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Iron-Catalyzed Cycloaddition of Alkynenitriles and Alkynes

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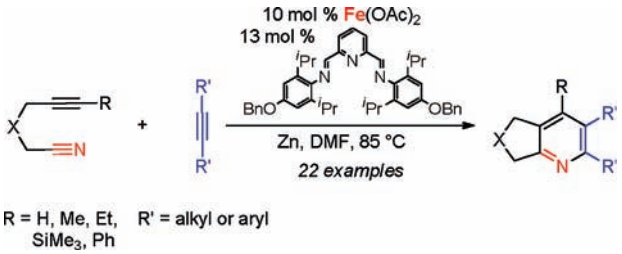
ABSTRACT



The combination of $Fe(OAc)_2$ and an electron-donating, sterically hindered pyridyl bisimine ligand catalyzes the cycloaddition of alkynenitriles and alkynes. A variety of substituted pyridines were obtained in good yields.

The abundance and affordability of iron makes it an attractive catalyst source. However, until recently, the number of catalytic processes (other than oxidation[1] and polymerization[2]) iron complexes could facilitate has been low. Over the past decade, the quantity of efficient iron-based catalyst systems has significantly risen.[3] For example, effective Fe-catalyzed cross-coupling chemistry[4] and cycloaddition chemistry[5] have emerged. To date, Fe-catalyzed cycloadditions have been mostly limited to the formation of carbocycles. In 1872, Sir Ramsay demonstrated that passing acetylene and hydrocyanic acid through a red-hot iron pipe led to the formation of pyridine.[6] Despite this very early observation, an effective and general Fe-based catalyst that mediates cycloadditions to form pyridines is still absent.[7] Herein, we describe a general iron catalyst that couples alkynenitriles and alkynes to form pyridines.[8]

Given the efficacy of Fe-catalyzed cycloadditions to generate carbocyclic structures, we surmised that the inability to prepare pyridines was due to limited reactivity of the nitrile (i.e., for either oxidative coupling or insertion). Thus,

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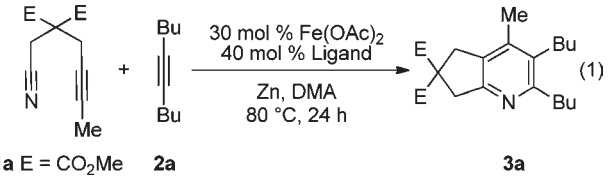
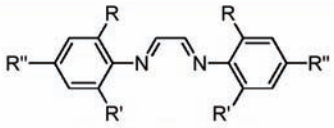
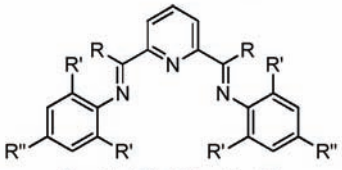
alkynenitrile **1a**, which tethers the nitrile to the alkyne, was chosen as a model substrate. Alkynenitrile **1a** and dec-5-yne **2a** were subjected to 30 mol % of $Fe(OAc)_2$,[9] 40 mol % of ligand, and Zn in DMA at 80 °C (eq 1).



1a E = CO_2Me **2a** **3a**

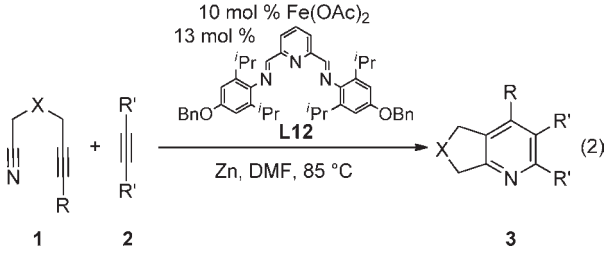
A variety of amines, phosphines, and NHCs (NHC = *N*-heterocyclic carbene) were evaluated as potential ligand arrays. The use of neither phosphines nor NHCs led to any detectable cycloaddition product. Imino-based ligands have successfully been employed in various Fe-mediated reactions.[10,11] As such, bisimines and pyridyl bisimines were also evaluated (Table 1). Although consumption of the alkynenitrile was observed, low or no pyridine was formed in most cases (entries 1−5). An appreciable amount of the desired pyridine product was formed when imine **L6** was used as the ligand (entry 6). Unfortunately, all attempts to optimize this reaction failed; yields above 50% were never obtained.

Table 1. Ligand Screen with Various Bisimine Ligands[a]

entry	ligand	conversion[b]	yield[b]
			
1	R = R' = R" = Me, L1	100	13
2	R = Me, R' = R" = H, L2	58	0
3	R = R' = ^{t}Bu, R" = H, L3	40	0
4	R = ^{t}Bu, R' = R" = H, L4	36	0
5	R = Et, R" = R" = H, L5	89	17
6	R = R' = ^{i}Pr, R" = H, L6	100	47
			
7	R = Me, R' = R" = Me, L7	43	0
8	R = Me, R' = ^{i}Pr, R" = H, L8	63	2
9	R = H, R' = R" = Me, L9	100	84
10	R = H, R' = ^{i}Pr, R" = H, L10	42	0
11	**R = H, R' = Me, R" = OBn, L11**	**100**	**62[c]**
12	**R = H, R' = ^{i}Pr, R" = OBn, L12**	**100**	**95[c]**

[a] Reaction conditions: 30 mol % of $Fe(OAc)_2$, 40 mol % of ligand, 40 mol % of Zn, 0.1 M DMA, 80 °C, 24 h. [b] Determined by gas chromatography with naphthalene as internal standard. [c] Reaction conditions: 20 mol % of $Fe(OAc)_2$, 27 mol % of ligand, 22 mol % of Zn, 0.1 M DMA, 80 °C.

We then turned our attention to pyridyl bisimines (entries 7−12). Reactions run with pyridyl bisimines derived from the corresponding pyridyl bisketones did not afford any pyridine cycloaddition product (entries 7 and 8). However, reactions run with pyridyl bisimines derived from the corresponding pyridyl bisaldehydes gave promising results. For example, quantitative conversion of the alkynenitrile was observed with **L9** (entry 9). Importantly, the pyridine product was observed in 84% GC yield. An increase in the steric bulk of the ligand seemed to have a dramatic deleterious effect on the reaction (entry 10). Specifically, reactions run with **L10** gave hardly any conversion and no desired pyridine product. Amazingly, the addition of an electron-donating group (i.e., −OBn) to the para position of the aryl rings had a profound effect on product formation (entries 11 and 12). When **L11** was used as the ligand, the desired pyridine product was formed in 62% yield despite employing a lower catalyst loading of 20 mol % (entry 11). Even more surprisingly, in contrast to the trend observed for neutral ligands, an increase in steric hindrance led to an *increase* in yield (entries 9−10 vs entries 11−12, respectively). That is, reactions run with **L12** provided the pyridine product in 95% yield, again while employing a lower catalyst loading (entry 12). Importantly, individual control reactions run without $Fe(OAc)_2$, ligand, or Zn resulted in no pyridine product formation. Further optimization ultimately led to the following reaction conditions: 10 mol % of $Fe(OAc)_2$, 13 mol % of bisimine **L12**, 0.4 M alkynenitrile, and 0.4 M alkyne in DMF, rather than DMA, at 85 °C (eq 2).



1 **2** **3**

The $Fe(OAc)_2$/**L12**-catalyzed cycloaddition of alkynenitriles and alkynes is a general reaction as a variety of alkynenitriles and alkynes can be used as substrates (Table 2). The reaction between alkynenitriles **1a** and **1b** with dec-5-yne (**2a**) afforded good isolated yields of the pyridine products (entries 1 and 2). Similarly, the reaction of phenyl-substituted alkynenitrile **1c** also afforded the corresponding pyridine in good yield (entry 3). Although the cycloaddition of terminal alkynenitrile **1d** resulted in low yield (entry 4),[5d] a reasonable yield was obtained when TMS-substituted alkynenitrile **1e** was employed (entry 5). Not surprisingly, 3-hexyne (**2b**) is an equally effective alkyne substrate (entry 6). Because of competing cyclotrimerization of the alkyne, the cycloaddition of

(9) Iron acetate (99.995% purity) was used: Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586.

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Table 2. $Fe(OAc)_2$/**L12**-Catalyzed Cycloaddition of Alkynenitriles and Symmetrical Alkynes[a]

entry	cyanoalkyne (**1**)	alkyne (**2**)	time (h)	product (% yield)[b]
1	R = Me, **1a**	**2a**	2h	**3a**, 70
2	R = Et, **1b**	**2a**	26h	**3b**, 86
3	R = Ph, **1c**	**2a**	5h	**3c**, 75
4	R = H, **1d**	**2a**	26h	**3d**, 30
5	R = $SiMe_3$, **1e**	**2a**	6h	**3e**, 57
6	**1a**	**2b**	6h	**3f**, 71
7	**1a**	**2c**	5h	**3g**, 54[c]
8	R = Et, **1f**	**2a**	4h	**3h**, 41
9	R = Ph, **1g**	**2a**	4h	**3i**, 45
10	**1h**	**2a**	4h	**3j**, 41
11	**1i**	**2a**	4h	**3k**, 65
12	**1j**	**2b**	4h	**3l**, 64
13	**1k**	**2a**	24h	**3m**, 40[d]

[a] Reaction conditions: 0.4 M **1**, 0.4 M **2**, 10 mol % of $Fe(OAc)_2$, 13 mol % of **L12**, 20 mol % of Zn, 85 °C. [b] Average of at least two reaction runs. [c] 2 equiv of alkyne. [d] Reaction conditions: 0.4 M **1**, 0.4 M **2**, 20 mol % of $Fe(OAc)_2$, 26 mol % of **L12**, 40 mol % of Zn, DMF, 85 °C.

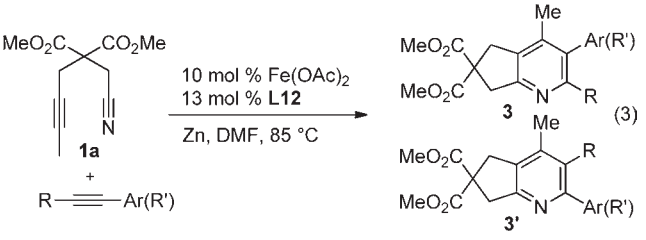
diphenylacetylene **2c** and alkynenitrile **1a** required 2 equiv of **2c** to afford the pyridine product in appreciable yield (entry 7). Alkynenitriles containing an either oxygen or a nitrogen backbone (**1f**–**h**) also reacted with decyne **2a** to afford the pyridine product, albeit in moderate yields (entries 8–10). In contrast, alkynenitrile **1h**, which possesses an all-carbon backbone, reacted with decyne **2a** and afforded better yields of the pyridine cycloaddition product (entry 11). A tricyclic indenylpyridine was prepared in good yield from the coupling of **1j** and **2b** (entry 12). In addition, the reaction of alkynenitrile **1k**, which possesses a 6-carbon chain that tethers an alkyne to the nitrile, and **2a** afforded bicycle **3k**, albeit in lower yields than the corresponding alkynenitrile which possesses a 5-carbon tether (entry 13 vs entry 1, respectively).

Table 3. Cycloaddition of **1a** and Unsymmetrical Alkynes[a]

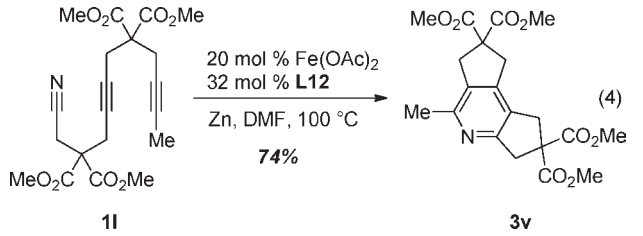
entry	alkyne (**2**)	reaction time	product % yield (**3**:**3'**)[b]
	R—≡—Ar		
1	Ar = Ph, R = Me **2d**	6h	**3n,** 69 (1.2:1)
2	Ar = *p*-$OMeC_6H_4$, R = Me, **2e**	6h	**3o,** 39 (3:2)
3	Ar = *p*-$CF_3C_6H_4$, R = Me, **2f**	6h	**3p,** 39 (4:1)
4	Ar = Py, R = Me, **2g**	16h	**3q,** 56 (7:3)
5	Ar = Ph, R = Bu, **2h**	5h	**3r,** 53 (2:3)
6	Ar = Ph, R = -$(CH_2)_2$NTsBoc **2i**	5h	**3s**, 44 (3:2)
	R—≡—R'		
7	R = Me, R' = Bu, **2j**	24h	**3t**, 62 (1:1)
8	R = Me, R' = ^{t}Bu, **2k**	6h	**3u**, 26 (0:1)

[a] Reaction conditions: 0.4 M **1**, 0.4 M **2**, 10 mol % of $Fe(OAc)_2$, 13 mol % of **L12**, 20 mol % of Zn, DMF, 85 °C. [b] Average of at least two reaction runs.

Unsymmetrical alkynes also reacted in the cycloaddition reaction (eq 3, Table 3). Methyl phenyl acetylene **2d** and alkynenitrile **1a** afforded the pyridine product with a 1.2:1 ratio of regioisomers (entry 1). Cycloaddition of an alkyne possessing an electron-withdrawing group (*p*-CF_3) (entry 3) afforded a higher ratio of the major regioisomer where the phenyl ring is distal from the pyridine nitrogen as compared to an alkyne possessing an electron-donating group (entry 2). The reaction of alkynenitrile **1a** and alkyne **2g**, possessing a pyridyl substituent, also afforded a mixture of pyridine products where the aryl ring is distal to the pyridine nitrogen in the major regioisomer (entry 4). A relatively equal mixture of regioisomers was obtained in the reactions of aryl-alkyl alkynes **2h** and **2i** (entries 5 and 6). As expected, the cycloaddition of unsymmetrical alkyl–alkyl alkyne **2j** and alkynenitrile **1a** afforded a 1:1 ratio of the pyridine products in a good yield (entry 7). Pyridine product was obtained as a single regioisomer in the reaction of a sterically hindered alkyne (i.e., methyl-^{t}Bu-acetylene **2k**, entry 8). Interestingly, the ^{t}Bu-group is proximal to the nitrogen of the pyridine (entry 8).

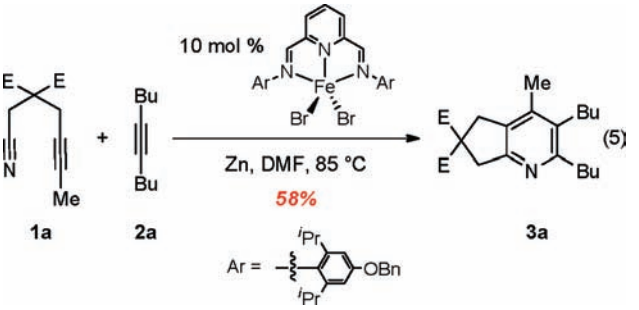


The catalytic system was also effective in the all-intramolecular cycloaddition. Specifically, addition of 20 mol % of $Fe(OAc)_2$ and 32 mol % of **L12** to substrate **1l** afforded tricyclic product **3v** in 74% isolated yield (eq 4).



Efforts to isolate an (**L12**)$Fe(OAc)_n$ complex[12] proved unsuccessful. However, the analogous (**L12**)$FeBr_2$[2a,b,d] complex was prepared and used as a catalyst for the cycloaddition of **1a** and **2a** (eq 5). Importantly, this well-defined Fe complex did catalyze the coupling and afforded pyridine **3a** in 58% isolated yield. For comparison, reactions run with 10 mol % of $FeBr_2$, in lieu of $Fe(OAc)_2$, provided pyridine **3a** in 54% (GC yield).[13]

(12) The $Fe(OAc)_2$ was only partially souble in most polar solvents.
(13) Reaction conditions: 0.4 M **1a**, 0.4 M **2a**, 10 mol % of $FeBr_2$, 13 mol % of **L12**, 20 mol % of Zn, DMF, 85 °C.



In conclusion, we have developed a methodology to prepare pyridines from alkynenitriles and alkynes by employing catalytic amounts of iron acetate and a pyridyl bisimine ligand. Efforts to understand the reactivity patterns of different pyridyl bisimine ligands in the cycloaddition reaction are currently underway.

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Supporting Information Available. All experimental procedures for new substrates and products as well as copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.