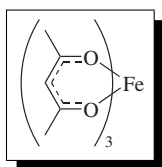


## Tris(acetylacetonato)iron(III)



[14024-18-1]  $C_{15}H_{21}O_6Fe$  (MW 353.21)  
 InChI = 1/3C5H8O2.Fe/c3\*1-4(6)3-5(2)7;/h3\*3,6H,1-2H3;/q;;;  
 +3/p-3/b3\*4-3-;/f3C5H7O2.Fe/h3\*6h;/q3\*-1;m  
 InChIKey = AQBLLJNPHDIAPN-HCVQTSIDDS

(organotransition metal catalyst used in the cross coupling of acid halides or vinyl bromides with Grignard reagents, the stereoselective epoxidation of steroidal alkenes, and the reductive decyanation of alkyl nitriles)

*Alternate Names:* ferric acetylacetonate; ferric triacetylacetonate; iron acetylacetonate.

*Physical Data:* mp 182–185 °C (191 °C by differential thermal analysis<sup>1</sup>).

*Solubility:* sol alcohols, chlorinated solvents.

*Form Supplied in:* deep red powder.

*Analysis of Reagent Purity:* CH analysis (calc 57.51% C, 5.96% H).<sup>1</sup>

*Purification:* recrystallization from ethanol<sup>2</sup> or methanol/H<sub>2</sub>O.<sup>1</sup>

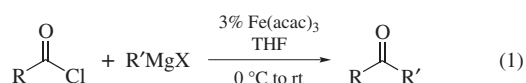
*Handling, Storage, and Precautions:* severe eye irritant and possible teratogen. Poor thermal stability in molten state.<sup>1</sup>

## Original Commentary

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The Dow Chemical Company, Midland, MI, USA

**Preparation of Ketones from Acyl Chlorides and Grignard Reagents.**<sup>3</sup> The inclusion of a catalytic amount of Fe(acac)<sub>3</sub> in the coupling reaction of acid chlorides and Grignard reagents gives the desired ketones without the significant formation of carbinols which accompanies the reaction in its absence (eq 1).<sup>4</sup> The use of other organometallic reagents<sup>5</sup> in place of Grignard reagents has also effected the formation of ketones without the accompanying formation of secondary and/or tertiary alcohols; however, these reagents lack the generality and convenience shown with the Fe(acac)<sub>3</sub> catalyzed reaction (Table 1). The reaction was also extended to aromatic acid chlorides and thiophenyl acid chlorides, which were coupled with long-chain di-Grignard reagents to produce symmetrical 1,*n*-diketones (*n* ≥ 8) and long-chain dicarboxylic thiol esters in moderate to good yield.<sup>6</sup>

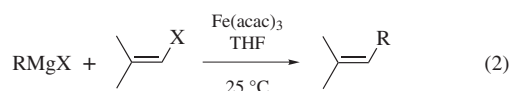


**Preparation of Alkenes: Cross Coupling of Vinyl Bromides,<sup>7</sup> Vinyl Sulfones,<sup>8</sup> and Vinyl Sulfoximines<sup>9</sup> with Grignard Reagents.** Fe<sup>III</sup> complexes containing β-diketonate ligands, such as Fe(acac)<sub>3</sub>, are useful catalysts for the cross coupling of vinyl

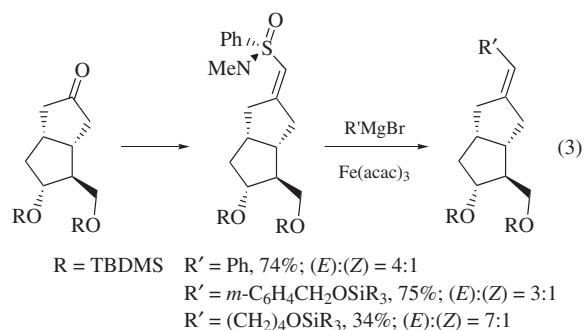
**Table 1** Fe(acac)<sub>3</sub> catalyzed cross coupling of acid halides with Grignard reagents

R	r'	Temp.	Yield(%)
Me	Me(CH <sub>2</sub> ) <sub>8</sub>	rt	82
Ph	Me	rt	80
Ph	Ph	0 °C	75
MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub>	Bu	rt	75
ClCO(CH <sub>2</sub> ) <sub>3</sub>	Et	rt	82
(R)(+)-PhC(CF <sub>3</sub> )(OMe)	Me	rt	(R)(+) 76
Cycloheptatrienyl	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	–	55

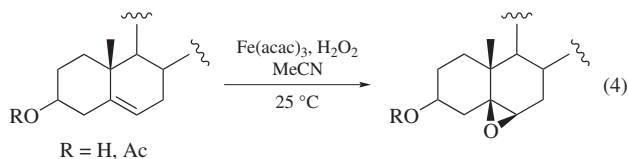
bromides with Grignard reagents (eq 2).<sup>7</sup> The coupling reactions with vinyl bromides proceed with primary, secondary, and tertiary Grignard reagents. It is proposed that Fe(acac)<sub>3</sub> is initially reduced by the Grignard reagent to form an active Fe<sup>I</sup> or Fe<sup>0</sup> catalyst,<sup>10</sup> which has been shown to undergo an irreversible deactivation during the course of the cross-coupling reaction. A similar reagent, **Tris(dibenzoylmethide)iron(III)**, has been shown to be more resistant to this deactivation and is the preferred iron catalyst for this reaction.<sup>7</sup>



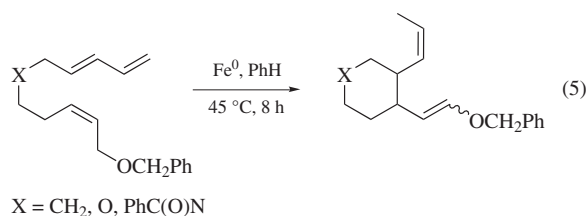
The cross coupling of Grignard reagents with vinyl sulfones in the presence of Fe(acac)<sub>3</sub> or **Nickel(II) Acetylacetonate** proceeds with some stereoselectivity; however, the reaction is complicated by reduction byproducts.<sup>8</sup> The stereoselective construction of exocyclic alkenes from the cross-coupling reaction of alkenyl-sulfoximines, prepared stereoselectively from the corresponding ketone, with Grignard reagents in the presence of stoichiometric amounts of Fe(acac)<sub>3</sub> and NiCl<sub>2</sub>(dppp) has also been reported (eq 3).<sup>9</sup> This serves as a useful alternative to standard Wittig-type alkenations for the construction of exocyclic alkenes.<sup>11</sup>



**Epoxidation of Steroidal Alkenes.**<sup>12</sup> Fe(acac)<sub>3</sub> is used to catalyze the stereoselective β-epoxidation of cholesterol derivatives (allylic alcohols) with excess **Hydrogen Peroxide** in acetonitrile under mild conditions (eq 4). This shows opposite stereoselectivity to epoxidation reactions using conventional organic peracids, where shielding by the angular methyl groups prevents epoxidation on the β-face. This method offers similar stereoselectivity to halohydrin methodology,<sup>13</sup> but the reaction is effected in a single step. The observed stereoselectivity is independent of R, unlike other methodologies.



**Preparation of *N*-Acylpiperidines: Ene Carbocyclization of Trienes.** The in situ generation of a (bipy)Fe<sup>0</sup>L<sub>n</sub> catalyst by the reaction of Fe(acac)<sub>3</sub> and *Triethylaluminum* is used to prepare cyclopentyl, cyclohexyl, and tetrahydropyranyl rings, as well as *N*-acylpiperidines by the formal [4 + 4] ene carbocyclization of trienes, triene ethers, and azatrienes (eq 5).<sup>14</sup>



**Miscellaneous Reactions.** Hydrocarbons are produced in good to excellent yield from alkyl nitriles upon treatment with Fe(acac)<sub>3</sub> and *Sodium* sand in benzene.<sup>15</sup> The best results for this reductive decyanation were obtained with saturated alkyl nitriles. Nontransition metal promoted cleavage of primary nitriles in liquid ammonia gives inferior results.<sup>16</sup> The Michael addition of ethyl acetoacetates to cyclic enones was catalyzed by Fe(acac)<sub>3</sub> and an electrophilic cocatalyst.<sup>17</sup> Other M(acac)<sub>n</sub> compounds were also examined.

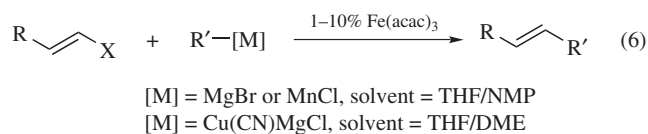
## First Update

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**C–C Bond Formation via Cross Coupling.** Over the past decade iron-catalyzed cross-coupling reactions have matured to be a major organometallic cross-coupling method.<sup>18</sup> Among the many iron complexes that have been reported, Fe(acac)<sub>3</sub> has been used most frequently due to its low cost and air and moisture stability. (For other catalyst choices, see also iron(III) trichloride and tris(dibenzoylmethide)iron(III).) Iron-catalyzed cross-coupling reactions are usually carried out using Grignard reagents, wherein an “inorganic Grignard reagent” [Fe(MgX)<sub>2</sub>] (Fe(-II) species) has been suggested as the active catalyst.<sup>19,20</sup> Other than Grignard reagents, the use of cuprate<sup>21,22</sup> and manganese<sup>23</sup> reagents have also been reported.

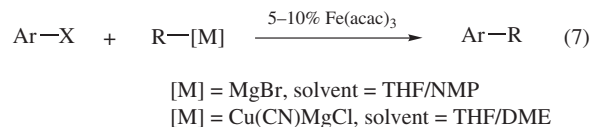
**Cross Coupling-alkenyl Electrophiles.** The iron-catalyzed cross-coupling reaction (eq 6) of Grignard, cuprate, or manganese reagents (alkyl, aryl, and alkenyl) with alkenyl electrophiles (vinyl halides, triflates, phosphates, or tosylates) has been a general method for C–C bond formation (entry 1–7, Table 2).<sup>22–26</sup> In most cases, the THF/NMP (*N*-methyl pyrrolidone) cosolvent has proven beneficial.<sup>23</sup> Alkenyl chlorides readily react under iron catalysis,

in contrast to their reluctance in the corresponding palladium- or nickel-catalyzed reactions.

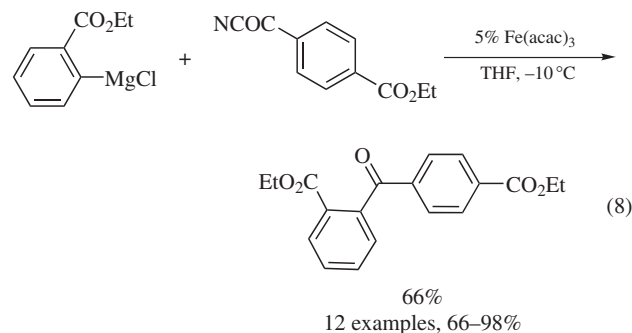


The iron-catalyzed cross-coupling reaction of Grignard reagents with aryl vinyl sulfides proceeds chemoselectively to provide the alkenylated, rather than arylated, product (entry 8).<sup>27</sup> 1,1-Dichloro-1-alkenes react smoothly to give 1,1-disubstituted alkenes (entry 9);<sup>28</sup> although the corresponding 1,1-dibromo-1-alkenes undergo hydrodebromination to yield *E*-bromo alkenes (entry 10).<sup>29</sup> Imidoyl chlorides have also been reported to react smoothly to give the cross-coupled adduct (entry 11).<sup>30</sup>

**Cross Coupling-aryl Electrophiles.** While alkenyl derivatives have been widely used as electrophiles in iron-catalyzed cross-coupling reactions, their aryl counterparts (eq 7) have demonstrated rather limited success. The scope of the organometallic partner is also less broad than in the alkenyl case: alkyl Grignard reagents can react smoothly with traditionally less reactive aryl electrophiles (aryl chlorides, triflates, or tosylates) (entry 1–3, Table 3);<sup>20,31</sup> aryl Grignard reagents efficiently cross couple only with electron-poor heterocyclic electrophiles due to competitive homodimerization of the electrophiles (entry 4);<sup>20</sup> and aryl cuprates cross couple with electron-poor arenes only when aryl iodides are used (entry 5).<sup>21</sup>



**Cross Coupling-acyl Electrophiles.** Acyl chlorides can be cross coupled with aryl- and alkyl Grignard reagents under iron catalysis.<sup>3,25</sup> Recently, acyl cyanides have been shown to be good substrates for diaryl ketone synthesis, in which good functional group tolerance has been demonstrated (eq 8).<sup>32</sup>



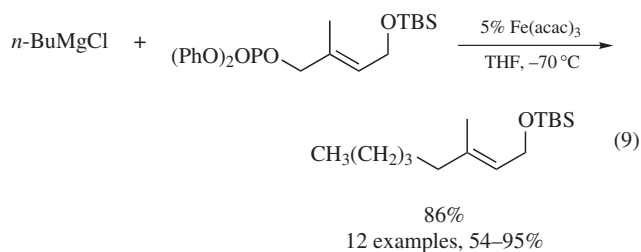
**Cross Coupling-allyl Electrophiles.** Allylic phosphates react with various Grignard reagents under iron catalysis, including sp<sup>3</sup>-, sp<sup>2</sup>-, and sp-hybridized carbon nucleophiles. High S<sub>N</sub>2-type regioselectivity is achieved when diphenylphosphate esters are used as electrophiles (eq 9).<sup>33</sup>

**Table 2** Fe(acac)<sub>3</sub>-catalyzed cross-coupling reaction with alkenyl electrophiles

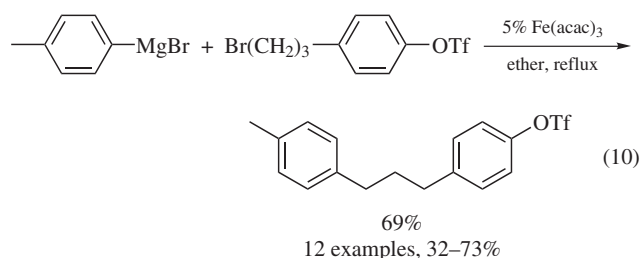
Entry	R-CH=CH-X	R'-[M]	R-CH=CH-R'	Yield(%)
1		MeMgCl		68
2		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> MgCl		80
3		<i>n</i> -BuMgCl		78
4		MeMgBr		70
5				60
6		PhMnCl		71
7				86
8				66
9		BrMg(CH <sub>2</sub> ) <sub>5</sub> MgBr		84
10				84
11		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> MgCl		89

**Table 3** Fe(acac)<sub>3</sub>-catalyzed cross-coupling reaction with aryl electrophiles

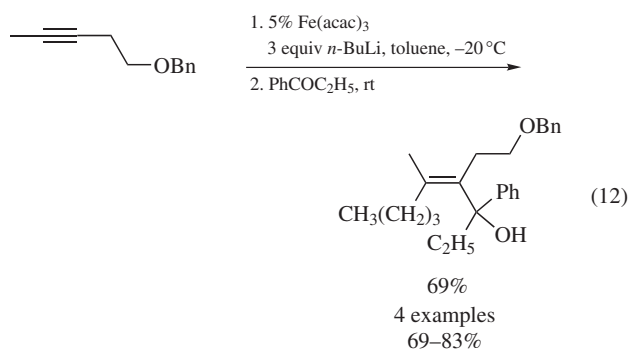
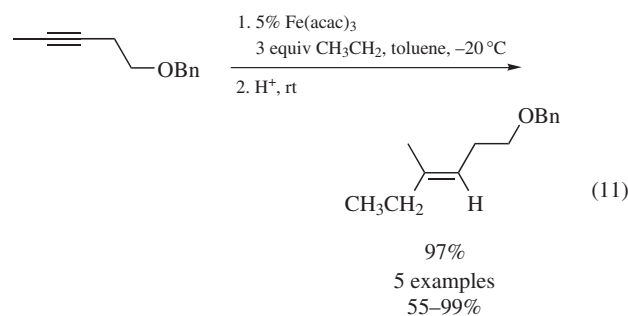
Entry	Ar-X	R-[M]	Ar-R	Yield(%)
1		<i>n</i> -C <sub>6</sub> H <sub>13</sub> MgBr		91 (X = Cl) 87 (X = OTf) 83 (X = OTs)
2				56
3		<i>n</i> -C <sub>14</sub> H <sub>29</sub> MgBr		41
4		PhMgBr		71
5		PhCu(CN)MgCl		82



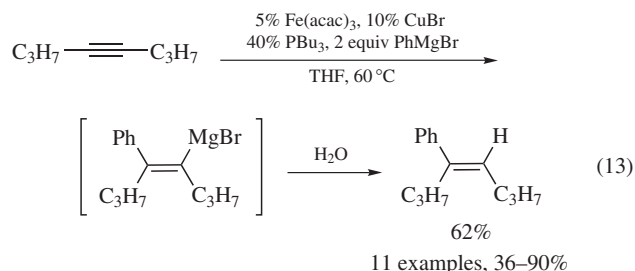
**Cross Coupling-alkyl Electrophiles.** Good results can be obtained in the iron-catalyzed cross-coupling reactions of aryl Grignard reagents with primary and secondary alkyl halides, in which the  $\beta$ -H elimination pathway is diminished. It proved critical to employ ether as the solvent, and aryl triflates were unreactive under these conditions (eq 10).<sup>34</sup> (See also iron(III) trichloride, where the cross coupling pathway is favored only when TMEDA is added.)<sup>35</sup>



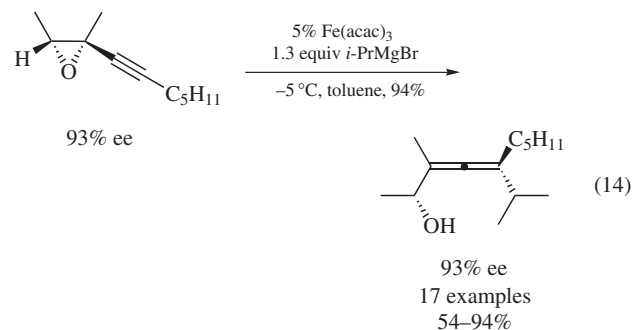
**Cross Coupling-additions to Alkynes.** Alkyl lithium reagents can undergo iron-catalyzed *syn*-addition to substituted alkynes bearing a Lewis basic directing group (OR or NR<sub>2</sub>) at the homopropargylic carbon. The resulting vinyl lithium intermediate can be trapped by protons (eq 11), chlorosilanes, aldehydes, or ketones (eq 12).<sup>36</sup>



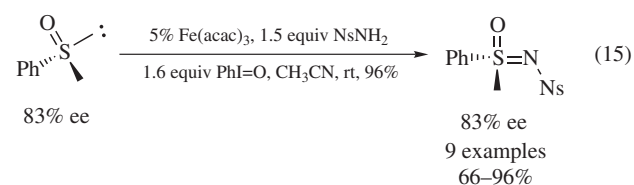
The complementary *syn*-arylation of an unfunctionalized alkyne may be achieved by the addition of an aryl Grignard reagent via Fe/Cu bimetallic catalysis. High *Z*-selectivity is observed with both electron-rich and electron-poor aryl Grignard reagents. Similarly, the intermediate vinyl metal species may be trapped by an aldehyde, a benzyl bromide, or a proton (eq 13).<sup>37</sup>



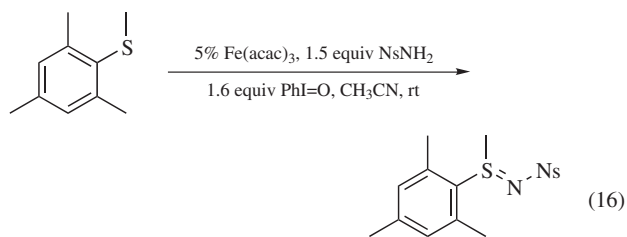
Propargylic epoxides react with alkyl- or aryl Grignard reagents under iron catalysis to yield 2,3-allenol derivatives. In this S<sub>N</sub>2'-type substitution reaction, the point chirality of the propargylic center is transferred to the axial chirality of the allene product with high stereochemical fidelity (eq 14).<sup>38</sup>



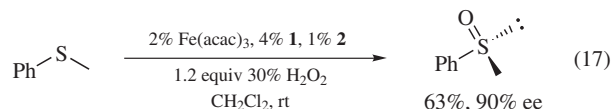
**Cross Coupling-imation of Sulfoxides and Sulfides.** The iron-catalyzed imination of sulfoxides can be achieved with sulfonylamides and iodobenzene. This reaction applies to both aryl and aliphatic sulfoxides, and retention of configuration at the sulfur center is observed (eq 15). Sulfides demonstrate greater reactivity toward imination than sulfoxides such that even substrates bearing a bulky substituent react smoothly, in contrast to the more reluctant sulfoxides (eq 16).<sup>39</sup>



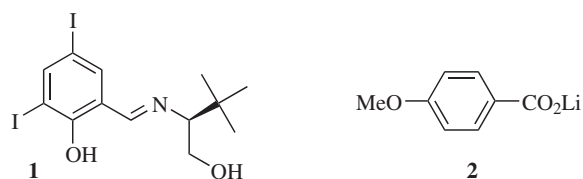
**Cross Coupling-asymmetric Oxidation of Sulfides.** The catalytic asymmetric oxidation of sulfides has been developed with a catalyst comprised of Fe(acac)<sub>3</sub> and a chiral Schiff base (**1**), using aqueous hydrogen peroxide as the oxidant.<sup>40</sup> This reaction works well regardless of the electronic properties of the sulfides, but enantioselectivity drops dramatically in the absence of an aryl substituent. The yield and enantioselectivity of the reaction can be boosted by the addition of carboxylic acids or carboxylates, among which the carboxylate (**2**) proves most effective (eq 17).<sup>41,42</sup>



74%  
6 examples  
45–91%



63%, 90% ee  
16 examples  
36–78%  
23–96% ee



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