

Iron-catalyzed Suzuki–Miyaura Coupling Reaction of Unactivated Alkyl Halides with Lithium Alkynylborates

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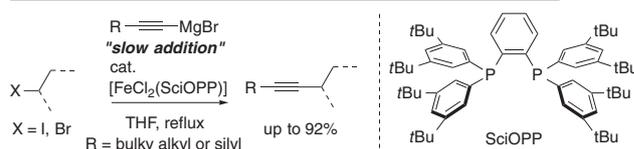
A Suzuki–Miyaura coupling reaction between unactivated alkyl halides and lithium alkynylborates was performed using an iron–bisphosphine catalyst. The reaction shows high chemoselectivity and is applicable to a broad scope of substrates bearing electrophilic functional groups. A radical probe experiment using cyclopropylmethyl bromide was conducted to investigate the nature of the intermediate in the reaction, showing that an alkyl radical species is generated from the alkyl halide substrate.

The Suzuki–Miyaura coupling reaction has been widely used for the synthesis of functional organic molecules, such as pharmaceuticals, agrochemicals, and electronic materials.¹ In particular, the Suzuki–Miyaura coupling of alkynyl borate reagents has become recognized as a powerful tool for installing a C–C triple bond moiety without altering other reactive functional groups on the substrates.² Since Soderquist and Fürstner independently reported the palladium-catalyzed alkylation between alkynyl borate reagents and aryl or alkenyl halides,^{2b,2c} the reaction has been successfully applied as a key step in the synthesis of natural products.³ However, while aryl and alkenyl halides have been widely employed in this alkylation reaction, the use of unactivated alkyl halides has remained challenging due to their reluctance to oxidative addition and the competing nonproductive β -hydrogen elimination from the alkyl–metal intermediate. Consequently, there has been no report on the use of alkynylborates in $C_{sp}-C_{sp^3}$ bond-forming reactions with unactivated alkyl halides, despite extensive studies using various combinations of alkynyl donors and transition-metal catalysts such as palladium,^{4a,4b,5a} nickel,^{4c,4d,5b} cobalt,^{5c–5f} and iron.^{5g,5h}

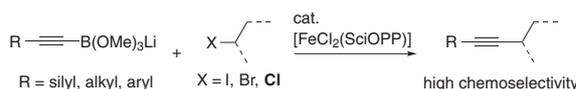
We have previously reported a Sonogashira-type coupling between alkyl halides and alkynyl Grignard reagents with the iron–bisphosphine catalyst $[\text{FeCl}_2(\text{SciOPP})]$ ^{5g,6} (Scheme 1A). Although this reaction demonstrated the potential of the iron catalyst in the alkylation of alkyl halides, significant synthetic limitations have remained, i.e., low functional group compatibility, the inapplicability of the reaction to secondary alkyl chlorides, and the need for overly elaborate protocols such as the slow addition of Grignard reagents at refluxing temperature. Herein we present the first example of Suzuki–Miyaura coupling between alkynylborates and unactivated alkyl halides in the presence of an iron catalyst,^{7,8} which overcomes these limitations to provide a facile route to alkyl-substituted functionalized alkynes in good to excellent yields (Scheme 1B).

We began our investigation by evaluating the coupling reaction of chlorocycloheptane (**1**) and lithium (triisopropyl-

(A) Previous work: Iron-catalyzed Sonogashira-type coupling of alkyl halides



(B) This work: Iron-catalyzed Suzuki–Miyaura coupling of alkyl halides



Scheme 1. Iron–bisphosphine-catalyzed $C_{sp}-C_{sp^3}$ bond-forming reaction of unactivated alkyl halides.

Table 1. Effect of reaction parameters on iron-catalyzed alkylation

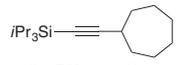
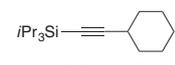
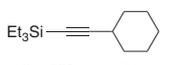
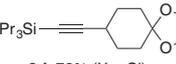
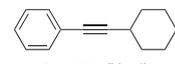
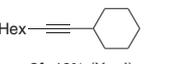
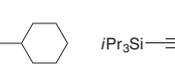
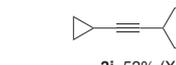
Optimal condition

Entry ^a	Variations from the optimal conditions	Yield/% ^b			Recovery of 1 / ^b
		3	4	5	
1	none	80	16	3	<1
2	without $[\text{FeCl}_2(\text{SciOPP})]$	0	0	0	>99
3	5 mol % of FeCl_2^c	10	4	5	74
4	5 mol % of $[\text{FeCl}_2(\text{dppbz})_2]$	0	0	0	>99
5	5 mol % of FeCl_2 and DPPE ^c	<1	<1	<1	94
6	5 mol % of FeCl_2^d with NMP (2 mL)	8	5	1	63
7	$\text{B}(\text{OiPr})_3$ instead of $\text{B}(\text{OMe})_3$ in 2	0	1	1	97
8	9-MeO-9-BBN instead of $\text{B}(\text{OMe})_3$ in 2	0	<1	<1	94

^aReactions were carried out at the 0.50 mmol scale. ^bYields were determined by quantitative GC analyses using dodecane as an internal standard. ^c $\text{FeCl}_2(\text{thf})_{1.5}$ was used. ^dAnhydrous FeCl_2 was used.

silyl)ethynyltrimethoxyborate (**2**),⁹ readily prepared from the terminal alkyne, BuLi, and trimethyl borate, and found that by using 5 mol % of $[\text{FeCl}_2(\text{SciOPP})]$ the target coupling product **3** was obtained in 80% yield, along with cycloheptene (**4**) and cycloheptane (**5**) (Table 1, Entry 1). Further investigation into the reaction conditions was conducted by altering individual reaction parameters from those considered to be optimal.¹⁰ In the absence of the iron catalyst, **1** was recovered quantitatively and no other products were observed (Table 1, Entry 2). Without the SciOPP ligand, the coupling reaction gave **3** in only 10%

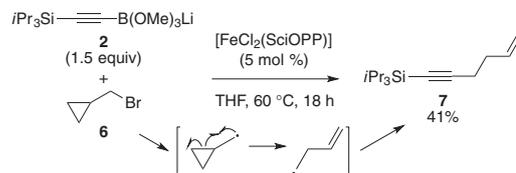
Table 2. Scope of substrates in iron-catalyzed Suzuki–Miyaura coupling with lithium alkynylborates^a

$\text{R}-\text{C}\equiv\text{C}-\text{B}(\text{OMe})_3\text{Li} + \text{X}-\text{R}' \xrightarrow[\text{THF/hexane or toluene, 40–80 }^\circ\text{C, 5–28 h}]{[\text{FeCl}_2(\text{SciOPP})] \text{ (5 mol \%)}} \text{R}-\text{C}\equiv\text{C}-\text{R}'$		
(1.5 equiv)	X = I, Br, Cl	
in THF/hexane		
 3a , 76% (X = Cl) 80 °C, 5 h	 3b , 81% (X = Cl) 80 °C, 12 h	 3c , 83% (X = Br) 60 °C, 12 h
 3d , 73% (X = Cl) 80 °C, 28 h	 3e , 25% (X = I) 60 °C, 6 h	 3f , 46% (X = I) 40 °C, 8 h
 3g , 53% (X = I) 40 °C, 8 h	 3h , 83% (X = Br) 60 °C, 18 h	
in toluene		
 3i , 53% (X = Br) 80 °C, 24 h [0% in THF]	 3j , 98% (X = Br) ^b 80 °C, 22 h [$<20\%$ in THF]	
 3k , 67% (X = I) ^b 60 °C, 18 h	 3l , 44% (X = Br) ^b 70 °C, 24 h	

^aReactions were carried out at the 0.50 mmol scale. Yields of isolated products are reported. ^b10 mol % of $[\text{FeCl}_2(\text{SciOPP})]$ and 2 equivalents of **2** were used.

yield, and showed diminished selectivity (Table 1, Entry 3). DPPBz,^{7c–7g} DPPE,¹¹ and NMP,^{5h,7a} which are well-recognized modifiers for iron-catalyzed cross-coupling reactions, were totally ineffective (Table 1, Entries 4–6). Other alkynylborates derived from $\text{B}(\text{O}i\text{Pr})_3$ ^{2c} and 9-MeO-9-BBN^{2b,2c} did not take part in the cross-coupling reaction (Table 1, Entries 7 and 8).

We next investigated the scope of the current protocol and found that it was applicable to various combinations of alkyl halides and alkynylborates (Table 2). (Triethylsilyl)ethynylborate also showed good reactivity toward bromocyclohexane, affording the target alkyne **3c** in 83% yield. A cyclic acetal was tolerant to the reaction conditions to give **3d** in 73% yield. (Phenyl)ethynylborate reacted to give **3e** albeit in a low yield. Reactions of primary alkyl-substituted alkynylborates were also found to be sluggish, yet they reacted with primary or secondary alkyl iodides to afford the coupling products **3f** and **3g** in moderate yields. The reaction of 1-bromo-4-(2-bromoethyl)benzene with **2** occurred selectively at the C_{sp^3} -Br position to afford **3h** in 83% yield, leaving the C_{sp^2} -Br bond completely intact. In the case of sterically small alkyne substituents, such as the (cyclopropyl)ethynyl group, the target product **3i** was not obtained, even with refluxing in THF. We assumed that even the borate reagent, which possesses a small substituent on the alkyne carbon, could form inert iron intermediates such as ferrate complexes in a polar solvent like THF (Table 2 and



Scheme 2. Radical probe experiment.

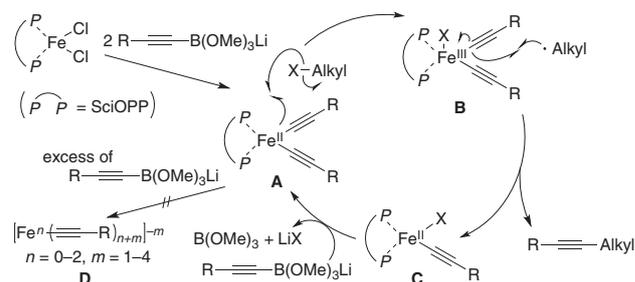


Figure 1. A plausible catalytic cycle for the current reaction.

Figure 1). We thus replaced the THF solvent with toluene, and found that the coupling reaction worked well even with the sterically unhindered alkynylborate and obtained the cyclopropylethynylated compound **3i** in 53% yield. Toluene solvent was effective also for the alkyl halides possessing a reactive functional group, such as nitrile, imide, and ketone (**3j–3l**). We reasoned that the low polarity of the toluene solvent prevented the side reactions on these functional groups with alkynyl iron species.¹²

To investigate the reaction mechanism, we conducted the reaction of (bromomethyl)cyclopropane (**6**) with **2** (Scheme 2). The linear 1,5-enyne **7** formed in 41% yield selectively, suggesting that the reaction proceeds via formation of an alkyl radical species. Based on the experimental observations described above, and accumulated knowledge of iron-catalyzed cross-coupling reactions,^{5g,7,8} we present a possible catalytic cycle, shown in Figure 1. We assume that the dialkynyl-iron-SciOPP intermediate **A** is responsible for the selective cross coupling through the putative iron intermediates **B** and **C**, whilst the ferrate complexes **D** that can form in the presence of an excess of the Grignard reagent¹³ do not possess sufficient reactivity towards the alkyl halides. Presumably, the steric bulk of SciOPP prevents the formation of the undesired ferrate formation.

In summary, we have developed the iron-catalyzed Suzuki–Miyaura coupling of unactivated alkyl halides with alkynylborate reagents. The reaction has synthetic advantages over more traditional methods, such as its simple operation, its applicability to a broad scope of alkyl halides including chlorides, and its high functional group compatibility. At present, details of the reaction mechanism are unclear, and evaluation of the postulated catalytic cycle is imperative. Further efforts on the elucidation of the mechanism are currently underway.

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Supporting Information is available electronically on J-STAGE.

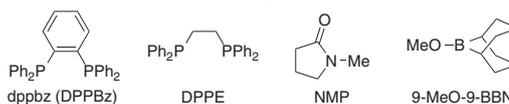
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- 10 Ligand, additive, and boron reagent structure abbreviations:



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