Cross-Coupling

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Iron-Catalyzed Alkyl–Alkyl Suzuki–Miyaura Coupling**

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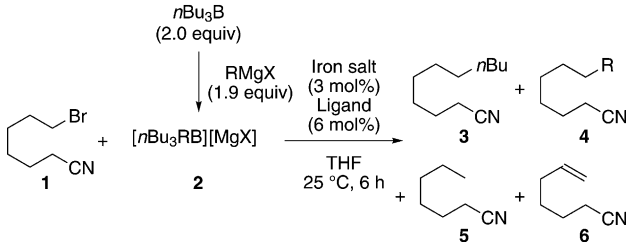
The Suzuki–Miyaura coupling reaction is one of the most practical and reliable synthetic reactions for the production of functional molecules, such as drug/agrochemical intermediates and organic electronic materials.[1] Although palladium, nickel, and iron can catalyze the Suzuki–Miyaura coupling reaction, catalysts based on the nontoxic and most abundant transition metal, iron, have not been studied extensively. Despite the renaissance of iron-catalyzed cross-coupling reactions,[2–4] there are only a few reports on iron-catalyzed Suzuki–Miyaura coupling. Although three iron-catalyzed biaryl cross-coupling reactions have been reported, two have been retracted.[5] Bedford's research group and our group have reported iron-catalyzed Suzuki–Miyaura coupling reactions of aryl- or alkenylboron reagents with the aid of iron-bisphosphine catalysts.[6] Herein we report the first iron-catalyzed alkyl–alkyl Suzuki–Miyaura coupling reaction wherein alkylboron compounds and non-activated alkyl halides are cross-coupled in high yields with a catalyst combination of an iron salt and a bisphosphine with a large bite angle, Xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene), thereby providing a new method for the most challenging combination of cross-coupling partners.[7]

During our studies on Suzuki–Miyaura coupling under iron catalysis,[6b,c] we identified transmetalation in the catalytic cycle as a critical step, requiring combinations of a carbanionic activator and a Lewis acidic metal salt. Therefore, to accomplish alkyl–alkyl coupling, we carefully screened organoboron reagents and their activators and found that *iso*-propylmagnesium chloride (*i*PrMgCl) acts as an efficient activator for trialkylboranes.[8] Table 1 summarizes the screening results of various iron salts, ligands, and activators used in the coupling reaction between tri(*n*-butyl)borane and 7-bromoheptanenitrile (**1**; Scheme 1). As shown in entry 1 of Table 1, the optimum yield (82%) of the desired butylation product **3** was achieved by using a stoichiometric amount of *i*PrMgCl in the presence of $[Fe(acac)_3]$ (3 mol%) and Xantphos (6 mol%), previously reported as the unselective catalyst combination for cross-coupling of alkyl Grignard reagents and alkyl halides.[7e] The cyano group remained untouched under the reaction conditions, thereby reflecting the quantitative formation of magnesium tetraalkylborate **2**.[9] The other secondary alkyl Grignard reagents also gave the desired product **3** but in slightly lower yields.[10] The reaction with *n*BuMgCl gave a high yield (85%) although it was inapplicable to other trialkylboranes (Table 1, entry 2).[11] Notably, the reaction with *n*BuLi did not give any product (Table 1, entry 3). We confirmed the formation of lithium tetrabutylborate ($[nBu_4B][Li]$),[9] suggesting that the lithium borate is stable and unreactive toward the transmetalation step. Interestingly, the reaction with MeMgBr gave methylation product **4** (73%) rather than **3** (8%, Table 1, entry 4). These results clearly show that the transfer rate of alkyl groups from the boron center to the iron center decreased in the order of methyl > primary alkyl > secondary alkyl group.[12] The reaction of a magnesium borate prepared with $TMSCH_2MgBr$ did not give **3** but gave heptanenitrile **5** and hept-6-enenitrile **6** in 19% and 49% yields, respectively, thus suggesting the selective transfer of the $TMSCH_2$ group from the borate $[nBu_3(TMSCH_2)B][MgCl]$ (Table 1, entry 5).[13] Similarly, the reaction with *t*BuMgCl did not give **3** but gave **5** and **6** (19% and 12% yields, respectively, Table 1, entry 6). NMR spectroscopy studies indicate that *t*BuMgCl partially reacts with nBu_3B to give a small amount of the corresponding borate ($[nBu_3tBuB][MgCl]$).[9] We assumed that the reaction with the remaining *t*BuMgCl took place prior to the coupling reaction with the activated alkyl boron compound, leading to the production of **5** and **6**. Note



Scheme 1. Iron-catalyzed Suzuki–Miyaura coupling between **1** and **2** (R = alkyl).

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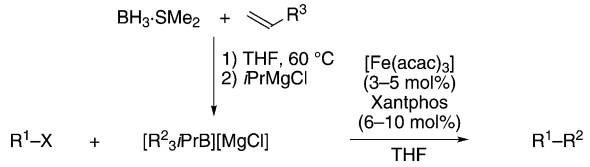
Table 1: Cross-coupling between **1** and **2** in the presence of iron salts and ligands.[a]

Entry	Iron salt	Ligand	RMgX or RLi	Yield [%][b]				Recovery of **1** [%][b]
				3	**4**	**5**	**6**	
1	$[Fe(acac)_3]$	Xantphos	*i*PrMgCl	82	0	11	<1	0
2	$[Fe(acac)_3]$	Xantphos	*n*BuMgCl	85	–	11	3	0
3	$[Fe(acac)_3]$	Xantphos	*n*BuLi	0	–	0	0	99
4	$[Fe(acac)_3]$	Xantphos	MeMgBr	8	73	5	10	0
5	$[Fe(acac)_3]$	Xantphos	$TMSCH_2MgCl$	0	0	19	49	28
6	$[Fe(acac)_3]$	Xantphos	*t*BuMgCl	0	0	19	12	9
7	$[Fe(acac)_3]$	–	*i*PrMgCl	3	0	9	<1	80
8	$[Fe(acac)_3]$	dppe	*i*PrMgCl	2	0	<1	<1	88
9	$[Fe(acac)_3]$	dppp	*i*PrMgCl	3	0	<1	<1	89
10	$[Fe(acac)_3]$	dppf	*i*PrMgCl	3	0	<1	<1	81
11	$[Fe(acac)_2]$	Xantphos	*i*PrMgCl	77	0	14	<1	0
12	$Fe(OAc)_2$	Xantphos	*i*PrMgCl	75	0	16	<1	0
13	$FeCl_2$	Xantphos	*i*PrMgCl	69	0	16	<1	0
14	$FeCl_3$	Xantphos	*i*PrMgCl	54	0	11	<1	16

[a] Reactions were carried out according to the procedure shown in Scheme 1 by using 3 mol% $[Fe(acac)_3]$ on a 0.3 mmol scale. [b] Yields and recovery of **1** were determined by gas–liquid chromatography (GLC) with the use of undecane as an internal standard. TMS = trimethylsilyl, dppe = 1,2-bis(diphenylphosphanyl)ethane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, dppp = l,3-bis(diphenylphosphanyl)propane, acac = acetylacetonate.

that a small amount (<1%) of homocoupling product of **1** was formed in most cases. The choice of ligand is also crucial: bisphosphines of smaller bite angles such as dppe, dppp, and dppf gave **3** in only 2–3% yields (Table 1, entries 8–10).[14] $[Fe(acac)_2]$, $Fe(OAc)_2$, $FeCl_2$, and $FeCl_3$ showed rather low or comparable catalytic activities (Table 1, entries 11–14).

To expand the scope of substrates, we conducted the coupling reaction of various alkyl halides with magnesium tetraalkylborates prepared from olefins, $BH_3{\cdot}SMe_2$, and *i*PrMgCl under optimized conditions (Scheme 2 and Table 2).[16] The reaction is applicable not only to primary but also to secondary alkyl bromides possessing functional

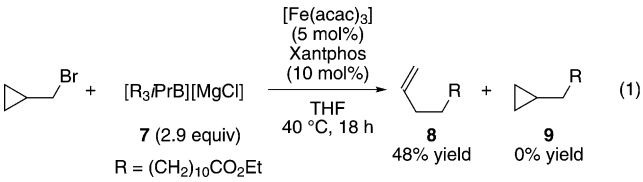


Scheme 2. Iron-catalyzed Suzuki–Miyaura coupling between alkyl halides and magnesium tetraalkylborates prepared from olefins, $BH_3{\cdot}SMe_2$, and *i*PrMgCl. R^1, R^2, R^3 = alkyl groups carrying functional groups as shown in Tables 2 and 3.

groups (Table 2, entries 1–7).[17] As shown in entry 7, the loss of stereochemistry observed for the secondary alkyl bromide indicates that a radical process takes place (see below).[18] Note that alkanes, reduction products of alkyl bromides, were formed as a major side product in the cases that the yield of the coupling compound is moderate. 1-Bromo-4-(2-bromoethyl)benzene underwent coupling with tetraalkylborate through a selective C_{sp^3}–Br bond cleavage (Table 2, entry 8); however, the C_{sp^2}–Br bond cleavage product was not observed. This selective cleavage can be attributed to the radical character of the organoiron species (see above) and the difference in the stabilities of the resulting radical intermediates (alkyl vs. aryl).

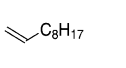
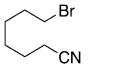
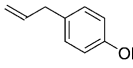
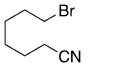
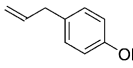
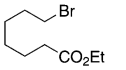
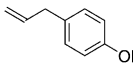
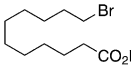
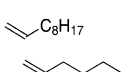
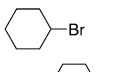
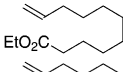
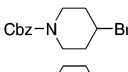
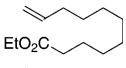
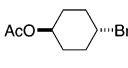
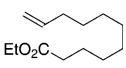
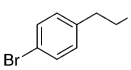
Because of the functional-group compatibility of the hydroboration/alkyl–alkyl coupling, which are not tolerated by the Grignard-based method,[7e] we were able to synthesize long-chain fatty acid derivatives, which constitute an important class of biomaterials that include nutrients and constituents of the cell membrane (Table 3). Ethyl-nonacosanoate, ethyl-17-cyanoheptadecanoate, diethyl-docosanedioate, and ethyl-22-chlorodocosanoate were synthesized in good yields (Table 3, entries 1–4).

The radical clock experiment shown in Equation (1) gave a mechanistic insight: the reaction of (bromomethyl)cyclopropane with **7**



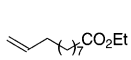
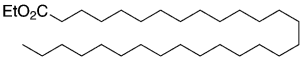
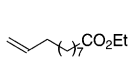
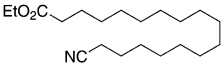
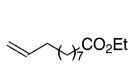
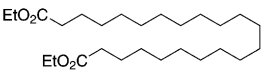
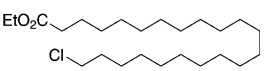
gave the ring-opening/cross-coupling product **8** as a sole product, thus indicating the intermediacy of alkyl radicals reported in the iron-catalyzed Suzuki–Miyaura coupling of

Table 2: Scope of substrates in the alkyl–alkyl cross-coupling.[a]

Entry	Olefin	Alkyl halide	Yield [%][b] (Conditions)
1			82 (25 °C, 6 h)
2			66 (60 °C, 6 h)
3			71 (60 °C, 12 h)
4			75 (60 °C, 12 h)
5			48[c] (25 °C, 18 h)
6[d]			54 (25 °C, 12 h)
7[d]			68[c,e] (25 °C, 28 h)
8			56 (40 °C, 18 h)

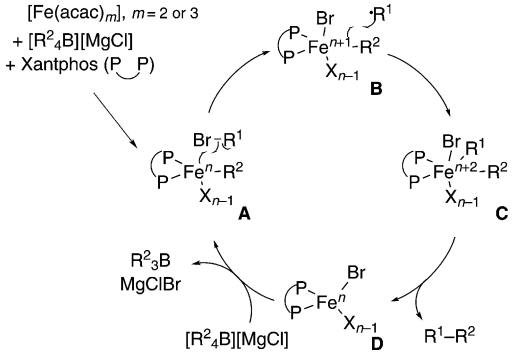
[a] Unless otherwise noted, reactions were carried out according to the procedure shown in Scheme 2 using 3–5 mol% $[Fe(acac)_3]$ on a scale of 0.3–0.6 mmol. [b] Yield of isolated product. [c] Yield was determined by GLC analysis using undecane as an internal standard. [d] 10 mol% $[Fe(acac)_3]$ was used. [e] *trans*/*cis* = 67:33. Cbz = benzyloxycarbonyl.

Table 3: Synthesis of ethyl esters of long-chain fatty acid derivatives.[a]

Entry	Olefin	Alkyl halide	Product Yield [%][b] (Conditions)
1		$C_{18}H_{37}$–Br	 68 (25 °C, 19 h)
2[c]		NC$(CH_2)_6$Br	 84 (40 °C, 12 h)
3		$EtO_2C(CH_2)_{10}$Br	 79 (40 °C, 18 h)
4		$EtO_2C(CH_2)_{10}$Br	 65[d] (25 °C, 24 h)

[a] Unless otherwise noted, reactions were carried out according to the procedure shown in Scheme 2 using 3–5 mol% $[Fe(acac)_3]$ on a scale of 0.3–0.6 mmol. [b] Yield of isolated product. [c] 10 mol% $[Fe(acac)_3]$ was used. [d] Yield was determined by GLC analysis with the use of undecane as an internal standard.

alkyl halides with aryl- and alkenylboron reagents.[6b,c] On the basis of the experimental results and the resemblance to alkyl–aryl(alkenyl) Suzuki–Miyaura coupling,[6b,c] we propose a possible catalytic cycle for the present alkyl–alkyl coupling (Scheme 3). The starting iron salt, $[Fe(acac)_2]$ or $[Fe(acac)_3]$, reacts with magnesium tetraalkylborate ($[R^2{}_4B][MgCl]$) to



Scheme 3. Possible catalytic cycle for the present alkyl–alkyl Suzuki–Miyaura coupling. X_{n-1} = Br or Cl.

form alkyliron(n) complex **A**, where n may be +2, +1, or even a lower formal oxidation number.[19] Thus, the catalytic cycle begins with the homolytic cleavage of the C_{sp^3}–halogen bond of the alkyl halide by **A** to form an alkyl radical ($R^{1\bullet}$) and Fe^{n+1} species **B**; this reaction is known as a fundamental step in metal-catalyzed living radical polymerization.[20,21] The alkyl radical ($R^{1\bullet}$) may be added to the iron center of **B** to form the Fe^{n+2} intermediate **C**, which can undergo reductive elimination to give **D**. Transmetalation with magnesium tetraalkylborate regenerates the reactive species **A** to complete the catalytic cycle. We have proposed the direct addition/substitution of the alkyl radical ($R^{1\bullet}$) to an aryl ligand on the iron(II) center (an *ipso* substitution) in the cross-coupling of alkyl halides and aryl metal reagents in the presence of bisphosphine ligands with a small bite angle (cf. SciOPP).[14] However, we suggest that the recombination of the alkyl radical to the iron center is presumably favored in the present system because of the lack of an *ipso* substitution pathway with the alkyl ligand. The intermediate alkyl iron species **A** and **C** are resistant to β-hydride elimination and subsequent by-product formation owing to the effect of the ligand with a large bite angle, Xantphos.[22]

In summary, we have demonstrated that alkyl–alkyl Suzuki–Miyaura coupling of primary and secondary alkyl halides can be realized by using a $[Fe(acac)_3]$/Xantphos catalyst in a highly chemoselective manner. The key to success is the use of *i*PrMgCl as an activator for trialkylboranes. The practicable functional-group compatibility and nonhazardous nature of the iron catalyst suggest that the present reaction is suitable for the facile synthesis of various functional molecules, particularly biomaterials, as illustrated by the synthesis of long-chain fatty acid derivatives.

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