Synthesis of 6*H*-Indolo[2,3-*b*][1,6]naphthyridines and Related Compounds as the 5-Aza Analogues of Ellipticine Alkaloids

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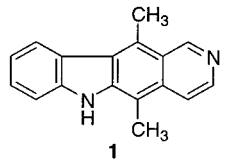
Treatment of 2-(1-alkynyl)phenyl isocyanates **6** with the iminophosphorane **14** produced in situ the benzoenynyl carbodiimides **15**. Thermolysis of **15** under refluxing *p*-xylene furnished the 6*H*-indolo[2,3-*b*][1,6]naphthyridines **5**, which could be regarded as the 5-aza analogues of ellipticine alkaloids. Similarly, condensation of **6** with the iminophosphorane **20** led to the formation of the 6*H*-indolo[2,3-*b*][1,5]naphthyridines **25** as the major isomer and the 10*H*- indolo[2,3-*b*][1,7]-naphthyridines **26** as the minor isomer. The indolonaphthyridines **32**, **33**, and **34** having a methoxyl substituent were likewise synthesized. Treatment of the diisocyanate **43** with 2 equiv of the iminophosphorane **7** furnished **45** having two indoloquinoline units incorporated in a seven-fused-ring system.

Introduction

Ellipticine (**1**) and 9-methoxyellipticine (**2**) are two naturally occurring 6*H*-pyrido[4,3-*b*]carbazole alkaloids isolated from the leaves of *Ochrosia elliptica* Labill (family Apocynaceae).[1] The discovery of their antitumor activities in 1967[2] has led to an explosion of synthetic, biological, and pharmacological studies of ellipticine and its derivatives.[3] Several ellipticine derivatives have been used in clinical trials.[3a−c] More recently, 5-methyl-5*H*-indolo[2,3-*b*]quinoline (**3a**), an indoloquinoline alkaloid isolated from the West African plant *Cryptolepis sanguinolenta*,[4] was reported to display a strong antiplasmodial activity.[5] Similarly, **3b** having a methyl substituent at the C11 position exhibited a strong antibacterial, antimycotic, and cytotoxic activity in vitro as well as significant antitumor properties in vivo.[6] Methylation of 6*H*-indolo[2,3-*b*]quinolines **4** with dimethyl sulfate followed by treatment with sodium hydroxide led to **3** directly (eq 1).[6,7] The interesting biological activities of ellipticines and indoloquinolines prompted us to develop a new synthetic route to the 6*H*-indolo[2,3-*b*][1,6]naphthyridines **5**, which could be regarded as the 5-aza analogues of ellipticines merging the heterocyclic frameworks of both ellipticine and indoloquinoline. Only one synthetic route involving a seven-step synthesis of 3-acetyl-4-(methylamino)pyridine from 3-acetylpyridine followed by condensation with oxindole to form 5,11-dimethyl-5*H*-



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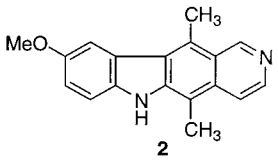

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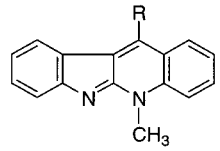

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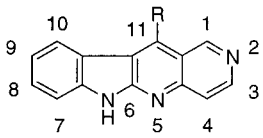
3b: R = Me



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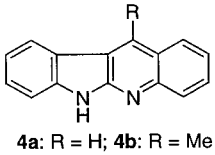
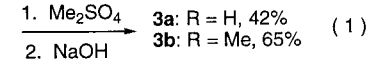


4a: R = H; **4b**: R = Me



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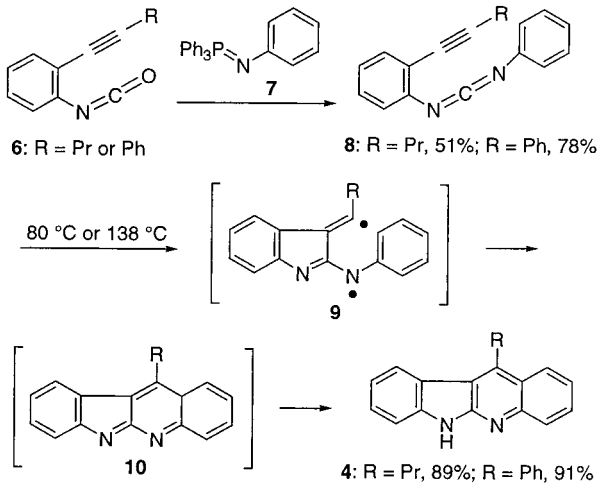
Scheme 1



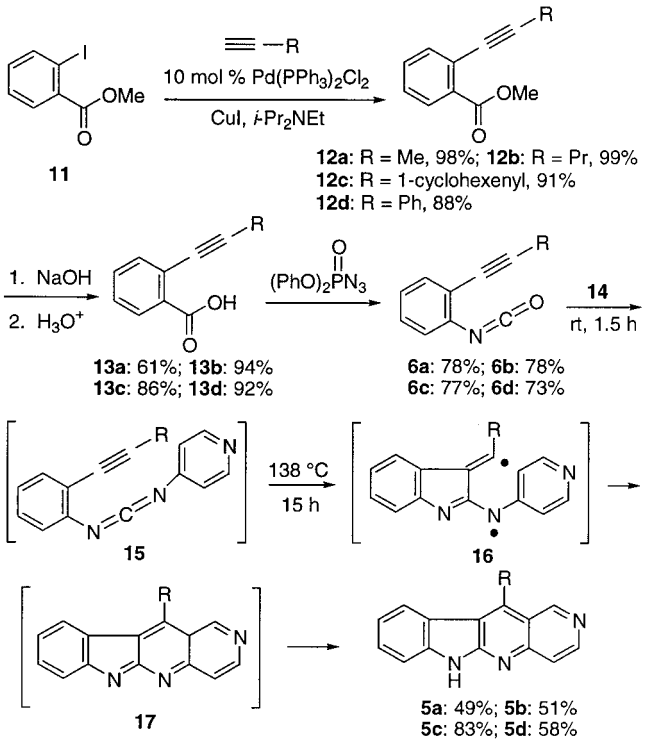
indolo[2,3-*b*][1,6]naphthyridine as the 5-aza analogue of ellipticine had been reported previously.[8]

We recently reported an efficient synthetic route to the 6*H*-indolo[2,3-*b*]quinolines **4** via thermolysis of the benzoenynyl carbodiimides **8**, derived from the aza-Wittig reaction between the 2-(1-alkynyl)phenyl isocyanates **6** and the iminophosphorane **7** (Scheme 1).[9a] Presumably the reaction proceeds either through a two-step biradical pathway involving an initial C2−C6 cyclization of **8** to form the biradicals **9** followed by an intramolecular radical−radical coupling or through a concerted intramolecular Diels−Alder reaction to furnish **10**. A subsequent tautomerization then provided **4**. We envisioned that by replacing the phenyl group in the iminophosphorane **7** with a pyridyl group, the synthetic sequence outlined in Scheme 1 could lead to a variety of indolonaphthyridines as the 5-aza analogues of ellipticines and the much less studied isoellipticines[10] in which the pyridine nitrogen is at a different ring D position.

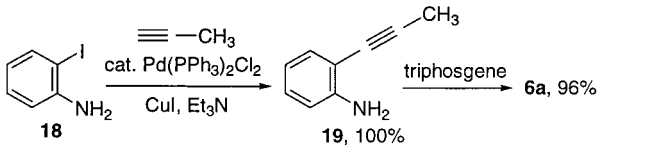
Results and Discussion

The requisite 2-(1-alkynyl)phenyl isocyanates **6** were prepared from methyl 2-iodobenzoate (**11**) according to the reported procedure (Scheme 2).[9a] The Pd-catalyzed cross-coupling reaction between **11** and 1-alkynes provided the methyl 2-(1-alkynyl)benzoates **12**. Hydrolysis of **12** gave the corresponding 2-(1-alkynyl)benzoic acids **13**. Treatment of **13** with diphenyl phosphorazidate then furnished **6** via a modified Curtius rearrangement.[11] Alternatively, **6a** was also obtained by the Pd-catalyzed

Scheme 2

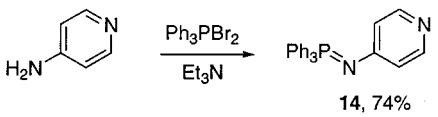


cross-coupling reaction between 2-iodoaniline (**18**) and propyne to afford **19** followed by treatment of **19** with triphosgene (eq 2).[12] The iminophosphorane **14** was a



(2)

known compound, and several synthetic procedures had been reported.[13] The procedure for the preparation of iminophosphoranes by treatment of primary arylamines with dibromotriphenylphosphorane (Ph_3PBr_2) appeared to offer the most direct route to **14**.[13e,f,14] Indeed, the use of 4-aminopyridine to react with Ph_3PBr_2 produced **14** (74% yield) in a single step (eq 3).



(3)

The aza-Wittig reaction between **6** and **14** produced in situ the benzoenynyl carbodiimides **15**. Thermolysis of **15** under refluxing *p*-xylene then furnished the 6*H*-indolo[2,3-*b*][1,6]naphthyridines **5** in a single operation from **6**. Again, the transformation from **15** to **17** could

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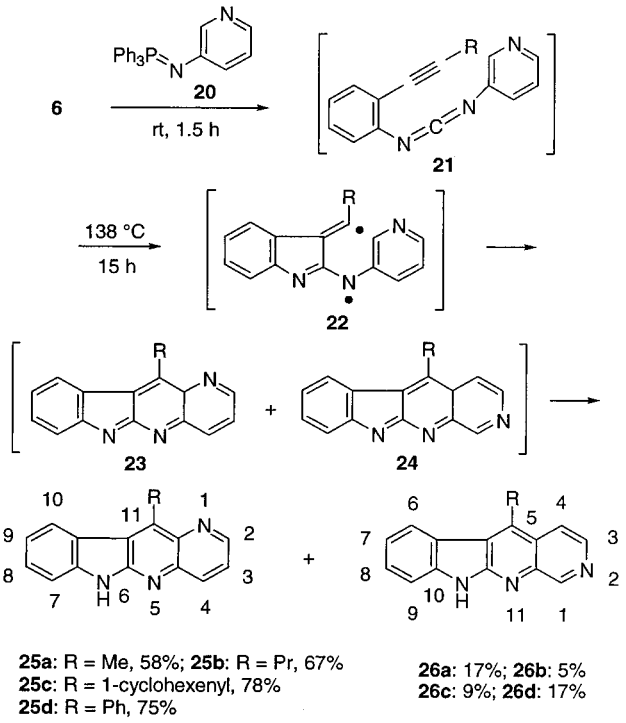
Scheme 3

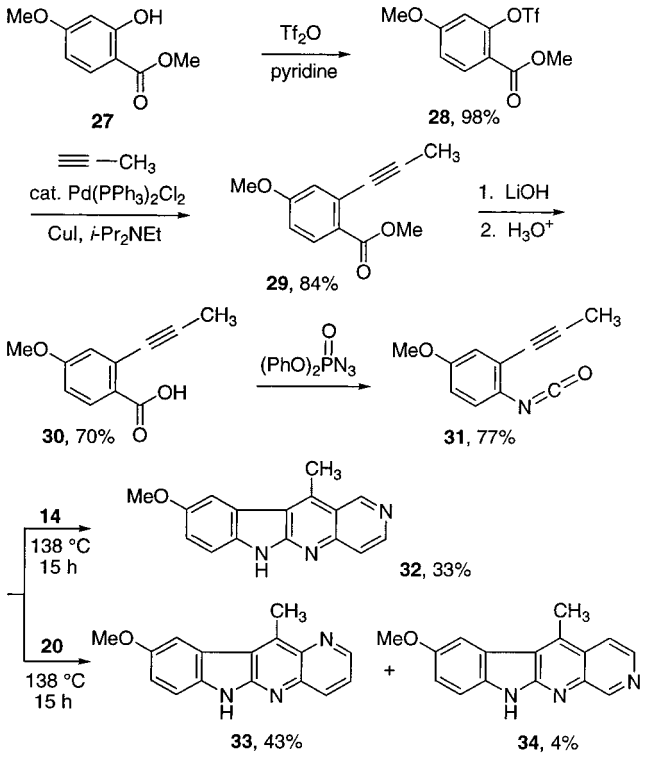


proceed either through a two-step biradical pathway or through a concerted intramolecular Diels−Alder reaction. It is worth noting that the synthetic sequence outlined in Scheme 2 allows easy introduction of an alkyl, an alkenyl, or an aryl substituent as the R group at the C11 position of **5**.

The iminophosphorane **20**,[13e] prepared from 3-aminopyridine and Ph_3PBr_2 in 76% yield, was also used for the aza-Wittig reaction with **6** to produce in situ the benzoenynyl carbodiimides **21** (Scheme 3). Subsequent thermolysis under refluxing *p*-xylene furnished the 6*H*-indolo[2,3-*b*][1,5]naphthyridines **25** as the major isomer and the 10*H*-indolo[2,3-*b*][1,7]naphthyridines **26** as the minor isomer. Apparently, cyclization of **21** furnished the formal Diels−Alder adducts **23** preferentially, leading to **25** as the major isomer. The reason for such a preference is not clear at this time. The structures of **25** and **26** represent two rare heterocyclic systems that could be regarded as the aza analogues of isoellipticines. There was only one earlier report of a indolonaphthyridine derivative having the heterocyclic structure of **25**.[15] The indolonaphthyridine **26a** was previously synthesized by condensation of 4-acetyl-3-aminopyridine with oxindole.[16]

Several ellipticine derivatives having either a 9-hydroxyl or a 9-methoxyl substituent were found to possess potent antitumor activities.[3a−c] Transformation of these derivatives to the corresponding quinone imines to allow subsequent attack by a nucleophilic substrate was reported to be responsible for their antitumor activities.[3a−c,17]

Scheme 4



It was straightforward to introduce a methoxyl group at the C9 position of **5** by starting from the readily available methyl 4-methoxysalicylate (**27**). Treatment of **27** with trifluoromethanesulfonic anhydride produced the corresponding triflate **28** in 98% yield (Scheme 4). A Pd-catalyzed cross-coupling reaction with propyne then furnished **29**.[18] The remaining sequence of reactions resembles those outlined in Scheme 2. The aza-Wittig reaction between **31** and **14** followed by thermolysis produced **32** having a 9-methoxyl substituent in 33% yield. Similarly, **33** and **34** were obtained by treatment of **31** with **20**.

We reported earlier the use of 1,4-phenylene diisocyanate (**35**) for the aza-Wittig reaction with 2 equiv of the iminophosphorane **36** to produce in situ **37** for subsequent thermolysis to furnish **38** having two indoloquinoline units incorporated in a seven-fused-ring system with a helical twist (Scheme 5).[9a] The strategy of using a diisocyanate for the construction of the seven-fused-ring systems was also adopted in the current study. The commercially available diethyl 2,5-dihydroxyterephthalate (**39**) was readily transformed to **43** having two benzoenynyl isocyanate units (Scheme 6). Unfortunately, attempts to produce **44** by treatment of **43** with 2 equiv of **14** for the aza-Wittig reaction followed by thermolysis afforded a dark brown solid which was difficult to characterize by spectroscopic methods because of its low solubility in common organic solvents. On the other hand, treatment of **43** with 2 equiv of **7**[9a,14b] led to the formation of a slightly soluble solid to allow characterization by HRMS and ^{1}H NMR. The spectroscopic data support the formation of **45** having two linearly fused indoloquinoline units in its structure.

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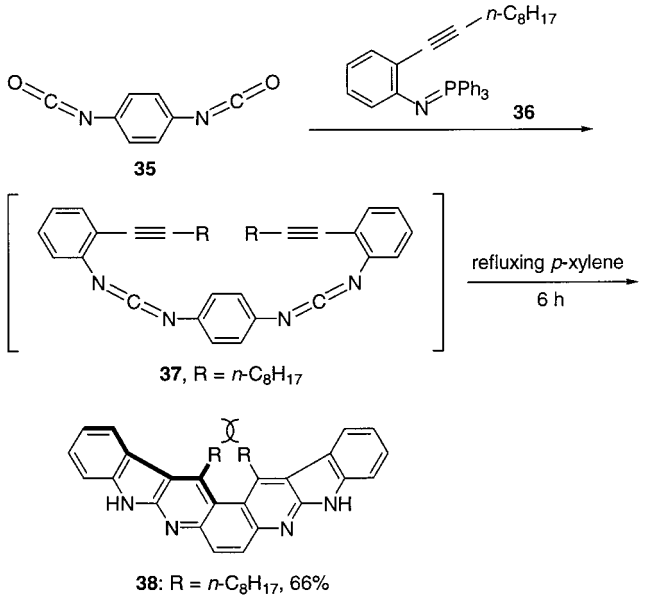
Scheme 5



Conclusions

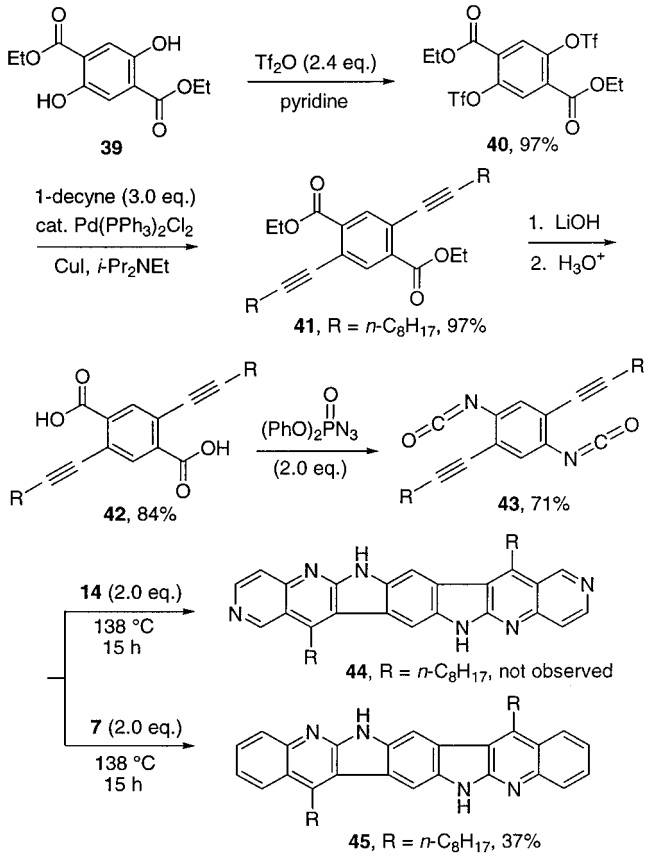
A new and efficient synthetic pathway to indolonaphthyridines has been developed. The synthetic route is convergent and allows easy placement of a variety of substituents around the periphery of the heterocyclic ring system. The structures of indolonaphthyridines resemble those of ellipticine alkaloids, making them good candidates as DNA intercalating agents with potentially interesting biological activities.

Experimental Section

Diethyl ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl prior to use. Triethylamine was distilled from CaH_2. 2-Iodoaniline was purchased from Oakwood Products, Inc. and was used as received. 1-Alkynes were obtained from GFS Chemicals, Inc. and were used without further purification. Dibromotriphenylphosphorane (Ph_3PBr_2), diphenyl phosphorazidate (DPPA), $Pd(PPh_3)_2Cl_2$, *p*-xylene (anhydrous), *N*,*N*-dimethylformamide (DMF), *N*,*N*-diisopropylethylamine, 1-ethynylcyclohexene, triphosgene, 3-aminopyridine, 4-aminopyridine, methyl 4-methoxysalicylate (**27**), trifluoromethanesulfonic (triflic) anhydride, and diethyl 2,5-dihydroxyterephthalate (**39**) were purchased from Aldrich and were used as received. Methyl 2-iodobenzoate (**11**) was purchased from Lancaster. Melting points are uncorrected. ^{1}H (270 MHZ) and ^{13}C (67.9 MHZ) NMR spectra were recorded in $CDCl_3$ using $CHCl_3$ (^{1}H δ 7.26) or $CDCl_3$ (^{13}C δ 77.0) as internal standard unless otherwise indicated.

Methyl 2-(1-Propynyl)benzoate (12a).[19] The following procedure for the preparation of **12a** is representative. To a degassed solution of 1.53 g of $Pd(PPh_3)_2Cl_2$ (2.18 mmol), 0.414 g of CuI (2.18 mmol), 6.55 g of methyl 2-iodobenzoate (**11**, 25.0 mmol), and 13.8 mL of *N*,*N*-diisopropylethylamine (79.0 mmol) in 80 mL of DMF was added 1.0 L of gaseous propyne (41 mmol) introduced with a gastight syringe. After 24 h at room temperature, the reaction mixture was poured into a flask containing 100 mL of a saturated NH_4Cl solution and 100 mL of pentane. After filtration, the organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel/5% diethyl ether in hexanes) to afford **12a** (4.26 g, 24.5 mmol, 98%) as a light yellow liquid: IR (neat) 2244, 1731, 1250, 757 cm^{-1}; ^{1}H δ 7.89 (1 H, dd, J = 7.9 and 1.4 Hz), 7.52 (1 H, dd, J = 7.7 and 1.3 Hz), 7.42 (1 H, td, J = 7.6 and 1.4 Hz), 7.31 (1 H, td, J = 7.3 and 1.4 Hz), 3.92 (3 H, s), 2.13 (3 H, s); ^{13}C δ 166.9, 134.3, 131.8, 131.6, 130.1, 127.1, 124.6, 91.5, 78.3, 52.1, 4.8; MS *m*/*z* 174 (M^+), 159, 143, 131, 115; HRMS calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0686.

Scheme 6



2-(1-Propynyl)benzoic Acid (13a).[20] The following procedure for the preparation of **13a** is representative. A solution of 3.934 g (22.61 mmol) of **12a** in 100 mL of THF and 99 mL of a 1 N NaOH solution was heated at 50 °C for 12 h. The reaction mixture was cooled in an ice−water bath and acidified with a dilute HCl solution. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by recrystallization from 50% of diethyl ether in hexanes to afford **13a** (2.20 g, 13.8 mmol, 61%) as a light yellow solid: mp 87.5−88 °C (lit.[20] 87−90 °C); IR 3300−2400 (br), 1675, 1284, 754 cm^{-1}; ^{1}H δ 11.82 (1 H, br OH), 8.05 (1 H, dd, J = 8.0 and 1.3 Hz), 7.54 (1 H, dd, J = 7.9 and 1.4 Hz), 7.48 (1 H, td, J = 7.7 and 1.5 Hz), 7.35 (1 H, td, J = 7.7 and 1.5 Hz), 2.14 (3 H, s); ^{13}C δ 171.5, 134.4, 132.4, 131.0, 130.6, 127.3, 124.9, 92.7, 78.1, 4.8; MS *m*/*z* 160 (M^+), 145, 131, 118, 89; HRMS calcd for $C_{10}H_8O_2$ 160.0524, found 160.0523.

2-(1-Propynyl)phenyl Isocyanate (6a). The following procedure for the preparation of **6a** is representative. To a solution of 2.163 g (13.52 mmol) of **13a** in 30 mL of anhydrous benzene were added 1.9 mL of triethylamine and 2.9 mL (13.5 mmol) of DPPA. After 3 h at room temperature, the reaction mixture was heated under reflux for 2 h until the nitrogen gas evolution had ceased. The reaction mixture was then washed with a saturated NH_4Cl solution and water, dried over $MgSO_4$, and concentrated. The reside was purified by flash chromatography (silica gel/5% diethyl ether in hexanes) to afford **6a** (1.65 g, 10.5 mmol, 78%) as a light yellow liquid: IR (neat) 2241, 1723, 755 cm^{-1}; ^{1}H δ 7.37 (1 H, dd, J = 7.5 and 1.6 Hz), 7.21 (1 H, td, J = 7.7 and 1.7 Hz), 7.10 (1 H, td, J =

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7.5 and 1.3 Hz), 7.00 (1 H, dd, J = 7.9 and 1.5 Hz), 2.13 (3 H, s); ^{13}C δ 135.4, 131.8, 128.6, 127.7, 125.2, 123.3, 121.5, 95.4, 75.7, 4.4; MS m/z 157 (M^+), 129, 102; HRMS calcd for $C_{10}H_7NO$ 157.0528, found 157.0525.

Alternatively, **6a** was also prepared from triphosgene and 2-(1-propynyl)aniline (**19**), which was readily obtained in essentially quantitative yield by using the $Pd(PPh_3)_2Cl_2$-catalyzed cross-coupling reaction between 2-iodoaniline and propyne as described previously.[9a] To a solution of 1.089 g of triphosgene (3.67 mmol) in 20 mL of anhydrous benzene was added dropwise a mixture of 1.310 g of **19** (10.0 mmol) and 2.78 mL of anhydrous triethylamine (20.0 mmol) in 30 mL of anhydrous benzene under a nitrogen atmosphere at room temperature. After 2 h at 70 °C, the white precipitate of triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel/10−20% of diethyl ether in hexanes) to give 1.507 g of **6a** (9.60 mmol, 96%).

Iminophosphorane 14.[13e,f] A reaction mixture of 0.753 g (8.0 mmol) of 4-aminopyridine, 3.72 g (8.8 mmol) of Ph_3PBr_2, 2.46 mL of anhydrous triethylamine, and 60 mL of anhydrous benzene was heated under reflux for 5 h. Triethylammonium bromide was removed by filtration, and the filtrate was concentrated. The residue was purified by passing through a short column (silica gel/20% ethanol in diethyl ether) to furnish **14** (2.096 g, 5.921 mmol, 74%) as a light brown solid: IR 1585, 1495, 1360, 1109, 719, 694 cm^{-1}; ^{1}H δ 8.04 (2 H, d, J = 5.0 Hz), 7.77−7.67 (6 H, m), 7.55 (3 H, td, J = 7.2 and 1.7 Hz), 7.5−7.4 (6 H, m), 6.59 (2 H, d, J = 5.7 Hz); ^{13}C δ 158.9 (d, J = 2 Hz), 149.4, 132.5 (d, J = 9.8 Hz), 132.1 (d, J = 2.6 Hz), 129.5 (d, J = 99.4 Hz), 128.8 (d, J = 11.9 Hz), 118.7 (d, J = 19.2 Hz); MS m/z 355 (MH^+), 279; HRMS calcd for $C_{23}H_{20}N_2P$ (MH^+) 355.1364, found 355.1386.

11-Methyl-6*H*-indolo[2,3-*b*][1,6]naphthyridine (5a). The following procedure for the preparation of **5a** is representative. To 0.354 g (1.00 mmol) of **14** in 40 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.157 g (1.00 mmol) of **6a** in 10 mL of anhydrous *p*-xylene under a nitrogen atmosphere at room temperature. After 1.5 h, the reaction mixture was heated under reflux for 15 h. The reaction mixture was then concentrated to yield a solid residue. After three cycles of washing the residue with 40 mL of diethyl ether followed by centrifugation and decanting the supernatant liquid, the remaining solid was pumped to dryness in vacuo to afford **5a** (0.114 g, 0.49 mmol, 49%) as a brown solid: compound turns black without melting at 290 °C; IR 1604, 1237, 740 cm^{-1}; ^{1}H δ 9.68 (1 H, s), 8.73 (1 H, d, J = 5.9 Hz), 8.29 (1 H, d, J = 7.9 Hz), 7.85 (1 H, d, J = 5.9 Hz), 7.58 (1 H, t, J = 7 Hz), 7.53 (1 H, d, J = 7 Hz), 7.38 (1 H, ddd, J = 8, 6, and 1.5 Hz), 3.31 (3 H, s); ^{13}C δ (DMSO-d_6) 155.0, 150.2, 149.4, 145.8, 141.8, 140.9, 128.7, 124.6, 121.5, 121.0, 120.8, 117.7, 111.7, 14.8; MS m/z 233 (M^+), 205, 179; HRMS calcd for $C_{15}H_{11}N_3$ 233.0953, found 233.0963.

11-Propyl-6*H*-indolo[2,3-*b*][1,6]naphthyridine (5b). The same procedure was repeated as described for **5a** except that to 0.354 g (1.00 mmol) of **14** in 40 mL of anhydrous *p*-xylene was treated with a solution of 0.185 g (1.00 mmol) of **6b**[9a] in 10 mL of anhydrous *p*-xylene. Purification by flash column chromatography (silica gel/5% ethanol and 20% diethyl ether in hexanes) afforded **5b** (0.133 g, 0.51 mmol, 51%) as a brown solid: compound turns black without melting at 249 °C; IR 1602, 1574, 1462, 817, 734 cm^{-1}; ^{1}H δ 12.09 (1 H, br s, NH), 9.59 (1 H, s), 8.60 (1 H, d, J = 5.9 Hz), 8.06 (1 H, d, J = 7.9 Hz), 7.77 (1 H, d, J = 5.6 Hz), 7.42 (2 H, m), 7.31 (1 H, ddd, J = 7.9, 5.2, and 2.7 Hz), 3.62 (2 H, t, J = 8.0 Hz), 1.96 (2 H, sextet, J = 7.5 Hz), 1.23 (3 H, t, J = 7.3 Hz); ^{13}C δ (DMSO-d_6) 155.1, 150.1, 149.5, 145.8, 145.2, 141.9, 128.7, 124.2, 121.1, 120.9, 119.4, 117.2, 111.8, 29.7, 23.7, 14.7; MS m/z 261 (M^+), 244, 232, 205; HRMS calcd for $C_{17}H_{15}N_3$ 261.1266, found 261.1260; Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.01; H, 5.78; N, 16.04.

Iminophosphorane 20.[13e] The same procedure was repeated as described for **14** except that a mixture of 1.412 g (15.0 mmol) of 3-aminopyridine, 7.281 g (17.2 mmol) of Ph_3PBr_2, 4.61 mL of anhydrous triethylamine, and 80 mL of anhydrous benzene was heated under reflux for 5 h. The reaction mixture was purified by flash chromatography (silica gel/10% ethanol in hexanes) to furnish **20** (4.04 g, 11.4 mmol, 76%) as a brown solid: IR 713, 694 cm^{-1}; ^{1}H δ 8.11 (1 H, d, J = 2.7 Hz), 7.87 (1 H, dd, J = 4.6 and 1.4 Hz), 7.78−7.69 (6 H, m), 7.57−7.41 (9 H, m), 7.05 (1 H, dm, J = 8.2 and 1 Hz), 6.91 (1 H, ddm, J = 8.2, 4.6, and 1 Hz); ^{13}C δ 147.7 (d, J = 2 Hz), 145.1 (d, J = 17.6 Hz), 138.3, 132.4 (d, J = 9.8 Hz), 131.9 (d, J = 2.6 Hz), 130.3 (d, J = 99.4 Hz), 129.4 (d, J = 18.1 Hz), 128.7 (d, J = 11.9 Hz), 123.3; MS m/z 355 (MH^+), 279, 201; HRMS calcd for $C_{23}H_{20}N_2P$ (MH^+) 355.1364, found 355.1368.

11-Methyl-6*H*-indolo[2,3-*b*][1,5]naphthyridine (25a) and 5-Methyl-10*H*-indolo[2,3-*b*][1,7]naphthyridine (26a).[16] To a solution of 0.708 g of **20** (2.00 mmol) in 3 mL of anhydrous benzene was added 0.314 g of **6a** (2.00 mmol) in 7 mL of anhydrous benzene via cannula under a nitrogen atmosphere at room temperature. After 2 h at room temperature, the reaction mixture was filtered through a short silica gel column to remove triphenylphosphine oxide. The column was further eluded with *p*-xylene. The combined benzene and *p*-xylene solutions were concentrated in vacuo to remove benzene. The remaining *p*-xylene solution was heated to reflux under a nitrogen atmosphere for 12 h. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (silica gel/12:7:1 of hexanes:diethyl ether: methanol) followed by preparative thin-layer chromatography to furnish 0.272 g (1.17 mmol, 58%) of **25a** and 0.081 g (0.35 mmol, 17%) of **26a** as pale yellow crystals. **25a:** IR (KBr) 1610, 1407, 734 cm^{-1}; ^{1}H δ 9.73 (1 H, br, s, NH), 8.95 (1 H, dd, J = 4.0 and 1.7 Hz), 8.33 (1 H, dd, J = 8.6 and 1.7 Hz), 8.30 (1 H, d, J = 7.7 Hz), 7.62 (1 H, dd, J = 8.5 and 4.1 Hz), 7.55 (1 H, td, J = 7.5 and 1.1 Hz), 7.50 (1 H, d, J = 7.2 Hz), 7.35 (1 H, ddd, J = 7.5, 6.9, and 1.6 Hz), 3.37 (3 H, s); ^{13}C δ (DMSO-d_6) 152.1, 146.2, 141.7, 141.3, 140.0, 139.0, 135.0, 128.1, 124.0, 123.5, 121.0, 120.0, 118.6, 110.9, 13.4; MS m/z 233 (M^+), 205, 152; HRMS calcd for $C_{15}H_{11}N_3$ 233.0953, found 233.0954. Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 76.95; H, 4.83; N, 17.76. **26a:** IR (KBr) 1615, 742 cm^{-1}; ^{1}H δ (DMSO-d_6) 11.97 (1 H, s), 9.32 (1 H, s), 8.51 (1 H, d, J = 5.7 Hz), 8.39 (1 H, d, J = 7.7 Hz), 8.21 (1 H, d, J = 5.7 Hz), 7.60 (1 H, t, J = 7.5 Hz), 7.54 (1 H, d, J = 7.2 Hz), 7.32 (1 H, t, J = 7.3 Hz), 3.18 (3 H, s); ^{13}C δ (DMSO-d_6) 152.8, 151.7, 142.0, 139.6, 137.8, 128.7, 126.3, 124.5, 120.4, 120.1, 119.1, 117.0, 111.0, 14.4; MS m/z 233 (M^+), 205, 151; HRMS calcd for $C_{15}H_{11}N_3$ 233.0953, found 233.0950.

11-Propyl-6*H*-indolo[2,3-*b*][1,5]naphthyridine (25b) and 5-Propyl-10*H*-indolo[2,3-*b*][1,7]naphthyridine (26b). To 0.354 g (1.0 mmol) of **20** in 40 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.185 g (1.0 mmol) of **6b**[9a] in 10 mL of anhydrous *p*-xylene under a nitrogen atmosphere at room temperature. After 1.5 h, the reaction mixture was heated under reflux for 15 h. The reaction mixture was then concentrated, and the residue was purified by column chromatography (silica gel/10% ethanol and 20% diethyl ether in hexanes) to afford **25b** (0.174 g, 0.667 mmol, 67%) and **26b** (0.013 g, 0.050 mmol, 5%) as brown solids. **25b**: mp 234−236 °C (dec); IR 1613, 1457, 764, 720 cm^{-1}; ^{1}H δ 11.32 (1 H, br s, NH), 8.91 (1 H, dd, J = 4.1 and 1.6 Hz), 8.27 (1 H, dd, J = 8.4 and 1.4 Hz), 8.12 (1 H, d, J = 7.9 Hz), 7.55−7.45 (3 H, m), 7.30 (1 H, ddd, J = 8.1, 5.7, and 2.7 Hz), 3.82 (2 H, t, J = 8.0 Hz), 1.92 (2 H, sextet, J = 7.6 Hz), 1.20 (3 H, t, J = 7.4 Hz); ^{13}C δ 152.7, 146.5, 146.4, 141.4, 141.2, 139.5, 134.6, 128.1, 124.1, 123.4, 121.5, 120.7, 119.1, 110.9, 29.6, 22.8, 14.7; MS m/z 261 (M^+), 246, 233, 219; HRMS calcd for $C_{17}H_{15}N_3$ 261.1266, found 261.1265. Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.27; H, 5.79; N, 16.05. **26b**: IR 1472, 797, 726 cm^{-1}; ^{1}H δ 9.72 (1 H, br s, NH), 9.56 (1 H, s), 8.60 (1 H, d, J = 5.9 Hz), 8.22 (1 H, d, J = 7.6 Hz), 8.06 (1 H, d, J = 5.9 Hz), 7.65−7.57 (2 H, m), 7.38 (1 H, ddd, J = 8.1, 5.2, and 2.4 Hz), 3.64 (2 H, t, J = 8.0 Hz), 1.96 (2 H, sextet, J = 7.7 Hz), 1.22 (3 H, t, J = 7.4 Hz); ^{1}H δ (DMSO-d_6) 12.02 (1 H, s), 9.36 (1 H, s), 8.51 (1 H, d, J = 4.2 Hz), 8.28 (1 H, d, J = 7.9 Hz), 8.23 (1 H, d, J = 5.9 Hz), 7.61 (1 H, t, J = 7.4 Hz), 7.56 (1 H, d, J = 7.3 Hz), 7.35 (1 H, t, J = 7.3 Hz), 3.64 (2 H, t, J = 7.7 Hz), 1.83 (2 H, sextet, J = 7.6 Hz), 1.12 (3 H, t, J =

7.4 Hz); ^{13}C δ (DMSO-d_6) 153.6, 152.3, 142.7, 140.1, 129.3, 126.3, 124.7, 120.9, 120.3, 119.3, 117.5, 111.8, 30.0, 23.1, 14.7; MS *m*/*z* 261 (M^+), 232, 205; HRMS calcd for $C_{17}H_{15}N_3$ 261.1266, found 261.1261.

Triflate 28. To a solution of 0.547 g (3.00 mmol) of methyl 4-methoxysalicylate (**27**) and 1.53 mL of pyridine (18.9 mmol) at 0 °C was added dropwise 0.555 mL (3.34 mmol) of trifluoromethanesulfonic anhydride. After 5 min of stirring at 0 °C followed by an additional 2 h of stirring at room temperature, the reaction mixture was heated at 40 °C for 24 h. The reaction mixture was then poured into a flask containing 20 mL of H_2O and 20 mL of Et_2O. The organic layer was separated, washed with water, a 10% aq HCl solution, water, and a saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel/20% diethyl ether in hexanes) to furnish **28** (0.923 g, 2.94 mmol, 98%) as a pale yellow liquid: IR (neat) 1727, 1618, 1427, 1277, 1210, 1142, 832 cm^{-1}; ^{1}H δ 8.04 (1 H, d, J = 9.0 Hz), 6.94 (1 H, dd, J = 8.8 and 2.4 Hz), 6.76 (1 H, d, J = 2.2 Hz), 3.92 (3 H, s), 3.87 (3 H, s); ^{13}C δ 163.94, 163.90, 149.6, 134.1, 118.7 (q, J = 320.5 Hz), 116.2, 113.4, 108.8, 56.0, 52.3; MS *m*/*z* 314 (M^+), 283, 219, 153; HRMS calcd for $C_{10}H_9F_3O_6S$ 314.0072, found 314.0086.

Methyl 4-Methoxyl-2-(1-propynyl)benzoate (29). The same procedure was repeated as described for **12a** except that a mixture of 2.10 g of $Pd(PPh_3)_2Cl_2$ (3.0 mmol), 0.57 g of CuI (3.0 mmol), 9.08 g of **28** (29.0 mmol), and 16.5 mL of *N*,*N*-diisopropylethylamine (95 mmol) in 120 mL of DMF was treated with 1.3 L of gaseous propyne (53 mmol) to afford **29** (4.983 g, 24.4 mmol, 84%) as a light yellow liquid: IR (neat) 2235, 1727, 1598, 779, 699 cm^{-1}; ^{1}H δ 7.88 (1 H, d, J = 8.7 Hz), 6.99 (1 H, d, J = 2.5 Hz), 6.82 (1 H, dd, J = 8.8 and 2.7 Hz), 3.87 (3 H, s), 3.82 (3 H, s), 2.13 (3 H, s); ^{13}C δ 166.0, 161.8, 132.1, 126.5, 123.6, 118.5, 113.4, 91.3, 78.4, 55.2, 51.6, 4.5; MS *m*/*z* 204 (M^+), 189, 173, 161, 145; HRMS calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0796.

4-Methoxy-2-(1-propynyl)benzoic Acid (30). To a flask containing 0.214 g of LiOH monohydrate (5.1 mmol) in 20 mL of methanol and 10 mL of water was added a solution of 0.208 g (1.02 mmol) of **29** in 10 mL of methanol. The resulting mixture was heated at 35 °C for 24 h before it was allowed to cool to room temperature. The flask was then placed in an ice−water bath. A dilute NH_4Cl solution at 0 °C was added until the pH of the solution became ca. 8. The solution was then treated dropwise with a dilute aqueous acetic acid solution until the pH reached ca. 5. At this point a white solid appeared. The solution was further acidified with a dilute HCl solution until the pH reached ca. 4. The white solid precipitate was collected by filtration followed by washing with water and pumping to dryness to afford 0.137 g of **30** (0.721 mmol, 70%) as a white solid: mp 171−173 °C; IR 1671, 1594, 1210, 849, 778 cm^{-1}; ^{1}H δ 8.05 (1 H, d, J = 9.0 Hz), 7.02 (1 H, d, J = 2.5 Hz), 6.88 (1 H, dd, J = 8.8 and 2.7 Hz), 3.86 (3 H, s), 2.15 (3 H, s); ^{13}C δ 169.6, 162.6, 133.6, 126.5, 122.8, 118.8, 114.0, 93.2, 78.3, 55.5, 4.8; MS *m*/*z* 190 (M^+), 173, 161, 147, 135; HRMS calcd for $C_{11}H_{10}O_3$ 190.0630, found 190.0625.

4-Methoxy-2-(1-propynyl)phenyl Isocyanate (31). The same procedure was repeated as described for **6a** except that 0.785 g (4.13 mmol) of **30** was treated with 0.58 mL of triethylamine and 0.89 mL (4.13 mmol) of DPPA to afford **31** (0.596 g, 3.19 mmol, 77%) as a white solid: IR (neat) 1513, 1204, 1032 cm^{-1}; ^{1}H δ 6.92 (1 H, d, J = 9.0 Hz), 6.89 (1 H, d, J = 3.9 Hz), 6.75 (1 H, dd, J = 8.7 and 3.1 Hz), 3.77 (3 H, s), 2.12 (3 H, s); ^{13}C δ 156.8, 128.2, 127.3, 124.2, 122.1, 116.3, 114.9, 95.1, 75.7, 55.5, 4.5; MS *m*/*z* 187 (M^+), 172, 159, 144; HRMS calcd for $C_{11}H_9NO_2$ 187.0633, found 187.0640.

9-Methoxy-11-methyl-6*H*-indolo[2,3-*b*][1,6]naphthyridine (32). The same procedure was repeated as described for **5a** except that 0.076 g (0.404 mmol) of **31** was treated with 0.157 g (0.445 mmol) of **14**. After three cycles of washing the concentrated residue with diethyl ether, centrifugation, and decanting the supernatant liquid, the residual solid was heated under reflux in 40 mL of benzene for 1 h. The mixture was allowed to cool to room temperature followed by centrifugation and decanting the supernatant liquid. The remaining solid was pumped to dryness in vacuo to afford **32** (0.035 g, 0.133 mmol, 33%) as a brown solid: compound turns black without melting at 284 °C; IR 1603, 1481, 1298, 1212, 811 cm^{-1}; ^{1}H δ (DMSO-d_6) 11.92 (1 H br s, NH), 9.72 (1 H, s), 8.62 (1 H, d, J = 6.2 Hz), 7.86 (1 H, d, J = 2.2 Hz), 7.80 (1 H, d, J = 5.9 Hz), 7.47 (1 H, d, J = 8.7 Hz), 7.23 (1 H, dd, J = 8.7 and 2.5 Hz), 3.91 (3 H, s), 3.29 (3 H, s); ^{13}C δ (DMSO-d_6) 155.8, 154.8, 150.2, 148.6, 142.1, 142.0, 136.1, 129.8, 121.8, 118.5, 116.8, 112.6, 108.9, 56.4, 15.0; MS *m*/*z* 263 (M^+), 248, 220; HRMS calcd for $C_{16}H_{13}N_3O$ 263.1059, found 263.1051.

9-Methoxy-11-methyl-6*H*-indolo[2,3-*b*][1,5]naphthyridine (33) and 7-Methoxy-5-methyl-10*H*-indolo[2,3-*b*][1,7]-naphthyridine (34). The same procedure was repeated as described for **25b** and **26b** except that 0.056 g (0.299 mmol) of **31** was treated with 0.117 g (0.329 mmol) of **20.** Purification by washing the crude residual three times with 30 mL of diethyl ether afforded **33** (0.034 g, 0.128 mmol, 43%) as a yellow solid. The combined diethyl ether solutions were pumped to dryness in vacuo, and the residue was further purified by flash chromatography (silica gel/10% ethanol and 20% diethyl ether in hexanes) to afford **34** (0.0031 g, 0.012 mmol, 4%) as a yellow solid. **33**: compound turns black without melting at 285 °C; IR 1490, 1463, 831, 788 cm^{-1}; ^{1}H δ 8.95 (1 H, d, J = 3.1 Hz), 8.34 (1 H, d, J = 8.1 Hz), 7.78 (1 H, d, J = 2.0 Hz), 7.63 (1 H, dd, J = 8.6 and 4.1 Hz), 7.44 (1 H, d, J = 8.7 Hz), 7.18 (1 H, dd, J = 8.7 and 2.2 Hz), 3.96 (3 H, s), 3.35 (3 H, s); ^{1}H δ (DMSO-d_6) 11.78 (1 H, s), 8.91 (1 H, dd, J = 1.5 and 2.5 Hz), 8.34 (1 H, dd, J = 1.3 and 7.3 Hz), 7.80 (1 H, d, J = 2.5 Hz), 7.74 (1 H, dd, J = 3.9 and 8.4 Hz), 7.46 (1 H, d, J = 8.7 Hz), 7.22 (1 H, dd, J = 2.4 and 7.6 Hz), 3.91 (3 H, s), 3.28 (3 H, s); ^{13}C δ (DMSO-d_6) 154.3, 152.6, 146.5, 141.3, 141.0, 138.8, 136.6, 135.4, 124.2, 121.8, 119.5, 116.8, 112.3, 108.5, 56.3, 14.0; MS *m*/*z* 263 (M^+), 248, 220; HRMS calcd for $C_{16}H_{13}N_3O$ 263.1059, found 263.1052. **34**: ^{1}H δ (DMSO-d_6) 12.23 (1 H, s), 9.69 (1 H, s), 8.69 (2 H, br s), 7.96 (1 H, d, J = 2.2 Hz), 7.56 (1 H, d, J = 8.7 Hz), 7.36 (1 H, dd, J = 8.7 and 2.2 Hz), 3.94 (3 H, s), 3.28 (3 H, s); MS *m*/*z* 263 (M^+), 248, 220; HRMS calcd for $C_{16}H_{13}N_3O$ 263.1059, found 263.1057.

Triflate 40. The same reaction procedure was repeated as described for **28** except that 3.76 g of diethyl 2,5-dihydroxyterephthalate (**39**, 14.8 mmol) in 15 mL of pyridine was treated with 10.05 g (35.6 mmol) of triflic anhydride to afford **40** (7.41 g, 14.3 mmol, 97%) as white crystalline needles: mp 109−111 °C; IR (KBr) 1732, 796, 713 cm^{-1}; ^{1}H NMR δ 7.98 (2 H, s), 4.49 (4 H, q, J = 7.2 Hz); 1.44 (6 H, t, J = 7.2 Hz); ^{13}C δ NMR 161.4, 146.4, 129.8, 127.2, 118.6 (q, J = 320.6 Hz), 63.4, 13.9; MS *m*/*z* 519 (MH^+), 518, 490, 473; HRMS calcd for $C_{14}H_{12}F_6O_{10}S_2$ 517.9776, found 517.9754.

Diethyl 2,5-Di(1-decynyl)terephthalate (41). The same procedure was repeated as described for **29** except that a solution of 0.340 g of $Pd(PPh_3)_2Cl_2$ (0.484 mmol), 0.092 g of CuI (0.48 mmol), 1.794 g of **40** (3.46 mmol), and 3.6 mL of *N*,*N*-diisopropylethylamine (20.8 mmol) in 10 mL of DMF and 11 mL of THF was treated with 1.87 mL (1.435 g) of 1-decyne (10.4 mmol) to afford **41** (1.656 g, 3.35 mmol, 97%) as a wax: mp 45−47 °C; IR 2229, 1735 cm^{-1}; ^{1}H δ 7.96 (2 H, s), 4.38 (4 H, q, J = 7.1 Hz); 2.46 (4 H, t, J = 7.0 Hz), 1.67−1.57 (4 H, m), 1.5−1.2 (20 H, m), 1.40 (6 H, t, J = 7.1 Hz), 0.87 (6 H, t, J = 6.9 Hz); ^{13}C δ 165.4, 135.7, 134.4, 122.9, 98.1, 78.5, 61.4, 31.8, 29.2, 29.1, 29.0, 28.5, 22.6, 19.9, 14.2, 14.1; MS *m*/*z* 494 (M^+), 465, 396, 367, 341; HRMS calcd for $C_{32}H_{46}O_4$ 494.3396, found 494.3406.

2,5-Di(1-decynyl)terephthalic Acid (42). The same procedure was repeated as described for **30** except that a solution of 2.048 g of **41** (4.15 mmol) in 40 mL of THF was treated with a solution of 1.52 g of LiOH monohydrate (36.2 mmol) in 70 mL of methanol and 70 mL of water to afford 1.526 g (3.48 mmol, 84%) of **42** as a white solid: mp 147−153 °C; IR 3300−2300 (br, OH), 2229, 1704 cm^{-1}; ^{1}H δ (DMSO-d_6) 13.35 (2 H, br s), 7.79 (2 H, s), 2.42 (4 H, t, J = 6.7 Hz), 1.57−1.35 (8 H, m), 1.23 (16 H, br), 0.83 (6 H, t, J = 6.4 Hz); ^{13}C δ (DMSO-d_6) 166.3, 135.6, 134.7, 122.0, 98.0, 78.6, 31.4, 28.7, 28.6, 28.3, 28.0, 22.2, 19.1, 14.0; MS *m*/*z* 438 (M^+), 421, 393, 363, 340; HRMS calcd for $C_{28}H_{38}O_4$ 438.2770, found 438.2756.

Diisocyanate 43. The same procedure was repeated as described for **31** except that 1.086 g (2.48 mmol) of **42** was treated with 0.70 mL of triethylamine and 1.07 mL (4.96 mmol) of DPPA to afford **43** (0.755 g, 1.75 mmol, 71%) as a white solid: mp (sealed tube) 64−66 °C; IR 2261, 2222 cm^{-1}; ^1H δ 6.99 (2 H, s), 2.46 (4 H, t, $J = 7.2$ Hz), 1.62 (4 H, quintet, $J = 7.2$ Hz), 1.48−1.23 (20 H, m), 0.88 (6 H, t, $J = 6.5$ Hz); ^{13}C δ 132.3, 127.6, 126.4, 121.7, 102.0, 75.5, 31.8, 29.2, 29.1, 29.0, 28.0, 22.6, 19.7, 14.1; MS *m*/*z* 432 (M^+), 406, 205; HRMS calcd for $C_{28}H_{36}N_2O_2$ 432.2777, found 432.2771.

Indoloquinoline 45. To a solution of 0.455 g of the iminophosphorane **7**[9a,14b] (1.288 mmol) in 40 mL of anhydrous *p*-xylene was introduced via cannula a solution of 0.278 g of **43** (0.644 mmol) in 10 mL of *p*-xylene under a nitrogen atmosphere. After 1.5 h at room temperature, the reaction mixture was heated under reflux for 6 h before it was allowed to cool to room temperature and concentrated. After three cycles of washing the residue with ethanol, centrifugation, and decanting the supernatant liquid, the remaining solid was washed with diethyl ether and then pumped to dryness in vacuo to afford 0.140 g of **45** (0.241 mmol, 37%) as a yellow solid: mp >360 °C; IR (KBr) 1626, 1609, 1586 cm^{-1}; ^1H δ (DMSO-d_6) 11.46 (2 H, s), 8.34 (2 H, d, $J = 7.9$ Hz), 8.27 (2 H, s), 7.97 (2 H, d, $J = 8.4$ Hz), 7.71 (2 H, td, $J = 7.6$ and 1 Hz), 7.50 (2 H, td, $J = 7.5$ and 1 Hz), 3.74 (4 H, t, $J = 7.9$ Hz), 1.92 (4 H, quintet, $J = 7.3$ Hz), 1.69 (4 H, quintet, $J = 7.5$ Hz), 1.44 (4 H, quintet, $J = 7.1$ Hz), 1.38−1.22 (12 H, m), 0.84 (6 H, t, $J = 6.9$ Hz); MS *m*/*z* 583 (MH^+), 483, 385; HRMS calcd for $C_{40}H_{47}N_4$ 583.3801 (MH^+), found 583.3820.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for **5c**,**d**, **6c**, **12c**, **13c**, **25c**,**d**, and **26c**,**d**, and ^1H and/or ^{13}C NMR spectra for compounds **5a**−**d**, **6a**,**c**, **12a**,**c**, **13a**,**c**, **14**, **20**, **25a**−**d**, **26a**−**d**, **28**−**34**, **40**−**43**, and **45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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