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# Iron-Catalyzed, Directed Oxidative Arylation of Olefins with Organozinc and Grignard Reagents

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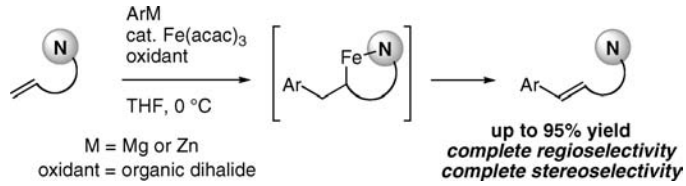
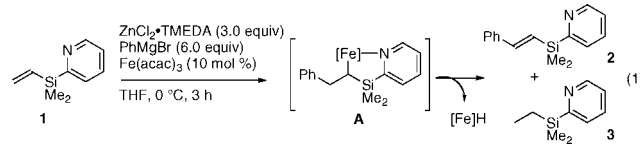
## ABSTRACT




**Chelation-controlled arylation of olefins with organozinc or Grignard reagents proceeds in the presence of an iron catalyst, under mild conditions and typically without the need of external ligands, to afford substituted olefins in high yield and with complete regio- and stereocontrol.**

The cross-coupling of olefins with organometallic reagents has recently emerged[1] as an attractive alternative to the Mizoroki−Heck reaction[2] to selectively construct polysubstituted olefins, compounds of interest for bioactive molecules and materials science. The catalyst of choice utilized so far for this "oxidative Heck" reaction was a late transition metal such as palladium or rhodium.[1] Iron is attracting much attention recently,[3] but its application for the Heck-type coupling of olefins has been largely neglected.[4] We report herein the iron-catalyzed arylation of olefins with organozinc and Grignard reagents, where we achieved complete regio- and stereoselectivity by designing the reaction to proceed through a putative ferracycle intermediate (such as **A** in eq 1).




On the basis of our previous work on pyridine- and imine-directed C−H bond activation,[5] we assumed that formation of a ferracycle such as **A** would facilitate addition of a phenyl

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(1) Selected examples: (a) Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 2424. (b) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270. (c) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980. (d) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, 5, 2231. (e) Martinez, R.; Voica, F.; Genet, J.-P.; Darses, S. *Org. Lett.* **2007**, *9*, 3213. (f) Hirabayashi, K.; Ando, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Synlett* **1999**, 99. (g) Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 7893. (h) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774.

(2) (a) Bräse, S.; de Meijere, A. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 5. (b) Heck, R. F. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(3) (a) *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, Germany, 2008. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (c) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (d) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (e) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Jacobi von Wangelin, A. *ChemSusChem* **2009**, *2*, 396. (f) Sarhan, A. A. O.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 2730. (g) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108.

(4) Loska, R.; Volla, C. M. R.; Vogel, P. *Adv. Synth. Catal.* **2008**, *350*, 2859.

(5) (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2975. (c) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Synlett* **2010**, 313.

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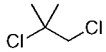
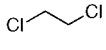
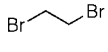
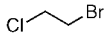
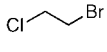
iron species[6,7] to 2-pyridyldimethylvinylsilane (**1**),[8,9] and following $\beta$-hydride elimination would afford a phenylated olefin **2** (eq 1). The reaction of **1** with diphenylzinc generated in situ from phenylmagnesium bromide and $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine)[10] in the presence of a catalytic amount of Fe(III) salt[11] afforded **2** as a single regio- and stereoisomer in moderate yield, together with reduced starting material **3**, and a trace amount of the reduction product of **2** (eq 1 and Table 1, entry 1). By

**Table 1.** Screening of Oxidants To Suppress the Formation of the Reduced Byproduct **3**[a]

| entry | oxidant | **2** (%)[b] | **3** (%)[b] |
|---|---|---|---|
| 1 | none | 37 | 39 |
| 2 |  | 41 | 39 |
| 3 |  | 43 | 48 |
| 4 |  | 70 | 1 |
| 5 |  | 76 | 11 |
| 6[c] |  | 92 (89) | 3 |
| 7 | $O_2$ | 51 | 20 |
| 8 |  | 72 | 6 |

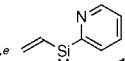
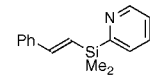
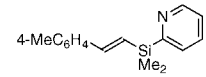
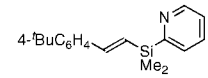
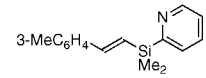
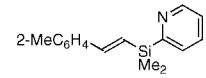
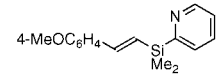
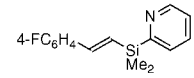
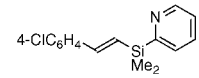
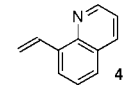
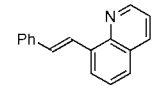
[a] Reaction of **1** (0.5 mmol) with $Ph_2Zn$ generated from $ZnCl_2$·TMEDA (3.0 equiv) and PhMgBr (6.0 equiv), in the presence of $Fe(acac)_3$ (10 mol %), oxidant (1.5−2.0 equiv) in THF at 0 °C for 3 h. [b] $^1H$ NMR yield. Isolated yield in parentheses. [c] Reaction performed at room temperature for 20 h.

comparison, substrates without a directing group (e.g., 1-octene, styrene, dimethylphenylvinylsilane), substrates possessing an oxygen-directing group (e.g., vinyl acetate), or substrates possessing a pyridine group unsuitable for forming a ferracycle (e.g., 2-vinylpyridine) did not react at all.

We assumed that the reduced byproduct **3** was formed from the reduction of **1** with an iron hydride species generated via $\beta$-hydride elimination of **A**, and hence we investigated several oxidants to suppress the formation of **3** (Table 1). 1,2-Dichloroisobutane, a compound we previously used to oxidize iron intermediate species,[5a,b] was not effective in this case (entry 2), nor was its linear congener, 1,2-dichloroethane (entry 3). The use of 1,2-dibromoethane significantly suppressed the reduction of **1** (entry 4), and 1-bromo-2-chloroethane was found to be an optimal oxidant (entry 5), allowing the formation of **2** in 92% NMR yield, when the reaction was performed at room temperature for 20 h (entry 6). Molecular oxygen could also be utilized, but it was less efficient (entry 7). Acetophenone also largely suppressed the reduction (entry 8).

With the optimized conditions in hand, we investigated the scope and limitations of the present reaction (Table 2).

**Table 2.** Iron-Catalyzed Directed Oxidative Arylation of Olefins with Organozinc and Grignard Reagents[a]

| entry | substrate | ArM | product[b] | yield (%)[c] |
|---|---|---|---|---|
| 1 |  **1** | $Ph_2Zn$ |  | 89 |
| 2[d,e] | | PhMgBr | | 70 |
| 3 | **1** | $(4\text{-}MeC_6H_4)_2Zn$ |  | 90 |
| 4 | **1** | $(4\text{-}^tBuC_6H_4)_2Zn$ |  | 86 |
| 5 | **1** | $(3\text{-}MeC_6H_4)_2Zn$ |  | 79 |
| 6 | **1** | $(2\text{-}MeC_6H_4)_2Zn$ |  | 39 |
| 7 | **1** | $(4\text{-}MeOC_6H_4)_2Zn$ |  | 71 |
| 8 | **1** | $(4\text{-}FC_6H_4)_2Zn$ |  | 54 |
| 9 | **1** | $(4\text{-}ClC_6H_4)_2Zn$ |  | 75 |
| 10 |  **4** | $Ph_2Zn$ |  | 68 |
| 11[d] | | PhMgBr | | 95 |

[a] Reaction conditions: starting material, $Ar_2Zn$ or PhMgBr (4.0 equiv), $Fe(acac)_3$ (10 mol %), 1-bromo-2-chloroethane (2.0 equiv) in THF at rt. [b] The product was obtained as a single regio- and stereoisomer. [c] Isolated yield. [d] 1,2-Dichloroisobutane was used as an oxidant. [e] $PPh_3$ (20 mol %) was used as a ligand.

Grignard reagents could also be utilized, albeit the yield was lower (entry 2). Both electron-rich (entries 3, 4, and 7) and electron-deficient (entries 8 and 9) organozinc reagents reacted with good yields, whereas sterically demanding

(6) (a) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050. (b) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621.

(7) (a) Yamagami, T.; Shintani, R.; Shirakawa, E.; Hayashi, T. *Org. Lett.* **2007**, *9*, 1045. (b) Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164. (c) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978.

(8) Itami, K.; Mitsudo, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2337.

(9) (a) Itami, K.; Mitsudo, K.; Kamei, T.; Koike, T.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 12013. (b) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577.

(10) The reaction did not proceed with pristine $Ph_2Zn$, and TMEDA played a beneficial role (Supporting Information).

(11) $Fe(acac)_3$ of various purities and anhydrous $FeCl_3$ gave similar results. Fe(II) salts could also be used. The reaction did not proceed in the absence of an iron salt (Supporting Information).

reagents gave lower yields (entry 6). It should be noted that the reaction proceeded with complete regio- and stereoselectivity, and in all cases, the product was obtained as a single *trans* isomer. Diarylated compounds were not observed in any cases, even when excess organometallic reagent was used.[12] The obtained compounds can be utilized as a versatile platform for further functionalization.[13]

8-Vinylquinoline also reacted smoothly to give the corresponding phenylated product in excellent yield and with complete selectivity, and in this case the Grignard reagent was higher yielding than the corresponding zinc reagent (entries 10 and 11). It should be noted that a product resulting from the addition of the Grignard reagent to quinoline in a 1,2-fashion[14] was not observed. Quinolines are a ubiquitous motif for natural products and bioactive compounds, such as antimalarial drugs.[15]

(12) Under these conditions, substituted olefins such as (*E*)-2-pyridyldimethyl-1-hexenylsilane did not react.

(13) (a) Itami, K.; Yoshida, J. *Synlett* **2006**, 157. (b) Itami, K.; Ohashi, Y.; Yoshida, J. *J. Org. Chem.* **2005**, *70*, 2778.

(14) For example: Goldstein, S. W.; Dambek, P. J. *Synthesis* **1989**, 221.

(15) Weissbuch, I.; Leiserowitz, I. *Chem. Rev.* **2008**, *108*, 4899.

In conclusion, we have developed an iron-catalyzed, chelation-controlled reaction of olefins with organozinc and Grignard reagents. This reaction proceeds with catalytic amounts of iron salt, typically without the need for expensive ligands, and affords a variety of olefin derivatives with perfect control of regio- and stereoselectivity. To the best of our knowledge, this is the first application of iron catalysis for an oxidative Heck-type reaction, which allows the use of organozinc reagents and Grignard reagents as a nucleophilic partner.

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**Supporting Information Available:** Experimental details and characterization of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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