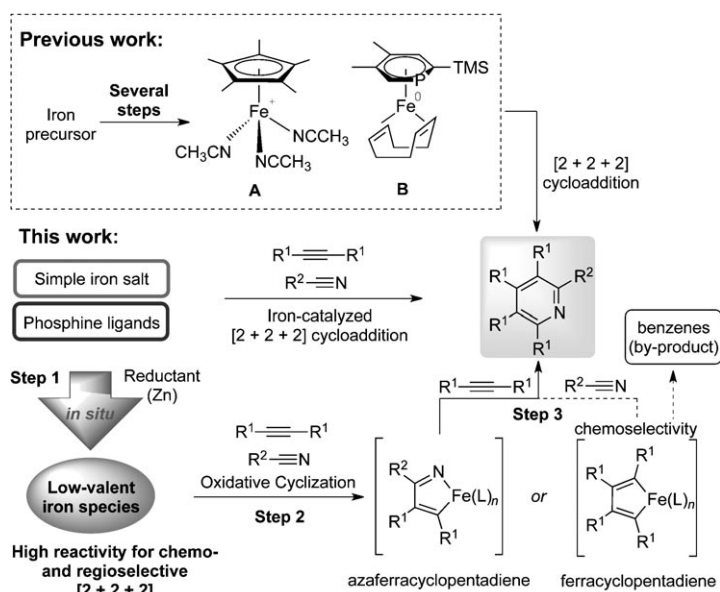


A Simple and Highly Efficient Iron Catalyst for a [2+2+2] Cycloaddition to Form Pyridines**

Chunxiang Wang, Xincheng Li, Fan Wu, and Boshun Wan*

Transition-metal-catalyzed [2+2+2] cycloaddition reactions that use two alkynes and a nitrile is the most straightforward and powerful strategy for the construction of multisubstituted pyridines with high atom efficiency.^[1,2] The iron-catalyzed [2+2+2] cycloaddition to form pyridines remains a great challenge in this field,^[3,4] although significant efforts have been made in various catalytic systems (e.g. Co,^[5] Ru,^[6] Rh,^[7] Ni,^[8] Ti,^[9] Zr/Ni^[10]) in the last few decades. Guerchais and co-workers described a stoichiometric reaction between an Fe^I complex (Scheme 1, structure A) and alkynes with a 73 % yield.^[4a] Meanwhile, Zenneck and co-workers developed a cycloaddition reaction catalyzed by an Fe⁰ complex (Scheme 1, structure B),^[4b,c] however, this approach gave low chemoselectivity and had a complicated procedure for catalyst preparation. A very recent example revealed that no pyridine products were observed from alkynes under iron catalyst even when nitrile was used as the solvent.^[11] Therefore, the development of a simple and highly efficient iron catalyst to exclusively generate pyridine compounds would be a useful contribution to this area. Herein, we disclose the [2+2+2] cycloaddition of diynes and unactivated nitriles at room temperature using a simple iron salt as the catalyst precursor, thus resulting in the production of pyridines with up to 98 % yield of isolated product.

Two important steps are generally involved in [2+2+2] cycloaddition: 1) formation of a metallacycle intermediate by oxidative cyclization and 2) subsequent reductive elimination to produce pyridines (the “common mechanism”).^[2] The formation of a metallacycle intermediate^[12,13] from a low-valent metal species plays a crucial role in the whole process. Inspired by an investigation by Holland and co-workers revealing that alkynes bind more tightly than phosphines to low-valent iron center,^[14] we envisioned that low-valent iron catalysts generated in situ from an inorganic



Scheme 1. Iron catalysts used for the [2+2+2] cycloaddition to form pyridines. TMS = trimethylsilyl.

iron salt and phosphine ligands might initiate the reaction through ligand exchange, and thereby promote the oxidative cyclization between an alkyne and an alkyne or a nitrile followed by the formation of metallacycle intermediate (Scheme 1, Step 2). Considering that the formation of benzene rings can be somewhat inhibited in the presence of a certain amount of nitrile compounds^[4a]—the nature of the ligand has a dramatic effect on the reaction product—it is possible to generate pyridines with high efficiency when the appropriate iron salt and ligand are used.

Initially, diyne **1a** and benzonitrile **2a** were used as model substrates for the optimization of the cycloaddition reaction conditions, and the results are summarized in Table 1. In the first instance, we employed the iron salt FeCl₃ as the catalyst precursor, 1,2-bis(diphenylphosphino)ethane (dppe) as the ligand, and **2a** as the solvent (Table 1, entries 1–4). No desired product was observed in the absence of dppe, as expected, and only trace amounts of **3a** were obtained when FeCl₃/dppe was used as the catalyst in a 1:1 ratio (6 % yield, entry 2).^[15] Given that the amount of ligand can strongly affect the catalytic efficiency, different metal/ligand ratios were screened. The yield was dramatically improved to 97 % when a 1:2 mixture of metal and ligand was used (entry 3), however, further increasing the ratio to 1:3 drastically decreased the yield (entry 4, 38 %). Sequential investigations of other iron salts, solvents, and ligands (entries 5–9) showed that the combination of FeBr₂ or FeI₂ with 1,3-bis(diphenylphosphino)propane

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[**] Financial support from the National Basic Research Program of China (2010CB833300) is gratefully acknowledged. We also thank Dr. Chunqing Liu (UOP), Prof. Yonggui Zhou, and Dr. Wei Wang for proof-reading this manuscript as well as Prof. Sentaro Okamoto (Kanagawa University) for helpful discussion on experiment details.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201102001>.

Table 1: Screening of reaction conditions.^[a]

| Entry | Iron salt | Ligand | Cat. loading [mol %] ^[b] | Conv. [%] ^[c] | Yield of 3a [%] ^[c] |
|--------------------|-------------------|--------|-------------------------------------|--------------------------|---------------------------------------|
| 1 ^[d,e] | FeCl ₃ | – | 20 | 0 | 0 |
| 2 ^[e,f] | FeCl ₃ | dppe | 20 | 29 | 6 |
| 3 ^[e] | FeCl ₃ | dppe | 20 | 99 | 97 |
| 4 ^[e,g] | FeCl ₃ | dppe | 20 | 45 | 38 |
| 5 | FeCl ₃ | dppe | 20 | 97 | 92 |
| 6 | FeCl ₃ | dppp | 20 | 100 | 97 |
| 7 | FeBr ₃ | dppp | 20 | 99 | 89 |
| 8 | FeBr ₂ | dppp | 20 | 100 | quant. |
| 9 | FeI ₂ | dppp | 20 | 100 | quant. |
| 10 | FeCl ₃ | dppp | 10 | 16 | 9 |
| 11 | FeBr ₂ | dppp | 10 | 75 | 68 |
| 12 | FeI ₂ | dppp | 10 | 100 | quant. |
| 13 | FeI ₂ | dppp | 5 | 100 | quant. |
| 14 | FeI ₂ | dppp | 2.5 | 13 | 6 |
| 15 ^[h] | FeI ₂ | dppp | 5 | 54 | 50 |
| 16 ^[d] | FeI ₂ | dppp | 5 | 0 | 0 |

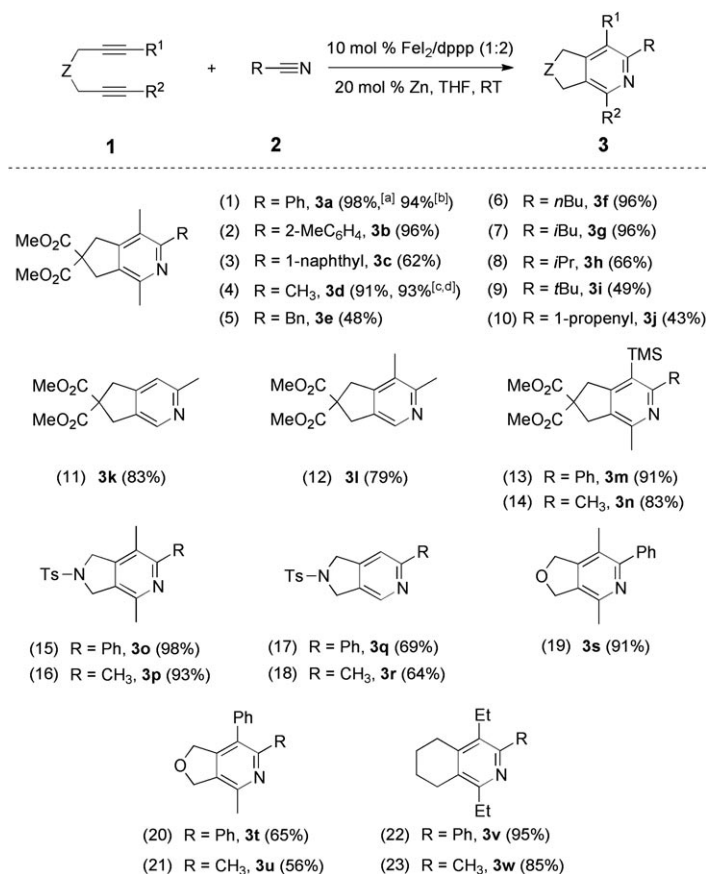
[a] Reaction conditions: 0.25 mmol of **1a**, 10 equiv of **2a**, *x* mol % of iron salt, 2*x* mol % of ligand, 2*x* mol % of Zn, 1 mL of THF at RT for 24 h unless otherwise stated. [b] Catalyst loading was based on the iron salt. [c] Determined by GC using a pyridine derivative as the internal standard; average of two runs. [d] Without Zn. [e] **2a** was used as the solvent. [f] FeCl₃/dppe = 1:1. [g] FeCl₃/dppe = 1:3. [h] 5 equiv of **2a** was used. THF = tetrahydrofuran.

(dppp) in THF gave a quantitative yield of **3a**, even when 10 equivalents of nitriles were employed.^[16] Lowering the catalyst loading to 10 mol % resulted in a remarkable decrease in the product yield for FeCl₃ and FeBr₂ (entries 10 and 11). In contrast, excellent results were obtained using only 5 mol % FeI₂ as the catalyst (entry 13). However, further decreasing the catalyst loading jeopardized the yield (entry 14), and reaction with either a lower amount of nitrile or without a reductant proved less efficient (entries 15 and 16). On the basis of the product yield, we chose the optimized reaction conditions as follows: 10 mol % of FeI₂ as the catalyst precursor, 20 mol % of dppp as the ligand, and 20 mol % of Zn dust as the reductant with 10 equivalents of nitrile in THF at room temperature for 24 hours.

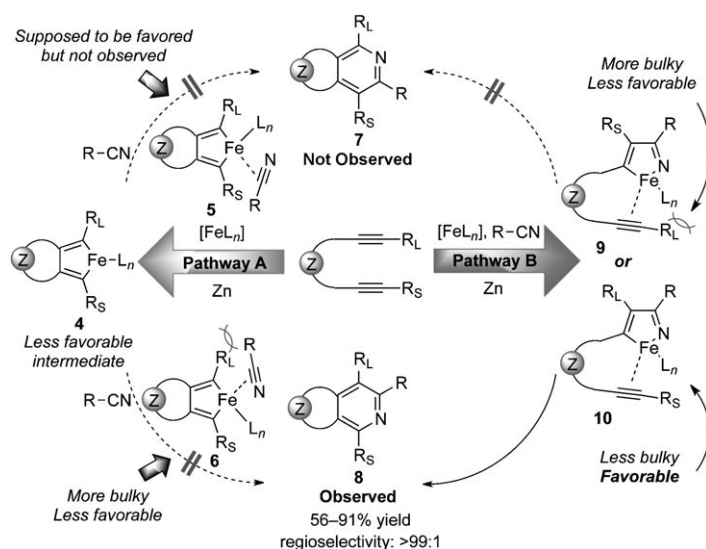
With the optimized reaction conditions in hand, we tested the scope of the reaction using various diynes and unactivated nitriles. As shown in Scheme 2, both aryl and alkyl nitriles reacted efficiently and produced the desired pyridines with good to excellent yields. Notably, the reactions with benzonitrile and acetonitrile proceeded effectively even when 5 mol % of catalyst was used (Scheme 2, (1) and (4)). In addition, nitriles bearing longer chains (Scheme 2, (6) and (7)) or sterically hindered moieties (Scheme 2, (2), (3), (8), and (9)) also produced the cycloadducts with reasonable yields. Interestingly, when (*Z*)-2-butenenitrile was used as the coupling partner, diyne **1a** selectively reacted with its cyano group to give the target product with a moderate yield without the formation of the 1,3-cyclohexadiene derivative (Scheme 2, (10)).^[17] Diynes

with internal substituents (Scheme 2, (11) and (18)) or without a tertiary center on the tether chain (Scheme 2, (19)–(21)) each furnished the corresponding pyridines with good yields, although slightly lower yields were observed for the terminal diynes (Scheme 2, (11), (17), and (18)). Importantly, diynes with unsymmetrical terminal substituents produced the corresponding pyridines as a single regioisomer when using this catalytic system (Scheme 2, (12), (13), (14), (20), and (21)).^[18]

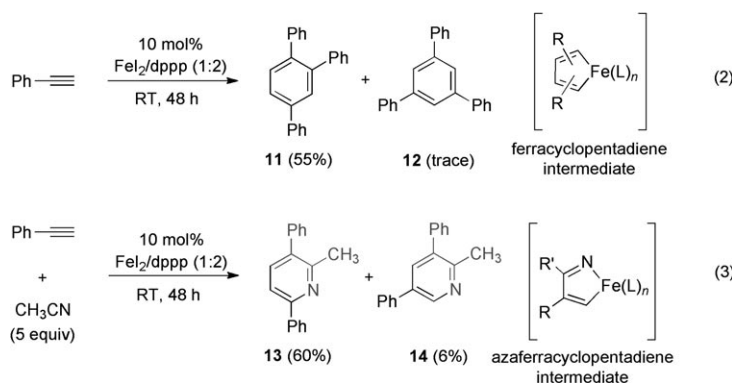
After determining the efficiency of the present iron catalysis, we then turned our attention to the mechanism. Two possible pathways are proposed in Scheme 3. To gather evidence to support one of these hypotheses, two intermolecular [2+2+2] cycloaddition reactions were carried out (Scheme 4). As expected, cyclotrimerization of monoalkynes exclusively produced the 1,2,4-trisubstituted benzene **11** in 55 % yield, and indicated that a ferracyclopentadiene intermediate^[12] was formed during cycloaddition [Scheme 4, Eq. (2)]. In addition, intermolecular cyclotrimerization of phenylacetylene with 5 equivalents of CH₃CN gave two pyridine isomers,^[19] **13** and **14**, in 60 % and 6 % yield, respectively, thus suggesting that the formation of an azaferrocyclopentadiene intermediate^[20,21] is responsible for the regioselectivity [Scheme 4, Eq. (3)]. Therefore, both path-



Scheme 2. Iron-catalyzed cycloaddition of diynes and unactivated nitriles. Reaction conditions: **1** (0.5 mmol), **2** (5 mmol), FeI₂ (10 mol %), dppp (20 mol %), Zn (20 mol %), 2 mL THF at RT for 24 h unless otherwise stated. [a] Yield of isolated product (average of two runs). [b] 5 mol % of catalyst. [c] 20 equiv of nitrile. Bn = benzyl, Ts = 4-toluenesulfonyl.



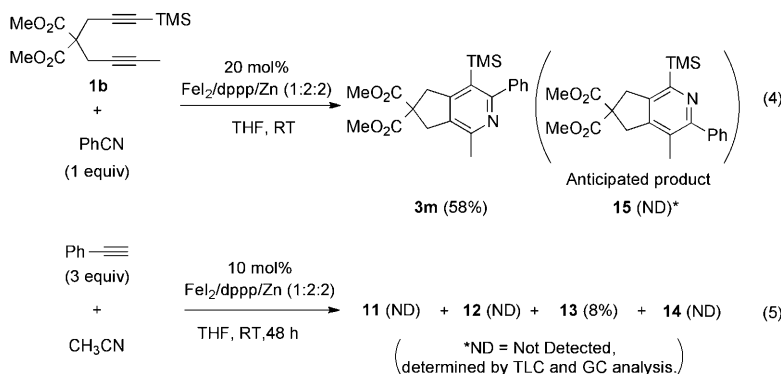
Scheme 3. Possible pathways to form pyridines.



Scheme 4. Intermolecular [2+2+2] cycloaddition reactions.

ways in Scheme 3 are feasible for the production of pyridine compounds.

To further understand the mechanism, a regioselective cycloaddition reaction of unsymmetrical diyne **1b** and 1 equivalent of benzonitrile was performed [Scheme 5, Eq. (4)]. When **1b** was exposed to the iron catalyst in the presence of 1 equivalent of nitrile, intramolecular oxidative cyclization of **1b** rather than intermolecular oxidative cycli-



Scheme 5. Competition experiments.

zation of the diyne and benzonitrile was preferred. Thus, both cycloadducts **3m** and **15** should be obtained, and the latter should be the major product because of its minor steric repulsion. However, **3m** was the only observed product, thus revealing that the ferracyclopentadiene intermediate was not formed in this process and that Pathway A (Scheme 3) was not accessible. Subsequently, another competition experiment between acetonitrile and 3 equivalents of phenylacetylenes was conducted [Scheme 5, Eq. (5)], and this reaction only provided a small amount of pyridine product **13** (8%). No desired product **11** was formed.^[22] Based on these results, we envision that the formation of the ferracyclopentadiene intermediate is strongly inhibited in the presence of nitrile [Eq. (2) vs. Eq. (5)] and that Pathway B is more favorable. As outlined in Scheme 2, although intramolecular cycloaddition of azaferracyclopentadiene intermediates **9** and **10** showed a reversed regioselectivity (Scheme 3, Pathway B), intermediate **10** is preferred to produce the observed product **8** as a result of the relatively minor interaction between the bulky ligand and the terminal alkyne substituent.

In summary, for the first time we have developed a simple and highly efficient method for the iron-catalyzed [2+2+2] cycloaddition of diynes and unactivated nitriles leading to pyridine compounds at room temperature. The catalyst is generated in situ from an inorganic iron salt and a diphosphine ligand and exhibited high reactivity and regioselectivity. The appropriate ligand as well as the metal/ligand ratio plays a crucial role on the catalytic efficiency. Further investigation of the mechanism is currently underway.

Experimental Section

Representative procedure: FeI_2 (15.6 mg, 0.05 mmol) and dppp (42.4 mg, 0.10 mmol) were weighed in the glove box and placed in a dried Schlenk tube. Subsequently, distilled THF (2 mL) was added. The resulting mixture was stirred at RT for 30 min to afford an orange/yellow clear solution, at which time Zn dust (6.5 mg, 0.10 mmol) was added. After stirring for an additional 30 min, diyne (0.5 mmol) was added followed by the nitrile (5 mmol), and the reaction was kept stirring for 24 h until the majority of the starting diyne was consumed. The solvent was evaporated and the crude product was directly purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to give the desired pyridine.

Received: March 22, 2011

Published online: June 22, 2011

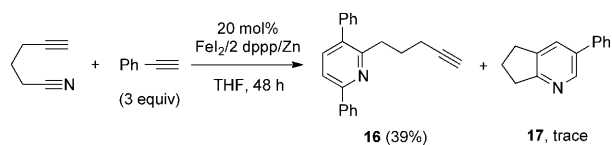
Keywords: cycloaddition · heterocycles · iron · nitriles · pyridines

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diyne analogue 3,9-dodecadiyne with benzonitrile afforded the desired product in 95 % yield (**3v**), whereas 3-hexyne only gave trace amounts of the product. The reason for these reaction outcomes is still unknown.

- [20] An azaruthenacyclopentadiene intermediate has been previously reported: see Ref. [6c] and [6e].
- [21] In related studies, the reaction of 5-hexynenitrile with excess phenylacetylene (3 equiv) was tested. Unexpectedly, the complete intermolecular cycloadduct **16** was obtained in 39 % yield, and only trace amounts of the anticipated cycloadduct **17** was observed (monitored by TLC and GC-MS analysis). This outcome may ascribe to the competitive reactivity of different alkynes towards the nitrile.



- [22] When prolonging the reaction time to 96 h, both 2,3,6-trisubstituted pyridine **13** and 1,2,4-triphenyl benzene **11** were detected, in 47 % and 7 % yield, respectively.