Iron Thiolate Complexes: Efficient Catalysts for Coupling Alkenyl Halides with Alkyl Grignard Reagents

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Recently, iron-catalyzed C-C coupling reactions have been extensively studied because they are an interesting way to avoid using palladium or nickel complexes, which are toxic and/or expensive. Valuable advances have been made in this field over the last few years by our group^[1] and others,^[2] however, there is currently a reduction in the rate of discovery and improvement of iron-catalyzed coupling reactions. In fact, most reactions reported until now use FeCl₃ or most frequently $[Fe(acac)_3]$ (acac=acetylacetonate) as catalysts and only a few original ligands have been proposed.^[3] Moreover, the majority of the ligands tested were chosen by analogy with palladium or nickel chemistry and ligands specially designed for use with iron are rare. On the basis of this observation it seemed to us that the discovery of specific new ligands is the next challenge to improve the couplings previously described and to widen the scope of the application of iron catalysis in organic synthesis.

It is well known that iron-sulfur protein complexes are involved in numerous biological processes occurring through redox reactions and exhibit remarkable properties.^[4] Even if the catalytic intermediates involved in cross-coupling reactions are quite different, we thought that it could be interesting to use thiolates as ligands to modify the redox potential of the catalytic species formed during the iron-catalyzed Grignard reactions and, consequently, their reactivity. Previously, we have shown that alkyl Grignard reagents react with alkenyl halides chemo- and stereoselectively in the presence of [Fe(acac)₃] to give excellent yields of the crosscoupling product when N-methylpyrrolidone (NMP) is used as a cosolvent (Scheme 1).^[1c]

This procedure is very efficient, however, NMP was recently identified to be a reprotoxin $^{\left[5\right] }$ and, in the future, it would be preferable to limit its use for industrial applications as a part of sustainable development. Therefore, we decided to select this reaction to perform our investigations

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- Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200184.

Scheme 1. The influence of NMP on the iron-catalyzed coupling between alkenyl halides and alkyl Grignard reagents.[1c]

and we report herein our results concerning an efficient new catalytic system based on iron(II) thiolates.

In the first set of experiments, iron(II) thiolates were prepared by mixing FeCl₃ or FeCl₂ with 3 or 2 equivalents, respectively, of RSMgCl^[6] in THF at 0°C (see the Supporting Information). These compounds were then directly used^[7] as precatalysts to perform the coupling of 1-bromo-2-methylpropene with OctMgCl at between -5 and 0°C (Table 1).

Table 1. Cross-coupling of 1-bromo-2-methylpropene with nOctMgCl in the presence of various iron-based catalytic systems. Fe catalyst

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	Br + OctMgCl THF, 0 °C, 1 h	T Oct	2
	Catalytic system		Yield [%] ^[a]
1	$[Fe(acac)_3]$ (5%)		39
2	$[Fe(acac)_3]$ (5%), NMP (9 equiv) ^[b]		82 (76) ^[c]
3	$[Fe(SOct)_2]^{[d]}(5\%)$		51
4	$[Fe(SPh)_2]^{[d]}(5\%)$		88
5	$[Fe(S-2-naphthyl)_2]$ (5%)		87, ^[d] 90 ^[e]
6	$[Fe(S-2-naphthyl)_2]^{[e]}$ (1%)		86

[a] Determined by GC analysis. Pentadecane (C₁₅H₃₂) was used as the internal standard. [b] Based on (CH₃)₂C=CHBr. [c] Yield of the isolated product, see ref. [1c]. [d] Precatalyst prepared from FeCl₃. [e] Precatalyst prepared from FeCl₂.

Iron(II) octylthiolate led to a 51% yield of 2-methylundec-2-ene (Table 1, entry 3). This yield is not as good as with [Fe(acac)₃] in the presence of NMP (Table 1, entry 2), but is better than with $[Fe(acac)_3]$ alone (Table 1, entry 1). The use of various iron alkylthiolates as ligands, however, did not allow us to obtain better results, and we, therefore, turned our attention to iron arylthiolates. These attempts were more successful since good yields (87-90%) were obtained by using a precatalyst prepared from thiophenol (Table 1, entry 4) or 2-naphthalenethiol (Table 1, entry 5). The iron arylthiolate can be successfully prepared from either FeCl₃

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or FeCl₂ (Table 1, entry 5). It is interesting to note that the yields obtained with iron arylthiolates are better than that previously obtained by using $[Fe(acac)_3]$ and NMP as a cosolvant (Table 1, entry 2). Interestingly, only 1% iron 2naphthylthiolate is enough to efficiently catalyze the reaction (Table 1, entry 6).

To study the scope and limitations of the reaction, we chose to use iron 2-naphthylthiolate as the precatalyst (Table 1, entries 5 and 6). Indeed, this iron thiolate always gave similar or slightly higher yields than $[Fe(SPh)_2]$. For instance, the coupling of (E)-1-bromooct-1-ene with BuMgCl led to a 90% yield of (E)-5-dodecene **3** with the 2-naphthylderived catalyst instead of 85% with the phenyl-derived one (Scheme 2).



Scheme 2. Stereoselectivity of the reaction.

Furthermore, we have found that the reaction is highly stereoselective (Scheme 2). Thus, (Z)- and (E)-1-bromooct-1-enes afforded the corresponding (Z)- and (E)-olefins **3** and **4**, respectively, with complete retention of configuration.

Moreover, the scope of the reaction is very wide and various mono- or disubstituted alkenyl bromides were successfully used (Table 2). Indeed, alkenyl bromides and iodides led to similar yields (Table 2, entries 6 and 7).

Table 2. Iron-catalyzed coupling of alkenyl bromides or iodides with primary alkyl Grignard reagents.

	Alkenyl halide	Product	Yield [%] ^[a]
1	ⁿ Br <i>E/Z</i> = 71:29	E/Z = 70:30 5	93
2	Ph Br E/Z = 85:15	Ph E/Z = 85:15 6	92
3	Br	-(-) ₅ 7	85
4	[~] Br <i>E/Z</i> = 44:56	E/Z = 44:56	87
5	Br	(-) ₅ 2	90
6	Bu Bu	Bu	93
7	Bu Bu	Bu 1	93

[a] Yield of the pure isolated product. Precatalyst: [Fe(S-2-naphthyl)₂].

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Table 3. Cross-coupling of 1-chlorodecene with nBuMgCl and iPrMgCl in the presence of various iron-based catalytic systems.

	Oct CI	+ RMgCl Fe catalyst Oct	
		1 HP, 0 °C, 1 h 9 (R= Bu) 10 (R= <i>i</i> Pr)	
	RMgCl	Catalytic System	Yield [%] ^[a]
1	BuMgCl	[Fe(acac) ₃] (5%), NMP (9 equiv) ^[b]	87
2	BuMgCl	$[Fe(S-2-naphthyl)_2]^{[c]}(5\%)$	87
3	BuMgCl	$[Fe(S-2-naphthyl)_2]^{[d]}(5\%)$	85
4	BuMgCl	$[Fe(S-2-naphthyl)_2]^{[d]}$ (5%), NMP (7.5%)	93
5	BuMgCl	$[Fe(S-2-naphthyl)_2]^{[d]}(5\%), LiCl^{[e]}(10\%)$	93
6	iPrMgCl	$[Fe(S-2-naphthyl)_2]^{[d]}(5\%)$	50
7	iPrMgCl	$[Fe(S-2-naphthyl)_2]^{[d]}(5\%), NMP(7.5\%)$	85
8	iPrMgCl	$[Fe(S-2-naphthyl)_2] (5\%), LiCl^{[e]} (10\%)$	86

[a] Determined by GC analysis. Hexadecane ($C_{16}H_{34}$) was used as the internal standard. [b] Based on OctCH=CHCl. [c] Prepared from FeCl₃. [d] Prepared from FeCl₂. [e] Prepared from FeCl₂•2LiCl, see ref. [9].

Alkenyl chlorides also react with alkyl Grignard reagents in the presence of iron 2-naphthylthiolate (Table 3, entries 2 and 3). However, they are less reactive than the corresponding bromides and generally gave slightly lower yields (about 5–7% less). However, we have determined that it is possible to improve these results by working with a precatalyst obtained by mixing iron 2-naphthylthiolate and NMP (1:1.5)^[8] (Table 3, entry 4). It is important to note that only 7.5% NMP is then necessary instead of the 900% (9 equiv) required when the reaction is performed with FeCl₃ or [Fe-(acac)₃] as the catalyst. Finally, we found that NMP can be completely eliminated because similar results were obtained by adding 2 equivalents of LiCl to the iron 2-naphthylthiolate^[9] (Table 3, entry 5).

The beneficial influence of NMP or LiCl is more important when the coupling is performed with a secondary alkyl Grignard reagent. Thus, the reaction of iPrMgCl with 1chlorodecene led to only a 50% yield of 2-methyldodec-3ene in the presence of iron 2-naphthylthiolate (Table 3, entry 6), whereas 85 and 86% yields were obtained in the presence of iron 2-naphthylthiolate complexed with NMP (Table 3, entry 7) or LiCl (Table 3, entry 8), respectively. It should be noted that the same coupling performed according to the previous procedure ([Fe(acac)₃] (5%)/NMP)^[1c] leads to only a 62% yield. Various alkenyl chlorides (Table 4, entries 1-3), as well as secondary alkyl Grignard reagents (Table 4, entries 3-5 and 7-9), were coupled successfully under these reaction conditions. It is also possible to introduce a tertiary alkyl group, although the yield is lower because a competitive β -hydrogen elimination reaction probably occurs (Table 4, entry 6). It should be noted that these results compare advantageously to those obtained with the previous procedure ($[Fe(acac)_3]$ (1%), NMP (9 equiv)).^[1c]

The reaction is highly chemoselective, and thus, various functionalized Grignard reagents were used successfully (Table 5). It is interesting to note that the use of a magnesi-

	R from	Alkenyl	Product	Yield
	RMgCl	halide		[%] ^[a]
1	Bu	CI	11	75 ^[b]
2	Bu	Bu Cl	Bu Bu 1	77 ^[c]
3	c-Hex	Oct	Oct12	84 ^[b]
4	<i>i</i> Pr	PhBr E/Z = 85:15	Ph E/Z = 85:15 13	78 ^[c]
5	c-Hex	Ph E 99	Ph <i>E</i> 99 14	76 ^[c]
6	tBu	Ph E 99	Ph <i>E</i> 99 15	59 ^[b]
7	sBu	Hex Br E/Z = 97:3	Hex E/Z = 97:3 16	90, ^[b] 87 ^[c]
8	sBu	Hex Br Z/E = 97:3	Hex Z/E = 97:3 17	89 ^[b]
9	c-Hex	Br	18	82 ^[b,c]

[a] Yield of the isolated product. [b] Precatalyst: $[Fe(S-2.naphthyl)_2]$ (5%), NMP (7.5%). [c] Precatalyst: $[Fe(S-2.naphthyl)_2]$ (5%), LiCl (10%).

Table 5. Iron-catalyzed alkenylation of functionalized alkyl Grignard reagents.

	Grignard reagent	Product	Yield [%] ^[a]
1	NMgCl	Ph <i>E/Z</i> = 86:14 ^[b] 19	94
2		E/Z = 72:28 ^[c] 20	88
3	CIMgO	Hex $4 - \frac{1}{2} + \frac{1}{4} + \frac{1}{4$	93
4		Bu Bu Bu 22	90
5	O_O_MgCl		79 ^[e]

[a] Yield of the isolated product. [b] From PhCH=CHBr, E/Z=85:15. [c] From MeCH=CHBr, E/Z=71:29. [d] From HexCH=CHBr, E/Z=97:3. [e] Overall yield after hydrolysis of the acetal.

um alcoholate did not perturb the reaction (Table 5, entries 2–4).

Functionalized alkenyl halides were also coupled in good yields (Table 6). For instance, ester (Table 6, entry 4), enone (Table 6, entries 1–3) and even ketone (Table 6, entry 5) groups are well tolerated by these reaction conditions.

Iron(II) 2-naphthylthiolate can also be used as the precatalyst to couple aryl halides with alkyl Grignard reagents (Scheme 3). As with alkenyl halides, the use of NMP is not necessary. However, the reaction is sometimes less chemoseTable 6. Selective iron-catalyzed coupling of functionalized alkenyl halides.







Scheme 3. Iron thiolate-catalyzed aryl-alkyl coupling reactions.

lective than the previous $[Fe(acac)_3]/NMP$ procedure.^[2a] For instance, coupling product **31**, prepared from 4-chlorobenzonitrile, was obtained in only 55% yield under these new reaction conditions.

In summary, we have shown that iron(II) arylthiolate complexes are effective precatalysts for the iron-catalyzed coupling reaction of alkenyl or aryl halides with alkyl Grignard reagents. The reaction proceeds highly chemo- and stereoselectively and, moreover, the yields are often slightly better than those obtained through the previously described procedure that uses [Fe(acac)₃] in the presence of NMP as a cosolvent. This is the first iron-catalyzed coupling procedure by using thiolates as ligands. It is important to note that, in contrast to the related previous procedures, NMP is not required as a cosolvent, which is especially interesting for industrial applications because NMP was recently identified as a reprotoxin.^[5]

Keywords: alkenes • alkenylation • cross-coupling • Grignard reaction • iron • iron-catalyzed reactions • thiolates

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- [6] RSH was deprotonated with a Grignard reagent, such as MeMgCl or BuMgCl, before adding FeCl₃ or FeCl₂ (see the Supporting Information). The precatalyst can also be prepared by adding RMgCl to a mixture of FeCl₃ and RSH, but the yields of coupling products are generally slightly lower if this procedure is utilized. Thus, under the same reaction conditions (Table 1, entry 5), 1-bromo-2-methylpropene then reacts with OctMgCl to afford 2-methyl-2-decene in 86 instead of 90 % yield.
- [7] A precatalyst stored for 24 h at room temperature led to the same results.
- [8] The complex [(FeCl₃)₂(dmf)₃] has been described. See: K. Ogura, T. Koyama, S. Seto, *J. Am. Chem. Soc.* **1972**, *94*, 307. We discovered that it is possible to prepare a similar complex with NMP: [(FeCl₃)₂-(nmp)₃]. The ratio FeCl₃/NMP is 1:1.5.
- [9] [Fe(S-2-naphthyl)₂] can be prepared from either of the ate complexes FeCl₂•2LiCl or FeCl₃•2LiCl. It should be noted that the addition of LiCl does not significantly improve the yield when the reaction is performed with 5 % FeCl₃. Thus, the coupling of OctCH=CHCl with BuMgCl led to a 56 % yield of OctCH=CHBu in the presence of 5 % FeCl₃ and a 57 % yield in the presence of 5 % FeCl₃•2LiCl.

Received: January 17, 2012 Published online: March 29, 2012