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Iron catalyzed highly regioselective dimerization of terminal aryl alkynes†

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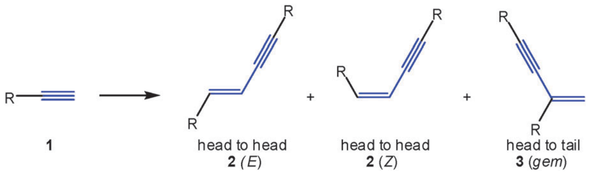
Iron can catalyze head-to-head dimerization of terminal aryl alkynes to give the corresponding (*E*) selective conjugated enynes in high yields. A variety of substituted aryl acetylenes underwent smooth dimerization using catalytic $FeCl_3$ and DMEDA in the presence of KO^tBu.

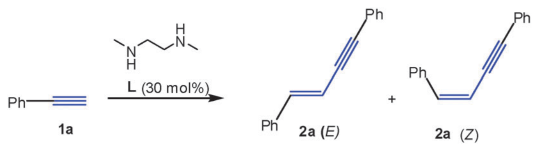
Conjugated enynes are the most versatile building blocks in organic synthesis found in bioactive molecules, drug intermediates, and organic electronic materials.[1,2] Dimerization of terminal alkynes is an atom-economical[3] and practical method to prepare conjugated enynes.[4–6] However, a highly selective synthesis of conjugated enynes by a dimerization is challenging[4–6] due to the competitive formation of other three possible (*E*), (*Z*), and *gem*-enyne[6] isomers (Scheme 1).[4–6] Although various transition metal[4] and f-element catalysts[5] are known to catalyze the dimerization of terminal alkynes, it is an important goal to develop clean and economically interesting processes for selective alkyne dimerization.

Recently iron-based catalytic systems have generated significant growing interests because iron salts are inexpensive and readily available.[7–10] Iron salts have been used as important alternatives to established transition metal-catalyzed carbon–carbon and carbon–hetero bond formation reactions[7] including Sonogashira[8] and Suzuki coupling.[9] In our efforts directed towards development of sustainable chemical procedures, we herein report *E*-selective head-to-head dimerization of terminal aryl alkynes catalyzed by a $FeCl_3$-bidentate chelating ligand system in the presence of KO^tBu.



Scheme 1 Dimerization of terminal alkyne.

Table 1 Screening of reagents for iron catalyzed dimerization of phenyl acetylene **1a**



Entry	Cat.[a]	Base[b]	Solvent, temp/°C, time	Ratio,[c] yield (%) of **2a** (*E*/*Z*)
1	$FeCl_3$	Cs_2CO_3	Toluene, 145, 48 h	89 : 11, 48
2	$FeCl_3$	K_2CO_3	Toluene, 145, 72 h	67 : 33, 50
3	$FeCl_3$	K_3PO_4	Toluene, 145, 72 h	86 : 14, 35
4	$FeCl_3$	KO^tBu^d	Toluene, 145, 2 h	78 : 22, 65
5	$\mathbf{FeCl_3}$	$\mathbf{KO^tBu}$	**Toluene, 145, 2 h**	**78 : 22, 73**
6	$FeCl_3$	KO^tBu	Toluene, 65,15 h	75 : 25, 50
7	$FeCl_3$	KO^tBu	THF, 85, 2 h	61 : 29, 67
8	$FeCl_3$	KO^tBu	CH_2Cl_2, 85, 2 h	NR
9	$FeCl_3$	KO^tBu	MeCN, 145, 2 h	NR
10	$FeCl_3$	KO^tBu	DMF, 145, 2 h	75 : 25, 55
11	$FeCl_3$	KO^tBu	DMSO, 145, 2 h	74 : 26, 50
12	$FeCl_3$	KO^tBu	Dioxane, 145, 2 h	72 : 28, 45
13	$FeCl_3$	KO^tBu	Neat, 145, 2 h	71 : 29, 45

[a] 30 mol% of $FeCl_3$ (98%), [b] 3 equiv. of base, [c] *E* : *Z* ratios were determined by ^1H NMR analysis of the crude reaction mixture. [d] 2 equiv. of KO^tBu.

When phenyl acetylene **1a** was treated with $FeCl_3$ (30 mol%) and DMEDA (**L**, 30 mol%) in the presence of Cs_2CO_3 for 48 h (Table 1, entry 1), the enyne **2a** (ratio *E*/*Z* = 89 : 11) was obtained in 48% yield.[11] Encouraged by this finding, we examined the efficiency of this $FeCl_3$ catalyzed ligand system for dimerization of phenylacetylene **1a** as a model system, and some of the representative results are summarized in Tables 1–3 (and ESI†).

After screening of different bases (entries 1–5), potassium *tert*-butoxide (3 equiv.) was found to be the most effective, and 73% yield of the desired product **2a** was obtained (*E*/*Z* = 78 : 22) using toluene as the solvent at 145 °C for 2 h (entry 5). The yield and selectivity of product **2a** decreased with further increasing of the reaction time (entry 6). All other tested bases, such as K_2CO_3, Cs_2CO_3 or K_3PO_4, took longer reaction time (48 to 72 h) and gave lower yield of enyne **2a** (entries 1–3). The reactions employing different solvents, such as THF (entry 7), DMF (entry 10), DMSO (entry 11) and dioxane (entry 12),

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† Electronic supplementary information (ESI) available: Detailed description of experimental procedures, characterization of all compounds. See DOI: 10.1039/c1cc10346f

gave the desired product in low yields, whereas no product was detected using CH_2Cl_2 (entry 8) and MeCN (entry 9). The dimer **2a** was obtained in 45% yield under solvent free conditions (entry 13).

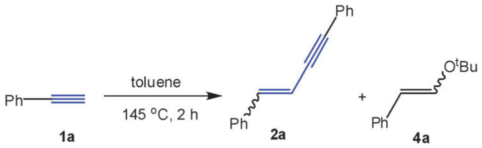
It is intriguing to note that KO^{t}Bu alone (entry 4, Table 2) without the addition of $FeCl_3$ and DMEDA (ESI†) could promote dimerization leading to 11% of the dimerized product **2a** along with 63% of the *tert*-butoxystyrene **4a** (E/Z = 17 : 83).[12,13] While in the presence of $FeCl_3$ (30 mol%), the dimer **2a** was obtained as the sole product (ESI†), which reveals the potential role of the iron catalyst in this transformation. In the absence of base, no reaction took place (entry 3, Table 2).

Recently Buchwald and Bolm reported that $FeCl_3$ catalyzed reactions may be influenced by trace amounts of copper impurities.[14] However, iron/copper promoted oxidative homo-coupling reaction of terminal alkynes has been reported to give the corresponding diynes.[15] We have carried out the dimerization of **1a** using copper salts in the presence of **L** and KO^{t}Bu. Copper salts were found to be ineffective to promote a dimerization of **1a** to give the desired product **2a** (entries 10 and 11, Table 2).

The yield of enyne **2a** was significantly decreased using $Fe(acac)_3$ (entry 6, Table 2) instead of $FeCl_3$ (entry 1). No product was obtained using $FeCl_3$ on silica gel (entry 5). Our results show that anhydrous iron salts are more effective (entries 7 and 8) to catalyze the transformation. We further found out that the purity of iron source does not play an important role in this reaction. Anhydrous $FeCl_2$ (beads, 99.99%, Aldrich) could promote the dimerization of **1a** to give the dimer **2a** in 63% yield (entry 8, Table 2). Similarly $FeCl_3$ (99.9%, Aldrich) gave comparable results with respect to reagent grade $FeCl_3$ (97%, SRL, entries 1 and 2, Table 2). On the basis of selectivity, reaction times and yields (Tables 1 and 2 and ESI†), the best result was achieved using 30 mol% $FeCl_3$, 30 mol% DMEDA, and 3 equiv. of KO^{t}Bu in toluene at 145 °C for 2 h.

We found that a series of aryl acetylenes **1** smoothly underwent dimerization to produce the head-to-head dimers **2** in good to excellent yield (Table 3). Both strongly electron-donating and electron-withdrawing groups were compatible

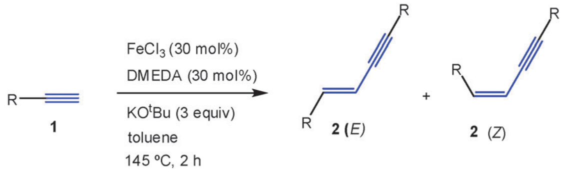
Table 2 Iron catalyzed dimerization of phenyl acetylene **1a**

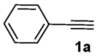
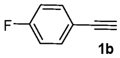
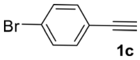
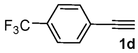
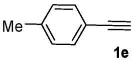
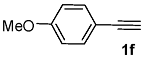
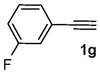
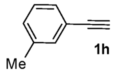
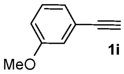
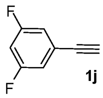
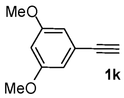
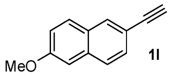
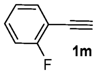
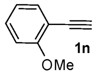


Entry	Cond.[a]	Ratio of **2 : 4**[b]	Ratio, yield of **2a** (E/Z)[b]	Ratio, yield of **4a** (E/Z)[b] (%)
1	**$FeCl_3$,[c] L, KO^{t}Bu**	**100 : 0**	**78 : 22, 73**	—
2	$FeCl_3$,[d] **L**, KO^{t}Bu	100 : 0	78 : 22, 71	—
3	$FeCl_3$,[c] **L**[d]	No isolated product		
4	KO^{t}Bu	26 : 74	77 : 23, 11	17 : 83, 63
5	$FeCl_3$ on silica gel,[e] **L**, KO^{t}Bu	No isolated product		
6	$Fe(acac)_3$,[f] **L**, KO^{t}Bu	82 : 18	80 : 20, 45	>99 *Z*, 12
7	$FeCl_2,6H_2O$,[g] **L**, KO^{t}Bu	85 : 15	78 : 22, 50	>99 *Z*, 7
8	$FeCl_2$,[h] **L**, KO^{t}Bu	100 : 0	67 : 33, 63	—
9	$FeCl_2$,[h] **L**, KO^{t}Bu[i]	100 : 0	55 : 45, 62	—
10	CuCl, **L**, KO^{t}Bu	5 : 95	—	—
11	$CuCl_2.2H_2O$, **L**, KO^{t}Bu	6 : 94	—	—

[a] 30 mol% of $FeCl_3$, 30 mol% of **L** and 3 equiv. of KO^{t}Bu were used. [b] Ratios were determined by ^{1}H NMR analysis of the unpurified reaction mixture. Purity and source of iron salts: [c] 99.9%, Aldrich, [d] 97%, Sisco Research Laboratory (SRL), [e] 5 wt%, Aldrich, [f] 97%, Aldrich, [g] 98%, Loba Chemie, [h] 99.99%, Aldrich, [i] Using 40 mol% of KO^{t}Bu for 15 h.

Table 3 Iron catalyzed dimerization of aryl acetylenes **1**[a,b]



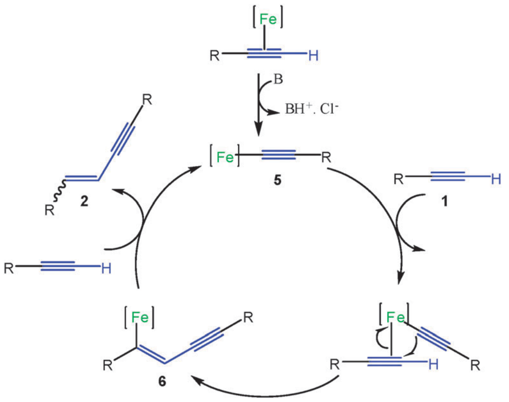
Entry	Substrate **1**	Conv.[a]	Ratio of **2** (E/Z)[a]	Yield (%) **2**
1	 **1a**	>99	78 : 22	73
2		>99	77 : 23[c]	42[c]
3	 **1b**	85	67 : 33	71
4	 **1c**	75	67 : 33	67
5	 **1d**	>99	67 : 33	55
6		>99	56 : 44[c]	29[c]
7	 **1e**	>99	73 : 27	99
8	 **1f**	>99	70 : 30	97
9	 **1g**	>99	73 : 27	55
10	 **1h**	>93	67 : 33	73
11	 **1i**	>99	75 : 25	57
12	 **1j**	>99	75 : 25	59
13	 **1k**	84	78 : 22	50
14	 **1l**	77	78 : 22	65
15	 **1m**	84	83 : 17	61
16	 **1n**	>95	71 : 29	90
17	C_5H_{12}—≡ **1o**	—	—	NR

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] All the reactions were carried out using 99.9% $FeCl_3$ (Aldrich). [c] In the absence of **L**.

with this procedure (Table 3). The yields for the dimerization ranged from 50 to 99% and the ratio of *E* and *Z* head-to-head dimers varies from 67 : 33 to 83 : 17 in favor of the *E* isomer. The dimerization of 4-fluorophenylacetylene **1b** in toluene gave a 67 : 33 mixture of the *E* and *Z* dimers in 71% yield (Table 3, entry 3). The 4-bromophenylacetylene **1c** was reacted under similar conditions (entry 4, Table 3) to give the corresponding product **2c** in 67% yield. When dimerization of aryl acetylene **1d** was carried out in the absence of ligand (entry 6), the corresponding product **2d** was obtained in 29% yield as nearly 1 : 1 ratio of *E*/*Z* isomers. While in the presence of ligand **L** (entry 5) the product **2d** was obtained in improved yield (55%) and selectivity (*E*/*Z* = 67 : 33), which confirms the key role of ligand in iron catalyzed dimerization. 4-Methyl and 4-methoxy phenylacetylenes (**1e,f**) furnished the corresponding dimers **2e,f** in near quantitative yield (*E*/*Z* = 2.5 : 1, entries 7 and 8).

The electron-donating substituents at *ortho* and *para* positions of phenyl acetylenes accelerated the reaction as evidenced by better yields (Table 3). Sterically hindered substrates bearing *ortho* substituents **1m** and **1n** (entries 15, 16) gave the desired products in good to high yields. Our results also show that substrates having *meta*-substituted phenylacetylenes reacted slower affording the corresponding products in moderate yields (entries 9–13). For example, 1-ethynyl-3,5-difluorobenzene (**1j**) was converted to the corresponding dimers in 59% yield with an *E*/*Z* ratio of 3 : 1. The 2-ethynyl-6-methoxynaphthalene (**1l**) furnished the desired product in 65% yield (entry 14). Under the reaction conditions employed, aliphatic alkyne **1o** did not yield the corresponding dimer **2o** at all (entry 17).

A plausible reaction mechanism is depicted in Scheme 2. The catalytic cycle may proceed with the formation of metal acetylide **5**.[16] Subsequent head-to-head insertion of alkyne **1** into the acetylide compound **5** would yield the alkenyl intermediate **6**. Another molecule of alkyne may react with **6** to yield the dimer **2** and regenerate the alkynide species **5**. While the reaction proceeds using catalytic KO^{t}Bu (40 mol%, Table 2, entry 8) in the case of **1a** to give **2a** in 62% yield, our results indicate that the proposed catalytic cycle requires excess KO^{t}Bu (2–3 equivalent) with other substrates to drive the reaction in forward direction.



Scheme 2 Proposed mechanism.

In summary, we have described a novel iron catalyzed regioselective dimerization of terminal aryl alkynes to prepare a variety of conjugated enyne compounds. This catalytic system represents an alternative to toxic and expensive transition metals. Further mechanistic investigation is currently underway.

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