propargylaniline **1u** was tested, the desired product **2u** was obtained in 78% yield. The structure of **2u** was also unambiguously confirmed by X-ray crystallography.[14]

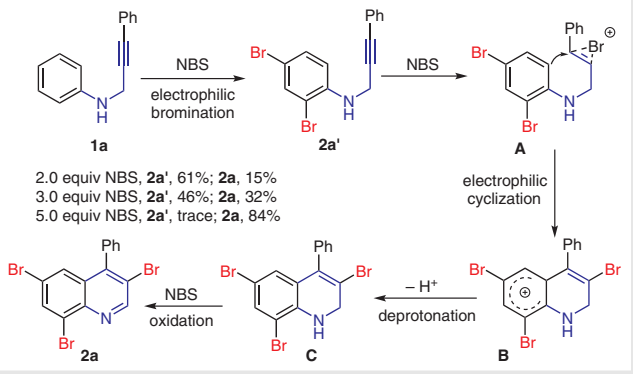
In order to elucidate the reaction mechanism, we revisited the optimization process as shown in Table 1. When 3.0 equivalents of NBS were added, products **2a** and **2a′** were obtained simultaneously, while compound **2a′** disappeared when adding 5.0 equivalents of NBS. These results indicated that the bromination of the benzene ring should occur before the ring closure, and **2a′** may be the key intermediate for this reaction. In order to verify this process, **2a′** was isolated and subjected to 3.0 equivalents of NBS in DCM. The desired product **2a** was obtained in 86% yield (Scheme 3a). When 4-phenylquinoline (**3**) was treated under the optimal conditions, bromination did not occur at any position of the quinoline (Scheme 3b). This result proved that undertaking the direct bromination of quinoline is difficult because of its electron deficiency. Furthermore, control experiments were also conducted under argon atmosphere, oxygen atmosphere or dark conditions. There was no obvious change in the yield of **2a** under these conditions (Scheme 3c). These results indicated that a radical process and oxygen might not be involved in this reaction.



Scheme 3 Control experiments

Based on literature reports and the above experiments, a possible reaction mechanism is proposed as shown in Scheme 4. Initially, the benzene ring is prone to undergo electrophilic substitution due to the presence of the amino group. Heterolysis of the N–Br bond of NBS forms Br^+ as an electrophile, which then attacks the aromatic ring to give the intermediate 2,4-dibromo-*N*-(3-phenylprop-2-ynyl)aniline (**2a′**). The benzene ring is deactivated by the electron-withdrawing action of two bromine atoms. Subsequently, **2a′** undergoes 6-*endo*-*dig* electrophilic bromocyclization to

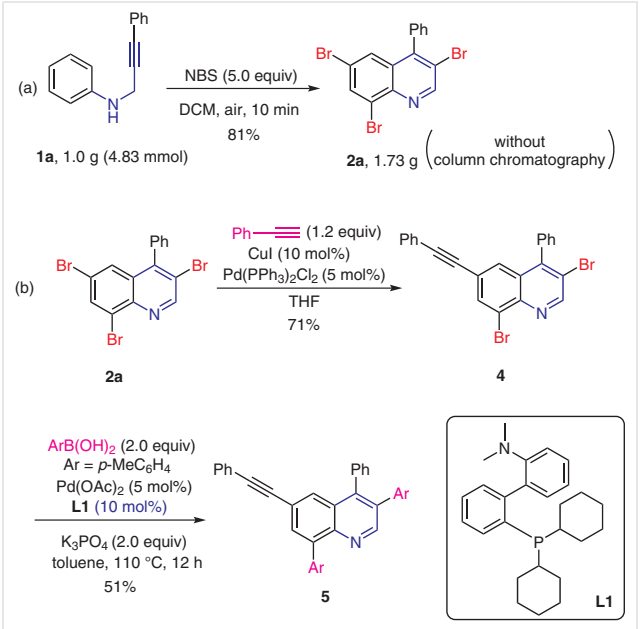
form intermediate **B**, followed by deprotonation to give intermediate **C**. Finally, the desired product **2a** is obtained by oxidative aromatization in the presence of NBS.



Scheme 4 Proposed reaction mechanism

Notably, an obvious advantage of our developed approach is that this reaction could be scaled up to gram quantities under the optimal reaction conditions, and the corresponding product **2a** was obtained in 81% yield (Scheme 5). Importantly, product **2a** can be precipitated out of solution without column chromatography, which might provide a potential application in organic synthesis (Scheme 5a). Furthermore, the synthetic application of the 3,6,8-tribromo-4-phenylquinolines was demonstrated by palladium-catalyzed cross-coupling reactions (Scheme 5b). Firstly, product **2a** underwent Sonogashira coupling with phenylacetylene to give product **4** in a highly regioselective way in 71% yield. Moreover, the Suzuki–Miyaura coupling of **4** with arylboronic acid also smoothly proceeded to give the corresponding product **5** in moderate yield (Scheme 5b).

In conclusion, we have developed a novel and efficient NBS-mediated cascade bromination/cyclization of *N*-(3-phenylprop-2-ynyl)anilines. The reaction can be completed in a few minutes to obtain a series of 3,6,8-tribromoquinoline compounds under mild conditions. The obtained multibromoquinoline products could then smoothly undergo the Sonogashira reaction at position C-6 in a highly regioselective way. Further application to construct a corresponding library of quinolines is under way in our laboratory.



Scheme 5 Gram-scale synthesis of **2a** and its cross-coupling derivatization

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. Dichloromethane (DCM) was purchased from Adamas Company (safe-dry, water <50 ppm). ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometers; chemical shifts are given in parts per million (ppm) relative to standard tetramethylsilane (0.00 ppm for ^{1}H NMR) or residual solvent peaks for ^{13}C NMR. HRMS was obtained using aQ-TOF instrument equipped with an ESI source. Standard column chromatography was performed on 200–300 mesh silica gel using flash column chromatography techniques.

2,4-Dibromo-*N*-(3-phenylprop-2-ynyl)aniline (2a'); Typical Procedure for Electrophilic Bromination

NBS (70.8 mg, 0.4 mmol) was added to a stirred solution of **1a** (41.4 mg, 0.2 mmol) in DCM (2 mL). The resulting mixture was stirred at rt for 10 min and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted and extracted with DCM (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give the corresponding product **2a'**.

Yellow solid; yield: 44.5 mg (61%); mp 55–56 °C.

IR (KBr): 3041, 2921, 2847, 1666, 1588, 1499, 1385, 1310, 1082, 1034, 867, 799, 757, 692, 538 cm^{-1}.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.59 (d, *J* = 2.0 Hz, 1 H), 7.41–7.30 (m, 6 H), 6.76 (d, *J* = 8.8 Hz, 1 H), 4.72 (s, 1 H), 4.22 (d, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 143.9, 134.8, 132.1, 131.6, 128.9, 128.8, 123.0, 113.7, 110.8, 109.5, 85.7, 83.8, 34.7.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}Br_2N$: 363.9331; found: 363.9334.

Cascade Electrophilic Bromination/Cyclization Reaction; General Procedure

NBS (177.0 mg, 1.0 mmol) was added to a stirred solution of **1a–1u** (0.2 mmol) in DCM (2 mL). The resulting mixture was stirred at rt for 10 min and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted and extracted with DCM (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give the corresponding product **2a–2u**.

3,6,8-Tribromo-4-phenylquinoline (2a)

White solid; yield: 74.2 mg (84%); mp 196–197 °C.

IR (KBr): 3045, 1890, 1584, 1461, 1345, 1112, 1082, 1032, 983, 853, 762, 700, 667, 614 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.15 (s, 1 H), 7.60–7.57 (m, 4 H), 7.28 (d, *J* = 5.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 147.5, 142.8, 136.1, 135.7, 130.7, 129.3, 129.2, 128.9, 128.4, 126.1, 121.3, 120.7.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_9Br_3N$: 439.8280; found: 439.8286.

3,6,8-Tribromo-4-(4-chlorophenyl)quinoline (2b)

White solid; yield: 77.2 mg (81%); mp 163–164 °C.

IR (KBr): 3039, 1721, 1597, 1579, 1490, 1461, 1347, 1112, 1084, 1016, 984, 859, 820, 770, 613, 524, 482 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.26 (s, 1 H), 8.43 (s, 1 H), 7.70 (d, *J* = 6.4 Hz, 2 H), 7.48–7.45 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.2, 146.0, 142.3, 135.8, 134.4, 134.3, 131.3, 130.2, 129.3, 127.9, 126.4, 121.1, 120.9.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_8Br_3ClN$: 473.7890; found: 473.7896.

3,6,8-Tribromo-4-*p*-tolylquinoline (2c)

White solid; yield: 66.6 mg (73%); mp 142–144 °C.

IR (KBr): 2918, 1721, 1597, 1579, 1490, 1461, 1347, 1112, 1084, 1016, 984, 859, 820, 770, 613, 524, 482 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.24 (s, 1 H), 8.41 (s, 1 H), 7.48 (s, 1 H), 7.43 (d, *J* = 6.0 Hz, 2 H), 7.28 (d, *J* = 6.4 Hz, 2 H), 2.45 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.3, 147.2, 142.4, 139.0, 135.7, 132.6, 130.5, 129.7, 129.2, 128.1, 126.3, 120.9, 120.8, 21.2.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{11}Br_3N$: 453.8436; found: 453.8437.

4-(3,6,8-Tribromoquinolin-4-yl)benzonitrile (2d)

Yellow solid; yield: 58.8 mg (63%); mp 263–265 °C.

IR (KBr): 3068, 3035, 2226, 1928, 1640, 1581, 1463, 1387, 1349, 1266, 1216, 1114, 1084, 983, 899, 869, 832, 791, 718, 615, 580, 528 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1 H), 8.19 (d, *J* = 2.0 Hz, 1 H), 7.90 (d, *J* = 7.6 Hz, 2 H), 7.45–7.43 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 145.1, 142.9, 140.3, 136.5, 132.8, 130.2, 129.8, 127.5, 126.6, 121.9, 120.2, 118.1, 113.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_8Br_3N_2$: 464.8232; found: 464.8235.

4-(3,6,8-Tribromoquinolin-4-yl)benzaldehyde (2e)

White solid; yield: 63.9 mg (68%); mp 198–199 °C.

IR (KBr): 3061, 1701, 1639, 1464, 1351, 1207, 1115, 988, 751, 616 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.15 (s, 1 H), 9.29 (s, 1 H), 8.45 (s, 1 H), 8.15 (d, *J* = 7.6 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.42 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.1, 153.2, 146.1, 142.3, 141.4, 136.7, 135.9, 130.3, 130.2, 129.8, 127.8, 126.4, 121.2, 120.4.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_9Br_3NO$: 467.8229; found: 467.8229.

3,6,8-Tribromo-4-(4-(trifluoromethyl)phenyl)quinoline (2f)

Yellow solid; yield: 70.4 mg (69%); mp 212–213 °C.

IR (KBr): 3073, 1620, 1584, 1465, 1382, 1327, 1267, 1219, 1165, 1125, 1069, 1022, 988, 790, 744, 626, 528 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.15 (s, 1 H), 8.18 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 2 H), 7.49 (s, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 145.7, 142.9, 139.4, 136.4, 131.4 (q, ^2J = 32.5 Hz), 130.1, 129.8, 127.7, 126.5, 126.0 (q, ^3J = 3.2 Hz), 123.8 (q, ^1J = 270.7 Hz), 121.7, 120.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_8Br_3F_3N$: 507.8153; found: 507.8155.

3,6,8-Tribromo-4-(4-methoxyphenyl)quinoline (2g)

White solid; yield: 38.7 mg (41%); mp 190–191 °C.

IR (KBr): 3033, 2933, 1609, 1583, 1509, 1459, 1346, 1290, 1247, 1176, 1111, 1027, 985, 868, 826, 798, 735, 613 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 8.15 (d, *J* = 2.4 Hz, 1 H), 7.66 (s, 1 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.8 Hz, 2 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 153.0, 147.3, 143.0, 136.0, 131.1, 130.6, 128.5, 127.8, 126.1, 121.2, 121.1, 114.3, 55.4.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{11}Br_3NO$: 469.8353; found: 469.8348.

4-([1,1′-Biphenyl]-4-yl)-3,6,8-tribromoquinoline (2h)

Yellow solid; yield: 46.6 mg (45%); mp 195–196 °C.

IR (KBr): 3070, 1938, 1640, 1579, 1457, 1402, 1343, 1107, 1088, 981, 937, 849, 765, 734, 722, 692, 613, 522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1 H), 8.17 (s, 1 H), 7.80 (d, *J* = 8.0 Hz, 2 H), 7.73–7.69 (m, 3 H), 7.51 (t, *J* = 7.6 Hz, 2 H), 7.44–7.36 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 147.1, 142.9, 142.0, 140.1, 136.1, 134.5, 130.7, 129.7, 129.0, 128.4, 127.9, 127.5, 127.2, 126.2, 121.3, 120.8.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{13}Br_3N$: 515.8593; found: 515.8596.

Ethyl 4-(3,6,8-Tribromoquinolin-4-yl)benzoate (2i)

Yellow solid; yield: 66.8 mg (65%); mp 185–186 °C.

IR (KBr): 3076, 2980, 2900, 1716, 1583, 1464, 1402, 1349, 1282, 1180, 1111, 1023, 988, 898, 863, 766, 710, 683, 616, 570, 527 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 8.25 (d, *J* = 8.4 Hz, 2 H), 8.15 (d, *J* = 2.4 Hz, 1 H), 7.49 (d, *J* = 2.0 Hz, 1 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 4.45 (q, *J* = 7.2 Hz, 2 H), 1.44 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 152.8, 146.3, 142.8, 140.1, 136.2 × 2, 131.3, 130.1, 129.3, 127.9, 126.3, 121.6, 120.3, 61.4, 14.4.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}Br_3NO_2$: 511.8491; found: 511.8493.

3,6,8-Tribromo-4-(3-methoxyphenyl)quinoline (2k)

White solid; yield: 48.1 mg (51%); mp 170–171 °C.

IR (KBr): 3081, 2990, 2831, 1845, 1608, 1581, 1463, 1430, 1380, 1346, 1288, 1219, 1162, 1114, 1053, 1002, 865, 782, 736, 707, 667, 643, 563 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 8.15 (s, 1 H), 7.62 (s, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.08 (d, *J* = 5.6 Hz, 1 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 6.80 (s, 1 H), 3.87 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 152.9, 147.2, 142.8, 137.0, 136.1, 130.6, 130.1, 128.4, 126.1, 121.3, 121.2, 120.6, 114.8, 114.6, 55.4.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{11}Br_3NO$: 469.8385; found: 469.8388.

3,6,8-Tribromo-4-(2-fluorophenyl)quinoline (2l)

White solid; yield: 80.0 mg (87%); mp 210–211 °C.

IR (KBr): 3075, 3042, 1881, 1616, 1585, 1462, 1385, 1350, 1246, 1217, 1096, 989, 892, 860, 815, 763, 665, 616, 532 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.19 (s, 1 H), 7.63–7.58 (m, 2 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.35–7.28 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (d, ^1J = 248.0 Hz), 152.8, 142.8, 141.9, 136.2, 131.7, 131.3 (d, ^3J = 7.8 Hz), 130.4, 127.7, 126.4, 124.7, 123.3 (d, ^2J = 15.6 Hz), 121.7, 121.6, 116.5 (d, ^2J = 20.8 Hz).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_8Br_3FN$: 457.8185; found: 457.8176.

3,6,8-Tribromo-4-(naphthalen-1-yl)quinoline (2m)

Yellow solid; yield: 60.0 mg (61%); mp 218–219 °C.

IR (KBr): 3041, 1639, 1581, 1384, 1345, 1271, 1213, 1159, 1125, 1084, 1045, 1014, 950, 861, 796, 773, 728, 651 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.22 (s, 1 H), 8.16 (s, 1 H), 8.07 (d, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.68–7.65 (m, 1 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.41–7.34 (m, 3 H), 7.10 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 146.4, 142.9, 136.3, 133.7, 133.4, 131.3, 130.7, 129.8, 128.8, 128.4, 127.3, 127.2, 126.7, 126.2, 125.5, 124.9, 122.1, 121.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{11}Br_3N$: 489.8436; found: 489.8439.

3,6,8-Tribromo-4-(3,5-dimethylphenyl)quinoline (2n)

Yellow solid; yield: 78.0 mg (83%); mp 153–154 °C.

IR (KBr): 3058, 2912, 1918, 1637, 1603, 1461, 1353, 1289, 1222, 1120, 1087, 1043, 856, 696, 627, 521 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.23 (s, 1 H), 8.40 (s, 1 H), 7.46 (s, 1 H), 7.21 (s, 1 H), 6.97 (s, 2 H), 2.37 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.2, 147.4, 142.3, 138.3, 135.7, 135.5, 130.8, 130.4, 128.1, 126.6, 126.3, 120.8, 120.7, 21.1.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}Br_3N$: 467.8593; found: 467.8596.

3,6,8-Tribromo-4-(3,5-dichlorophenyl)quinoline (2o)

White solid; yield: 88.9 mg (87%); mp 204–205 °C.

IR (KBr): 3075, 2912, 1637, 1586, 1561, 1435, 1385, 1342, 1119, 1092, 1019, 865, 787, 675 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 8.19 (s, 1 H), 7.57 (s, 1 H), 7.52 (s, 1 H), 7.18 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 144.4, 142.8, 138.5, 136.5, 135.9, 129.9, 129.6, 127.6, 126.5, 121.9, 120.6.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_7Br_3Cl_2N$: 507.7500; found: 507.7510.

3,6,8-Tribromo-4-(2-bromo-4-fluorophenyl)quinoline (2p)

Yellow solid; yield: 84.1 mg (78%); mp 180–181 °C.

IR (KBr): 3076, 1588, 1489, 1460, 1384, 1349, 1261, 1205, 1114, 1085, 1040, 988, 943, 866, 821, 746, 652, 615, 557, 525 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.25 (s, 1 H), 7.64–7.62 (m, 1 H), 7.47 (s, 1 H), 7.37–7.28 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9 (d, ^1J = 252.6 Hz), 152.9, 145.4, 142.8, 136.3, 132.9 (d, ^4J = 3.7 Hz), 131.7 (d, ^3J = 8.6 Hz), 130.0, 127.4, 126.5, 123.3 (d, ^3J = 9.7 Hz), 121.8, 121.5, 120.9 (d, ^2J = 24.5 Hz), 115.6 (d, ^2J = 21.5 Hz).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_7Br_4FN$: 535.7291; found: 535.7293.

3,6-Dibromo-4-(5-methylthiophen-2-yl)quinoline (2q)

Yellow solid; yield: 31.4 mg (41%); mp 144–145 °C.

IR (KBr): 3160, 3080, 2954, 1774, 1700, 1370, 1295, 1190, 1114, 1060, 1004, 934, 848, 822, 643, 558 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.13 (s, 1 H), 8.04 (d, *J* = 8.8 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.78 (s, 1 H), 7.10 (d, *J* = 3.6 Hz, 1 H), 7.02 (d, *J* = 4.0 Hz, 1 H), 2.57 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.5, 145.1, 142.8, 140.1, 133.4, 132.1, 131.8, 130.4, 130.1, 127.7, 126.4, 121.8, 121.2, 15.1.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}Br_2NS$: 381.8895; found: 381.8896.

3,8-Dibromo-6-methyl-4-phenylquinoline (2r)

Yellow solid; yield: 71.6 mg (95%); mp 113–115 °C.

IR (KBr): 3051, 2909, 1615, 1473, 1363, 1159, 1114, 1076, 1037, 994, 931, 856, 766, 735, 702, 631, 528 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.08 (s, 1 H), 7.90 (s, 1 H), 7.57–7.54 (m, 3 H), 7.30–7.27 (m, 2 H), 7.19 (s, 1 H), 2.39 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7, 147.4, 142.6, 138.3, 136.7, 135.3, 130.0, 129.2, 128.8, 128.7, 125.2, 124.6, 119.8, 21.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}Br_2N$: 375.9331; found: 375.9335.

3,8-Dibromo-6-chloro-4-phenylquinoline (2s)

Yellow solid; yield: 68.4 mg (86%); mp 170–171 °C.

IR (KBr): 3045, 1698, 1597, 1546, 1462, 1444, 1387, 1353, 1115, 1094, 1035, 902, 856, 795, 769, 763, 689, 625, 572, 533 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 8.01 (s, 1 H), 7.58–7.56 (m, 3 H), 7.43 (s, 1 H), 7.28 (d, *J* = 6.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 147.4, 142.6, 135.7, 133.6, 133.3, 130.1, 129.2, 129.1, 128.9, 126.0, 125.0, 120.7.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_9Br_2ClN$: 395.8785; found: 395.8786.

3,8-Dibromo-4-phenyl-6-(trifluoromethyl)quinoline (2t)

White solid; yield: 56.0 mg (65%); mp 178–179 °C.

IR (KBr): 3052, 2930, 1477, 1438, 1407, 1368, 1295, 1166, 1124, 1084, 1034, 990, 883, 798, 764, 699, 655, 606 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1 H), 8.23 (s, 1 H), 7.76 (s, 1 H), 7.60–7.59 (m, 3 H), 7.30–7.29 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 149.2, 145.1, 135.4, 129.6 (q, ^2J = 33.1 Hz), 129.5, 129.1, 129.0 × 2, 126.5, 124.1 (q, ^3J = 4.1 Hz), 124.0, 122.8 (q, ^1J = 271.6 Hz), 121.2.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_9Br_2F_3N$: 429.9048; found: 429.9053.

3,6-Dibromo-1-methyl-4-phenylquinolin-1-ium bromide (2u)

Yellow solid; yield: 71.4 mg (78%); mp >300 °C.

IR (KBr): 3650, 3310, 3090, 3052, 1605, 1556, 1513, 1366, 1319, 1259, 1165, 1134, 1077, 1036, 949, 881, 840, 754, 707, 616, 517 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.14 (s, 1 H), 8.55 (d, *J* = 9.6 Hz, 1 H), 8.49–8.46 (m, 1 H), 7.72 (d, *J* = 6.8 Hz, 4 H), 7.47–7.44 (m, 2 H), 4.70 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.4, 152.3, 137.7, 136.8, 133.9, 130.6, 130.3, 129.8, 129.4, 128.8, 124.6, 122.2, 118.3, 45.7.

HRMS (EI): *m*/*z* [M – Br]$^+$ calcd for $C_{16}H_{12}Br_2N$: 375.9331; found: 375.9328.

Gram-Scale Synthesis of 2a

NBS (4.27 g, 24.0 mmol) was added in one portion to a stirred solution of **1a** (1.0 g, 4.8 mmol) in DCM (20 mL). The resulting mixture was stirred at rt for 10 min under air atmosphere and the progress of the reaction was monitored by TLC. After completion, product **2a** precipitates out of the reaction mixture, and was then filtered, washed with water and dried in an oven to give **2a** as a white solid; yield: 1.73 g (81%).

3,8-Dibromo-4-phenyl-6-(phenylethynyl)quinoline (4)

Under argon atmosphere, 3,6,8-tribromo-4-phenylquinoline (**2a**; 0.703 g, 1.59 mmol), phenylacetylene (0.135 g, 1.33 mmol), CuI (0.025 g, 0.13 mmol) and bis(triphenylphosphine)palladium chloride (0.046 g, 0.066 mmol) were placed in a reaction flask. THF (20 mL) and Et_3N (7 mL) were added, and the mixture was stirred at 50 °C for 12 h. After that, phenylacetylene (0.135 g per time) was injected into the reaction solution at 12 h intervals until the starting material **2a** was consumed. After completion of the reaction, the reaction mixture was concentrated, and diluted and extracted with DCM. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give the corresponding product **4** (TLC; 2% EtOAc in petroleum ether).

Yellow solid; yield: 522.9 mg (71%); mp 191–192 °C.

IR (KBr): 3056, 2207, 1601, 1491, 1464, 1443, 1361, 1177, 1133, 1105, 940, 876, 755, 697, 630, 591 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 8.18 (s, 1 H), 7.59 (d, *J* = 7.2 Hz, 4 H), 7.51–7.49 (m, 2 H), 7.36–7.31 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 147.9, 143.6, 136.2, 135.6, 131.8, 129.8, 129.3, 129.1, 129.1, 129.0, 128.8, 128.5, 125.1, 123.4, 122.3, 120.5, 92.3, 87.6.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{14}Br_2N$: 461.9488; found: 461.9491.

4-Phenyl-6-(phenylethynyl)-3,8-di-*p*-tolylquinoline (5)

Under argon atmosphere, 3,8-dibromo-4-phenyl-6-(phenylethynyl)quinoline (**4**; 80.0 mg, 0.18 mmol), 4-tolylboronic acid (49.0 mg, 0.36 mmol), palladium acetate (2.0 mg, 0.009 mmol), **L1** (7.0 mg, 0.018 mmol) and potassium phosphate (77.0 mg, 0.36 mmol) were placed in a pressure tube. Toluene (2 mL) was added, and the mixture was stirred at 110 °C for 12 h. After the mixture was cooled to rt, the reaction mixture was quenched with water, and the product was extracted three times with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by silica gel column chromatography (4% EtOAc in petroleum ether) to afford **5**.

White solid; yield: 44.6 mg (51%); mp 65–67 °C.

IR (KBr): 3025, 2915, 1640, 1480, 1187, 1116, 1026, 882, 826, 757, 698, 606 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (d, *J* = 2.0 Hz, 1 H), 7.82 (s, 2 H), 7.64 (d, *J* = 6.4 Hz, 2 H), 7.52–7.51 (m, 2 H), 7.40–7.39 (m, 3 H), 7.35–7.33 (m, 5 H), 7.26–7.24 (m, 2 H), 7.04 (s, 4 H), 2.45 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 145.1, 144.9, 141.3, 137.4, 136.9, 136.5, 136.2, 135.0, 133.4, 132.3, 131.7, 130.6, 130.5, 129.9, 129.1, 128.9, 128.5, 128.4, 128.3 × 2, 127.8, 127.7, 123.0, 121.4, 90.4, 89.6, 21.3, 21.1.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{37}H_{28}N$: 486.2216; found: 486.2217.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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(14) CCDC 2048602 (**2a**), CCDC 2048406 (**2u**) and CCDC 2048600 (**4**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.