Synthesis C.-K. Chan, M.-Y. Chang Paper

N-Bromosuccinimide-Mediated Synthesis of Substituted Quinoxalines

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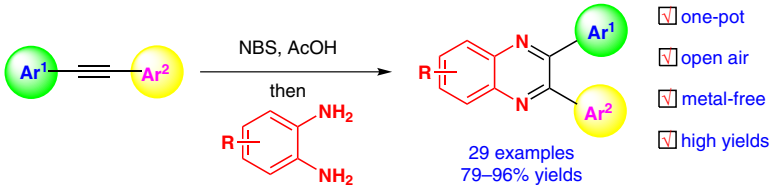

Ar^1, Ar^2 = Ph, 3-$MeOCH_2C_6H_4$, 3-$CF_3C_6H_4$, 4-PhC_6H_4, 4-$MeO_2CC_6H_4$, 4-ClC_6H_4, 2-thienyl
R = H, 3,4-Me_2, 3,4-Cl_2, naphthyl, 3-CO_2Me, 3-pyridyl, 3,3',4,4'-tetraaminobiphenyl

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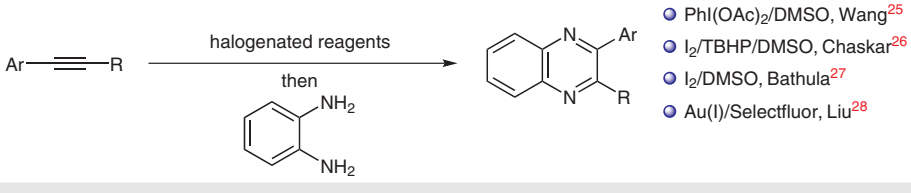
Abstract An efficient and simple *N*-bromosuccinimide-mediated two-step synthesis of substituted quinoxalines from 1,2-diarylacetylenes and 1,2-diaminobenzenes in boiling AcOH, during a one-pot procedure has been developed. All the structures of the substituted quinoxalines were confirmed, some by single-crystal X-ray crystallography. Possible reaction pathways were discussed, and some data were matched with the previous work.

Key words one-pot synthesis, *N*-bromosuccinimide, acetic acid, phenylacetylene, quinoxalines

Quinoxalines are ubiquitous nitrogen-containing heterocyclic compounds that play important roles in the organic field, such as efficient intermediates of some synthetic routes,[1] polymers,[2] and useful dyes.[3] In addition to these meaningful features, quinoxalines and their derivatives have a wide range of pharmaceutical uses, such as antimicrobial,[4] anticancer,[5] antiprotozoal,[6] antibacterial,[7] antimalarial,[8] and antileishmanial.[9] On the basis of these significant characteristics, many protocols have been developed for the synthesis of quinoxalines. According to relevant studies, the most popular procedures are derived from the condensation of 1,2-diamines with a number of polar *ortho*-carbon units, such as aldehydes,[10] ketones,[11] 1,2-diketones,[12] epoxides,[13] vicinal diols,[14] diazoketones,[15] alkenes,[16] and alkynes.[17]

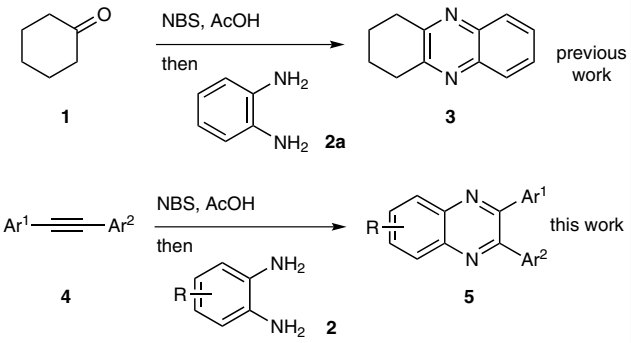
Recently, several research groups have used 1,2-phenyldiamines and alkynes, the latter being oxidized to carbonyl or hydroxyl groups like ketones[11,12] or vicinal diols[14] for the preparation of quinoxalines. For this purpose, a variety of oxidants and catalytic systems were employed, including $KMnO_4/NaHCO_3$,[18] PdX_2/DMSO,[17b,c,19] $PdBr_2/CuBr_2$/1,4-dioxane,[20] O_2/Cu,[21] $Ga(OTf)_3$,[22] SO_3/1,4-dioxane,[23] and $PdCl_2/CuCl_2$/PEG.[24] Despite the fact that these methods are effective in synthesizing substituted quinoxalines, we explored a novel one-pot, metal-free, rapid reaction to synthesize quinoxaline with cheaper reagents from alkynes.

Even if many efficient approaches for preparing substituted quinoxalines from alkynes using halogenated oxidants such as I_2/DMSO,[25] I_2/TBHP/DMSO,[26] IBX/DMSO,[27] and Au(I)/Selectfluor[28] have been well developed (Scheme 1), we envisioned that other halogen-containing reagents may also promote the one-pot condensation of alkynes with 1,2-diaminobenzenes. In particular, only few reports on the condensation of alkynes with 1,2-diaminobenzenes mediated by bromine-containing reagents are known. After further comparison of literature on the halogenated reagent-mediated synthesis of quinoxalines, no report on the system NBS/AcOH was found for this transformation.



Scheme 1 Halogenated-reagent-mediated synthesis of quinoxalines

In 2011, we developed a synthetic strategy from cyclohexanone (**1**) and 1,2-diaminobenzene (**2a**) toward substituted quinoxalines **3**.[11d] Herein, we conducted bromination of alkynes **4** followed by condensation of **2** using the experience of our previous work for the synthesis of quinoxaline analogues (Scheme 2).



Scheme 2 NBS-mediated synthesis of quinoxalines

Initially, 1,2-diphenylacetylene (**4a**) and 1,2-diaminobenzene (**2a**) were chosen as the model substrates to examine this one-pot transformation via NBS-mediated bromination. Other NXS (X = Cl or I) and equivalents were investigated on a 1.0 mmol scale of **4a** in acetic acid at reflux, and the results are summarized in Table 1. Obviously, 1.2 equivalents of NBS was an efficient additive in this step, and the yield of **6a** was 92% after 2 hours (Table 1, entries 1–3). NCS was also examined with 1.2 and 1.5 equivalents, but the reaction time was more than 6 hours for conducting chlorination (entries 4 and 5). NIS was not appropriate in this step, because the yields were 30% and 35%, with numerous recovered starting materials (entries 6 and 7). The structure of **6a** was determined by single-crystal X-ray crystallography (Figure 1).[29]

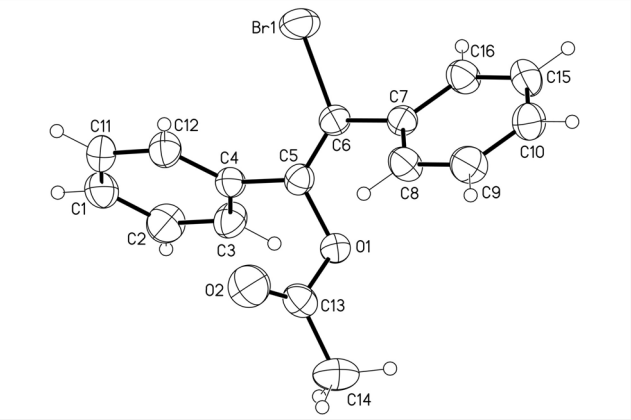
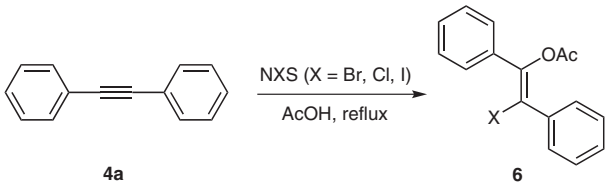


Figure 1 X-ray crystal structure of compound **6a**

Table 1 Reaction Conditions of **4a** with NXS (X = Br, Cl, I)[a]

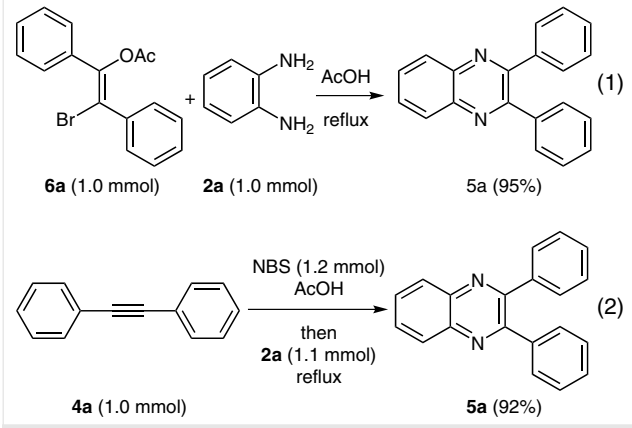


4a **6**

Entry	Additive	Equiv	**6**, Yield (%)[b]
1	NBS	1.0	**6a**, 80
2	NBS	1.2	**6a**, 95
3	NBS	1.5	**6a**, 85[c]
4	NCS	1.2	**6b**, 60[d]
5	NCS	1.5	**6b**, 55[c,d]
6	NIS	1.2	**6c**, 30[d]
7	NIS	1.5	**6c**, 35[d]

[a] The reactions were conducted on a 1.0 mmol scale with **4a**.
[b] Isolated yields.
[c] Trace amounts (<5%) of unknown products were obtained.
[d] Recovered **4a**: entry 4, 20%; entry 5, 18%, entry 6, 55%, entry 7, 60%.

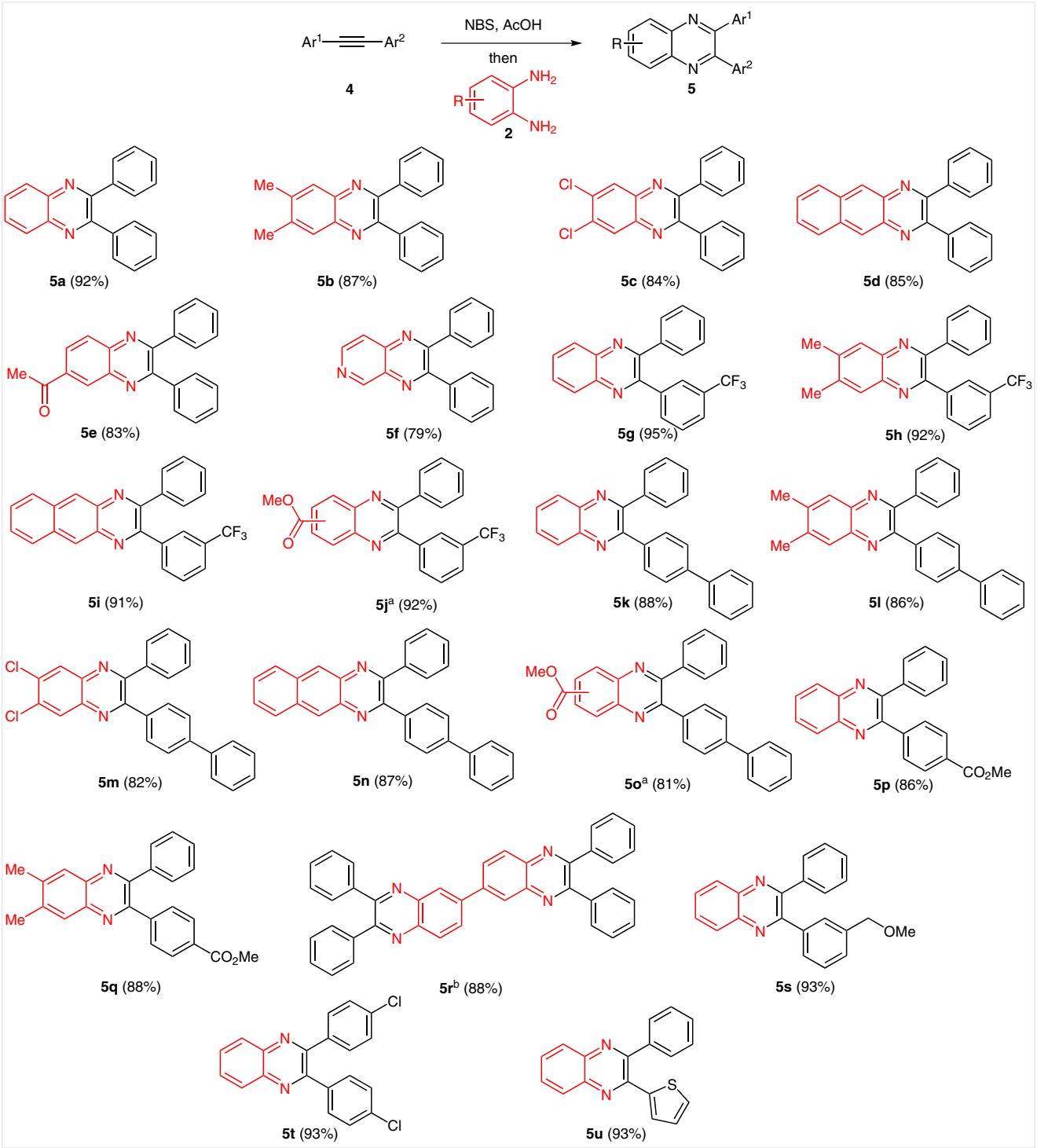
As expected, the reaction between **6a** and 1.1 equivalents of **2a** smoothly afforded the corresponding quinoxaline **5a** in AcOH at reflux in good yield. To our delight, this two-step strategy produced **5a** in 90% total yield in 5 hours (Scheme 3, eq. 1). Owing to acetic acid acting as a solvent in both the bromination and condensation reactions of synthesizing substituted quinoxaline **5a**, the combined reaction deserved further exploration. However, considering the convenience of the NBS-mediated synthesis of substituted quinoxaline **5a**, we wished to develop a convenient, one-pot protocol to elevate efficiency and shorten the reaction time.



Scheme 3 Synthesis of **5a**

Subsequently, **4a** was first investigated via NBS-mediated bromination in acetic acid at reflux, until the reaction was terminated after 2 hours. Then **2a** was added directly

to the reaction mixture and the progress of the reaction was followed by TLC. Fortunately, the above-mentioned one-pot reaction strategy was complete in four hours, and **5a** was obtained in high yield (Scheme 3, eq. 2).



Scheme 4 Synthesis of **5**. *Reagents and conditions*: 1,2-diarylacetylene **4** (1.0 mmol), NBS (1.2 mmol) in AcOH (8 mL) at reflux for 2 h, then 1,2-diaminobenzenes **2** (1.1 mmol) was added and the mixture was stirred another 2 h. The isolated products were >95% pure as determined by ^{1}H NMR analysis. [a] Two isomers (**5j**, 1:1; **5o**, 1:1). [b] 1,2-Diphenylacetylene **4a** (2.0 mmol), NBS (2.4 mmol) in AcOH (10 mL) at reflux for 2 h, then 3,3′,4,4′-tetraaminobiphenyl **2g** (1.1 mmol) was added and the mixture was stirred for another 2.5 h.

On the basis of the optimized reaction conditions, a study on the substrate scope was carried out, and is shown in Scheme 4. Initially, a variety of symmetric diamines **2a**–**d** with a range of substituents were used in the reaction, followed by the NBS-mediated bromination of **4a**. The corresponding quinoxalines **5a**–**d** were isolated in 84–92% yields. Asymmetric methyl 3,4-diaminobenzoate (**2e**) and heterocyclic 2,3-diaminopyridine (**2f**) were also used in this reaction to give the products **5e** and **5f** in good isolated yields (83% and 79%, respectively). Asymmetric **4b** was tested in this reaction with 1,2-diamines **2** and the desired products **5g**–**i** were obtained in high yields between 91–95%. When methyl 3,4-diaminobenzoate (**2e**) was used in this reaction with **4b**, the product **5j** was obtained in 90% yield as two isomers in a 1:1 ratio. The reactions of 1-phenyl-4-(2-phenylethynyl)benzene (**4c**) with **2a**–**e** afforded substituted quinoxalines **5k**–**n** in good yields (82–88%) and **5o** in 81% yield in a 1:1 ratio. 1-(4-Methoxycarbonylphenyl)-2-phenylacetylene (**4d**) also reacted with **2a** and **2b**; the desired **5p** and **5q** were isolated in high yields (86% and 88%, respectively). It is noteworthy that 3,3′,4,4′-tetraaminobiphenyl (**2g**), tested in this condensation with **4a** afforded **5r** in good to excellent yield of 88%. The reaction of 1-(methoxymethyl)-3-(phenylethynyl)benzene (**4e**) with **2b** gave **5s** in 93% yield. The reaction of 1,2-bis(4-chlorophenyl)ethyne (**4f**) with **2a** was also examined, and **5t** was obtained in 93% yield. Much to our satisfaction, 2-(phenylethynyl)thiophene (**4g**), which contains a thiophene ring, was tested with **2b** and produced the quinoxaline **5u** in 93% yield. The structures of substituted quinoxalines **5d**, **5f**, and **5r** were determined by single-crystal X-ray crystallography,[29] and that of **5r** is shown in Figure 2.

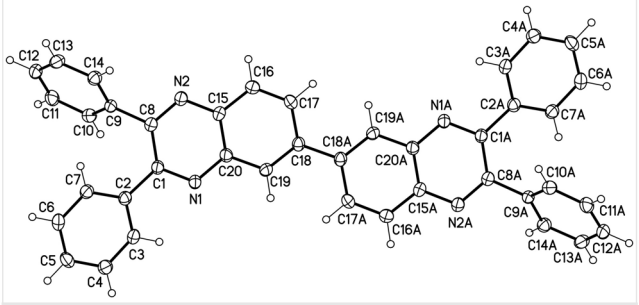
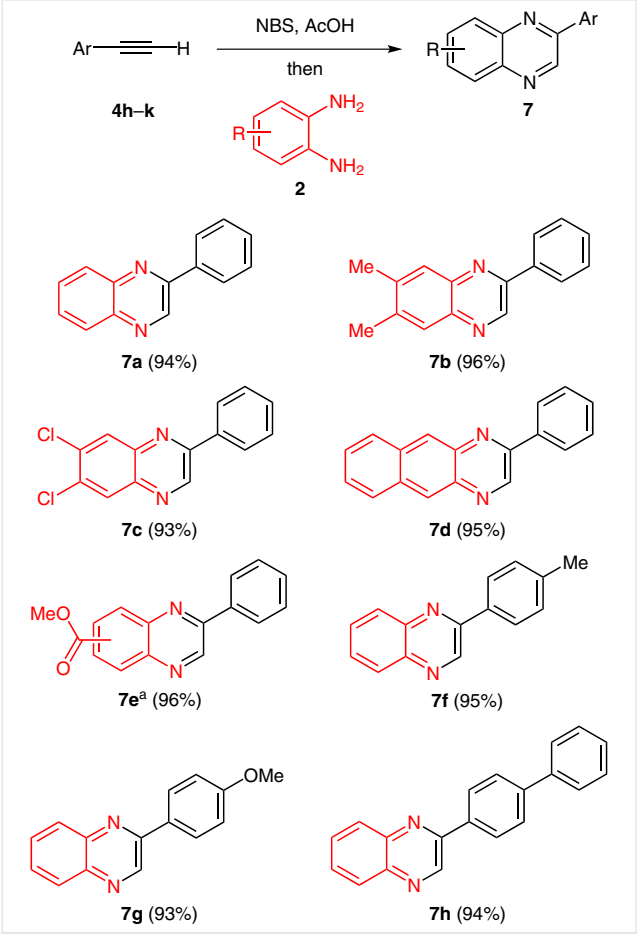


Figure 2 X-ray crystal structure of **5r**

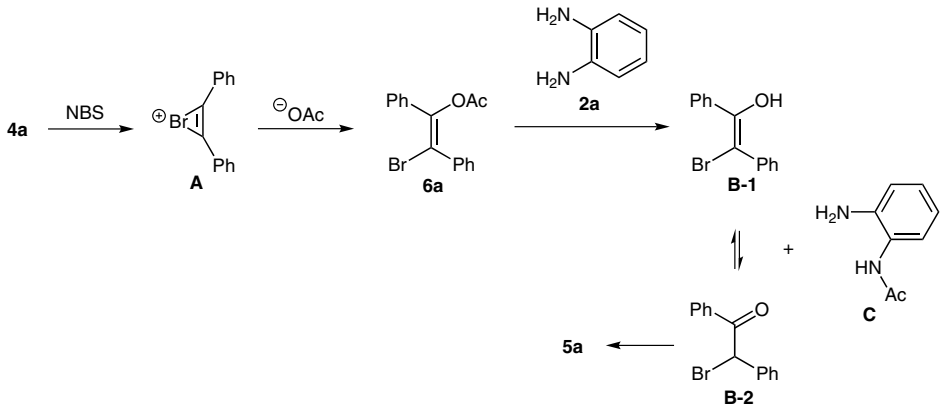
From the above observation, the substrate scope of alkynes **4** was further investigated from 1,2-diarylacetylenes **4a**–**g** to monoarylacetylenes **4h**–**k**. Phenylacetylene (**4h**) was reacted with **2a** under the above optimized reaction conditions and the corresponding **7a** was obtained in 94% yield. Based on the success of obtaining **7a**, other 1,2-diamines **2b**–**e** were also tested with **4h** and provided the desired quinoxalines **7b**–**e** in high yields (93–96%). Subsequently, **4i**–**k** were reacted with **2a** affording the desired quinoxalines **7f**–**h** in yields ranging from 93–95%. The results of this two-step one-pot synthetic route toward monosubstituted quinoxalines **7a**–**h** are shown in Scheme 5. In particular, monosubstituted quinoxaline derivatives **7b** and **7d** have shown the ability to selectively block EGFR kinase.[30]



Scheme 5 Synthesis of **7**. *Reagents and conditions*: **4h**–**k** (1.0 mmol), NBS (1.2 mmol) in AcOH (8 mL) at reflux, 2 h, then **2** (1.1 mmol), reflux, 2 h. The isolated products were >95% pure as determined by ^{1}H NMR analysis. [a] Two isomers with a ratio 1:1.

According to the aforementioned results, a plausible reaction pathway is proposed in Scheme 6. First, bromination of 1,2-diphenylacetylene (**4a**) in the presence of NBS afforded the intermediate **A**, and acetic acid underwent a nucleophilic substitution to furnish acetate **6a**. Then, **2a** was added to form enol **B-1** and acetamide **C**. By the enol-keto tautomerism, **B-1** gets transformed to **B-2**. Finally, the desired quinoxaline **5a** was obtained via a condensation of **B-2** with **C** followed by a sequential aromatization.

In summary, a facile one-pot strategy for the synthesis of substituted quinoxalines has been successfully developed from 1,2-diarylacetylenes with 1,2-diaminobenzenes in high yields. This convenient protocol goes through a bromination step via NBS in boiling AcOH giving intermediate



Scheme 6 Plausible reaction pathway

acetates, which are then condensed with 1,2-diaminobenzenes smoothly affording substituted quinoxaline derivatives in good to excellent yields. A possible reaction pathway was also discussed using the single-crystal X-ray crystallography of the intermediate acetate **6a**. Some quinoxaline data matched with the previous literature.

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry N_2 with magnetic stirring. Products in organic solvents were dried with anhyd $MgSO_4$ before concentration in vacuum. Melting points were determined with a SMP3 melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and at 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are given in hertz. High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF-Q mass spectrometer. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

Quinoxalines 5 and 7; General Procedure

NBS (214 mg, 1.2 mmol) was added to a solution of the appropriate alkyne **4** (1.0 mmol) in AcOH (8 mL) at r.t. The reaction mixture was stirred at reflux for 2 h, then the respective diamine **2** (1.1 mmol) was added to the reaction mixture directly. The mixture was stirred at 120 °C for 2 h continuously, cooled to r.t., and the solvent was concentrated. The residue was diluted with aq $NaHCO_3$ (95%, 10 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product. Purification on silica gel (hexanes/EtOAc: 10:1 to 6:1) afforded quinoxaline **5** or **7**.

2,3-Diphenylquinoxaline (5a)[17b]

Yield: 260 mg (92%); colorless solid; mp 120–121 °C (hexanes/EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.18 (m, 2 H), 7.80–7.75 (m, 2 H), 7.55–7.52 (m, 4 H), 7.39–7.32 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.39 (2 ×), 141.15 (2 ×), 138.99 (2 ×), 129.92 (2 ×), 129.80 (4 ×), 129.13 (2 ×), 128.76 (2 ×), 128.21 (4 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{20}H_{15}N_2$: 283.1235; found: 283.1229.

6,7-Dimethyl-2,3-diphenylquinoxaline (5b)[31]

Yield: 270 mg (87%); colorless solid; mp 174–175 °C (hexanes/EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 2 H), 7.51–7.49 (m, 4 H), 7.34–7.29 (m, 6 H), 2.52 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.45 (2 ×), 140.50 (2 ×), 140.16 (2 ×), 139.33 (2 ×), 129.80 (4 ×), 128.49 (4 ×), 128.14 (4 ×), 20.38 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{22}H_{19}N_2$: 311.1548; found: 311.1544.

6,7-Dichloro-2,3-diphenylquinoxaline (5c)[32]

Yield: 294 mg (84%); colorless solid; mp 111–112 °C (hexanes/EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 2 H), 7.52–7.49 (m, 4 H), 7.41–7.33 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.49 (2 ×), 139.95 (2 ×), 138.39 (2 ×), 134.43 (2 ×), 130.26 (2 ×), 129.78 (4 ×), 129.28 (2 ×), 128.35 (4 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{20}H_{13}Cl_2N_2$: 351.0456; found: 351.0452.

2,3-Diphenylbenzo[g]quinoxaline (5d)[33]

Yield: 282 mg (85%); colorless solid; mp 183–184 °C (hexanes/EtOAc)

^1H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 2 H), 8.13–8.11 (m, 2 H), 7.59–7.57 (m, 6 H), 7.42–7.34 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.17 (2 ×), 139.10 (2 ×), 137.92 (2 ×), 134.07 (2 ×), 129.83 (4 ×), 129.01 (2 ×), 128.54 (2 ×), 128.24 (4 ×), 127.52 (2 ×), 126.73 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{24}H_{17}N_2$: 333.1392; found: 333.1388.

X-ray Crystallographic Data[29]

Single-crystal of **5d** was grown by slow diffusion of EtOAc into a solution of **5d** in CH_2Cl_2 to give colorless prisms. The compound crstallized in the monoclinic crystal system, space group C 2/c, *a* = 25.127(2) Å, *b* = 7.7380(7) Å, *c* = 21.2747(19) Å, *V* = 3436.0(5) Å^3, *Z* = 8, d_{calcd} = 1.285 g/cm^3, *F*(000) = 1392, 2θ range 1.95–26.44°, *R* indices (all data) *R*1 = 0.0561, w*R*2 = 0.1009.

Methyl 2,3-Diphenylquinoxaline-6-carboxylate (5e)[34]

Yield: 282 mg (83%); colorless solid; mp 115–116 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (d, *J* = 2.0 Hz, 1 H), 8.36 (dd, *J* = 2.0, 8.8 Hz, 1 H), 8.21 (d, *J* = 8.8 Hz, 1 H), 7.56–7.53 (m, 4 H), 7.41–7.32 (m, 6 H), 4.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.28, 155.08, 154.37, 143.10, 140.36, 138.57, 131.87 (2 ×), 131.16, 129.83 (4 ×), 129.79 (2 ×), 129.42, 129.36, 129.21, 129.09, 128.29 (2 ×), 52.54.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{22}H_{17}N_2O_2$: 341.1290; found: 341.1287.

2,3-Diphenylpyrido[3,4-*b*]pyrazine (5f)[35]

Yield: 224 mg (79%); colorless solid; mp 180–181 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1 H), 8.83 (d, *J* = 5.6 Hz, 1 H), 8.01 (dd, *J* = 0.8, 5.6 Hz, 1 H), 7.56–7.53 (m, 4 H), 7.44–7.34 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.08, 155.49, 154.23, 147.00, 143.68, 138.21 (2 ×), 136.30, 129.87 (2 ×), 129.78 (2 ×), 129.74, 129.46, 128.43 (4 ×), 121.50.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{19}H_{14}N_3$: 284.1188; found 284.1181.

X-ray Crystallographic Data[29]

Single-crystal of **5f** was grown by slow diffusion of EtOAc into a solution of **5f** in CH_2Cl_2 to give colorless prisms. The compound crstallized in the monoclinic crystal system, space group P 21/n, *a* = 13.9951(9) Å, *b* = 7.1280(4) Å, *c* = 14.7290(9) Å, *V* = 1435.17(15) Å^3, *Z* = 4, d_{calcd}= 1.311 g/cm^3, *F*(000) = 592, 2θ range 2.27–26.47°, *R* indices (all data) *R*1 = 0.0531, w*R*2 = 0.0943.

2-Phenyl-3-[3-(trifluoromethyl)phenyl]quinoxaline (5g)

Yield: 333 mg (95%); colorless solid; mp 107–108 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.18 (m, 2 H), 7.87 (s, 1 H), 7.84–7.79 (m, 2 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.62 (d, *J* = 7.6 Hz, 1 H), 7.51–7.48 (m, 2 H), 7.45–7.34 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.30, 151.70, 141.39, 141.21, 139.72, 138.51, 133.17, 130.48, 130.27, 129.76 (2 ×), 129.26 (2 ×), 129.24 (2 ×), 129.11, 128.60, 128.50 (2 ×), 126.90 (q, *J* = 3.8 Hz), 125.48 (q, *J* = 3.8 Hz).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{21}H_{14}F_3N_2$: 351.1109; found: 351.1102.

6,7-Dimethyl-2-phenyl-3-[3(trifluoromethyl)phenyl]quinoxaline (5h)

Yield: 348 mg (92%); colorless solid; mp 96–97 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (s, 1 H), 7.94 (s, 1 H), 7.84 (s, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.48–7.45 (m, 2 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.40–7.32 (m, 3 H), 2.53 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.27, 150.70, 141.25, 141.00, 140.30, 140.21, 139.96, 138.71, 133.17, 129.77 (4 ×), 128.85, 128.50, 128.42 (2 ×), 128.17 (2 ×), 126.87 (q, *J* = 3.8 Hz), 125.21 (q, *J* = 3.8 Hz), 20.48, 20.44.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{23}H_{18}F_3N_2$: 379.1422; found: 379.1417.

2-Phenyl-3-[3-(trifluoromethyl)phenyl]benzo[*g*]quinoxaline (5i)

Yield: 364 mg (91%); colorless solid; mp 161–162 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 1 H), 8.76 (s, 1 H), 8.14–8.11 (m, 2 H), 7.93 (s, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.61–7.57 (m, 2 H), 7.55–7.53 (m, 2 H), 7.47–7.37 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.75, 152.38, 139.71, 138.51, 137.83, 137.76, 134.30, 134.14, 133.14, 129.74 (4 ×), 129.27, 128.55 (4 ×), 128.44, 127.71, 127.60, 126.99, 126.92, 126.86 (q, *J* = 3.8 Hz), 125.64 (q, *J* = 3.8 Hz).

HRMS (ESI): (M^+ + H) calcd for $C_{25}H_{16}F_3N_2$: 401.1266; found: 401.1261.

Methyl 2-Phenyl-3-[3-(trifluoromethyl)phenyl]quinoxaline-6-carboxylate and Methyl 3-Phenyl-2-[3-(trifluoromethyl)phenyl]quinoxaline-6-carboxylate (5j)

Two isomers, ratio = 1:1; yield: 376 mg (92%); colorless solid; mp 159–160 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92–8.91 (m, 1 H), 8.41–8.38 (m, 1 H), 8.24–8.21 (m, 1 H), 7.89–7.87 (m, 1 H), 7.70–7.63 (m, 2 H), 7.52–7.36 (m, 6 H), 4.031–4.029 (m, 3 H).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{23}H_{16}N_2O_2$: 409.1164; found: 409.1159.

2-([1,1′-Biphenyl]-4-yl)-3-phenylquinoxaline (5k)[36]

Yield: 315 mg (88%); colorless solid; mp 116–117 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.17 (m, 2 H), 7.80–7.75 (m, 2 H), 7.64–7.56 (m, 8 H), 7.45–7.42 (m, 2 H), 7.39–733 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.39, 152.99, 141.50, 141.18, 141.11, 140.30, 138.98, 137.80, 130.30 (2x), 130.01, 129.99, 129.83 (2 ×), 129.12 (2 ×), 128.87, 128.78 (2 ×), 128.35 (2 ×), 127.59, 127.05 (2 ×), 126.92 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{26}H_{19}N_2$: 359.1548; found: 359.1540.

2-([1,1′-Biphenyl]-4-yl)-6,7-dimethyl-3-phenylquinoxaline (5l)

Yield: 332 mg (86%); colorless solid; mp 147–148 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 2 H), 7.63–7.54 (m, 8 H), 7.47–7.42 (m, 2 H), 7.38–7.34 (m, 4 H), 2.53 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.39, 151.96, 141.26, 140.72, 140.39 (2 ×), 140.11, 140.05, 139.18, 138.01, 130.01 (2 ×), 129.85 (2 ×), 128.78 (2 ×), 128.65, 128.29 (2 ×), 128.08, 128.07, 127.54, 127.05 (2 ×), 126.86 (2 ×), 20.45 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{28}H_{23}N_2$: 387.1861; found: 387.1857.

2-([1,1′-Biphenyl]-4-yl)-6,7-dichloro-3-phenylquinoxaline (5m)

Yield: 349 mg (82%); transparent gel.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1 H), 8.30 (s, 1 H), 7.65–7.55 (m, 9 H), 7.47–7.35 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.46, 154.05, 142.00, 140.13, 139.98, 139.88, 138.41, 137.17, 134.45, 134.40, 130.28 (2 ×), 129.77 (2 ×), 129.75 (2 ×), 129.34, 128.85 (2 ×), 128.46 (2 ×), 127.77, 127.08 (2 ×), 126.99 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{26}H_{17}Cl_2N_2$: 427.0769; found: 427.0764.

2-([1,1′-Biphenyl]-4-yl)-3-phenylbenzo[*g*]quinoxaline (5n)

Yield: 355 mg (87%); colorless solid; mp 168–169 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (s, 1 H), 8.77 (s, 1 H), 8.15–8.11 (m, 2 H), 7.68–7.57 (m, 10 H), 7.48–7.36 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.12, 153.71, 141.75 (2 ×), 140.29 (2 ×), 139.04, 137.82, 134.10, 134.09, 130.34 (2 ×), 129.85 (2 ×), 129.12, 128.83 (2 ×), 128.55 (2 ×), 128.35 (2 ×), 127.67, 127.50, 127.47, 127.09 (2 ×), 126.91 (2 ×), 126.79 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{30}H_{21}N_2$: 409.1705; found: 409.1696.

Methyl 3-([1,1′-Biphenyl]-4-yl)-2-phenylquinoxaline-6-carboxylate and Methyl 2-([1,1′-Biphenyl]-4-yl)-3-phenylquinoxaline-6-carboxylate (5o)

Two isomers, ratio = 1:1; yield: 337 mg (81%); colorless solid; mp 153–154 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92–8.91 (m, 1 H), 8.39–8.36 (m, 1 H), 8.24–8.22 (m, 1 H), 7.65–7.58 (m, 8 H), 7.47–7.35 (m, 6 H), 4.03 (s, 3 H).

HRMS (ESI): *m*/*z* (M^+ + 1) calcd for $C_{28}H_{21}N_2O_2$: 417.1603; found: 417.1601.

Methyl 4-(3-Phenylquinoxalin-2-yl)benzoate (5p)[17b]

Yield: 292 mg (86%); colorless solid; mp 151–152 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.20 (m, 2 H), 8.01 (d, *J* = 8.4 Hz, 2 H), 7.84–7.79 (m, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.52–7.49 (m, 2 H), 7.41–7.32 (m, 3 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.71, 153.21, 152.31, 143.28, 141.16, 141.06, 138.33, 130.57, 130.33, 130.22, 129.92 (2 ×), 129.83 (2 ×), 129.50 (2 ×), 129.18, 129.14, 129.11, 128.46 (2 ×), 52.25.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{22}H_{17}N_2O_2$: 341.1290; found: 341.1284.

Methyl 4-(6,7-Dimethyl-3-phenylquinoxalin-2-yl)benzoate (5q)

Yield: 324 mg (88%); colorless solid; mp 91–92 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.8 Hz, 2 H), 7.95 (s, 1 H), 7.93 (s, 1 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 7.48–7.46 (m, 2 H), 7.35–7.31 (m, 3 H), 3.92 (s, 3 H), 2.53 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.81, 152.33, 151.31, 143.80, 141.22, 140.95, 140.31, 140.12, 138.83, 129.91 (2 ×), 129.81 (2 ×), 129.44 (2 ×), 128.80, 128.37 (2 ×), 128.18 (2 ×), 121.37, 52.21, 20.50, 20.47.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{24}H_{21}N_2O_2$: 369.1603; found: 369.1596.

2,2′,3,3′-Tetraphenyl-6,6′-biquinoxaline (5r)[37]

Yield: 495 mg (88%); colorless solid; mp 253 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J*= 2.0 Hz, 2 H), 8.33 (d, *J* = 8.8 Hz, 2 H), 8.24 (dd, *J* = 2.0, 8.4 Hz, 2 H), 7.59–7.56 (m, 8 H), 7.41–7.34 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.16 (2 ×), 153.73 (2 ×), 141.42 (2 ×), 141.23 (2 ×), 140.91 (2 ×), 138.90 (2 ×), 133.61 (2 ×), 130.14 (2 ×), 129.90 (2 ×), 129.86 (8 ×), 129.52 (2 ×), 128.96 (2 ×), 128.30 (8 ×), 127.43 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{40}H_{27}N_4$: 563.2236; found: 563.2228.

X-ray Crystallographic Data[29]

Single-crystal of **5r** was grown by slow diffusion of EtOAc into a solution of **5r** in CH_2Cl_2 to yield colorless prisms. The compound crstallizes in the monoclinic crystal system, space group P 21/c, *a* = 6.2940(7) Å, *b* = 7.6457(9) Å, *c* = 29.753(4) Å, *V* = 1426.6(3) Å^3, *Z* = 2, d_{calcd}= 1.310 g/cm^3, *F*(000) = 588, 2θ range 1.37–26.36°, *R* indices (all data) *R*1 = 0.0658, w*R*2 = 0.1592.

2-[3-(Methoxymethyl)phenyl]-3-phenylquinoxaline (5s)

Yield: 303 mg (93%); colorless solid; mp 76–77 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.19 (m, 2 H), 7.81–7.77 (m, 2 H), 7.53–7.51 (m, 3 H), 7.42–7.29 (m, 6 H), 4.43 (s, 2 H), 3.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.43, 153.23, 141.05, 138.86, 138.83, 138.42, 130.09 (2 ×), 129.83 (2 ×), 129.18, 129.15, 129.09 (2 ×), 129.08, 128.84, 128.34, 128.29 (2 ×), 128.15, 74.23, 57.93.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{22}H_{19}N_2O$: 327.1497; found: 327.1491.

2,3-Bis(4-chlorophenyl)quinoxaline (5t)[12c]

Yield: 326 mg (93%); colorless solid; mp 188–189 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.14 (m, 2 H), 7.82–7.78 (m, 2 H), 7.47 (d, *J* = 8.8 Hz, 4 H), 7.35 (d, *J* = 8.8 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.92 (2 ×), 141.21 (2 ×), 137.20 (2 ×), 135.35 (2 ×), 131.17 (4 ×), 130.40 (2 ×), 129.18 (2 ×), 128.73 (4 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{20}H_{13}Cl_2N_2$: 351.0456; found: 351.0452.

2-Phenyl-3-(thiophen-2-yl)quinoxaline (5u)

Yield: 268 mg (93%); colorless solid; mp 97–98 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.10 (m, 2 H), 7.78–7.70 (m, 2 H), 7.63–7.60 (m, 2 H), 7.52–7.48 (m, 3 H), 7.41 (dd, *J* = 0.8, 5.2 Hz, 1 H), 6.88 (dd, *J* = 3.6, 5.2 Hz, 1 H), 6.77 (dd, *J* = 0.8, 3.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.51, 146.88, 142.68, 141.11, 139.34, 132.62, 130.20, 129.93, 129.75, 129.32, 129.24, 129.12 (2 ×), 129.02, 128.82, 127.74, 128.71 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{18}H_{13}N_2S$: 289.0800; found: 289.0794.

2-Phenylquinoxaline (7a)[38]

Yield: 194 mg (94%); colorless solid; mp 75–76 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.31 (s, 1 H), 8.19–8.10 (m, 4 H), 7.78–7.70 (m, 2 H), 7.57–7.48 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.70, 143.21, 142.18, 141.42, 136.63, 130.19, 130.09, 129.51, 129.45, 129.05 (2 ×), 128.99, 127.45 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{14}H_{11}N_2$: 207.0922; found: 207.0916.

6,7-Dimethyl-2-phenylquinoxaline (7b)[39]

Yield: 225 mg (96%); colorless solid; mp 130–131 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (s, 1 H), 8.17–8.14 (m, 2 H), 7.90 (s, 1 H), 7.85 (s, 1 H), 7.57–7.47 (m, 3 H), 2.50 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.96, 142.22, 141.19, 140.86, 140.35, 140.19, 137.01, 129.83, 129.04 (2 ×), 128.58, 127.99, 127.34 (2 ×), 20.36, 20.33.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{16}H_{15}N_2$: 235.1235; found: 235.1232.

6,7-Dichloro-2-phenylquinoxaline (7c)[32]

Yield: 255 mg (93%); colorless solid; mp 155–156 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 8.28 (s, 1 H), 8.24 (s, 1 H), 8.20–8.17 (m, 2 H), 7.61–7.54 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.64, 144.27, 141.09, 140.24, 135.97, 134.93, 134.01, 130.77, 130.18, 129.77, 129.27 (2 ×), 127.57 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{14}H_9Cl_2N_2$: 275.0143; found: 275.0135.

2-Phenylbenzo[*g*]quinoxaline (7d)[10]

Yield: 243 mg (95%); colorless solid; mp 158–159 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 8.79 (s, 1 H), 8.75 (s, 1 H), 8.29–8.26 (m, 2 H), 8.15–8.11 (m, 2 H), 7.63–7.56 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.68, 143.62, 138.48, 136.89, 136.20, 134.43, 133.84, 130.79, 129.29 (2 ×), 128.56, 128.52, 127.86, 127.75 (2 ×), 127.27, 127.14, 126.99.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{18}H_{13}N_2$: 257.1079; found: 257.1072.

Methyl 2-Phenylquinoxaline-6-carboxylate and Methyl 3-Phenylquinoxaline-6-carboxylate (7e)[40]

Two isomers, ratio = 1:1; yield: 254 mg (96%); colorless solid; mp 159–160 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40–9.38 (m, 1 H), 8.86–8.80 (m, 1 H), 8.37–8.30 (m, 1 H), 8.23–8.14 (m, 3 H), 7.60–7.52 (m, 3 H), 4.01 (br s, 3 H).

HRMS (ESI): *m*/*z* (M^+ + Na) calcd for $C_{16}H_{12}N_2O_2Na$: 287.0797; found: 287.0793.

2-(*p*-Tolyl)quinoxaline (7f)[32]

Yield: 209 mg (95%); colorless solid; mp 92–93 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1 H), 8.14–8.07 (m, 4 H), 7.78–7.69 (m, 2 H), 7.35 (d, *J* = 0.8, 8.4 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.70, 143.17, 142.22, 141.30, 140.42, 133.85, 130.12, 129.80 (2 ×), 129.44, 129.21, 128.98, 127.34 (2 ×), 21.35.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{15}H_{13}N_2$: 221.1079; found: 221.1075.

2-(4-Methoxyphenyl)quinoxaline (7g)[32]

Yield: 220 mg (93%); colorless solid; mp 95–96 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1 H), 8.15 (d, *J* = 9.2 Hz, 2 H), 8.12–8.07 (m, 2 H), 7.76–7.67 (m, 2 H), 7.06 (d, *J* = 9.2 Hz, 2 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.41, 151.34, 142.93, 142.21, 141.05, 130.15, 129.29, 129.14, 129.02, 128.94, 128.92 (2 ×), 114.52 (2 ×), 55.36.

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{15}H_{13}N_2O$: 237.1028; found: 237.1022.

2-([1,1′-Biphenyl]-4-yl)quinoxaline (7h)[32]

Yield: 265 mg (94%); colorless solid; mp 128–129 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 8.26 (d, *J* = 8.4 Hz, 2 H), 8.16 (dd, *J* = 1.6, 8.0 Hz, 1 H), 8.12 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 2 H), 7.75–7.65 (m, 4 H), 7.50–7.45 (m, 2 H), 7.42–7.37 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.19, 143.09, 142.76, 142.21, 141.43, 140.04, 135.39, 130.17, 129.49, 129.37, 129.00, 128.80 (2 ×), 127.80 (2 ×), 127.74, 127.65 (2 ×), 127.02 (2 ×).

HRMS (ESI): *m*/*z* (M^+ + H) calcd for $C_{20}H_{15}N_2$: 283.1235; found: 283.1230.

(*E*)-2-Bromo-1,2-diphenylethenyl Acetate (6a)

NBS (214 mg, 1.2 mmol) was added to a solution of 1,2-diphenylacetylene (**4a**; 178 mg, 1.0 mmol) in AcOH (8 mL) at r.t. The reaction mixture was stirred at reflux for 2 h, cooled to r.t., and the solvent was concentrated. The residue was diluted with aq $NaHCO_3$ (95%, 10 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc: 10:1 to 6:1) afforded compound **6a**; yield: 303 mg (96%); colorless solid; mp 113–114 °C (hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.68 (m, 2 H), 7.52–7.49 (m, 2 H), 7.45–7.31 (m, 6 H), 1.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.54, 144.52, 137.62, 135.26, 129.18, 129.14 (2 ×), 128.72, 128.61 (2 ×), 128.25 (2 ×), 128.05 (2 ×), 114.02, 20.53.

HRMS (ESI): *m*/*z* (M^+ + Na) calcd for $C_{16}H_{13}BrO_2Na$: 338.9997; found: 338.9989.

X-ray Crystallographic Data[29]

Single-crystal of **6a** was grown by slow diffusion of EtOAc into a solution of **6a** in CH_2Cl_2 to afford colorless prisms. The compound crstallizes in the triclinic crystal system, space group P-1, *a* = 8.1329(3) Å, *b* = 8.9362(3) Å, *c* = 10.0140(4) Å, *V* = 700.17(4) Å^3, *Z* = 2, d_{calcd}= 1.504 g/cm^3, *F*(000) = 320, 2θ range 2.11–26.47°, *R* indices (all data) *R*1 = 0.0318, w*R*2 = 0.0605.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561472.

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