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Effect of TMEDA on Iron-Catalyzed Coupling Reactions of ArMgX with Alkyl Halides

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The iron-catalyzed Grignard coupling reaction has received increasing interest from an environmental point of view. In this reaction, various types of Grignard reagents have been successfully coupled with alkyl, vinyl, and aryl halides to produce a variety of organic compounds, including complex natural products.[1,2] A special feature of the iron-catalyzed reaction, which is not easily accessible with commonly used nickel- and palladium-catalyzed reactions, is the successful coupling of alkyl halides with Grignard reagents, which is achieved either by catalysis of ferrates[2a] or by additive effects of amines[2b,c,3] and phosphorus compounds.[2d,e] Despite the great synthetic utility of these iron-catalyzed reactions, their mechanism has not been fully studied because of the paramagnetism and instability of the alkyliron intermediates. The mechanism of the "ate" catalyst has only recently been proposed by Fürstner and co-workers[1a−e,2a] on the basis of the isolation of possible ferrate intermediates. In contrast, the effect of additives, in particular that of tetramethylethylenediamine (TMEDA), requires further investigation.[2b,3] Although Sen and co-workers[4] and later Fürstner et al.[1c] reported the possible involvement of (TMEDA)Fe(CH_2Ph)$_2$ from detection of the coupling product in the reaction with allyl bromide, the fate of the iron species was not investigated fully. In this paper, we propose a mechanism for the iron-catalyzed cross-coupling reactions of ArMgX with alkyl halides using (TMEDA)FeAr_2 and (TMEDA)Fe(Ar)Br on the basis of the isolation and reaction of these organoiron intermediates.

The coupling reaction is generally performed by treatment of RX with a mixture of ArMgX and TMEDA (1 equiv with respect to ArMgX) in the presence of $FeCl_3$ (5 mol %) in THF. Slow addition of ArMgX/TMEDA increases the yield and selectivity of the coupling product. We selected the reaction between 2,4,6-$Me_3C_6H_2$MgBr (mesityl-MgBr) and 1-bromooctane, which are coupled by catalysis of $FeCl_3$ (5 mol %) in the presence of TMEDA to give 1-octyl-2,4,6-trimethylbenzene in 32% yield after 18 h at room temperature. A controlled experiment in 1:4 THF/C_6D_6 in the absence of 1-bromooctane provided evidence for the formation of (TMEDA)Fe(mesityl)$_2$ (**1**), the ^{1}H resonances of which were in accord with those of the same complex prepared according to the literature method.[5] This strongly suggests that **1** is involved in the catalytic cycle as an intermediate. The complex **1** was characterized by ^{1}H NMR spectroscopy and elemental analysis by Chirik and co-workers,[5] and we succeeded in preparing single crystals suitable for X-ray structure determination. The ORTEP drawing is depicted in Figure 1.

The reaction of isolated **1** with 2 equiv of 1-bromooctane revealed the formation of a new iron complex, suggested by NMR evidence to be (TMEDA)Fe(mesityl)Br (**2**), in ∼90% yield.[6] GC analysis of the organic products showed that 1-octyl-2,4,6-trimethylbenzene

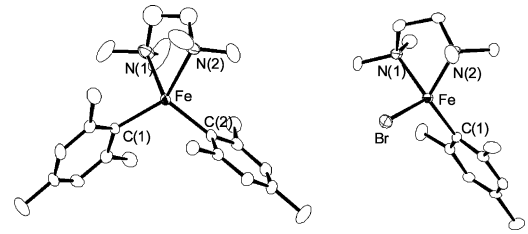

Figure 1. Molecular structures of complexes **1** (left) and **2** (right) shown using 50% probability ellipsoids.

was formed in 76% yield based on **1** along with unreacted 1-bromooctane (124% yield).[7] We found that **2** could be synthesized by treatment of **1** with (TMEDA)FeBr_2 in 51% yield. Identification of **2** was performed by X-ray crystallography. Figure 1 also shows the ORTEP view of **2**, in which the two nitrogen atoms in TMEDA, a mesityl group, and a bromine atom are arranged tetrahedrally. Elemental analysis and NMR spectra support the structure of **2** (see the Supporting Information).

Two significant findings were obtained from further reactions of **2** with another equivalent of 1-bromooctane or mesityl-MgBr. First, the reaction of **2** with 1-bromooctane was much slower than the reaction of **1** with 1-bromooctane. Second, **2** reacted with mesityl-MgBr to regenerate **1**. These results suggested the catalytic cycle shown in Figure 2, in which **1** (formed from $FeCl_3$, mesityl-

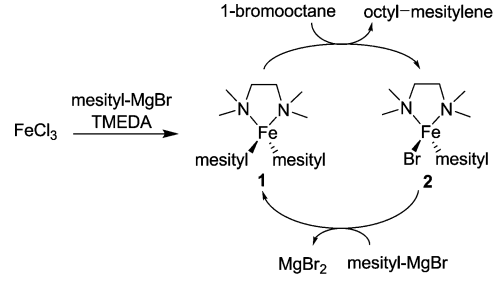

Figure 2. Possible catalytic cycle for the reaction of 1-bromooctane with mesityl-MgBr catalyzed by **1**.

MgBr, and TMEDA) reacts with 1-bromooctane to give the coupling product and **2**. The resulting **2** is allowed to react with mesityl-MgBr to regenerate **1**, which initiates the second run of the catalytic cycle in contact with 1-bromooctane.

The use of a "radical clock" provided further insights into the mechanism. Treatment of **1** with 1-bromo-5-hexene resulted in the exclusive formation of 2,4,6-$Me_3C_6H_2C_4H_8CH{=}CH_2$ with no radical cyclization (eq 1). A similar reaction of **1** with bromomethylcyclopropane gave a 17: 55 mixture of 2,4,6-$Me_3C_6H_2CH_2$(cyclopropyl) and 2,4,6-$Me_3C_6H_2C_2H_4CH{=}CH_2$ (eq 2).

It is known that estimated rates of the radical cyclization of 5-hexenyl radical and radical ring opening of cyclopropylmethyl

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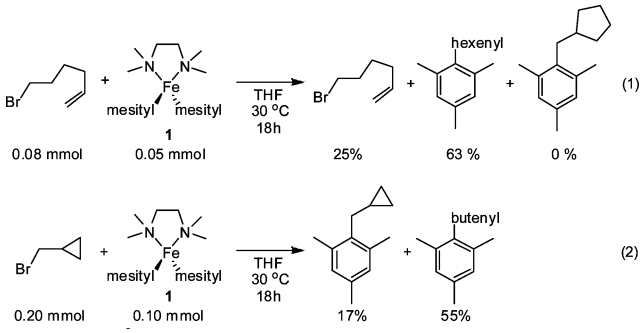

radical are 1.0×10^5 and 1.3×10^8 M^{-1} s^{-1}, respectively, at 25 °C.[8] The above results apparently suggest that one-electron oxidation of Fe(II) to Fe(III) is involved in the reaction of **1** with R−Br and that the lifetime of the radical intermediate is too short for the cyclization of 5-hexenyl radical to occur but long enough to promote partial ring opening of the cyclopropylmethyl radical. In other words, the radical species generated by reaction of R−X with Fe(II) quickly coupled with the mesityl group on the iron, as shown in Figure 3. In our previous paper, the product of the catalytic coupling

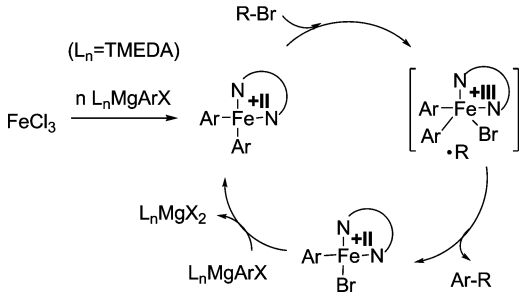

Figure 3. Possible catalytic cycle for the (TMEDA)$FeAr_2$-catalyzed cross-coupling reaction.

of PhMgBr with 1-bromo-5-hexene was dependent on the reaction conditions used. When PhMgBr, 1-bromo-5-hexene, TMEDA, and a catalytic amount of $FeCl_3$ were mixed at −78 °C and the resulting mixture was warmed to room temperature, the product was exclusively $PhCH_2$(cyclopentyl). In contrast, no radical cyclization was observed when a mixture of PhMgBr and TMEDA was added dropwise to a solution containing 1-bromo-5-hexene and $FeCl_3$ (the slow-addition method).[2b] These results suggest the existence of two processes, one involving a short-lived radical and the other a long-lived radical. The former selectively takes place in both the catalytic reaction using the slow-addition method and a stoichiometric reaction of **1** with 1-bromo-5-hexene. *In other words, addition of TMEDA as the additive contributes to formation of* **1***, and the slow-addition method plays a role in operating the catalytic cycle shown in Figure 3* with the long-lived radical pathway suppressed.

As the detailed and excellent report by Fürstner and co-workers showed, mechanisms of the iron-catalyzed coupling reactions are complicated, and there apparently exist several reaction pathways that give the coupling product. Catalyst design, such as the "ate" complex and the TMEDA complex, and careful choice of the reaction conditions (e.g., slow addition) can eliminate the other possible reaction pathways to increase the selectivity of the reactions. The present study clearly demonstrates that TMEDA coordinates to iron and that coordination to iron initiates the catalytic cycle shown in Figure 3.[9] We consider this to be clear evidence showing that there is a new, reasonable mechanism other than Fürstner's "ate" mechanism, which contributes to the design of better catalysts for iron-catalyzed coupling reactions.

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Supporting Information Available: Detailed experimental section, molecular structures of **1** and **2**, details of the crystallographic studies (including CIF files), and ^{1}H NMR data for **2** and ^{1}H and ^{13}C NMR data for cross-coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) Efficient cross-coupling of ArMgX with alkyl halides was achieved by using 2 mol % of [$(FeCl_3)_2$(TMEDA)$_3$] as the catalyst. See: Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364.

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(6) Since the signals were broadened by the paramagnetism, the yield of **2** could not be determined accurately.

(7) Transition-metal-catalyzed Grignard cross-coupling reactions of ArMgX with R−X are often accompanied by formation of Ar−Ar as an undesired side reaction. We found that **1** was unstable in solution with respect to formation of the homocoupling product (mesityl−mesityl) at room temperature under a nitrogen atmosphere. However, no bimesityl was detected in the reaction of freshly prepared **1** with 1-bromooctane.

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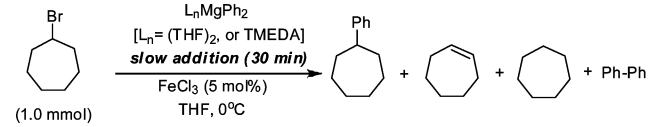
(9) It should be noted that TMEDA may play another role in the catalytic coupling of ArMgX with R−X. As described previously,[2b] application of the iron-catalyzed process to coupling of ArMgX with secondary alkyl halides resulted in undesired olefin formation via elimination of HX. In this case, the Grignard reagents behaved as both the nucleophile and the base. We suspect that coordination of TMEDA to Mg reduces the Lewis acidity of the Mg center, suppressing the elimination of HX. In fact, PhMgBr in THF-d_8 in the presence of TMEDA afforded a mixture of PhMgBr(TMEDA), Ph_2Mg(TMEDA), and $MgBr_2(TMEDA)_n(THF)_{2-n}$ (n = 1, 2) (see the Supporting Information). Since $Ph_2Mg(THF)_2$ and Ph_2Mg(TMEDA) can be synthesized by alternative routes,[10] these compounds were isolated and subjected to the iron-catalyzed coupling with bromocycloheptane. As summarized below, the reaction with $Ph_2Mg(THF)_2$ afforded cycloheptene exclusively. In sharp contrast, treatment of bromocycloheptane with Ph_2Mg(TMEDA) gave a mixture of phenylcycloheptane and cycloheptane, and application of the slow-addition method to this reaction increased the selectivity for phenylcycloheptane. A recent paper by Cahiez et al.[3] as well as our unpublished data suggests that only a catalytic amount of TMEDA based on Mg is necessary for effective suppression of the HX elimination as long as ArMgX and TMEDA are carefully added dropwise.



L_n = $(THF)_2$:	9	67	3	13
L_n = TMEDA * :	41	44	6	12
L_n = TMEDA :	72	10	<1	4

* : without slow addition

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