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Iron-Catalysed sp^3–sp^3 Cross-Coupling Reactions of Unactivated Alkyl Halides with Alkyl Grignard Reagents

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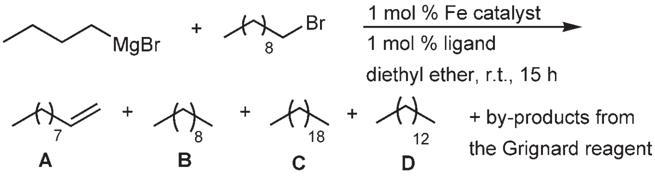
Abstract: Iron-catalysed sp^3–sp^3 Kumada coupling with primary and secondary alkyl halides (RX) and alkyl Grignard reagents has been achieved in low to good yields depending on the nature of the R group.

Keywords: alkyl halides; cross-coupling; Grignard reactions; iron

The direct carbon-carbon cross-coupling reaction of organometallic components with alkyl halides is one of the key chemical transformations in synthetic chemistry. The field is dominated by the use of catalysts such as nickel, palladium and copper with alkyl metals such as alkyl Grignards (Kumada coupling), alkyl borons (Suzuki–Miyaura coupling) and alkyl zincs (Negishi coupling).[1] Recently, there has been intensive interest in the development of iron catalysts for C−C bond formation.[2] This is in part due to the push towards the development of 'greener' and cheaper catalysts. The use of cheap, non-toxic and environmentally benign iron compounds as catalysts in Kumada coupling has been reported by Kochi[3] in 1971 but exploitation of this to synthesis was not realised until the work Cahiez,[4] Furstner,[5] Nakamura,[6] Hayashi[7] and Bedford.[8] To date, sp^2–sp^3 and sp^2–sp^2 couplings of Grignard reagents with alkyl or aryl halides have been achieved in synthetically viable yields. However the efficient cross-coupling of sp^3–sp^3 carbon centres, using iron catalysts, remains an exciting challenge. To our knowledge, there is only the report of Kochi's pioneering observations with coupling of activated alkyl halides,[3] while sp^3–sp^3 coupling of Grignard reagent with *unactivated* alkyl halides has not been reported. Our studies, reported herein, provide an important precedence for extending the scope of iron catalysed sp^3–sp^3 reactions with unactivated alkyl halides.

The obstacles to successful sp^3–sp^3 carbon-carbon cross coupling using Grignard reagents include the formation of undesired by-products such as that resulting from homocoupling, disproportionation and beta-elimination reactions. Thus for a reaction as outlined in Scheme 1, the desired cross-coupling reaction to form product **D** suffers from competition with the formation of decene **A**, decane **B** and eicosane **C**, the by-products that arise from the limiting reagent, the alkyl halide. By-products arising from the Grignard reagents are also likely but due to their volatility, these were not analysed.

Our initial studies focused on the use of iron(II) acetate as the catalyst in diethyl ether. A large number of ligands (Figure 1) were screened – these included the use of phosphines, phosphites, amines, butadiene. Of these, the use of Xantphos (**1**) gave moderate to good yields of the cross-coupling product. It is interesting to note that the use of **2**, a conformationally flexible diphosphine related to Xantphos gave much lower yields of the cross coupling product (5% *versus* 51% yield). Similarly the diphosphine **3** also gave poor yields of the desired cross-coupling product, indicating that the nature of the substitution on the phosphorus atom of the ligand is also crucial



Scheme 1. Iron-catalysed sp^3–sp^3 Kumada coupling.

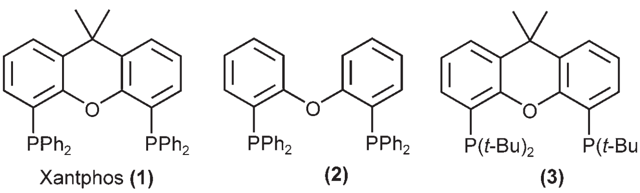


Figure 1. Structures of selected phosphine ligands.

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Table 1. Screening of ligands with $Fe(OAc)_2$ as catalyst.[a]

Ligands	**A** (%)	**B** (%)	**C** (%)	**D** (%)
No ligand	15	58	16	3
Triphenylphosphine, PPh_3	7	50	7	15
Tricyclohexylphosphine	18	57	0	2
2-(Di-*tert*-butylphosphino)biphenyl	11	62	12	4
2-(Dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl	15	51	16	8
1,2-Bis(dipentafluorophenylphosphino)ethane	10	64	6	5
1,2-Bis(diphenylphosphino)ethane	14	58	7	5
2,2-Bis(diphenylphosphino)-1,1-binaphthyl	10	43	11	18
9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (**1**)	2	31	10	51
Bis(2-diphenylphosphinophenyl) ether (**2**)	10	62	13	5
9,9-Dimethyl-4,5-bis(di-*tert*-butylphosphino)xanthene (**3**)	9	44	6	11
Tri-*n*-butyl phosphite	12	38	9	14
Tris(2,2,2-trifluoroethyl) phosphite	11	56	11	2

[a] The reaction was carried out under standard conditions as described in the Experimental Section with 1 mol% iron(II) acetate in the presence of 1 mol% ligand. The yields of the cross-coupling products were quantified using GC (relative to response curves with appropriate standards). In the control experiment without the iron catalyst, only the alkyl halide was recovered after work-up.

Table 2. Screening of Fe catalyst using Xantphos (**1**).[a]

Fe catalysts	**A** (%)	**B** (%)	**C** (%)	**D** (%)
$Fe(acac)_3$	18	36	11	9
$FeCl_2$	9	51	15	3
$FeCl_3$	32	54	9	2
FeF_3	9	31	5	15
$Fe(OAc)_2$	2	31	10	51
$Fe(CF_3COCH{=}COCH_3)_3$	15	27	6	3

[a] The reaction was carried out under standard conditions as described in the Experimental Section, with 1 mol% iron(II) catalyst in the presence of 1 mol% ligand. The yields of the cross-coupling products were quantified using GC (relative to response curves with appropriate standards).

in promoting the desired cross-coupling reactions. Some of the results are summarised in Table 1 below.

Using Xantphos as the ligand, the use of other iron complexes [Fe(II) and Fe(III)] as catalysts was also examined (Table 2). From these studies, $Fe(OAc)_2$ gave the best yields of the cross coupling product. Attempts to optimise the reaction conditions for the cross coupling reaction included the choice of solvents and temperature. The use of THF, DCM and 1,4-dioxane as solvents reduced the yield of the cross-coupled product. When the reaction was attempted under the reflux temperature of diethyl ether, no improvement in the yield of the desired cross coupled product **D** was obtained. The progress of reaction was also monitored over time and our studies showed that the reaction was completed in 15 min and that prolonged reaction times did not negatively or positively impact on the yields of the desired product. When the loading of the iron catalyst and ligand was increased to 3 mol% and 6 mol% respectively, the yields of the cross-coupled products showed marked improvements in some cases.

Under the best conditions ascertained so far [3 mol% $Fe(OAc)_2$, 6 mol% Xantphos in diethyl ether at room temperature for 15 min], the reactions of the R'MgBr with some primary and secondary alkyl halides were attempted (Scheme 2, Table 3). From these studies, for the primary alkyl halides utilised, the yields ranged from 46–64% of the desired cross coupled product. The yields of the desired cross-coupled product with secondary alkyl halides were low (*ca.* 8–43%) under these conditions.

Our preliminary investigation of the possible mechanism of cross-coupling of primary systems suggests the intermediacy of radical intermediates (Scheme 3). In particular, the reaction of 4-phenoxybutylmagnesium bromide with 6-bromohexene gave cross-coupling adducts **4** and **5** in a ratio of 95:5 with isolated yields

$$\mathrm{R'MgBr} \quad + \quad \mathrm{RBr} \xrightarrow[\substack{\text{6 mol \% Xantphos} \\ \text{diethyl ether, r.t., 15 mins}}]{\text{3 mol \% Fe(OAc)}_2} \mathrm{R'\text{-}R}$$

Scheme 2. ‘Best’ conditions to date for cross-coupling.

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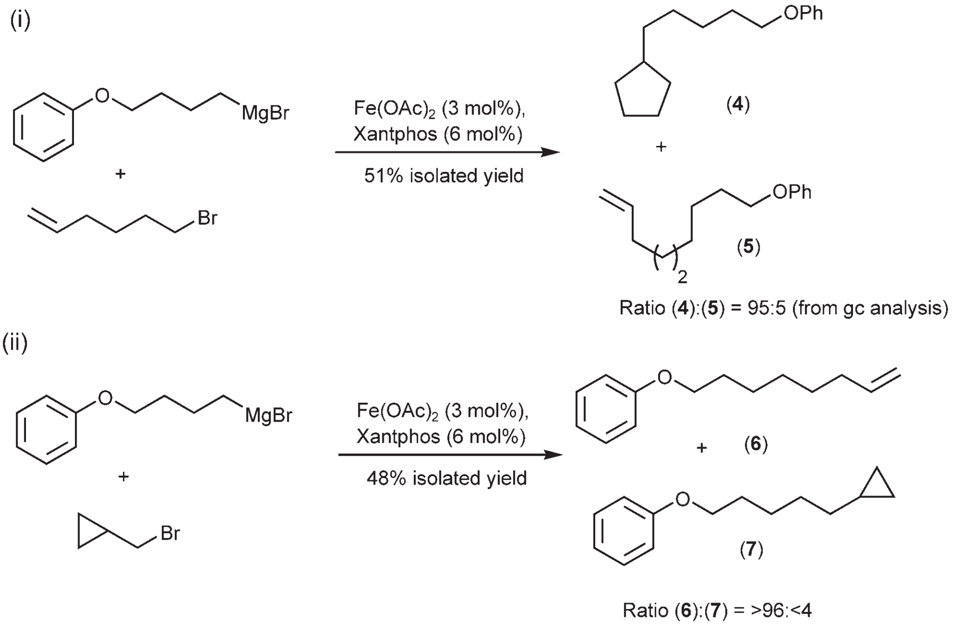
Table 3. Cross-coupling yields[a] under standard reaction conditions.

R-Br	R′	Yield [%] of R′-R
1-Bromodecane	*n*-butyl	64%
1-Bromododecane	*n*-butyl	63%
1-Bromotetradecane	*n*-butyl	63%
1-Bromohexadecane	*n*-butyl	64%
exo-2-Bromonorbornane	*n*-butyl	8%
1-Bromocyclohexane	*n*-butyl	34%
4-Bromo-1-butene	*n*-hexyl	46%
1-Bromodecane	*n*-hexyl	62%
1-Bromocyclohexane	1-propylbenzene	43%

[a] The reaction was carried out under the best conditions, using 3 mol% $Fe(OAc)_2$ as catalyst and 6 mol% Xantphos as ligand. The yields of the cross-coupling products were quantified using GC (relative to response curves with appropriate standards).



Scheme 3. Probing the mechanism of sp^3–sp^3 iron-catalysed cross-coupling reactions.

of 51%. Thus the cyclopentyl adduct **4** was formed as the near exclusive cross-coupling adduct. When bromomethylcyclopropane replaced 6-bromohexene, the cross-coupling adduct **6** was isolated in 48% yield. The cyclopropyl cross-coupled product **7** could not be readily detected by ^{1}H NMR spectroscopy or GC/MS techniques. Thus the near exclusive formation of both **4** and **6** suggest that alkyl radicals from the corresponding alkyl halides are formed during the reaction.

The present study remains, to our knowledge, the first exploitation of an sp^3–sp^3 cross-coupling reaction between primary alkylmagnesium bromides and unactivated primary alkyl bromides. Although further improvements should be realised for the secondary systems, the significance of this report should not be undermined. The potential scope for this transformation is tremendous and this report should provide the impetus for further development. The challenge is to understand the chemistry of these iron-catalysed cross-coupling reactions in order to enable further exploration of the scope and limitations of the reagents and substrates (structural and functional group tolerance).

Experimental Section

General Procedure for the Preparation of the Grignard Reagent

All apparatus must be thoroughly dried in a hot oven before use. A 2-necked round-bottomed flask equipped with a magnetic stirrer bar and a reflux condenser was evacuated and backfilled with argon repeatedly. This was followed by the addition of magnesium turnings (1.89 mmol). The magnesium turnings were covered with 2 mL of anhydrous diethyl ether which was removed *via* gentle vacuum, following which the Mg turnings were further dried under high vacuum with gentle heating. The flask was then backfilled with argon and anhydrous diethyl ether (2 mL) followed by a catalytic amount of iodine, and alkyl halide (1.35 mmol) were added. After approximately 2 min, the colour of the reaction mixture changed from brown to colourless. The reaction mixture was refluxed at 60 °C for 1 h following which the Grignard reagent was cooled to room temperature, after which the solution can either be filtered or cannulated under anhydrous conditions. The concentration of the Grignard reagent was determined by titration following the literature procedure.[9]

General Procedure for the Cross-Coupling Reactions

To a round-bottomed flask in a glove-box was added 3 mol% $Fe(OAc)_2$ and 6 mol% of ligand. The flask was evacuated and filled with argon (3 times) followed by the addition of anhydrous diethyl ether (1 mL). This was followed by the addition of 1.5 equivalents (0.68 mmol) of the Grignard reagent in diethyl ether (0.34 M)[9] and 0.45 mmol of the alkyl halide at room temperature. The reaction mixture was stirred for 15 min following which an internal standard was added to the reaction mixture and the reaction was quenched with 1 N HCl. The reaction mixture was diluted with pentane and analysed by gas chromatography (GC column: HP-5). The quantities of the products of the reaction were quantified using GC (relative to response curves with appropriate standards). In some cases, the products of the reaction were purified *via* column chromatography.

Acknowledgements

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