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Combination of iron salts with magnesium alkoxides: an efficient strategy for stereoselective cross-coupling of Grignard reagents and conjugated dienyl bromides.

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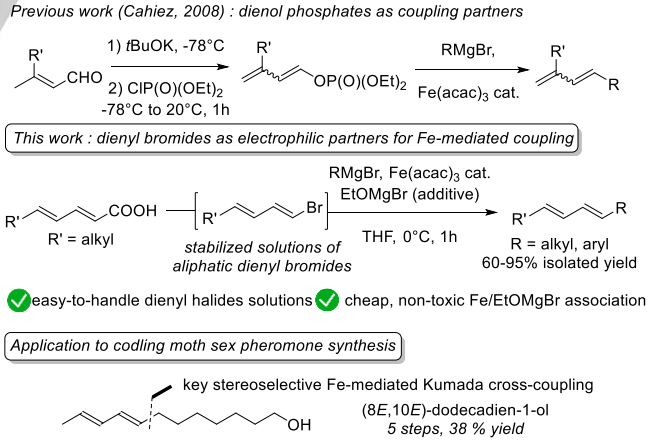
Abstract: A convenient procedure allowing iron-catalyzed cross-coupling of alkyl or aryl Grignard reagents and conjugated dienyl bromides is reported, relying on the use of cheap and non-toxic magnesium alkoxides as sole additives. An excellent stereoselectivity is observed in the alkyl-dienyl series. This sequence has been applied to the synthesis of the sex pheromone of codling moth, illustrating its applicability to the obtention of targets of industrial interest. Preliminary mechanistic studies carried out on the aryl-dienyl cross-coupling suggest that *in situ* generated *ate* homoleptic organoiron(II) species act as catalytically relevant intermediates. A modified preparative method for the realization of THF solutions of dienyl bromides as "ready-to-use" coupling partners is also discussed, circumventing the thermal instability of those derivatives.

Fe-catalyzed cross-coupling reactions have been intensely developed in the last decades.[1] Use of this cheap and abundant metal indeed led to a significant breakthrough in transition-metal catalysis owing to its ecologic and economic advantages.[1b] In this regard, efficient Kochi-type cross-couplings between Grignard reagents and organic halides in the absence of well-defined exogenous ligands were described at a preparative scale by Cahiez. Cross-coupling involving alkyl Grignard reagents and alkenyl halides can indeed be mediated using simple ferric salts such as $FeCl_3$ in the presence of *N*-methylpyrrolidinone (NMP) as a co-solvent.[1c] This method has moreover been broadly adapted to a great variety of Fe-catalyzed coupling patterns ever since, allowing the use of aliphatic halides, heteroaryl and aryl halides as electrophilic partners.[2] The state of the art however remains scarce regarding iron-mediated coupling methodologies involving dienyl halides as electrophilic partners. Yet, such substrates are particularly useful synthons in retrosynthetic analysis, a large variety of pharmaceutical or biological molecules featuring conjugated dienes. This statement is particularly true in the field of pheromone synthesis, such molecules often exhibiting conjugated dienes with controlled stereochemistry. However, dienyl halides display a strong tendency to polymerize, and require special storage and handling conditions.[3] Consequently, coupling methodologies involving dienyl halides as electrophiles are extremely rare.[4] Cahiez demonstrated that the use of dienol phosphates as electrophiles in alkyl-dienyl cross-coupling circumvented the drawbacks related to dienyl halides, the former being bench-stable. Moreover, such electrophiles can also lead to excellent coupling yields even in the absence of NMP, probably thanks to the ability of the phosphate leaving group to act as a stabilizing ligand to on-cycle iron intermediates.[5]
However, coupling strategies relying either on the use of NMP as a co-solvent or involving diethyl phosphate as a leaving group suffer from strong limitations for high-scale synthesis. On one hand, NMP was recently categorized as a reprotoxic reagent[6] and, on the other hand, the use of a dienol phosphate as a leaving group leads to overall sequences with a poor atom economy and also brings eco-toxicity issues.[7] Stereoselective synthesis of dienol phosphates moreover requires cryogenic temperatures (-78°C) as well as NMP-based methodologies,[5d] making difficult their preparation at high industrial scales (Scheme 1).



Scheme 1. Synthesis of dienyl electrophiles and their use as coupling partners in Fe-catalyzed cross-couplings.

In a recent work, we reported that the use of magnesium alkoxides as cheap and non-toxic additives led to high cross-coupling yields in alkyl-alkenyl and alkyl-aryl Kochi-type couplings involving organic halides as electrophiles.[8] This method thus appears as an appealing alternative to the use of the abovementioned coupling strategies involving either NMP or

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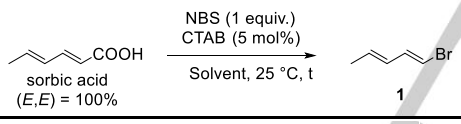
dienol phosphates (Scheme 1). Encouraged by those results, we developed a new efficient alkyl-dienyl and aryl-dienyl iron-mediated coupling method between Grignard reagents and dienyl bromides, which is reported herein. This transformation also relies on the use of a magnesium ethoxide as additive, and can be achieved with good to excellent retention of stereochemistry in the alkyl-dienyl series (Scheme 1). Moreover, we also describe a convenient modified procedure allowing an easy synthesis and handling of sensitive dienyl bromides, hampering their degradation and thus facilitating their use as coupling partners. A short convenient synthesis of codling moth sex pheromone has been performed to illustrate the synthetic potential of this strategy in terms of future industrial applications. Synthesis of this pheromone is of high industrial interest in the context of biocontrol products development targeting codling moth, since this insect is considered as a major pest to agricultural crops, mainly fruits such as apples and pears.[9]

In order to access stereocontrolled dienic halides scaffolds, a Hunsdiecker-Borodin decarboxylation of α,β,γ,δ-unsaturated aliphatic acids was performed, adopting the recent conditions developed by Rajanna et al. for the synthesis of alkenyl halides starting from α,β-unsaturated acids.[10] This transformation requires the halodecarboxylation of an unsaturated acid using association of *N*-bromosuccinimide (NBS) with a micellar medium (cetyl trimethyl ammonium bromide (CTAB) is used as surfactant); sorbic acid has been used as a benchmark substrate, affording 1-bromopenta-1,3-diene **1** (Table 1).

Table 1. Solvent screening for the bromodecarboxylation reaction of sorbic acid.[a]



Entry	Solvent	Reaction time (h)	Acid conversion (%)[b]	GC ratio (**1**) (*E*,*E*)/(*Z*,*E*)
1	Dichloroethane	2	> 95	90/10
2	Dichloromethane	1	> 95	91/09
3	1,2-Dichlorobenzene	4	> 95	90/10
4	THF	1	> 95	50/50
5	*t*BuOMe (MTBE)	> 48	50	50/50
6	DMF	2	> 95	32/68

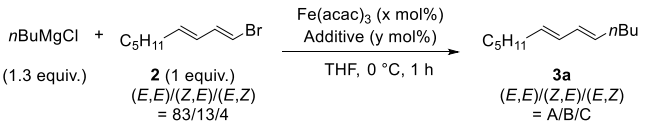
[a] Reaction scale: 10 mmol of sorbic acid, 10 mmol of NBS in solvent (10 mL).
[b] Followed by GC-MS.

Excellent conversions with a 90% retention of stereochemistry of the starting dienic acid were obtained in dichloroethane and dichloromethane (DCM) (Entries 1-2), with a faster reaction time in dichloromethane (1h). A high 95% conversion was also observed using 1,2-dichlorobenzene (Entry 3).

However, further purification of compound **1** could not be carried out successfully due to its high thermal instability. For example, evaporation of dichloromethane (Entry 2) proved to be problematic since a complete degradation of **1** was observed upon concentration *under vacuo* after 30 min at 40°C, a dark oil containing mostly polybrominated and polymeric byproducts being obtained. The separation of **1** by distillation from 1,2-dichlorobenzene (Entry 3) was unsuccessful for the same reasons. We then explored the possibility to carry out this transformation in solvents which would be compatible with further cross-coupling conditions, such as THF (Entry 4) or *t*BuOMe (MTBE, Entry 5). Our idea was to obtain directly THF or MTBE solutions of **1** after workup, with no need to further concentrate the latter. Those solutions would then be used directly under cross-coupling conditions, unlike their analogs involving chlorinated solvents used in Entries 1-3, which do not tolerate Grignard reagents. A high 95% conversion of sorbic acid was obtained in THF (Entry 4), comparable with those obtained in chlorinated solvents; however, an isomerization towards a 50/50 1*E*,3*E*/1*Z*,3*E* mixture was observed. A comparable isomerization has been observed using *t*BuOMe (50/50 1*E*,3*E*/1*Z*,3*E*, Entry 5) or DMF (32/68 1*E*,3*E*/1*Z*,3*E*, Entry 6) as solvents, with a much smaller 50% conversion for the former, and an almost quantitative conversion for the latter.

Therefore, the sole acceptable conditions which mostly retain the stereochemistry of the starting dienic acid require the use of chlorinated solvents (Entries 1-3). It was found that dilution of the dichloromethane reaction mixture obtained at the end of reaction (Entry 2) in THF (THF:DCM = 1:5) prior to concentration *under vacuo* and separation of the byproducts on alumina column inhibited the degradation of **1**, which was obtained as a DCM-free THF solution with a 0.45 M concentration. This solution was stored at -30°C away from light, and no further isomerization of **1** was observed after a few days; storage at -4°C resulted in isomerization towards a 85/15 1*E*,3*E*/1*Z*,3*E* mixture after 48h. Following the same experimental procedure, a 0.72 M THF solution of 1-bromonona-1,3-diene **2** (83/13/4 1*E*,3*E*/1*Z*,3*E*/1*E*,3*Z* mixture) could also be prepared from the corresponding α,β,γ,δ-unsaturated acid, and this substrate was used as a benchmark reactant in iron-catalyzed couplings (Table 2). **2** was preferred to **1** for this benchmark work due to its better thermal stability, allowing a more reproducible preparation of standard solutions.

Table 2. Optimization of alkyl-dienyl cross-coupling conditions.[a]



Entry	$Fe(acac)_3$ (mol%)	Additive (mol%)	GC yield[b] (%)	GC ratio A/B/C
1	5	-	75	81/13/6
2	5	NMP (900)	91	82/14/4
3	5	EtOMgBr (200)	87	82/14/4
4	5	*n*OctOMgBr (200)	78	81/13/6
5	**2.5**	**EtOMgBr (100)**	**87**	**82/14/4**
6	1	EtOMgBr (40)	79	82/13/5
7	2.5	EtOMgBr (50)	80	82/13/5

[a] Reaction scale: 0.5 mmol of **2**, 0.65 mmol of *n*BuMgCl in THF (1.0 mL).
[b] Measured in the crude using benzaldehyde as internal standard.

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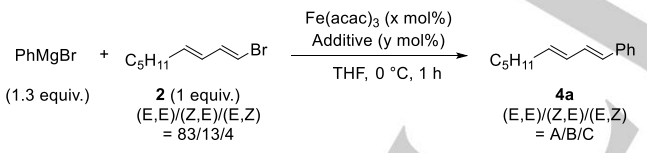
Cross-coupling with aliphatic Grignard reagents was first investigated, and *n*BuMgCl was used as a benchmark nucleophile in this alkyl-dienyl coupling series (see Table 2). Cross-coupling between **2** and *n*BuMgCl mediated by 5% $Fe(acac)_3$ in the absence of any additive led to formation of **3a** with a 75% yield after 1h at 0°C (Entry 1). Use of NMP as a co-solvent in the classic conditions described by Cahiez[1c] afforded 91% of coupling product (Entry 2). Those results are in line with what is reported in similar conditions for the coupling of alkyl Grignard reagents and alkenyl bromides. The same reaction was then carried out using magnesium alkoxides as additives. A high 87% yield (GC yield, 82% isolated yield) was obtained using 5% $Fe(acac)_3$ in combination with 200% EtOMgBr (which corresponds to a EtOMgBr:Fe = 40 ratio, Entry 3).This yield is comparable to what is obtained using NMP as co-solvent (Entry 2). Supplanting EtOMgBr by an aliphatic magnesium alkoxide bearing a longer chain (*n*-C_8H_{17}OMgBr) was slightly detrimental to the coupling efficiency (78% yield, Entry 4). To our delight, the catalytic load could be decreased to a low 2.5% $Fe(acac)_3$ quantity, associated with 100% EtOMgBr (EtOMgBr:Fe = 40), with an unchanged 87% coupling yield (Entry 5). Decreasing the iron catalytic load to 1% and maintaining a EtOMgBr:Fe ratio of 40 led to a weaker 79% yield (Entry 6). A similar decrease was observed when a 2.5% iron catalytic load was used associated with a smaller EtOMgBr:Fe = 20 ratio (Entry 7). It is remarkable that the stereochemistry of the starting mixture (83/13/4 mixture of 1*E*,3*E*/1*Z*,3*E*/1*E*,3*Z* isomers of **2**) is maintained in the distribution of coupling products (**3a**$_{1E,3E}$/**3a**$_{1Z,3E}$/**3a**$_{1E,3Z}$) in conditions described in Table 2, regardless of the nature of the additive (NMP, *n*-C_8H_{17}OMgBr, or EtOMgBr).

In a second time, we sought for optimal conditions allowing the coupling between **2** and aryl Grignard reagents. PhMgBr was used as a benchmark nucleophile (Table 3).

Table 3. Optimization of aryl-dienyl cross-coupling conditions.[a]



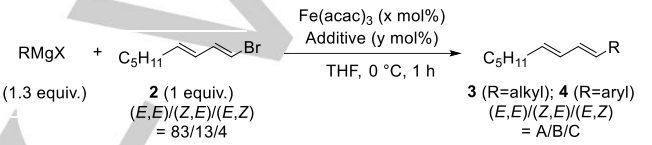
Entry	$Fe(acac)_3$ (mol%)	Additive (mol%)	GC yield[b] (%)	GC ratio A/B/C
1	5	-	31	66/26/8
2	5	EtOMgBr (200)	50	67/25/8
3	2.5	EtOMgBr (100)	41	67/25/8
4	1	EtOMgBr (40)	32	66/26/8
5	**8**	**EtOMgBr (200)**	**60**	**67/25/8**
6	8	EtOMgBr (100)	54	67/25/8

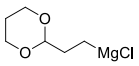
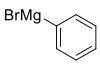
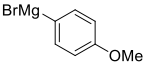
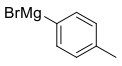
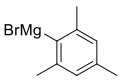
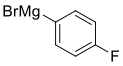
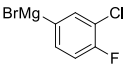
[a] Reaction scale: 0.5 mmol of **2**, 0.65 mmol of PhMgBr in THF (1.0 mL). [b] Measured in the crude using benzaldehyde as internal standard.

A EtOMgBr:Fe = 40 ratio was used, similarly to what was optimized for the alkyl-dienyl coupling. Product **4a** was obtained with a small 41% yield under the conditions optimized using *n*BuMgCl as nucleophile (that is : 2.5 mol% $Fe(acac)_3$, see Table 3, Entry 3). A higher catalytic load (8 mol% $Fe(acac)_3$ associated with 25 equiv. EtOMgBr with respect to Fe, Entry 5) was required to achieve a modest 60% yield. In all cases, an isomerization of the diene moiety was observed, leading to a 67/25/8 mixture of 1*E*,3*E*/1*Z*,3*E*,1*E*,3*Z* isomers of the coupling product **4a**. This loss of stereochemistry mostly originates from the aryl-dienyl conjugation in the latter.

Significant quantities of biphenyle PhPh (aryl Grignard homocoupling product) were also obtained, inhibiting the efficiency of the cross-coupling path (26% of PhMgBr was converted into PhPh in the absence of additive, Entry 1). Competition with homocoupling makes more challenging the aryl-dienyl cross-coupling, as attested by the low **4a** yield obtained in the absence of additive (31%, Table 3, Entry 1, to be compared with the analog alkyl-dienyl yield: **3a** was obtained with a 75% yield in the absence of additive, Table 2, Entry 1).

Table 4. Cross-coupling scope of alkyl and aryl Grignard reagents.[a]



Entry	Method[b]	RMgX	**3** and **4** (% isolated yield)[c]	GC ratio[d] A/B/C
1	a	*n*BuMgCl	**3a** (82)	82/14/4
2	a		**3b** (85)	81/14/5
3	b	ClMgO-$(CH_2)_6$-MgCl	**3c** (92)	82/14/4
4	c		**4a** (56)	67/25/8
5	c		**4b** (67)	74/19/7
6	c		**4c** (54)	71/21/8
7	c		**4d** (traces)	-
8	c		**4e** (71)	76/19/5
9	c		**4f** (73)	82/13/5
10	c		**4g** (72)	79/14/7

[a] Reaction scale: 0.5 mmol of **2**, 0.65 mmol of RMgX in THF (1.0 mL). [b] Method a : 2.5 mol% $Fe(acac)_3$, 100 mol% EtOMgBr; Method b : 2.5 mol% $Fe(acac)_3$; Method c : 8 mol% $Fe(acac)_3$, 200 mol% EtOMgBr [c] After silica gel column chromatography. [d] Just after reaction quench and before chromatography purification.

The addition of EtOMgBr allowed to partly inhibit the homocoupling process, since the amount of PhPh obtained in the presence of 200 equiv. EtOMgBr (Entry 2) dropped to 20% of the starting PhMgBr quantity. Optimized conditions (Entry 5) allowed to reduce the homocoupling to 16% of the starting Grignard.

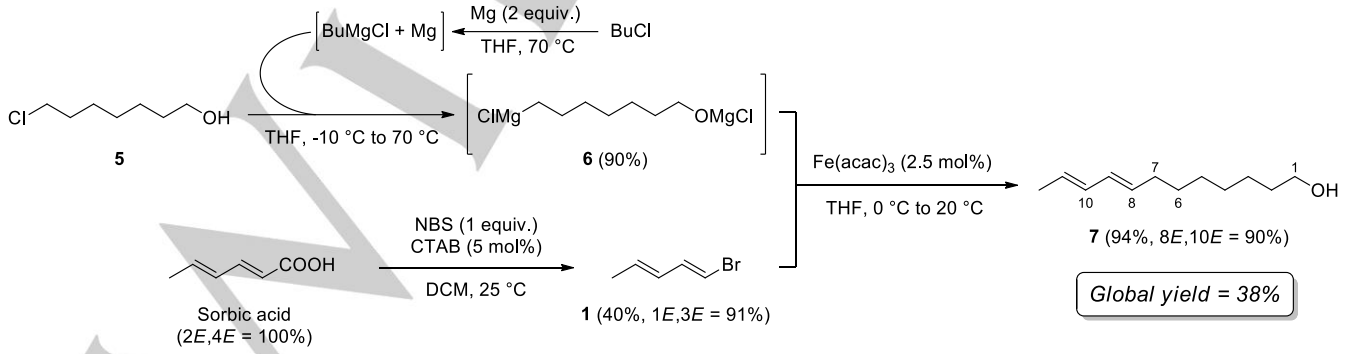
Those results in hands, the scope of the aliphatic and aromatic Grignard reagents suitable for such coupling conditions has been examined using **2** as electrophile (Table 4). Reaction of *n*-BuMgCl and of γ-substituted aliphatic Grignard acetal with **2** afforded **3a** and **3b** with similar 82% and 85% yields (Entries 1-2). Cross-coupling product **3c** was obtained in a high 92% yield when an aliphatic Grignard ω-substituted by a magnesium alkoxide moiety (Entry 3) was used. In that case, owing to a magnesium alkoxide moiety borne by the nucleophile, it is of note that no additional alkoxide additive was required, making this coupling sequence particularly efficient. In the aryl-dienyl series, modest to good yields were obtained using aryl nucleophiles substituted by electron-donating groups such as *p*-$MeOC_6H_4MgBr$ (formation of **4b**, 67% yield, Entry 5) or *p*-MeC_6H_4MgBr (**4c**, 54% yield, Entry 6). Bulky aryl nucleophiles such as MesMgBr only afforded traces of coupling product (**4d**, Entry 7). Higher yields were obtained for aryl Grignards bearing electron-withdrawing halides substituents. The use of *p*-FC_6H_4MgBr as a nucleophile afforded the expected coupling product **4e** with a 71% isolated yield (Entry 8). Similarly, disubstituted (*m*-Cl,*p*-F)-C_6H_3MgBr led to formation of **4f** with a 73% yield (Entry 9). In both latter cases, no substitution of the halide borne by the aryl ring was observed, thus opening possibility of late-stage functionalization of those positions by another coupling process. Finally, heteroaryl-dienyl coupling involving 2-thienylMgBr as a nucleophile also led to a good 72% coupling yield (formation of **4g**, Entry 10). The lower yields obtained for electron-rich aryl nucleophiles (involving *p*-OMe or *p*-Me substituents, Entries 5, 6) are due to the competition of the cross-coupling process with the homocoupling of the Grignard reagent, leading to high quantities of bisaryls. Formation of electron-rich symmetric bisaryls under transition-metal catalysis has already been described as a process which is significantly much faster than the formation of unsymmetrical analogs; a thorough study of the involved stereoelectronic effects has for example been reported by Hartwig regarding the reactivity trends of $(P,P)Pt^{II}(Ar)_2$ compounds in reductive elimination processes.[11]

In order to illustrate the potential of this methodology in terms of future industrial applications, we applied it to a new efficient and convergent synthesis of the codling moth (*Cydia pomonella*) sex pheromone, (8*E*,10*E*)-dodecadien-1-ol (**7**) (Scheme 2).

The majority of known and still currently used methods for the synthesis of **7** date back to the late 1970s and all rely on the introduction of the C_6-C_7 linkage as the key step.[12] The general methodology described by Samain[12f] is based on the introduction of the C_6-C_7 bond via a copper-catalyzed cross-coupling between sorbic alcohol derivatives, such as acetoxy derivative, and the Grignard reagent from 6-chlorohexan-1-ol where the hydroxyl group has been protected. This reaction affords, after deprotection, the expected pheromone with an excellent 98% isomeric ratio of (*E*,*E*) isomer. However, this methodology faces efficiency issues since the cross-coupling product is obtained with a modest 60% yield in the key step.

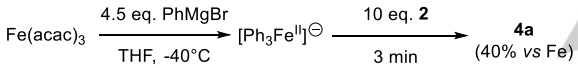
Encouraged by the results of the cross-coupling scope discussed in Table 4, we propose an alternative methodology for the synthesis of **7** relying on the introduction of the C_7-C_8 linkage by a key alkyl-dienyl coupling (Scheme 2). The global synthesis is a five-step convergent procedure leading to the sex pheromone **7** with an overall 38% yield with a diastereomeric purity of 90%. To prepare the C_1-C_7 synthon **6**, diethyl pimelate ($EtOOC(CH_2)_5COOEt$) was chosen as starting material and converted into 7-chloroheptan-1-ol (**5**) in two steps (85% yield) following the procedure described in our previous work.[5c] Preparation of the α,ω-magnesium alkoxide salt of Grignard reagent **6** was then performed by addition of **5** to a THF mixture containing *in situ*-synthesized *n*BuMgCl (1.0 equiv) and Mg (1.1 equiv) at -10 °C. Progressive heating at 70 °C allowed formation of the corresponding Grignard reagent **6** in an overall yield of 90%. **6** was then directly subjected to the reaction with **1** (1*E*,3*E*/1*Z*,3*E* = 91/09) in a one-pot strategy. The cross-coupling between the two synthons previously prepared was performed using $Fe(acac)_3$ and with a low 2.5 mol% catalytic loading. The reaction proceeded very quickly with a full consumption of **1** in one hour and the cross-coupling product **7** was then obtained in a high isolated 94% yield. Moreover, this coupling was highly stereoselective since the expected (8*E*,10*E*) isomer was obtained with 90% diastereomeric purity. It is also worth noting that the alkyl−dienyl Fe-catalyzed Kumada cross coupling between **6** and **1** remarkably proceeds without requiring additional ligands or any toxic additive, akin to the similar result reported in Table 4 (Entry 3).

We were then interested in delineating the nature of the organometallic species active in the coupling process. The question of the active oxidation state in iron-mediated couplings still remains a challenging issue, due to the short lifetime of the related species. A variety of couplings with aliphatic electrophiles was shown to involve a key single electronic transfer step featuring *in situ* generated organoiron(II) species.[13]



Scheme 2. Synthetic route to pheromone **7** described in this work.

However, the question is much less discussed in the case of sp2-hybridized electrophiles. In this regard, some of us recently demonstrated that *ate*-Fe^{II} complexes such as $[(PhCH_2)_3Fe^{II}]^-$ could be active in cross-coupling between benzylmanganese reagents and alkenyl bromides.[14] In the present case, low-temperature ^1H NMR monitoring performed at -40°C showed that the homoleptic complex $[Ph_3Fe^{II}]^-$ was formed when $Fe(acac)_3$ was treated with a slight excess of PhMgBr (4.5 equiv.). $[Ph_3Fe^{II}]^-$ was characterized by its paramagnetic signals at 126.6 and -42.7 ppm (Section S3).[15] This complex usually decomposes by reductive elimination to afford mixtures of Fe^0 and Fe^I species[15,16] above -20°C. However, it remains stable at -40°C for several hours. When an excess of **2** (10 equiv. per mole of iron) was added at -40°C onto $[Ph_3Fe^{II}]^-$, the signals of the latter fully disappeared after 3 minutes, and no other paramagnetic species could be observed. GC-MS analysis revealed that 40% of the coupling product **4a** were obtained after acidic quench at -40°C. This demonstrates that $[Ph_3Fe^{II}]^-$ can act as an on-cycle species in the coupling process, and that no reduction towards lower oxidation states is required (Scheme 3). This result is in line with the recently reported reactivity of the $[Me_3Fe^{II}]^-$ anion towards bromostyrene in Kochi-Kumada cross-coupling between the latter and MeMgBr.[17] Further mechanistic studies need to be performed regarding the alkyl-dienyl coupling mechanism; *ate*-alkyliron(II) species bearing β-hydrogens can indeed evolve towards polynuclear reduced species after β-elimination, making much more complex the related mechanistic studies.[18]



Scheme 3. Relevance of *in situ* generated *ate* species $[Ph_3Fe^{II}]^-$ as an on-cycle intermediate in cross-coupling with **2**.

An in-depth investigation of the exact role played by magnesium alkoxide additives in the efficiency of this coupling is currently in progress. It can reasonably be hypothesized that those salts contribute to a stabilization of the Fe^{II} oxidation state during the catalytic cycle, inhibiting its evolution towards lower oxidation states, thus contributing to limit the occurrence of off-cycle, reactant-consuming pathways.

In conclusion, we reported a convenient procedure for the synthesis and purification of thermally sensitive aliphatic dienyl bromides, obtained as stabilized THF solutions. Those mixtures can be used as an efficient electrophile source in Fe-catalyzed Kumada cross-couplings with a variety of aliphatic and aromatic Grignard reagents. The coupling yields can moreover be improved thanks to the use of magnesium alkoxides as additives, and a complete stereochemistry retention is observed in alkyl-dienyl couplings. This makes this sequence particularly useful for the synthesis of insect pheromones, as illustrated by the codling moth sex pheromone synthesis. In the aryl-dienyl coupling sequence, preliminary mechanistic studies suggest the implication of organoiron(II) species as key intermediates, showing that no reduction of the iron precursor at lower oxidation states is required to ensure catalytic activity.

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Keywords: iron • cross-coupling • pheromones • natural products • reaction mechanisms

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Synthesis of dienic scaffolds by Fe-mediated coupling between Grignard reagents and dienyl bromides is reported. This methodology involves the use of magnesium alkoxides as additives, and can be applied to targets of industrial interest, such as insect pheromones. Mechanistic studies suggest that the active species is an organoiron(II) complex, showing that no reduction of the precursor to low oxidation states is required.

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