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Iron-Catalyzed Suzuki−Miyaura Coupling of Alkyl Halides

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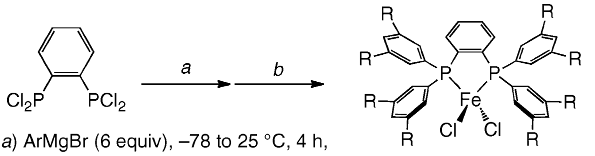
Abstract: In the presence of novel iron(II) chloride−diphosphine complexes and magnesium bromide, lithium arylborates react with primary and secondary alkyl halides to give the corresponding coupling products in good to excellent yields. High functional group compatibility is also demonstrated in the reactions of substrates possessing reactive substituents, such as alkoxycarbonyl, cyano, and carbonyl groups.

The transition-metal-catalyzed cross-coupling reaction of organoboron compounds, known as Suzuki−Miyaura coupling, is one of the most prevalent organic synthetic reactions for the production of functional molecules, such as drug intermediates and organic electronic materials.[1] Palladium and nickel have been widely used as catalysts for the coupling reaction in combination with numerous supporting ligands, which attain the desired reactivity and selectivity. On the other hand, only a few examples of the coupling reaction of organoboron compounds under iron catalysis have been reported,[2−4] despite the recent burst of progress in iron catalysis aimed at practical cross-coupling reactions.[5,6] Herein we report the synthesis of a series of new diphosphine ligands based on the *o*-phenylenediphosphine framework and the Suzuki−Miyaura coupling of alkyl halides in the presence of the corresponding iron−diphosphine complexes.[3,7]

On the basis of our recent study of the reaction between an iron−diamine complex, $FeAr_2$(TMEDA), and an alkyl halide,[8] we envisioned that the reactive iron species would have the following features: (1) divalent iron (+II oxidation state), (2) neutral complex, (3) coordinatively unsaturated, and (4) having sufficient spin density on the iron center. In order to fulfill these requirements, we designed novel iron−diphosphine complexes, such as **1** and **2**, that bear one *o*-phenylene-tethered diphosphine ligand possessing bulky substituents at the 3 and 5 positions of the diphenylphoshino groups. The bulky substituents were expected to introduce peripheral steric bulk around the iron center, preventing the formation of coordinatively saturated octahedral iron complexes. Scheme 1 shows the straightforward syntheses of the phosphine ligands and their subsequent complexation with iron(II) chloride.

Scheme 1. Synthesis of Iron−Diphosphine Complexes **1** and **2**



(*a*) ArMgBr (6 equiv), –78 to 25 °C, 4 h,
then H_3O^+
(*b*) $FeCl_2$•$4H_2O$, EtOH, 90 °C, 6 h

1 (R = *t*-Bu): 59 % yield
2 (R = $SiMe_3$): 54% yield

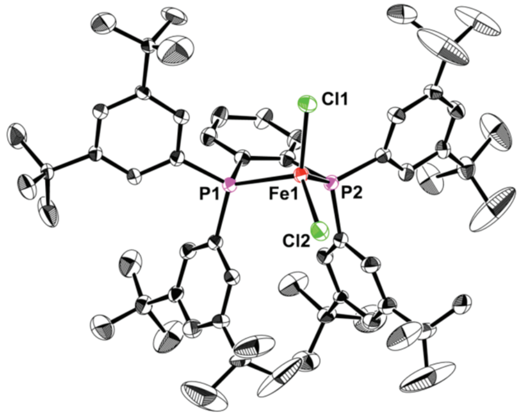


Figure 1. X-ray crystal structure of **1**. Thermal ellipsoids are shown at 50% probability; hydrogen atoms have been omitted for clarity. Selected bond lengths (Å): Fe−Cl1, 2.2190(14); Fe−Cl2, 2.2172(17); Fe−P1, 2.4623(14); Fe−P2, 2.4404(13). Selected bond angles (deg): Cl1−Fe−Cl2, 122.16(6); Cl1−Fe−P1, 109.37(6); Cl2−Fe−P2, 113.00(6); P1−Fe−P2, 80.63(4).

The distorted T_d structure of the $FeCl_2$−diphosphine complex **1** (R = *t*-Bu) was confirmed by X-ray crystal structure analysis, as shown in Figure 1. Solid-state magnetic measurements on **1** were performed using a SQUID magnetometer to confirm the paramagnetic nature, which obeyed the Curie−Weiss law for the temperature range 30−300 K. The magnetic moment for **1** was found to be $4.7\mu_B$, which is close to the spin-only value indicating the presence of four unpaired electrons ($S = 2$). The solution magnetic moment was determined by the Evans method;[9] the 9:1 THF-d_8/benzene solution magnetic moment of $5.1\mu_B$ measured at 23 °C indicated an $S = 2$ high-spin complex in the solution phase. Density functional theory calculations supported the high-spin nature of the T_d complex, which is in good accordance with the solid-state experimental structure as well as the solution-phase magnetism (see the Supporting Information). We anticipated that transmetalation between the iron complex and two molecules of arylmetal compounds would give rise to a diaryliron species with the desired reactivity toward alkyl halides.

Having the well-defined catalyst precursors in hand, we next examined the iron-catalyzed cross-coupling between alkyl halides and arylboron compounds. Our initial attempts using conventional base additives for the Suzuki−Miyaura coupling (e.g., KF, K_3PO_4, KO*t*-Bu, and Cs_2CO_3) did not promote the reaction,[10] probably because of the high affinity of the fluorine- and oxygen-centered anions for the iron metal center.[3,11] We therefore examined a variety of organoborates[12] and found that lithium arylborate **3** prepared from arylboronic acid pinacol ester and alkyllithium[13] can be effectively cross-coupled with alkyl halides in the presence of a catalytic amount of the iron complex (**1** or **2**) and $MgBr_2$ (Scheme 2).

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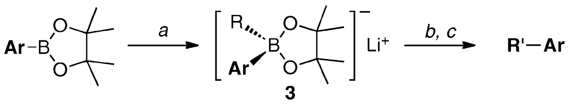
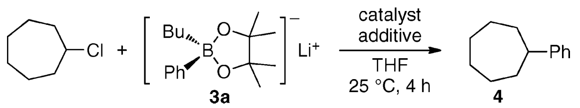
Scheme 2. Cross-Coupling of Organoboronates with Alkyl Halide in the Presence of a Catalytic Amount of **1** or **2**



(*a*) RLi, THF, –78 to 0 °C, 1 h, (*b*) **R'**X
(*c*) cat. **1** or **2**, 20 mol % of $MgBr_2$, THF, 0 to 40 °C

Table 1. Catalyst and Additive Screening for the Cross-Coupling



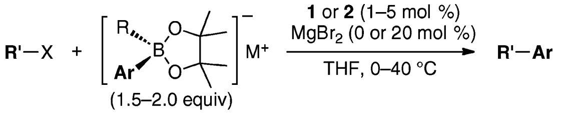
entry[a]	catalyst (3 mol %)	additive (mol %)	yield (%)[b]	recovery (%)[b]
1	$FeCl_3$	TMEDA (200)	0	>99
2	$FeCl_3$	TMEDA (200) + $MgBr_2$ (20)	0	>99
3	$FeCl_2(dppbz)_2$	none	0	>98
4	$FeCl_2(dppbz)_2$	$MgBr_2$ (20)	14	83
5	complex **1**	$MgBr_2$ (20)	**93**	0
6	complex **2**	$MgBr_2$ (20)	**91**	0
7	complex **2**	none	0	>99

[a] Reactions were carried out using 1.4 equiv of phenylborate **3a** on a 0.5 mmol scale. [b] The yield of **4** and the recovery of chlorocycloheptane were determined by GC analysis using undecane as an internal standard.

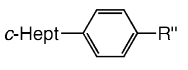
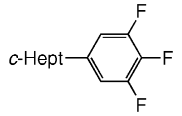
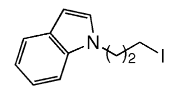
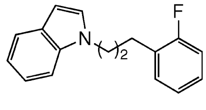
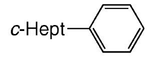
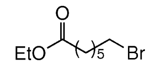
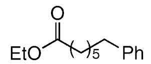
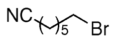
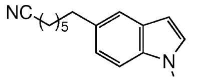
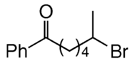
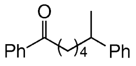
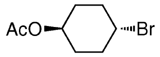
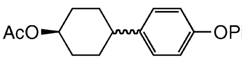
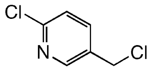
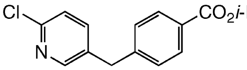
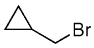
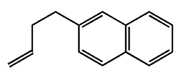
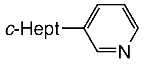
Table 1 summarizes the results of catalyst screening for the reaction of chlorocycloheptane with phenylborate **3a** prepared from phenylboronic acid pinacol ester and butyllithium. As shown in entries 1 and 2, $FeCl_3$ with *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA), the effective catalyst for other types of iron-catalyzed cross-couplings of alkyl halides,[6h,m,n,v] did not give the desired coupling product **4** regardless of the presence of $MgBr_2$. We recognized a promising indication of the desired reactivity in the combination of $FeCl_2(dppbz)_2$, an $FeCl_2$−1,2-bis(diphenylphosphino)benzene complex, and $MgBr_2$ (14% yield, entry 4). To our delight, use of the novel iron complexes **1** and **2** afforded the desired coupling product in 93 and 91% yield, respectively (entries 5 and 6).[14] $MgBr_2$ was found to be essential for the coupling reaction (entry 7).[15] We currently assume that $MgBr_2$ accelerates the transmetalation between borate **3a** and the iron catalyst.[16]

Table 2 summarizes the scope of the present iron-catalyzed Suzuki−Miyaura coupling reaction. As shown in entries 1−9, a variety of arylboronic acid pinacol esters possessing functional groups such as methoxy, dimethylamino, chloro, fluoro, and alkoxycarbonyl participate in the reaction via in situ borate formation with butyl- or *tert*-butyllithium. It should be noted that ethyl Grignard reagent was used for the activation of *p*-(alkoxycarbonyl)phenyl boronic acid pinacol esters because alkyllithium reagents can react with the alkoxycarbonyl groups (entries 5−7). The reaction with chlorocycloheptane proceeded smoothly to give the desired product in 93% yield (entry 10). Chemoselective reactions are demonstrated in entries 11−15: the ethoxycarbonyl, cyano, and carbonyl groups remained untouched. 2-Chloro-5-chloromethylpyridine reacted with arylboronic acid pinacol ester via a selective $C(sp^3)-Cl$ [vs $C(sp^2)-Cl$] bond cleavage (entry 15). The reaction of (bromomethyl)cyclopropane gave the ring-opening product 2-(but-3-enyl)naphthalene, which supports the intermediacy of alkyl radicals (entry 16). Pyridin-3-ylboronic acid pinacol ester was also a viable substrate (entry 17).

Table 2. Substrate Scope of the Coupling Reaction



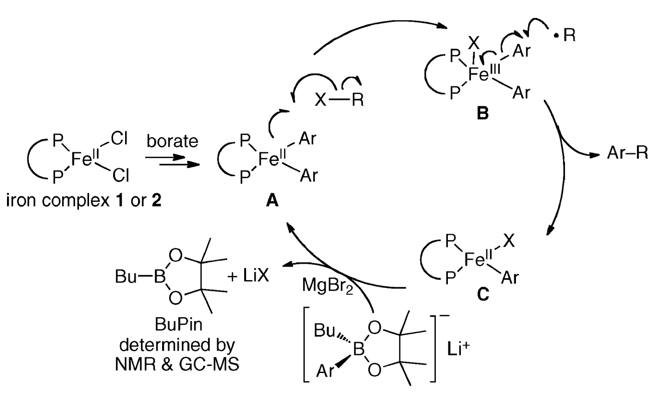
R' = 1°, 2° alkyl, R = Et, Bu, *t*-Bu, Ar = aromatic group, M = Li or MgBr

entry[a]	Alkyl–X	coupling product	yield (%)[b]
1[c]	*c*-Hept−Br		99 (R" = H)
2			98 (R" = OMe)
3			94 (R" = NMe_2)
4			77 (R" = Cl)
5[d,e,f]			90 (R" = CO_2Me)
6[d,e,f]			81 (R" = CO_2Et)
7[d,e,f]			74 (R" = CO_2i-Pr)
8			83
9			79
10[f,g]	*c*-Hept−Cl		93[h]
11			90
12[g]			96
13[e]			65
14[d,e]			83[i]
15[d,f]			86
16			99[j]
17[d]	*c*-Hept−Br		73

[a] Reactions were carried out at 40 °C for 3−4 h on a 0.44−1.0 mmol scale using 3 mol % **2**, unless otherwise noted. Arylborates were prepared from arylboronic acid pinacol ester and *t*-BuLi, unless otherwise noted. [b] Isolated yield. [c] Using 1 mol % **2**. [d] Using EtMgBr instead of *t*-BuLi. [e] Using 5 mol % **2**. [f] Reaction was carried out at 25 °C for 3−8 h. [g] Using BuLi instead of *t*-BuLi. [h] GC yield. **1** was used instead of **2**. [i] The *cis/trans* ratio was 42/58. [j] Isomerization of olefin (6%) was observed.

Scheme 3 shows a plausible mechanism. The starting complex **1** or **2** reacts with 2 equiv of arylborate to form diaryliron^{II} **A**. In view of the lack of biaryl formation during the coupling reactions as well as the results of mechanistic studies using an $FeAr_2$(TMEDA) complex,[8] we believe that reduction of the iron center does not take place during the reaction. The catalytic cycle thus starts with the homolytic cleavage of the sp^3-carbon−halogen bond of the alkyl halide to afford iron^{III} species in metal-catalyzed living radical polymerization reactions.[17] The trivalent interemediate **B** reacts with the alkyl radical (R•) via release of the aryl radical or, more likely, via *ipso* attack of the alkyl radical at one of the two aryl groups to give the cross-coupling product Ar−R and aryliron^{II} halide **C**.[18] Regeneration of the reactive species **A** completes the catalytic cycle via transmetalation with an arylborate with the help of the cocatalyst, $MgBr_2$. The peripheral steric bulk[19] of the iron complexes **1** and **2** would prevent the formation of ferrate complexes, which often show low selectivity in iron-catalyzed cross-coupling reactions.[20]

Scheme 3. Plausible Mechanism



In summary, we have developed an iron-catalyzed Suzuki−Miyaura coupling of nonactivated alkyl halides with arylboron compounds. The unique combination of the novel sterically demanding phosphine ligands and a magnesium cocatalyst enables the selective coupling reaction in high yield. The relationship between the spin state of the iron catalyst and its reactivity is being actively investigated in our group.

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Supporting Information Available: Details of the experimental procedure, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) In the presence of the diphoshine ligand, $FeCl_2$, $FeCl_3$, FeF_2, and $Fe(OEt)_2$ gave 88, 51, 1, and 0% yield, respectively. The fluoride and alkoxide ions may interfere with the coupling reaction. See the Supporting Information for details.

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