

Synthesis of Iron(III) Complex Bearing Tridentate β -Aminoketonato Ligand: Application to Iron-catalyzed Cross-coupling Reaction of Arylmagnesium Bromides with Alkyl Halides

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A tridentate β -aminoketonato iron complex was prepared by the reaction of lithium β -aminoketonato with FeCl_3 . This iron complex was found to be an efficient catalyst for the cross-coupling reaction between arylmagnesium bromides and alkyl halides.

Transition-metal-catalyzed C–C bond formation between organometallic reagents and organic halides is one of the most important reactions in modern organic synthesis. Various transition metals have been employed as an efficient catalyst for the reaction, for example, Pd, Ni, and Co.¹ Recently, iron complexes have been actively investigated as a catalyst in the reaction,^{2–9} because iron is a nearly ideal transition metal due to its low cost, nontoxicity, and availability. It has been reported that $[\text{Fe}(\text{acac})_3]$ (acac: acetylacetonato) acts as an effective catalyst for the cross-coupling reaction.^{4,7} Acetylacetonato is a β -diketonato ligand, which acts as not only a bidentate three-electron donor but also pseudo halogen, and various metal complexes bearing this ligand are commercially available and extensively used instead of halogeno complexes. On the other hand, a β -diketiminato ligand, which has bulky substituents on nitrogen atoms instead of oxygen atoms in β -diketonato, has attracted much attention because this ligand is able to stabilize coordinatively unsaturated metal complexes by the substituents.¹⁰ However, this steric feature might reduce the reactivity of the metal center with various organic molecules. We are interested in a β -aminoketonato ligand, which has both an organic nitrogen group and an oxygen atom as donor atoms of the ligand (Figure 1).¹¹ This ligand is expected to control favorably the stability and/or reactivity of the metal species. Furthermore, the proligand, β -aminoketone, can be easily prepared by the reaction of β -diketone with various primary amines, and thus modifications of steric and electronic factors might be possible.¹² Herein, we report the preparation of the β -aminoketonato complex of iron and its application to the catalyst for the cross-coupling reaction of arylmagnesium bromides and organic halides.

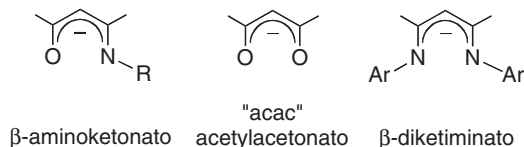
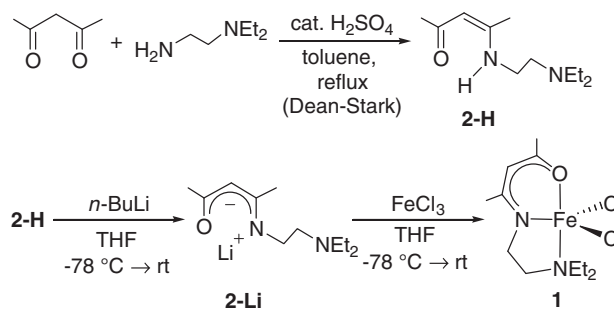


Figure 1. β -Aminoketonato ligand: comparison with acetylacetonato and β -diketiminato ligands.

First we prepared iron complex **1** bearing a tridentate β -aminoketonato ligand, as we expected that such a ligand could form a robust iron complex and prevent the additional interaction with solvent or substrates (Scheme 1). On treatment of acetylacetonato with *N,N*-diethylethylenediamine in the presence of a catalytic amount of H_2SO_4 under toluene refluxing conditions, tridentate β -aminoketone **2-H** was obtained as a yellow oil in 87% yield. The reaction of lithium β -aminoketonato **2-Li**, prepared from **2-H** with *n*-BuLi in situ, with one equivalent of FeCl_3 in THF afforded the desired iron complex **1** in 95% yield as a purple solid.¹³ The ^1H NMR spectrum of **1** showed broad signals due to a paramagnetic nature. Complex **1** was characterized by elemental analysis as well as X-ray diffraction.¹⁴ An ORTEP drawing of **1** is shown in Figure 2. The geometry of iron is distorted trigonal bipyramidal with equatorial angles in the range 113.93(3)–124.68(5) $^\circ$; the sum of angles is 359.79 $^\circ$. The apical O(1)–Fe(1)–N(2) angle exhibits a small nonlinearity (165.60(6) $^\circ$). The iron atom is nearly located on the coplane defined by O(1), N(1), and N(2); the iron atom is displaced 0.0359(2) Å out of the plane. A notable feature of the



Scheme 1.

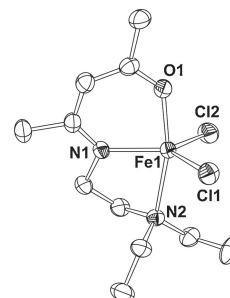


Figure 2. ORTEP drawing of complex **1** (30% probability of thermal ellipsoids). All hydrogen atoms are omitted for clarity.

Table 1. Optimization of the cross-coupling reaction catalyzed by **1**^a

Entry	Solvent	Catalyst /mol %	PhMgBr /equiv	Addition rate/min	Time /min	Temp /°C	Yield/% ^b	
							5a	6a
1	Et ₂ O	1.0	1.2	fast	60	4	88	11
2	CPME	1.0	1.2	fast	60	4	81	12
3	THF	1.0	1.2	fast	60	4	34	5
4	DME	1.0	1.2	fast	60	4	20	26
5	Et ₂ O	1.0	1.2	10	60	4	81	20
6	Et ₂ O	1.0	1.2	20	60	4	65	26
7	Et ₂ O	1.0	1.2	fast	60	rt	88	11
8	Et ₂ O	1.0	1.2	fast	60	35	84	12
9	Et ₂ O	0.5	1.2	fast	60	rt	83	16
10	Et ₂ O	2.0	1.2	fast	60	rt	88	15
11	Et ₂ O	3.0	1.2	fast	60	rt	81	14
12	Et ₂ O	5.0	1.2	fast	60	rt	79	18
13	Et ₂ O	1.0	1.0	fast	60	rt	78	18
14	Et ₂ O	1.0	1.5	fast	60	rt	84	14
15	Et ₂ O	1.0	2.0	fast	60	rt	85	11
16	Et ₂ O	1.0	1.2	fast	5	rt	87	11

^aThe reaction was carried out on a 1.8 mmol scale of **4a**.

^bCompounds **5a** and **6a** were isolated as a mixture. The ratio of **5a/6a** was determined by ¹H NMR. Yield of **5a** was based on **4a**. Yield of **6a** was based on **3a**.

bonding to the iron center is that the bond to the aminoketonato nitrogen N(1) (2.0345(15) Å) is substantially shorter than that of the amino nitrogen N(2) (2.2566(16) Å).

As the desired iron complex **1** was obtained and characterized, we evaluated the iron complex **1** in the cross-coupling reaction and optimized the reaction conditions using the reaction of phenylmagnesium bromide (**3a**) with bromocyclohexane (**4a**) (Table 1). To begin with, the reaction was conducted in some ethereal solvents (Entries 1–4). Diethyl ether (Et₂O) gave the best result, and phenylcyclohexane (**5a**) was obtained in a good yield (88%) along with the formation of biphenyl (**6a**) in 11% yield. CPME (cyclopentyl methyl ether) was also a suitable solvent, whereas the yield of the desired product decreased in THF or DME (1,2-dimethoxyethane) probably due to the strong coordination ability of THF and DME to iron and/or magnesium. In iron-catalyzed cross-coupling reactions, Nakamura and co-workers reported that the slow addition of Grignard reagent to the reaction mixture is effective for the formation of the desired compound.^{3a} We investigated the influence of addition rate of **3a** on the formation of **5a**. The yield of **5a** decreased and increase of the formation of **6a** was observed by decreasing the rate of addition (Entries 5 and 6). Therefore, the fast addition resulted in the effective formation of the desired product **5a** in our system (Entry 1). The reaction was also examined at several temperatures. The yield of **5a** decreased slightly when the reaction was conducted at 35 °C (Entries 1, 7, and 8). Regarding amounts of the catalyst **1** and the Grignard reagent **3a**, employments of 1.0 mol% of the catalyst and 1.2 equivalent of the magnesium reagent lead to a good result (Entries 7 and 9–15). Furthermore, the reaction was found to be complete within 5 min (Entry 16).¹³

Table 2. The reaction of various arylmagnesium bromides with cyclohexyl bromide catalyzed by **1**^a





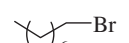

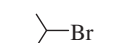
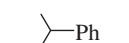

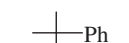
Entry	ArMgBr 3	Product 5	Yield/%
2		Cy-	57
3		Cy-	91
4		Cy-	33 ^b
5		Cy-	89
6		Cy-	85
7		Cy-	95

^aThe reaction was carried out with **3** (2.2 mmol) and **4a** (1.8 mmol) in the presence of the catalyst **1** (0.018 mmol). Arylmagnesium bromide **3** was added at once (fast addition). Cy: cyclohexyl. ^bReaction time was 1 h.

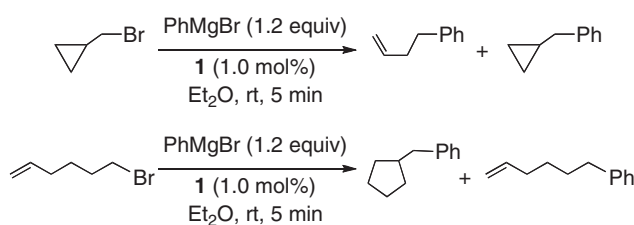
To demonstrate the efficiency of the cross-coupling reaction catalyzed by complex **1**, we investigated the scope of the reaction of various arylmagnesium bromides with bromocyclohexane under optimized reaction conditions. The results are summarized in Table 2. *para*-Substituted arylmagnesium bromides, such as 4-methyl-, 4-methoxy-, and 4-fluorophenylmagnesium bromides, afforded the desired products **5** in good yields (Entries 1, 3, and 5). However, the decrease of the product yield was observed in the reactions of *ortho*-substituted arylmagnesium bromides (Entries 2 and 4). In the case of 2-methoxyphenylmagnesium bromide, the desired product was obtained in 33% even after 1 h (Entry 4). By the reaction of 1- and 2-naphthylmagnesium bromide with bromocyclohexane, 1- and 2-cyclohexylnaphthalene were obtained in 85% and 95%, respectively (Entries 6 and 7).

Then, we examined the reaction of phenylmagnesium bromide with various alkyl halides (Table 3). In the case of iodocyclohexane, the desired product **5a** was obtained in a good yield (Entry 1). The chlorinated substrate resulted in the decrease of the product yield (43%) under the same reaction conditions, whereas elongation of the reaction time (3 h) led to the increase of the yield up to 77% (Entry 2). Acyclic bromoalkanes were also used in the cross-coupling reaction with phenylmagnesium bromide. In the case of 1-bromooctane as a primary alkyl halide, 1-phenyloctane was obtained in 77% yield (Entry 3). 2-Bromobutane, a secondary alkyl halide, afforded the product in 48% yield. The yield was not improved by elongation of the reaction time (Entry 4). In the case of 2-bromo-2-methylpropane, a tertiary alkyl halide, the desired product, was not obtained (Entry 5).

Table 3. The reaction of phenylmagnesium bromide with alkyl halides catalyzed by **1**^a

Entry	Alkyl halide 4	Product 5	Yield/%
1			87
2			43 (77) ^b
3			77
4			48 (47) ^c
5			—

^aThe reaction was carried out with **3a** (2.2 mmol) and **4** (1.8 mmol) in the presence of the catalyst **1** (0.018 mmol). Phenylmagnesium bromide **3a** was added at once (fast addition). ^bReaction time was 3 h. ^cReaction time was 1 h.

**Scheme 2.**

To obtain insight into the mechanism of the reaction, we examined reactions of (bromomethyl)cyclopropane or 6-bromo-1-hexene with phenylmagnesium bromide (Scheme 2). In the case of (bromomethyl)cyclopropane, the ring-opened product 4-phenyl-1-butene was obtained in 63% yield along with the simple coupled product benzylcyclopropane as a minor product (4% yield). With 6-bromo-1-hexene, both the ring-closed product benzylcyclopentane (23%) and the simple coupled product 6-phenyl-1-hexene (34%) were obtained. These results indicated that the cross-coupling reaction catalyzed by complex **1** could involve a radical mechanism in the reaction of alkyl halide with the iron species.^{6b,15,16}

In our system, the slow addition of phenylmagnesium bromide to the reaction mixture is unfavorable for the formation of the cross-coupled product (Table 1). This procedure resulted in increase of the formation of biphenyl, the homocoupled product. Moreover, although a large amount of arylmagnesium bromide was present in our catalytic system by fast addition, only a small quantity of the homocoupled product was formed. From these results, the high-oxidation-state iron species formed by the reaction of the low-oxidation-state iron with alkyl halide readily reacted with arylmagnesium bromide to give the cross-coupled product. Furthermore, the iron species consisting of the tridentate β -aminoketonato ligand might effectively prevent the formation of a polyphenyl ate-complex, which can be considered to produce the homocoupled product via reductive elimination.^{17,18}

In summary, we demonstrate the preparation of the tridentate β -aminoketonato iron complex **1** and its application to the iron-catalyzed cross-coupling reactions of arylmagnesium bromides with alkyl halides. Iron complex **1** acts as an effective catalyst for the reaction by the simple procedure, i.e., (i) without an additive such as TMEDA, (ii) without heating and/or cooling the reaction mixture, and (iii) within a short reaction time. Further investigations on the development of effective iron catalysts and the coupling reactions with various organometallic reagents are now in progress.

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