

Published in final edited form as:

Org Lett. 2011 June 3; 13(11): 2936–2939. doi:10.1021/ol2009939.

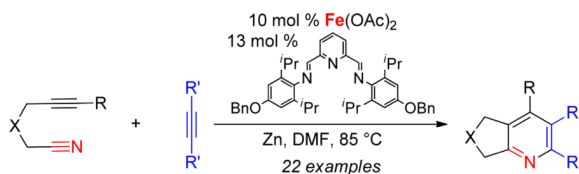
Iron Catalyzed Cycloaddition of Alkynenitriles and Alkynes

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Abstract


 R = H, Me, Et, SiMe₃, Ph R' = alkyl or aryl

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.

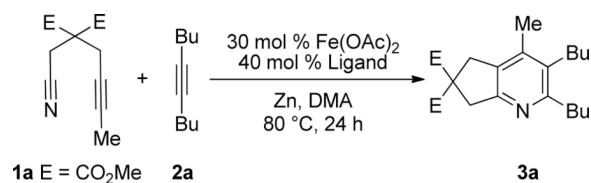
The abundance and affordability of iron makes it an attractive catalyst source. However, until recently, the number of catalytic processes (other than oxidation¹ and polymerization²) iron complexes could facilitate has been low. Over the past decade, the quantity of efficient iron-based catalyst systems has significantly risen.³ For example, effective Fe-catalyzed cross-coupling chemistry⁴ and cycloaddition chemistry⁵ has emerged. To date, Fe-catalyzed cycloadditions have been mostly limited to the formation of carbocycles. In 1872, Sir Ramsay demonstrated that the addition 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, alkynenitrile **1a**, which tethers the nitrile to the alkyne, was chosen as a model substrate. Alkynenitrile **1a** and butyne **2a** were subjected to 30 mol % Fe(OAc)₂,⁹ 40 mol % ligand, and Zn in DMA at 80 °C (eq 1).

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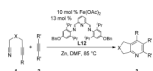
Supporting Information All experimental procedures for new substrates and products as well as copies of NMR spectra are available free of charge via the Internet at <http://pubs.acs.org>.



(1)

A variety of amines, phosphines, and NHCs (NHC = *N*-heterocyclic carbene) were evaluated as potential ligand arrays. Neither the use of phosphines or 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 alkyne nitrile 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.

We then turned our attention to pyridyl bisimines (entries 7–12). Reactions run with pyridyl bisimines derived from the corresponding pyridyl diketones did not afford any pyridine cycloaddition product (entries 7–8). However, reactions run with pyridyl bisimines derived from the corresponding pyridyl bisaldehydes gave promising results. For example, quantitative conversion of the alkyne nitrile 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 11–12). 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 hinderance 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%, 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 % Fe(OAc)₂, 13 mol % bisimine **L12**, 0.4 M alkyne nitrile, and 0.4 M alkyne in DMF, rather than DMA, at 85 °C (eq 2).



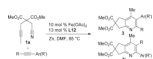
(2)

The Fe(OAc)₂/**L12**-catalyzed cycloaddition of alkyne nitriles and alkynes is a general reaction as a variety of alkyne nitriles and alkynes can be used as substrates (Table 2). The reaction between alkyne nitriles **1a** and **1b** with dec-5-yne (**2a**) afforded good isolated yields of the pyridine products (entries 1–2). Similarly, the reaction of phenyl-substituted alkyne nitrile **1c** also afforded the corresponding pyridine in good yield (entry 3).

Although the cycloaddition of terminal alkyne nitrile **1d** resulted in low yield (entry 4),^{5d} a reasonable yield was obtained when TMS-substituted alkyne nitrile **1e** was employed (entry 5). Not surprisingly, 3-hexyne (**2b**) is an equally effective alkyne substrate (entry 6). Due to

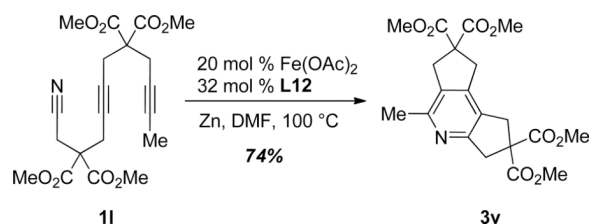
competing cyclotrimerization of the alkyne, the cycloaddition of diphenylacetylene **2c** and alkyne nitrile **1a** requires 2 equivalents of **2c** to afford the pyridine product in appreciable yield (entry 7). Alkyne nitriles containing an ether oxygen or a nitrogen backbone (**1f**, **g**, and **1h**) also react with decyne **2a** to afford the pyridine product, albeit in moderate yields (entries 8–10). In contrast, alkyne nitrile **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 alkyne nitrile **1k**, which possesses a 6-carbon chain that tethers an alkyne to the cyano group, and **2a** affords bicycle **3k**, albeit in lower yields than the corresponding alkyne nitrile which possesses a 5-carbon tether (entry 13 vs. entry 1, respectively).

Unsymmetrical alkynes also react in the cycloaddition reaction (eq 3, Table 3). Methyl phenyl acetylene **2d** and alkyne nitrile **1a** afford the pyridine product with 1.2:1 ratio of regioisomers (entry 1). Cycloaddition of an alkyne possessing an electron withdrawing group (*p*-CF₃) (entry 3) affords 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 alkyne nitrile **1a** and alkyne **2g**, possessing a pyridyl substituent, also affords 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 were obtained in the reactions of aryl-alkyl alkynes **2h** and **2i** (entries 5–6). As expected, the cycloaddition of unsymmetrical alkyl-alkyl alkyne **2j** and alkyne nitrile **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-^tBu-acetylene **2k**, entry 8). Interestingly, the ^tBu-group is proximal to the nitrogen of the pyridine (entry 8).



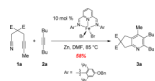
(3)

The catalytic system is also effective in the all-intramolecular cycloaddition. Specifically, addition of 20 mol % Fe(OAc)₂ and 32 mol % **L12** to substrate **1l** afforded tricyclic product **3v** in 74% isolated yield (eq 4).



(4)

Efforts to isolate an (**L12**)Fe(OAc)_n complex¹² proved unsuccessful. However, the analogous (**L12**)FeBr₂^{2a,b} 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 % FeBr₂, in lieu of Fe(OAc)₂, provided pyridine **3a** in 54% (GC yield).¹³



(5)

In conclusion we have developed a methodology to prepare pyridines from alkyne nitriles 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the NSF and NIGMS (5R01GM076125) for support of this research.

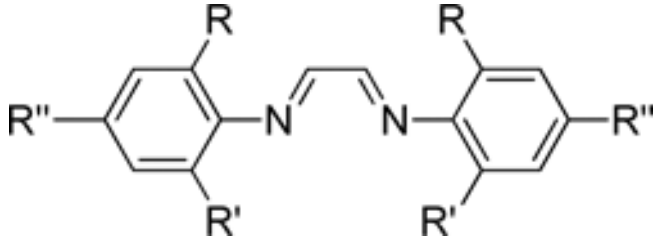
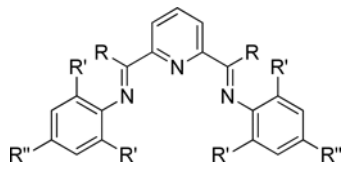
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12. The Fe(OAc)₂ was only partially soluble in most polar solvents.
13. Reaction conditions: 0.4M **1a**, 0.4M **2a**, 10 mol % FeBr₂, 13 mol % **L12**, 20 mol % Zn, DMF, 85 °C.

Table 1

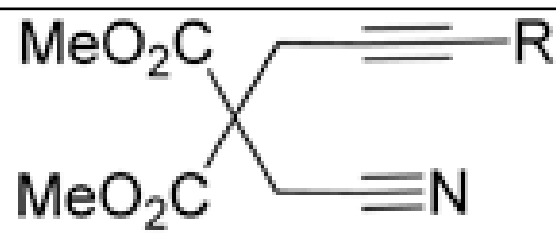
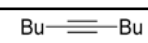


Ligand screen with various bisimine ligands^a

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' = <i>t</i> Bu, R'' = H, L3	40	0
4	R = <i>t</i> Bu, R' = R'' = H, L4	36	0
5	R = Et, R' = R'' = H, L5	89	17
6	R = R' = <i>i</i> Pr, R'' = H, L6	100	47
			
7	R = Me, R' = R'' = Me, L7	43	0
8	R = Me, R' = <i>i</i> Pr, R'' = H, L8	63	2
9	R = H, R' = R'' = Me, L9	100	84
10	R = H, R' = <i>i</i> Pr, R'' = H, L10	42	0
11	R = H, R' = Me, R'' = OBn, L11	100	62^c
12	R = H, R' = <i>i</i>Pr, R'' = OBn, L12	100	95^c

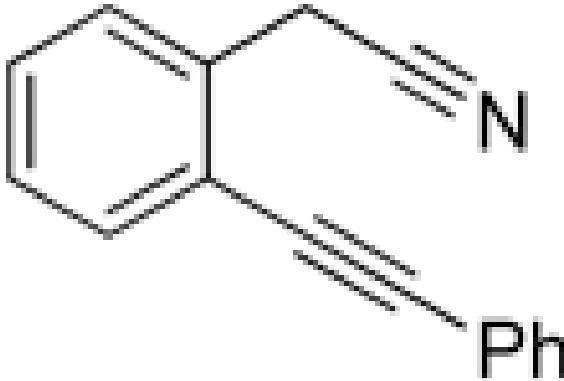
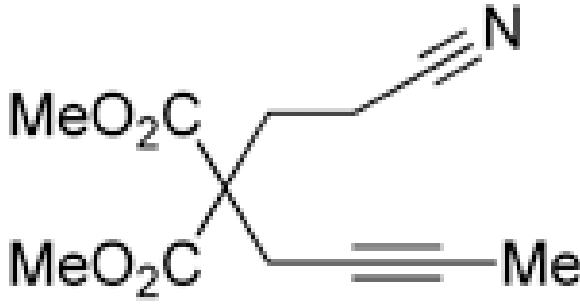
^aReaction conditions: 30 mol % Fe(OAc)₂, 40 mol % Ligand, 40 mol % Zn, 0.1 M DMA, 80 °C, 24 h.^bDetermined by gas chromatography with naphthalene as internal standard.^cReaction conditions: 20 mol % Fe(OAc)₂, 27 mol % Ligand, 22 mol % Zn, 0.1 M DMA, 80 °C.

Table 2

Fe(OAc)₂/L12-catalyzed cycloaddition of cyanoalkynes and symmetrical alkynes^a

entry	cyanoalkyne (1)	alkyne (2)	time(h)
			
1	R = Me, 1a	2a	2h
2	R = Et, 1b	2a	26h
3	R = Ph, 1c	2a	5h
4	R = H, 1d	2a	26h
5	R = SiMe ₃ , 1e	2a	6h
			
6	1a	2b 	6h
7	1a	2c	5h

entry	cyanoalkyne (1)	alkyne (2)	time(h)
8	R = Et, 1f	2a	4h
9	R = Ph, 1g	2a	4h,
10	1h	2a	4h
11	1i	2a	4h

entry	cyanoalkyne (1)	alkyne (2)	time(h)
12	 1j	2b	4h
13	 1k	2a	24h

^aReaction Conditions: 0.4 M **1**, 0.4 M **2**, 10 mol % Fe(OAc)₂, 13 mol % **L12**, 20 mol % Zn, DMF, 85 °C.

^bAverage of at least two reaction runs.

^c2 equiv of alkyne.

^dReaction Conditions: 0.4 M **1**, 0.4 M **2**, 20 mol % Fe(OAc)₂, 26 mol % **L12**, 40 mol % Zn, DMF, 85 °C.

Table 3

Cycloaddition of **1a** and unsymmetrical alkynes^a

entry	alkyne (2)	reaction time	product % yield (3:3') ^b
1	Ar = Ph, R = Me 2d	6h	3n , 69 (1.2:1)
2	Ar = <i>p</i> -OMeC ₆ H ₄ , R = Me, 2e	6h	3o , 39 (3:2)
3	Ar = <i>p</i> -CF ₃ C ₆ H 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)
7	R = Me, R' = Bu, 2j	24h	3t , 62 (1:1)
8	R = Me, R' = ^t Bu, 2k	6h	3u , 26 (0:1)

^aReaction Conditions: 0.4 M **1**, 0.4 M **2**, 10 mol % Fe(OAc)₂, 13 mol % **L12**, 20 mol % Zn, DMF, 85 °C.^bAverage of at least two reaction runs.