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Iron(III) Catalyzed Coupling of Aryl Halides: Synthesis of Terphenyl and Biphenyl Derivatives

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Abstract

Iron(III) mediated coupling of arylmagnesium halides with other aryl halides produced both homo- and cross-coupled products. The reaction of phenylmagnesium bromide with 1,4-dibromobenzene as well as with 4-chlorobromobenzene in presence of $FeCl_3$ catalyst produced both cross-coupled *p*-terphenyl and homo-coupled biphenyl. Under the same condition only homo-coupled 4,4′-dipropoxybiphenyl was obtained from 4-propoxyphenylmagnesium bromide. The coupling of 4-bromophenylmagnesium bromide with bromobenzene produced both homo- and cross-coupled biaryls.

Keywords: Coupling; Aryl halides; Terphenyl; Biphenyl.

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1. Introduction

Aryl-aryl bond formation is one of the most powerful tools in modern organic synthesis [1-4]. Biaryls as well as their heteroaromatic analogues are some of the attractive structural units in natural products, bio-active compounds, functional polymers, ligands in catalysts etc. For the synthesis of biaryls, transition-metal-mediated coupling reactions have been used in most cases. Palladium and nickel catalysts have been the major choice for aryl-aryl cross-coupling reactions and are widely used in the laboratory as well as in industry. Palladium(0) catalysts are reliably used [5-8], especially if appropriate ligands such as sterically hindered phosphines are present [9-12]. Nickel(0) complexes had also found useful applications, but appear to have less general scope [13-17].

Following the pioneering work of Kochi and co-workers [18-22] iron catalysts have recently been very actively investigated for their performance in cross-coupling reactions

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[23-29]. Because of competition of homo-coupling over cross-coupling, there remained a challenge of using iron-catalyst for aryl-aryl cross-coupling. Although highly efficient cross-coupling reactions could be realized between a range of alkyl magnesium reagents and aryl halides or aryl sulfonates, iron-catalyzed cross-coupling between two aryl moieties remained problematic owing to extensive homo-coupling reactions of the aryl magnesium species. Nakamura *et al*. reported a selective biaryl synthesis based on iron(III) fluoride catalyzed cross-coupling of aryl chlorides with aryl Grignard reagents where the fluoride ion remarkably suppresses the homocoupling in presence of additive like 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (SIPr.HCl) [30]. Very recently Knokhel and co-workers reported iron(III) bromide mediated coupling of N-heterocyclic chlorides and bromides with arylmagnesium bromide lithium chloride complex [31]. Herein, we report the formation of cross-coupled biaryls along with homo-coupled products through iron(III) chloride catalyzed reactions of aryl Grignard reagents and aryl halides without using any additives.

2. Experimental

2.1. *General*

Melting points were determined with Yanaco MP-500D melting point apparatus. NMR spectra were recorded on Bruker Biospin 500 spectrometer using tetramethylsilane as the internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP2010 spectrometer. All solvents were dried and purified by the usual techniques: tetrahydrofuran was distilled from benzophenone ketyl under a nitrogen atmosphere; *n*-hexane and dichloromethane were simply distilled without using any drying agent.

2.2. *General Procedure for the cross-coupling of arylmagnesium bromide and aryl halide (typical for coupling of phenylmagnesium bromide with 1,4-dibromobenzene)*

A solution of bromobenzene (785 mg, 5.0 mmol) in dry THF (3 mL) was added dropwise to a portion of Mg turnings (132 mg, 5.5 mmol) in dry THF (3 mL) under a nitrogen atmosphere at room temperature. Exothermic reaction started within few minutes. The reaction mixture was stirred at room temperature for 1.5 h to complete the formation of Grignard reagent. With the help of a syringe the Grignard reagent thus formed was transferred to a 50 mL two-necked round-bottomed flask under nitrogen atmosphere. A 5 mL portion dry THF was added to dilute the Grignard reagent and then it was cooled to 0 °C. Then anhydrous $FeCl_3$ (41 mg, 5 mol%) and 1,4-dibromobenzene (590 mg, 2.5 mmol) were added to the reaction mixture and was allowed to stand at room temperature. It was then stirred overnight to complete the reaction. Methanol (10 mL) was added followed by the addition of CH_2Cl_2 (20 mL) and water. The organic layer was separated and the aqueous layer was extracted with more CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed in a vacuum rotary evaporator to give a crude product. The crude was chromatographed on a silica gel column eluting with hexane to afford 218 mg (38%) of *p*-terphenyl as cross-coupled product and 65 mg (17%) of biphenyl as homo-coupled product.

p-Terphenyl **(5):** white solid, mp 211.0-212.0°C (lit [32] mp 210-211.5°C); EI MS: m/z 230 (M^+); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.68 (s, 4H), 7.65 (d, J = 7.8 Hz, 4H), 7.45 (t, J = 7.8 Hz, 4H), 7.36 (t, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 140.7, 140.1, 128.8, 127.5, 127.3, 127.0.

Biphenyl **(6)*:*** Colorless crystal, mp 69.0-70.0 °C (lit [33] mp 69.0-69.5 °C); EI MS m/z 154 (M^+); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.61 (d, J = 8.4 Hz, 4H), 7.45 (t, J = 7.8 Hz, 4H), 7.36 (t, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 141.2, 128.7, 127.2, 127.1.

2.2.1. *Coupling of 4-bromophenylmagnesium bromide with bromobenzene*

Starting materials and reagents used were 1,4-dibromobenzene (1.180 g, 5.0 mmol), Mg turnings (134 mg, 5.6 mmol), $FeCl_3$ (40 mg, 5 mol%) and bromobenzene (786 mg, 5.0 mmol). Products were 4,4′-dibromobiphenyl (47 mg, 8%), 4-bromobiphenyl (186 mg, 16%) and *p*-terphenyl (34 mg, 3%).

4,4′-Dibromobiphenyl **(8)*:*** Colorless crystal, mp 165.0-166. 0 °C (lit [34] mp 166.5-167.0°C); EI MS: m/z 310/312/314 (1:2:1) (M^+); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.56 (d, J = 8.4 Hz, 4H), 7.41 (d, J = 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 138.9, 132, 128.5, 121.9.

4-Bromobiphenyl **(7)*:*** White solid, mp 88.0-89.0°C (lit [35] mp 89.0-90.0°C); EI MS: m/z 232/234 (1:1) (M^+); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.60-7.51 (m, 4H), 7.48-7.36 (m, 4H), 7.35 (t, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 140.2, 140.0, 131.9, 128.9, 128.8, 127.6, 127.0, 121.6.

p-Terphenyl **(5)*:*** white solid, mp 211.0-212. 0 °C (lit [32] mp 210-211. 5 °C); EI MS: m/z 230 (M^+); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.68 (s, 4H), 7.65 (d, J = 7.8 Hz, 4H), 7.45 (t, J = 7.8 Hz, 4H), 7.36 (t, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 140.7, 140.1, 128.8, 127.5, 127.3, 127.0.

2.2.2. *Coupling of 4-propoxyphenylmagnesium bromide with 1,4-dibromobenzene*

Starting materials and reagents used were 4-propoxybromobenzene (1.075 g, 5.0 mmol), Mg turnings (132 mg, 5.5 mmol), $FeCl_3$ (40 mg, 5 mol%) and 1,4-dibromobenzene (592 mg, 2.5 mmol). Product is 4,4′-dipropoxybiphenyl (492 mg, 73%).

4,4′-Dipropoxybiphenyl **(9)*:*** White solid, mp 146-147 °C, EI MS: m/z 270 (M^+); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.46 (d, J = 8.8 Hz, 4H), 6.94 (d, J = 8.8 Hz, 4H), 3.95 (t, J = 6.6 Hz, 2H), 1.82 (sextet, J = 7.0 Hz, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 158.2, 133.3, 127.6, 114.7, 69.6, 22.6, 10.5.

2.2.3. *Coupling of phenylmagnesium bromide with 4-chlorobromobenzene*

Starting materials and reagents used were bromobenzene (786 mg, 5.0 mmol), Mg turnings (130 mg, 5.4 mmol), $FeCl_3$ (42 mg, 5 mol%) 1-bromo-4-chlorobenzene (480 mg, 2.5 mmol) Products were *p*-terphenyl (58 mg, 10%), biphenyl (181 mg, 47%).

p-Terphenyl* (5)*: white solid, mp 211.0-212.0 °C (lit [32] mp 210-211.5 °C); EI MS: m/z 230 (M^+); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.68 (s, 4H), 7.65 (d, J = 7.8 Hz, 4H), 7.45 (t, J = 7.8 Hz, 4H), 7.36 (t, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 140.7, 140.1, 128.8, 127.5, 127.3, 127.0.

Biphenyl* (6)*: Colorless crystal, mp 69.0-70.0 °C (lit [33] mp 69.0-69.5 °C); m/z 154 (M^+); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.61 (d, J = 8.4 Hz, 4H), 7.45 (t, J = 7.8 Hz, 4H), 7.36 (t, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 141.2, 128.7, 127.2, 127.1.

3. Results and Discussion

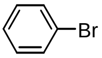
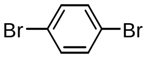
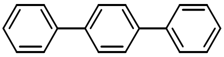
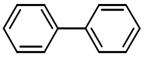
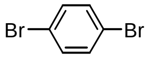
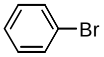
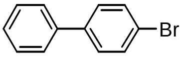
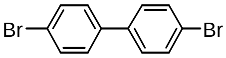
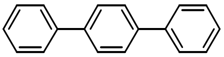
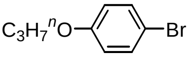
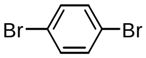
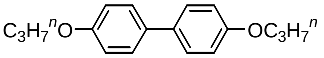
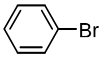
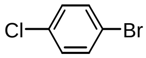
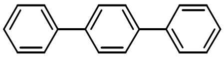
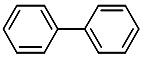
Iron-catalysts being environmentally friendly and inexpensive have been extensively studied for the carbon-carbon bond formation. Iron(III) catalysts are capable of forming ferrate complex possessing excess aryl groups with appropriate reagents. The reductive elimination of these complexes might lead to the formation of both homo- and or cross-coupled products under suitable conditions.

In the present study, cross-coupled biaryls are produced along with homo-coupled products during reactions between aryl Grignard reagent and aryl halides in presence of Fe(III) catalyst. All Grignard reagents were prepared from pure aryl bromides and activated Mg turnings in dry THF under nitrogen atmosphere. The Grignard reagents so produced were diluted with dry THF before addition of another aryl halide and $FeCl_3$ catalyst (5 mol%). The results of the coupling reactions are summarized in the Table 1.

The reaction of phenylmagnesium bromide with half-equivalent (0.5 equiv.) of 1,4-dibromobenzene **2** in presence of Fe(III) catalyst as well as in the absence of any additive produced the cross-coupled product *p*-terphenyl **5** as the major product along with homo-coupled product biphenyl **6**. However the Grignard reagent prepared from 1,4-dibromobenzene **2** and Mg turnings (1.1 equiv.), when coupled with bromobenzene **1** (1.0 equiv.), produced cross-coupled 4-bromobiphenyl **7** (16%), *p*-terphenyl **5** (3%) along with homo-coupled 4,4′-dibromobiphenyl **8** (8%). In this case, the Grignard reagent 4-bromophenylmagnesium bromide, which already contains a bromine atom in its *para* position, might produce mixture of *p*-oligophenyl derivatives under the reaction condition. The formation *p*-terphenyl **5** in this case can be explained by the coupling of di-Grignard derivative of 1,4-dibromobenzene (formed from excess Mg turnings) with bromobenzene **1**. The Grignard reagent from 4-propoxybromobenzene **3**, when treated with 1,4-dibromobenzene **2** (0.5 equiv.) in presence of iron catalyst produced only homo-coupled 4,4′-dipropoxybiphenyl **9** (73%). In this case, probably the electron donating alkoxy group in *para* position might accelerate the formation of ferrate complexes containing excess 4-propoxyphenyl group (such as Ar^1_4Fe, $Ar^1_3Ar^2Fe$ and $Ar^1_2Ar^2Fe$), which undergo reductive elimination to produce only the homo-coupled product. However, the coupling between phenylmagnesium bromide and 4-chlorobromobenzene **4** (0.5 equiv.) produced only 10% of the expected cross-coupled product *p*-terphenyl **5** along with homo-coupled biphenyl **6** (47%).

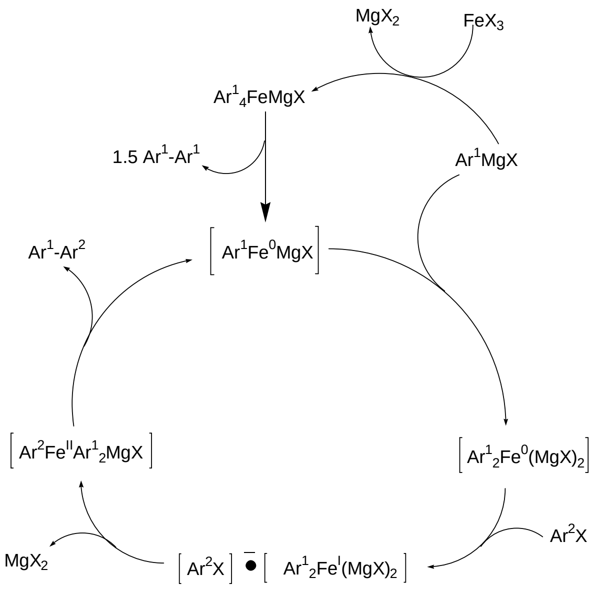
Table 1. Coupling of aryl halides using iron(III) catalyst.

$$Ar^1Br \xrightarrow[THF]{Mg} Ar^1MgBr \xrightarrow[FeCl_3,\ 0\ ^oC - rt]{Ar^2Br} Ar^1{-}Ar^2 + Ar^1{-}Ar^1$$

Entry	Ar^1Br	Ar^2Br^a	Products
1	 **1**	 **2**	 **5** (38%)  **6** (17%)
2	 **2**	 **1**	 **7** (16%)  **8** (8%)  **5** (3%)
3	 **3**	 **2**	 **9** (73%)
4	 **1**	 **4**	 **5** (10%)  **6** (47%)

[a] In entry 1, 3 and 4 dihalobenzenes were used 0.5 equivalent in each case.

In a plausible catalytic cycle (Scheme 1) an addition of Fe(III) to an arylmagnesium halide to form a tetrakis(aryl)iron(III) intermediate is involved. This then undergoes reduction, losing two aryl groups as the homo-coupled product, and forms aryliron(0). Addition of one equivalent arylmagnesium halide forms a low-valent, Fe^0 species which serves as a reductant for the other aryl halide substrate. This forms an aryl radical and an open-shell Fe^I radical which rapidly combines to create a tris(aryl)iron(II) species having two different kinds of aryl moieties. This then undergoes reductive elimination to yield the cross-coupled product and regenerate the active catalyst complex.



Scheme 1. Plausible mechanism for the iron(III) catalyzed coupling reaction

4. Conclusion

In summary, iron(III) chloride catalyzed coupling of aryl Grignard reagents with aryl halides produced both homo- and cross-coupled products. Coupling of phenylmagnesium bromide with half-equivalent of either 1,4-dibromobenzene or 1-bromo-4-chlorobenzene in presence of iron(III) catalyst produced both cross-coupled *p*-terphenyl and homo-coupled biphenyl. Only homo-coupled 4,4′-dipropoxybiphenyl was obtained from 4-propoxyphenylmagnesium bromide under the same condition. In this case, electron-donating propoxy group in *para* position might accelerate the formation of ferrate complexes containing excess aryl group that may undergo reductive elimination to produce only the homo-coupled product. The Grignard reagent prepared from 1,4-dibromobenzene and Mg turnings (1.1 equiv.) when coupled with bromobenzene produced cross-coupled 4-bromobiphenyl and *p*-terphenyl along with homo-coupled 4,4′-dibromobiphenyl.

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