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Iron-Catalyzed Formation of 2-Aminopyridines from Diynes and Cyanamides

Timothy K. Lane, Brendan R. D'Souza, and Janis Louie

Henry Eyring Building, Department of Chemistry, University of Utah, 315 S 1400 E, Salt Lake City, Utah 84112-0850

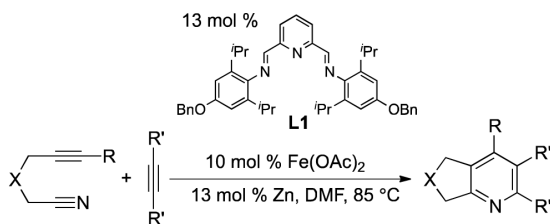
Abstract

Diynes and cyanamides undergo an iron-catalyzed [2+2+2] cycloaddition to form highly substituted 2-aminopyridines in an atom-efficient manner that is both high yielding and regioselective. This system was also used to cyclize two terminal alkynes and a cyanamide to afford a 2,4,6-trisubstituted pyridine product regioselectively.

Introduction

The introduction of complex substitution patterns onto pyridine rings can require multiple synthetic steps. Alternatively, metal catalyzed [2+2+2] cycloadditions can create highly substituted pyridines in a single step from simple starting materials.¹ This remarkably powerful method allows for the efficient and regioselective construction of pyridines in addition to bi- and tricyclic-fused pyridine ring systems. Despite the abundance and low cost of iron salts, only a few examples of iron-catalyzed pyridine formation exist.²

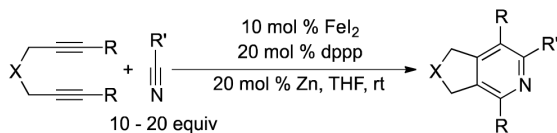
We recently developed the first general iron-catalyzed method for pyridine synthesis.³ In our initial report, the strong tendency for iron to cyclotrimerize alkynes was overcome using alkynenitrile substrates along with a unique bis(aldimino)pyridine ligand (**L1**) (eq 1).⁴ Shortly after our initial report, Wan and co-workers published an iron-catalyzed synthesis of pyridines from diynes and nitriles (eq 2).⁵ Unfortunately, relatively high catalyst loadings were required in both systems. In addition, these systems either gave pyridines in moderate yields (former) or required ten to twenty molar equivalents of nitrile (latter).⁶ Although these reports are an important step forward, an efficacious iron-catalyzed route to pyridines that utilizes low catalyst loading yet affords high yield of pyridine remains scarce.



(1)

*louie@chem.utah.edu.

Supporting Information Available Experimental details, ¹H and ¹³C NMR spectra, and crystal structure data for (**L2**)FeBr₂. This material is available free of charge via the Internet at <http://pubs.acs.org>.



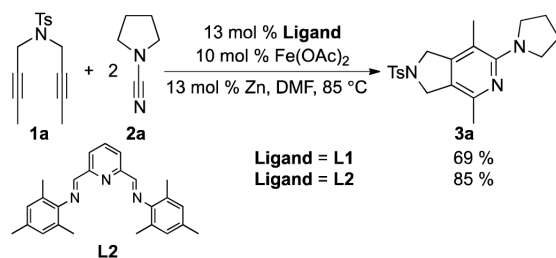
(2)

Attempts to react unactivated nitriles with diynes using our system afforded only traces of pyridine products. Reactions with electron deficient nitriles were also unsuccessful. Our recent work with cyanamides suggested that they could be suitable partners in Fe-catalyzed cycloaddition chemistry as they appeared to be more reactive in Ni-catalyzed cycloadditions.⁷ Thus, 2-aminopyridines could potentially be prepared by our iron bisiminopyridine catalyst without requiring a large excess of cyanamide or having to tether the cyanamide to an alkyne.

Variations on the 2-aminopyridine core have been studied extensively due to their potential as medicinally useful compounds.⁸ 2-Aminopyridines are also a central structural motif in α -carboline natural products⁹ as well as in a variety of chromophores,¹⁰ pharmacophores,¹¹ OLED's,¹² and inorganic ligands.¹³ These broadly applicable compounds are commonly synthesized by Buchwald-Hartwig type aminations,¹⁴ nucleophilic aromatic substitutions,¹⁵ and multi-component condensations.¹⁶ Such methods are useful for the creation of simple 2-aminopyridines, but more complex substitution patterns require additional synthetic manipulations. For more complex aminopyridines, Co, Ni, Rh, and Ti catalysts and a photocatalytic system have all been used to mediate [2+2+2] cycloadditions.¹⁷ However, in most of these studies (i.e., Ni, Rh, and Ti), only a single example of a [2+2+2] cycloaddition with a cyanamide was demonstrated. In an effort to improve the conditions and expand the scope of these reactions, we recently developed a Ni/NHC-catalyzed system for the [2+2+2] formation of 2-aminopyridines from diynes and cyanamides.⁷ Although this system was high yielding and regioselective, the low cost and environmentally-benign nature of iron compares favorably to nickel. Additionally we felt that highly reactive cyanamides presented an opportunity to improve on iron-catalyzed pyridine formation. Herein, we report the successful development of an iron catalyst for the cycloaddition of diynes and cyanamides to afford 2-aminopyridines.

Results and Discussion

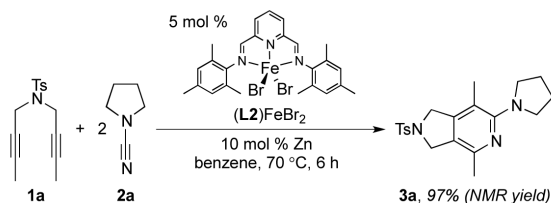
We were delighted when our first attempt to make 2-aminopyridine **3a** from diyne **1a** and 2 equivalents of cyanamide **2a** using our original catalyst system (10 mol % Fe(OAc)₂, 13 mol % Zn and 13 mol % **L1** in DMF) afforded 2-aminopyridine **3a** in 69% isolated yield at 85 °C (eq 3). Furthermore, the use of a simpler ligand (**L2**) led to an increase in isolated yield (85%).¹⁸ Further optimization led to conditions employing 5 mol % catalyst loading of inexpensive FeCl₂, 10 mol % Zn and 10 mol % **L2** in benzene over 4 hours at room temperature. Evaluation of other ligands (N-heterocyclic carbenes, phosphines, and pyridyl diimines) provided no product.¹⁹



(3)

Unfortunately, the mild conditions that worked for the model substrates (i.e., **1a** and **2a**) were not amenable to other diynes. Although increasing the reaction temperature to 70 °C led to good reactivity of the substrates, diyne dimerization accounted for as much as half of substrate conversion. An excess of cyanamide (10 equiv) led to no reactivity suggesting that cyanamide binding out-competes alkyne binding at high concentrations. Gratifyingly, slow addition of diyne over the course of 3 hours solved this problem and provided a general method for coupling a variety of diynes. Slow addition of the diyne also allowed us to decrease the cyanamide:diyne ratio to 1.2:1 with no deleterious effects on the yield.

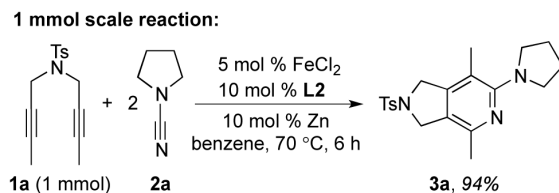
Control studies to establish the necessity of iron for the reaction were carried out. Importantly, removing any part of the catalytic system renders the reaction ineffective. Additionally, (**L2**)FeBr₂ was independently synthesized and used directly as an all-in-one catalyst precursor to provide a 97 % NMR yield (eq 4). That is, the combination of (**L2**)FeBr₂ and Zn dust provided a catalytically competent system. No reaction occurred in the absence of zinc dust.²⁰



(4)

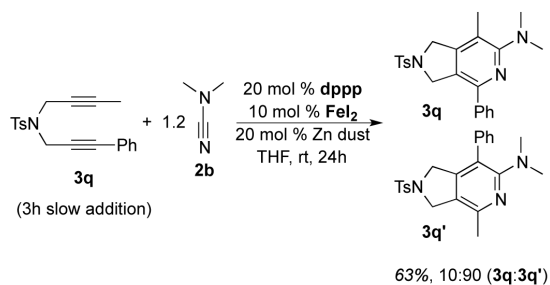
A broad range of diynes and cyanamides were successfully converted to their respective 2-aminopyridines (Table 1). The protected nitrogen backbone diyne **1a** and malonate backbone diyne **1b** both afforded products (**3a** and **3b**) in excellent yield (entries 1-2). The challenging terminal diyne **1c** provided **3c** in good yield (entry 3). However, other difficult substrates such as phenyl and TMS substituted diynes (**1d** and **1e** respectively, entries 4-5) were unreactive. The lack of Thorpe-Ingold effect in substrates **1f** and **1g** did not effect cycloaddition as products **3f** and **3g** were both obtained in 84% yield (entries 6-7). Notably, entries 1 and 6 demonstrate that heteroatom tethers, which were problematic in the previous iron systems,^{3,5} are well tolerated by this system. Diyne **1h** successfully provided the 6,6-bicyclic pyridine (**3h**) in good yield (entry 8). High yields of 2-aminopyridine were obtained with methyl-phenyl (**2d**) and dimethyl (**2b**) substituted cyanamides substrates (entries 9 and 11). Surprisingly, cycloaddition of diethyl cyanamide **2c** afforded a lower yield of product (entry 10). Cyclic cyanamides N-cyanopiperidine (**2e**) and N-cyanomorpholine (**2f**) reacted readily (entries 12-13). Despite the apparent negative effect of cyanamide sterics in entry 10,

the large dibenzazepinyl cyanamide provided **3n** in good yield (entry 14). This result compares well with the 19% yield afforded by cobalt.^{17c} Attempts to react (dimethylamino)acetonitrile with diyne **1b** were unsuccessful, which may indicate that the inherent electronic structure of cyanamides, not a chelation effect, is the source of their high reactivity in this system.²¹ To demonstrate the synthetic utility of this methodology, entry 1 was repeated on a 1 mmol scale leading to a comparable yield of 94 % (eq 5).



(5)

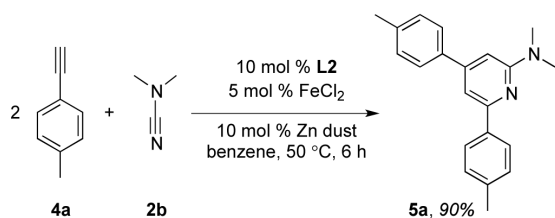
For future synthetic application, an understanding of regioselectivity of unsymmetrical coupling partners is paramount. Dienes **1i-k** were evaluated under our optimized conditions and the results are summarized in Table 2. In each of these cases, good yields of 2-aminopyridine products were obtained. What is surprising, however, is that each of the reactions shows a strong preference to place the larger substituent proximal to the pyridine nitrogen. For example, the cycloaddition of H, Me substituted diyne **1i** and cyanamide **2b** provided an 85:15 ratio of **3o** and **3o'** in 72% combined yield (entry 1). A similar product ratio was obtained in the cycloaddition of a bulkier diyne (**1j**, entry 2) as well as aryl/alkyl diyne (**1k**, entry 3). These regioselectivity trends provide an alternative to nickel-catalyzed systems where the larger substituent is placed at the 3-position of the 2-aminopyridine ring.⁷ Additionally, this Fe-catalyzed method is milder than the cobalt-catalyzed system which is primarily limited to terminal alkynes.^{17c} Notably, the regioselectivity is the reverse of that observed in the previous Fe-catalyzed system involving diynes and nitriles wherein the larger alkyne substituent was placed ortho to the nitrile substituent.⁵ To verify that this trend is a result of the catalyst and not the type of nitrile, we reacted diyne **3q** with dimethyl cyanamide **2b** under the catalyst developed by Wan and co-workers (eq 6). The FeI₂/dppp system provided the product in a 63% combined yield but with **3q'** as the major regioisomer in a 10:90 (**3q**, **3q'**) ratio, the opposite selectivity of our system.



(6)

The fully intermolecular [2+2+2] cycloaddition of alkynes and nitriles to form pyridines is a challenging reaction. To date, intermolecular reactions with cyanamides are limited to cobalt catalysts, and these systems provide a mixture of products when using unsymmetrical

internal alkynes.²² Furthermore, no reports of [2+2+2] cycloadditions involving aryl acetylenes and cyanamides exist. Terminal aryl acetylenes are particularly challenging substrates since these tend to undergo rapid oligomerization to provide unwanted side products.^{1,23} Despite this potential pitfall, as well as the possibility of forming multiple regioisomers, we found the reaction of two equivalents of alkyne **4a** and one equivalent of cyanamide **2b** afforded **5a** as a single regioisomer in 90 % yield (eq 4). This mild and efficient route to 2-amino-4,6-aryl pyridines may provide an alternative to multi-step syntheses of biologically active compounds²⁴ and is the topic of further investigation in our lab.



(7)

The contrast in regioselectivity between our $\text{FeCl}_2/\text{L2}$ system and the FeI_2/dppp system is the first example of ligand-dependent regioselectivity in metal-catalyzed [2+2+2] pyridine formation. The regioselectivity observed in our Fe system mirrors that observed in Co-catalyzed protocols. As such, this suggests that the $\text{L2}/\text{Fe}$ -catalyzed cycloaddition of cyanamides follows a similar mechanism to that of the well-established mechanism for Co-catalyzed pyridine formation.²⁵ Following in-situ ligand coordination and reduction by zinc, a reduced Fe catalyst binds the diyne and facilitates oxidative coupling of the two alkyne units to form a ferracyclopentadiene (Scheme 2). Insertion of cyanamide and reductive elimination subsequently afford the pyridine product. Interestingly, the FeI_2/dppp catalyst system, which follows the regioselectivity patterns of nickel, has been proposed to undergo a mechanism involving initial oxidative coupling between an alkyne and a nitrile instead.⁵ This is in agreement with the proposed mechanism for nickel-catalyzed pyridine formation.²⁶ The regioselectivity results of this study, combined with what is known about cobalt and nickel systems, may indicate that iron is capable of following either mechanistic pathway and is dependent on ligand choice. Studies to gain further insight into the mechanistic difference between these two Fe based systems are currently underway.

Conclusions

The iron catalyzed [2+2+2] cycloaddition of alkynes and cyanamides is a high yielding, atom efficient and regioselective method to obtain 2-aminopyridines. Iron catalyzed pyridine synthesis is no longer limited by alkynenitrile substrates or large excesses of nitrile. We are continuing our efforts to expand this chemistry to other nitrile substrates.

Experimental

General Experimental

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2 filled glove-box unless otherwise noted. Benzene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. Iron Chloride (99.95% purity) was purchased from Alfa Aesar. Dienes **1a**,²⁷ **1b-c**,²⁸ **1d**,²⁹ **1e**,³⁰ **1f**,³¹ **1g**,³² **1h**,³³ **1i**,³⁴ and **1j-k**³⁵ were prepared from known literature procedures. Liquid cyanamides were degassed

using three sequential freeze-pump-thaw cycles. Slow addition of diyne was performed using a syringe pump 22 from a disposable 1 mL syringe with a 6 inch stainless steel 24 gauge needle. The needle was dried overnight at 160 °C and was fitted to the syringe while hot. The syringe/needle joint was then wrapped tightly with Teflon tape.

¹H and ¹³C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ¹H and to the center line of a triplet at 77.23 ppm for ¹³C. The abbreviations s, d, dd, dt, dq, td, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet of doublets, triplet, quartet, and quintet, respectively. All ¹³C NMR spectra were proton decoupled. Gas Chromatography was performed using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 10 °C/min.; final temperature: 300 °C held for 12 minutes; detector temperature: 250 °C.

General Procedure for the Cycloaddition

In a nitrogen filled glove box, 5 mol % FeCl₂, 10 mol % **L2** and benzene was added to a vial. The mixture was stirred for 10 to 15 minutes at which time 1.2 equivalents of cyanamide **2** (2.7 M in benzene) and 10 mol % Zn dust was added. The vial was then capped with a Teflon lined septum screw cap and removed from the glove box. The vial was stirred in a 70 °C oil bath and a solution of diyne **1** (0.49 M in benzene) was slowly added to the vial over 3 hours (unless otherwise noted) via syringe pump. (The final concentration of the diyne after addition was 0.4 M.)

Purification Procedure A

For 2-aminopyridines with an R_f > 0.3 (20 % ethyl acetate in hexanes) **L2** (R_f = 0.51, 20% ethyl acetate in hexanes) may co-elute with and contaminate the final product. This method was devised to avoid this issue. Once the reaction was complete, as determined by GC, the crude mixture was stirred in aqueous HCl for 10 minutes to protonate the 2-aminopyridine product. The aqueous layer was collected and the organic layer was further extracted with 4 × 15 mL portions of aqueous HCl. The aqueous extracts were collected then a saturated aqueous NaHCO₃ solution was carefully added until the pH >7 causing the product to precipitate. The aqueous layer was then extracted with 3 × 25 mL portions of diethyl ether. The organic extracts were collected, dried over Na₂SO₄, filtered and the solvent was removed *in vacuo*. The crude product was then purified via silica gel flash chromatography.

Purification Procedure B

For 2-aminopyridines with R_f < 0.3 (20 % ethyl acetate in hexanes). Once the reaction was complete, as determined by GC, the crude mixture was purified via flash silica gel chromatography. The product often contained unreacted cyanamide at this point so the product was stirred in aqueous HCl for 10 minutes. The aqueous layer was collected and the organic layer was further extracted with 4 × 15 mL portions of aqueous HCl. The aqueous extracts were collected then a saturated aqueous NaHCO₃ solution was carefully added until the pH >7 causing the product to precipitate. The aqueous layer was then extracted with 3 × 25 mL portions of diethyl ether. The organic extracts were collected, dried over Na₂SO₄, filtered and the solvent was removed *in vacuo*.

Synthesis of 4,7-dimethyl-6-(pyrrolidin-1-yl)-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (3a)

Compound **3a** was prepared using the general procedure with **2a** (42 mg, 4.4 × 10⁻¹ mmol), FeCl₂ (2.3 mg, 1.8 × 10⁻² mmol), **L2** (13.4 mg, 3.6 × 10⁻² mmol), and zinc (2.4 mg, 3.6 × 10⁻² mmol) in 418 μL of benzene. Diyne **1a** (100 mg, 3.6 × 10⁻¹ mmol), dissolved in 490

μL benzene was added over 3 h at 70 °C. The reaction was stirred an additional 1 h for a total reaction time of 4 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 10 % ethyl acetate in hexanes followed by an acid/base extraction with 3M HCl to yield **3a** (126 mg, 93 %) as a white solid. $R_f = 0.19$ (20 % ethyl acetate in hexanes). ^1H and ^{13}C NMR spectral data was compared with known literature values.^{7a}

Synthesis of dimethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (3b)

Compound **3b** was prepared using the general procedure with **2a** (49 mg, 5.1×10^{-1} mmol), FeCl_2 (2.7 mg, 2.1×10^{-2} mmol), **L2** (16 mg, 4.2×10^{-2} mmol), and zinc (2.8 mg, 4.2×10^{-2} mmol) in 560 μL of benzene. Diyne **3b** (100 mg, 4.2×10^{-1} mmol), dissolved in 498 μL benzene, was added over 3 h at 70 °C. The reaction mixture was stirred for an additional 3 h for a total reaction time of 6 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 20 % ethyl acetate in hexanes followed by an acid/base extraction with 1M HCl to yield **3b** (127 mg, 90 %) as a yellowish solid. $R_f = 0.27$ (20 % ethyl acetate in hexanes). ^1H and ^{13}C NMR spectral data was compared with known literature values.^{7a}

Synthesis of dimethyl 3-(pyrrolidin-1-yl)-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (3c)

Compound **3c** was prepared using the general procedure with **2a** (55 mg, 5.7×10^{-1} mmol), FeCl_2 (3.0 mg, 2.4×10^{-2} mmol), **L2** (18 mg, 4.8×10^{-2} mmol), and zinc (3.1 mg, 4.8×10^{-2} mmol) in 194 μL of benzene. Diyne **1c** (99 mg, 4.8×10^{-1} mmol), dissolved in 1 mL benzene, was added over 3 h at 70 °C. The reaction was stirred at 70 °C for an additional 15h for a total reaction time of 18 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 2 % methanol in dichloromethane followed by an acid/base extraction with 1M HCl to yield **3c** (94 mg, 65 %) as a white solid. $R_f = 0.01$ (20 % ethyl acetate in hexanes). ^1H and ^{13}C NMR spectral data was compared with known literature values.^{7a}

Synthesis of 4,7-diethyl-6-(pyrrolidin-1-yl)-1,3-dihydrofuro[3,4-c]pyridine (3f)

Compound **3f** was prepared using the general procedure with **2a** (36 mg, 3.8×10^{-1} mmol), FeCl_2 (2.0 mg, 1.6×10^{-2} mmol), **L2** (12 mg, 3.2×10^{-2} mmol), and zinc (2.1 mg, 3.2×10^{-2} mmol) in 292 μL of benzene. Diyne **1f** (47 mg, 3.2×10^{-1} mmol), dissolved in 497 μL benzene, was added over 5 h at 70 °C. The reaction was stirred an additional 1 h for a total reaction time of 6 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure A with an acid/base extraction using 1M HCl then silica gel flash chromatography using 5 % ethyl acetate in hexanes (500 mL), then 10 % ethyl acetate in hexanes (500 mL) to yield **3f** (65 mg, 84 %) as a yellow oil. $R_f = 0.52$ (20 % ethyl acetate in hexanes). ^1H (300 MHz, CDCl_3): δ (ppm) 1.14 (t, $J = 7.7$ Hz, 3H), 1.23 (t, $J = 7.5$ Hz, 3H), 1.93 (quint, $J = 3.3$ Hz, 4H), 2.51-2.60 (m, 4H), 3.52 (quint, $J = 3.2$ Hz, 4H), 5.05 (s, 4H). ^{13}C (75 MHz, CDCl_3) δ (ppm) 158.0, 150.3, 149.8, 122.9, 116.2, 72.8, 72.4, 50.3, 29.2, 25.8, 23.0, 13.8, 12.5. IR (cm^{-1}): 2966, 2932, 2869, 1761, 1600, 1428, 1381, 1343, 1311, 1228, 1143, 1053, 906, 783. HRMS (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 247.1810, found 247.1814.

Synthesis of 1,4-dimethyl-3-(pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[c]pyridine (3g)

Compound **3g** was prepared using the general procedure with **2a** (55 mg, 5.7×10^{-1} mmol), FeCl_2 (3.0 mg, 2.4×10^{-2} mmol), **L2** (18 mg, 4.8×10^{-2} mmol), and zinc (3.1 mg, $4.8 \times$

10^{-2} mmol) in 429 μL of benzene. Diyne **1g** (57 mg, 4.8×10^{-1} mmol), dissolved in 765 μL benzene, was added over 5 h at 70 °C. The reaction was stirred an additional 2 h for a total reaction time of 7 hours. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure A with an acid/base extraction using 1M HCl then silica gel flash chromatography using 5 % ethyl acetate in hexanes (500 mL), then 10 % ethyl acetate in hexanes (500 mL) to yield **3g** (86 mg, 84 %) as a yellow oil. $R_f = 0.49$ (20 % ethyl acetate in hexanes). ^1H (300 MHz, CDCl_3): δ (ppm) 1.89-1.92 (m, 4H), 2.06, (quint, $J = 7.4$ Hz, 2H), 2.17 (s, 4H), 2.33 (s, 3H), 2.80 (t, $J = 7.5$ Hz, 4H), 3.44 (t, $J = 6.5$ Hz, 4H). ^{13}C (75 MHz, CDCl_3) δ (ppm) 154.5, 147.4, 129.1, 129.0, 114.3, 50.4, 32.3, 30.6, 25.6, 24.8, 22.0, 16.0. IR (cm^{-1}): 2953, 2868, 1595, 1425, 1347, 1204, 1137, 1063, 938, 858, 756. HRMS (ESI) m/z calcd. for $\text{C}_{14}\text{H}_{21}\text{N}_2$ $[\text{M}+\text{H}]^+$ 217.1705, found 217.1709.

Synthesis of tetraethyl-1,4-dimethyl-3-(pyrrolidin-1-yl)isoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**3h**)

Compound **3h** was prepared using the general procedure with **2a** (18 mg, 1.9×10^{-1} mmol), FeCl_2 (1.0 mg, 0.8×10^{-2} mmol), **L2** (5.8 mg, 1.5×10^{-2} mmol), and zinc (1.0 mg, 1.5×10^{-2} mmol) in 100 μL of benzene. Diyne **1h** (67 mg, 1.6×10^{-1} mmol) dissolved in 300 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 3 h for a total reaction time of 6 h. After the reaction was complete (reaction monitored by GC), the crude product was isolated with only silica gel flash chromatography (no acid/base extraction) using 10 % ethyl acetate in hexanes (200 mL), then 15 % ethyl acetate in hexanes (400 mL) to yield **3h** (65 mg, 80 %) as a yellow oil. $R_f = 0.19$ (20 % ethyl acetate in hexanes). ^1H (400 MHz, CDCl_3): δ (ppm) 1.23 (td, $J_1 = 3.2$, $J_2 = 3.2$, $J_3 = 3.2$ Hz, 12H), 1.86-1.92 (m, 4H), 2.12 (s, 3H), 2.34 (s, 3H), 3.30 (s, 2H), 3.36 (m, 6H), 4.13-4.25 (m, 8H). ^{13}C (100 MHz, CDCl_3) δ (ppm) 170.2, 170.1, 157.9, 150.2, 141.7, 118.2, 115.8, 62.2, 62.0, 61.9, 57.4, 57.1, 50.4, 33.1, 31.8, 25.5, 22.3, 14.8, 13.9. IR (cm^{-1}): 2981, 2937, 2871, 2361, 1735, 1571, 1429, 1367, 1326, 1270, 1241, 1202, 1096, 1052, 942, 864, 784, 703, 650, 614, 580. HRMS (ESI) m/z calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_4$ 455.1971, found 455.1969.

Synthesis of dimethyl 3-(dimethylamino)-1,4-dimethyl-5H-cyclopenta[*c*]pyridine-6,6(7H)-dicarboxylate (**3i**)

Compound **3i** was prepared using the general procedure B with **2b** (20 mg, 2.8×10^{-1} mmol), FeCl_2 (1.5 mg, 1.2×10^{-2} mmol), **L2** (8.8 mg, 2.4×10^{-2} mmol), and zinc (1.6 mg, 2.4×10^{-2} mmol) in 103 μL of benzene. Diyne **1b** (56 mg, 2.4×10^{-1} mmol) dissolved in 489 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 2 h for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 5 % ethyl acetate in hexanes (500 mL), then 10 % ethyl acetate in hexanes (500 mL), then 20 % ethyl acetate in hexanes (500 mL) followed by an acid/base extraction with 1M HCl to yield **3i** (71 mg, 97 %) as a yellow oil. $R_f = 0.27$. ^1H and ^{13}C NMR spectral data was compared with known literature values.^{7a}

Synthesis of dimethyl-3-(diethylamino)-1,4-dimethyl-5H-cyclopenta[*c*]pyridine-6,6(7H)-dicarboxylate (**3j**)

Compound **3j** was prepared using the general procedure with **2c** (22 mg, 2.8×10^{-1} mmol), FeCl_2 (1.5 mg, 1.2×10^{-2} mmol), **L2** (8.8 mg, 2.4×10^{-2} mmol), and zinc (1.6 mg, 2.4×10^{-2} mmol) in 103 μL of benzene. Diyne **1b** (56 mg, 2.4×10^{-1} mmol) dissolved in 489 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 2 h for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash

chromatography using 10 % ethyl acetate in hexanes followed by an acid/base extraction with 1M HCl to yield **3j** (28 mg, 35 %) as a yellow oil. $R_f = 0.27$ (20 % ethyl acetate in hexanes). ^1H and ^{13}C NMR spectral data was compared with known literature values.^{7a}

Synthesis of dimethyl 1,4-dimethyl-3-(methyl(phenyl)amino)-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (**3k**)

Compound **3k** was prepared using the general procedure with **2d** (22 mg, 1.8×10^{-1} mmol), FeCl_2 (1.0 mg, 7.5×10^{-2} mmol), **L2** (5.5 mg, 1.5×10^{-2} mmol), and zinc (1.0 mg, 1.5×10^{-2} mmol) in 65 μL of benzene. Diyne **1b** (35 mg, 1.5×10^{-1} mmol) dissolved in 310 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 2 hours for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 5 % ethyl acetate in hexanes (250 mL), then 10 % ethyl acetate in hexanes (250 mL), 20 % ethyl acetate in hexanes (500 mL) followed by an acid/base extraction with 1M HCl to yield **3k** (39 mg, 70 %) as a yellowish oil. $R_f = 0.16$ (20 % ethyl acetate in hexanes). ^1H and ^{13}C NMR spectral data was compared with known literature values.^{7a}

Synthesis of dimethyl-1,4-dimethyl-3-(piperidin-1-yl)-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (**3l**)

Compound **3l** was prepared using the general procedure with **2e** (31 mg, 2.8×10^{-1} mmol), FeCl_2 (1.5 mg, 1.2×10^{-2} mmol), **L2** (8.8 mg, 2.4×10^{-2} mmol), and zinc (1.6 mg, 2.4×10^{-2} mmol) in 121 μL of benzene. Diyne **1b** (56 mg, 2.4×10^{-1} mmol) dissolved in 471 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 2 hours for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 5 % ethyl acetate in hexanes (250 mL), then 10 % ethyl acetate in hexanes (250 mL), and 20 % ethyl acetate and hexanes (250 mL) followed by an acid/base extraction with 1M HCl to yield **3l** (78 mg, 97 %) as a yellowish oil. $R_f = 0.27$ (20 % ethyl acetate in hexanes). ^1H (400 MHz, CDCl_3): δ (ppm) 1.58 (q, $J = 7.2$ Hz, 2H) 1.68 (quint, $J = 6$ Hz, 4H), 2.14 (s, 3H), 2.33 (s, 3H), 3.0 (t, $J = 4.8$ Hz, 4H), 3.48 (s, 2H), 3.50 (s, 2H), 3.77 (s, 6H). ^{13}C (100 MHz, CDCl_3) δ (ppm) 172.3, 161.8, 150.2, 148.3, 127.6, 118.3, 59.7, 53.3, 51.7, 40.1, 38.9, 26.6, 24.9, 21.9, 14.5. IR (cm^{-1}): 2930, 2851, 1738, 1586, 1432, 1371, 1266, 1199, 1163, 1114, 1062, 1028, 963, 858, 610. HRMS (ESI) m/z calcd. for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 347.1971, found 347.1980.

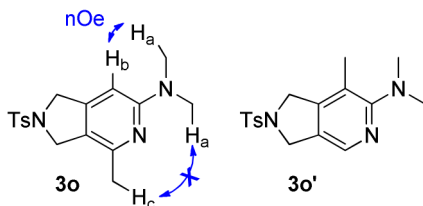
Synthesis of dimethyl-1,4-dimethyl-3-morpholino-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (**3m**)

Compound **3m** was prepared using the general procedure with **2f** (48 mg, 4.7×10^{-1} mmol), FeCl_2 (2.7 mg, 2.1×10^{-2} mmol), **L2** (16 mg, 4.2×10^{-2} mmol), and zinc (2.8 mg, 4.2×10^{-2} mmol) in 200 μL of benzene. Diyne **2b** (50 mg, 2.1×10^{-1} mmol) dissolved in 400 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 2 h for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure A with an acid/base extraction using 1M HCl then silica gel flash chromatography using 20 % ethyl acetate in hexanes (200 mL), then 30 % ethyl acetate in hexanes (400 mL) to yield **3m** (49 mg, 67 %) as a yellowish oil. $R_f = 0.38$ (20 % ethyl acetate in hexanes). ^1H and ^{13}C NMR spectral data was compared with known literature values.^{7a}

Synthesis of dimethyl-3-(5H-dibenzo[b,f]azepin-5-yl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3n**)

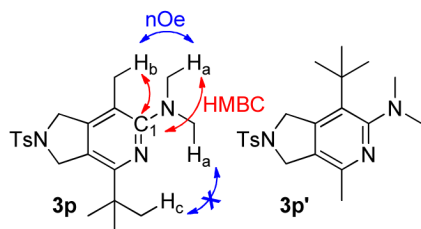
Compound **3n** was prepared using the general procedure with **2g** (83 mg, 4.7×10^{-1} mmol), FeCl_2 (2.68 mg, 2.1×10^{-2} mmol), **L2** (15.6 mg, 4.2×10^{-2} mmol), and zinc (2.8 mg, 4.2×10^{-2} mmol) in 121 μL of benzene. Diyne **1b** (50 mg, 2.1×10^{-1} mmol) dissolved in 471 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 19 h for a total reaction time of 22 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 10 % ethyl acetate in hexanes followed by an acid/base extraction with 1M HCl to yield **3n** (133 mg, 69 %) as a red oil. $R_f = 0.29$ (20 % ethyl acetate in hexanes). ^1H (400 MHz, CDCl_3): δ (ppm) 1.78 (s, 3H), 2.44 (s, 3H), 3.44 (s, 2H), 3.54 (s, 2H), 3.75 (s, 6H), 6.85 (s, 2H), 7.07 (dt, $J = 7.2$ Hz, 0.8 Hz, 2H), 7.16 (dd, $J = 8$ Hz, 1.6 Hz, 2H), 7.22 (dd, $J = 8$ Hz, 1.6 Hz, 2H), 7.71 (dd, $J = 8$ Hz, 0.8 Hz, 2H). ^{13}C (100 MHz, CDCl_3) δ (ppm) 172.2, 156.1, 151.7, 148.4, 148.1, 135.1, 132.4, 129.6, 128.8, 127.3, 124.7, 120.4, 59.8, 53.3, 40.3, 39.0, 22.1, 14.9. IR (cm^{-1}): 3020, 2953, 2923, 2854, 2361, 1737, 1589, 1482, 1432, 1340, 1266, 1200, 1163, 1113, 1060, 950, 922, 865, 794, 767, 735, 662, 559. HRMS (ESI) m/z calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 455.1971, found 455.1982.

Synthesis of N,N,4-trimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-amine (**3o**)



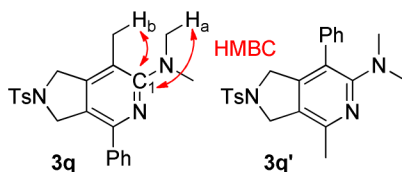
Compounds **3o** and **3o'** were prepared using the general procedure with **2b** (13 mg, 1.9×10^{-1} mmol), FeCl_2 (1.0 mg, 7.9×10^{-2} mmol), **L2** (5.8 mg, 1.6×10^{-2} mmol), and zinc (1.0 mg, 1.6×10^{-2} mmol) in 93 μL of benzene. Diyne **1i** (41 mg, 1.6×10^{-1} mmol), dissolved in 303 μL benzene was added over 3 h at 70 °C. The reaction was stirred an additional 5 h for a total reaction time of 8 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 20 % ethyl acetate in hexanes followed by an acid/base extraction with 3M HCl to yield **3o** and **3o'** (38 mg, 72 %, 85:15) as a white solid. $R_f = 0.11$ (20 % ethyl acetate in hexanes). **3o**: ^1H (400 MHz, CDCl_3): δ (ppm) 2.26 (s, 3H), 2.42 (s, 3H), 3.02 (s, 6H), 4.45 (s, 2H), 4.51 (s, 2H), 6.12 (s, 1H), 7.32 (d, $J = 8$, 2H), 7.77 (d, $J = 8$, 2H). ^{13}C (100 MHz, CDCl_3) δ (ppm) 159.4, 150.6, 147.2, 143.9, 134.0, 130.0, 118.2, 96.4, 53.9, 51.9, 38.4, 22.3, 21.7. MP 176-178 °C. 2-D NOESY (500 MHz, CDCl_3): H_b (6.12 ppm) correlates to H_a (4.51 ppm). H_c (2.56 ppm) shows no correlation to H_a . IR (cm^{-1}): 2918, 2849, 1614, 1579, 1503, 1408, 1342, 1309, 1159, 1099, 815, 669, 579, 543. HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 332.1433, found 332.1433.

Synthesis of 4-(tert-butyl)-N,N,7-trimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-amine (3p)



Compounds **3p** and **3p'** were prepared using the general procedure with **2b** (13 mg, 1.9×10^{-1} mmol), FeCl_2 (1.0 mg, 7.9×10^{-2} mmol), **L2** (5.8 mg, 1.6×10^{-2} mmol), and zinc (1.0 mg, 1.6×10^{-2} mmol) in 59 μL of benzene. Diyne **1j** (50 mg, 1.6×10^{-1} mmol), dissolved in 336 μL benzene was added over 3 h at 70 °C. The reaction was stirred an additional 3 h for a total reaction time of 6 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 10 % ethyl acetate in hexanes followed by an acid/base extraction with 3M HCl to yield **3p** and **3p'** (49 mg, 80 %, 88:12) as a white solid. $R_f = 0.27$ (20 % ethyl acetate in hexanes). **3p**: ^1H (500 MHz, CDCl_3): δ (ppm) 1.29 (s, 9H), 2.10 (s, 3H), 2.42 (s, 3H), 2.79 (s, 6H), 4.24 (s, 2H), 2.74 (s, 2H), 7.34 (d, $J = 8$ Hz, 2H), 7.80 (d, $J = 8$ Hz, 2H). ^{13}C (125 MHz, CDCl_3): δ (ppm) 160.2, 157.6, 148.0, 143.9, 134.0, 123.1, 127.8, 121.0, 114.6, 53.6, 52.3, 42.3, 38.6, 29.5, 21.7, 14.9. MP 101-102 °C. 2-D NOESY (800 MHz, CDCl_3): H_a (2.84 ppm) correlates to H_b (2.09 ppm). H_c (1.28 ppm) does not correlate to H_a . HMBC (800 MHz, CDCl_3): C (161.1 ppm) couples with H_a (2.84 ppm) and H_b (2.09 ppm). IR (cm^{-1}): 3633, 2954, 2866, 2792, 2361, 1726, 1599, 1566, 1478, 1453, 1416, 1392, 1351, 1315, 1251, 1204, 1165, 1099, 1066, 955, 930, 816, 772, 737, 711, 665, 607, 570, 548, 513. HRMS (ESI) m/z calcd. for $\text{C}_{21}\text{H}_{30}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 388.2059, found 388.2069.

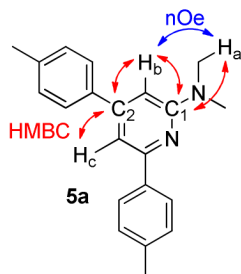
Synthesis of N,N,7-trimethyl-4-phenyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-amine (3q)



Compounds **3q** and **3q'** were prepared using the general procedure with **2b** (13 mg, 1.9×10^{-1} mmol), FeCl_2 (1.0 mg, 7.9×10^{-2} mmol), **L2** (5.8 mg, 1.6×10^{-2} mmol), and zinc (1.0 mg, 1.6×10^{-2} mmol) in 93 μL of benzene. Diyne **1k** (53 mg, 1.6×10^{-1} mmol), dissolved in 302 μL benzene was added over 3 h at 70 °C. The reaction was stirred an additional 3 h for a total reaction time of 6 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B with silica gel flash chromatography using 10 % ethyl acetate in hexanes followed by an acid/base extraction with 3M HCl to yield **3q** and **3q'** (43 mg, 67 %, 86:14) as a white solid. $R_f = 0.14$ (20 % ethyl acetate in hexanes). **3q**: ^1H (400 MHz, CDCl_3): δ (ppm) 2.18 (s, 3H), 2.42 (s, 3H), 2.87 (s, 6H), 4.53 (s, 2H), 4.82 (s, 2H), 7.28-7.47 (m, 5H), 7.76 (dd, $J = 6.5, 7.5$ Hz, 4H). ^{13}C (125 MHz, CDCl_3): δ (ppm) 161.9, 148.2, 147.1, 144.0, 139.4, 134.0, 130.1, 128.8, 128.7, 127.9, 127.8, 122.5, 116.9, 53.7, 52.9, 42.2, 21.7, 15.3. HMBC (800 MHz, CDCl_3): C_1 (165.2 ppm) couples with H_a (2.86 ppm) and H_b (2.17 ppm). MP 176-177 °C. IR (cm^{-1}): 2924, 2854, 2361, 1733, 1595, 1491, 1458, 1400, 1349, 1161, 1098, 1065, 913, 816, 753, 703, 673, 614, 581, 548. HRMS (ESI) m/z calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 408.1746,

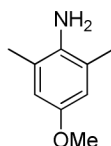
found 408.1752. A crystal of **3q'** suitable for x-ray analysis was grown by slow evaporation from an ether solution (see supporting information).

Synthesis of N,N-dimethyl-4,6-di-p-tolylpyridin-2-amine (**5a**)



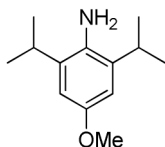
Compound **5a** was prepared using the general procedure with **2b** (22 mg, 3.2×10^{-1} mmol), FeCl₂ (2.0 mg, 1.6×10^{-2} mmol), **L2** (11.7 mg, 3.2×10^{-2} mmol), and zinc (2.1 mg, 3.2×10^{-2} mmol) in 108 μ L of benzene. 4-ethynyltoluene (73 mg, 6.3×10^{-1} mmol), dissolved in 287 μ L benzene was added over 3 h at 50 °C. The reaction was stirred an additional 2 h for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure A with an acid/base extraction using 1M HCl then silica gel flash chromatography using 5 % ethyl acetate in hexanes (500 mL to yield **5a** (86 mg, 90 %) as a white solid. $R_f = 0.57$ (20 % ethyl acetate in hexanes). ¹H-NMR (500 MHz, CD₂Cl₂) δ (ppm) 2.41 (d, $J = 4.0$ Hz, 6H), 3.20 (s, 6H), 6.67 (s, 1H), 7.24 (s, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz, 2H), 7.56 (d, $J = 8.5$ Hz, 2H), 8.0 (d, $J = 7.0$ Hz, 2H). ¹³C (125 MHz, CDCl₃) δ (ppm) 159.9, 155.8, 150.7, 138.51, 138.48, 137.8, 137.7, 129.7, 129.3, 127.2, 127.0, 107.1, 102.2, 38.3, 21.5, 21.4. 2-D NOESY (800 MHz, CDCl₃): H_a (3.24 ppm) correlates with H_b (6.66 ppm). HMBC (800 MHz, CDCl₃): C₁ (159.6 ppm) couples with H_a (3.24 ppm) and H_b (6.66 ppm). C₂ (137.6 ppm) couples with H_b (6.66 ppm) and H_c (7.30 ppm). MP 99 °C. IR (cm⁻¹): 3026, 2920, 1599, 1543, 1511, 1416, 1401, 1250, 1181, 1114, 986, 836, 807, 602, 559. HRMS (ESI) m/z calcd. for C₂₁H₂₃N₂ [M+H]⁺ 303.1861, found 303.1864.

Ligand Synthesis



L1,³ **L2**,³⁶ and **L4**²⁹ were synthesized according to the literature methods.

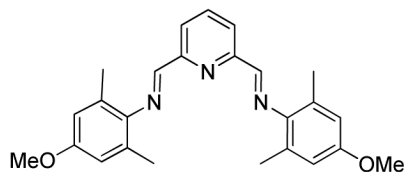
Synthesis of 4-(methoxy)-2,6-dimethylaniline



4-(methoxy)-2,6-dimethylaniline was prepared using a similar literature procedure.³⁰ In a nitrogen glove box, a 20 mL scintillation vial was filled with CuI (353.8 mg, 1.86 mmol) 3,4,7,8-tetramethyl-1,10-phenanthroline (877.4 mg, 3.71 mmol), Cs₂CO₃ (21.5g, 111.4 mmol), and 4-iodo-2,6-dimethyl aniline^{4a} (9.17 g, 37.1 mmol). The vial was sealed with a rubber septum, removed from the glove box then evacuated and backfilled with Argon three

times. Toluene (14 mL) was added and the mixture was stirred at 80 °C for 20 minutes. Methanol (3.6 mg, 111.4 mmol) was added and the rubber septum was quickly replaced with a vial cap. The reaction was stirred for 24 hours at 80 °C then cooled to room temperature, filtered through a silica gel plug and flushed with 150 mL of ethyl acetate. The resulting solution was reduced in vacuo and purified via silica gel flash chromatography with 10% ethyl acetate in hexanes to yield **4-(methoxy)-2,6-dimethylaniline** (3.90 g, 51%) as a blue solid. $R_f = 0.12$ (20 % ethyl acetate in hexanes). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 2.20 (s, 6H), 3.23 (s, 2H), 3.75 (s, 3H), 6.58 (s, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ (ppm) 152.23, 134.61, 123.4, 114.1, 55.9, 18.2. MP 38 °C. IR (cm^{-1}): 3449, 3371, 1923, 2835, 1604, 1490, 1378, 1328, 1300, 1243, 1192, 1150, 1064, 949, 854, 728, 599. HRMS (ESI) m/z calcd. for $\text{C}_9\text{H}_{14}\text{NO}$ $[\text{M}+\text{H}]^+$ 152.1075, found 152.1083.

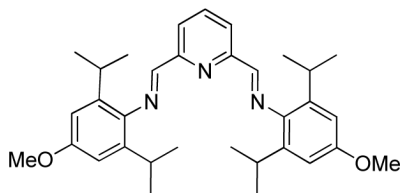
Synthesis of 4-(methoxy)-2,6-diisopropylaniline



L3

4-(methoxy)-2,6-diisopropylaniline was prepared using a similar literature procedure.³⁷ In a nitrogen glove box, a 20 mL scintillation vial was filled with CuI (91.9 mg, 0.48 mmol) 3,4,7,8-tetramethyl-1,10-phenanthroline (228 mg, 0.95 mmol), Cs_2CO_3 (5.58 g, 28.9 mmol), and 4-iodo-2,6-diisopropylaniline^{4a} (2.93 g, 9.65 mmol). The vial was sealed with a rubber septum, removed from the glove box then evacuated and backfilled with Argon three times. Toluene (5 mL) was added and the mixture was stirred at 80 °C for 20 minutes. Methanol (869 mg, 28.9 mmol) was added and the rubber septum was quickly replaced with a vial cap. The reaction was stirred for 24 hours at 80 °C then cooled to room temperature, filtered through a silica gel plug and flushed with 150 mL of ethyl acetate. The resulting solution was reduced in vacuo and purified via silica gel flash chromatography with 10% ethyl acetate in hexanes to yield **4-(methoxy)-2,6-diisopropylaniline** (1.83 g, 91%) as a blue oil. $R_f = 0.28$ (20 % ethyl acetate in hexanes). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 1.32 (d, $J = 6.5$ Hz, 12H), 3.01 (quint $J = 7.5$ Hz, 2H), 3.50 (s, 2H), 3.82 (s, 3H), 6.70 (s, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ (ppm) 152.9, 134.4, 134.0, 108.8, 55.7, 28.3, 22.6. IR (cm^{-1}): 3459, 3382, 2961, 2871, 2832, 2361, 1600, 1466, 1435, 1383, 1348, 1311, 1242, 1219, 1172, 1123, 1103, 1042, 939, 865, 760, 669. HRMS (ESI) m/z calcd. for $\text{C}_{13}\text{H}_{22}\text{NO}$ $[\text{M}+\text{H}]^+$ 208.1701, found 208.1700.

Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene))bis(4-methoxy-2,6-dimethylaniline) (L3)



L5

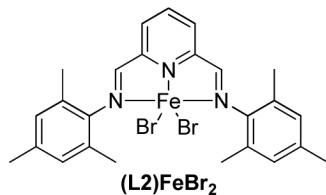
L3 was prepared from the similar literature procedure³⁶ with 4-methoxy-2,6-methyl aniline (1.54 g, 10.2 mmol) and 2,6-pyridinedicarboxaldehyde (673 mg, 4.98 mmol) and 10 drops of glacial acetic acid in 15 mL 100% ethanol. The reaction was stirred overnight at room temperature. The mixture was then cooled to 0 °C, filtered and rinsed with cold 100%

ethanol to yield **L3** (1.9 g, 95 %) as a yellow solid. $R_f = 0.37$ (20 % ethyl acetate in hexanes). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ (ppm) 2.21, (s, 12H), 3.81 (s, 6H), 6.67 (s, 4H), 7.97 (t, $J = 7.8$ Hz, 1H), 8.37–8.40 (m, 4H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ (ppm) 163.4, 156.4, 154.8, 143.9, 137.4, 128.8, 122.8, 113.7, 55.53, 19.0. MP 190 °C. IR (cm^{-1}): 3044, 2924, 2863, 2300, 1608, 1545, 1518, 1491, 1459, 1421, 1388, 1263, 1226, 1157, 1034, 996, 948, 879, 818, 736, 638, 573, 516. HRMS (ESI) m/z calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 402.2182, found 402.2189.

Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene))bis(4-(benzyloxy)-2,6-diisopropylaniline) (L5)

L5 was prepared from the similar literature procedure³⁶ with 4-N methoxy-2,6-diisopropylaniline (807 mg, 3.89 mmol) and 2,6-N N pyridinedicarboxaldehyde (263 mg, 1.95 mmol) and 5 drops of MeO OMe glacial acetic acid in 5 mL 100% ethanol. The reaction was stirred overnight at room temperature. The mixture was then cooled to 0 °C, filtered and rinsed with cold 100% ethanol to yield **L3** (891 mg, 89 %) as a yellow solid. $R_f = 0.61$ (20 % ethyl acetate in hexanes). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ (ppm) 1.20 (d, $J = 6.7$ Hz, 24H), 3.03 (quint, $J = 6.9$ Hz, 4H), 3.85 (s, 6H), 6.74 (s, 4H), 7.99 (t, $J = 7.8$ Hz, 1H), 8.36–8.40 (m, 4H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ (ppm) 163.4, 157.0, 154.7, 142.1, 139.1, 137.5, 122.8, 108.8, 55.5, 28.4, 23.7. MP 181 °C. IR (cm^{-1}): 3046, 2961, 2871, 2836, 1638, 1601, 1582, 1462, 1383, 1327, 1289, 1238, 1198, 1169, 1125, 1107, 1076, 1039, 990, 942, 866, 763, 739, 625, 526. HRMS (ESI) m/z calcd. for $\text{C}_{33}\text{H}_{44}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 514.3434, found 514.3441.

Synthesis of (L2)FeBr₂



Adapted from the literature procedure.^{19b} In a nitrogen filled glove box, **L2 N** (109 mg, 5.1×10^{-1} mmol), FeBr_2 (111 mg, 5.1×10^{-1} mmol), and 3.0 mL of THF were combined in a vial and stirred at room temperature overnight. Pentane was added to the mixture creating a green precipitate. This green solid was filtered and rinsed with pentane then dried *in vacuo* yielding a dark green solid (299.3 mg, >99 %). A crystal suitable for x-ray analysis was grown from slow diffusion of pentane into a solution of **(L2)FeBr₂** in THF. Elemental Analysis calculated: C, 51.31 H, 4.65 N, 7.18 found: C, 51.59 H, 4.88 N, 7.19.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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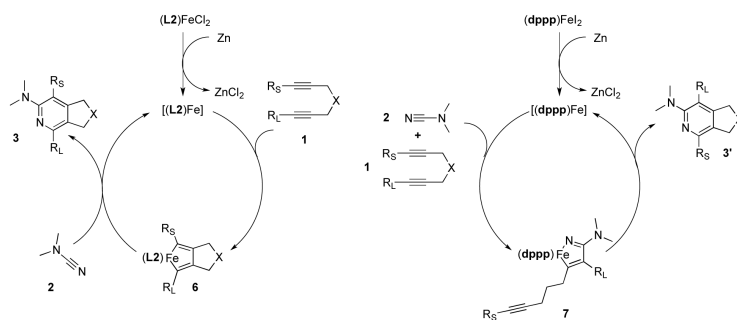
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Scheme 1.
Proposed mechanism.

Table 1

Fe-catalyzed cycloaddition of diynes and cyanamides

a, b

entry	diyne	cyanamide	product	yield	entry	diyne	cyanamide	product	yield
1 ^c				93	9				97
				90	10				35
2				65	11				70
3				NR					
4				NR					
5 ^d				NR					
				84	12				95
6				84					
7 ^b				84					
				80	13 ^f				67
8				80					
				80	14				69

^a 5 mol % FeCl₂, 10 mol % **L2**, 10 mol % Zn dust, diyne (0.4 M), cyanamide (0.48 M), benzene, 70 °C.

^b 3 h slow addition of diyne unless otherwise noted.

^c TS = *p*-toluenesulfonyl.

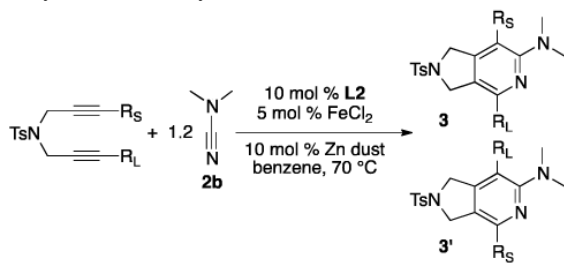
^d TMS = trimethylsilyl.

^e 5 h slow addition of substrate.

^f 10 mol % FeCl₂, 20 mol % **L2**, 20 mol % Zn dust.

Table 2

Unsymmetrical Diynes



entry	substrate	product	yield ^a (3 : 3') ^b
1	1i , $R_S = \text{H}$, $R_L = \text{Me}$	3o	72(85:15)
2	1j , $R_S = \text{Me}$, $R_L = \text{tBu}$	3p	80(86:14)
3	1k , $R_S = \text{Me}$, $R_L = \text{Ph}$	3q	67(88:12)

^aYields reported as a combination of both regioisomers.

^bProduct ratios determined by $^1\text{H NMR}$