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Iron-catalyzed Alkyl-Alkyl Negishi Coupling of Organoaluminum Reagents

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The first iron-catalyzed cross-coupling reaction of alkyl halides with alkylaluminum reagents (alkyl-alkyl Negishi coupling) is developed using an iron/bisphosphine catalyst system. The reaction shows high functional group tolerance: various primary alkyl halides possessing a non-protected indole, carboxyl, or hydroxy group are coupled with primary alkylaluminums in good yields. Potassium fluoride plays a key role to promote the reaction by generating an aluminate species which facilitates the transmetalation between the organoaluminum and the iron catalyst.

Keywords: Iron, Cross coupling, Organoaluminum

Cross-coupling reaction forming C_{sp3}-C_{sp3} bonds is one of the key chemical transformations in synthetic organic chemistry.¹ In the last two decades, transition-metal-catalyzed alkyl-alkyl cross-coupling reactions have been extensively developed by mainly nickel and palladium catalysts (Figure 1a).²⁻⁷ The first alkyl-alkyl coupling was reported by Knochel and co-workers using dialkylzinc reagents and alkyl iodides bearing a terminal olefin in the presence of nickel catalyst.³ This achievement has led to the development of a variety of alkyl-alkyl cross-coupling reactions with not only alkylzinc,⁴ but also alkyl Grignard,⁵ and alkylboron reagents,⁶ applied in the synthesis of bio-active natural products and pharmaceuticals.^{4d,6c}

Recently, increasing attention has been focused on iron as a sustainable catalyst in organic synthesis due to its non-toxic, environmentally benign nature, and high-abundance in the Earth's crust.^{8,9} Considerable efforts have thus been devoted to developing iron-catalyzed cross-coupling reactions forming C_{sp2}-C_{sp3}, C_{sp2}-C_{sp2}, C_{sp}-C_{sp2}, and C_{sp}-C_{sp3} bonds to date.¹⁰⁻¹² However, there are only limited reports for C_{sp3}-C_{sp3} bond-forming reactions. Chai, Cárdenas, and Kambe reported iron-catalyzed Kumada-type alkyl-alkyl coupling between alkyl Grignard reagents and alkyl halides (Figure 1b).¹³ Our group previously reported the Suzuki-type alkyl-alkyl coupling by using alkylboronates as nucleophiles.¹⁴ There is still room for improvement in functional group tolerance and substrate scope on electrophiles and/or nucleophiles, because these reactions require the use of Grignard reagents and highly reactive organolithium to activate the organoboron nucleophiles. In contrast, we previously reported the synthetic utility of organoaluminum reagents in iron-catalyzed Negishi-type coupling reactions, which enable the compatibility with a range of functional groups under mild activation condition.¹² Therefore, we envisioned the applicability of organoaluminum reagents to iron-catalyzed alkyl-alkyl coupling to overcome the above limitations.

Previous work

(a) Pd, Ni, Co, or Cu catalyst (X = I, Br, Cl, F, OTs, etc.; M = Mg, Zn, B)

(b) Fe catalyst (X = I, Br, F, OTs; M = Mg, B)

Kumada-type coupling (M = Mg) : low functional group tolerance

Suzuki-type coupling (M = B) : require *i*-PrMgCl to activate alkylborane

(c) This work

✓ high functional group tolerance: CN, CO₂R, CO₂H, OH, NHR

Scheme 1. Transition-metal-catalyzed cross coupling between alkyl electrophiles and alkylmetal reagents.

Herein, we report a new iron-catalyzed alkyl-alkyl cross-coupling reaction of non-activated alkyl halides with alkylaluminum reagents by using catalytic amounts of Fe(OAc)₂ and Bn-Nixantphos **1**¹⁵ (Figure 1c). The addition of potassium fluoride^{12c} was found to be the key to attain the facile coupling reaction. This reaction system shows high functional group compatibility, which has not been achieved by previous iron catalysts.

We chose the coupling reaction between (6-bromohexyl)benzene (**2a**) and trioctylaluminum as a model reaction. After the screening of catalyst precursors, ligands, additives, and reaction conditions, a wide bite angle bisphosphine **1** was found to give the desired coupling product **3a** in 83% yield (entry 1). Comparable catalytic activities (64 and 72%) were observed by using its congeners, TBS-Nixantphos and Xantphos (entries 2 and 3).¹⁶ It should be noted that these reaction conditions suppressed the undesired β-hydrogen elimination completely and olefin **4a** and 1-octene were not observed at all (see SI, Table S1). On the other hand, a structurally flexible bisphosphine ligand, DPEphos, resulted in low selectivity, likely due to the dissociation of one phosphine from the iron center, which enables competitive side reactions such as the β-hydrogen elimination (entry 4). A narrow bite angle bisphosphine, SciOPP, did not give the desired product **3a**, despite its effectiveness in the iron-catalyzed cross-coupling reaction of alkyl halides (entry 5).^{10b} When *i*-Pr-Pybox^{4c} and N-heterocyclic carbene (NHC) precursor IPr·HCl^{4b} were used, almost no desired product **3a** was obtained (entries 6 and 7). Other mono- and bisphosphine, diamine,^{10a} and NHC precursors^{13b} were

Table 1. Effect of reaction parameters in iron-catalyzed cross coupling of **2a** with trioctylaluminum^a

Entry	Changes from the optimal conditions	Yield (%) ^b			
		3a	4a	5a	RSM ^c
1	none	83	0	16	0
2	TBS-Nixantphos instead of 1	64	0	7	12
3	Xantphos instead of 1	72	0	15	0
4	DPEphos instead of 1	20	23	37	0
5	SciOPP instead of 1	0	29	50	0
6	<i>i</i> -Pr-Pybox instead of 1	0	1	9	84
7	IPr-HCl instead of 1	4	21	35	7
8	FeCl ₂ instead of Fe(OAc) ₂	17	17	33	26
9	Fe(OPiv) ₂ instead of Fe(OAc) ₂	70	0	16	0
10	Fe(OTf) ₂ instead of Fe(OAc) ₂	70	0	16	4
11 ^d	FeCl ₂ and KOAc (30 mol %) instead of Fe(OAc) ₂	76	0	8	0
12	without 1	<1	23	36	37
13	without Fe(OAc) ₂	0	0	5	92
14	without KF	<1	0	5	95

^aReactions were carried out on 0.2–0.8 mmol scale. ^bDetermined by quantitative GC analysis using undecane as an internal standard. ^cRecovery of starting material **2a**. ^dFeCl₂ (5 mol %) was treated with KOAc (30 mol %) in MeOH/THF for 1 h and then the solvent was removed in vacuo.

ineffective in this reaction, where significant amounts of by-products, **4a**, **5a**, and 1-octene were formed (see SI, Table S1). The present coupling reaction thus requires the use of wide bite angle bisphosphine ligands possessing rigid framework to achieve high selectivity of the coupling product.

The counter anion of the iron salts showed remarkable influence on the product yield and selectivity. As shown in entry 8, FeCl₂ showed lower reactivity and selectivity than Fe(OAc)₂. On the other hand, the iron salts having oxoanions, Fe(OPiv)₂ and Fe(OTf)₂^{10e} resulted in much higher yields than the chloride, albeit displaying lower selectivity than Fe(OAc)₂ (entries 9 and 10, see also SI, Table S2). As shown in entry 11, pretreatment of FeCl₂ with potassium acetate dramatically improved the yield and selectivity compared with FeCl₂ alone. In the absence of bisphosphine ligand **1**, Fe(OAc)₂, or KF, almost no desired

product was obtained (entries 12–14). Notably, the addition of fluoride anion is critical for attaining the rapid conversion of the alkyl bromide, which can be accounted for facilitating the transmetalation step by the formation of a highly reactive aluminate species.^{12c,17} These results indicate that the Fe(OAc)₂/**1** catalyst with KF is crucial to achieve high catalytic activity and suppress undesired side reactions.

Table 2 illustrates the scope and limitations of the present reaction under optimal conditions. A variety of

Table 2. Substrate scope of alkyl halides and alkylaluminum reagents^a

Entry	Alkyl-X	Product	Yield (%) ^b
1			77
2			65
3			12
4			73 (48)
5			87 (30)
6			62 (54)
7 ^c			37
8 ^c			90 (44)
9 ^c			(60)
10 ^c			(38)
11			62 (49)
12			0
13			37
			0

^aReactions were carried out on a 1 mmol scale using Fe(OAc)₂ (5 mol %), **1** (10 mol %), and alkylaluminum reagents (1.5 equiv) in THF at 40 °C for 8–44 h, see the SI for details of the reaction conditions for each entry. ^bDetermined by quantitative GC analysis using undecane as an internal standard. Isolated yields are given in parentheses. ^cTrioctylaluminum (2.5 equiv) was used.

1 alkylaluminum reagents were cross-coupled with 1-
2 bromodecane (**2b**). The reactions of trioctylaluminum or
3 triethylaluminum with **2b** gave the corresponding coupling
4 products **3ba** and **3bb** in 77% and 65% yields, respectively
5 (entries 1 and 2). In contrast, trimethylaluminum afforded
6 only 12% yield of product **3bc**, where decene was obtained
7 as the major by-product (entry 3).¹⁸

8 We then studied the scope of alkyl halides and to our
9 delight the present reaction showed high functional group
10 tolerance. Alkyl bromides bearing a reactive functional
11 group, such as cyano or ester group, reacted with
12 alkylaluminum reagents to give the corresponding coupling
13 products **3ca-d** in good yields (62–87%, entries 4–6).
14 Importantly, alkyl halides possessing a non-protected indole,
15 carboxyl, and hydroxy group¹⁹ also participated in the
16 reactions to afford the corresponding products **3e-g** in 37–
17 90% yield, despite the catalyst poisoning effect of these
18 functional groups in iron-catalyzed coupling reactions of
19 alkyl halides (entries 7–9).^{10b} An even more challenging
20 primary alkyl chloride bearing a hydroxy group **2g-Cl** can
21 also be cross-coupled with trioctylaluminum reagent to give
22 the product **3g** in 38% yield (entry 10). We consider that
23 organoaluminum reagent deprotonate the acid proton and
24 the resulting aluminum salts of the substrate undergo facile
25 cross-coupling reaction.^{12b,20} The reaction of 1-bromo-6-
26 chlorohexane (**2h**) showed high chemoselectivity and
27 proceeded exclusively at the bromide site to afford **3h** in
28 62% yield (entry 11). The reaction of secondary alkyl
29 bromide, bromocycloheptane (**2i**) with trioctylaluminum
30 reagent did not produce the desired coupling product,
31 whereas undesired by-products, cycloheptane, cycloheptene,
32 and 1,1'-bi(cycloheptane) were obtained in 14%, 46%, and
33 12% yields, respectively (entry 12). The reaction of
34 (bromomethyl)cyclopropane (**2j**)²¹ gave the corresponding
35 ring-opening/coupling product **3ja** in 37% yield without the
36 formation of **3jb** indicating the intermediacy of alkyl
37 radicals (entry 13).^{11,13b}

38 We further conducted a sequential
39 hydroalumination²²/cross-coupling reaction. Addition of
40 DIBAL-H to olefin **6** and the subsequent iron-catalyzed
41 cross-coupling reaction with **2b** proceeded in a one-pot
42 manner to give the desired coupling product **3ka** in 36%
43 yield along with the formation of minor by-product **3kb**
44 (Scheme 2). Although there is still room for improving the
45

47 **Scheme 2.** Cross coupling of alkyl halides with terminal alkenes via
48 hydroalumination with diisobutylaluminum hydride.

49 product yield and selectivity, this consecutive
50 transformation displays the synthetic potential of the
51 present coupling reaction.²³

52 Based on the above-described results and previous
53 mechanistic studies on iron-catalyzed cross-coupling
54 reactions,^{11d–f} a plausible reaction mechanism featuring an
55 Fe^I/Fe^{II}/Fe^{III} manifold is presented in Figure 1. The catalytic
56 cycle starts from the bisphosphine-iron(I) intermediate **A**
57 which forms by the reduction of Fe(OAc)₂ in the presence of
58 ligand **1**.^{11b,24} The reaction of **A** with the alkyl halide **2**
59 forms the alkyl radical intermediate and the **iron(II)**
60 **intermediate B**. Transmetalation of **B** with the
61 organoaluminum species generates the organoiron(II)
62 intermediate **C**, which can undergo rapid recombination
63 with the alkyl radical to produce the organoiron(III)
64 intermediate **D**.^{11d–f} The catalytic cycle then completes by
65 reductive elimination to give the C_{sp3}–C_{sp3} coupling product
66 **3**, regenerating the **iron(I) intermediate A**. We consider that
67 the wide bite angle ligand promotes the reductive
68 elimination and the acetate ligand occupying the vacant
69 coordination sites²⁵ suppresses the undesired β-hydrogen
70 elimination.

72 **Figure 1.** A possible reaction mechanism.

74 In conclusion, the first example of iron-catalyzed
75 alkyl–alkyl Negishi coupling of organoaluminum has been
76 achieved employing an Fe(OAc)₂/1 catalyst system.
77 Stoichiometric potassium fluoride was identified as the
78 critical additive that facilitates the coupling reactions by the
79 formation of highly nucleophilic aluminate species. This
80 new coupling method features the simple and mild
81 activation of organoaluminum nucleophiles, resulting in
82 high functional group tolerance, and thus demonstrates
83 synthetic advantages especially in high product selectivity
84 over previously reported iron-catalyzed alkyl–alkyl coupling
85 reactions.

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7
8 Supporting Information is available electronically on J-
9 STAGE.

10 References and Notes

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110 0.7%, and 24% yields, respectively. Unfavorable low-valent or
111 peralkylated iron species would be easily generated by the less
112 bulky trimethylaluminum, leading to undesired side reactions.
- 113 19 The aluminum alkoxide species is known to enhance the cross-
114 coupling reaction of 1-chlorohexanol (ref. 12b), however the
115 reaction between 1-chlorohexanol and triethylaluminum did not
116 proceed without KF.
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124 were observed in 18%, 8%, 13%, and 13% yields, respectively.
125 We assume that the β-hydrogen elimination from isobutyliron
126 intermediates affords iron hydride intermediates which cause the
127 undesired side reactions.
- 128 24 The reduction of iron(II) acetate by organoaluminum reagent in
129 THF may give dimeric iron(I) acetate species, which can
130 generate the monomeric iron(I) acetate **A** in an equilibrium
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You are requested to put a brief abstract (50-60 words, one paragraph style) with the graphical abstract you provided, so that readers can easily understand what the graphic shows.

Graphical Abstract	
Textual Information	
A brief abstract (required)	A novel alkyl-alkyl Negishi coupling of organoaluminum reagents is developed employing an iron(II) acetate/bisphosphine (Bn-Nixantphos) catalyst system. Potassium fluoride plays a key role for promoting the coupling reaction, enabling various alkyl-alkyl coupling reaction to afford the desired products in good to high yields. The present reaction exhibits high functional group compatibility even with non-protected indole, carboxyl, hydroxy groups.
Title(required)	Iron-catalyzed Alkyl-Alkyl Negishi Coupling of Organoaluminum Reagents
Authors' Names(required)	Ryosuke Agata, Shintaro Kawamura, Katsuhiko Isozaki, and Masaharu Nakamura
Graphical Information	
<p><Please insert your Graphical Abstract: The size is limited within 100 mm width and 30 mm height, or 48 mm square>(required)</p> <div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;"> <p>Alkyl-X + R₂Al-Alkyl</p> <p>(X = Br, Cl) (R = Alkyl or <i>i</i>-Bu)</p> </div> <div style="text-align: center; margin: 0 10px;"> <p>cat. Fe(OAc)₂ cat. Bn-Nixantphos KF</p> <p>→</p> </div> <div style="text-align: center;"> <p>Alkyl-Alkyl</p> <p>up to 90% 14 examples</p> </div> </div> <p>✓ first example of alkyl-alkyl coupling using organoaluminum reagents ✓ high functional group tolerance</p> <div style="text-align: center; margin-top: 10px;"> <p>Bn-Nixantphos</p> </div>	