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Iron-Catalyzed Stereospecific Activation of Olefinic C−H Bonds with Grignard Reagent for Synthesis of Substituted Olefins

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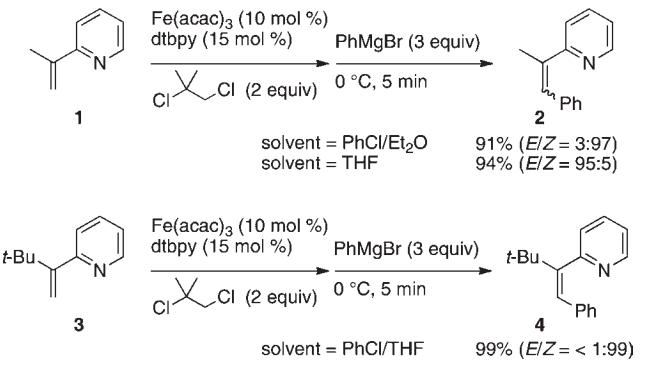
Supporting Information

ABSTRACT: The reaction of an aryl Grignard reagent with a cyclic or acyclic olefin possessing a directing group such as pyridine or imine results in the stereospecific substitution of the olefinic C−H bond syn to the directing group. The reaction takes place smoothly and without isomerization of the product olefin in the presence of a mild oxidant (1,2-dichloro-2-methylpropane) and an aromatic cosolvent. Several lines of evidence suggest that the reaction proceeds via iron-catalyzed olefinic C−H bond activation rather than an oxidative Mizoroki−Heck-type reaction.

Among numerous methods for the stereoselective synthesis of olefins,[1] an attractive but undeveloped methodology is the stereospecific substitution of a C−H bond, as represented by the stereoselective coupling of an olefin possessing a directing group with an aromatic compound bearing an electro- or nucleofugal group[2,3] or with alkene, alkyne, carbonyl, or carbon monoxide.[4] These recently reported reactions have been catalyzed by precious metals such as Ru, Rh, and Pd and require an elevated reaction temperature. The Mizoroki−Heck reaction[5] formally belongs to this class of reactions but lacks the stereospecificity, because of the intermediacy of a metal hydride species. We report herein a new synthetic transformation for the coupling of an aryl Grignard reagent with an olefin bearing a directing group such as pyridine or imine, in which a hydrogen atom syn to the directing group can be replaced stereospecifically with an aryl group (Scheme 1). Attractive features include the use of a catalytic amount of inorganic iron complex[6,7] and a convenient Grignard reagent, mild conditions (0 °C), and a short reaction time (<5 min). The reaction adds to the rapidly increasing repertoire of C−H bond activation reactions using a first-row group 8 or 9 metal as the catalyst.[8,9]

Scheme 1 describes the reaction conditions that allowed us to achieve the stereospecific arylation of an olefin, as illustrated by the reaction of 2-isopropenylpyridine (**1**) with 3 equiv of PhMgBr in the presence of 10 mol % $Fe(acac)_3$ and 15 mol % 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy). Application of the conditions that we previously developed[9a] for the iron-catalyzed C−H bond activation of 2-phenylpyridine with in situ-prepared Ph_2Zn resulted in a very slow and low-yielding reaction (see the Supporting Information) despite the use of a large amount of zinc halide (3 equiv) and Grignard reagent (6 equiv). Therefore, we carefully reoptimized[10] the catalytic system and found that slow addition (during 5 min) of a diethyl ether solution of PhMgBr (3 equiv) to a mixture of **1**, 1,2-dichloro-2-methylpropane

Scheme 1. Control of Selectivity in the Iron-Catalyzed Oxidative Phenylation of 1-Substituted Vinylpyridines



(2 equiv), $Fe(acac)_3$ (10 mol %), and dtbpy (15 mol %) in chlorobenzene afforded the syn-arylated product (*Z*)-**2** and its isomer (*E*)-**2** in 91% overall yield with an *E*:*Z* ratio of 3:97. It should be noted that 1 equiv of PhMgBr accepted the hydrogen atom removed from the olefin.[11] The dtbpy ligand and the slow addition of the Grignard reagent retarded the otherwise fast iron-catalyzed homocoupling of PhMgBr.[12] The ratio dropped to 10:90 (92% yield) when chlorobenzene was used as the solvent for the Grignard reagent, after solvent exchange from a solution of PhMgBr in THF. When THF was used for both the Grignard preparation and the coupling reaction, we predominantly obtained (*E*)-**2** (*E*:*Z* = 95:5) in 94% overall yield. To date we have been unable to introduce alkyl (methyl, *n*-butyl, or cyclohexyl) or alkenyl groups (vinyl, 2-propenyl, or 2-methylpropenyl) under the present conditions.

Without the 1,2-dichloro-2-methylpropane oxidant, the reaction was not catalytic in $Fe(acac)_3$, and olefin isomerization (see below) became the major reaction. The phenylation reaction took place only at the 2-position of the olefin. When the vinylpyridine substrate had a *tert*-butyl group at the 1-position (substrate **3**), the reaction was entirely syn-selective, giving **4** in 99% isolated yield.

The *Z*-selective formation of **2** and **4** when chlorobenzene was used as a cosolvent suggests that the C−H bond activation is intrinsically stereospecific. Indeed, as illustrated in Scheme 2, the reaction of PhMgBr with (*Z*)-2-(1-phenylprop-1-en-2-yl)pyridine [(*Z*)-**2**], which lacks the syn hydrogen atom, did not give any of the expected C−H bond activation product **5** but instead gave a trace amount of (*E*)-**2** because of in situ *E*/*Z* isomerization of the

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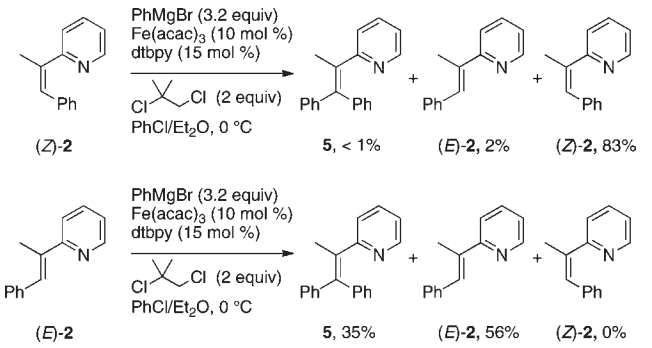
Scheme 2. Different Reactivities of the *Z* and *E* Isomers of 2



starting material. On the other hand, (*E*)-**2** gave the desired product **5** in 35% yield with no (*Z*)-**2**. The observed stereospecificity is a signature of C−H bond activation, as opposed to the expected lack of stereospecificity in the Heck-type reaction involving carbometalation and metal hydride elimination.

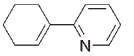
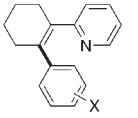
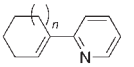
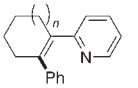
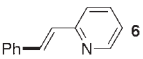
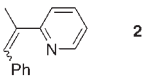
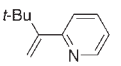
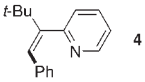
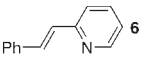
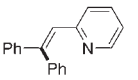
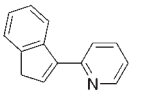
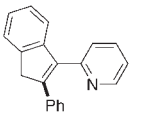
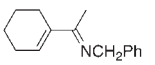
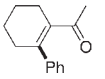
The in situ isomerization of (*Z*)-2-styrylpyridine [(*Z*)-**6**, 100% *Z*] was briefly probed using a 4-MeOC$_6$H$_4$MgBr reagent. A congener of **6** without a nitrogen atom [i.e., (*Z*)-stilbene] did not isomerize at all under the conditions in Scheme 1. Using (*Z*)-**6** and THF as the solvent under otherwise similar conditions, we obtained an E/Z mixture of 89:11, as opposed to the 42:58 ratio (100:0 with PhMgBr) obtained when chlorobenzene/THF was used. When we did not add the oxidant (1,2-dichloro-2-methylpropane), the *E*:*Z* ratio became 100:0, suggesting that a reduced iron species catalyzes the isomerization. Indeed, no isomerization took place in the absence of the Grignard reagent, which presumably serves as a reducing agent to generate a reactive iron species from Fe(acac)$_3$.

This low-valent iron species is not likely to be iron hydride, because we detected no hydrogenation products in any of the reactions reported here, even when the reaction was performed in the absence of an oxidant. This observation stands in contrast to a seemingly similar iron-catalyzed oxidative Heck reaction[13] that produces a large amount of reduced products unless suitable measures are taken. In the light of the stability of isolated iron−arene π complexes,[14] we speculate that the aromatic solvent acts as a ligand for the low-valent iron species, thereby inhibiting its interaction with the olefin product and thus the *E*/*Z* isomerization.

The scope of the arylation reaction is illustrated in Table 1. The reaction of 2-(cyclohex-1-en-1-yl)pyridine with phenyl (entry 1) and *p*-biphenyl (entry 2) Grignard reagents proceeded in quantitative yield. Aryl Grignard reagents possessing an electron-withdrawing (entries 3 and 7) or electron-donating (entries 4 and 5) group also reacted well. Meta-substituted Grignard reagents (entries 6 and 7) reacted in high yield, whereas ortho substitution suppressed the reaction (entry 8).

A variety of cyclic and acyclic olefins possessing a 2-pyridyl directing group took part in this reaction (entries 9−16). Cyclopentenyl to cycloheptenyl pyridines illustrate the generality (entries 1, 9, and 10). Notably, the reaction did not produce any of the olefin regioisomers known to form in the palladium-catalyzed Heck reaction of cyclohexene substrates.[15] 2-Vinylpyridine took part in the reaction, but the product was found to have isomerized in situ to an *E* isomer (entry 11). Careful monitoring of the reaction after 1, 3, and 5 min of addition of the Grignard reagent allowed us to observe the in situ isomerization quantitatively (*E*:*Z* = 35:65, 65:35, and 96:4, respectively). This isomerization

Table 1. Iron-Catalyzed Oxidative Arylation of Alkenylpyridines and Ketimines with Aryl Grignard Reagents[a]

entry	substrate	RMgBr	product	yield (%)[b] (*E*:*Z*)[c]
1		XC_6H_4MgBr		96 (X = H)
2				96 (X = 4-Ph)
3				85 (X = 4-F)
4				83 (X = 4-Me)
5				68 (X = 4-MeO)
6				91 (X = 3-Ph)
7				90 (X = 3-F)
8				0 (X = 2-Ph)
9		PhMgBr		88 (n = 0)
10		PhMgBr		87 (n = 2)
11		PhMgBr	 **6**	50 (96:4)
12[d]	 **1**	PhMgBr	 **2**	91 (3:97)
13[e]		PhMgBr		94 (95:5)
14	 **3**	PhMgBr	 **4**	99 (< 1:99)
15	 **6**	PhMgBr		40
16		PhMgBr		77[f]
17[g]		PhMgBr		85

[a] Reaction conditions: olefin (0.4 mmol), Fe(acac)$_3$ (10 mol %), dtbpy (15 mol %), and 1,2-dichloro-2-methylpropane (2 equiv) in PhCl with slow addition of PhMgBr in THF (3.2 equiv) at 0 °C over 5 min. [b] Isolated yield. The newly formed bond is shown in bold. [c] Determined by ^{1}H NMR analysis. [d] PhMgBr in Et$_2$O was used. [e] THF was used instead of PhCl. [f] 2-Phenyl-1-(2-pyridyl)indene was also obtained in 18% yield as an inseparable mixture with the desired product. [g] 4 equiv of PhMgBr was used. The imine product was hydrolyzed with HCl in THF/H$_2$O at 60 °C.

was suppressed by the presence of a substituent at the 1-position of the olefin, as discussed in Scheme 1. It is also notable that the product yield also increased as the 2-substituent became bulkier (from H to Me to *tert*-butyl; entries 11−14). A substituent at the 2-position of the olefin appeared to be unfavorable for the reaction (entry 15 and Scheme 2). An indene derivative, of recent interest for materials science,[16] could also be employed as the starting material (entry 16).

Unsaturated imines also took part in this reaction. Under similar conditions, an *N*-benzyl cyclic ketimine (entry 17) was smoothly arylated, and after hydrolysis, the corresponding unsaturated ketone was obtained in high yield. The imines derived from substituted anilines and alkylamines served as modest directing groups, while an *N*-diphenylphosphinylimine gave none of the desired product (see the Supporting Information). Acyclic ketimines reacted sluggishly (<20% yield) under these conditions.

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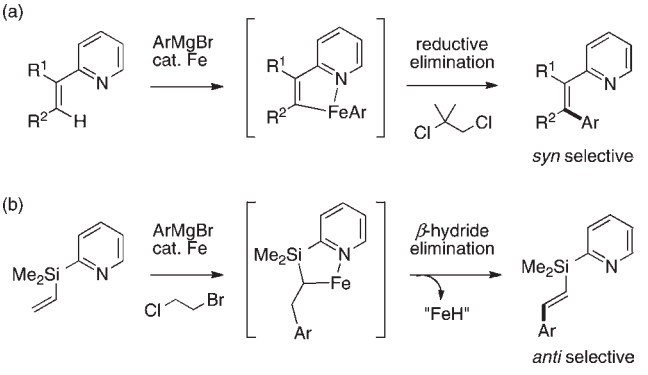
Scheme 3. Different Reaction Pathways: (a) C−H Bond Cleavage Followed by Reductive Elimination (This Reaction) and (b) Carbometalation Followed by β-Hydride Elimination[13]



It may be useful to consider briefly the reaction mechanism, although the whole catalytic cycle appears to be too complex to be studied at this time. On the basis of the necessary presence of a directing nitrogen group and the favorable effects of the 1-substituent illustrated in Scheme 1, we surmise that the reaction involves a five-membered metallacycle resulting from C−H bond activation (Scheme 3a) and that this intermediate then undergoes reductive elimination, perhaps after interaction with 1,2-dichloro-2-methylpropane, to give the syn-substituted olefin. The oxidative Heck reaction that we reported recently (Scheme 3b)[13] formally resembles the present reaction; however, it is mechanistically different. Thus, the addition of an aryliron species to the olefinic bond generates a five-membered metallacycle, which undergoes β-hydride elimination to produce the desired product (as the sterically more stable *E* isomer) together with an iron hydride species. The latter competitively reduces the starting material or the product, which was the major side reaction. Such reductive products were never detected in the present reaction, even when an oxidant was not present. We therefore consider that the C−H bond activation reported here and the oxidative Heck reaction are different reactions. The lack of regioisomeric olefinic products in entries 1−10 (which are inherent in the Heck-type reaction)[15] and the fact that only the (*E*)-**2** isomer was arylated (Scheme 2) also suggest that the present reaction does not involve the Heck-type carbometalation/β-hydride elimination mechanism.

In conclusion, we have developed a directed substitution reaction of an olefinic C−H bond with Grignard reagents using iron catalysis under very mild conditions. The reaction takes place in a syn-specific manner; however, the product may be allowed to isomerize to the more stable isomer when possible. To our knowledge, this is the first report of an iron-catalyzed olefin functionalization via stereospecific C−H bond activation. In view of the recent rush of reports on iron- and cobalt-catalyzed C−H bond activation reactions,[8,9] we suspect that the first-row transition metals will soon secure an important position in C−H bond activation chemistry, where only precious metals have played the dominant role in the past decades.[17,18]

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and physical properties of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698–4745. (b) Negishi, E.-i.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474–1485.

(2) (a) Oi, S.; Sakai, K.; Inoue, Y. *Org. Lett.* **2005**, *7*, 4009–4011. (b) Ackermann, L.; Born, R.; Álvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364–6367. (c) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836. (d) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115–6124. (e) Kim, M.; Kwak, J.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8935–8939. (f) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035.

(3) (a) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355–5357. (b) Zhou, H.; Chung, W.-J.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2009**, 3472–3474.

(4) For selected examples, see: (a) Fujii, N.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 939–940. (b) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *Chem. Commun.* **1996**, 585–586. (c) Chatani, N.; Kamitani, A.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7014–7018. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 5604–5605. (e) Kuninobu, Y.; Fujii, Y.; Matsuki, T.; Nishina, Y.; Takai, K. *Org. Lett.* **2009**, *11*, 2711–2714.

(5) (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 5. (b) Heck, R. F. In *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*, 3009–3066. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.

(6) (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*, 6217–6254. (c) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317–3321. (d) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511. (e) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Jacobi von Wangelin, A. *ChemSusChem* **2009**, *2*, 396–417.

(7) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061–6067.

(8) (a) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293–1314.

(9) (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928. (c) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Synlett* **2010**, 313–316. (d) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568–5569. (e) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428–429. (f) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221–5223.

(10) The reaction proceeded with comparable yield using various Fe(II) and Fe(III) salts having different purities. The presence of the iron catalyst and of the diamine ligand was mandatory. Without the oxidant, the reaction was stoichiometric in iron, and no reduction of the double bond was observed. See the Supporting Information for details.

(11) The amount of PhMgBr could be reduced to 2.4 equiv without an appreciable decrease in yield (73%).

(12) (a) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943–1946. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491–493.

(13) Ilies, L.; Okabe, J.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2010**, *12*, 2838–2840.
(14) (a) Bart, S. C.; Hawrelak, E. J.; Lobkovsky, E.; Chirik, P. J. *Organometallics* **2005**, *24*, 5518–5527. (b) Radonovich, L. J.; Eyring, M. W.; Groshens, T. J.; Klabunde, K. J. *J. Am. Chem. Soc.* **1982**, *104*, 2816–2819.
(15) For example, see: Hartung, C. G.; Köhler, K.; Beller, M. *Org. Lett.* **1999**, *1*, 709–711.
(16) Zhu, X.; Mitsui, C.; Tsuji, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 13596–13597.
(17) *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005.
(18) Nakamura, E.; Sato, K. *Nat. Mater.* **2011**, *10*, 158–161.