Simple iron-amine catalysts for the cross-coupling of aryl Grignards with alkyl halides bearing β-hydrogens

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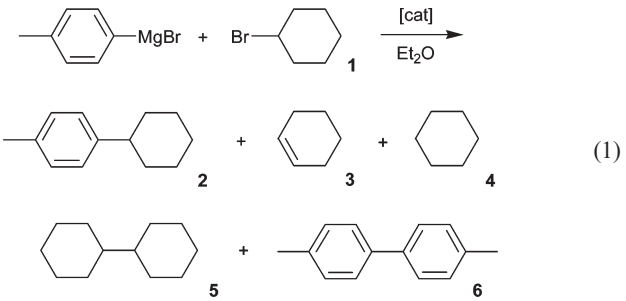
Mixtures of iron(III) chloride and appropriate amine ligands are active catalysts for the coupling of aryl Grignard reagents with primary and secondary alkyl halide substrates bearing β-hydrogens, under mild and simple reaction conditions.

The transition metal catalysed Grignard cross-coupling reaction is a powerful tool for the formation of C–C bonds.[1] The use of primary, and particularly, secondary alkyl halides as substrates poses problems in that they tend to be less reactive than aryl halides and the intermediate alkyl complexes formed tend to be prone to rapid β-elimination reactions generating alkene products.[2] Recent studies show that the problem of β-elimination is surmountable.[3] For instance Ni and Pd complexes have been shown to catalyse the coupling of primary alkyl halide substrates with appropriate nucleophilic coupling partners,[3] while Co,[4] Ni[5] and Fe[6,7] catalysts have all recently shown activity in coupling reactions of primary and secondary alkyl substrates, typically without large amounts of β-eliminated by-product formation.

Of particular note are recent reports of the use of iron(III) complexes as pre-catalysts in the cross-coupling of both primary and secondary alkyl halides with aryl Grignard reagents. Nagano and Hayashi showed that [Fe(acac)$_3$] can be used to good effect,[6] while Martin and Fürstner showed the ferrate complex [Li(tmeda)$_2$][Fe(C$_2$H$_4$)$_4$] to be effective in the coupling of a large range of alkyl halides with diverse functionality.[8] We found that simple iron–salen complexes can also be exploited.[9] Nakamura and co-workers demonstrated that iron(III) chloride can be employed in the presence of stoichiometric amounts of appropriate amines, particularly TMEDA, provided the Grignard is added slowly *via* a syringe pump.[7] While this latter method is particularly attractive, due to the simplicity of the catalyst and the excellent results obtained, it currently suffers from three limitations. Firstly, a greater than stoichiometric amount of amine is required, which is added with the Grignard reagent. Secondly, for optimal performance the Grignard/amine mixture must be added slowly *via* the use of a syringe pump and thirdly, typically, the reactions must be cooled to 0 °C or lower. If it were possible to circumvent these limitations then this would represent a very powerful technique, due to the simplicity of the catalyst systems. We find that these problems are indeed surmountable: amines can be used in catalytic quantities; the reactions can be performed at elevated temperatures and there is no requirement for slow addition of the Grignard. The preliminary findings of this study are reported below.



(1)

For the initial screening of catalyst performance, we chose the reaction outlined in eqn. (1) as a typical example of aryl Grignard–secondary alkyl coupling.† Fig. 1 shows the conversion to coupled

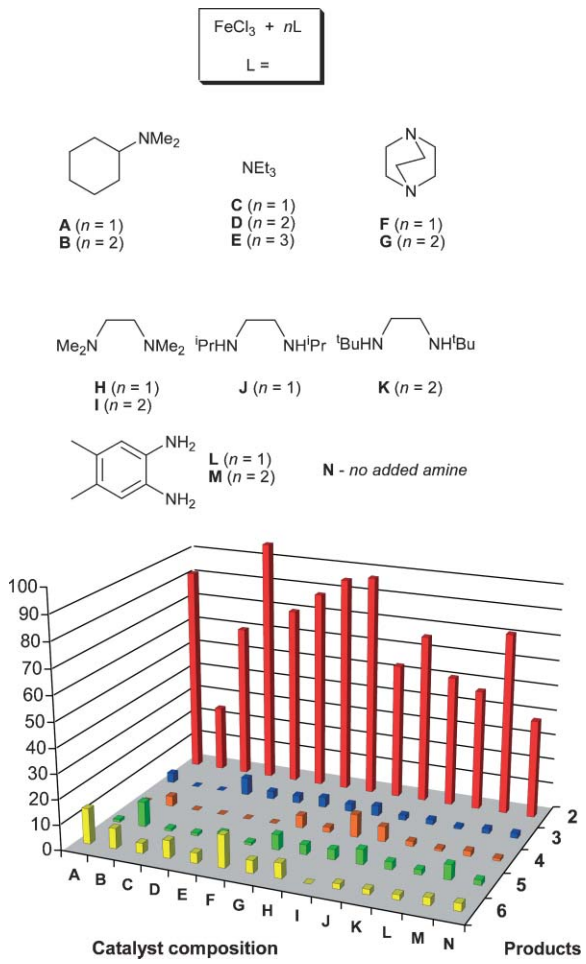


Fig. 1 Screening of activity of Fe–amine catalysts in the coupling of 4-tolylMgBr with cyclohexyl bromide.†

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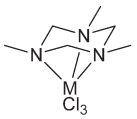
product **2** along with the formation of the elimination product – cyclohexene (**3**), the hydrodehalogenated product – cyclohexane (**4**), and the two homo-coupled products dicyclohexyl (**5**) and bitolyl (**6**) with a range of amine–Fe catalysts. Surprisingly, we found that, under these conditions, even $FeCl_3$ in the absence of added amine shows some activity – 39% (catalyst entry **N**). This is in contrast with the findings of Nakamura and co-workers who found very little hetero-coupling *versus* large amounts of elimination product under their conditions.[7] The addition of amine ligands in catalytic loadings leads to substantial improvement in activity.

As can be seen, most of the amines tested show good to excellent conversions to coupled product **2** with minimum levels of contamination by **3** and **4**. The best activities tend to be obtained with either mono- or bidentate tertiary amines, with chelating primary and secondary bis-amine ligands typically showing lower performance. Interestingly, the use of triethylamine as the ligand (entries **C–E**) proved effective; by contrast Nakamura and co-workers found this ligand to be very poor under their conditions.[7] There does not appear to be a general trend in performance on the ratio of Fe to N-donors across the series, rather any effect seems to be ligand-specific.

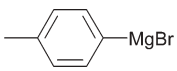
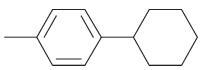
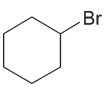
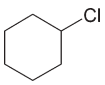
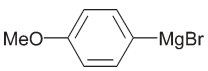
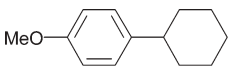
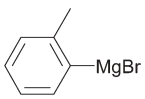
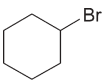
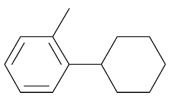
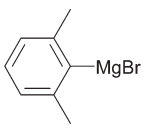
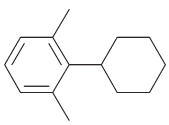
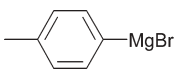
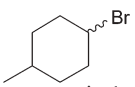
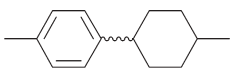
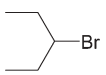
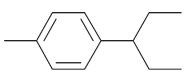
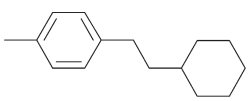
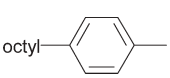
The pre-formed iron(III) 1,3,5-trimethylhexahydro-1,3,5-triazine complex **7**[10] gives a healthy 86% conversion to the hetero-coupled product **2** under the same conditions as in Fig. 1. By contrast its chromium analogue **8**[10] gives none of the desired product.



7: M = Fe
8: M = Cr

The three best ligands – triethylamine, DABCO and TMEDA – were then screened against a range of substrates and the results are summarised in Table 1.‡ In all cases the Fe : N ratio was kept at 1 : 2.

Table 1 Cross-coupling of alkyl with aryl Grignard reagents

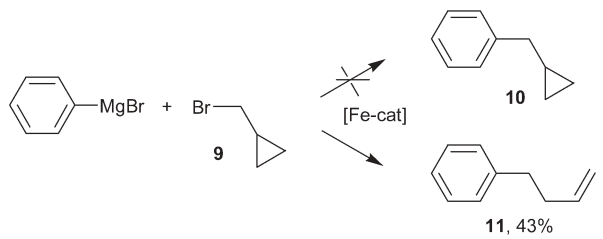
				Conversion (%)[a] with catalyst system		
Entry	ArMgBr	Alkyl halide	Product	$FeCl_3$ + 2 NEt_3	$FeCl_3$ + TMEDA	$FeCl_3$ + DABCO
1				75	90	100
2				79	79	88
3				69	60	74
4				84	59	62
5				75	62	70
6				0	0	0
7		 (*cis* : *trans* ratio 1 : 3.2)		85 (*cis* : *trans* ratio 1 : 1.5)	75 (*cis* : *trans* ratio 1 : 1.8)	93 (*cis* : *trans* ratio 1 : 1.9)
8				66	49	40
9				74	44	61
10		octyl–Br		70	63	62

[a] Conversion to product determined by ^1H NMR spectroscopy (mesitylene internal standard).

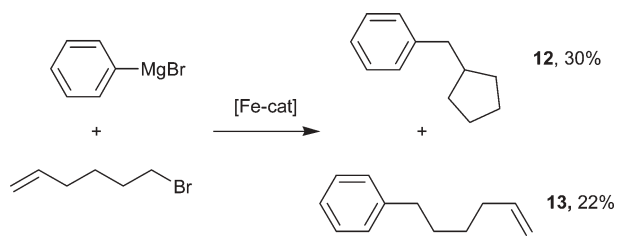
As can be seen, in contrast with the results obtained by Nakamura and co-workers under their conditions,[7] the TMEDA system fared least well in nearly all reactions. With cyclohexyl substrates, the best catalyst proved to be that based on $FeCl_3$/DABCO in nearly all cases (entries 1–3 and 7), except in the reaction of the hindered aryl Grignard, 2-tolyl magnesium bromide, with bromocyclohexane. In this instance the best catalyst was that based on $FeCl_3$/NEt_3. None of the catalysts tested were able to couple the hindered substrate 2-*meta*-xylylmagnesium bromide (entry 6). In the coupling of 4-tolyl magnesium bromide with 4-methylcyclohexyl bromide (entry 7) the DABCO/$FeCl_3$ catalyst system gives not only the highest conversion to coupled product but also the greatest *trans*-selectivity. The variation in *cis* : *trans* ratio compared to that of the starting alkyl bromide and the difference in selectivity with varying catalysts tend to argue against a simple oxidative addition of the alkyl halide to the metal centre during the catalytic cycle, a point that will be discussed further later. When either primary alkyl halides or open-chain secondary alkyl halides are used, the best catalyst system tested proves to be $FeCl_3$/NEt_3 (entries 8–10).

With regards to a possible mechanism, Nagano and Hayashi suggest that Fe-based couplings of alkyl halides with aryl Grignards may proceed *via* oxidative addition of the alkyl halide to a reduced iron complex,[6] that is to say a two-electron redox pathway is involved. By contrast Nakamura and co-workers invoke a radical pathway in which the reduced iron catalyst enters a one-electron redox pathway and an alkyl radical is formed from the alkyl halide.[7] It was proposed that any alkyl radical formed in such a pathway may not be free, but rather remains 'associated' with the metal centre.[11] Their observation that an enantio-pure secondary alkyl bromide is converted to a racemic mixture of coupled product is strongly supportive of a radical pathway.

In order to probe further whether the mechanism proceeds *via* a classical oxidative addition manifold or by a radical pathway, we investigated the coupling of phenylmagnesium bromide with (bromomethyl)cyclopropane, **9**, (Scheme 1). If an oxidative addition pathway is operative then it would be expected that the simple coupled product **10** would form.[12] However this is not the case, instead the ring-opened product 4-phenylbutene, **11**, is obtained, lending support to a radical pathway.[13] Further evidence for an alkyl radical intermediate is provided by the reaction of phenylmagnesium bromide with 6-bromohexene (Scheme 2); this predominantly yields the ring-closed product **12** as well as the simple coupled product **13**.[14]



Scheme 1 *Conditions*: PhMgBr (4.0 mmol), **9** (2.0 mmol), cat = $FeCl_3$/2 Et_3N (5 mol%), Et_2O/THF (3 : 2), 45 °C, 30 min. Yield determined by ^1H NMR spectroscopy.



Scheme 2 *Conditions*: PhMgBr (4.0 mmol), 6-bromohexene (2.0 mmol), cat = $FeCl_3$/2 Et_3N (5 mol%), Et_2O/THF (3 : 2), 45 °C, 30 min. Yields determined by ^1H NMR spectroscopy.

In summary, we have found that simple iron catalysts formed *in situ* from $FeCl_3$ and appropriate amines are active catalysts for the coupling of primary and secondary alkyl halides with aryl Grignard reagents without the need for excess amine, slow addition of the Grignard or low reaction temperatures. Research is ongoing to try to establish the nature of the true active catalyst species.

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Notes and references

† The appropriate amount of amine in CH_2Cl_2 (2 ml) was added to anhydrous $FeCl_3$ (0.1 mmol) and then after standing (2 min) the solvent was removed *in vacuo*. Et_2O (3 ml) was added and the solution was stirred (~ 2 min). CyBr (1.0 mmol) was added, the solution stirred for 5 minutes, then heated to reflux temperature (external temperature 45 °C; reaction temperature ~ 36–38 °C) and 4-MeC_6H_4MgBr (1.0 M solution in Et_2O, 2.0 ml) was added in one portion. The reaction was then heated for 30 min, quenched with H_2O (5 ml), extracted with CH_2Cl_2 (3 × 5 ml) and dried ($MgSO_4$). Mesitylene (internal standard, 0.1439 M in CH_2Cl_2, 1.00 ml) was added and the conversion to products **2–6** was determined by GC analysis.
‡ Reactions performed as above with appropriate alkyl halide (2.0 mmol), ArMgBr (4.0 mmol) and catalyst (5 mol% Fe). Reactions were quenched (H_2O, 5 ml), extracted with CH_2Cl_2 (3 × 5 ml) and dried ($MgSO_4$). Mesitylene (internal standard, 0.667 M in CH_2Cl_2, 1.00 ml) was added, an aliquot (2 ml) was removed from which the solvent was removed at room temperature under reduced pressure. The residue was dissolved in $CDCl_3$ (~ 0.7 ml) and the conversion to coupled product was determined by ^1H NMR spectroscopy.

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14 Interestingly, Nakamura and co-workers found that with greater than stoichiometric amounts of amine additive, **13** predominates with little or no **12** observed, depending on precise conditions. See ref. 7.