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Kumada–Tamao–Corriu Coupling of Alkyl Halides Catalyzed by an Iron–Bisphosphine Complex

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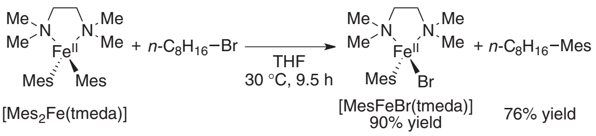
An iron(II) chloride complex possessing a sterically demanding *ortho*-phenylene-tethered bisphosphine ligand shows a high catalytic activity in the *Kumada–Tamao–Corriu* coupling of nonactivated alkyl halides with aryl Grignard reagents. Primary, secondary, and tertiary alkyl halides can participate as an electrophilic coupling partner. A radical clock experiment using (iodomethyl)cyclopropane exclusively gives the corresponding ring-opening coupling product, suggesting intermediacy of alkyl radical species.

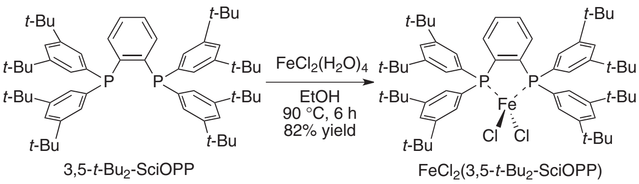
Transition-metal-catalyzed cross-coupling is one of the most powerful tools in organic synthesis.[1] After dormancy for decades, iron has attracted renewed attention as a practical coupling catalyst due to its economic and ecological advantages over the other rare metal catalysts.[2,3] Moreover, iron catalyst displays characteristic reactivities and selectivities, which cannot be easily attained by the prevalent Ni- and Pd-catalysts: several research groups, including us, have reported the cross-coupling reactions of nonactivated alkyl halides with Grignard reagents by using iron catalysts.[3h–3j,3m–3o,3t,3u] In 2004, we introduced TMEDA as a Lewis basic additive into the iron-catalyzed cross-coupling reaction to obtain the desired reactivity toward the alkyl halides.[3h] Although high selectivity and reactivity were achieved by using TMEDA with the optimized experimental procedure, large excess of the additive was required. In order to control the reaction by using a catalytic amount of additives instead of TMEDA, we continued the study and have developed new *ortho*-phenylene–bisphosphine ligands, which bear peripheral steric bulk around the iron center.[4] We report herein a new *Kumada–Tamao–Corriu* coupling between various nonactivated alkyl halides and aryl Grignard reagents effected by low catalyst loading (0.5 to 3 mol %) of the iron–bisphosphine complex.

According to Nagashima's report on the reaction of dimesityliron(II)-*N*,*N*,*N*′,*N*′-tetramethylethylenediamine, [$\mathrm{Mes_2Fe^{II}(tmeda)}$], with an alkyl halide (eq 1), it was suggested that the reactive iron species should adopt a tetrahedral geometry in high-spin state ($S = 2$).[5]



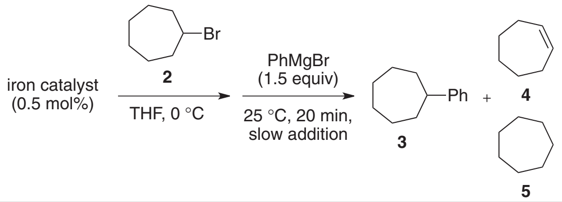
(1)

As shown in Scheme 1, we designed and synthesized a novel *ortho*-phenylene-tethered bisdphosphine ligand possessing bulky substituents at the 3,5-positions of phenyl groups on the phosphorus atoms, 1,2-bis{bis[3,5-di(*t*-butyl)phenyl]phosphino}benzene[6] (hereafter named 3,5-*t*-Bu$_2$-SciOPP[4c,7]) and also prepared its iron(II) chloride complex [$\mathrm{FeCl_2}$(3,5-*t*-Bu$_2$-SciOPP)].[4] The iron complex exhibited the above-mentioned properties of the catalytically active iron species, and we anticipated that the bulky substituents would bring about peripheral steric bulkiness around the iron center to maintain the desired properties upon transmetalation with aryl Grignard reagents, emulating Nagashima's [$\mathrm{Mes_2Fe^{II}(tmeda)}$].



Scheme 1. Synthesis of an iron complex.

Table 1. Screening of iron catalyst

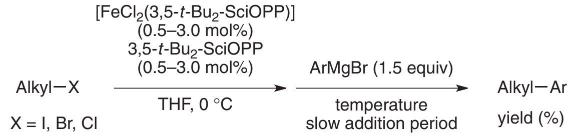


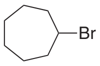
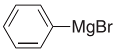
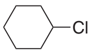
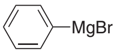
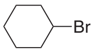
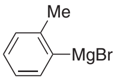
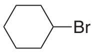
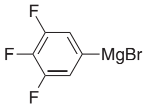
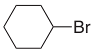
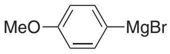
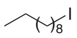
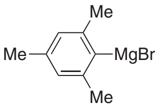
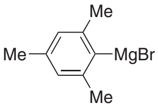
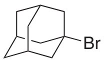
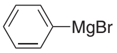
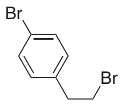
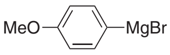
Entry	Iron catalyst	Yield/%[a]			Recovery/%[a]
		3	4	5	2
1	$\mathrm{FeCl_3}$	21	69	6	0
2[b]	[$\mathrm{FeCl_2(dppbz)_2}$]	50	20	4	25
3[b]	[$\mathrm{FeCl_2}$(3,5-*t*-Bu$_2$-SciOPP)]	84	14	0	1
4[c]	[$\mathrm{FeCl_2}$(3,5-*t*-Bu$_2$-SciOPP)]	92	8	0	0

[a] The yield and recovery were determined by GC analysis using undecane as an internal standard. [b] All data are the average of two or three experiments. [c] 0.5 mol % of 3,5-*t*-Bu$_2$-SciOPP was used as an additive.

Having the iron complex in hand, we examined the coupling reaction of alkyl halides with aryl Grignard reagents in the presence of catalytic amounts of [$\mathrm{FeCl_2}$(3,5-*t*-Bu$_2$-SciOPP)]. Table 1 summarizes the results of catalyst screening for the reaction of bromocycloheptane (**2**) with the phenyl Grignard reagent. To a THF solution of **2** and the iron complex was added dropwise the Grignard reagent over 20 min at 25 °C according to a procedure we reported previously.[3h] In the absence of the phosphine ligand, coupling product (**3**) was obtained in 21%

Table 2. Substrate scope

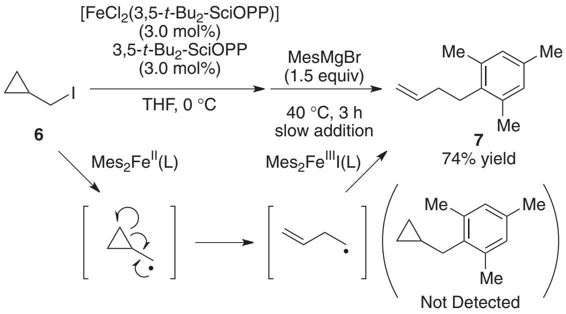


Entry[a]	Alkyl–X	ArMgBr	Time/°C	Period	Yield[b]/%
1[c]			25	20 min	92[d]
2			40	3 h	82
3			40	20 min	95
4			40	20 min	98
5			25	20 min	98
6			40	3 h	93
7			40	3 h	76
8			40	3 h	81
9			40	3 h	78

[a]The reactions were carried out by using 3.0 mol % of [FeCl$_2$(3,5-t-Bu$_2$-SciOPP)] and 3.0 mol % of 3,5-t-Bu$_2$-SciOPP unless otherwise noted. [b]Isolated yield. [c]0.5 mol % of [FeCl$_2$(3,5-t-Bu$_2$-SciOPP)] and 0.5 mol % of 3,5-t-Bu$_2$-SciOPP were used. [d]The yield was determined by GC analysis using undecane as an internal standard.

yield along with the undesired formation of cycloheptene (**4**) and cycloheptane (**5**) in 69% and 6% yield, respectively (Entry 1). [FeCl$_2$(dppbz)$_2$], which is an efficient catalyst for Negishi coupling reactions,[8] gave **3** in a modest yield (Entry 2). [FeCl$_2$(3,5-t-Bu$_2$-SciOPP)] gave **3** in 84% yield and further improvement has been achieved by using 0.5 mol % of the free ligand along with 0.5 mol % of the iron complex (Entries 3 and 4). We assume that partial dissociation of the ligand followed by nonselective reaction is presumably suppressed by the addition of the free ligand.

Under the optimized conditions (Entry 4, Table 1), the scope of the reaction was further examined (Table 2). Most of the reactions proceeded in good to excellent yield in the presence of 0.5–3.0 mol % of the iron catalyst. Less reactive substrates require higher reaction temperature (40 °C) and/or slower addition of the Grignard reagent (3 h) in general.[9,10] Notably, electron-deficient and sterically demanding aryl Grignard reagents can participate in the reaction (Entries 4, 6, and 7). Not only primary and secondary alkyl halides but also a tertiary alkyl halide gave the coupling product in good yield (Entry 8). 1-Bromo-4-(2-bromoethyl)benzene possessing two potential reactive sites, $\mathrm{C_{sp}}^2$–Br and $\mathrm{C_{sp}}^3$–Br, reacted with the p-anisyl Grignard reagent via a selective $\mathrm{C_{sp}}^3$–Br bond cleavage, providing the corresponding coupling product in 78% yield (Entry 9).



Scheme 2. Radical clock experiment using (iodomethyl)-cyclopropane.

As shown in Scheme 2, the intermediacy of alkyl radical species in the present coupling reaction was confirmed by the reactions of (iodomethyl)cyclopropane (**6**): in the presence of 3.0 mol % of the iron catalyst, the reaction with mesityl Grignard reagent proceeded at 40 °C to give the ring-opening product (**7**) exclusively in 74% yield.

In summary, we have developed highly efficient iron-catalyzed cross-coupling of alkyl halides with aryl Grignard reagents with the aid of *ortho*-phenylene-tethered bisphosphine ligand possessing bulky substituents at the 3,5-positions of the diphenylphosphino groups (SciOPPs). The present method provides a facile and nonhazardous access to a variety of substituted aromatics in laboratory as well as industry.

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6 1,2-Bis{bis[3,5-di(*t*-butyl)phenyl]phosphino}benzene (3,5-*t*-$\mathrm{Bu_2}$-SciOPP) is commercially available from Wako Pure Chemical Industries, Ltd.

7 SciOPP is the abbreviation of spin-control-intended *ortho*-phenylene–diphosphine.

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9 Slow addition of Grignard reagents often provides higher selectivity in iron-catalyzed cross-coupling, being supposed to suppress the ferrate formation; see refs. 3h, 3j, and 3o.

10 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.