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Iron-Catalyzed Cycloaddition Reaction of Diynes and Cyanamides at Room Temperature

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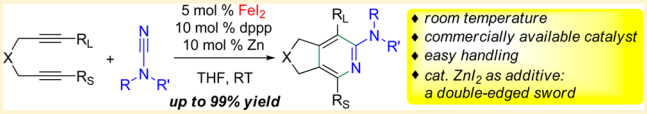
Supporting Information

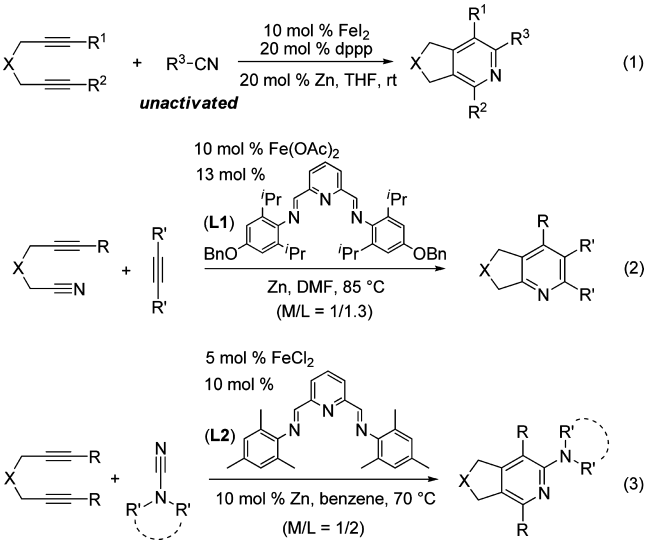
ABSTRACT: An iron-catalyzed [2 + 2 + 2] cycloaddition reaction of diynes and cyanamides at room temperature is reported. Highly substituted 2-aminopyridines were obtained in good to excellent yields with high regioselectivity. Insights toward the reaction process were investigated through in situ IR spectra and control experiments. In this iron-catalyzed cycloaddition reaction, the active iron species was generated only in the presence of both alkynes and nitriles. The lower reaction temperature, broad substrates scope, and inversed regioselectivity make it a complementary method to the previously developed iron catalytic system.



INTRODUCTION

Transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction of two molecular of alkynes and one molecular of nitrile is one of the most powerful methods to construct pyridine cores.[1] Compared with other traditional methods,[2] the cycloaddition reaction is extremely atom-efficient and can generate two C−C bonds and one C−N bond simultaneously in a single step. Simple modification on the substituents of the alkyne or nitrile moieties makes it possible to synthesize multisubstituted pyridines. However, despite numerous studies in this field,[3,4] only a few examples based on the iron catalysis have been reported.[5]

Iron is generally regarded as a cheap, benign, relatively nontoxic, and abundant metal compared with other late transition metals. Many transformations can be effectively promoted by iron catalysis.[6] Recently, we have reported a simple and efficient iron catalyst for the cycloaddition reaction of diynes and unactivated nitriles at room temperature (eq 1).[4a] The appropriate ligand as well as the metal/ligand ratio plays a crucial role on the reactivity. Preliminary results indicated that the formation of benzene byproducts[7] was strongly inhibited in the presence of nitriles, but a certain amount of nitrile and relatively long reaction time were necessary in our system. Independently, Louie and coworkers reported an iron-catalyzed cycloaddition reaction of alkynenitriles and alkynes using a similar strategy (eq 2).[8a] Later, they applied the catalyst system to the reaction of diynes and cyanamides with slight modification by increasing the metal/ligand ratio from 1:1.3 to 1:2 (eq 3).[8b] Reactions of diynes with unactivated nitriles under Louie's system afforded only trace amount of pyridine products.[8b] In contrast, cyanamides were good substrates for the formation of 2-aminopyridines where only 5 mol % catalyst and 1.2 equiv of cyanamide were required to afford the desired products in good yields.



Synthesis of 2-aminopyridines from [2 + 2 + 2] cycloaddition of alkynes and cyanamides has been reported as a part or a single example in most previous works, including the cobalt,[9] rhodium,[10] nickel,[3m] and titanium[11] catalytic systems and a photocatalytic system.[12] In contrast, systematic studies on the formation of 2-aminopyridines via cycloaddition reaction of alkynes with cyanamides have rarely been reported.[8b,13] Maryanoff and co-workers described the cycloaddition of diynes with cyanamides using $CpCo(CO)_2$ as a catalyst at high temperature (*ca.* 100 °C).[13a] More recently, Louie and coworkers developed a Ni/NHC-catalyzed system for the formation of 2-aminopyridines at room temperature[13b] and later reported a Fe/bis(aldimino)pyridine (**L2**) catalytic system.[8b] The 2-aminopyridine products were obtained in moderate to excellent yields in both cases. However, in the case of Ni, air-sensitive $Ni(COD)_2$ must be stored at −20 °C and can be easily decomposed. In the case of Fe, high reaction temperature was generally required, and benzene[14] was selected as solvent. Therefore, a milder and more environmentally benign method is desired.

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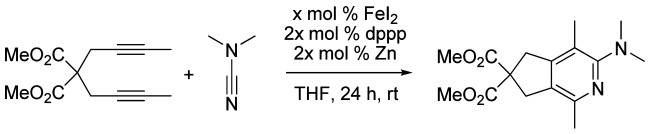
In the course of our study on the metal-catalyzed cycloaddition reactions,[4] we found that FeI_2/dppp/Zn is an efficient catalyst for the cycloaddition of diynes and unactivated nitriles to give pyridines.[4a] In view of the fact that the use of cyanamides instead of unactivated nitriles as coupling partners can show higher reactivity in the cycloaddition reaction, herein we report the iron-catalyzed [2 + 2 + 2] cycloaddition reaction of diynes and cyanamides *at room temperature* to afford 2-aminopyridines. The high reactivity of this catalyst allows the synthesis of 2-aminopyridines at ambient temperature with lower catalyst loading or without requiring a large excess of cyanamide. The use of commercial available iron salt and ligand makes this method more elegant.

RESULTS AND DISCUSSION

Initially, diyne **1a** and cyanamide **2a** were selected as the model substrates to screen reaction conditions. We were delighted to find that 2-aminopyridine **3a** was obtained in 99% yield (Table 1, entry 1) at room temperature using our previous developed catalytic system (10 mol % FeI_2, 20 mol % dppp, and 20 mol % Zn in THF). Reducing the catalyst loading and nitrile amount by half, the reaction took place smoothly without any loss of yield (entry 2). Further decreasing the nitrile amount to 2 equiv led to a lower but acceptable yield (83%, entry 3). This result suggested that an excess amount of nitrile was required to achieve satisfactory yield; however, this problem can be fixed by prolonging the reaction time to 36 h (97%, entry 4) or using higher catalyst loading (99%, entry 5). Considering that changing additive senquence by slow addition of diyne into cyanamide does not essentially alter the reactivity of catalyst, we tested the scope of the reaction under the following conditions without using the inconvenient syringe pump technique: 5 mol % catalyst, 5 equiv of cyanamide or 10 mol % catalyst, 2 equiv of cyanamide at room temperature for 24 h.

Table 1. Screening Reaction Conditions[a]



1a **2a** **3a**

entry	x	**2a** (equiv)	conv (%)[b]	yield (%)[b]
1	10	10	100	99
2	5	5	100	99
3	5	2	86	83
4[c]	5	2	100	97
5	10	2	100	99

[a]0.25 mmol **1a**, x mol % FeI_2, 2x mol % dppp, 2x mol % Zn, 1 mL THF, rt, 24 h [dppp = 1,3-bis(diphenylphosphino)propane]. [b]Determined by GC. Naphthalene was used as internal standard. [c]36 h.

Reactions of various diynes and cyanamides to give 2-aminopyridine derivatives were examined under the optimized reaction conditions above. The results are summarized in Table 2. Dialkylcyanamides **2a**−**2f** reacted efficiently with malonate backbone diyne **1a** to afford products in good to excellent yields (entries 1−6). Notably, cycloaddition of diethyl cyanamide **2e**, which was a problematic substrate in the previous iron system,[8b] successfully provided the product **3e** in good yield (entry 5). Specifically, the substrates diisopropylcyanamide **2f** and diallylcyanamide **2g**, completely unreactive toward cycloaddition in the previous nickel system,[13b] also gave the desired products (entries 6 and 7), albeit a lower yield of product **3g** was observed under 5 mol % catalyst. In addition to dialkylcyanamides, methylphenyl (**2h**) and dibenzyl (**2i**) substituted cyanamides were evaluated to produce 2-aminopyridines in excellent yields (entries 8 and 9). The reactions of various diynes with model cyanamide **2a** were also tested and afforded good to excellent yields. Diynes without a tertiary center on the tether chain furnished the corresponding 2-aminopyridines with good yields (entries 11 and 12); however, only trace amount of product **3l** was obtained in the presence of 5 mol % catalyst. In addition, the challenging terminal diyne **1e** gave 2-aminopyridine **3m** in good yield (entry 13). It is worth noting that the difficult substrate phenyl-substituted diyne (**1f**), which showed no reactivity in the previous iron system,[8b] was compatible with our catalytic system to give 2-aminopyridine **3n** in excellent yield (entry 14). Nevertheless, in accordance with previous work,[8b] TMS substituted diyne (**1g**) was completely unreactive (entry 15).

To further evaluate the reactivity of our catalytic system, unsymmetrical diynes were subjected to the cycloaddition reaction with 2 equiv of cyanamide **2a** (entries 16−18). Moderate to good yields were obtained in these cases. Nevertheless, slightly different from our previous results,[4a] the 2-aminopyridine product was not produced as a single regioisomer. For example, the reaction of Me, H substituted diyne **1h** and cyanamide **2a** afforded 2-aminopyridine **3p** as the major product in 67% yield with a 94:6 ratio of **3p**:**3p**′ (entry 16). This result may ascribe to the inherent electronic structure of cyanamides. A similar regioselectivity was observed in the reaction with NTs-based Ph, Me substituted diyne **1j**. (*Note*: malonate backbone Ph, Me substituted diyne provided a similar product ratio in 94% combined yield, but the two regioisomers failed to be separated due to the same polarity.) Interestingly, a bulkier TMS, Me substituted diyne **1i** gave the product as a single regioisomer (entry 17). In consistency with our previous observations,[4a] the larger alkyne substituent of the major product was placed ortho to the nitrile substituent. As demonstrated by the reaction of diyne **1j** and cyanamide **2a** under different catalytic systems in Louie's report,[8b] the contrast in regioselectivity between our system and their system showed an interesting example of ligand-dependent regioselectivity. Unfortunately, the reason is still unknown and will be a topic of further investigation.

In our previous work, we have shown that the intermolecular reaction of phenylacetylene and CH_3CN successfully took place to afford two regioisomers in a 66% combined yield with a 10:1 ratio, and no unwanted side products were detected.[4a] Following this avenue, the complete intermolecular [2 + 2 + 2] cycloaddition of monoyne **1k** and cyanamide **2a** was conducted under our system (eq 4) and Louie's system (eq 5), respectively. Different products (**3s** and **3t**) were obtained in comparable yields (70% versus 62%). This result suggested that these two iron-based systems may provide a complementary method to exclusively synthesize 2-amino-3,6-diaryl pyridines or 2-amino-4,6-diaryl pyridines from the same starting materials.

Regarding the mechanism, early studies indicate that Louie's system follows the mechanism of cobalt-catalyzed pyridine formation via a ferracyclopentadiene intermediate **4**, whereas our system follows the mechanism of nickel-catalyzed pyridine formation via an azaferracyclopentadiene intermediate **5**, as shown in Scheme 1.[8b] However, the real reaction process is completely a black box in these catalytic systems.[4a,8] To gain insight into the mechanism, we monitored the reaction of **1a** and **2a** (2 equiv) by using in situ IR spectra (Figure 1). Disappointedly, no intermediate

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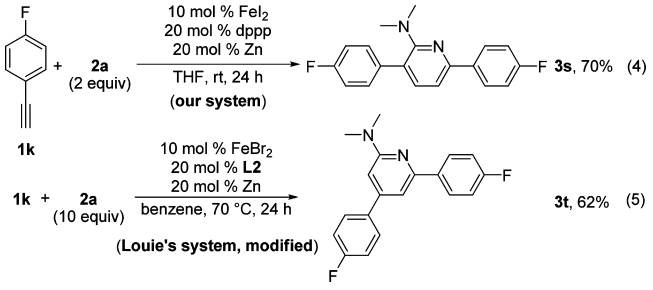
Table 2. Iron-Catalyzed Cycloaddition of Diynes and Cyanamides[a]

entry	diyne	cyanamide	product	yield (%)[b] A[c]	yield (%)[b] B[d]
1	**1a** X = $C(CO_2Me)_2$	**2a**	**3a**	92	88
2	**1a**	**2b**	**3b**	82	85
3	**1a**	**2c**	**3c**	86	96
4	**1a**	**2d**	**3d**	78	95
5	**1a**	**2e**	**3e**	76	83
6[e,f]	**1b**	**2f**	**3f**	83	91
7	**1a**	**2g**	**3g**	40	75
8	**1a**	**2h**	**3h**	91	99
9[f]	**1b**	**2i**	**3i**	98	90
10	**1b**	**2a**	**3j**	96	95
11	**1c**	**2a**	**3k**	81	78
12	**1d** X = $C(CO_2Me)_2$	**2a**	**3l**	trace	75
13	**1e**, $R^1 = R^2 = H$	**2a**	**3m**	70	73
14	**1f**, $R^1 = R^2 = Ph$	**2a**	**3n**	94	98
15[g]	**1g**, $R^1 = R^2 = TMS$	**2a**	**3o**	NR	NR
16	**1h**, $R^1 = Me$, $R^2 = H$	**2a**	**3p** (**3p'**: $R^1 = H$, $R^2 = Me$)	– 67%[h]	**3p/3p'** = 94/6[i]
17	**1i**, $R^1 = TMS$, $R^2 = Me$	**2a**	**3q**	– 59%[h]	**3q/3q'** = 100/0[i]
18	**1j**, X = NTs, $R^1 = Ph$, $R^2 = Me$	**2a**	**3r** (**3r'**: $R^1 = Me$, $R^2 = Ph$)	– 71%[h]	**3r/3r'** = 90/10[i]

[a]0.5 mmol diyne, 2 mL THF, rt, 24 h, with protocol A or protocol B. [b]Isolated yields. [c]Protocol A: 5 mol % FeI_2, 10 mol % dppp, 10 mol % Zn dust, 5 equiv of cyanamide. [d]Protocol B: 10 mol % FeI_2, 20 mol % dppp, 20 mol % Zn dust, 2 equiv of cyanamide. [e]Ts = *p*-toluenesulfonyl. [f]Cycloaddition of diyne **1a** with cyanamide **2f** or **2i** also reacted efficiently; however, the products were difficult to purify because of the similar polarity as the starting materials. [g]TMS = trimethylsilyl. [h]Isolated yield of the major product. [i]Product ratio (major/minor) determined by ^1H NMR or GC before separation.



was caught in our system during the reaction process. Instead, typical bands associated with C–O–C bond stretching vibration (1212 cm^{-1}) on diyne **1a** and C–N bond stretching vibration (1271 cm^{-1}) on 2-aminopyridine **3a** were observed (Figure 1, left). After careful investigation of this spectra, we found that almost no consumption of diyne **1a** was detected in the first 5 h (Figure 1, right, red line), and a new peak at 1271 cm^{-1} was gradually accumulated at very low speed (Figure 1, right, blue line). In the next 9 h, the peak at 1212 cm^{-1} decreased rapidly, and the peak at 1271 cm^{-1} was simultaneously formed. It seems that an induction period is required to initialize the reaction in the first few hours; this phenomenon promoted us to gain more detailed information about the reaction process.

Control experiments on the catalyst preparation were conducted. The model reaction of **1a** and **2a** (2 equiv) was tested in the presence of 10 mol % catalyst with different pretreatments. The standard catalyst was first stirred for 12 h and filtrated. Subsequently, diyne **1a** and cyanamide **2a** were added into the resulting solution (eq 6). To our surprise, no pyridine product was formed. Similarly, when diyne **1a** (eq 7) or cyanamide **2a** (eq 8) was separately added with catalyst before filtration, the same result was observed. In contrast, when diyne **1a** was divided into two portions (eq 9), 10 mol % of **1a** was added first with cyanamide **2a** and stirred for 8 h. After filtration, the rest 90 mol % of **1a** was added, and we were pleased to find that product **3a** was obtained in 18% yield. From these results, we hypothesized that the reduction process occurred only in the presence of both diyne and nitrile (Scheme 2). The direct reduction of precatalyst **6** to generate active species **8** by zinc dust was not operative, which did not agree with the previous assumption (Scheme 1).[8b] This result showed the first example

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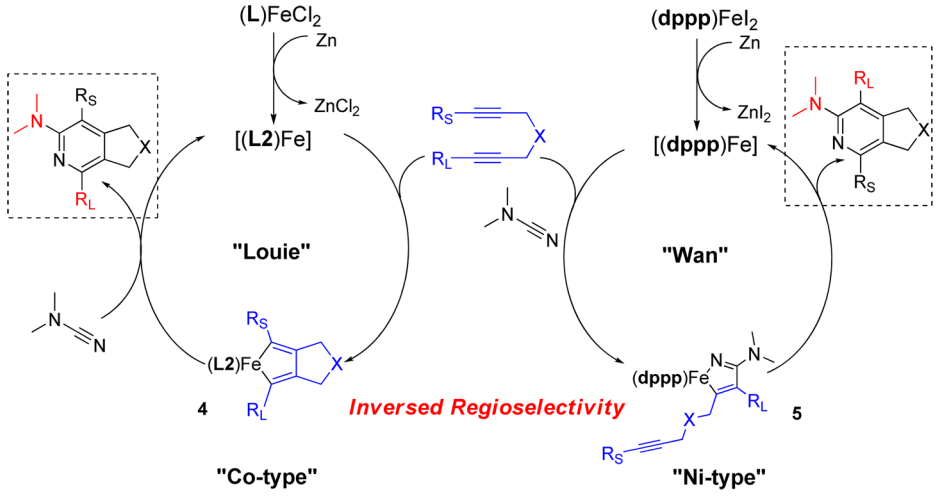
Scheme 1. Proposed Mechanism under Different Systems



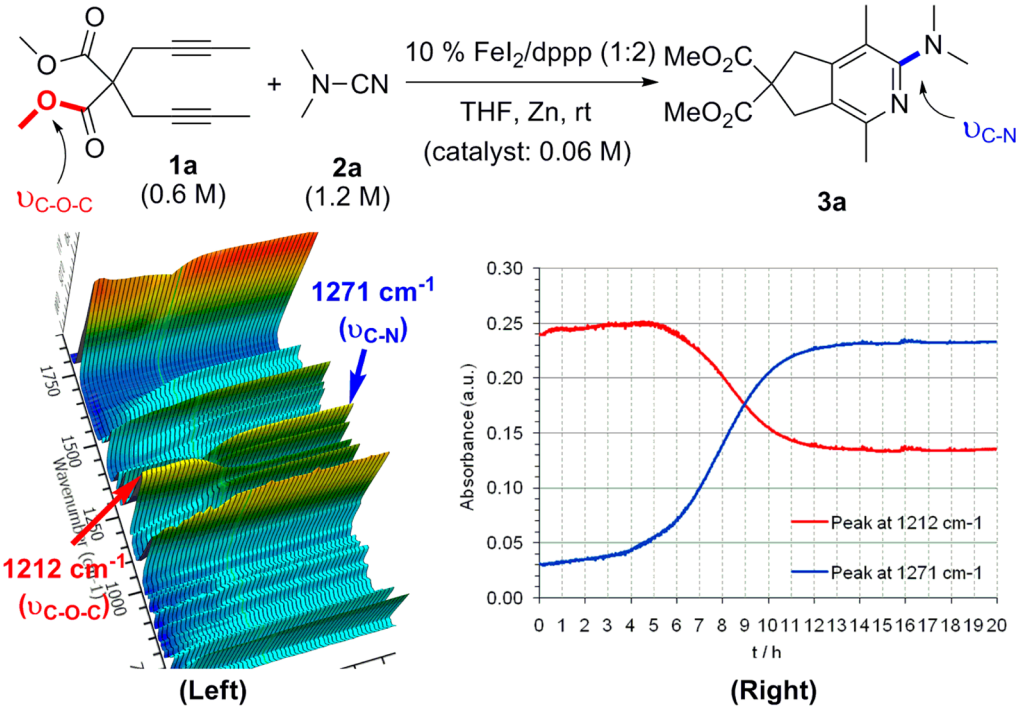
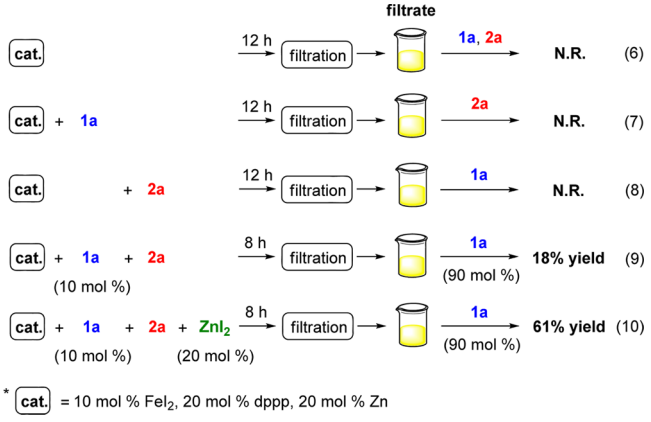


Figure 1. In situ IR spectra.



of substrate-participated active species generation in the metal-catalyzed [2 + 2 + 2] cycloaddition reactions, which may have been neglected for a long period of time in the previous studies of in situ generated catalysts.

Considering that ZnI_2 in situ generated from the reduction process is not only a spectator, we added 20 mol % of ZnI_2 into the reaction solution performed in eq 9 and surprisingly found that the yield of pyridine product was improved to 61% (eq 10, versus eq 9, 18%). This result indicated that ZnI_2 might act as a Lewis acid by activating the alkyne or nitrile moieties,[15] thus allowing the generation of active low-valent iron species to be much easier. This assumption was further supported by the reaction of **1d** and **2a** under 5 mol % catalyst. After adding 10 mol % of ZnI_2, 2-aminopyridine **3l** was obtained in 49% yield (eq 11).

Encouraged by this result, we proceeded to evaluate the reactivity in the presence of 5 mol % catalyst and 1.2 equiv of cyanamide with 10 mol % ZnI_2 as additive, as shown in Table 3. For those reactive cyanamides (e.g., **2a** and **2b**), the addition of ZnI_2 failed to show any beneficial effect on the product yield

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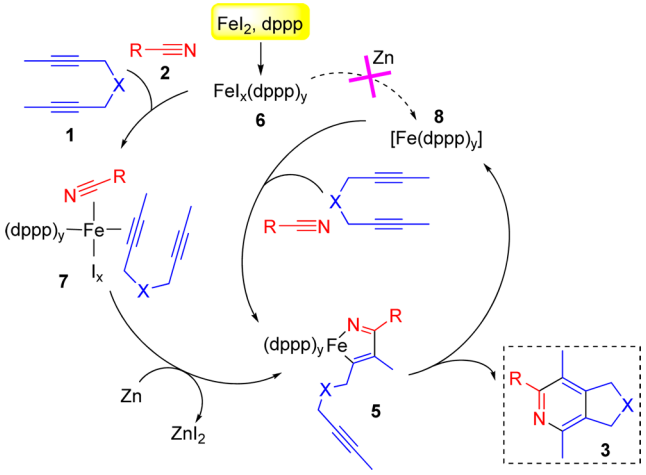
Scheme 2. Modified Mechanism



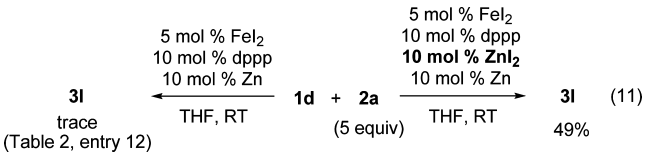
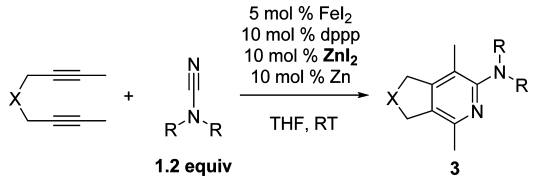


Table 3. Cycloaddition with 1.2 equiv of Cyanamide under 5 mol % Catalyst[a]



entry	diyne	cyanamide	product	yield (%)[b,c]	yield (%)[b]	lit. yield (%)[d]
1	**1a**	**2a**	**3a**	91	**84**	97
2	**1a**	**2b**	**3b**	88	**81**	90
3	**1a**	**2c**	**3c**	16	**79**	95
4	**1a**	**2d**	**3d**	6	**88**	67[e]
5	**1a**	**2e**	**3e**	9	**51**	35
6	**1a**	**2h**	**3h**	tr	**82**	70
7	**1b**	**2a**	**3j**	94	**82**	
8	**1c**	**2a**	**3k**	52	**73**	

[a]Reaction conditions: 0.5 mmol diyne, 5 mol % FeI_2, 10 mol % dppp, 10 mol % ZnI_2, 10 mol % Zn, 1.2 equiv of cyanamide, 2 mL THF, rt, 24 h. [b]Isolated yields. [c]Without adding 10 mol % ZnI_2 as additive. [d]Yield reported in ref 8b: 5 mol % catalyst, 1.2 equiv of cyanamide, 70 °C. [e]10 mol % catalyst.

(Table 3, entries 1, 2, and 7). On the contrary, slight decrease on the yield was observed, although 100% of diyne conversion was detected in these cases. This may ascribe to the diyne dimerization resulting from the activation of alkyne moieties by ZnI_2. For less reactive cyanamides (e.g., **2c**, **2d**, **2e**, and **2h**) or diyne (e.g., **1c**), the product yields were greatly improved after adding catalytic amount of ZnI_2 (Table 3, entries 3, 4, 5, 6, and 8). It seems that the catalytic amount of ZnI_2 acts as a double-edged sword in this cycloaddition reaction, improving the product yield while promoting the diyne dimerization. It is noteworthy that the yields obtained under the modified catalyst were comparable with the results of the previous iron catalytic system,[8b] but without using syringe pump technique or requiring high reaction temperature.

Although these data showed an important step forward, the modified mechanism is still far from its mature state. For example, the coordination mode of the substrates in intermediate **7** (Scheme 2), the role of ZnI_2, and the real reduction process are still unclear at this time and must await further study. Future work based on these points is currently underway.

CONCLUSIONS

In summary, we presented an efficient iron catalyst for the [2 + 2 + 2] cycloaddition reaction of alkynes and cyanamides to form 2-aminopyridines at room temperature with good to excellent yields. The regioselectivity as well as the broad substrates scope makes it a complementary method to the previous developed systems. Importantly, the presence of both alkynes and nitriles is the key to the generation of active iron species. Interestingly, the reactivity of the catalyst can be improved by adding a small amount of Lewis acid ZnI_2. We are currently expending this method to other cycloaddition reactions.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under an atmosphere of argon using standard Schlenk techniques or in an argon-filled glovebox unless otherwise noted. Column chromatography was carried out on silica gel (300−400 mesh) using a forced flow of eluent at 0.3−0.5 bar pressure. For TLC, silica gel GF254 was used and visualized by fluorescence quenching under UV light. THF was dried according to the standard procedure and was distilled prior to use. FeI_2 (99.99% purity) was purchased from Sigma Aldrich. Diynes were prepared according to literature procedures.[10,16] Cyanamides were also prepared according to literature procedures.[13b] Liquid cyanamides were degassed using three sequential freeze−pump−thaw cycles.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at 400, 100, and 377 MHz respectively. The chemical shifts for ^{1}H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard (7.26 ppm for $CDCl_3$ or 2.05 ppm for CD_3COCD_3). The chemical shifts for ^{13}C NMR were recorded in ppm downfield using the central peak of $CDCl_3$ (77.16 ppm) or CD_3COCD_3 (29.84 ppm) as the internal standard. Coupling constants (J) are reported in hertz and refer to apparent peak multiplications. The abbreviations s, d, t, q, and m stand for singlet, doublet, triplet, quartet, and multiplet, respectively. All ^{13}C NMR spectra were proton decoupled. In situ IR spectra were recorded with a diamond probe head. Gas chromatography was performed using the following conditions: initial oven temperature, 150 °C, held for 3 min; temperature ramp rate 10 °C/min; final temperature, 180 °C, held for 4 min; temperature ramp rate 50 °C/min; final temperature, 280 °C, held for 8 min; detector temperature, 280 °C.

General Procedure for the Cycloaddition. *General Procedure A.* FeI_2 (5 mol %, 7.8 mg, 0.025 mmol) and dppp (10 mol %, 21.2 mg, 0.05 mmol) were weighed in the glovebox and placed in a dried Schlenk tube. Subsequenly, 2 mL distilled THF was added. The resulting mixture was stirred at room temperature for 30 min to afford an orange-yellow clear solution, at which time Zn dust (10 mol %, 3.3 mg, 0.05 mmol) was added. After an additional 30 min of stirring, diyne (0.5 mmol) was added followed by cyanamide (2.5 mmol, 5 equiv), and the mixture was stirred for 24 h until most of the starting diyne was consumed. The solvent was evaporated, and the crude product was directly purified by silica gel flash column chromatography to give the desired product.

General Procedure B. Procedure for the reaction with 10 mol % catalyst and 2 equiv cyanamide was similar to the above method except for the amount of each reactant: diyne (0.5 mmol), FeI_2 (10 mol %, 15.6 mg, 0.05 mmol), dppp (20 mol %, 42.4 mg, 0.1 mmol), Zn dust (20 mol %, 6.5 mg, 0.10 mmol), cyanamide (1 mol, 2 equiv).

General Procedure C. FeI_2 (5 mol %, 7.8 mg, 0.025 mmol) and dppp (10 mol %, 21.2 mg, 0.05 mmol) were weighed in the glovebox and

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placed in a dried Schlenk tube. Subsequenly, 2 mL distilled THF was added. The resulting mixture was stirred at room temperature for 30 min to afford an orange-yellow clear solution, at which time ZnI_2 (10 mol %, 16.0 mg, 0.05 mmol) and Zn dust (10 mol %, 3.3 mg, 0.05 mmol) were added. After an additional 30 min of stirring, diyne (0.5 mmol) was added followed by cyanamide (0.6 mmol, 1.2 equiv), and the mixture was stirred for 24 h until most of the starting diyne was consumed. The solvent was evaporated, and the crude product was directly purified by silica gel flash column chromatography to give the desired product.

*Dimethyl 3-(Dimethylamino)-1,4-dimethyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3a**).*[8b] White solid: 141 mg, 92% yield (procedure A) or 135 mg, 88% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.31 (s, 3H), 2.76 (s, 6H), 3.47 (s, 2H), 3.48 (s, 2H), 3.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 161.4, 150.2, 147.8, 127.1, 117.1, 59.8, 53.1, 42.4, 40.0, 38.6, 21.7, 14.9.

*Dimethyl 1,4-Dimethyl-3-(pyrrolidin-1-yl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3b**).*[8b] White solid: 136 mg, 82% yield (procedure A) or 141 mg, 85% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 4H), 2.15 (s, 3H), 2.29 (s, 3H), 3.43 (s, 4H), 3.47 (s, 4H), 3.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 159.0, 150.2, 147.4, 124.6, 113.4, 59.9, 53.1, 50.3, 40.1, 38.6, 25.6, 21.8, 15.8.

*Dimethyl 1,4-Dimethyl-3-(piperidin-1-yl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3c**).*[8b] Colorless oil: 149 mg, 86% yield (procedure A) or 166 mg, 96% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 2H), 1.65 (s, 4H), 2.12 (s, 3H), 2.31 (s, 3H), 2.98 (s, 4H), 3.46 (s, 2H), 3.48 (s, 2H), 3.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 161.6, 150.0, 148.0, 127.4, 118.0, 59.7, 53.1, 51.5, 39.9, 38.6, 26.4, 24.7, 21.7, 14.3.

*Dimethyl 1,4-Dimethyl-3-morpholino-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3d**).*[8b] White solid: 136 mg, 78% yield (procedure A) or 165 mg, 95% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.31 (s, 3H), 3.05 (t, J = 4 Hz, 4H), 3.47 (s, 2H), 3.49 (s, 2H), 3.74 (s, 6H), 3.80 (t, J = 4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 160.1, 150.4, 148.4, 128.2, 117.8, 67.3, 59.8, 53.2, 50.7, 39.9, 38.6, 21.7, 14.4.

*Dimethyl 3-(Diethylamino)-1,4-dimethyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3e**).*[8b] Colorless oil: 131 mg, 76% yield (procedure A) or 143 mg, 83% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 6H), 2.12 (s, 3H), 2.32 (s, 3H), 3.11 (t, J = 4 Hz, 4H), 3.50 (s, 4H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 160.4, 150.0, 147.9, 127.3, 119.3, 59.7, 53.2, 45.7, 40.1, 38.8, 21.8, 14.6, 13.4.

*N,N-Diisopropyl-4,7-dimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo-[3,4-c]pyridin-6-amine (**3f**).* White solid: 167 mg, 83% yield (procedure A) or 183 mg, 91% yield (procedure B); mp 97−98 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 8 Hz, 12H), 2.10 (s, 3H), 2.27 (s, 3H), 2.41 (s, 3H), 3.51 (m, 2H), 4.49 (s, 2H), 4.54 (s, 2H), 7.31 (s, J = 8 Hz, 2H), 7.79 (s, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 147.5, 145.7, 143.9, 134.1, 130.0, 127.7, 126.1, 124.0, 53.5, 52.7, 49.6, 21.8, 21.7, 21.3, 14.9; HRMS (ESI, m/z) calcd for $C_{22}H_{31}N_3O_2SNa$ $[M + Na]^+$ 424.2035, found 424.2040.

*Dimethyl 3-(Diallylamino)-1,4-dimethyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3g**).* Colorless oil: 72 mg, 40% yield (procedure A) or 134 mg, 75% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.31 (s, 3H), 3.48 (s, 2H), 3.49 (s, 2H), 3.76 (s, 6H), 5.07 (d, J = 1.6 Hz, 1H), 5.10 (d, J = 1.6 Hz, 1H), 5.16 (d, J = 1.6 Hz, 1H), 5.20 (d, J = 1.6 Hz, 1H), 5.48−5.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 160.0, 150.3, 147.8, 136.2, 127.4, 117.9, 116.5, 59.8, 53.7, 40.1, 38.7, 21.8, 14.7; HRMS (ESI, m/z) calcd for $C_{20}H_{26}N_2O_4Na$ $[M + Na]^+$ 381.1790, found 381.1806.

*Dimethyl 1,4-Dimethyl-3-(methyl(phenyl)amino)-5H-cyclopenta-[c]pyridine-6,6(7H)-dicarboxylate (**3h**).*[8b] Yellowish oil: 168 mg, 91% yield (procedure A) or 182 mg, 99% yield (procedure B); R_f = 0.2 (petroleum ether/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.40 (s, 3H), 3.35 (s, 3H), 3.54 (s, 2H), 3.59 (s, 2H), 3.79 (s, 6H), 6.62 (d, J = 8 Hz, 2H), 6.77 (t, J = 8 Hz, 1H), 7.17 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 156.6, 151.1, 150.3, 148.7, 130.7, 129.0, 122.3, 118.7, 115.7, 59.7, 53.3, 40.0, 38.94, 38.88, 21.8, 14.5.

*N,N-Dibenzyl-4,7-dimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]-pyridin-6-amine (**3i**).* White solid: 244 mg, 98% yield (procedure A) or 224 mg, 90% yield (procedure B); mp 159−160 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.22 (s, 3H), 2.40 (s, 3H), 4.25 (s, 4H), 4.48 (s, 4H), 7.18 (t, J = 8 Hz, 2H), 7.23−7.33 (m, 10 H), 7.78 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.2, 146.8, 143.9, 139.4, 133.9, 130.0, 128.4, 128.2, 127.7, 126.8, 124.6, 117.3, 55.3, 53.4, 52.5, 21.6, 21.5, 14.5; HRMS (ESI, m/z) calcd for $C_{30}H_{31}N_3O_2SNa$ $[M + Na]^+$ 520.2035, found 520.2017.

*N,N,4,7-Tetramethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]-pyridin-6-amine (**3j**).* White solid: 166 mg, 96% yield (procedure A) or 164 mg, 95% yield (procedure B); mp 155−156 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.26 (s, 3H), 2.40 (s, 3H), 2.76 (s, 6H), 4.48 (s, 2H), 4.50 (s, 2H), 7.32 (d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 146.9, 146.6, 143.9, 133.9, 130.0, 127.6, 123.4, 115.3, 53.3, 52.5, 42.2, 21.6, 14.9; HRMS (ESI, m/z) calcd for $C_{18}H_{23}N_3O_2SNa$ $[M + Na]^+$ 368.1409, found 368.1412.

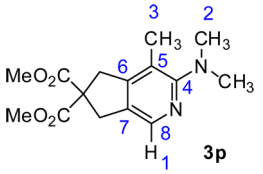
*N,N,4,7-Tetramethyl-1,3-dihydrofuro[3,4-c]pyridin-6-amine (**3k**).* White solid: 78 mg, 81% yield (procedure A) or 75 mg, 78% yield (procedure B); mp 66−67 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.30 (s, 3H), 2.81 (s, 6H), 4.99 (s, 2H), 5.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 149.9, 145.5, 126.4, 114.2, 73.1, 72.7, 42.3, 21.9, 15.1; HRMS (ESI, m/z) calcd for $C_{11}H_{16}N_2ONa$ $[M + Na]^+$ 215.1160, found 215.1161.

*N,N,1,4-Tetramethyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-amine (**3l**).* Colorless oil: trace (procedure A) or 71 mg, 75% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (m, 2H), 2.17 (s, 3H), 2.35 (s, 3H), 2.79−2.81 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 154.6, 147.8, 131.5, 117.5, 42.6, 32.1, 30.6, 24.7, 21.9, 14.9; HRMS (ESI, m/z) calcd for $C_{12}H_{19}N_2$ $[M + H]^+$ 191.1548, found 191.1552.

*Dimethyl 3-(Dimethylamino)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3m**).* White solid: 97 mg, 70% yield (procedure A) or 102 mg, 73% yield (procedure B); mp 101−102 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 6H), 3.47 (s, 4H), 3.73 (s, 6H), 6.38 (s, 1H), 7.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 159.2, 151.2, 142.9, 123.7, 101.3, 60.7, 53.1, 40.5, 38.6, 37.5; HRMS (ESI, m/z) calcd for $C_{14}H_{18}N_2O_4Na$ $[M + Na]^+$ 301.1164, found 301.1160.

*Dimethyl 3-(Dimethylamino)-1,4-diphenyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3n**).* White solid: 202 mg, 94% yield (procedure A) or 211 mg, 98% yield (procedure B); mp 142−143 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, CD_3COCD_3) δ 2.67 (s, 6H), 3.38 (s, 2H), 3.65 (s, 6H), 3.80 (s, 2H), 7.35−7.52 (m, 8H), 7.91 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 172.0, 159.8, 152.8, 149.7, 141.0, 139.4, 129.9, 129.5, 129.2, 129.0, 128.9, 127.9, 125.5, 122.0, 61.2, 53.2, 41.7, 40.7, 40.5; HRMS (ESI, m/z) calcd for $C_{26}H_{27}O_4N_2$ $[M + H]^+$ 431.1965, found 431.1966.

*Dimethyl 3-(Dimethylamino)-4-methyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3p**).*[3m]



3p

Colorless oil: 98 mg, 67% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.73 (s, 6H), 3.43 (s, 2H), 3.51 (s, 2H), 3.70 (s, 6H), 7.90 (s, 1H);

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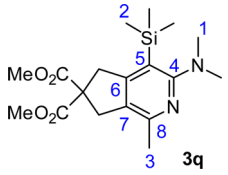
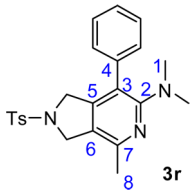
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 161.7, 150.5, 139.6, 129.3, 119.9, 60.2, 53.0, 42.3, 39.6, 38.1, 15.0; HMBC (400 MHz, $CDCl_3$) H_1 (7.90 ppm) couples with C_7 (129.3 ppm), H_2 (2.73 ppm) couples with C_4 (161.7 ppm), H_3 (2.14 ppm) couples with C_4 (161.7 ppm), C_5 (119.9 ppm) and C_6 (150.5 ppm); HRMS (ESI, m/z) calcd for $C_{15}H_{20}N_2O_4Na$ $[M + Na]^+$ 315.1321, found 315.1327.

*Dimethyl 3-(Dimethylamino)-1-methyl-4-(trimethylsilyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3q**).*



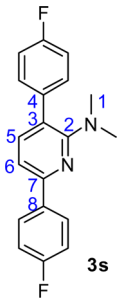
Colorless oil: 108 mg, 59% yield (procedure B); R_f = 0.3 (petroleum ether/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.32 (s, 9H), 2.35 (s, 3H), 2.62 (s, 6H), 3.44 (s, 2H), 3.58 (s, 2H), 3.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 169.2, 157.8, 152.7, 129.3, 120.9, 59.8, 53.1, 44.9, 42.5, 37.7, 22.0, 1.6; HMBC (400 MHz, $CDCl_3$) H_1 (2.62 ppm) couples with C_4 (169.2 ppm), H_2 (0.32 ppm) couples with C_4 (169.2 ppm); HRMS (ESI, m/z) calcd for $C_{18}H_{28}N_2O_4NaSi$ $[M + Na]^+$ 387.1716, found 387.1723.

*N,N,4-Trimethyl-7-phenyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]-pyridin-6-amine (**3r**).*



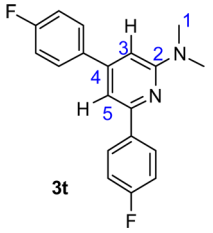
White solid: 145 mg, 71% yield (procedure B); mp 194–195 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.40 (s, 3H), 2.61 (s, 6H), 4.34 (s, 2H), 4.52 (s, 2H), 7.22–7.39 (m, 7H), 7.70 (d, J = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 148.6, 146.5, 143.8, 138.1, 133.7, 129.9, 128.9, 128.5, 127.6, 127.2, 121.3, 117.5, 53.7, 52.2, 41.3, 29.8, 21.9, 21.6; HMBC (400 MHz, $CDCl_3$) H_8 (2.31 ppm) couples with C_6 (121.3 ppm) and C_7 (148.6 ppm), H_1 (2.61 ppm) couples with C_2 (159.1 ppm); HRMS (ESI, m/z) calcd for $C_{23}H_{26}N_3O_2S$ $[M + H]^+$ 408.1740, found 408.1722.

*3,6-Bis(4-fluorophenyl)-N,N-dimethylpyridin-2-amine (**3s**).*



Pale yellow solid: 109 mg, 70% yield (procedure B); mp 116–117 °C; R_f = 0.5 (petroleum ether/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, CD_3COCD_3) δ 2.77 (s, 6H), 7.23 (dt, J = 4, 8 Hz, 4H), 7.44 (d, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.60 (t, J = 4 Hz, 2H), 7.22 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 164.6 (J_{C-F} = 147 Hz), 162.2 (J_{C-F} = 145 Hz), 160.2, 152.7, 141.4, 137.7 (J_{C-F} = 3 Hz), 136.6 (J_{C-F} = 3 Hz), 130.6 (J_{C-F} = 7 Hz), 129.4 (J_{C-F} = 8 Hz), 123.6, 116.2 (J_{C-F} = 210 Hz), 112.0, 41.5; HMBC (400 MHz, CD_3COCD_3) H_1 (2.77 ppm) couples with C_6 (160.2 ppm), H_5 (7.56 ppm) couples with C_3 (152.7 ppm) and C_3 (160.2 ppm), H_6 (7.56 ppm) couples with C_3 (152.7 ppm) and C_3 (160.2 ppm); ^{19}F NMR (377 MHz, CD_3COCD_3) δ −115.8, −117.4; HRMS (ESI, m/z) calcd for $C_{19}H_{17}F_2N_2$ $[M + H]^+$ 311.1354, found 311.1335.

*4,6-Bis(4-fluorophenyl)-N,N-dimethylpyridin-2-amine (**3t**).*



Compound **3t** was prepared using the modified procedure of Louie's system[8b] with **2a** (407.0 μL, 5 mmol), $FeBr_2$ (10.8 mg, 0.05 mmol), **L2** (37.0 mg, 0.10 mmol), and zinc (6.5 mg, 0.10 mmol) in 2 mL benzene. **1k** (117 μL, 1 mmol) was then added into the solution. The reaction was stirred at 70 °C for 24 h, after which time the product was isolated via silica gel flash chromatography (eluent, petroleum ether/ethyl acetate = 400/1). White solid: 96 mg, 62% yield; mp 128–129 °C; R_f = 0.5 (petroleum ether/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, CD_3COCD_3) δ 3.20 (s, 6H), 6.76 (s, 1H), 7.23 (dt, J = 4, 8 Hz, 4H), 7.35 (s, 1H), 7.83 (dt, J = 4, 8 Hz, 2H), 8.23 (dt, J = 4, 8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 165.2 (J_{C-F} = 9 Hz), 162.8 (J_{C-F} = 10 Hz), 160.5, 155.0, 150.2, 137.3 (J_{C-F} = 3 Hz), 137.0 (J_{C-F} = 4 Hz), 129.9 (J_{C-F} = 8 Hz), 129.6 (J_{C-F} = 8 Hz), 116.4 (J_{C-F} = 22 Hz), 115.8 (J_{C-F} = 21 Hz), 106.9, 102.9, 38.2; HMBC (400 MHz, CD_3COCD_3) H_1 (3.20 ppm) couples with C_2 (160.5 ppm), H_3 (6.76 ppm) couples with C_2 (160.5 ppm) and C_4 (137.7 ppm), H_5 (7.35 ppm) couples with C_4 (137.7 ppm); ^{19}F NMR (377 MHz, CD_3COCD_3) δ −115.7, −116.0; HRMS (ESI, m/z) calcd for $C_{19}H_{17}F_2N_2$ $[M + H]^+$ 311.1354, found 311.1336.

Procedure for in Situ IR Spectra. Under the protection of nitrogen gas, to a Schlenk tube were added FeI_2 (10 mol %), dppp (20 mol %), Zn (20 mol %), diyne **1a** (1 equiv), and cyanamide **2a** (2 equiv) successively. Reactions were carried out with [cat.] = 0.06 M, [**1a**] = 0.6 M, [**2a**] = 1.2 M with continuous stirring at room temperature. The reaction was monitored by in situ IR.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and ^{19}F NMR spectra, HMBC and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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