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Short Communication

Highly regioselective cyclotrimerization of terminal alkynes catalyzed by Fe(II) complexes bearing 2-(benzimidazolyl)-6-(1-(arylimino)ethyl)pyridines

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ABSTRACT

$FeCl_2$ ligated with 2-(benzimidazolyl)-6-(1-(arylimino)ethyl)pyridine in the presence of zinc powder and zinc iodide could effectively catalyze cyclotrimerization of intermolecular alkynes to afford benzene derivatives in high regioselectivity. The synthetic usefulness of this catalytic system consisting of Fe(II) complex **C1**, Zn and ZnI_2 in acetonitrile was tested with various terminal alkynes. In the cases of using aryl substituted alkynes, the 1,2,4-trisubstituted benzenes **2** were found to be the major products.

1. Introduction

Since the first transition-metal-catalyzed trimerization of alkynes to benzene has been demonstrated by Reppe in 1948 [1], the [2 + 2 + 2] cycloaddition of alkynes was extensively studied [2–5]. Although this approach has become one of the most powerful methods to assemble a benzene ring, it suffers from serious chemo- and regioselectivity problems which normally lead to a complex mixture of products, thus severely limiting synthetic utility of this reaction. Alternative approaches have been proposed to circumvent the lack of selectivity. Indeed, intramolecular [6,7] or partially intramolecular reactions of α,ω-diynes with an excess of monoalkynes [8,9] have been successfully employed to solve the selective problems and have been elegantly used in the total synthesis of complexly natural and artificial compounds. On the other hand, several elaborately catalytic systems involving palladium [10], ruthenium [11], rhodium [12], cobalt [13–15], iridium [16], and other transition metals [17–19] with rational ligands have been described to overcome this problem. Nonetheless, the selectivity of catalytic intermolecular cyclotrimerization of alkynes has remained a crucial issue.

Iron is an ideal transition metal, given its low price, non-toxicity and environmentally benign character. Recently, iron complexes are used as catalysts in synthetic chemistry for carbon–heteroatom [20] and carbon–carbon bond-forming reactions [21,22]. Low-valent iron complexes can induce cross-coupling [23], isomerization, and cycloaddition [21,24–26]. In addition, iron complexes ligated by bidentate *N,N*-ligands, and tridentate *N,N,N*-ligands were proven to be efficient catalyst precursors for the ethylene oligomerization and polymerization reaction [27–30]. To our knowledge, iron-catalyzed highly regioselective cyclotrimerization of intermolecular alkynes has been rarely explored, although iron-catalyzed cyclotrimerizations of intramolecular alkynes have been reported [31,32]. We report herein $FeCl_2$/2-(benzimidazolyl)-6-(1-(arylimino)ethyl)pyridine complex catalyzed cyclotrimerization of terminal alkynes with high regioselectivity (Scheme 1).

2. Results and discussion

The 2-(benzimidazolyl)-6-(1-(arylimino)ethyl)-pyridyliron dichlorides (**C1**–**C5**, Fig. 1) were readily prepared by the reaction of $FeCl_2 \cdot 4H_2O$ with the corresponding 2-(benzimidazolyl)-6-(1-(arylimino)ethyl)-pyridines (**L**) in ethanol according to the literature [29], whilst the 2,6-bis(1-(2,6-dimethylphenylamino)ethyl)pyridyliron chloride (**C6**, Fig. 1) was prepared by the literature procedure [33].

To examine the catalytic activity of complex **C1**–**C5** on cyclotrimerization of intermolecular alkyne, we tested the cyclotrimerization of phenylacetylene as a model reaction, which resulted in a quantitative yield of product **2a** with complex **C1** in excellent regioselectivity (Table 1, entry 1). The complexes as precatalyst both with electron-donating groups (entries 1, and 2) and electron-withdrawing groups (entries 4, and 5) on the benzene ring of ligands showed high activities. Complex **C3** having bulky group on the benzene ring showed moderate activity (entry 3) compared with complexes **C1** and **C2**. When complex **C6** was used as a precatalyst under the same conditions, the reaction proceeded in 80% yield with lower regioselectivity (entry 6). Since many modifications of the

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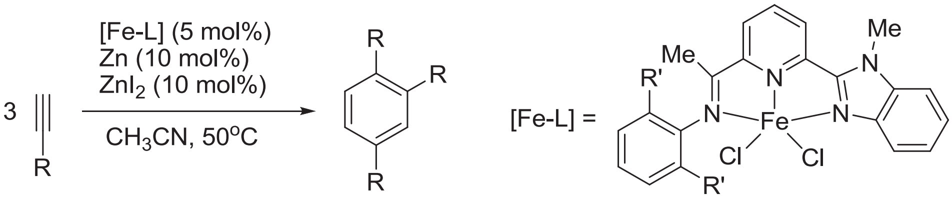


Scheme 1. Iron-catalyzed cyclotrimerization of terminal alkynes.

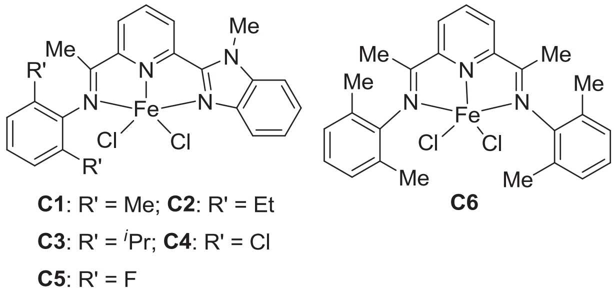
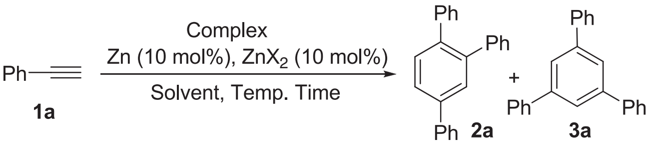


Fig. 1. Iron complexes.

complexes as precatalyst can be envisaged, we identified the complex **C1** as the precatalyst. Decreasing the temperature from 50 °C to room temperature, longer reaction time was required to accomplish the reaction (entry 8). The applicability of solvents was also evaluated (entries 1 and 9–12). Among several solvents tested, acetonitrile as solvent afforded asymmetric benzene **2a** in almost quantitative yield. We then examined other zinc salts, for instance, $ZnBr_2$ and $ZnCl_2$ decreased the yield to 57% and 56% yield, respectively (entries 13–14). It is noteworthy that without addition of any zinc salt, the reaction proceeded in low yield (entry 15). These results indicated that in the reaction ZnI_2 may be necessary for activation of precatalyst **C1** presumably by ligand exchange [34]. On the other hand, the reaction did not proceed without using iron complex (entry 16). Furthermore, when the $FeCl_2 \cdot 4H_2O$ and ligand **L1** were blended together as a precatalyst, the reaction did not proceed (entry 17). Therefore, we found the following optimized conditions: using complex **C1** as a precatalyst, the model reaction proceeded smoothly in 94% yield with excellent regioselectivity in acetonitrile at 50 °C for 8 h under nitrogen atmosphere.

The synthetic usefulness of the catalytic system consisting of Fe(II) complex **C1**, Zn and ZnI_2 in acetonitrile was tested with various terminal alkynes (Table 2). In all cases the 1,2,4-trisubstituted benzenes **2** were found to be the major products. The aryl substituted terminal alkynes gave the 1,2,4-trisubstituted benzenes **2** in good to excellent yields (entries 1–10). Aryl group could be borne as both an electron-donating group (entries 2–4) and electron-withdrawing group (entries 5–8). When 4-ethynyl-*N*,*N*-dimethylaniline **1d** was used as a substrate and the desired product was formed in 53% yield (entry 4). Cyclotrimerization of 4-ethynylbiphenyl **1i** gave 1,2,4-trisubstituted benzene **2i** in 89% yield (entry 9). Cyclotrimerization of 3-ethynylthiophene **1j** also gave 1,2,4-trisubstituted benzene **2j** in 90% yield (entry 10). When alkyl substituted terminal alkynes were used, the cyclotrimerization products formed in moderate yields with lower regioselectivity (entries 11–13). When ethyl propiolate **1n** was used, the product **2n** formed in 46% yield with high regioselectivity (entry 14). Cyclotrimerization of ethynyltrimethylsilane **1o** afforded product in low yield (entry 15). That may attribute to bulky TMS

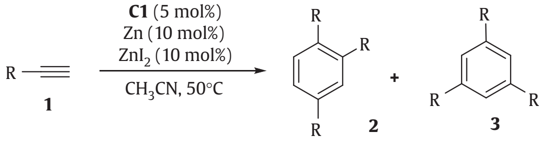
Table 1
Optimization of the reaction conditions.[a]

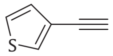


Entry	Complex	Solvent	Temp. Time		ZnX2	Yield of **2a + 3a**(%)[b]	Ratio of **2a/3a**[c]
			(°C)	(h)			
1	C1	CH_3CN	50	8	ZnI_2	94	98/2
2	C2	CH_3CN	50	8	ZnI_2	91	98/2
3	C3	CH_3CN	50	8	ZnI_2	48	98/2
4	C4	CH_3CN	50	8	ZnI_2	93	98/2
5	C5	CH_3CN	50	8	ZnI_2	89	98/2
6	C6	CH_3CN	50	8	ZnI_2	80	79/21
7	C1	CH_3CN	50	1	ZnI_2	55	98/2
8	C1	CH_3CN	rt	24	ZnI_2	83	98/2
9	C1	THF	50	8	ZnI_2	Trace	-
10	C1	CH_2Cl_2	50	8	ZnI_2	0	-
11	C1	Toluene	50	8	ZnI_2	0	-
12[d]	C1	DMF	50	8	ZnI_2	9	-
13	C1	CH_3CN	50	8	$ZnBr_2$	57	98/2
14	C1	CH_3CN	50	8	$ZnCl_2$	56	98/2
15[e]	C1	CH_3CN	50	8	-	16	-
16	-	CH_3CN	50	8	ZnI_2	0	-
17	$FeCl_2$ $4H_2O/L_1$	CH_3CN	50	8	ZnI_2	0	-

[a] Conditions: Phenylacetylene (110 mL, 1 mmol), complex (0.05 mmol), zinc powder (6.5 mg, 0.10 mmol), ZnX_2 (0.10 mmol), solvent (2.0 mL).
[b] Isolated yield.
[c] The isomeric ratio was determined via careful integration of ^1H NMR spectra.
[d] 1,4-Diphenylbuta-1,3-diene was obtained in 10% yield.
[e] Mixture of **2a**, **3a**, 1,4-Diphenylbuta-1,3-diene.

Table 2
Fe(II) complex **C1** catalyzed cyclotrimerization of terminal alkynes.



Entry	R—≡		Times (h)	Yield (%)[a]	Ratio of **2:3**[b]
1	Ph—≡	**1a**	8	94	98:2
2	p-$\mathrm{MeC_6H_4}$—≡	**1b**	8	91	97:3
3	p-$\mathrm{MeOC_6H_4}$—≡	**1c**	8	81	97:3
4	p-$\mathrm{Me_2NC_6H_4}$—≡	**1d**	8	53	92:8
5	p-$\mathrm{ClC_6H_4}$—≡	**1e**	8	92	98:2
6	p-$\mathrm{FC_6H_4}$—≡	**1f**	8	80	98:2
7	p-$\mathrm{AcC_6H_4}$—≡	**1g**	8	91	> 99
8	p-$\mathrm{MeO_2CC_6H_4}$—≡	**1h**	8	94	> 99
9	p-$\mathrm{PhC_6H_4}$—≡	**1i**	8	89	> 99
10		**1j**	8	90	95:5
11	$\mathrm{Cl(CH_2)_3}$—≡	**1k**	24	54	59:41
12	$\mathrm{Ph(CH_2)_2}$—≡	**1l**	24	30	58:42
13	$\mathrm{NC(CH_2)_3}$—≡	**1m**	24	45	62:38
14[c]	$\mathrm{EtO_2C}$—≡	**1n**	8	46	> 99
15	TMS—≡	**1o**	24	11	> 99

[a] Isolated yield.
[b] The isometric ratio was determined via careful integration of ^1H NMR spectra.
[c] (E)-Diethyl hex-2-en-4-ynedioate was obtained with 23% isolated yield.

group. When the internal alkynes were treated under this reaction conditions, the fully substituted benzene was not observed.

Although confirmation of the reaction mechanism must await further study, we postulate the reaction course as illustrated in Scheme 2, which based on reported metal-catalyzed reactions [2]. Firstly, the complex **C** ($\mathrm{LFeCl_2}$) may react with $\mathrm{ZnI_2}$ to afford $\mathrm{LFeI_2}$, which can be reduced by Zn powder to give possible intermediates **4** [30,31]. The complex **4** can quickly react with two equivaluents of alkyne to give metallacyclopentadienes **5** [35]. In some cases of the reaction, a trace amount of 1,4-diphenylbuta-1,3-diene was detected. That result confirmed that di(α-aryl)-ferrocyclopentadiene **5** would be favorable than (α-aryl)-(β-aryl) ones. The intermediate **5** can further be cyclized to **6** and/or **7** through an insertion or [4+2]-cycloaddition pathway, respectively. Reductive elimination reaction of **6** and/or **7** yields benzene derivative **2** and regenerates the low valent complex **4**.

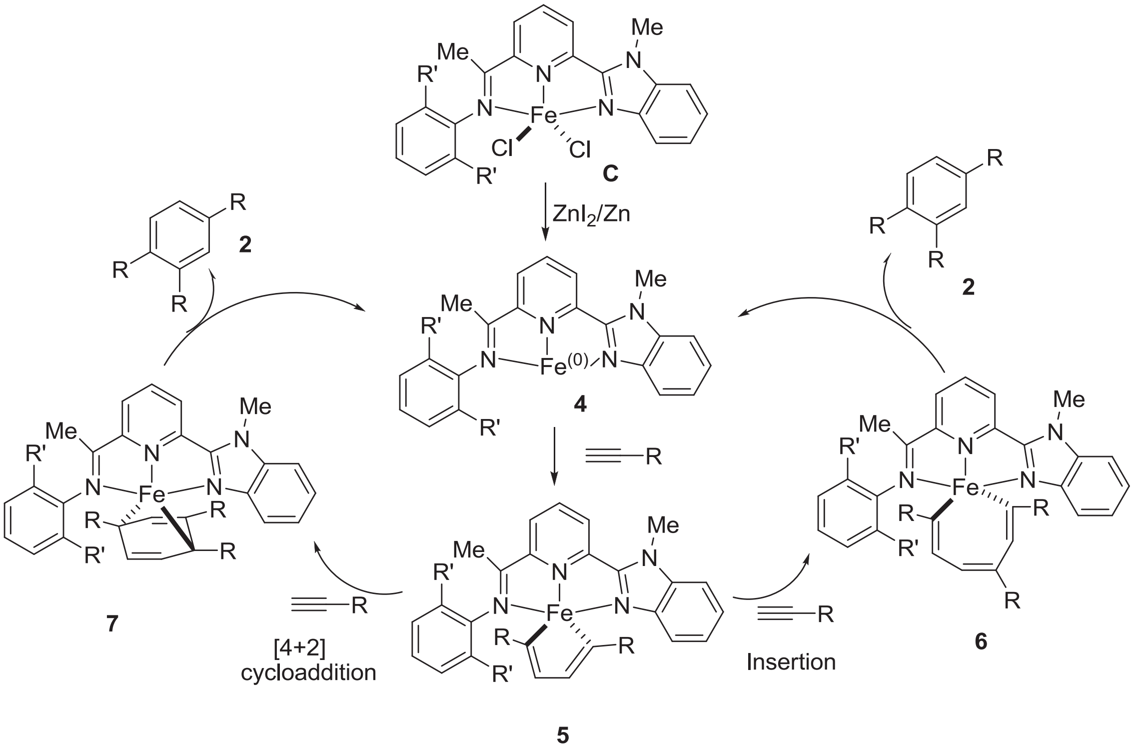
3. Conclusion

We have shown that the cyclotrimerization of aromatic terminal alkynes can be efficiently catalyzed by iron complexes in acetonitrile to afford 1,2,4-trisubstituted benzene derivatives in good to excellent yields. Further investigations of mechanism and applications are still in progress.

4. Experimental

4.1. Procedure for the preparation of complexes **C1**–**C6**

The complexes **C1**–**C6** were synthesized by the reaction of $\mathrm{FeCl_2 \cdot 4H_2O}$ with the corresponding ligands in ethanol. A typical synthetic procedure for **C1** was described as follows: the ligand 2,6-dimethyl-N-(1-(6-(1-methyl-1 H-benzo[d]imidazol-2-yl)pyridin-2-yl)ethylidene)aniline (74 mg, 0.21 mmol) and $\mathrm{FeCl_2 \cdot 4H_2O}$ (79.5 mg, 0.20 mmol) were added to a Schlenk tube, followed by the addition of freshly distilled ethanol (5 mL) with rapid stirring at room temperature. The solution turned green immediately, and a blue precipitate formed. The reaction mixture was stirred for 12 h, and then the precipitate was washed with diethyl ether twice and dried to give the pure product as a blue powder in 89% yield. IR (KBr; cm^{-1}): 3448 (m), 3066 (m), 2952 (w), 2915 (w), 1560 (vs), 1495 (m), 1472 (s), 1419 (s), 1372 (m), 1323 (s), 1273 (m), 1211 (s), 1100 (m), 1021 (w),



Scheme 2. Possible reaction mechanism.

813 (m), 793 (w), 764 (m), 746 (s). Anal. Calcd for $C_{23}H_{22}Cl_2FeN_4$ (481.20): C, 57.41.56; H, 4.61; N, 11.64. Found: C, 57.37.56; H, 4.64; N, 11.61.

4.2. General procedure for the catalytic cyclotrimerization of terminal alkynes

Iron(II) complex **C1** (24.1 mg, 0.05 mmol), zinc powder (6.5 mg, 0.10 mmol), zinc iodide (32 mg, 0.10 mmol), terminal alkyne (1 mmol), and acetonitrile (2.0 mL) were added to a pre-dried screw capped test tube. The mixture was stirred at 50 °C for an indicated time. The reaction mixture was quenched with hydrochloric acid (3 M) and extracted with ethyl ether. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of petroleum ether and ethyl acetate as eluent to afford desired product.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2010.11.013.

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