

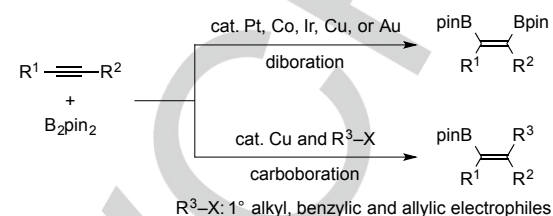
Iron-Catalyzed Diboration and Carboboration of Alkynes**

Naohisa Nakagawa^[a,b], Takuji Hatakeyama^[a,c], and Masaharu Nakamura^{*[a]}

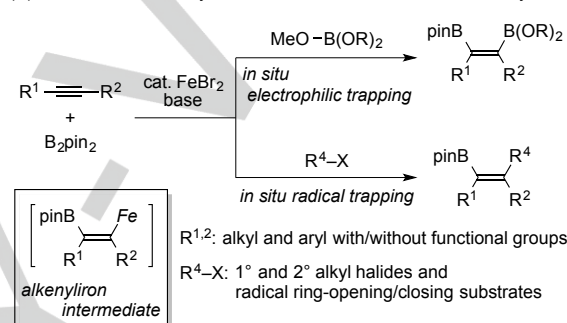
Abstract: We have developed an iron-catalyzed diboration reaction of alkynes with bis(pinacolato)diboron (B_2pin_2) and external borating agents ($MeOB(OR)_2$), affording diverse symmetrical or unsymmetrical *cis*-1,2-diborylalkenes. The simple protocol for the diboration reaction can be extended to the iron-catalyzed carboboration of alkynes with primary and unprecedented secondary alkyl halides, affording various tetrasubstituted monoborylalkenes in a highly stereoselective manner. DFT calculations indicate that a boryliron intermediate adds across the triple bond of an alkyne to afford an alkenyliron intermediate, which can react with electrophiles, the borylation and alkylation agents. In situ trapping experiments support the intermediacy of the alkenyl iron species.

With the development of Suzuki–Miyaura cross-coupling reactions, alkenylboron compounds have attracted the attention as the key intermediates for the synthesis of diverse functional molecules for use as electronic materials and bioactive natural products.^[1] Diborylalkenes are particularly attractive building blocks for substituted alkenes^[2] and π -extended polyarenes,^[3] and their expedient synthesis has attracted much attention from synthetic chemists. The transition-metal-catalyzed diboration of alkynes has been investigated intensively^[4] since its discovery by Suzuki and Miyaura,^[5a] and diverse transition metals such as platinum, cobalt, iridium, copper, and gold proved to be effective catalysts^[5] (Scheme 1-A, upper reaction). Recently, copper-catalyzed diboration of alkynes has been extended to a novel carboboration reaction,^[6,7] furnishing diverse tetrasubstituted borylalkenes,^[7d–h] which are valuable synthetic intermediates (Scheme 1-A, lower reaction). The discovery of a new diboration and carboboration catalyst has enhanced the synthetic efficacy of the reaction. In this communication, we report that simple iron salts, which are one of the most promising practical catalysts, can catalyze the diboration and carboboration of internal alkynes (Scheme 1-B). The trapping experiments and DFT calculations suggest that the diboration and carboboration reactions occur

(A) Previous works: Transition-metal-catalyzed diboration of alkynes and copper-catalyzed carboboration of alkynes



(B) This work: Iron-catalyzed diboration and carboboration of alkynes



Scheme 1. Transition-metal-catalyzed diboration and carboboration of alkynes. through the formation of an alkenyliron species, which reacts with borating agents and unactivated alkyl halides, respectively, to provide the above two reactions, which have not been achieved by the existing methods.

Based on our previous studies on iron-catalyzed cross-coupling^[8,9] and carbometallation reactions,^[10] we screened iron catalysts and reaction conditions and found that a simple iron salt can catalyze the diboration reaction of alkynes^[11] under particular conditions: In the presence of 10 mol% $FeBr_2$, 10 mol% $LiOMe$, and 1.5 equiv of 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ($MeOBpin$) **3a**, the diboration reaction of 4-octyne **1** with bis(pinacolato)diboron (B_2pin_2) **2** afforded *cis*-1,2-diborylalkene **4a** in 99% yield with exclusive *cis*-selectivity (Table 1, optimal conditions). Table 1 summarizes the effects of deviating from the optimal conditions. In the absence of the iron catalyst, no reaction occurred (entry 2). A reduced catalyst loading afforded **4a** in a sufficient yield (93%), albeit with the formation of 4% of the corresponding hydroboration product^[12] (entry 3). The counteranions (I and Cl) of the iron precatalyst strongly affected the diboration reaction to decrease the yield (entries 4 and 5). $FeBr_3$ also worked as an efficient catalyst and afforded **4a** in 92% yield (entry 6). The base, $LiOMe$, was essential for the reaction (entry 7). Increasing the amount of $LiOMe$ (20 mol%) led to a faster conversion, but lowered the overall yield of **4a** (entry 8). The use of other alkali metal alkoxides also afforded **4a** in high yields (entries 9–11). In the absence of $MeOBpin$ **3a**, the yield of **4a** decreased to 53%, and **1** was recovered in 36% yield (entry 12).

We next investigated diverse alkynes and found that the reactions of internal alkynes afforded the corresponding *cis*-1,2-diboryl alkenes in good yields and with excellent stereoselectivity (Scheme 2).^[13] The reactivity of alkynes was

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highly influenced by the terminal substituents: The reactions of

Table 1. Effect of reaction parameters on iron-catalyzed diboration of 4-octyne.

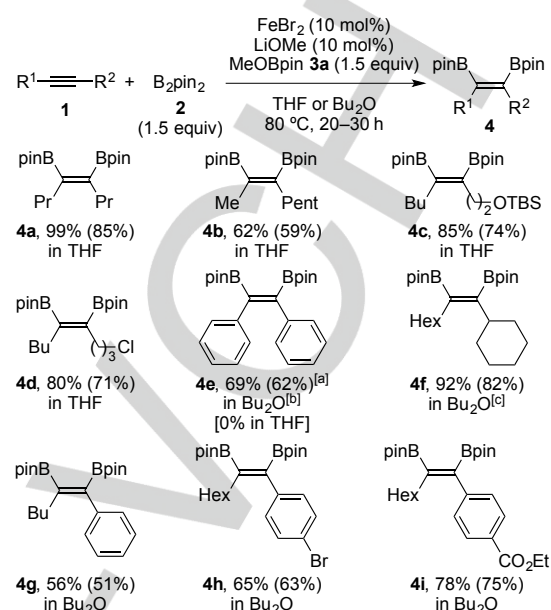
Optimal conditions			
$\text{Pr}-\text{C}\equiv\text{C}-\text{Pr} + \text{B}_2\text{pin}_2 \xrightarrow[\text{THF, 80 }^\circ\text{C, 20 h}]{\text{FeBr}_2 (10 \text{ mol\%}), \text{LiOMe} (10 \text{ mol\%}), \text{MeOBpin } \mathbf{3a} (1.5 \text{ equiv})} \text{pinB}-\text{C}(\text{Pr})=\text{C}(\text{Pr})-\text{Bpin}$			
Entry ^[a]	Changes from the optimal conditions	Yield of 4a [%] ^[b]	Recovery of 1 [%] ^[c]
1	None	99	0
2	Without FeBr ₂	0	99
3	5 mol% of FeBr ₂ and LiOMe, 40 h	93 ^[c]	0
4	FeI ₂	55	15
5	FeCl ₂	5	88
6	FeBr ₃	92	0
7	without LiOMe	0	98
8	20 mol% of LiOMe, 9 h	87 ^[d]	0
9	LiOtBu	63	33
10	NaOMe, 48 h	96	0
11	KOMe, 48 h	99	0
12	without 3a	53	36

[a] Reactions were carried out on a 0.50 mmol scale. [b] Yields were determined by quantitative GC analyses using decane as an internal standard. [c] The hydroboration product was obtained in ca. 4% yield. [d] Yield was determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The hydroboration product was obtained in 6% yield.

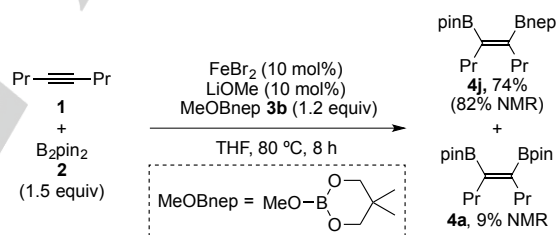
internal alkynes with alkyl substituents afforded the desired diborylalkenes in good-to-excellent yields (**4a–4d**). Because aryl or bulky alkyl substituents were found to retard the diboration reaction under the optimal conditions, we screened solvents and found that dibutyl ether (Bu₂O) is an effective solvent in these cases. For example, diborylalkenes **4e** and **4f** were obtained successfully in Bu₂O, but not in THF. We assume that Bu₂O, a weaker coordinating solvent than THF, does not hamper the coordination of alkynes to the iron center (see the DFT calculations shown below). Similarly, the reactions of monoaryl-substituted internal alkynes in Bu₂O afforded the desired diborylalkenes **4g–4i** in fair-to-good yields. Notably, reactive functional groups such as C_{sp2}-Br and ethyl ester remained intact under the reaction conditions (**4h** and **4i**).

In the present study, the diboration reaction proceeded smoothly with an additional borating agent. To understand the role of the borating agent, we conducted the diboration of **1** in the presence of 2-methoxy-5,5-dimethyl-1,3,2-dioxaborinane **3b** (MeOBnep) (Scheme 3). MeOBnep **3b** participated in the diboration reaction to afford an unsymmetrical diborylalkene **4j** as a major product. Meanwhile, only a small amount of symmetrical diborylalkene **4a** was observed. This result suggests that the second

incorporation of the boryl unit into **1** occurs by an electrophilic substitution reaction with **3a** or **3b**.^[14]



Scheme 2. Iron-catalyzed diboration of diverse alkynes. Reactions were carried out on a 1.0 mmol scale. Yields were determined by ¹H NMR analyses using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. [a] 85% *cis*-selectivity was confirmed by GC and ¹H NMR analyses. [b] Reaction was carried out at 100 °C and stirred for 12 h. [c] 20 mol% of FeBr₂ and 20 mol% of LiOMe were used.

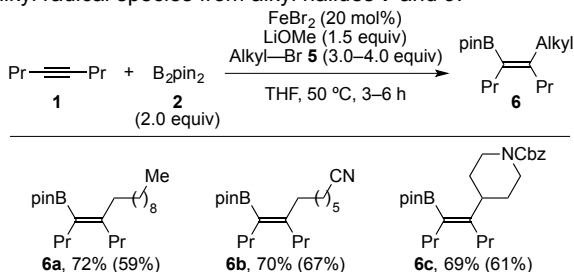


Scheme 3. Diboration of 4-octyne in the presence of MeOBnep.

Based on our previous work on iron-catalyzed cross-coupling reactions, we envisaged that a carbon electrophile such as unactivated alkyl halides could also trap the alkenyliron intermediate in a stereospecific manner.^[15] In the presence of alkyl halides **5** and a stoichiometric amount of LiOMe, the carboboration reaction occurred preferentially, affording monoborylalkenes **6** (Scheme 4). Notably, a secondary alkyl bromide also participated in the present iron-catalyzed reaction to afford the corresponding carboboration product **6c**.^[16] The carboboration of 1-phenyl-1-hexyne with **2** and bromocyclohexane proceeded in a regioselective manner to some extent.^[17]

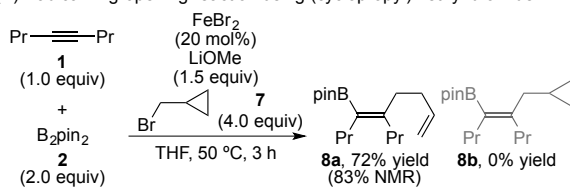
We assumed that the carboboration of secondary alkyl bromide involves the homolytic cleavage of the C–Br bond, as observed in the previously reported iron-catalyzed cross-coupling reactions of alkyl halides.^[8,9,15] To confirm the intermediacy of alkyl radical species, the carboboration reaction was conducted using (cyclopropyl)methyl bromide **7** (Scheme 5-A). The reaction afforded ring-opened monoborylalkene **8a** as the sole coupling product. In contrast, the copper-catalyzed

carboration of an alkyne with **7** afforded allyl(cyclopropyl) monoborylalkene such as **8b** through an S_N2 pathway.^[7] Carboration using diethyl 2-allyl-2-(2-bromoethyl)malonate **9**, possessing a terminal double bond, was accompanied by a cyclization reaction (Scheme 5-B). These results strongly indicate that iron-catalyzed carboration involves the formation of alkyl radical species from alkyl halides **7** and **9**.

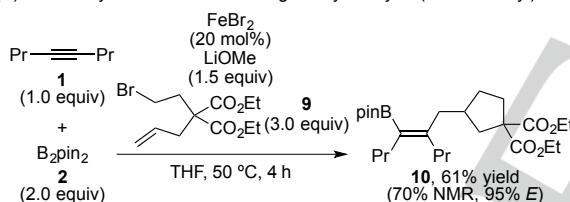


Scheme 4. Iron-catalyzed carboration of 4-octyne. Reactions were carried out on a 0.50 mmol scale. Yields were determined by ¹H NMR analyses using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses.

(A) Radical ring-opening reaction using (cyclopropyl)methyl bromide



(B) Radical cyclization reaction using diethyl 2-allyl-2-(2-bromoethyl)malonate

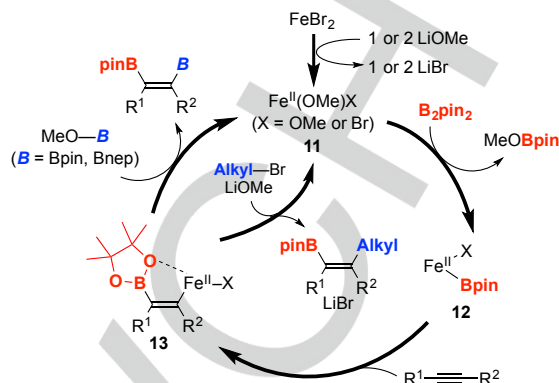


Scheme 5. Radical clock experiments.

Scheme 6 shows a plausible reaction mechanism based on the results obtained: FeBr₂ initially undergoes transmetalation with LiOMe to form methoxyiron(II) intermediate **11**,^[18] which reacts with B₂pin₂ to afford boryliron(II) intermediate **12**. The coordination of an alkyne to intermediate **12** followed by the insertion of alkyne to the Fe–B bond generates a reactive alkenyliron(II) intermediate **13**. Then, intermediate **13** undergoes an electrophilic substitution reaction with a borating agent, MeOBpin or MeOBnep, affording the diboration product *cis*-selectively and starting methoxyiron(II) intermediate **11**, thus completing the catalytic cycle. The presence of an alkyl electrophile may divert intermediate **13** into the carboration reaction by the formation of alkyl radical species.

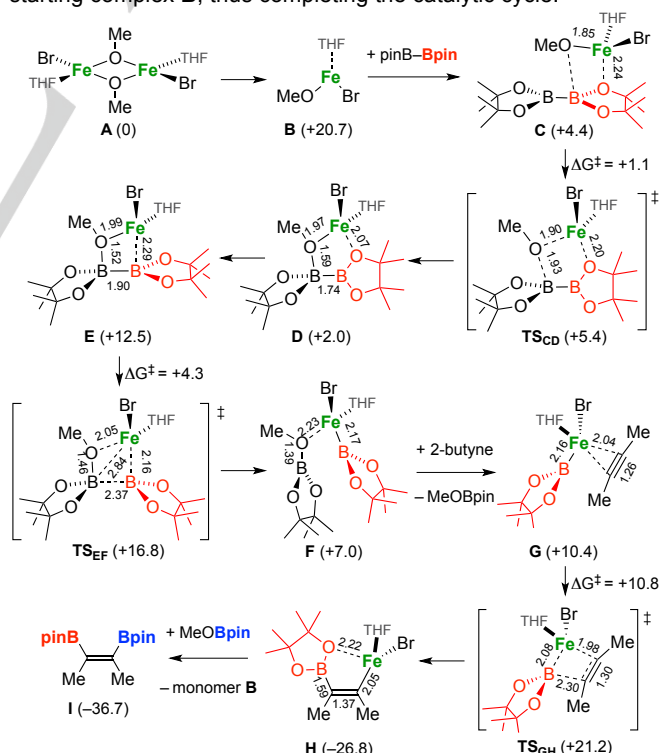
To evaluate the postulated pathway shown in Scheme 6, we performed a set of DFT calculations to determine the energetically feasible reaction pathway^[19] that connect iron alkoxide models **A** (dimer) and **B** (monomer) to alkenyl iron intermediate **H** (Scheme 7). Monomer **B** and B₂pin₂ form adduct **C**, in which the methoxy and pinacol oxygen atoms coordinate to one of the boron atoms and iron, respectively. The transfer of the methoxy group from the iron center to the other boron atom occurs through TS_{CD} with a small activation energy (1.1 kcal/mol),

forming borate intermediate **D**. Intermediate **D** interconverts to intermediate **E** with the loss of the coordination of the pinacol oxygen atom to the iron center and facilitates intramolecular σ-



Scheme 6. Plausible pathway for iron-catalyzed diboration and carboration reactions.

bond metathesis between the Fe–O and B–B bonds through TS_{EF} to afford methoxyiron intermediate **F**. The ligand exchange of the iron center from MeOBpin to 2-butyne affords alkyne π-complex **G**. Borylmatalation proceeds via TS_{GH} with 10.8 kcal/mol activation energy; this TS is the highest energy barrier in the entire process (+21.2 kcal/mol compared to **A**). The *syn*-borylmatalation reaction leads to the stereoselective formation of alkenyliron(II) intermediate **H** with 26.8 kcal/mol exothermicity. Intermediate **H** may undergo an electrophilic trapping reaction with MeOBpin to afford 1,2-*cis*-diborylalkene and regenerate starting complex **B**, thus completing the catalytic cycle.



Scheme 7. DFT pathway for the iron-catalyzed diboration reaction. Gibbs free energies (ΔG, calculated at the MP2/6-311G(d)//B3LYP/6-31G(d) level) relative to **A** are given in kcal/mol in parentheses.

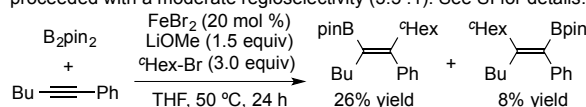
In summary, we developed novel iron-catalyzed diboration and carboboration reactions of internal alkynes, featuring exclusive *cis*-selectivity and high chemoselectivity, without using any precious metals and ligands. The synthetic advantages of our protocol over the conventional ones were demonstrated by unsymmetrical diboration and carboboration using a secondary alkyl halide. Moreover, the intermediacy of alkyl radical species enabled us to develop ring-opening and ring-closing carboboration reactions. The results of DFT calculations indicate that the reaction involves a methoxyiron species, which undergoes transmetalation with B₂pin₂ to form a boryliron intermediate, followed by the insertion of an alkyne. Further investigation is underway in our laboratory to expand the synthetic scope of these reactions and to elucidate the detailed mechanism and nature of boryliron intermediates.

Acknowledgements

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Keywords: alkyl halides • alkynes • carboboration • diboration • iron

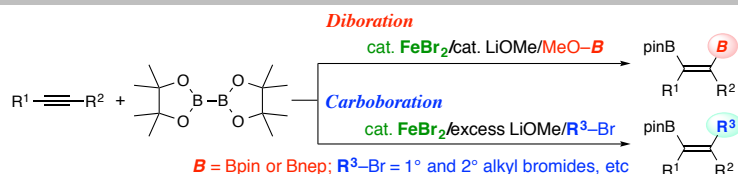
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COMMUNICATION



Naohisa Nakagawa, Takuji Hatakeyama,
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**Iron-Catalyzed Diboration and
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Iron-catalyzed diboration and carboboration of internal alkynes have been developed. These processes feature the unique reactivity of iron catalyst: diboration takes place through a borylmetalation/electrophilic substitution reaction and carboboration through a borylmetalation/radical reaction, both providing the products in a highly *cis*-selective and chemoselective manner.