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IRON CATALYZED CROSS-COUPLING REACTIONS. SYNTHESIS OF ARYLETHENES.

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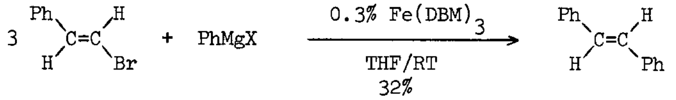
Abstract: Iron (III) complexes have been found to effectively catalyze the coupling of alkenyl halides with aryl Grignard reagents to provide arylethenes in excellent yields.

Elegant mechanistic studies by Kochi and co-workers have pointed to the potential of iron (III) complexes as efficient catalysts for the cross-coupling of a variety of organic halides and organometallic substrates.[1] Yet in spite of these studies, little synthetic effort has been expended to delineate the scope of iron-catalyzed cross-coupling reactions and their utility in organic synthesis.[2] This is in stark contrast to the tremendous efforts devoted to the use of palladium and nickel catalysts for similar processes.[3]

Even from the few studies that have thus far been related, enticing features of the iron-catalyzed coupling reactions have been exposed. For example, among the metals used as catalysts for cross-coupling, iron appears to be among the most efficient at coupling halides with alkyl organometallics, and in particular tertiary alkyl reagents.[1e,4] Iron has also been found to catalyze the coupling of substrates such as vinylsulfones,[2a] and seems bound to find utility with other novel substrates as well. Furthermore, iron catalysts offer several advantages in terms of their practical use. Perhaps foremost, the iron catalysts are very inexpensive. This is a consequence not only of the price of the metal, but also of the ligands utilized to solubilize the metal. Thus the 2,4-pentanedione-derived ligands utilized in conjunction with the iron catalysts are much less costly than the exotic phosphine ligands utilized for some of the nickel and palladium catalysts. Finally, these iron complexes are all air- and moisture-stable compounds, readily handled and stored for long periods of time. This is again in contrast to some of the corresponding nickel and palladium catalysts, many of which are air-, moisture- and even light-sensitive.

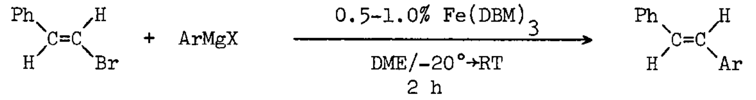
Although the main focus of our studies in iron-catalyzed coupling reactions is concentrated on the use of these catalysts in processes complimentary to or unique from those of other metal catalysts, we found it necessary to establish some general synthetic conditions and features of these catalysts using more established substrates. As a consequence, we report here on the iron-catalyzed cross-coupling reaction of alkenyl halides with aryl Grignard reagents.

Kochi has reported that this particular process occurs in poor yield (32%) in THF at room temperature utilizing tris(dibenzoylmethido)iron(III) [$Fe(DBM)_3$] as a catalyst (0.3 mole %) and a three-fold excess of alkenyl halide.[1d]



We have undertaken a systematic study of this reaction utilizing the same substrates and catalyst [0.5-1.0 mole % of Fe(DBM)$_3$] to determine the optimum conditions for the synthetic reaction. We have found that of four solvents tested (diethyl ether, THF, DME and dioxane), DME consistently provides the highest yields. Furthermore, use of excess alkenyl halide proved to be unnecessary for the reaction. Finally, a lower initial reaction temperature (-20°C) is beneficial, and under these conditions nearly quantitative yields of cross-coupled products could be achieved (Table 1).

Table 1. Reaction of α-Styrylbromide with Aryl Grignard Reagents.



1 2 3

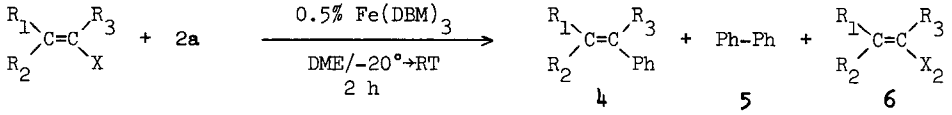
Entry	ArMgX	% GC Yield (Isolated)[a] 3	m.p. or b.p. (mmHg)
1	Phenyl (2a)	90(68)	122-123°C
2	1-Naphthyl (2b)	83(56)	71-71.5°C[5]
3	3-Methoxyphenyl (2c)	75	119°C(0.1)[6]
4	4-Chlorophenyl (2d)	(75)	125-126°C[7]
5	2-Methylphenyl (2e)	100	158-159°C[8]
6	2,4,6-Trimethylphenyl (2f)	0	-

[a] Satisfactory ^{1}H NMR, IR, and mass spectral data were obtained for all compounds.

Only with the sterically hindered mesitylmagnesium bromide (entry 6) was no coupling observed.

A variety of alkenyl halides[9] have been demonstrated to provide synthetically useful yields of cross-coupled product (Table 2). However, while E-alkenyl halides provide excellent yields of product in all cases, the corresponding Z-isomers provide either low yields of coupled product (entry 2), or give isomeric mixtures of products (entries 6 and 7). Similar results have been observed by Kochi and co-workers in other systems, and to a certain degree the percentage of isomerization appears to be a function of the steric bulk of the Grignard reagent. Thus t-butyl- and cyclohexylmagnesium halides give rise to substantial isomerization in cross-coupling reactions with Z-alkenyl halides, while primary alkyl Grignard reagents provide nearly complete stereoselectivity in the same process. It may not be too surprising, therefore, that the relatively bulky arylmagnesium halides also provide isomeric mixtures. In all cases, the desired product was contaminated by 10-25% of homo-coupled by-products.

Table 2. Reaction of Alkenyl Halides with Phenylmagnesium Bromide.

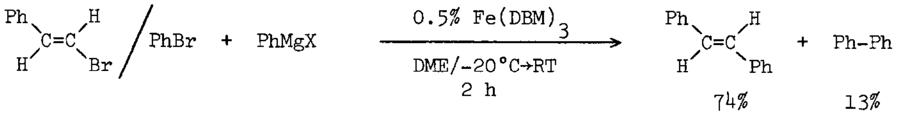


Entry	R_1	R_2	R_3	X	% GC Yield of Products[a] **4**	**5**	**6**
1	Ph	H	H	Br	90	10	10
2	H	Ph	H	Br	52[b]	17	-
3	H	H	Ph	Br	75	14	2
4	Bu	H	H	I	77	14	11
5	Bu	H	H	Br	65	12	8
6	H	Bu	H	I	93[c]	2	7
7	H	Bu	H	Br	83[d]	9	8

[a] Satisfactory ^{1}H NMR, IR mass spectral data and physical constants were obtained for all compounds. Isomeric purity was established by GC and/or ^{13}C NMR analyses. [b] Exclusive formation of the Z-isomer. 15% Alkenyl halide remained. [c] 1:2 mixture of Z:E isomers. [d] 2:1 mixture of Z:E isomers.

The following procedure is representative. To a dry, argon-flushed 50 ml flask equipped with a septum inlet was added 0.018g (0.025 mmol) of $Fe(DBM)_3$. This was dissolved in 10mL of dry DME and the resulting solution was cooled to 0°C. The active catalyst was generated by the addition of 6.6mL (10 mmol) of phenylmagnesium bromide (1.5M in Et_2O). The resulting deep blue solution was cooled to -20°C, and 1.83g (10 mmol) of β-bromostyrene was slowly added. The reaction mixture was stirred at -20°C for 0.5h, then allowed to warm to room temperature and stirred for an additional 2h. The reaction was quenched by adding 5mL of saturated NH_4Cl. Diethyl ether was added and the layers were separated. The aqueous layer was extracted with ether and the combined organic extracts were dried ($MgSO_4$). The volatiles were removed *in vacuo* and the residue was taken up in a minimum of hexane and passed through a Florisil column, eluting with hexane to remove the iron salts. After removal of the hexane, the product was recrystallized from ethanol to provide 1.22g (68%) of a colorless solid, m.p.122-123°C. This was identical in every respect to an authentic sample of *trans*-stilbene.

While the yields and stereoselectivity of the iron-catalyzed cross-coupling reaction do not compare particularly favorably with comparable palladium- and nickel-catalyzed process,[10] we have found that the cross-coupling of alkenyl halides takes place selectively in the presence of aryl halides. We have been unable to find similar selectivity documented for other catalysts. Thus β-styryl bromide couples with phenylmagnesium bromide in the presence of bromobenzene to provide nearly 80% of *trans*-stilbene. Nearly all of the bromobenzene can be recovered, and only slightly more biphenyl is detected under these conditions (13% vs. 10%).



We are continuing our investigations in the area of iron catalysis, which include the study of novel coupling reactions and the development of new iron catalysts that we hope may alleviate some of the problems encountered in the present work.

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