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An unprecedented iron-catalyzed cross-coupling of primary and secondary alkyl Grignard reagents with non-activated aryl chlorides

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ABSTRACT

The use of N-heterocyclic carbene ligands in the iron-catalyzed cross-coupling of alkyl Grignards has allowed, for the first time, coupling of non-activated, electron rich aryl chlorides. Surprisingly, the tetrahydrate of FeCl₂ was found to be a better pre-catalyst than anhydrous FeCl₂. Primary Grignard reagents coupled in excellent yields while secondary Grignard reagents coupled in modest yields. The use of acyclic secondary Grignard reagents resulted in the formation of isomers in addition to the desired product. These isomeric products were formed via reversible β -hydrogen elimination, indicating that the crosscoupling proceeds through an ionic pathway.

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The search for catalysts which are capable of forming aryl-alkyl C-C bonds but are less expensive and more benign than palladiumbased catalysts has resulted in a significant body of work describing iron-catalyzed cross-coupling reactions utilizing both alkyl and aryl Grignard reagents.^{1,2} The cross-couplings of alkyl halides with aryl Grignard reagents have been demonstrated using simple iron salts as catalyst precursors in the presence of ligands including acac,¹¹ amines,^{1d,m} phosphines,^{1a} phosphites,^{1a} arsines,^{1a} N-hetero-cyclic carbenes,^{1a} and amine-bis(phenolates).^{1f} These catalytic systems allow for the couplings of primary and secondary alkyl halides including those containing β-hydrogens. Studies have shown that the cross-couplings of alkyl halides with aryl Grignard reagents occur through a radical-based mechanism.^{1a,o,q} The crosscouplings of aryl chlorides with alkyl Grignard reagents, on the other hand, have been shown to couple using simple iron salts as catalyst in the presence of additives such as N-methyl-2-pyrrolidone (NMP) via an ionic mechanism.^{10,3} These cross-couplings are highly efficient and rapid for primary alkyl Grignard reagents with activated, electron poor heteroaryl, and aryl chlorides, but chlorobenzene and more electron rich aryl chlorides do not couple. Moreover, secondary alkyl Grignard reagents failed to couple using simple iron salts, and only one example utilizing the reactive 2-chloropyridine with an iron-salen complex was reported in poor yield.^{2a} Heteroaryl sulfamates and phosphates⁴ as well as vinyl and aryl carboxylates⁵ have since been reported to participate in similar coupling reactions as those reported using aryl chlorides.

The development of cross-coupling reactions involving nonactivated aryl chlorides expands the scope of iron-catalyzed cross-coupling reactions, and the ability to couple secondary alkyl Grignard reagents through an ionic pathway would prove significant as it paves the way toward the development of an asymmetric variant. This paper describes the use of N-heterocyclic carbenes (NHC's) as ligands in the iron-catalyzed cross-coupling of non-activated aryl chlorides with primary and secondary alkyl Grignard reagents.

In order to test the viability of using N-heterocyclic carbenes as ligands in the iron-catalyzed cross-coupling of alkyl Grignard reagents and aryl chlorides, butylmagnesium chloride was added to THF solutions containing chlorobenzene, anhydrous FeCl₂ (5 mol %), and imidazolium chlorides or imidazolinium tetrafluoroborates (10 mol %). The imidazolium and imidazolinium salts were converted into the corresponding imidazol-2-ylidines and imidazolin-2-ylidines in situ upon reaction with the basic Grignard reagent. The different NHC's that were generated in situ and used in this study are shown in Scheme 1.

Reaction progress was followed by GC using naphthalene as an internal standard. All of the ligands tested resulted in some noticeable coupling, but ligand **2** (IPr), bearing the bulky diisopropylphenyl groups, gave the best overall result at 80% as shown in Scheme 2. We were delighted with these results as non-activated aryl chlorides like chlorobenzene have yet to be demonstrated in iron-catalyzed cross-coupling reactions with alkyl Grignard reagents.

Cross-coupling reactions using **2** and other alkyl Grignard reagents were then attempted, but the results were often variable,





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Scheme 2. Ligand screening.

2

3

4

5

6

80

14

24

66

12

THF. RT. 24h

especially when different batches of anhydrous FeCl₂ were used. Recently, Biscoe et al. reported that fresh anhydrous NiCl₂ did not perform as well in cross-coupling reactions involving tertiary alkyl Grignard reagents as NiCl₂ which had been exposed to lab air for some time.⁶ They found that it was necessary to have water present in order for the reaction to proceed efficiently and so they resorted to using NiCl₂·(H₂O)_{1.5} as the catalyst precursor. We decided to see if the same observations could be made in our iron-catalyzed cross-coupling. The reaction of *p*-chloroanisole with isobutylmagnesium chloride using 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (H-IPr) as a ligand precursor was chosen to test the effects of having water present as shown in Scheme 3. The tetrahydrate of FeCl₂ was found to be a superior catalyst in cross-couplings of alkyl Grignard reagents which is analogous to the observations made by Biscoe et al. utilizing NiCl₂: $(H_2O)_{1.5}$.

The cross-coupling of a series of alkyl Grignard reagents was then carried out with three non-activated aryl chlorides in THF at 70 °C using FeCl₂·(H₂O)₄ and H-IPr as catalyst and ligand precursors, respectively, (Table 1). Overall, two different methods were employed. In method A, all of the Grignard was added at once at





Table 1 Cross-coupling results



| Entry | R | Y | eq RMgCl | Time (h) | Method ^a | % Yield ^b |
|-------|------------|------------------|----------|----------|---------------------|----------------------|
| 1 | Isobutyl | Н | 2 | 0.5 | А | 87 |
| 2 | Isobutyl | Н | 3 | 0.5 | Α | 98 |
| 3 | Isobutyl | Н | 4 | 0.5 | Α | 95 |
| 4 | Isobutyl | Н | 6 | 0.5 | Α | 84 |
| 5 | Isobutyl | Н | 3 | 3 | Α | 92 ^c |
| 6 | Isobutyl | CH_3 | 3 | 1 | Α | 97 |
| 7 | Isobutyl | CH_3 | 3 | 3 | Α | 91 ^c |
| 8 | Isobutyl | OCH_3 | 3 | 2.5 | Α | 98 |
| 9 | Isobutyl | OCH_3 | 3 | 3 | Α | 86 ^c |
| 10 | Butyl | Н | 3 | 1 | Α | 96 |
| 11 | Butyl | Н | 3 | 3 | Α | 89 ^c |
| 12 | Butyl | CH_3 | 3 | 3 | Α | 89 |
| 13 | Butyl | CH_3 | 3 | 3 | Α | 81 ^c |
| 14 | Butyl | OCH_3 | 3 | 3 | Α | 83 |
| 15 | Butyl | OCH_3 | 4 | 3 | В | 88 |
| 16 | Butyl | OCH_3 | 3 | 3 | Α | 81 ^c |
| 17 | Propyl | Н | 3 | 3 | Α | 98 |
| 18 | Propyl | CH_3 | 3 | 3 | Α | 84 |
| 19 | Propyl | CH_3 | 4 | 3 | В | 94 |
| 20 | Propyl | OCH_3 | 3 | 3 | Α | 79 |
| 21 | Propyl | OCH_3 | 4 | 3 | В | 90 |
| 22 | Cyclohexyl | Н | 3 | 3 | Α | 58 |
| 23 | Cyclohexyl | Н | 4 | 3 | В | 65 |
| 24 | Cyclohexyl | CH_3 | 3 | 3 | Α | 47 |
| 25 | Cyclohexyl | CH_3 | 4 | 3 | В | 50 |
| 26 | Cyclohexyl | CH_3 | 4 | 19 | В | 50 |
| 27 | Cyclohexyl | OCH ₃ | 3 | 3 | А | 45 |
| 28 | Cyclohexyl | OCH ₃ | 4 | 3 | В | 43 |

^a In method A all of the Grignard is added at once at the beginning of the reaction, while in method B, half of the Grignard is added initially, and the other half is added after 1 h.

^b Yields determined by GC using naphthalene as an internal standard.

^c Isolated yield.

the beginning of the reaction, while in method B half of the Grignard was added initially and the second half was added after one hour. The cross-coupling of chlorobenzene with varying equivalents of isobutylmagnesium chloride demonstrated that using 3 equiv of Grignard relative to the aryl chloride gave the best results as shown in entries 1-4. A single addition of Grignard in excess of 3 equiv generally gave lower yields, but an improvement could be achieved by reacting the aryl chloride with 4 equiv of Grignard using method B when the use of 3 equiv of Grignard using method A gave yields below 85%. This improvement was observed in a number of cases throughout Table 1, but is exemplified by comparing entries 18 and 19. In general, primary Grignard reagents coupled in excellent yields for all three non-activated aryl chlorides including the challenging 4-chloroanisole.



Scheme 4. Formation of reduced arene.



Scheme 5. Cross-coupling of secondary alkyl Grignard reagents.

Gratifyingly, the secondary cyclohexyl Grignard coupled with all three aryl chlorides, although the yields were moderate (entries 22–28). It was found that reaction times longer than 3 h did not offer any improvement in the yields involving secondary alkyl Grignards (entries 25 and 26). Substantial amounts of the arene formed from reduction of the aryl chloride were observed in the couplings involving the cyclohexyl Grignard. A plausible explanation for the formation of the reduced arene is that a cyclohexylaryliron species undergoes reversible β -hydrogen elimination, producing an intermediate arylalkenylhydridoiron complex which, in turn, gives the arene upon reductive elimination as shown in Scheme 4.

We then attempted the coupling of isopropyl- and sec-butylmagnesium chloride with chlorobenzene in THF at 70 °C with the expectation that some of the isomeric *n*-propyl- and *n*-butylbenzene would be produced, thereby supporting the hypothesis that β -hydrogen elimination occurs during the coupling. The linear *n*alkyl isomers (L) were observed in both cases as shown in Scheme 5. This result is not surprising, as β -hydrogen elimination is known to occur in the coupling of secondary organometallics using other metal catalysts.⁷ Moreover, formation of the *n*-alkyl isomers indicates that the cross-coupling reaction occurs via an ionic mechanism since these isomers would not be expected in a radical-based reaction. In the couplings of both isopropyl- and secbutylmagnesium chloride, the desired branched isomer (B) was formed as the major product giving branched to linear ratios (B:L) greater than one. Increasing the equivalents of the Grignard reagent used improved the branched-to-linear ratios substantially at the expense of the yield. Although the yields of these cross-couplings were modest, the results are promising, considering that iron-catalyzed cross-couplings involving non-activated aryl chlorides were previously unreported and non-activated aryl chlorides have only recently been coupled with reasonable yields and branched to linear ratios using palladium.^{7a}

In conclusion, we report here the first iron-catalyzed cross-coupling of non-activated aryl chlorides with alkyl Grignard reagents. The bulky 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene **2** was found to function as the best ligand. Primary Grignard

reagents coupled in excellent yields while the use of secondary Grignard reagents resulted in significantly lower yields. Undesired *n*-alkyl isomers were formed in couplings involving acyclic secondary Grignard reagents, suggesting that reversible β -hydrogen elimination occurs in competition with the desired reductive elimination. Reversible β -hydrogen elimination can also explain the formation of reduced arenes in the couplings involving secondary alkyl Grignard reagents. Catalyst optimization for cross-coupling reactions involving secondary alkyl Grignard reagents allowing for asymmetric variants and further elucidation of the mechanistic details of these reactions will be the focus of future studies in our lab.

Representative cross-coupling procedure

1,3-Bis-(2,6-diisopropylphenyl)imidazoliumchloride (0.1 mmol, 10 mol %) was added to Vial 1 containing a stir bar which was then fitted with a septum. $FeCl_2(H_2O)_4$ (9.9 mg, 0.05 mmol, 5 mol %) was added to Vial 2 containing a stir bar which was then fitted with a septum. Both Vial 1 and Vial 2 were evacuated and backfilled with argon. Chlorobenzene (102 µL, 1 mmol) was then added via syringe to Vial 2. Freshly distilled THF (10.5 mL) was added via syringe to Vial 1, and isobutylmagnesium chloride (1.5 mL of a 2 M solution in THF, 3 mmol) was added with stirring. Vial 1 was placed in an oil bath at 70 °C and stirred for 10 min. Then the contents of Vial 1 were transferred to Vial 2 via syringe, and Vial 2 was placed in the oil bath at 70 °C. After 3 h, the reaction was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was poured into a separatory funnel followed by 15 mL of 1 M HCl and 15 mL of pentane. The pentane layer was washed with water $(1 \times 15 \text{ mL})$ and brine $(1 \times 15 \text{ mL})$. The pentane laver was dried over Na₂SO₄ and the solvent was removed in vacuo. The crude oil was purified by distillation resulting in a colorless oil (122 mg, 92%). ¹H NMR and GC-MS were consistent with known material.

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References and notes

- 1. (a) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danapoulos, A. A.; Frost, R. M.; Hird, M. J. Org. Chem 2006, 71, 1104-1110; (b) Bedford, R. B.; Betham, M.; Bruce, D. W.; Davis, S. A.; Frost, R. M.; Hird, M. Chem. Commun. 2006, 1398-1400; (c) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. Chem. Commun. 2004, 24, 2822-2823; (d) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. Chem. Commun. 2005, 4161-4163; (e) Bica, K.; Gaertner, P. Org. Lett. 2006, 8(4), 733-735; (f) Chowdhury, R. R.; Crane, A. K.; Fowler, C.; Kwong, P.; Kozak, C. M. Chem. Commun. 2008, 94-96; (g) Czaplik, W. M.; Mayer, M.; Grupe, S.; von Wangelin, A. J. Pure Appl. Chem. 2010, 82(7), 1545-1553; (h) Czaplik, W. M.; Mayer, M.; von Wangelin, A. J. Angew. Chem., Int. Ed. 2009, 48, 607-610; (i) Fürstner, A.; Krause, H.; Lehmann, C. W. Angew. Chem., Int. Ed. 2006, 45, 440-444; (j) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. J. Am. Chem. Soc. 2008, 130, 8773-8787; (k) Martin, R.; Fürsner, A. Angew. Chem., Int. Ed. 2004, 43, 3955-3957; (l) Nagano, T.; Hayashi, T. Org. Lett. 2004, 6(8), 1297-1299; (m) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. J. Am. Chem. Soc. 2004, 126, 3686-3687; (n) Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. J. Am. Chem. Soc. 2009, 131, 6078-6079; (o) Sherry, B. D.; Fürsner, A. Acc. Chem. Res. 2008, 41(11), 1500-1571; (p) Tamura, M.; Kochi, J. K. J. Am. Chem. Soc. 1971, 93(6), 1487-1489; (q) Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M. Org. Lett. 2012, 14(4), 1066-1069.
- (a) Fürstner, A.; Leitner, A. Angew. Chem., Int. Ed. 2002, 41(4), 609–612; (b) Fürstner, A.; Leitner, A. M. M.; Krause, H. J. Am. Chem. Soc. 2002, 124, 13856– 13863; (c) Seidel, G.; Laurich, D.; Fürstner, A. J. Org. Chem. 2004, 69, 3950–3952.

- (a) Kleimark, J.; Hedström, A.; Larsson, P.-F.; Johansson, C.; Norrby, P.-O. ChemCatChem 2009, 1, 152–161; (b) Kleinmark, J.; Larsson, P.-F.; Emamy, P.; Hedström, A.; Norrby, P.-O. Adv. Synth. Catal. 2012, 354, 448–456.
- Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. Org. Lett. 2009, 11(21), 4886–4888.
 Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. J. Am. Chem. Soc. 2009, 131, 14656–14657.
- Joshi-Pangu, A.; Wang, C.-Y.; Biscoe, M. R. J. Am. Chem. Soc. 2011, 133, 8478– 8481.
- (a) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. J. Am. Chem. Soc.
 2008, 130, 9257–9259; (b) Han, C.; Buchwald, S. L. J. Am. Chem. Soc. 2009, 131, 7532–7533; (c) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. J. Am. Chem. Soc. 1984, 106, 158–163; (d) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. J. Am. Chem. Soc. 1972, 94(26), 9268–9269.