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Journal:	<i>Organic &amp; Biomolecular Chemistry</i>
Manuscript ID	OB-COM-02-2020-000357.R1
Article Type:	Communication
Date Submitted by the Author:	23-Mar-2020
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## Regio and stereoselective synthesis of 1,4-enynes by iron-catalysed Suzuki–Miyaura coupling of propargyl electrophiles under ligand-free condition

sReceived 00th January 20xx,  
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

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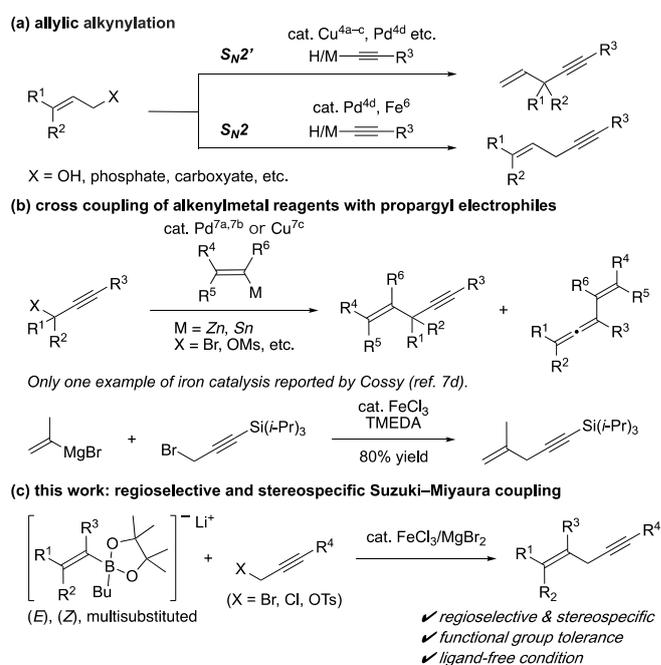
**The first iron-catalysed cross coupling of propargyl electrophiles with lithium alkenylborates has been developed. Various propargyl electrophiles can be cross-coupled with lithium (*E*)- or (*Z*)-alkenylborates in a stereospecific manner to give the corresponding 1,4-enynes in good to excellent yields. The reaction features high *S<sub>N</sub>2*-type regioselectivity and functional group compatibility.**

1,4-Enynes are versatile synthetic building blocks for complex molecular frameworks of natural and non-natural bioactive compounds.<sup>1–3</sup> While various synthetic approaches to 1,4-enynes have therefore been developed to date,<sup>4–11</sup> several limitations remain in the state-of-the-art. For example, the synthesis of densely substituted 1,4-enynes by allylic alkylation is highly challenging due to the lack of suitable methods for simultaneous control of regioselectivity and alkene geometry, and no precedent exists for the installation of tetrasubstituted alkene moieties with this method (Scheme 1a).<sup>4</sup> Cross-coupling reactions between a propargyl electrophile and an alkenylmetal is an alternate approach that provides a diverse array of stereochemically-defined multi-substituted 1,4-enynes (Scheme 1b).<sup>7</sup> Despite its high synthetic potential, this cross-coupling approach suffers from narrow substrate scope, poor functional group compatibility, and most importantly, poor control over regioselectivity (i.e., *S<sub>N</sub>2* vs. *S<sub>N</sub>2'* selectivity).<sup>12–16</sup>

We previously reported the Suzuki–Miyaura coupling of various organoborates with alkyl halides in the presence of iron catalysts, which proceeded with high functional group compatibility to afford the coupling products.<sup>17</sup> We thus envisioned that the iron-catalysed cross-coupling reaction of

propargyl electrophiles with alkenylborates would enable expedient synthesis of varied 1,4-enynes. Herein, we report the first iron-catalysed Suzuki–Miyaura coupling of lithium alkenylborates with propargyl electrophiles, which furnishes densely substituted and functionalised 1,4-enynes in a highly regioselective and stereospecific manner (Scheme 1c).

Our study began with the screening of metal catalysts and reaction conditions for the cross coupling of lithium alkenylborate (**1a** or **1a'**) with propargyl bromide **2a\_Br**, as shown in Table 1. The reaction was carried out as follows: Borate **1a** or **1a'** was prepared by the treatment of the corresponding alkenylboronate with *t*-BuLi or BuLi, respectively, and used for the coupling reaction without isolation/purification. To the mixture of the borate and the



**Scheme 1** Synthesis of 1,4-enynes through allylic alkylation and transition-metal-catalysed cross-coupling reactions of alkenylmetal reagents with propargyl electrophiles.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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propargyl bromide, catalytic amounts of transition-metal salts and MgBr<sub>2</sub> were added and stirred at 0 °C for 1 hour.

In the case of FeCl<sub>3</sub>, the stereospecific cross-coupling reaction proceeded selectively at the Csp<sup>3</sup>-Br position to give the desired product **3a** in quantitative yield without the formation of allene isomer **4a** (entry 1, Table 1).<sup>17b</sup> Notably, the (*Z*)-configuration of **1a** is entirely retained in the transformation. BuLi could also activate alkenylboronate for cross coupling to give **3a** in 95% yield (entry 2). In the absence of either the FeCl<sub>3</sub> or MgBr<sub>2</sub>, no coupling product was formed (entries 3 and 4). Precious or rare metal salts, such as PdCl<sub>2</sub> and NiCl<sub>2</sub>, did not catalyse the present reaction at all (entries 5 and 6).<sup>7a,7b,12,13</sup> whereas CoCl<sub>2</sub>, MnCl<sub>2</sub>, and CuCl showed lower catalytic activity and selectivity than that with the iron catalyst (entries 7–9).<sup>14</sup> This successful conversion represents the first example of the alkenylation of propargyl electrophiles with lithium alkenylboronates. Since *t*-BuLi is air-sensitive and flammable, we adopted the conditions in entry 2 as the optimal ones.

With the optimal conditions in hand, we studied the scope of lithium alkenylboronates **1** and propargyl bromides **2** in the cross coupling, as shown in Table 2. Various lithium (*Z*)-alkenylboronates<sup>18</sup> smoothly cross-coupled with **2a-Br** to give the corresponding 1,4-enynes **3a–3d**, in good to excellent yields. The scalability of the method was demonstrated by conducting the reaction on a gram-scale, in which 9.45 mmol of **1a'** reacted with **2a-Br** to afford 2.92 g of **3a** in 87% yield. When lithium (*E*)-alkenylboronate<sup>19,20</sup> was used, the yield of **3e** was much lower than that using the corresponding (*Z*)-alkenylboronate; nevertheless, the yield reached 82% upon increasing the catalyst loading of FeCl<sub>3</sub> from 1 to 10 mol %. Lithium alkenylboronates bearing an electron-rich and an electron-deficient aryl group participated in the reaction to give **3f** and **3g** in 78% and 86% yields, respectively.

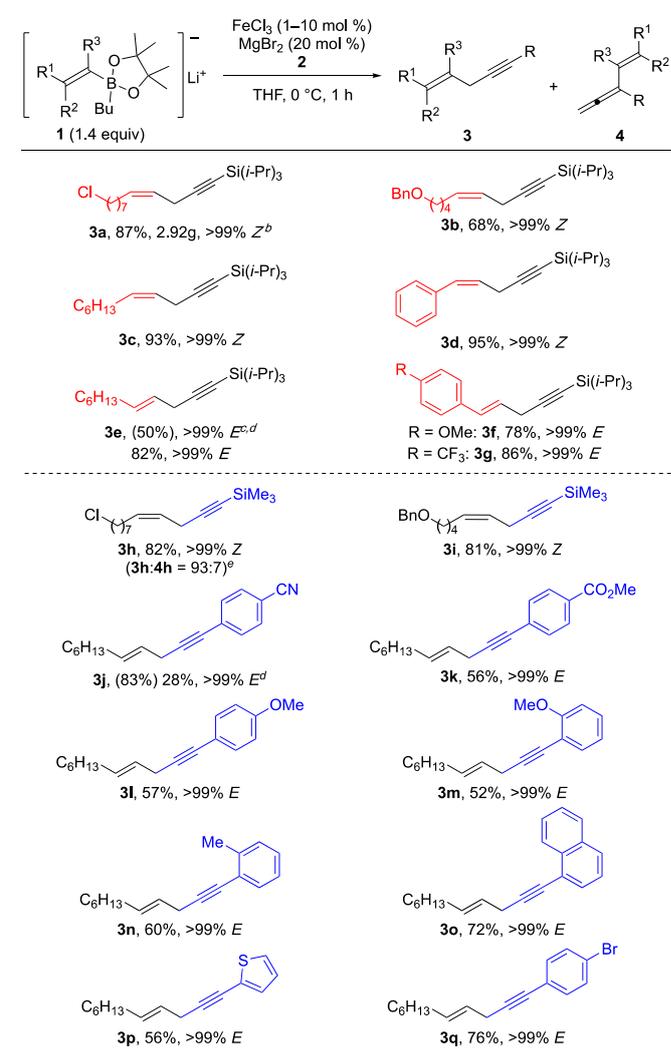
**Table 1** Optimisation of reaction conditions for cross-coupling reaction of lithium alkenylboronate (**1a** or **1a'**) with propargyl bromide **2a-Br**<sup>a</sup>

Entry	Catalyst	Alkenylboronate	Yield (%) <sup>b</sup>		
			<b>3a</b>	<b>4a</b>	RSM <sup>c</sup>
1	FeCl <sub>3</sub>	<b>1a</b>	>99	N.D.	N.D.
2	FeCl <sub>3</sub>	<b>1a'</b>	95	N.D.	N.D.
3 <sup>d</sup>	FeCl <sub>3</sub>	<b>1a</b>	N.D.	N.D.	90
4	none	<b>1a</b>	N.D.	N.D.	91
5	PdCl <sub>2</sub>	<b>1a</b>	3	N.D.	66
6	NiCl <sub>2</sub>	<b>1a</b>	N.D.	N.D.	93
7	CoCl <sub>2</sub>	<b>1a</b>	18	N.D.	78
8	MnCl <sub>2</sub>	<b>1a</b>	42	N.D.	46
9	CuCl	<b>1a</b>	62	10	N.D.

<sup>a</sup>Reactions were carried out on a 0.3–0.5 mmol scale. N.D. denotes not detected.

<sup>b</sup>Determined by <sup>1</sup>H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. <sup>c</sup>Recovered starting material **2a-Br**. <sup>d</sup>Without MgBr<sub>2</sub>.

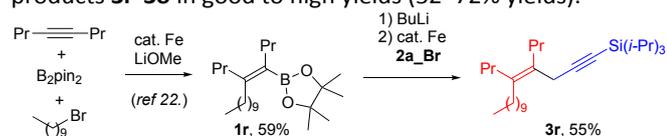
**Table 2** Substrate scope<sup>a</sup>



<sup>a</sup>Reactions of lithium (*Z*)- and (*E*)-alkenylboronates were carried out using 1 mol % and 10 mol % of FeCl<sub>3</sub>, respectively, unless otherwise noted; see the experimental section for details of the reaction conditions for each entry. *E:Z* ratio were determined by <sup>1</sup>H NMR analysis. Isolated yields are given. <sup>b</sup>Reaction was carried out on a 9.45 mmol scale. <sup>c</sup>FeCl<sub>3</sub> (1 mol %) was used. <sup>d</sup>NMR yield is given in parentheses. GPC purification lowered the isolated yield of **3j**. <sup>e</sup>GC peak area ratio.

Next, the scope of propargyl halides was examined with a range of lithium (*Z*)- or (*E*)-alkenylboronates. The reactions of trimethylsilyl-substituted propargyl bromide with lithium (*Z*)-alkenylboronates efficiently provided **3h** and **3i** in excellent yield with high S<sub>N</sub>2-type selectivity (**3h:4h** = 93:7), where the selectivity of 1,4-enyne **3h** versus allene **4h** was determined by GC analysis of the crude product. After purification, **3h** was obtained in 82% yield. The reactions between various aryl-substituted propargyl bromides and lithium (*E*)-alkenylboronates were examined to provide the corresponding 1,4-enynes **3j–3q** in good to high yields without the formation of allene byproducts. Functional groups, such as nitrile and ester, were compatible with this reaction, giving the corresponding

products **3j** and **3k** in 28% and 56% yields, respectively.<sup>21,22</sup> Electron-rich and sterically demanding substrates delivered the products **3l–3o** in good to high yields (52–72% yields).



**Scheme 2** Synthesis of tetrasubstituted 1,4-enyne (See SI for detailed reaction conditions).

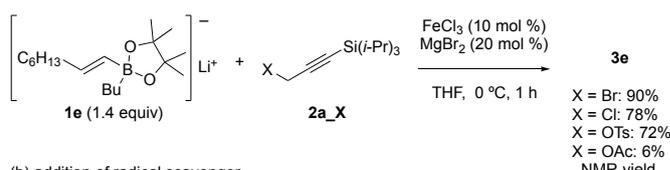
A heteroaryl-containing substrate, 2-thiophenyl-substituted propargyl bromide, also participated in this reaction to give the product **3p** in 56% yield. *p*-Bromophenyl-substituted propargyl bromide was cross-coupled selectively at the Csp<sup>3</sup>–Br position without generating the Csp<sup>2</sup>-coupling product.

Scheme 2 shows the synthesis of a tetrasubstituted 1,4-enyne via a sequential iron-catalysed carboboration<sup>23</sup>/cross-coupling reaction. Notably, the tetrasubstituted 1,4-enyne **3r**, which has not been achieved by conventional methods, was synthesised successfully through this sequential method.

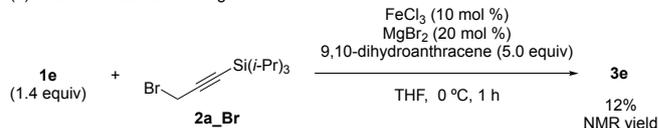
Having examined the substrate scope extensively, we then carried out a set of reactions for probing the origin of the distinct reactivity of the catalyst system toward a range of propargyl electrophiles. As shown in Scheme 3a, propargyl halides **2a\_Br** and **2a\_Cl** participated in the reaction to give **3e** in high yield. Propargyl tosylate **2b\_OTs** also provided **3e** in 72% yield owing to its *in situ* conversion to **2a\_Br** by halogen exchange (see SI).<sup>24</sup> While propargyl acetate **2a\_OAc** afforded **3e** in extremely low yield due to its low reactivity. Generally, homolytic cleavage of the C–OR bond does not occur under cross-coupling reaction. Thus, the present reaction can be interpreted to proceed via *in situ* formation of the propargyl bromide and the subsequent propargyl radical formation. A brief mechanistic study also supported the radical mechanism. In the presence of five equivalents of 9,10-dihydroanthracene as the radical scavenger,<sup>25</sup> the coupling reaction slowed down dramatically and the coupling product **3e** formed only in 12% yield (Scheme 3b).

Fig. 1 shows a possible reaction mechanism based on the above results and previous mechanistic studies on iron-catalysed cross couplings of alkyl halides.<sup>26</sup> Before its participation in the catalytic cycle, the reactive halogenated iron(I) intermediate **A** is generated by the transmetalation/reduction of iron precatalyst FeCl<sub>3</sub> with lithium alkenylborate **1** and the subsequent reaction with propargyl halide **2**. The reactive species **A** abstracts a halogen atom from

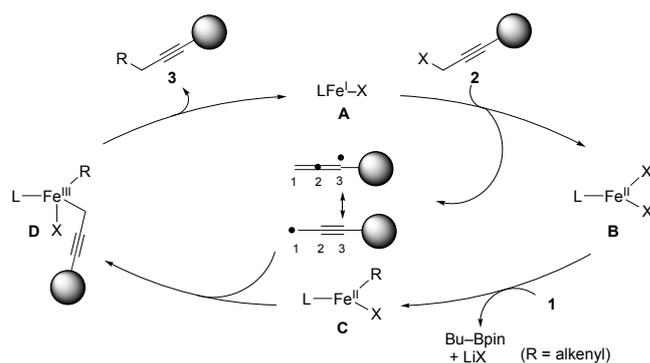
(a) comparison of leaving groups



(b) addition of radical scavenger



**Scheme 3** Mechanistic study.



**Fig. 1** Possible reaction mechanism.

propargyl halide **2**, forming a propargyl radical intermediate and iron(II) intermediate **B**. The transmetalation of intermediate **B** with the alkenylborate **1** forms the organoiron(II) intermediate **C**. Although the spin density of the propargyl radical delocalises both on C1 and C3 positions, the radical recombination of organoiron(II) intermediate **C** with the propargyl radical takes place predominantly at the C1 position likely due to the steric hindrance of the terminal substituents, affording the organoiron(III) intermediate **D**. The subsequent reductive elimination gives 1,4-enyne **3** and regenerates iron(I) intermediate **A**. It should be noted that the reaction is considered to involve a radical chain mechanism,<sup>26b,c</sup> and hence, intermediate **C** trapping a propargyl radical is not necessarily the same iron species which generates the intermediate **D**.

In summary, we have developed an efficient stereoselective synthesis of 1,4-enynes by the iron-catalysed Suzuki–Miyaura coupling between propargyl electrophiles and alkenylborates. This reaction features high functional group compatibility, excellent regioselectivity (S<sub>N</sub>2-type) and stereoselectivity, and is high yielding with a broad range of substrates, providing versatile building blocks to advance the synthesis of complex bioactive molecules. Applications of the present coupling reaction in natural product syntheses and development of the enantioselective variant are underway in our laboratory.

This work was supported in part by the Advanced Low Carbon Technology Research and Development Program (ALCA JPMJAL1504) from the Japan Science and Technology Agency (JST), and New Energy and Industrial Technology Development Organization (NEDO). R.A. thanks ‘Research Fellowships of Japan Society for the Promotion of Science for Young Scientists’

(JSPS 11488). This work was also supported by Integrated Research Consortium on Chemical Sciences (IRCCS). FT-ICR-MS and 800 MHz NMR analyses were supported by the JURC at ICR, Kyoto University. We thank Tosoh Finechem Corporation and Nissan Chemical Corporation for their financial support.

### Conflicts of interest

There are no conflicts to declare.

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