JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

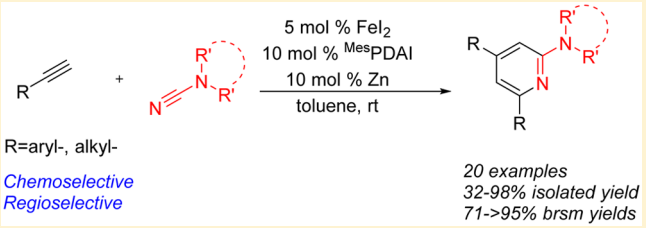
Regioselective Iron-Catalyzed [2 + 2 + 2] Cycloaddition Reaction Forming 4,6-Disubstituted 2-Aminopyridines from Terminal Alkynes and Cyanamides

Nathan A. Spahn, Minh H. Nguyen, Jonas Renner, Timothy K. Lane, and Janis Louie*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States

Supporting Information

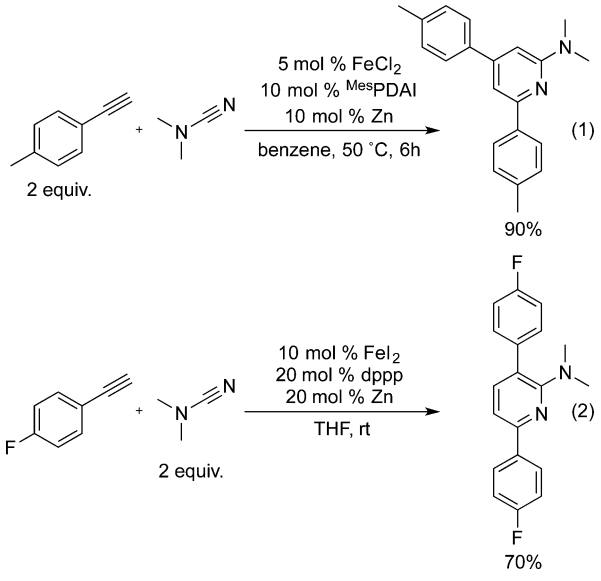
ABSTRACT: Iron complexes bound by redox-active pyridine dialdimine (PDAI) ligands catalyze the cycloaddition of two terminal alkynes and one cyanamide. The reaction is both chemo- and regioselective, as only 4,6-disubstituted 2-aminopyridine products are formed in moderate to high yields. Isolation of an iron azametallacycle (**4**) suggests that catalyst deactivation occurs with a large excess of cyanamide over longer reaction times. Fe-catalyzed cycloaddition allowed for a straightforward synthesis of a variety of aminopyridines, including known estrogen receptor ligands.



INTRODUCTION

Metal-catalyzed [2 + 2 + 2] cycloaddition reactions represent a powerful synthetic tool for the construction of cyclic aromatic compounds in a single step.[1−6] Indeed, a variety of substituted aromatic compounds including benzenes,[7−9] pyridines,[4,5,10−15] pyrimidines,[16] and pyranones[17−19] have been prepared through the use of transition-metal catalysts based on Ru,[14,20,21] Rh,[22,23] Co,[24−28] Ir,[29−31] Mo,[32] Ni,[13,15,19] Ti,[33] Pd,[34−36] and Fe.[10−12,16,37−42] Of these metals, Co, Ni, and Fe are particularly interesting because of their lower cost and wide availability. Despite the utility of this transformation, almost all examples require the use of tethered π systems, typically in the form of a diyne, due to the inherent difficulties in controlling both chemo- and regioselectivity. This is particularly true for synthetic strategies that convert two alkynes and a nitrile into pyridine products, as alkynes are inherently more reactive than nitrile substrates.[20,26,40−42] Furthermore, when terminal alkynes are coupled with a nitrile in a [2 + 2 + 2] cycloaddition, four different pyridine regioisomers and two benzene isomers are possible, as well as other alkyne oligomers. For example, Rh-catalyzed cycloaddition of two terminal alkynes and cyanamides, an activated nitrile, produced a 1.3:1 mixture of 4,6- and 3,6-disubstituted 2-aminopyridines.[23] Similarly, equal amounts of 3,6- and 4,6-disubstituted 2-aminopyridine products were formed in $CoCp(CO)_2$-catalyzed cycloadditions.[26] Some recent metal-free reports of regioselective [2 + 2 + 2] cycloaddition reactions coupling ynamides and nitriles to give the corresponding pyridines in high yields have been reported.[43,44] Nevertheless, the development of a more general chemo- and regioselective cycloaddition method for pyridine formation would represent a significant synthetic advance.

Our laboratory recently developed a $Ni(COD)_2$/SIPr (SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidene) system that successfully catalyzes the cycloaddition reaction of terminal alkynes and cyanamides to provide the 3,5-disubstituted 2-aminopyridine regioisomer as the major product with reasonable regiocontrol.[15] Additionally, two isolated reports of intermolecular Fe-catalyzed cycloaddition demonstrate that chemo- and regioselective cycloadditions between alkynes and nitriles may be possible (eqs 1 and 2).[11,12] Interestingly, these two Fe systems



suggest that the regioselectivity may be controlled by the choice of ligand. As such, we sought to define the generality of our chemo- and regioselective three-component methodology catalyzed by

Received: September 28, 2016
Published: November 17, 2016

DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234−242

^{Mes}PDAI-bound (^{Mes}PDAI = (1*E*,1′*E*)-1,1′-(pyridine-2,6-diyl)-bis(*N*-mesitylmethanimine) Fe complexes. Herein, we report reaction conditions that afford 4,6-disubstituted 2-aminopyridine products regioselectively.

RESULTS AND DISCUSSION

We initially focused on establishing a general cycloaddition protocol on the basis of our Fe/PDAI system (eq 1) using alkyne **1a** and cyanamide **2a** as model substrates (Table 2). Many [2 + 2 + 2] cycloaddition reactions that couple two alkynes and a nitrile yield substituted benzenes as common side products. Thus, we initially ran reactions with excess cyanamide **2a**. However, increasing the amount of cyanamide had no effect on the yield of pyridine product **3aa** or reduction in the amount of alkyne trimers formed.[45,46] Instead, increased amounts of cyanamide led to the formation of complex **4**, an iron azametallacycle incorporating two cyanamides, over long reaction times. It is important to note that only trace amounts of complex **4** are obtained after the first 1 h. An ORTEP diagram of complex **4** is shown in Figure 1, and selected bond lengths are shown in Table 1.

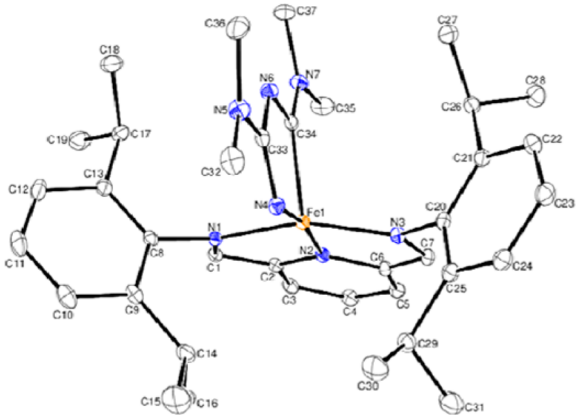


Figure 1. ORTEP diagram of (^{iPr}PDAI)Fe(NCNMe$_2$)$_2$ (**4**).

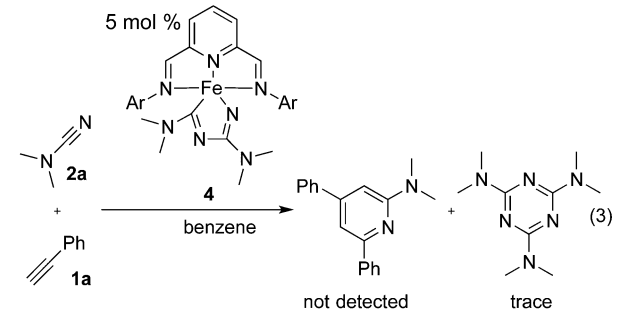
Table 1. Comparison of Selected Bond Lengths (Å) for (^{iPr}PDAI)Fe(NCNMe$_2$)$_2$ and (^{iPr}PDAI)Fe(DMAP)[47]

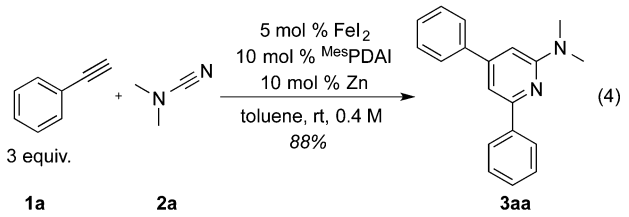
	(^{iPr}PDAI)Fe(NCNMe$_2$)$_2$	(^{iPr}PDAI)Fe(DMAP)[a]
N_{imine}–C_{imine}	1.334(2), 1.242(2)	1.339(3), 1.355(3)
C_{imine}–C_{ipso}	1.416(2), 1.407(3)	1.407(4), 1.406(4)
C_{ipso}–N_{py}	1.383(2), 1.389(2)	1.379(3), 1.373(3)
Fe_{cycle}–N_{cycle}	1.9684(15)	
Fe_{cycle}–C_{cycle}	1.9956(17)	

[a]Data taken from ref 47.

Interestingly, complex **4** shares important ligand bond lengths with an (^{iPr}PDAI)Fe(DMAP) complex developed by Chirik and co-workers,[47] which suggests that the complex possesses a radical dianionic ligand and an iron(IV) center. The geometry of complex **4** is a distorted square pyramid with the four iron-bound nitrogen atoms slightly out of the square plane with iron and the axial carbon offset toward the azametallacycle nitrogen. Complex **4** represents the only example of an isolated iron azametallacycle.

When alkyne **1a** and cyanamide **2a** were subjected to catalytic amounts of complex **4**, only trace hexamethyl-1,3,5-triazine-2,4,6-triamine was observed along with unreacted starting materials (eq 3). As such, we believe complex **4** is a catalyst sink, and large amounts of cyanamide relative to Fe catalyst must be avoided to reduce formation of azametallacycle **4**.





In contrast, increasing the amount of alkyne relative to cyanamide successfully increased the yield of pyridine products. Three equivalents of alkyne led to greater consumption of cyanamide, while further amounts of alkyne failed to increase the pyridine yields (eq 4). We also determined that zinc serves as a reductant for the iron halide precatalyst. That is, when **1a** and **2a** were combined with 5 mol % (^{Mes}PDAI)Fe(C_4H_6)[47] in the absence of zinc, **3aa** was obtained in an isolated yield of 80%. Nevertheless, we felt our optimized cycloaddition protocol with in situ formation of the Fe catalyst in the presence of zinc would be more practical and employed these conditions for a variety of alkynes and cyanamides (Table 2). The iron system is effective at coupling both aryl- and alkyl-substituted alkynes, which is a marked improvement over our Ni/IPr system that preferentially reacts with alkyl-substituted alkynes.[15] The substitution patterns of the pyridine regioisomers were easily determined by 1D-NOESY NMR spectroscopy (see the Supporting Information). Yields in parentheses are adjusted relative to unreacted cyanamide. The unreacted cyanamide suggests that alkyne trimerization rates are comparable to the rate of cyclization between alkyne and cyanamide, resulting in alkyne consumption prior to complete cyanamide conversion. Aryl alkynes reacted with dimethyl cyanamide **1a** to exclusively afford 4,6-aminopyridine products in high yields (Table 2, entries 1–6). Ortho substitution (**1c**) on the aryl alkyne did not affect the product yield. However, no conversion was observed when a doubly ortho substituted aryl alkyne such as 2,4,6-trimethylphenylacetylene was used as the cycloaddition partner. Both electron-donating and electron-withdrawing groups on the aryl ring were tolerated (entries 4 and 5), though slightly lower yields were obtained with electron-withdrawing substituents. Although low-valent Fe complexes are known to activate aryl halides,[48,49] both 4-fluoro-1-ethynylbenzene and 4-chloro-1-ethynylbenzene were amenable substrates (entries 5 and 6). Not surprisingly, high yields of 2-aminopyridine products were obtained when diethyl cyanamide **2b** and pyrrolidine-1-carbonitrile **2c** were used (entries 7 and 8). Interestingly, lower yields were obtained when six-membered cyanamides, such as piperidine-1-carbonitrile **2d** and morpholine-4-carbonitrile **2e**, were used as coupling partners. Cyanamides possessing easily removable groups, such as allyl (**2f**) and benzyl (**2g**), were also successfully converted to pyridine products (entries 11 and 12). However, attempts at using other protected cyanamides, such as *tert*-butyl carbamate and *N*-tosyl cyanamide, did not yield pyridine product, which is

DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234–242

Table 2. Iron-Catalyzed [2 + 2 + 2] Cycloaddition of Terminal Alkynes and Cyanamides

Entry	Alkyne	Cyanamide	Product	Yield(%)[c]
1[a]	R=H, R'=H **1a**	**2a**	R=H, R'=H **3aa**	88 (93)
2[a]	R=Me, R'=H **1b**	**2a**	R=Me, R'=H **3ba**	82 (83)
3[a]	R=H, R'=Me **1c**	**2a**	R=H, R'=Me **3ca**	89
4[a]	R=OMe, R'=H **1d**	**2a**	R=OMe, R'=H **3da**	98
5[a]	R=F, R'=H **1e**	**2a**	R=F, R'=H **3ea**	69 (91)
6[a]	R=Cl, R'=H **1f**	**2a**	R=Cl, R'=H **3fa**	62 (82)
7[a]	**1a**	**2b**	**3ab**	70 (>95)
8[a]	**1a**	**2c**	**3ac**	86 (87)
9[a]	**1a**	R=CH_2 **2d**	R=CH_2 **3ad**	44 (83)
10[a]	**1a**	R=O **2e**	R=O **3ae**	48 (>95)
11[a]	**1a**	R=allyl **2f**	R=allyl **3af**	32 (71)
12[a]	**1a**	R=Bn **2g**	R=Bn **3ag**	78(82)
13[b]	R=CH_2CH_3 **1g**	**2a**	R=CH_2CH_3 **3ga**	55 (92)
14[b]	R=OTBS **1h**	**2a**	R=OTBS **3ha**	83 (89)
15[b]	R=CH_2OTBS **1i**	**2a**	R=CH_2OTBS **3ia**	69 (>95)
16[c]	R=CH_2Ph **1j**	**2a**	R=CH_2Ph **3ja**	59 (>95)
17[b]	**1k**	**2a**	**3ka**	60 (89)
18[b]	**1l**	**2a**	**3la**	54 (76)
19[b]	**1m**	**2a**	**3ma**	69 (>95)

[a]Conditions: 5 mol % of FeI_2, 10 mol % of ^{Mes}PDAI, 10 mol % of Zn, 3 equiv of alkyne, 0.4 M cyanamide, toluene, room temperature. [b]Conditions: 5 mol % of FeI_2, 10 mol % of ^{Mes}PDAI, 10 mol % of Zn, 3 equiv of alkyne added dropwise over 3 h, 0.4 M cyanamide, toluene, room temperature. [c]Isolated yields, with brsm yields in parentheses.

likely due to lower electron density at the nitrile nitrogen. In addition, when acetonitrile was used instead of cyanamide, only alkyne oligomers were observed.

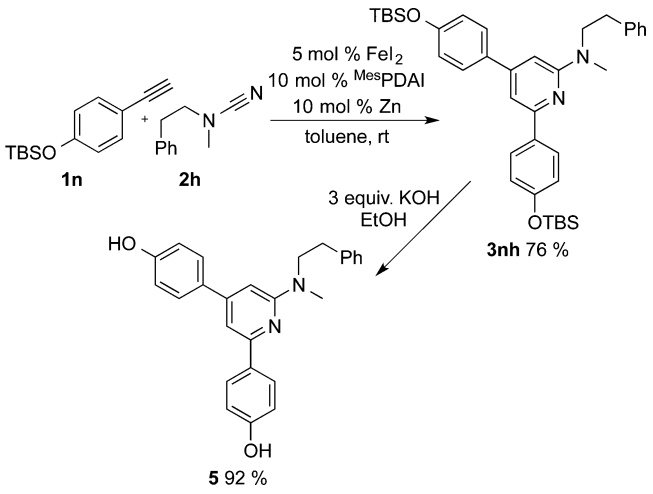
Unlike our Ni system which preferentially converted alkyl alkynes over aryl alkynes, the Fe/PDAI combination effectively catalyzes the cycloaddition of both aryl alkynes and alkyl alkynes. For alkyl alkynes, slow addition of the alkyne over the course of 3 h ensured pyridine product formation over cyclotrimerization of alkyl alkynes. Catalyst deactivation through complex **4** does not occur because it does not appreciably form at shorter reaction times. Oxygen functional groups, such as protected alcohols **1h**, **1i**, and alkynes possessing a distal aromatic group (**1j**) were successfully employed in the cycloaddition reaction to yield the corresponding 2-aminopyridines in good yields (Table 2, entries 14−16). Pyridine products were also formed from the use of trimethylsilyl-protected acetylene (entry 17) and ethynylcyclopropane (entry 18). The use of propargyl chloride as a coupling partner shut down the cycloaddition, which is likely due to irreversible oxidation of the Fe catalyst. Adding substitution at the 3-position of the terminal alkynes and using methyl propiolate afforded only alkyne oligomers, despite slow addition of the alkyne. To our surprise, sulfur-containing 3-ethynylthiophene **1m** was also converted to pyridine product, despite iron's propensity to bind sulfur compounds (entry 19).[50]

4,6-Diaryl-2-aminopyridine pyridines are known estrogen receptor ligands for both the α and β receptor proteins (ERα and ERβ).[51] We believed that we could apply our Fe-catalyzed cycloaddition methodology to construct the pyridine core of one of these compounds in a single step. Thus, we subjected *tert*-butyl(4-ethynylphenoxy)dimethylsilane and *N*-methyl-*N*-phenethylcyanamide to the standard cycloaddition conditions, and, gratifyingly, the corresponding protected estrogen receptor was isolated in 76% yield (Scheme 1). After deprotection with KOH, the estrogen receptor ligand was isolated in 70% overall yield over two steps. This Fe-catalyzed cycloaddition protocol is a marked improvement over the previous synthetic pathway, which is a four-step process with an overall yield of 35%.[51]

In conclusion, we have presented a general [2 + 2 + 2] cycloaddition that exhibits unprecedented exclusive selectivity for 4,6-disubstituted 2-aminopyridines. The reaction is synthetically practical and tolerant of both aryl- and alkyl-substituted alkynes as well as a variety of functional groups. Additional experiments are being conducted to determine selectivity for mixed pyridine products when two different terminal alkynes are employed. In addition, the regioselective Fe-catalyzed cycloaddition protocol

DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234−242

Scheme 1. Fe-Catalyzed Cycloaddition Approach to an Estrogen Receptor Ligand



was used to prepare known estrogen substitutes and ligands for the ERα and ERβ proteins. The mechanism of this catalyst system and the origin of the regioselectivity are currently being explored by our laboratory.

EXPERIMENTAL SECTION

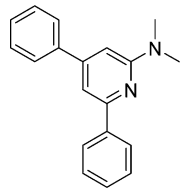
General Experimental Considerations. All reactions were conducted in a N_2-filled glovebox unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. FeI_2 was purchased from Sigma-Aldrich and used without further purification. ^{Mes}PDAI was synthesized via literature methods.[11] All alkynes and cyanamides were purchased from commercial sources. Liquid cyanamides and alkynes were degassed using three sequential freeze−pump−thaw cycles. ^{1}H and ^{13}C nuclear magnetic resonance spectra of pure compounds were acquired at 400 and 101 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.26 ppm for ^{1}H and to the center line of a triplet at 77.0 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, quartet, and quintet, respectively. All ^{13}C NMR spectra were proton decoupled. Preparatory TLC was performed on silica gel TLC plates 60 F256 from Merck. IR spectra were obtained using a Bruker Tensor 27 spectrometer on KBr disks. Calculated HRMS data were obtained from ChemDraw software.

Method A. In a nitrogen-filled glovebox, a 2 mL vial was charged with iron iodide (0.05 equiv) and MesPDAI ((1*E*,1′*E*)-1,1′-(pyridine-2,6-diyl)bis(*N*-mesitylmethanimine)) (0.10 equiv) and toluene to bring the final molarity to 0.4 M. The catalyst solution was stirred for 20 min, at which time cyanamide (1 equiv) was added. The reaction mixture was stirred for 5 min before zinc (0.1 equiv) was added. The reaction mixture was stirred for another 5 min, and alkyne (3 equiv) was added. The reaction mixture was stirred overnight, and the crude reaction mixture was passed through a Celite plug. The product was isolated by preparatory TLC.

Method B. In a nitrogen-filled glovebox, a 2 mL vial was charged with iron iodide (0.05 equiv) and MesPDAI ((1*E*,1′*E*)-1,1′-(pyridine-2,6-diyl)bis(*N*-mesitylmethanimine)) (0.10 equiv) and toluene to bring the final molarity to 0.4 M. The catalyst solution was stirred for 20 min, at which time cyanamide (1 equiv) was added. The reaction mixture was stirred for 5 min before zinc (0.1 equiv) was added. The reaction mixture was stirred for another 5 min, and alkyne (3 equiv) was added by syringe pump over 3 h. The reaction mixture was stirred overnight, and the crude reaction mixture was passed through a Celite plug. The product was isolated by preparatory TLC.

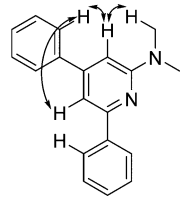
Synthesis of Complex 4. In a nitrogen-filled glovebox, a vial was charged with (^{iPr}PDAI)$FeBr_2$ (1 equiv., 100 mg, 0.15 mmol) and 0.25 mL of toluene, and a stir bar was placed in the vial. Cyanamide **1a** (10 equiv, 121 μL, 1.5 mmol) was added to the vial, and the resulting reaction mixture was stirred for 30 min. Sodium mercury amalgam or zinc (2.5 equiv) was placed in the vial, and the reaction mixture was stirred overnight. The resulting solution was passed through Celite, and residual reactant in the reaction vial was dissolved with THF and also passed through Celite. All solvents were removed in vacuo. Pentane was added to the residue, and the heterogeneous solution was again passed through Celite. Pentane was allowed to slowly evaporate at room temperature to give green crystals of complex **4**.

Synthesis of *N*,*N*-Dimethyl-4,6-diphenylpyridin-2-amine (3aa).

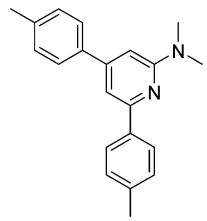


Method A for the cycloaddition was used with iron iodide (2.8 mg, 0.0091 mmol), ^{Mes}PDAI (6.7 mg, 0.0182 mmol), alkyne **1a** (60 μL, 0.546 mmol), and cyanamide **2a** (14.8 μL, 0.182 mmol). The product was isolated by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.6) in 88% (43.9 mg) yield of pyridine **3aa** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 7.5 Hz, 2H), 7.70 (d, J = 7.3 Hz, 2H) 7.52−7.39 (m, 6H), 7.29 (s, 1H), 6.68 (s, 1H), 3.25 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 155.5, 150.6, 140.3, 140.2, 128.8, 128.5, 128.4, 127.1, 126.9 (2C), 107.2, 102.5, 38.1. IR (cm^{-1}): 3059, 3035, 2925, 2853, 1598, 1547, 1499, 1250, 1183. HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2$ $[M + H]^+$ 275.1543, found 275.1541.

1D NOESY Relationships.

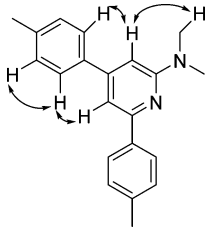


Synthesis of *N*,*N*-Dimethyl-4,6-di-*p*-tolylpyridin-2-amine (3ba).[11]



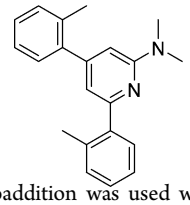
Method A for the cycloaddition reaction was used with iron iodide (2.5 mg, 0.00825 mmol), ^{Mes}PDAI (6.1 mg, 0.0165 mmol), alkyne **1b** (62.8 μL, 0.495 mmol), and cyanamide **2a** (13.4 μL, 0.165 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.6) in 82% (41.0 mg) yield of pyridine **3ba** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 7.8 Hz, 2H), 7.57 (d, J = 7.7 Hz, 2H), 7.25−7.23 (m, 5H), 6.61 (s, 1H), 3.20 (s, 6H), 2.41 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 155.5, 138.3, 137.5, 137.4, 129.5, 129.1, 126.9, 126.7, 106.8, 101.9, 38.1, 21.3, 21.2. IR (cm^{-1}): 3027, 2922, 2858, 2803, 1600, 1545, 1512, 1417, 1401, 1182. HRMS (ESI): m/z calcd for $C_{21}H_{23}N_2$ $[M + H]^+$ 303.1856, found 303.1863.

1D NOESY Relationships.



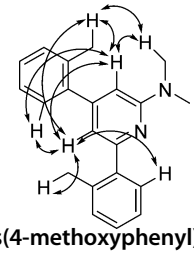
DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234−242

Synthesis of *N,N*-Dimethyl-4,6-di-*o*-tolylpyridin-2-amine (3ca).

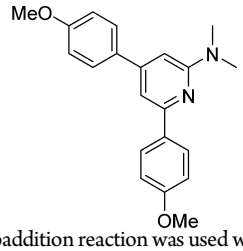


Method A for the cycloaddition was used with iron iodide (2.5 mg, 0.00825 mmol), ^{Mes}PDAI (6.1 mg, 0.0165 mmol), alkyne **1c** (62.4 μL, 0.495 mmol), and cyanamide **2a** (13.4 μL, 0.165 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.6) in 89% (44.5 mg) yield of pyridine **3ca** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, J = 5.3, 1.8 Hz, 1H) 7.47−7.22 (m, 7H), 6.70 (s, 1H), 6.44 (s, 1H), 3.18 (s, 6H), 2.54 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 157.7, 151.1, 141.2, 140.9, 136.1, 135.1, 130.7, 130.4, 129.7, 129.1, 127.74, 127.71, 125.8, 125.6, 113.1, 104.0, 38.1, 20.9, 20.4. IR (cm^{-1}): 3060, 3019, 2924, 2855, 1595, 1574, 1547, 1497, 1401, 1379, 1122. HRMS (ESI): m/z calcd for $C_{21}H_{22}N_2$ $[M + H]^+$ 303.1856, found 303.1861.

1D NOESY Relationships.

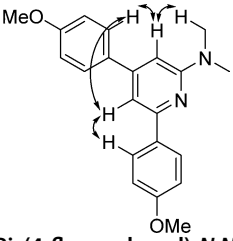


Synthesis of 4,6-Bis(4-methoxyphenyl)-*N,N*-dimethylpyridin-2-amine (3da).

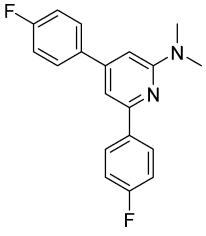


Method A for the cycloaddition reaction was used with iron iodide (2.3 mg, 0.0075 mmol), ^{Mes}PDAI (5.5 mg, 0.015 mmol), alkyne **1d** (58.4 μL, 0.450 mmol), and cyanamide **2a** (12.2 μL, 0.150 mmol). The product was isolated by preparatory TLC (10% ethyl acetate and hexanes, R_f = 0.6) in 98% (49.0 mg) yield of pyridine **3da** as a yellow solid. Mp: 122−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.8 Hz, 2H), 7.67−7.60 (m, 2H), 7.19 (s, 1H), 7.05−6.96 (m, 4H), 6.59 (s, 1H), 3.97 (s, 6H), 3.22 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.1, 160.0, 159.6, 155.2, 150.1, 133.0, 132.8, 128.2, 128.1, 114.2, 113.7, 106.2, 101.3, 55.34, 55.29, 38.1. IR (cm^{-1}): 3027, 2922, 2855, 1601, 1546, 1513, 1417, 1400, 1183. HRMS (ESI): m/z calcd for $C_{21}H_{22}N_2O_2$ $[M + H]^+$ 335.1754, found 335.1758.

1D NOESY Relationships.

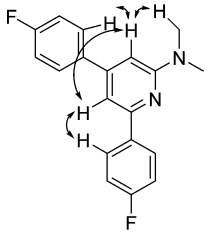


Synthesis of 4,6-Bis(4-fluorophenyl)-*N,N*-dimethylpyridin-2-amine (3ea).[12]

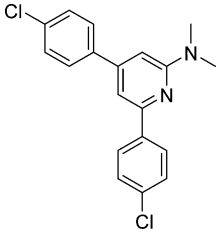


Method A for the cycloaddition reaction was used with iron iodide (2.5 mg, 0.00805 mmol), ^{Mes}PDAI (5.9 mg, 0.0161 mmol), alkyne **1e** (55.4 μL, 0.483 mmol), and cyanamide **2a** (13.1 μL, 0.161 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.5) in 69% (34.5 mg) yield of pyridine **3ea** as a white solid. Mp: 128−129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16−8.03 (m, 2H), 7.73−7.58 (m, 2H), 7.24−7.07 (m, 5H), 6.58 (s, 1H), 3.22 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3 (J_{C-F} = 246.0 Hz), 163.1 (J_{C-F} = 246.0 Hz), 159.5, 154.6, 149.7, 136.3 (J_{C-F} = 3.3 Hz), 136.2 (J_{C-F} = 3.0 Hz), 128.8 (J_{C-F} = 8.2 Hz), 128.6 (J_{C-F} = 8.2 Hz), 115.7 (J_{C-F} = 21.5 Hz), 115.3 (J_{C-F} = 21.5 Hz), 106.6, 102.2, 38.1. IR (cm^{-1}): 3068, 2926, 2854, 1607, 1550, 1508, 1399, 1294, 1185, 1156. HRMS (ESI): m/z calcd for $C_{19}H_{16}F_2N_2$ $[M + H]^+$ 311.1354, found 311.1358.

1D NOESY Relationships.

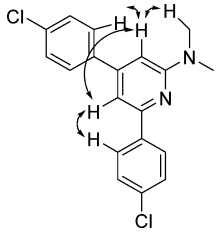


Synthesis of 4,6-Bis(4-chlorophenyl)-*N,N*-dimethylpyridin-2-amine (3fa).

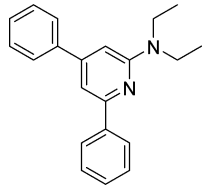


Method A for the cycloaddition reaction was used with iron iodide (2.3 mg, 0.0073 mg), ^{Mes}PDAI (5.4 mg, 0.0146 mmol), alkyne **1f** (59.8 mg, 0.438 mmol), and cyanamide **2a** (11.9 μL, 0.146 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.4) in 62% (31.0 mg) yield of pyridine **3fa** as a white solid. Mp: 157−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.45−7.50 (m, 4H), 7.15 (s, 1H), 6.59 (s, 1H), 3.22 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 154.5, 149.5, 138.5, 138.4, 134.6, 134.5, 129.0, 128.6, 128.4, 128.1, 106.6, 102.4, 38.1. IR (cm^{-1}): 2924, 2852, 1603, 1546, 1490, 1417, 1396. HRMS (ESI): m/z calcd for $C_{19}H_{16}Cl_2N_2$ $[M + H]^+$ 343.0763, found 343.0771.

1D NOESY Relationships.



Synthesis of *N,N*-Diethyl-4,6-diphenylpyridin-2-amine (3ab).[52]

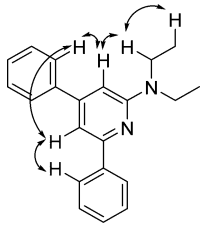


Method A for the cycloaddition was used with iron iodide (2.8 mg, 0.0090 mmol), ^{Mes}PDAI (6.7 mg, 0.0180 mmol), alkyne **1a** (59.3 μL, 0.540 mmol), and cyanamide **2b** (20.9 μL, 0.180 mmol). The product was isolated by preparatory TLC (5% ethyl acetate in hexanes, R_f = 0.6) in 70% (35.0 mg) yield of pyridine **3ab** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15−8.07 (m, 2H), 7.71−7.64 (m, 2H), 7.52−740

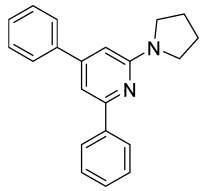
DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234−242

(m, 6H), 7.22 (s, 1H), 6.60 (s, 1H), 3.68 (q, J = 7.0 Hz, 4H), 1.29 (t, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7, 155.7, 150.6, 140.6, 140.4, 131.3, 128.8, 128.4, 128.3, 127.1, 126.8, 106.7, 102.2, 42.7, 13.2. IR (cm^{-1}): 2959, 2923, 2852, 1596, 1511, 1482, 1452, 1440, 1287. HRMS (ESI): m/z calcd for $C_{21}H_{22}N_2$ $[M + H]^+$ 303.1856, found 303.1857.

1D NOESY Relationships.

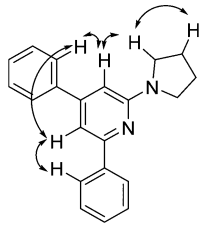


Synthesis of 2,4-Diphenyl-6-(pyrrolidin-1-yl)pyridine (3ac).[52]

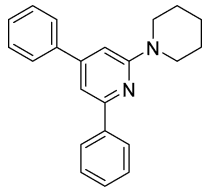


Method A for the cycloaddition was used with iron iodide (2.6 mg, 0.00825 mmol), ^{Mes}PDAI (7.0 mg, 0.0165 mmol), alkyne **1a** (54.3 μL, 0.495 mmol), and cyanamide **2c** (16.6 μL, 0.165 mmol). The product was isolated by preparatory TLC (10% ethyl acetate in hexanes) in 87% (43.5 mg) yield of pyridine **3ac** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15−8.06 (m, 2H), 7.72−7.64 (m, 2H), 7.54−7.33 (m, 6H) 7.24 (d, J = 1.0 Hz, 1H), 6.51 (s, 1H), 3.63 (t, J = 6.5 Hz, 4H), 2.06 (t, J = 6.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7, 155.9, 150.3, 140.3 (2C), 128.8, 128.41, 128.39, 128.36, 127.1, 126.9, 106.9, 103.0, 46.8, 25.6. IR (cm^{-1}): 3060, 2925, 2855, 1605, 1542, 1453, 1385, 1271. HRMS (ESI): m/z calcd for $C_{21}H_{20}N_2$ $[M + H]^+$ 301.1699, found 301.1698.

1D NOESY Relationships.

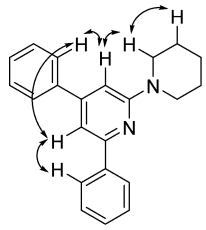


Synthesis of 2,4-Diphenyl-6-(piperidin-1-yl)pyridine (3ad).[52]

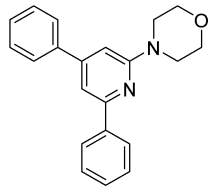


Method A for the cycloaddition was used with iron iodide (3.4 mg, 0.0079 mmol), ^{Mes}PDAI (5.8 mg, 0.0159 mmol), alkyne **1a** (52.3 μL, 0.477 mmol), and cyanamide **2d** (18.4 μL, 0.159 mmol). The product was isolatd by preparatory TLC (5% ethyl acetate in hexanes, R_f = 0.6) in 83% (41.5 mg) yield of pyridine **3ad** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dt, J = 8.3, 1.8 Hz, 2H), 7.71−7.62 (m, 2H), 7.53−7.34 (m, 6H), 7.37 (s, 1H), 6.80 (s, 1H) 3.71 (t, J = 5.6 Hz, 4H), 1.74−1.68 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.9, 155.7, 140.3, 140.2, 128.8, 128.5, 128.4, 127.1, 126.9 (2C), 108.1, 103.8, 46.4, 25.6, 24.9. IR (cm^{-1}): 3060, 2931, 2852, 1595, 1545, 1495, 1447, 1243. HRMS (ESI): calcd for $C_{22}H_{22}N_2$ $[M + H]^+$ 315.1856, found 315.1856.

1D NOESY Relationships.

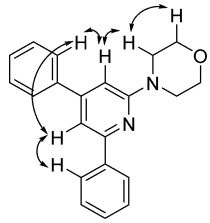


Synthesis of 4-(4,6-Diphenylpyridin-2-yl)morpholine (3ae).[52]

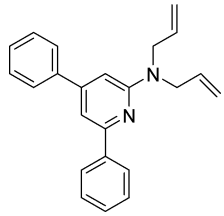


Method A for the cycloaddition was used with iron iodide (2.4 mg, 0.0079 mmol), ^{Mes}PDAI (5.8 mg, 0.0158 mmol), alkyne **1a** (52.0 μL, 0.474 mmol), and cyanamide **2e** (16.0 μL, 0.158 mmol). The product was isolated by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.3) in 48% (24.0 mg) yield of pyridine **3ae** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 7.4 Hz, 2H), 7.66 (d, J = 7.2 Hz, 2H), 7.54−7.35 (m, 7H), 3.90 (t, J = 4.0 Hz, 4H) 3.69 (t, J = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.8, 155.8, 151.2, 139.9, 139.8, 128.9, 128.7, 128.6, 128.5, 127.1, 126.9, 109.4, 103.6, 66.9, 45.8. IR (cm^{-1}): 3061, 2961, 2921, 2852, 1595, 1546, 1497, 1447, 1425, 1238. HRMS (ESI): m/z calcd for $C_{21}H_{20}N_2O$ $[M + H]^+$ 317.1648, found 317.1649.

1D NOESY Relationships.

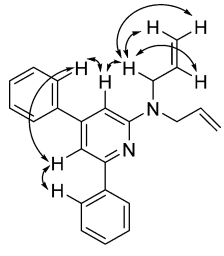


Synthesis of *N,N*-Diallyl-4,6-diphenylpyridin-2-amine (3af).



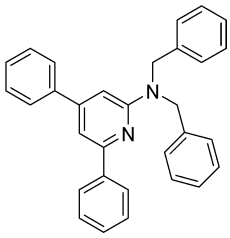
Method A for the cycloaddition was used with iron iodide (2.8 mg, 0.0090 mmol), ^{Mes}PDAI (6.7 mg, 0.0180 mmol), alkyne **1a** (59.3 μL, 0.540 mmol), and cyanamide **2f** (24.4 μL, 0.180 mmol). The product was isolated by preparatory TLC (5% ethyl acetate in hexanes, R_f = 0.6) in 32% (16.0 mg) yield of pyridine **3af** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, J = 5.3, 3.3 Hz, 2H), 7.68−7.62 (m, 2H), 7.52−7.34 (m, 8H), 7.28 (d, J = 1.0 Hz, 1H) 6.62 (d, J = 1.0 Hz, 1H), 5.97 (ddt, J = 17.1, 10.4, 5.3 Hz, 2H), 5.33−5.15 (m, 4H), 4.28 (d, 4.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_2$): δ 158.2, 155.5, 150.7, 140.3, 140.1, 134.4, 128.8, 128.5, 128.4, 127.1, 126.8 (2C), 116.2, 107.5, 102.9, 50.4. IR (cm^{-1}): 3061, 3034, 2979, 2922, 2853, 1596, 1546, 1480, 1223. HRMS (ESI): m/z calcd for $C_{23}H_{22}N_2$ $[M + H]^+$ 327.1856, found 327.1851.

1D NOESY Relationships.



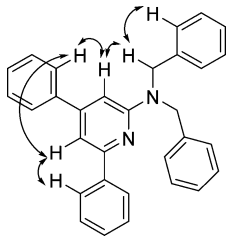
DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234−242

Synthesis of *N*,*N*-Dibenzyl-4,6-diphenylpyridin-2-amine (3ag).

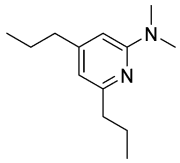


Method A for the cycloaddition was used with iron iodide (2.8 mg, 0.0090 mmol), ^{Mes}PDAI (6.7 mg, 0.0180 mmol), alkyne **1a** (59.3 μL, 0.540 mmol), and cyanamide **2g** (40 mg, 0.180 mmol). The product was isolated by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.6) in 78% (39.0 mg) yield of pyridine **3ag** as a yellow-green solid. Mp: 106−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17−8.09 (m, 2H), 7.61−7.54 (m, 2H), 7.49−7.36 (m, 15H), 7.34−7.28 (m, 2H), 6.68 (s, 1H), 4.99 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8, 155.5, 151.0, 140.0, 139.9, 138.8, 128.8, 128.6, 128.4, 128.2, 128.1, 127.3, 127.1, 126.9, 126.8, 107.9, 102.6, 51.1. IR (cm^{-1}): 3084, 3061, 3030, 2919, 2855, 1596, 1547, 1496, 1480, 1450, 1361, 1221. HRMS (ESI): *m*/*z* calcd for $C_{31}H_{26}N_2$[M + H]$^+$ 427.2169, found 427.2171.

1D NOESY Relationships.

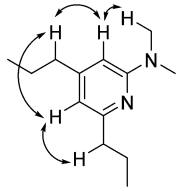


Synthesis of *N*,*N*-Dimethyl-4,6-dipropylpyridin-2-amine (3ga).[15]

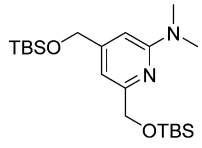


Method B for the cycloaddition reaction was used with iron iodide (3.7 mg, 0.0121 mmol), ^{Mes}PDAI (9 mg, 0.0242 mmol), alkyne **1g** (49.5 mg, 0.726 mmol), and cyanamide **2a** (17.0 mg, 0.242 mmol). The crude product was isolated by preparatory TLC (5% ethyl acetate in hexanes, R_f = 0.4) in 55% (27.5 mg) yield of pyridine **3ga** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (s, 1H), 6.15 (s, 1H), 3.06 (s, 6H), 2.58 (t, *J* = 8 Hz, 2H), 2.46 (t, *J* = 8 Hz, 2H), 1.81−1.55 (m, 4H), 0.98−0.92 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.1, 159.5, 152.5, 111.2, 102.6, 40.4, 38.0, 37.9, 23.7, 22.6, 14.0, 13.9. IR (cm^{-1}): 2959, 2930, 2871, 1604, 1564, 1498, 1420, 1185. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{22}N_2$ [M + H]$^+$ 207.1856, found 207.1862.

1D NOESY Relationships.

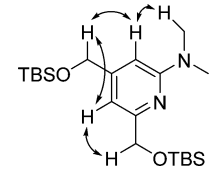


Synthesis of 4,6-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-dimethylpyridin-2-amine (3ha).[15]

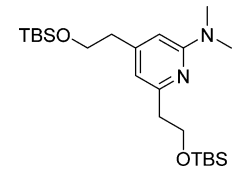


Method B for the cycloaddition reaction was used with iron iodide (2.8 mg, 0.00915 mmol), ^{Mes}PDAI (6.8 mg, 0.083 mmol), alkyne **1h** (111.3 μL, 0.459 mmol), and cyanamide **2a** (14.9 μL, 0.183 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.6) in 83% (62.3 mg) yield of pyridine **3ha** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.43 (s, 1H), 4.68 (s, 4H), 3.07 (s, 6H), 0.96 (s, 9H), 0.97 (s, 9H), 0.12 (s, 6H), 0.11 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1, 159.0, 104.9, 100.7, 66.3, 64.3, 38.1, 26.0, 25.9, 18.43, 18.37, −5.31 (2C). IR (cm^{-1}): 2955, 2929, 2857, 1610, 1569, 1501, 1471, 1421, 1391, 1255, 1147, 1107. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{42}N_2O_2Si_2$ [M + H]$^+$ 411.2858, found 411.2864.

1D NOESY Relationships.

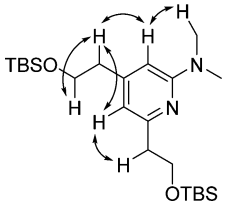


Synthesis of 4,6-Bis(2-(((*tert*-butyldimethylsilyl)oxy)ethyl)-*N*,*N*-dimethylpyridin-2-amine (3ia).[15]

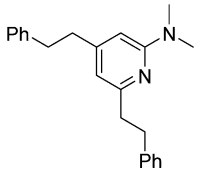


Method B for the cycloaddition reaction was used with iron iodide (2.6 mg, 0.00855 mmol), ^{Mes}PDAI (6.3 mg, 0.0171 mmol), alkyne **1i** (105.9 μL, 0.513 mmol), and cyanamide **2a** (13.9 μL, 0.171 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.6) in 69% (51.8 mg) yield of pyridine **3ia** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (s, 1H), 6.20 (s, 1H), 3.96 (t, *J* = 7.1 Hz, 2H), 3.78 (t, *J* = 7.0 Hz, 2H), 3.05 (s, 6H), 2.82 (t, *J* = 7.1 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 0.88 (s, 9H), 0.87 (s, 9H), 0.01 (s, 6H), 0.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 156.9, 149.1, 112.6, 103.8, 63.7, 63.2, 41.8, 39.4, 38.0, 26.0, 25.9, 18.33, 18.29, −5.33, −5.37. IR (cm^{-1}): 2955, 2930, 2886, 2858, 1607, 1564, 1472, 1421, 1389, 1255, 1099. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{46}N_2O_2Si_2$ [M + H]$^+$ 439.3171, found 439.3175.

1D NOESY Relationships.



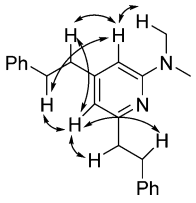
Synthesis of *N*,*N*-Dimethyl-4,6-diphenethylpyridin-2-amine (3ja).[15]



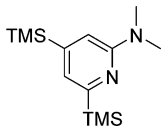
Method B for the cycloaddition was used with iron iodide (2.3 mg, 0.0076 mmol), ^{Mes}PDAI (5.6 mg, 0.0151 mmol), alkyne **1j** (63.7 μL, 0.453 mmol), and cyanamide **2a** (12.3 μL, 0.151 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.6) in 59% (29.5 mg) yield of pyridine **3ja** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.2 (m, 10H), 6.29 (s, 1H), 6.16 (s, 1H), 3.10−3.07 (m, 8H), 2.89−2.98 (m, 4H), 2.81 (dd, *J* = 10.0, 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.5, 159.2, 151.7, 142.5, 141.5, 128.5, 128.4, 128.3, 128.2, 125.9, 125.6, 111.1, 102.9, 40.0, 38.0, 37.7, 36.9, 35.5. IR (cm^{-1}): 3084, 3062, 3026, 2924, 2857, 1603, 1563, 1496, 1454, 1419, 1192. HRMS (ESI): *m*/*z* calcd for $C_{23}H_{26}N_2$ [M + H]$^+$ 331.2169, found 331.2174.

DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234−242

1D NOESY Relationships.

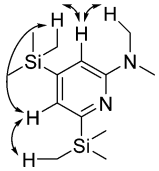


Synthesis of *N,N*-Dimethyl-4,6-bis(trimethylsilyl)pyridin-2-amine (3ka).

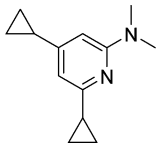


Method B for the cycloaddition was used with iron iodide (2.9 mg, 0.0094 mmol), ^{Mes}PDAI (6.9 mg, 0.0188 mmol), alkyne **1k** (79.7 μL, 0.564 mmol), and cyanamide **2a** (15.3 μL, 0.188 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.5) in 60% (30.0 mg) yield of pyridine **3ka** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.57 (s, 1H), 3.11 (s, 6H), 0.29 (s, 9H), 0.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.1, 157.9, 148.0, 121.0, 109.5, 37.8, −1.5, −1.7. IR (cm^{-1}): 2956, 2898, 2855, 2802, 1574, 1520, 1486, 1396, 1334, 1248, 1184. HRMS (ESI): *m/z* calcd for $C_{13}H_{26}N_2Si_2$ $[M + H]^+$ 267.1707, found 267.1712.

1D NOESY Relationships.

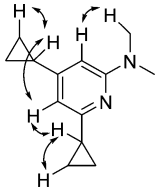


Synthesis of 4,6-Dicyclopropyl-*N,N*-dimethylpyridin-2-amine (3la).[15]

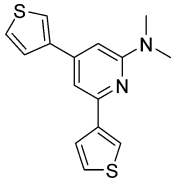


Method B for the cycloaddition was used with iron iodide (3.9 mg, 0.0124 mmol), ^{Mes}PDAI (9.1 mg, 0.247 mmol), alkyne **1l** (62.7 μL, 0.741 mmol), and cyanamide **2a** (20.1 μL, 0.247 mmol). The crude product was purified by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.6) in 54% (27.0 mg) yield of pyridine **3la** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 1H), 6.02 (s, 1H), 3.01 (s, 6H), 1.88−1.79 (m, 1H), 1.79−1.71 (m, 1H), 1.04−0.91 (m, 4H), 0.85−0.78 (m, 2H), 0.78−0.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.3, 159.4, 154.2, 106.3, 99.6, 37.8, 16.9, 15.3, 9.3, 8.7. IR (cm^{-1}): 3085, 3005, 2927, 2856, 2801, 1603, 1561, 1498, 1422, 1400, 1177. HRMS (ESI): *m/z* calcd for $C_{13}H_{18}N_2$ $[M + H]^+$ 203.1543, found 203.1551.

1D NOESY Relationships.

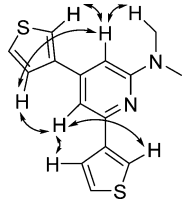


Synthesis of *N,N*-Dimethyl-4,6-bis(thiophen-3-yl)pyridin-2-amine (3ma).

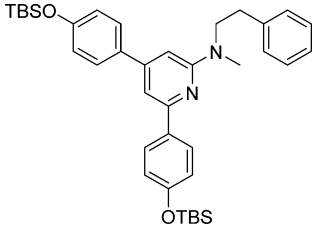


Method B for the cycloaddition was used with iron iodide (2.7 mg, 0.00875 mmol), ^{Mes}PDAI (6.5 mg, 0.0175 mmol), alkyne **1m** (51.7 μL, 0.525 mmol), and cyanamide **2a** (14.2 μL, 0.175 mmol). The product was isolated by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.5) in 69% (34.5 mg) yield of pyridine **3ma** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 3.0, 0.9 Hz, 1H), 7.71 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.71 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.62 (dd, *J* = 2.8, 1.2 Hz, 1H) 7.50−7.33 (m, 3H), 7.13 (s, 1H), 6.61 (s, 1H), 3.20 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 151.9, 144.7, 143.2, 141.3, 126.40, 126.35, 126.2, 125.6, 122.9, 122.1, 106.4, 101.3, 38.0. IR (cm^{-1}): 3102, 2924, 2852, 2801, 1603, 1554, 1526, 1418, 1186, 1173. HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_2S_2$ $[M + H]^+$ 287.0671, found 287.0677.

1D NOESY Relationships.

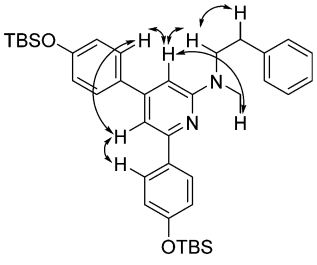


Synthesis of 4,6-Bis(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-*N*-methyl-N-phenethylpyridin-2-amine (3nh).

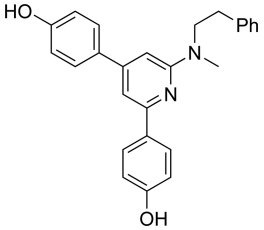


Method A for the cycloaddition was used with iron iodide (1.2 mg, 0.0040 mmol), ^{Mes}PDAI (3.0 mg, 0.008 mmol), *tert*-butyl(4-ethynylphenoxy)dimethylsilane (55.8 mg, 0.240 mmol), and *N*-methyl-*N*-phenethylcyanamide (12.8 mg, 0.08 mmol). The product was isolated by preparatory TLC (10% ethyl acetate in hexanes, R_f = 0.5) in 76% (38 mg) yield of pyridine **3nh** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.27−7.10 (m, 6H), 6.88−6.83 (m, 4H), 6.45 (s, 1H), 3.84 (t, *J* = 7.5 Hz, 2H), 3.03 (s, 3H), 2.92 (t, *J* = 7.5 Hz, 2H), 0.95 (s, 18H), 0.18−0.17 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 156.3, 156.2, 155.2, 150.2, 140.2, 133.6, 133.4, 128.9, 128.4, 128.1, 128.0, 126.1, 120.3, 120.0, 106.2, 101.2, 52.6, 36.9, 33.8, 29.7, 25.72, 25.69, 18.3, 4.4 (2C). IR (cm^{-1}): 2955, 2929, 2857, 1604, 1545, 1510, 1264, 1168. HRMS (ESI): *m/z* calcd for $C_{38}H_{52}N_2O_2Si_2$ $[M + H]^+$ 625.3640, found 625.3646.

1D NOESY Relationships.



Synthesis of 4,4′-(6-(Methyl(phenethyl)amino)pyridine-2,4-diyl)diphenol (5).[51]



A 2 mL vial was charged with 4,6-bis(4-((*tert*-butyldimethylsilyl)oxy)-phenyl)-*N*-methyl-*N*-phenethylpyridin-2-amine (39 mg, 0.03 mmol),

DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234−242

potassium hydroxide (10.6 mg, 0.189 mmol), and ethanol (0.5 mL), with a magnetic stir bar. The reaction mixture was stirred for 4 h and filtered through Celite. Solvent was removed in vacuo, and the crude product was purified by preparatory TLC (50% ethyl acetate in hexanes, R_f = 0.5) to give 92% (35.9 mg) yield of deprotected pyridine **5** as a green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.45−7.30 (m,6H), 7.06−6.99 (m, 4H) 6.63 (s, 1H), 4.02 (t, J = 8 Hz), 3.22 (s, 3H), 3.10 (t, J = 8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.5, 156.1, 156.0, 155.2, 150.1, 140.1, 133.1, 133.0, 128.9, 128.5, 128.4, 128.3, 126.1, 115.7, 115.3, 106.1, 101.2, 52.6, 36.9, 33.8. IR (cm^{-1}): 3368 (br), 3084, 3064, 3026, 2928, 1603, 1545, 1513, 1453, 1233, 1172. HRMS (ESI): m/z calcd for $C_{26}H_{24}N_2O_2$ $[M + H]^+$ 397.1916, found 397.1918.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02374.

Experimental details, characterization data, X-ray crystallographic data, and spectra (PDF)
Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for J.L.: louie@chem.utah.edu.

ORCID

Janis Louie: 0000-0003-3569-1967

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Institutes of Health (GM076125) for financial support. We also thank James G. Muller and Dr. Atta M. Arif of the University of Utah for providing HRMS and for X-ray analysis of compound **4**, respectively.

■ REFERENCES

(1) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787−3802.
(2) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741−4767.
(3) Chopade, P. R.; Louie. *Adv. Synth. Catal.* **2006**, *348*, 2307−2327.
(4) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085−1094.
(5) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, *6*, 1317−1323.
(6) Varela, J. A.; Saá, C. *Synlett* **2008**, 2571−2578.
(7) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830−2834.
(8) Ardizzoia, G. A.; Brenna, S.; LaMonica, G.; Maspero, A.; Masciochi, N. *J. Organomet. Chem.* **2002**, *649*, 173−180.
(9) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835−2841.
(10) D'Souza, B. R.; Lane, T. K.; Louie, J. *Org. Lett.* **2011**, *13*, 2936−2939.
(11) Lane, T. K.; D'Souza, B. R.; Louie, J. *J. Org. Chem.* **2012**, *77*, 7555−7563.
(12) Wang, C.; Wang, D.; Xu, F.; Pan, B.; Wan, B. *J. Org. Chem.* **2013**, *78*, 3065−3072.
(13) Stolley, R. M.; Maczka, M. T.; Louie, J. *Eur. J. Org. Chem.* **2011**, 3815−3824.
(14) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **2003**, *68*, 8595−8598.
(15) Zhong, Y.; Spahn, N. A.; Stolley, R. M.; Minh, H. N.; Louie, J. *Synlett* **2015**, *26*, 307−312.
(16) Lane, T. K.; Nguyen, M. H.; D'Souza, R. B.; Spahn, N. A.; Louie, J. *Chem. Commun.* **2013**, *49*, 7735−7737.
(17) Inoue, T.; Itoh, Y.; Kazama, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3329.
(18) Tsuda, T.; Sumiya, R.; Saegusa, T. *Synth. Commun.* **1987**, *17*, 147.
(19) Tsuda, T.; Morikawa, S.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 3140−3145.
(20) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem. - Eur. J.* **2006**, *12*, 5618−5631.
(21) Xu, F.; Wang, C.; Li, X.; Wan, B. *ChemSusChem* **2012**, *5*, 854−857.
(22) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917−3922.
(23) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Mol. Catal.* **1987**, *40*, 337−357.
(24) Diversi, P.; Ingrosso, G.; Lucherini, A.; Malquori, S. *J. Mol. Catal.* **1987**, *40*, 267−280.
(25) Sugiyama, Y.; Okamoto, S. *Synthesis* **2011**, 2247−2254.
(26) Boñaga, L. V. R.; Zhang, H.; Maryanoff, B. E. *Chem. Commun.* **2004**, 2394−2395.
(27) Weding, N.; Jackstell, R.; Jiao, H.; Spannenberg, A.; Hapke, M. *Adv. Synth. Catal.* **2011**, *353*, 3423−3433.
(28) Thiel, I.; Jiao, H.; Spannenberg, A.; Hapke, M. *Chem. - Eur. J.* **2013**, *19*, 2548−2554.
(29) Auvinet, A.-L.; Michelet, V.; Ratovelomanana-Vidal, V. *Synthesis* **2013**, *45*, 2003−2008.
(30) Onodera, G.; Suto, M.; Takeuchi, R. *J. Org. Chem.* **2012**, *77*, 908−920.
(31) Hashimoto, T.; Okabe, A.; Mizuno, T.; Izawa, M.; Takeuchi, R. *Tetrahedron* **2014**, *70*, 8681−8689.
(32) Ardizzoia, G. A.; Brenna, S.; LaMonica, G.; Maspero, A.; Masciocchi, N. *J. Organomet. Chem.* **2002**, *649*, 173−180.
(33) Ozerov, O. V.; Ladipo, F. T.; Patrick, B. O. *J. Am. Chem. Soc.* **1999**, *121*, 7941−7942.
(34) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835−2941.
(35) Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* **2001**, *66*, 3627−3629.
(36) Radhakrishnan, K. V.; Yoshikawa, E.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 7533−7535.
(37) tom Dieck, H.; Diercks, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 1138−1146.
(38) Breschi, C.; Piparo, L.; Pertici, P.; Caporusso, A. M.; Vitulli, G. *J. Organomet. Chem.* **2000**, *607*, 57−63.
(39) Richard, V.; Ipouck, M.; Mérel, D. S.; Gaillard, S.; Whitby, R. J.; Witulski, B.; Renaud, J.-L. *Chem. Commun.* **2014**, *50*, 593−595.
(40) Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 7162−7166.
(41) Nakajima, K.; Liang, W.; Nishibayashi, Y. *Org. Lett.* **2016**, *18*, 5006−5009.
(42) Nakajima, K.; Takata, S.; Sakata, K.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 7597−7601.
(43) Zhang, J.; Zhang, Q.; Xia, B.; Wu, J.; Wang, X.-N.; Chang, J. *Org. Lett.* **2016**, *18*, 3390−3393.
(44) Wang, Y.; Song, L.-J.; Zhang, X.; Sun, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 9704−9708.
(45) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organomet. Chem.* **2006**, *691*, 3129−3136.
(46) Liu, Y.; Yan, X.; Yang, N.; Xi, C. *Catal. Commun.* **2011**, *12*, 489−492.
(47) Russell, S. K.; Milsmann, C.; Lobkovsky, E.; Weyhermüller, T.; Chirik, P. *Inorg. Chem.* **2011**, *50*, 3159−3169.
(48) Lefévre, G.; Jutand, A. *Chem. - Eur. J.* **2014**, *20*, 4796−4805.
(49) Huang, Y.; Moret, M.-E.; Gebbink, R. J. M. K. *Eur. J. Org. Chem.* **2014**, 3788−3793.
(50) Arabczyk, W.; Moszyński, D.; Narkiewicz, U.; Pelka, R.; Podsiadly, M. *Catal. Today* **2007**, *124*, 43−48.
(51) Henke, B. R.; Drewry, D. H.; Jones, S. A.; Stewart, E. L.; Weaver, S. L.; Wiethe, R. W. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1939−1942.
(52) Katritzky, A. R.; Belyakov, S. A.; Sorochinsky, A. E.; Henderson, S. A.; Chen, J. *J. Org. Chem.* **1997**, *62*, 6210−6214.

DOI: 10.1021/acs.joc.6b02374
J. Org. Chem. 2017, 82, 234−242