Iron nanoparticles in the coupling of alkyl halides with aryl Grignard reagents†

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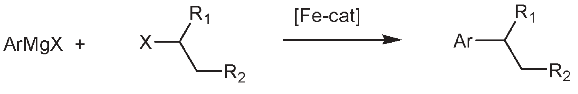
Iron nanoparticles, either formed *in situ* stabilized by 1,6-bis(diphenylphosphino)hexane or polyethylene glycol (PEG), or preformed stabilized by PEG, are excellent catalysts for the cross-coupling of aryl Grignard reagents with primary and secondary alkyl halides bearing β-hydrogens and they also prove effective in a tandem cyclization/cross-coupling reaction.

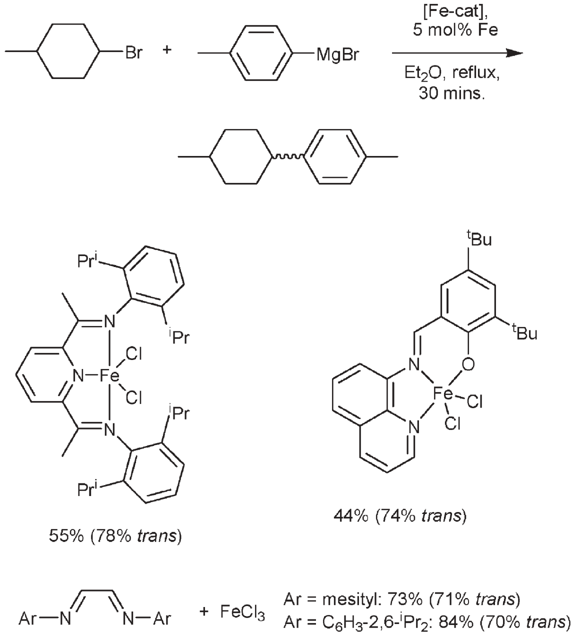
The coupling of Grignard reagents with alkyl halide substrates bearing β-hydrogens can prove problematic. This is because the intermediate metal–alkyl complexes formed are prone to rapid competitive β-elimination reactions that generate unwanted alkenic by-products. Recent studies show that the issue of β-elimination is surmountable in a range of coupling reactions.[1] Building on Kochi's seminal observations that iron-based catalysts can be employed in cross-coupling reactions of vinyl halides,[2] several notable reports have recently appeared on the use of iron pre-catalysts in the cross-coupling of both primary and secondary *alkyl* halides with aryl Grignard reagents (Scheme 1).

Nagano and Hayashi showed that [Fe(acac)$_3$] can be used to good effect,[3] while Martin and Fürstner demonstrated that the ferrate complex [Li(tmeda)$_2$][Fe(C$_2$H$_4$)$_4$] performs well in the coupling of a range of substrates with diverse functionality.[4] We have shown that certain iron-salen based systems are also active.[5]

Particularly simple, yet highly active catalyst systems based on FeCl$_3$ and either stoichiometric or catalytic quantities of amine additives have been reported.[6,7] While Nakamura and co-workers took precautions in order to prevent their reaction mixtures turning black (low temperature, slow addition of ArMgX, stoichiometric amine additive),[6] we found that these measures are not always necessary for good activity, indeed a far larger range of pre-catalysts, not only with amine[7] but also phosphine, arsine, phosphite and carbene ligands,[8] can be employed *if the reactions are allowed to turn black*. Furthermore we now find that the four imine-based iron catalysts shown in Scheme 2 are also active; again the reactions turn black immediately on addition of the Grignard reagent.[9] The breadth of pre-catalysts structures that



Scheme 1



Scheme 2 Coupling of 4-methylcyclohexyl bromide with 4-tolylmagnesium bromide catalysed by Fe-imine-based species.

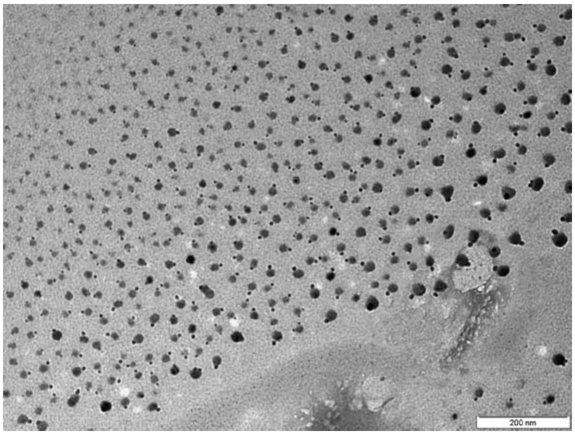


Fig. 1 TEM image of the mixture obtained on reacting FeCl$_3$–dpph with **2**.

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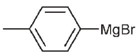
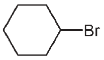
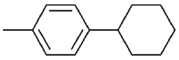
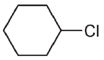
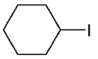
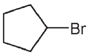
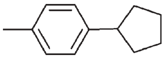
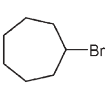
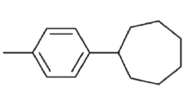
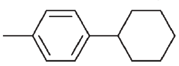
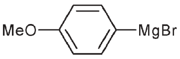
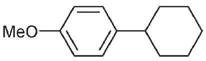
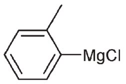
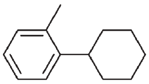
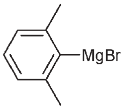
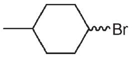
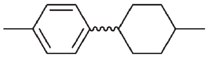
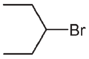
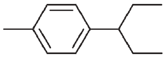
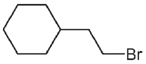
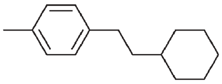
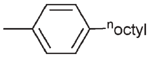
Table 1 Coupling of aryl Grignard reagents with alkyl halides catalysed by *in situ* generated Fe–PEG catalyst^{a}

Entry	ArMgX	AlkX	Product	PEG M_W	PEG/Fe^{b}	Conv., %^{c}
1	 2	 1		14000	100	0
2					10	0
3					2.5	80
4					1	$94^{d,e,}$ (78)^{f}
5					0.1	67
6				35000	1	79
7				2000		63
8				14000		79 (r.t.)^{e}
9					2.5	77
10						82^{e}
11					1	78^{e}
12						79^{e}
13	2	1				$91^{d,e,h}$
14	 *g*					$78^{d,e}$
15						$72^{d,e,h}$
16	 *i*					$30^{d,e}$
17						
18	2					$91^{d,e,k}$
19						$81^{d,e}$
20						$91^{d,e}$
21		Br–^{n}octyl				$85^{d,e,}$ (80)^{f}

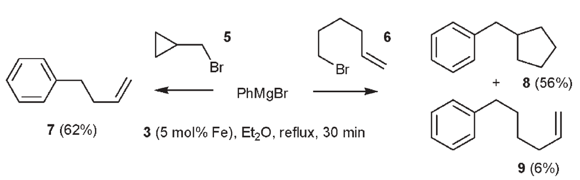
^{a} Conditions: RX (1.0 mmol), ArMgBr (1 M, Et_2O, 2.0 mmol), $FeCl_3$ (0.05 mmol), Et_2O (3 ml), 45 °C (external temp.; internal ~35–38 °C), 0.5 h. ^{b} Based on PEG monomer. ^{c} Conv. to coupled product determined by ^{1}H NMR (mesitylene internal standard). ^{d} Pre-dried PEG (toluene azeotrope). ^{e} Average of two runs. ^{f} Isolated yield. ^{g} 0.5 M in THF. ^{h} Hg (100–150 eq.) added. ^{i} 1 M in THF. ^{j} 1 M in THF. ^{k} *trans* : *cis* = 70 : 30.

prove active led us to wonder whether there was in fact a common catalytic species in all these cases; the black colouration suggested that this may be nanoparticulate iron.[10]

In order to test this hypothesis we subjected the reaction mixture obtained in the coupling of cyclohexyl bromide, **1**, with 4-MeC_6H_4MgBr, **2**, catalyzed by $FeCl_3$–dpph to TEM (Fig. S1).‡[11] This shows fairly small (typically 5–12 nm) iron nanoparticles associated with larger particles of MgX_2.[12,13] Similar iron nanoparticles, typically in the range of 4–9 nm and associated with larger MgX_2 particles, are obtained on the reaction of an $FeCl_3$–dpph mixture with **2** in the absence of alkyl halide (Fig. 1), indicating that the Grignard reagent acts as the reductant.

The catalytically active nanoparticles are presumably stabilized by the phosphine ligand, prompting us to see whether we could use a simpler stabilizing additive, namely polyethylene glycol (PEG). We were delighted to find that this indeed proves to be the case; Table 1 summarizes the catalytic data obtained in a brief survey with this system.‡

As can be seen, the best activity is obtained with PEG of M_w 14,000 g mol^{-1} and an Fe-to-monomer ratio of between 1 : 1 and 1 : 2.5. Higher activity is obtained if the PEG is pre-dried. Slightly better performance is seen at reflux temperature (~35–38 °C) than at room temperature. Both cyclohexyl iodide and chloride are coupled equally as effectively as the bromide (compare entries 3, 9 and 10), while increasing the bulk of the ArMgBr is deleterious to the reaction with no activity observed using 2,6-$Me_2C_6H_3MgBr$. As far as we are aware there are no reports of the iron-catalyzed coupling of such hindered, di-*ortho*-substituted aryl Grignard



Scheme 3

reagents with secondary alkyl halides.[14] Primary and open chain secondary alkyl halides can also be coupled effectively. TEM analysis of a sample taken from the coupling of **1** with **2** again shows iron nanoparticles.‡ Interestingly, the addition of a large excess of Hg does not prevent catalysis (entries 13 and 15).

Encouraged by the activity of the *in situ*-reduced $FeCl_3$–PEG system, we wondered if we could produce pre-formed iron nanoparticles that function as equally active catalysts. Treatment of an ether solution of $FeCl_3$ and PEG with 5 equiv. of **2** gives a black suspension, **3**,[15] which shows only a partial settling out of some black precipitate over several days. TEM analysis of **3** shows iron nanoparticles with a typical size range of about 7–13 nm in an MgX_2 matrix.‡ Suspension **3** is air sensitive, turning yellow-brown within minutes of exposure to air. GC analysis of a water-quenched sample of **3** indicates the presence of 1.5 equiv. of 4,4′-bitolyl per Fe, formed on the reduction of the $FeCl_3$; exactly consistent with the reduction of Fe(III) to Fe(0). The use of BuLi instead of **2** gives a suspension **4** from which LiCl settles out within a few hours.[16]

Suspension **3** shows very similar activity to the catalyst formed *in situ* in the coupling of **1** with **2** (91%; compare with entry 4). The use of **3** in the reaction of **2** with 4-$MeC_6H_{10}Br$ gives the coupled product (80%) with a *trans*-selectivity of 72% – very close to that obtained with $FeCl_3$–PEG (entry 18). Repeating the coupling of **1** with **2** catalyzed by samples of **3** aged for 1 and 15 days shows only a moderate reduction in activity (70% and 71% conversion respectively).[17,18] In stark contrast with the activity shown by **3**, **4** performs very poorly in the coupling of **1** with **2** (4%), possibly due to the observed particle aggregation.[19]

As for the mechanism of coupling of AlkX with ArMgX catalyzed by iron nanoparticles, we currently favour a radical process[4,6] rather than a ‘classical’ coupling mechanism.[3] This preference is based on the results of the reactions of PhMgBr with **5** and **6** catalyzed by **3**, both of which give products expected from a radical-based mechanism (Scheme 3). The former reaction yields the ring-opened product **7** only,[20,21] while the latter reaction produces the ring-closed product **8** as the major species. The formation of **8** is an example of a tandem radical ring-closing/cross-coupling reaction; to the best of our knowledge the first reported for a nanoparticulate iron catalyst.

In summary we have demonstrated that iron nanoparticles, both pre-formed or formed *in situ*, are excellent catalysts for the coupling of aryl Grignard reagents with alkyl halides. In addition, the nanoparticles can be exploited for tandem ring-closing/cross-coupling. To the best of our knowledge this is the first time that iron nanoparticles have been used in *any* cross-coupling or related reactions.[22] The facile synthesis of the particles, their thermal stability and their ease of handling make them highly attractive for use in a wide range of catalytic reactions. We are currently examining the full scope of this new catalyst paradigm and the results from this study will be presented later.

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Notes and references

‡ See electronic supporting information for details.

1 For reviews see: (*a*) A. C. Frisch and M. Beller, *Angew. Chem., Int. Ed.*, 2005, **44**, 674; (*b*) M. R. Netherton and G. C. Fu, *Adv. Synth. Catal.*, 2004, **346**, 1525; (*c*) D. J. Cárdenas, *Angew. Chem., Int. Ed.*, 2003, **42**, 384; (*d*) T.-Y. Luh, M.-K. Leung and K.-T. Wong, *Chem. Rev.*, 2000, **100**, 3187.

2 Recent overview: J. K. Kochi, *J. Organomet. Chem.*, 2002, **653**, 11.

3 T. Nagano and T. Hayashi, *Org. Lett.*, 2004, **6**, 1297.

4 (*a*) R. Martin and A. Fürstner, *Angew. Chem., Int. Ed.*, 2004, **43**, 3955; (*b*) See also the structural characterisation, reactivity and catalytic activity of an unusual iron “super ate” complex: A. Fürstner, H. Krause and C. W. Lehmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 440.

5 R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby and M. Hird, *Chem. Commun.*, 2004, 2822.

6 M. Nakamura, K. Matsuo, S. Ito and E. Nakamura, *J. Am. Chem. Soc.*, 2004, **126**, 3686.

7 R. B. Bedford, D. W. Bruce, R. M. Frost and M. Hird, *Chem. Commun.*, 2005, 4161.

8 R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost and M. Hird, *J. Org. Chem.*, 2006, **71**, 1104.

9 For syntheses of pre-formed iron complexes see: (*a*) G. J. P. Britovsek, M. Bruce, V. C. Gibson, B. S. Kimberley, P. J. Maddox, S. Mastroianni, S. J. McTavish, C. Redshaw, G. A. Solan, S. Strömberg, A. J. P. White and D. J. Williams, *J. Am. Chem. Soc.*, 1999, **121**, 8728; (*b*) R. K. O’Reilly, V. C. Gibson, A. J. P. White and D. J. Williams, *J. Am. Chem. Soc.*, 2003, **125**, 8450.

10 Suspensions of iron nanoparticles are typically black, see, for example: (*a*) Y. Koltypin, N. Perkas and A. Gedanken, *J. Mater. Chem.*, 2004, **14**, 2975; (*b*) L. Guo, Q. Huang, X.-Y. Li and S. Yang, *Phys. Chem. Chem. Phys.*, 2001, **3**, 1661.

11 dpph = 1,6-bis(diphenylphosphino)hexane. This reaction gives 91% conversion to 4-MeC_6H_4Cy, see ref. 8.

12 EDX analysis reveals the presence of Mg, Cl and Br.

13 No special precautions were taken to prevent oxidation of the iron nanoparticles in the TEM analyses, so it is likely that the majority of the iron is in the form of an amorphous oxide phase in all cases.

14 Hayashi and co-workers showed that the similarly sized 2,4,6-$Me_3C_6H_2MgBr$ reacts with a *primary* alkyl halide, see ref. 3.

15 As in ref. 10*b*, powder XRD of a dried sample of **3** is inconclusive, probably because the particles are small and amorphous.

16 TEM analysis of a sample of **4** shows much larger aggregates of more polydisperse particles – see supporting information.

17 This decrease may correspond to some catalyst precipitation.

18 At this stage it is not possible to say whether the catalysis occurs at the nanoparticle surface, or whether the nanoparticles act as a ‘reservoir’ for soluble catalytic species as is probably the case when palladium nanoparticles are used in coupling reactions. See for instance: A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx and J. G. de Vries, *Org. Lett.*, 2003, **5**, 3285.

19 The MgX_2 salts in **3** and catalyst systems formed *in situ* from $FeCl_3$–PEG may play a role in nanoparticle stabilization with respect to aggregation beyond that played by the PEG, which may explain the low catalytic activity of **4**.

20 **5** as a radical probe, see: Y. Ikeda, T. Nakamura, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2002, **124**, 6514 and references therein.

21 A simple oxidative addition pathway would give $PhCH_2$-*cyclo*-C_3H_5. See: J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu and N. Kambe, *J. Am. Chem. Soc.*, 2002, **124**, 4222.

22 To the best of our knowledge, catalytic organic applications of iron nanoparticles are limited to Fischer–Tropsch synthesis, simulation of coal liquefaction, the hydrogenation of naphthalene, the hydroformylation of an alkene, denitrogenation of nitrogen compounds and the degradation of trichloroethylene. For leading references see: *Small*, 2005, **1**, 482.