Use of Hydrogen Bonds to Control Molecular Aggregation. Behavior of a Self-Complementary Dipyridone Designed to Self-Replicate

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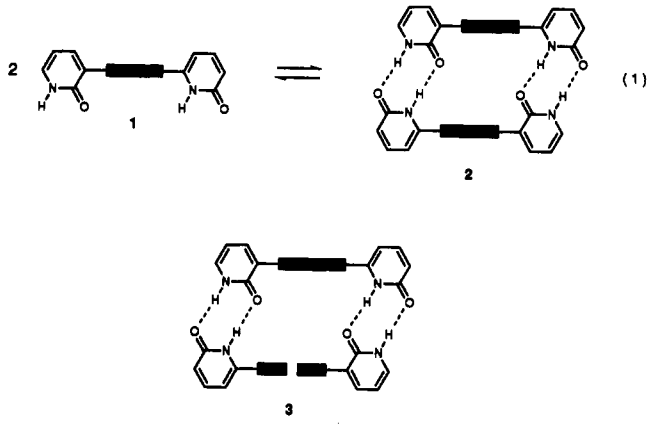
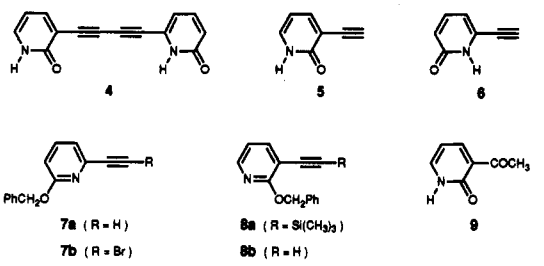
In principle, the simple dipyridone **4** encodes enough chemical information to allow it to self-replicate by acting as a template for the assembly and controlled oxidative coupling of ethynylpyridone subunits **5** and **6**. This could occur by the formation of ternary hydrogen-bonded complex **18**, followed by copper-induced oxidative coupling of the bound ethynylpyridone subunits. In fact, treatment of an equimolar mixture of compounds **5** and **6** with excess CuCl·TMEDA and O_2 in a variety of solvents produced only a normal statistical ratio of dipyridone **4** and symmetric isomers **10** and **11**. This is presumably because dipyridone **4** is too highly self-associated to permit the formation of significant amounts of ternary complex **18**. Moreover, even if dipyridone **4** can act as a template for the juxtaposition of its subunits, it may not be able to promote the subsequent copper-induced oxidative coupling that joins them together.

The tendency of 2-pyridones and related heterocycles to form cyclic hydrogen-bonded dimers allows them to be used as sticky sites that compel molecules in which they are incorporated to associate in predictable ways.[2] For example, pyridones can be linked by spacers to create self-complementary molecules **1** that are able to form strong duplexes **2** joined by multiple hydrogen bonds (eq 1).[2b,c] Despite its structural simplicity, dipyridone **1** nevertheless



encodes enough chemical information to control its own replication.[3] In principle, this can be achieved by treating dipyridone **1** with linkable monopyridone subunits, which should lead to the temporary assembly of ternary aggregate **3**. Proximity-induced linkage of the bound subunits can then generate a new molecule of dipyridone **1**. In this article, we analyze the ability of self-complementary diynyldipyridone **4** to act as a template for its own replication by directing the assembly of its constituent parts, the ethynylpyridones **5** and **6**.



Ethynylpyridone **6** was prepared in 89% yield by debenzylation (CF_3COOH, 72 °C, 90 min)[4] of the known ether **7a**.[2c] Isomer **5** proved to be more difficult to synthesize. Precursor **8a** could be prepared in 93% yield by coupling 3-bromo-2-(phenylmethoxy)pyridine[2c] with (trimethylsilyl)acetylene ($N(C_2H_5)_3$, 3 mol % $PdCl_2(PPh_3)_2$, 5 mol % CuI).[5] Desilylation (KOH, CH_3OH) then provided acetylene **8b** in nearly quantitative yield. Unfortunately, normal debenzylation using trifluoroacetic acid caused hydration of the triple bond and led to the isolation of acetylpyridone **9**[6] under a variety of conditions. In contrast, treatment of compound **8b** with trimethylsilyl iodide[7] cleaved the benzyl ether cleanly and produced pyridone **5** in 60% yield.

Self-complementary dipyridone **4** and non-self-complementary isomers **10** and **11** were prepared from acetylenes **7a** and **8b**. Direct oxidative coupling of compound **7a** by a variation of the Hay procedure (O_2, CuCl·TMEDA)[8] provided an 88% yield of diyne **12**, which was then converted into dipyridone **10** in 92% yield by normal debenzylation (CF_3COOH, 72 °C, 3 h). Similarly, Eglinton coupling ($Cu(OAc)_2$, pyridine)[9] converted acetylene **8b** into diyne **13** in 76% yield. In this case, standard debenzylation

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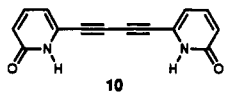
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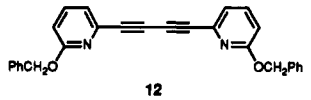
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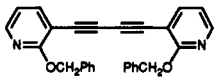
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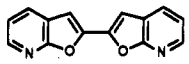
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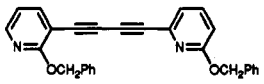
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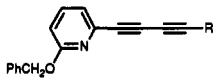
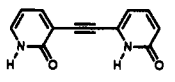
using hot trifluoroacetic acid did not permit isolation of the corresponding dipyridone 11; instead, the diyne unit participated in a double cyclization that yielded bifuropyridine 14.[10] Fortunately, debenzylation using trifluoroacetic acid under milder conditions (25 °C, 3 h) provided dipyridone 11 in 88% yield.

Synthesis of self-complementary dipyridone 4 proved to be more troublesome, since the corresponding benzyl ether 15 is unsymmetric and therefore cannot be prepared by the simple oxidative self-coupling of identical acetylenes. As an alternative, we explored the direct introduction of an intact diyne unit. Diyne 16 could be prepared


16 (R = $Si(CH_3)_3$)

in 48% yield by treating 1,4-bis(trimethylsilyl)butadiyne with an equimolar amount of butyllithium and then with $ZnCl_2$, followed by the addition of 2-bromo-6-(phenylmethoxy)pyridine[2c] and a catalytic amount of $PdCl_2(PPh_3)_2$.[11] Unfortunately, we were unable to couple diyne 16 with 3-bromo-2-(phenylmethoxy)pyridine[2c] by a similar procedure. Target 15 was finally synthesized by using a catalytic version of the Cadiot–Chodkiewicz reaction[9,12] to cross-couple bromoacetylene 7b with acetylene 8b. Compound 7b was prepared in quantitative yield by brominating acetylene 7a (Br_2, NaOH),[13] and the desired coupling was achieved in 87% yield by mixing compounds 7b and 8b in $N(C_2H_5)_3$ in the presence of catalytic amounts of CuI and $PdCl_2(PPh_3)_2$. Careful debenzylation of diyne 15 (CF_3COOH, 72 °C, 1 h) then provided self-complementary dipyridone 4 in 81% yield.

Compound 4 closely resembles acetylene 17, which has been shown to form a hydrogen-bonded duplex in the solid state and in solution.[2c] The association constant is greater than $6 \times 10^4\ M^{-1}$ in $CHCl_3$ at 25 °C. By analogy, compound 4 should show very similar properties of aggregation. This suggests that solutions prepared by mixing dipyridone 4 with monopyridones 5 and 6 should consist of free dipyridone and its dimer, in rapid equilibrium with other species including ternary complexes formed by the association of dipyridone 4 with two monopyridones. However,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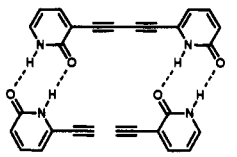
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only ternary complex 18, which incorporates nonidentical monopyridone subunits 5 and 6, can adopt a conformation in which the relative orientation of the two terminal acetylenes permits coupling. Proximity-induced coupling of monopyridones 5 and 6 in complex 18 would reproduce dipyridone 4 at the expense of symmetric dipyridones 10 and 11. In this way, dipyridone 4 could serve as a template for its own replication by directing the assembly of its constituent parts.

This intriguing possibility can be tested by analyzing the oxidative coupling of equimolar mixtures of monopyridones 5 and 6. Coupling without the benefit of template effects should produce a statistical 1:2:1 mixture of dipyridones 10, 4, and 11; in contrast, coupling controlled by template effects that specifically favor or disfavor one isomer would be revealed by an increasingly nonstatistical distribution of products.[14] Treatment of an equimolar solution of monopyridones 5 and 6 in CH_2Cl_2 (0.4 M) with excess CuCl·TMEDA and O_2[8] produced a mixture of dipyridones 4, 10, and 11 in 87% yield. Analysis by ^1H NMR spectroscopy showed a normal statistical ratio of the three products. We suspected that the low solubility of the dipyridones in CH_2Cl_2 might prevent them from exerting measurable template effects or that the high self-association constant of dipyridone 4 would suppress the assembly of ternary complex 18, so we repeated the cross-coupling experiment in other solvents chosen to increase solubility and decrease association. In both acetone and DMSO, however, we again observed statistical mixtures of the three dipyridones.

Although dipyridone 4 encodes enough chemical information to identify its constituent parts, bind them, and orient them in close proximity, it nevertheless fails to orchestrate its self-replication. This is presumably because dipyridone 4 is too highly self-associated to permit the formation of kinetically significant amounts of ternary complex 18. In addition, even if dipyridone 4 can act as a template for the juxtaposition of its subunits, it may not be able to promote the subsequent reactions that actually join them together. The mechanism of copper-induced oxidative coupling of acetylenes is not known in detail, but it is likely to involve elimination from mixed-valence clusters of copper acetylides.[15,16] Key steps in the template-directed self-replication of dipyridone 4 would therefore be the formation of an intermediate copper complex similar to structures 19 or 20, followed by elimination of copper and coupling. The structures of

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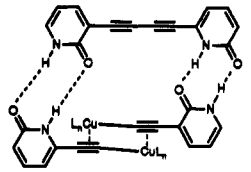

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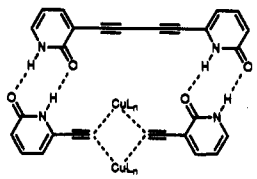

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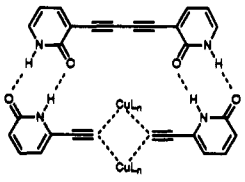
these hypothetical intermediates are not unreasonable; however, in order to accommodate the atoms of copper, both structures are forced to accept various distortions, particularly in the network of hydrogen bonds. This is because the two central acetylenic carbons in diyne 4 are separated by the length of a carbon–carbon sp–sp single bond (1.38 Å),[17] whereas the corresponding carbons in the acetylide subunits of putative intermediates 19 and 20 should be separated by 2.0–3.0 Å.[18] The resulting strain can be relieved by eliminating copper, thereby providing a supplementary driving force for the final step of the hypothetical self-replication of dipyridone 4. Nevertheless, the high energy of intermediates 19 and 20 appears to help prevent the overall process of template-directed self-replication of dipyridone 4 from being more rapid than random coupling of monopyridones 5 and 6 without the benefit of a template. In contrast, isomeric dipyridone 11 should be able to serve as an effective template for binding 2 equiv of monopyridone 6 and assembling ternary complex 21 without introducing significant strain in the network



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of hydrogen bonds; in this case, however, subsequent acetylenic coupling becomes the difficult step because the final product and the template are not complementary.

Our observations underscore the enormous challenge of devising small self-complementary molecules that can act as autocatalytically effective templates for their own replication. If the templates are flexible, they will not have excessively high constants of self-association, and they may be able to recognize their constituent parts, bind them, and accommodate the transition state of the reaction that joins them together. However, the entropic cost of achieving a suitable orientation of the components may prevent template-directed assembly from being much faster than uncontrolled processes. In contrast, rigid templates can be designed to be perfectly self-complementary and to orient the subunits in close juxtaposition. Unfortunately, templates of this type cannot normally be effective promoters of the coupling step because of their high degree of self-association. Moreover, they are unlikely to achieve effective autocatalysis by being perfectly complementary to the transition state of the reaction that couples the subunits. For these reasons, it will be difficult to devise small self-complementary molecules that act as highly efficient templates for self-replication except in special cases when coupling occurs without major changes in geometry.

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Experimental Section

$N(C_2H_5)_3$ and pyridine were dried by distillation from CaH_2, CH_2Cl_2 was dried by distillation from P_2O_5, and tetrahydrofuran (THF) was dried by distillation from the sodium ketyl of benzophenone. All other reagents were commercial products of the highest purity available.

6-Ethynyl-2(1*H*)-pyridinone (6). A solution of 2-ethynyl-6-(phenylmethoxy)pyridine (**7a**; 481 mg, 2.30 mmol)[2c] in CF_3COOH (15 mL) was heated at reflux for 90 min. Volatiles were then removed by evaporation under reduced pressure. The residue was dried azeotropically by the distillation of added benzene, and saturated aqueous $NaHCO_3$ (10 mL) was then added. This yielded a precipitate of 6-ethynyl-2(1*H*)-pyridinone (**6**), which was isolated by filtration as a white solid (244 mg, 2.05 mmol, 89%). An analytically pure sample was prepared by sublimation (85 °C/0.10 Torr): mp 180–185 °C dec; IR (KBr) 3700–2700, 2100, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 1 H), 6.48 (dd, ^3J = 6.9 Hz, ^4J = 1.0 Hz, 1 H), 6.67 (dd, ^3J = 9.3 Hz, ^4J = 1.0 Hz, 1 H), 7.38 (dd, ^3J = 9.3 Hz, ^3J = 6.9 Hz, 1 H), 12.2 (bs, 1 H); HRMS (EI) calcd for C_7H_5NO 119.0371, found 119.0371.

2-(Phenylmethoxy)-3-[(trimethylsilyl)ethynyl]pyridine (8a). A stirred mixture of 3-bromo-2-(phenylmethoxy)-pyridine (2.0 g, 7.6 mmol),[2c] CuI (0.077 g, 0.40 mmol), and $PdCl_2(PPh_3)_2$ (0.18 g, 0.26 mmol) in $N(C_2H_5)_3$ (15 mL) was heated at reflux under dry N_2 and treated with (trimethylsilyl)acetylene (0.89 g, 9.1 mmol). After 2 h, the mixture was cooled to 25 °C, diluted with H_2O, and extracted with $CHCl_3$. Volatiles were removed from the combined extracts by evaporation under reduced pressure. Flash chromatography (silica, hexane (75%)/$CHCl_3$ (25%))[19] of the residue provided 2-(phenylmethoxy)-3-[(trimethylsilyl)ethynyl]pyridine (**8a**) as a pale yellow liquid (2.0 g, 7.1 mmol, 93%): IR (liquid film) 2150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 9 H), 5.46 (s, 2 H), 6.86 (dd, ^3J = 7.4 Hz, ^3J = 5.0 Hz, 1 H), 7.3–7.6 (m, 5 H), 7.72 (dd, ^3J = 7.4 Hz, ^4J = 2.0 Hz, 1 H), 8.11 (dd, ^3J = 5.0 Hz, ^4J = 2.0 Hz, 1 H); HRMS (EI) calcd for $C_{17}H_{19}NOSi$ 281.1236, found 281.1236.

3-Ethynyl-2-(phenylmethoxy)pyridine (8b). 2-(Phenylmethoxy)-3-[(trimethylsilyl)ethynyl]pyridine (**8a**; 1.1 g, 3.9 mmol) was treated with CH_3OH (20 mL) and aqueous KOH (1 N, 20 mL). The resulting mixture was stirred at 25 °C for 12 h and was then extracted with $CHCl_3$. Volatiles were removed from the combined extracts by evaporation under reduced pressure. This left a residue of pure 3-ethynyl-2-(phenylmethoxy)pyridine (**8b**) as a pale yellow liquid (0.78 g, 3.7 mmol, 95%): IR (liquid film) 2110; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 1 H), 5.50 (s, 2 H), 6.88 (dd, ^3J = 7.4 Hz, ^3J = 5.0 Hz, 1 H), 7.3–7.6 (m, 5 H), 7.75 (dd, ^3J = 7.4 Hz, ^4J = 2.0 Hz, 1 H), 8.13 (dd, ^3J = 5.0 Hz, ^4J = 2.0 Hz, 1 H).

3-Ethynyl-2(1*H*)-pyridinone (5). A solution of 3-ethynyl-2-(phenylmethoxy)pyridine (**8b**; 159 mg, 0.760 mmol) and trimethylsilyl iodide (197 mg, 0.985 mmol) in CH_2Cl_2 (1 mL) was stirred at 25 °C for 3 h under dry N_2, and the resulting mixture was poured into CH_3OH (3 mL). Volatiles were then removed by evaporation under reduced pressure. Flash chromatography (silica, ethyl acetate)[19] of the residue provided 3-ethynyl-2(1*H*)-pyridinone (**5**) as a beige solid (54.2 mg, 0.455 mmol, 60%): mp 139–141 °C; IR 3600–2700, 2100, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 1 H), 6.32 (dd, ^3J = 6.9 Hz, ^3J = 6.7 Hz, 1 H), 7.52 (dd, ^3J = 6.7 Hz, ^4J = 2.1 Hz, 1 H), 7.74 (dd, ^3J = 6.9 Hz, ^4J = 2.1 Hz, 1 H); HRMS (EI) calcd for C_7H_5NO 119.0371, found 119.0371. Anal. Calcd for C_7H_5NO: C, 70.58; H, 4.23. Found: C, 70.21; H, 4.47.

2,2′-(1,3-Butadiyne-1,4-diyl)bis[6-(phenylmethoxy)pyridine] (12). A catalyst solution was prepared by stirring a mixture of CuCl (126 mg, 1.27 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (55.8 mg, 0.480 mmol) in acetone (2 mL) at 25 °C for 1 h. Precipitated solids were allowed to settle, and the supernatant solution was used in the following step.

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A solution of 2-ethynyl-6-(phenylmethoxy)pyridine (**7a**; 100 mg, 0.478 mmol)[2c] in acetone (4 mL) was warmed at 35 °C and saturated with O_2, and then the previously prepared catalyst solution was added. The resulting mixture was stirred at 35 °C for 3 h under an atmosphere of O_2, and then volatiles were removed by evaporation under reduced pressure. $CHCl_3$ was added to the residue, and the mixture was extracted with 3 N aqueous HCl. Volatiles were removed from the organic phase by evaporation under reduced pressure. The residue was recrystallized from benzene to provide 2,2′-(1,3-butadiyne-1,4-diyl)bis[6-(phenylmethoxy)pyridine] (**12**) as a colorless solid (176 mg, 0.423 mmol, 88%): mp 157–160 °C dec; IR (KBr) 1585, 1565, 1440, 1310, 1260, 1020, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (s, 4 H), 6.83 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 2 H), 7.18 (dd, ^3J = 7.3 Hz, ^4J = 0.8 Hz, 2 H), 7.3–7.5 (m, 10 H), 7.56 (dd, ^3J = 8.4 Hz, ^3J = 7.3 Hz, 2 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 67.9, 72.7, 81.0, 112.8, 122.1, 127.9, 128.2, 128.4, 136.7, 138.4, 138.5, 163.2; MS (EI) *m/e* 416, 325, 91; HRMS (EI) calcd for $C_{28}H_{20}N_2O_2$ 416.1525, found 416.1499.

6,6′-(1,3-Butadiyne-1,4-diyl)bis-2(1*H*)-pyridinone (10). A solution of 2,2′-(1,3-butadiyne-1,4-diyl)bis[6-(phenylmethoxy-)pyridine] (**12**; 107 mg, 0.257 mmol) in CF_3COOH (5 mL) was heated at reflux for 3 h. Volatiles were then removed by evaporation under reduced pressure, and the residue was dried azeotropically by the distillation of added benzene. A 10% solution of $N(C_2H_5)_3$ in acetone (5 mL) was added, and the resulting suspension was stirred briefly and then centrifuged. The supernatant was removed, and the remaining solid was washed with acetone and dried. This yielded a pure sample of 6,6′-(1,3-butadiyne-1,4-diyl)bis-2(1*H*)-pyridinone (**10**) as a yellow powder (55.7 mg, 0.236 mmol, 92%): mp 220 °C dec; IR (KBr) 3600–2600, 1650 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.58 (d, ^3J = 9.0 Hz, 2 H), 6.83 (d, ^3J = 6.8 Hz, 2 H), 7.50 (dd, ^3J = 9.0 Hz, ^3J = 6.8 Hz, 2 H), 11.9 (bs, 2 H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 74.8, 78.2, 115.8, 120.9, 129.4, 140.3, 162.6; MS (EI) *m/e* 236; HRMS (EI) calcd for $C_{14}H_8N_2O_2$ 236.0586, found 236.0553.

3,3′-(1,3-Butadiyne-1,4-diyl)bis[2-(phenylmethoxy)pyridine] (13). A mixture of 3-ethynyl-2-(phenylmethoxy)pyridine (**8b**; 266 mg, 1.27 mmol) and $Cu(OOCCH_3)_2$ (558 mg, 3.07 mmol) in pyridine (30 mL) was heated at reflux for 6 h. Volatiles were then removed by evaporation under reduced pressure. Flash chromatography (silica, hexane (50%)/$CHCl_3$ (50%))[19] of the residue yielded 3,3′-(1,3-butadiyne-1,4-diyl)bis[2-(phenylmethoxy)pyridine] (**13**) as a colorless solid. Recrystallization from benzene yielded an analytically pure sample (201 mg, 0.483 mmol, 76%): mp 118–120 °C; IR (KBr) 2140; ^1H NMR (300 MHz, $CDCl_3$) δ 5.51 (s, 4 H), 6.88 (dd, ^3J = 7.4 Hz, ^3J = 5.0 Hz, 2 H), 7.3–7.6 (m, 10 H), 7.78 (dd, ^3J = 7.4 Hz, ^4J = 1.9 Hz, 2 H), 8.14 (dd, ^3J = 5.0 Hz, ^4J = 1.9 Hz, 2 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 67.2, 78.5, 105.8, 116.1, 126.9, 127.1, 127.8, 136.5, 142.3, 146.4, 163.4; MS (EI) *m/e* 416, 325, 91; HRMS (EI) calcd for $C_{28}H_{20}N_2O_2$ 416.1525, found 416.1562. Anal. Calcd for $C_{28}H_{20}N_2O_2$: C, 80.75; H, 4.84. Found: C, 80.66; H, 4.86.

3,3′-(1,3-Butadiyne-1,4-diyl)bis-2(1*H*)-pyridinone (11). A solution of 3,3′-(1,3-butadiyne-1,4-diyl)bis[2-(phenylmethoxy-)pyridine] (**13**; 68.0 mg, 0.163 mmol) in CF_3COOH (5 mL) was kept at 25 °C for 3 h. A workup similar to the one used to isolate dipyridone **10** provided pure 3,3′-(1,3-butadiyne-1,4-diyl)bis-2(1*H*)-pyridinone (**11**) as a yellow powder (33.9 mg, 0.144 mmol, 88%): mp 255 °C dec; IR (KBr) 3600–2600, 2140, 1650 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.22 (dd, ^3J = 7.1 Hz, ^3J = 6.2 Hz, 2 H), 7.54 (dd, ^3J = 6.2 Hz, ^4J = 2.0 Hz, 2 H), 7.79 (dd, ^3J = 7.1 Hz, ^4J = 2.0 Hz, 2 H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 82.5, 104.6, 111.6, 120.9, 131.7, 145.6, 161.6; HRMS (EI) calcd for $C_{14}H_8N_2O_2$ 236.0586, found 236.0630. Anal. Calcd for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41. Found: C, 70.04; H, 3.91.

2,2′-Bifuro[2,3-*b*]pyridine (14). A solution of 3,3′-(1,3-butadiyne-1,4-diyl)bis-2(1*H*)-pyridinone (**11**; 45.6 mg, 0.193 mmol) in CF_3COOH (10 mL) was heated at reflux for 3 h. Volatiles were then removed by evaporation under reduced pressure, and the residue was dried azeotropically by the distillation of added benzene and then washed with small amounts of acetone. The remaining solid was dried to give a pure sample of 2,2′-bifuro[2,3-*b*]pyridine (**14**) as a pale yellow powder (39.7 mg, 0.168 mmol, 87%): mp 266–268 °C; IR (KBr) 1600, 1400, 1250, 1110, 810, 760 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.44 (dd, ^3J = 7.7 Hz, ^3J = 4.8 Hz, 2 H), 7.58 (s, 2 H), 8.22 (dd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 2 H), 8.38 (dd, ^3J = 4.8 Hz, ^4J = 1.7 Hz, 2 H); MS (EI) *m/e* 236; HRMS (EI) calcd for $C_{14}H_8N_2O_2$ 236.0586, found 236.0590.

2-(Phenylmethoxy)-6-[4-(trimethylsilyl)-1,3-butadiynyl]pyridine (16). A solution of (1,3-butadiyne-1,4-diyl)bis-[trimethylsilane] (38.4 mg, 0.198 mmol) in THF (2 mL) was stirred at −78 °C under dry N_2 and treated dropwise with a solution of butyllithium (124 μL, 1.56 M in hexane, 0.193 mmol). The resulting mixture was kept at −78 °C for 1 h, and then a solution of $ZnCl_2$ (26.9 mg, 0.197 mmol) in THF (1 mL) was added. The cooling bath was removed, and the stirred mixture was treated with a solution of 2-bromo-6-(phenylmethoxy)pyridine (52.2 mg, 0.198 mmol)[2c] and $PdCl_2(PPh_3)_2$ (15.4 mg, 0.0219 mmol) in THF (2 mL). The resulting mixture was kept at 25 °C for 4 h, and then volatiles were removed by evaporation under reduced pressure. Flash chromatography (silica, hexane (95%)/ethyl acetate (5%))[19] of the residue provided a pure sample of 2-(phenylmethoxy)-6-[4-(trimethylsilyl)-1,3-butadiynyl]pyridine (**16**) as a yellow oil (28.1 mg, 0.0920 mmol, 48%): IR (liquid film) 2100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 9 H), 5.38 (s, 2 H), 6.80 (d, ^3J = 8.3 Hz, 1 H), 7.12 (d, ^3J = 7.2 Hz, 1 H), 7.3–7.5 (m, 5 H), 7.53 (dd, ^3J = 8.3 Hz, ^3J = 7.2 Hz, 1 H); HRMS (FAB) calcd for $C_{19}H_{20}NOSi$ 306.1314, found 306.1295.

2-(Bromoethynyl)-6-(phenylmethoxy)pyridine (7b). A mixture of 2-ethynyl-6-(phenylmethoxy)pyridine (**7a**; 0.718 g, 3.43 mmol),[2c] Br_2 (0.776 g, 4.85 mmol), and NaOH (1.25 g, 31.3 mequiv) in H_2O (3.3 mL) was stirred in the dark at 25 °C for 48 h. The resulting mixture was then extracted with $CHCl_3$, and volatiles were removed from the combined organic extracts by evaporation under reduced pressure. The residue, a yellow oil, was 2-(bromoethynyl)-6-(phenylmethoxy)pyridine (0.975 g, 3.38 mmol, 99%). It was used immediately in the following step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 2 H), 6.81 (d, ^3J = 8.4 Hz, 1 H), 7.08 (d, ^3J = 7.3 Hz, 1 H), 7.3–7.5 (m, 5 H), 7.46 (dd, ^3J = 8.4 Hz, ^3J = 7.3 Hz, 1 H).

2-(Phenylmethoxy)-3-[4-[6-(phenylmethoxy)-2-pyridinyl]-1,3-butadiynyl]pyridine (15). A mixture of 2-(bromoethynyl)-6-(phenylmethoxy)pyridine (**7b**; 160 mg, 0.56 mmol), 3-ethynyl-2-(phenylmethoxy)pyridine (**8b**; 110 mg, 0.53 mmol), CuI (3.9 mg, 0.020 mmol), and $PdCl_2(PPh_3)_2$ (7.3 mg, 0.010 mmol) in $N(C_2H_5)_3$ (1.2 mL) was stirred at 25 °C for 12 h under dry N_2. Volatiles were then removed by evaporation under reduced pressure. Flash chromatography (silica, hexane (85%)/ethyl acetate (15%))[19] of the residue provided 2-(phenylmethoxy)-3-[4-[6-(phenylmethoxy)-2-pyridinyl]-1,3-butadiynyl]pyridine (**15**) as a pale yellow solid (190 mg, 0.46 mmol, 87%). An analytical pure sample was prepared by recrystallization from benzene: mp 111–113 °C; IR (KBr) 2200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 2 H), 5.52 (s, 2 H), 6.81–6.92 (m, 2 H), 7.19 (m, 1 H), 7.3–7.6 (m, 11 H), 7.77–7.80 (m, 1 H), 8.15–8.18 (m, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 67.3, 67.4, 72.7, 78.3, 81.0, 105.6, 112.2, 116.1, 121.6, 126.9, 127.0, 127.2, 127.4, 127.6, 127.7, 127.8, 127.9, 136.4, 138.2, 142.5, 146.4, 146.7, 162.8, 163.5; MS (EI) *m/e* 416, 325, 91; HRMS (EI) calcd for $C_{28}H_{20}N_2O_2$ 416.1525, found 416.1548. Anal. Calcd for $C_{28}H_{20}N_2O_2$: C, 80.75; H, 4.84. Found: C, 80.76; H, 4.77.

3-[4-(1,6-Dihydro-6-oxo-2-pyridinyl)-1,3-butadiynyl]-2(1*H*)-pyridinone (4). A solution of 2-(phenylmethoxy)-3-[4-[6-(phenylmethoxy)-2-pyridinyl]-1,3-butadiynyl]pyridine (**15**; 193 mg, 0.463 mmol) in CF_3COOH (10 mL) was heated at reflux for 1 h. A workup similar to the one used to isolate dipyridone **10** yielded a pure sample of 3-[4-(1,6-dihydro-6-oxo-2-pyridinyl)-1,3-butadiynyl]-2(1*H*)-pyridinone (**4**) as a yellow powder (88.7 mg, 0.375 mmol, 81%): mp 210 °C dec; IR (KBr) 3650–2600, 2200, 1650 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.26 (t, 1 H), 6.51 (d, 1 H), 6.70 (d, 1 H), 7.45 (t, 1 H), 7.59 (d, 1 H), 7.88 (d, 1 H); MS (EI) *m/e* 237; HRMS (EI) calcd for $C_{14}H_8N_2O_2$ 236.0586, found 236.0567. Anal. Calcd for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41. Found: C, 69.94; H, 3.99.

Oxidative Coupling of Equimolar Mixtures of 3-Ethynyl-2(1*H*)-pyridinone (5) and 6-Ethynyl-2(1*H*)-pyridinone (6). A catalyst solution was prepared in acetone (6 mL) from CuCl (150 mg, 1.5 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (58 mg, 0.50 mmol) as described previously for the synthesis of dipyridine **12**. A stirred mixture of 6-ethynyl-2(1*H*)-pyridinone

(6; 50 mg, 0.42 mmol) and 3-ethynyl-2(1*H*)-pyridinone (5; 50 mg, 0.42 mmol) in acetone (1 mL) was warmed at 35 °C, saturated with O_2, treated with the catalyst solution, and kept under O_2 for 3 h. Volatiles were then removed by evaporation under reduced pressure, and the residue was washed with acetone until the extracts were colorless. The remaining solid was washed with 2% aqueous HNO_3 and again with acetone. The product, a yellow powder, was a mixture of the three dipyridones **4**, **10**, and **11** (44 mg, 0.19 mmol, 90%). The entire sample was dissolved in DMSO-d_6 and analyzed by ^1H NMR spectroscopy. Integration of the well-resolved signals at δ 6.70 (**4**), 6.83 (**10**), and 7.79 (**11**) showed that the three dipyridones were present in the statistical ratio. Similar experiments were performed by using CH_2Cl_2 and DMSO for the preparation of the catalyst solution and for the cross-coupling reaction.

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