## Iron-Catalyzed Enyne Cross-Coupling Reaction

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In the presence of 0.5-1 mol % of FeCl<sub>3</sub> with lithium bromide as a crucial additive, alkynyl Grignard reagents, prepared from the corresponding alkynes and methylmagnesium bromide, react with alkenyl bromides or triflates to give the corresponding conjugated enynes in high to excellent yields. The reaction shows wide applicability to various terminal alkynes and alkenyl electrophiles.

Conjugated enyne is a key structural and often functional unit of various bioactive molecules, drug intermediates, and organic electronic materials.<sup>1</sup> Development of Pd-catalyzed Csp–Csp<sup>2</sup> coupling reactions (cf., the Negishi coupling, the Sonogashira coupling, and the Heck reactions) have significantly contributed to selective and efficient syntheses of the unsaturated structure.<sup>2</sup> Recent investigations aimed toward the development of inexpensive and practical methods for enyne coupling revealed that cobalt,<sup>3a</sup> nickel,<sup>3b–d</sup> and copper<sup>3e–g</sup> can be effective catalysts for such a purpose. Herein, we wish to disclose another practical enyne coupling reaction, in which alkenyl halides or triflates and alkynyl-magnesium reagents are cross-coupled by iron catalyst with the aid of concomitant lithium halides.

Despite the recent remarkable progress in the field of ironcatalyzed cross-coupling reactions,<sup>4–7</sup> no successful example of enyne coupling has been reported to date. Even though various combinations of an alkenyl electrophile and an organomagnesium reagent have already been examined in the pioneering work of Kochi<sup>8</sup> and the breakthrough work of Cahiez,<sup>5a</sup> they were limited to alkyl and aryl metal reagents. This is very likely due to the stability of the Fe–C bond of alkynyl iron species, which allows the formation of stable ferrate complexes to halt the catalytic cross-coupling process.<sup>9,10</sup> Based on our previous studies on iron catalysis, we envisioned that suitable Lewis basic or acidic additives could facilitate the reductive decomposion of the ferrate to produce a catalytically active iron species.

We thus conducted a catalyst and promoter screening by using the reaction between octynyl magnesium bromide **1a** and  $\beta$ -bromostyrene **2** as a benchmark reaction (Scheme 1). 1-Octynylmagnesium bromide **1a** was prepared from 1-octyne and an equimolar amount of methylmagnesium bro-

**Scheme 1.** Preparation of 1-Octynyl Magnesium Bromide and Iron-Catalyzed Cross-Coupling Reaction with  $\beta$ -Bromostyrene



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mide<sup>11</sup> at 60 °C for 4 h. FeCl<sub>3</sub><sup>12</sup> (0.5 mol %) and  $\beta$ -bromostyrene **2** (*E*:*Z* = 85:15) were added at 0 °C to the THF solution of **1a** (1.2 equiv). The reaction mixure was stirred at 50 °C for 24 h, and the yield of the desired enyne **3** was determined by <sup>1</sup>H NMR.

Table 1 summarizes the result of the screening of Lewis basic or acidic promoters. As in entry 1, conversion of  $\beta$ -bromostyrene was sluggish without any addives to give **3** in 12% yield. Previously reported effective additives for the iron-catalyzed coupling reactions were tested. Those additives are the following: *N*-methyl-2-pyrrolidone<sup>5a-d</sup> (9.0 equiv, NMP), tricyclohexylphosphine<sup>6g</sup> (1 mol %, PCy<sub>3</sub>), 1,3-bis(2,6-*i*-propylphenyl)imidazolinium hydrochloride<sup>6g</sup> (2 mol %, SIPr·HCl), hexamethylenetetramine<sup>6i</sup> (5 mol %, HMTA), and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (10 mol %, TME-DA). These additives, however, did not improve the product yield (entries 2–5). A stoichiometric amount of TMEDA<sup>6a</sup> (1.2 equiv) accerelated the reaction to give **3** in 60% yield

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(10) Bolm et al. recently reported an iron-catalyzed Sonogashira coupling of terminal alkynes and iodoarenes, under less basic or nucleophilic conditions than those described here. The present enyne coupling reaction did not proceed with Bolm's iron-catalyst system. Carril, M.; Correa, A.; Bolm, C. Angew. Chem., Int. Ed 2008, 47, 4862–4865.

(11) Deprotonation can be achieved at room temperature by using ethylmagnesium bromide.

(12) FeCl<sub>2</sub>, Fe(acac)<sub>3</sub>, and other iron salts showed comparable catalytic activity as described in entry 1, Table 2.

Table 1. Effect of Lewis Basic and Acidic Additives

$entry^a$	additive (X mol %)	yield of $3~(\%)^b$	recovery of <b>2</b> (%)
1	none (–)	12	83
2	NMP (900)	2	69
3	HMTA/TMEDA (5/10)	15	76
4	SIPr•HCl (2)	11	76
5	$PCy_3(1)$	17	75
6	TMEDA (120)	60	36
7	LiCl (120)	82	18
8	LiBr (120)	85	9
9	LiBr (60)	27	71
10	LiBr (20)	21	72
11	$MgBr_2$ (120)	28	65
12	$ZnCl_{2}$ (120)	1	93

 $^a$  Reactions were carried out on a 1.0 mmol scale.  $^b$  The yield was determined by  $^1\!\mathrm{H}$  NMR analysis by using dibromomethane as an internal standard.

(entry 6). Note that additional TMEDA or prolonged reaction time did not improve the yield.

We next examined a series of metal salts and found that a considerable improvement of the yield could be achieved with 120 mol % of LiCl or LiBr<sup>13</sup> (entries 7 and 8). It is noteworthy that 1-octynyllithium, prepared from 1-octyne and *n*-BuLi, did not give enyne **3** under the same conditions. Reduced amount of LiBr (20 and 60 mol %) or use of additional magnesium salts was not effective (entries 9–11). In sharp contrast to Negishi coupling, addition of ZnCl<sub>2</sub> (transmetalation to zinc)<sup>2b</sup> did not work at all under the present conditions (entry 12). In all cases, enyne **3** was obtained as a 88:12 mixture of geometrical isomers (*E:Z*) along with the formation of hexadeca-7,9-diyne in 1–5%.

To examine the substrate scope of the reaction, we carried out the cross-coupling reaction using a variety of alkenyl electrophiles and alkynyl magnesium bromides (1a-1f, Figure 1) in the presence of FeCl<sub>3</sub> (0.5-3 mol %) and LiBr (120 mol %).





Table 2 illustrates the iron-catalyzed cross-coupling reactions under the optimum conditions described above. As shown in entry 1, the reaction between 1a and 2 completed at 60 °C for 24 h to give enyne 3 in 95% yield. Iron(II)

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<sup>(13)</sup> Other lithium salts were also examined: LiI (32%), LiOTf (86%), LiClO<sub>4</sub> and LiBF<sub>4</sub> (0%). The combined use of lithium salt and TMEDA was not as effective as lithium salt itself.

**Table 2.** Iron-Catalyzed Enyne Coupling in the Presence of Lithium Bromide

entry <sup>a</sup>	RMgBr	electrophile	product	yield $(\%)^b$
1	1a	<b>2</b> <sup>c</sup>	C <sub>6</sub> H <sub>13</sub>	95 <sup>d, e</sup> (89 <sup>f</sup> 86 <sup>g</sup> )
2	1a	Br	C <sub>6</sub> H <sub>13</sub>	(02, 602) 76
3	1a	Br	$C_6H_{13}$ $\sim$ TMS	> 99 <sup>d, h</sup>
4	1a	TfO 8 C <sub>6</sub> ⊢	$C_6H_{13}$ <b>9</b> $C_6H_{13}$	75
5	1b	<b>2</b> <sup>c</sup>	TBDMSO 10 Pr	82 <sup>i</sup>
6	1c	<b>2</b> <sup>c</sup>		Ph <sup>91<sup>j</sup></sup>
7	1c	6		88 S
8	1d	6	TBDMS	87 <sup>k</sup>
9	1e	6	TIPS — ( 14 TMS	$84^d$
10	1d	8	TBDMS	83
11	1f	4	$\sum_{16}$	60 <sup>1</sup>
12	1f	6		91 <sup>d</sup>
13	1c	Br	TBDPSO-(/)2 19 <i>E</i>	92 - (93% E)
14	1c	Br	TBDPSO-()2	92 (65% Z)

<sup>*a*</sup> Reactions were carried out at 60 °C for 24 h on a 1.0 mmol scale in the presence of 1 mol % of FeCl<sub>3</sub> unless otherwise noted. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> E:Z = 85:15 <sup>*d*</sup> 0.5 mol % of FeCl<sub>3</sub> was used. <sup>*e*</sup> E:Z = 88:12 <sup>*f*</sup> 0.5 mol % of FeCl<sub>3</sub> was used. <sup>*k*</sup> Reaction time was 12 h. <sup>*i*</sup> E:Z = 92:8 <sup>*i*</sup> E:Z = 85:15 <sup>*k*</sup> 3 mol % of FeCl<sub>3</sub> was used. <sup>*l*</sup> Reaction time temperature was 80 °C.

salts, FeCl<sub>2</sub> and Fe(acac)<sub>3</sub>, showed comparable catalytic activity to give **3** in 89% and 86% yield, respectively. The reactions with 2-bromopropene and 1-trimethylsilylpropene smoothly took place to give enynes **5** and **7** in 76% and >99% yield, respectively (entries 2 and 3).

Alkenyltriflate **8** also took part in the coupling reaction (entry 4).<sup>3a</sup> Silylethers remained intact under the present reaction conditions (entries 5–7). This method can be applicable for silylethynyl Grignard reagents<sup>14</sup>1d and 1e (entries 8–10). Phenylethynylmagnesium bromide 1f, slightly

less reactive than 1a-1e, reacted with 4 and 6 to give enynes 16 and 17 in 60% and 91% yield, respectively (entries 11 and 12). As shown in entries 13 and 14, the present reaction turned out to be stereoselective<sup>15</sup> to some degree: *trans*-1-bromopropene 18*E* (99% *E*) gave *trans*-isomer 19*E* as a major product (93% *E*), and 18*Z* (99% *Z*) gave *cis*-isomer 19*Z* as a major (65% *Z*).





A possible mechanism of the iron-catalyzed enyne coupling is shown in Scheme 2. Based on the initial formation of the divne upon mixing the alkynyl metal and the precatalyst FeCl<sub>3</sub>, a trivalent iron salt would presumably be first reduced to a low-valent state (A), such as Fe(0) or Fe(I), which probably possesses one or a few alkynyl groups. In the absence of a lithium salt, the initial reduction is rather sluggish and highly dependent on the strucure of the alkynyl moiety because of the notable stability of Fe(II) alkynyl ate complexes.<sup>3a,9</sup> Oxdative addition of an alkenyl bromide to the low-valent ferrate complex A gives the higher-valent ferrate complex **B**, which undergoes reductive elimination to produce the corresponding enyne. The resulting ferrate complex C reacts with alkynylmagnesium bromide to regenerate A. The partial loss of the stereochemical purity of (E)- and (Z)-propenyl bromides indicates the involvement of an electron transfer process at the oxidative addition step.<sup>16</sup>

In summary, we have found a pronounced acceleration effect of lithium salts on the cross-coupling of alkynylmagnesium reagents under iron catalysis to achieve a new transition-metal-catalyzed enyne coupling reaction. The present reaction possesses several synthetically attractive

<sup>(14) (2-</sup>Trimethylsilyl)ethynylmagnesium bromide shows lower reactivity to give the corresponding enyne in 39% yield.

<sup>(15)</sup> The iron-catalyzed coupling reactions between alkylmagnesium bromide and alkenyl halide take place stereoselectively. See refs 5a and 8a-e.

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features: (1) simple procedure, (2) high selectivity, (3) high yield, and (4) freedom from expensive metals and ligands. The acceleration effect of certain lithium salts would also be helpful for further development of iron-catalyzed cross-coupling reactions.

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**Supporting Information Available:** Experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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