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Iron-catalyzed 1,6-addition of aryl Grignard reagents to 2,4-dienoates and -dienamides

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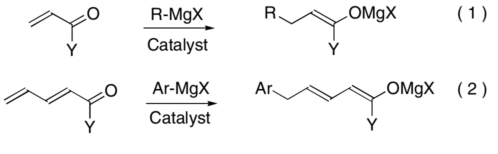
Abstract—1,6-Addition of aryl Grignard reagents to 2,4-dienoates or -dienamides was nicely catalyzed by iron salt to give 5-aryl-3-enoates or the corresponding amides in a highly regio- and stereoselective manner.

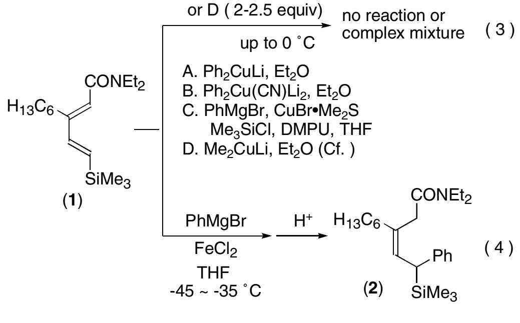
Conjugate addition of Grignard reagents to unsaturated carbonyl compounds is a fundamental transformation in organic synthesis (Scheme 1, Eq. 1). Copper salts are exclusively used as an excellent catalyst to effect this transformation, and their broad applicability has been firmly established.[1] However, it may also be true that the copper methodology is not necessarily almighty. In fact, we encountered difficulty in performing conjugate addition of aryl Grignard reagents to certain 2,4-dienoates or -dienamides in the 1,6-fashion under copper catalysis (Scheme 1, Eq. 2, Y = OR or NR_2). In order to make this reaction viable, we sought an alternative to copper reagents and found that an iron salt nicely promotes this type of conjugate addition.

Although the 1,6-addition of organocopper reagents to 2,4-unsaturated carbonyl compounds has been reported,[2] its generality is much less explored than that of the usual 1,4-type reactions. When we attempted reaction between phenylmetal reagents and the 2,4-dienamide **1**,[3] several representative copper-assisted systems did not furnish the desired product at all (Scheme 2, Eq. 3).[4] However, to our surprise, switching the copper-based reagents to an iron-based one[5,6] led to a smooth addition of phenyl Grignard reagent exclusively in 1,6-fashion to give the desired product **2** (Eq. 4).

Table 1 summarizes the variation of reaction conditions and stoichiometry of the substrates and reagents. The addition of PhMgBr in the absence of or even in the presence of a stoichiometric amount of $FeCl_2$ did not occur (entries 1 and 2). However, the catalytic use of $FeCl_2$ now promoted the 1,6-addition (entries 3–9). Considering the possible difference in reactivity from substrate to substrate, we adopted the conditions of entry 6, which consists of PhMgBr (1.8 equiv) and $FeCl_2$ (0.1 equiv), for the collection of data in Table 2. It is noteworthy that the geometry of the trisubstituted olefin of product



Scheme 1. 1,4- and 1,6-addition of Grignard reagent.



Scheme 2. Copper- versus iron-mediated conjugate addition.

Keywords: Grignard reagents; Iron; 1,6-Addition; 2,4-Dienoate and -dienamide; *cis*-Olefin.

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Table 1. Iron-mediated conjugate addition to **1** (Scheme 2, Eq. 4)

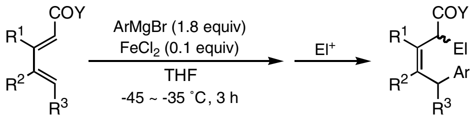
Entry	PhMgBr (equiv)	$FeCl_2$ (equiv)	Period (h)	Yield (%)[a]	
				Recvd. **1**	Product **2**
1	2.5	0	3	Quant.	
2	1.0	1.0	3	Quant.	
3	1.8	1.0	3	15	76
4	1.3	0.1	5		90 (75)
5	1.5	0.1	3		72
6	1.8	0.1	3		83 (72)
7	1.3	0.05	3		28
8	1.5	0.05	3		72
9	1.8	0.05	3		83

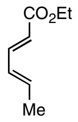
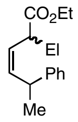
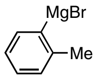
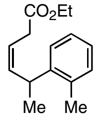
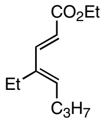
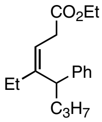
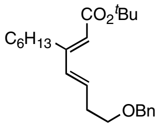
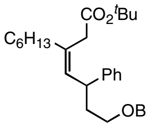
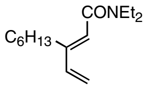
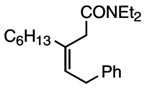
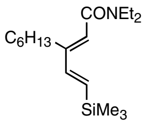
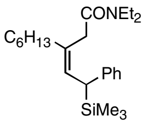
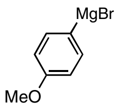
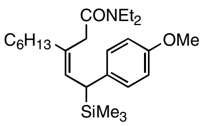
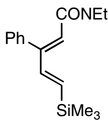
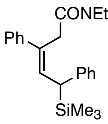
[a] Yield determined by ^1H NMR. Isolated yield in parentheses.

2 was exclusively controlled to be (*Z*) (vide infra), which was established by NOE experiments.

This 1,6-addition appears reasonably general, and dienoates and dienamides with various substitution patterns afforded the desired products.[7] Other results are summarized in Table 2. Ethyl sorbate (**3**)[2a,b] (and its homologues[2a,c–e]) has been used as a probe for copper-mediated 1,4-/1,6-addition of Grignard reagents, but the addition of an aryl group has not been reported so far. The present iron-catalyzed reaction enabled the delivery of the phenyl group in a 1,6-fashion to give the desired product **4** (entry 1). The olefin geometry of

Table 2. Iron-catalyzed 1,6-addition of aryl Grignard reagents



Entry	Substrate	ArMgBr	El^+	Product[a]	Yield (%)[b] [Ds][c]
1	 (**3**)	PhMgBr	H^+	 EI = H (**4**)	78
2			D^+	= D (**5**)	>98% d [58:42]
3			MeI	= Me (**6**)	70 [61:39]
4	**3**		H^+	 (**7**)	65
5	 (**8**)	PhMgBr	H^+	 (**9**)	84
6	 (**10**)	PhMgBr	H^+	 (**11**)	86
7	 (**12**)	PhMgBr	H^+	 (**13**)	86
8	 (**1**)	PhMgBr	H^+	 (**2**)	72
9	**1**		H^+	 (**14**)	73
10	 (**15**)	PhMgBr	H^+	 (**16**)	79

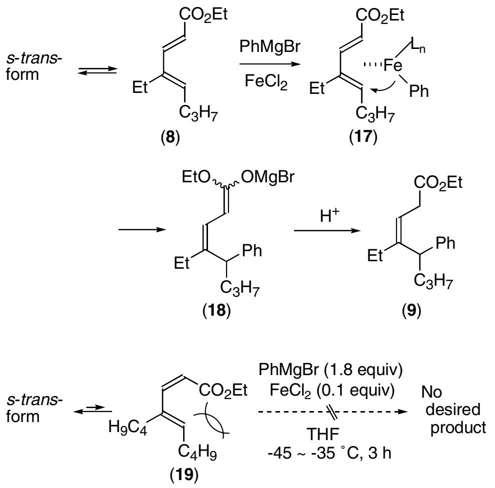
[a] A single olefinic isomer was obtained in all cases. Its stereochemistry was confirmed as depicted for **2**, **4**, **5**, **6**, **7**, **9**, **11**, and **13**.

[b] Isolated yields.

[c] Diastereoselectivity with respected to the introduction of El^+. The relative stereochemistry has not been determined.

the product observed herein was exclusively (*Z*), which is in stark contrast to the previously reported alkyl transfer by organocopper-based reactions, where the products always have (*E*)-olefinic configuration with high stereoselectivity.[2a–d] The intermediate dienolate species before aqueous workup was identified by deuteriolysis (to give **5**) and, more importantly, it could be used for further transformation such as methylation, giving the product **6** in good yield (entries 2 and 3). A sterically demanding aryl Grignard reagent could participate in the reaction to afford **7** (entry 4). Other esters **8** and **10** having more substituents afforded the expected products **9** and **11** as well under iron catalysis (entries 5 and 6). As already exemplified in Eq. 4, various 2,4-dienamides **1**, **12**, and **15** behaved like the esters to give the corresponding products **2**, **13**, **14**, and **16** in good yields (entries 7–10). In all cases, virtually a single trisubstituted olefin was produced. Its geometry was established in representative cases, where the carbonyl group and the incoming aryl group occupy *cis* position. This observation was again different from that of the known relevant copper-mediated alkyl transfer reactions, where the relationship is always *trans*.[2a,c,d,f] The resultant stereodefined olefins should facilitate further synthetic transformations.

The following experiments in Scheme 3 could provide some insight into the mechanism of this reaction. The phenyl addition proceeded successfully to (2*E*)-4,5-dialkyl-2,4-pentadienoate **8** as shown in entry 5, Table 2. However, a similar substrate **19**, despite having (2*Z*)-olefin geometry, did not afford the desired product. These facts suggest that availability of the *s-cis* form of the diene **8**, which is less favorable in **19**, is essential for the conjugate addition. Then, the initial formation of the *s-cis*-diene-iron complex like **17**[8] is followed by the aryl transfer from iron to the terminal position of the dienoate system to give the dienolate **18**. This was finally protonated to give the olefinic product **9**, the stereochemistry of which is consistent with that observed.[9]



Scheme 3. Rationale for the reactivity of the starting dienoates and the stereochemistry of the product.

In conclusion, a new role of iron catalyst in the Grignard conjugate addition was disclosed.[10] As iron is an inexpensive, non-toxic, and ubiquitous metal, the use of its salt as reagent enhances the synthetic convenience and fulfills the recent demand for an environmentally friendly process.

Acknowledgements

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7. Typical procedure: Ethyl (*Z*)-5-phenyl-3-hexenoate (**4**). To a stirred solution of ethyl sorbate (70.1 mg, 0.5 mmol) and $FeCl_2$ (6.40 mg, 0.05 mmol) in 3 mL of THF was added a 1.09 M solution of PhMgBr in THF (0.826 mL, 0.9 mmol) at −50 °C under argon to give a dark brown to black homogeneous solution. Then the solution was stirred at −50 to −40 °C for 2 h. The reaction was terminated at that temperature by the addition of a saturated NH_4Cl aqueous solution (5 mL). The organic products were extracted with ether (6–7 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude oil, ^1H NMR analysis of which did not show the peaks of other regio- and stereoisomers. The crude product was chromatographed on silica gel (hexane–ether) to afford the title compound (85.5 mg, 78%) as an isomerically pure form.
8. For *s-cis*-diene-iron complexes, which are well known as a reactive intermediate, see: Ref. 5c–e.
9. For other types of Grignard reagents, 2-propenyl Grignard reagent underwent the same 1,6-addition to **3** so far in a low yield, and alkyl Grignard reagents afforded neither 1,6- nor 1,4-addition products.
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