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Iron(III) salen-type catalysts for the cross-coupling of aryl Grignards with alkyl halides bearing β-hydrogens†

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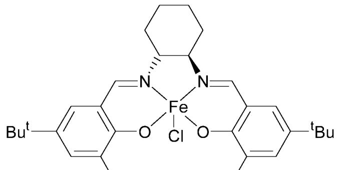
Received (in Cambridge, UK) 7th September 2004, Accepted 11th October 2004
First published as an Advance Article on the web 27th October 2004

Iron(III) salen and related complexes are active catalysts for the coupling, under mild and simple reaction conditions, of aryl Grignard reagents with primary and secondary alkyl halide substrates bearing β-hydrogens.

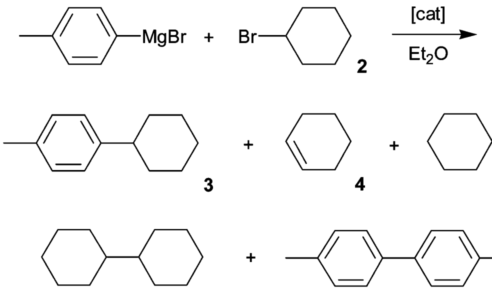
The transition metal catalysed Grignard cross-coupling reaction is a powerful tool for the formation of C–C bonds.[1] The use of primary, and particularly, secondary alkyl halides as substrates poses problems in that they tend to be less reactive than aryl halides and the intermediate alkyl complexes formed tend to be prone to rapid β-elimination reactions generating alkene products. Recent studies show that the problem of β-elimination is surmountable. For instance Ni and Pd complexes have been shown to catalyse the coupling of primary alkyl halide substrates with appropriate nucleophilic coupling partners,[2] while Co,[3] Ni[4] and Fe[5,6] 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. Nakamura and Hayashi showed that [Fe(acac)$_3$] can be used to good effect, while Nakamura and co-workers demonstrated that iron(III) chloride can also be employed in the presence of stoichiometric amounts of appropriate amines, provided the Grignard is added very slowly *via* a syringe pump.

Fürstner and co-workers had shown previously that the Fe^{III} salen complex **1** can be used to couple alkyl Grignards with aryl halides.[7] We were interested to see whether related complexes could be used to realise the coupling of aryl Grignards with alkyl halides containing β-hydrogens. This indeed proves to be the case and the preliminary results of this study are presented 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. In the first instance we screened a range of first-row TM–salen complexes and the results obtained are summarised in Fig. 1. As can be seen, most of the complexes performed very poorly, except for [FeCl(salen)], **8**, which gave a healthy conversion of 68% to the desired product whilst maintaining low levels of both the β-eliminated product **4** (1%) and the hydrodehalogenated product **5** (1%). It is interesting to note that while [Co^{II}(salen)] did not prove active for the heterocoupling reaction, it shows moderate activity in the homocoupling of the aryl Grignard reagent. The salen ligand on its own shows no activity. Reducing the loading of complex **8** (Table 1) leads to a decrease in conversion to the coupled product **3**, as expected. In addition, the relative amounts of side-products tend to increase, this being particularly true for the formation of cyclohexane, **5**. At 0.1 mol% Fe loading there is essentially no activity.



(1)

Interestingly, we find that when the catalyst is added as a solution in dichloromethane and the solvent subsequently removed *in vacuo*, then its performance often increases compared with when it is added as a solid. Thus when the reaction is performed at 5 mol% loading of [FeCl(salen)] introduced in this manner, the conversion to **3** increases from 68 to 84%.

Next we investigated the effect of structural modification of the Schiff base ligands and the results are summarised in Fig. 2. This series of experiments was performed at 1 mol% Fe loading in order to highlight differences in activity.

Increasing the size of the diamino linker proves to be highly deleterious with **9** and **10** showing very poor activity. Replacing the ethylene backbone with an aromatic spacer is also highly detrimental to performance with **11**–**13** showing little or no activity. We then investigated the effect of changing the phenolate groups, keeping

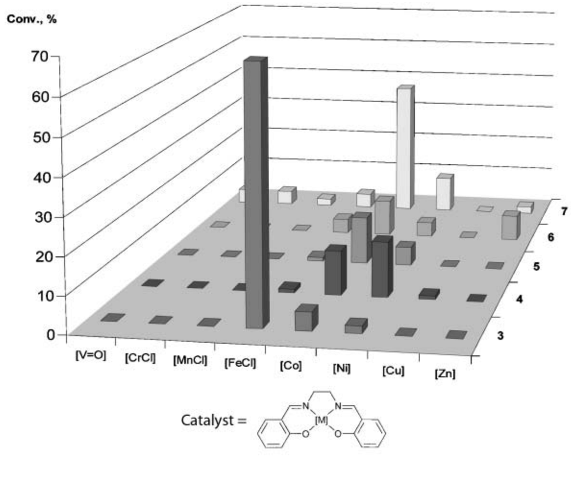


Fig. 1 Screening of activity of TM–salen complexes in the Grignard coupling of 4-tolylmagnesium bromide with cyclohexylbromide. Conditions: CyBr (1.0 mmol), 4-MeC$_6$H$_4$MgBr (2.0 mmol), catalyst (5 mol%), Et$_2$O, 45 °C, 30 min. Conversion determined by GC (mesitylene standard).

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† Electronic supplementary information (ESI) available: full quantification of side-products with varying catalysts. See http://www.rsc.org/suppdata/cc/b4/b413790f/

DOI: 10.1039/b413790f

Table 1 Effect of decreasing loading of [FeCl(salen)], **8**, on the coupling of 4-tolylmagnesium bromide with cyclohexylbromide[a]

Catalyst loading (mol% Fe)	Conversion to (%): **3**	**4**	**5**	**6**	**7**
5	68	1	1	4	4
1	52	3	5	1	6
0.5	24	3	9	2	4
0.1	0	0	0	0	1

[a] Conditions as in Fig. 1 but with variable catalyst loading.

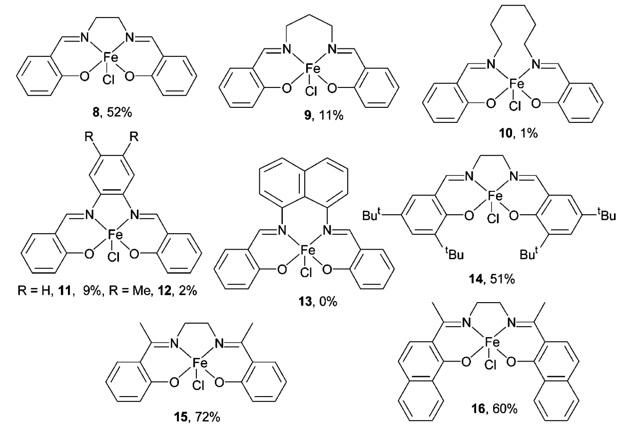


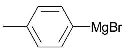
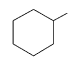
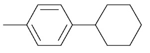
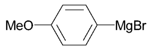
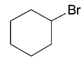
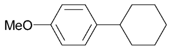
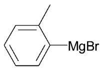
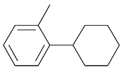
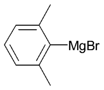
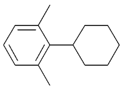
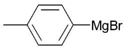
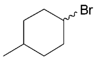
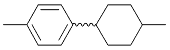
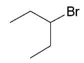
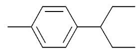
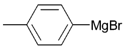
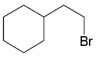
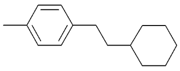
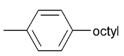
Fig. 2 Effect of variation of ligand structure on the coupling of 4-tolylMgBr with CyBr. Conditions: as above with 1 mol% Fe loading.

ethylene as the backbone. The bulky ^{t}Bu–modified analogue, **14** shows essentially the same conversion as the unmodified system **8**, however far greater amounts of dicyclohexane, **6**, are observed with the bulky system (10% *v.* 1% with **8**).† By contrast, catalyst **14** gives essentially no cyclohexane by-product, compared with 5% obtained with **8**. Switching to ketone-derived Schiff base ligands proves beneficial with complex **15** giving a 72% conversion to the desired product. The more hindered naphthyl analogue **16** displays lower activity than **15**, but still out-performs **8**.

Having established that complex **15** shows optimal activity, this catalyst was then used for the remainder of the studies with varying substrates, the results of which are summarised in Table 2.‡ The catalyst loading was not optimised, rather it was kept at 2.5 mol% iron throughout. Under these conditions, the conversion to coupled product **3** in the 'standard' reaction rises to 90% (entry 1). In comparison [Fe(acac)$_3$] gives only 69% conversion under similar conditions and 5 mol% loading.[5] While Nakamura's Fe^{III}–TMEDA system gives 99% yield in this reaction, the need to add greater than stoichiometric amounts of the amine, coupled with the need for slow addition of the Grignard with a syringe pump, detracts from its appeal.[6] Slightly lower activity is seen if bromocyclohexane is replaced by the iodo- or chloro-counterparts (entries 2 and 3). The electron-rich 4-MeOC$_6$H$_4$MgBr also gives a good conversion (entry 4). While an *ortho*-methyl function is tolerated in the aryl Grignard substrate (entry 5) the introduction of two *ortho* substituents leads to a complete loss in activity (entry 6). While this result was obtained in THF, it is not a solvent effect. When the reaction was repeated in THF–ether, no conversion was observed in contrast with results obtained in entry 1. Further, when 10% 4-MeC$_6$H$_4$MgBr is added, a small amount of **3** forms, demonstrating the competence of the catalyst, but none of the bulky cross-coupled product is observed. Interestingly, a small amount of 2,2′,6′6′-tetramethylbiphenyl is also formed suggesting that formation of an iron–aryl complex is not disfavoured completely in this case.

The coupling of 4-bromomethylcyclohexane (mixture of *cis* and *trans* isomers) with 4-tolylmagnesium bromide gives a mixture of stereoisomers (1 : 1.8 *cis* : *trans*). The ratio in the starting material is 1 : 3.3, indicating poor stereocontrol. The low selectivity observed is presumably a result of the modest steric influence of the remote methyl function. By contrast, Nakamura *et al.* observed a high stereoselectivity for the *trans*-isomer when the considerably more encumbered substrate 4-bromo-*tert*-butylcyclohexane is coupled with 4-MeOC$_6$H$_4$MgBr.[6]

Table 2 Cross-coupling of ArMgBr with alkyl halides[a]

Entry	ArMgBr	Alkyl halide	Product	Conv.,[b] %
1				90 (84)[c] (41)[d]
2	"	X=I	"	76
3	"	X=Cl	"	80
4				81 (77)[e]
5				61
6				0[a or c]
7				83[f]
8	"			56
9				69
10	"	Octyl—Br		89

[a] Conditions: alkyl halide (2.0 mmol), ArMgBr (4.0 mmol), catalyst **15** (2.5 mol%), Et$_2$O, 45 °C, 30 min. [b] Conversion to coupled product, determined by ^{1}H NMR (mesitylene internal standard). [c] THF : ether (2 : 3) used as solvent. [d] 2.0 mmol aryl Grignard used. [e] Isolated yield. [f] Mixture of stereoisomers, 1 : 1.8.

The reaction is tolerant of open chain secondary alkyl halides (entry 8), and good to excellent activities are seen with primary alkyl bromides (entries 9 and 10).

In summary, easily synthesised and handled Fe^{III}–salen-type complexes are excellent catalysts for the cross-coupling of aryl Grignard reagents with primary and secondary alkyl halides.

We thank the COMIT Faraday partnership and Kingston Chemicals for support.

Notes and references

‡ **General method for catalysis in Table 2**. Catalyst **15** (2.5 mol%) in CH$_2$Cl$_2$ (3 mL) was added to the reaction flask under N$_2$ and then the solvent was removed *in vacuo*. AlkX (2.0 mmol) and Et$_2$O (6 mL) were added and the solution was stirred at rt for 2 min. ArMgBr (1 M in Et$_2$O or THF) was added and the resultant black mixture was heated at 45 °C (external) for 30 min. HCl (aq., 2 M, 5 mL) was added, the organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and dried (MgSO$_4$). Mesitylene (internal standard, 0.667 M, 1.00 mL) was added, the solvent was carefully removed on a rotary evaporator and conversion to coupled product was determined by ^{1}H NMR.

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