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Iron-Catalyzed Cross-Coupling of Alkenyl Sulfides with Grignard Reagents

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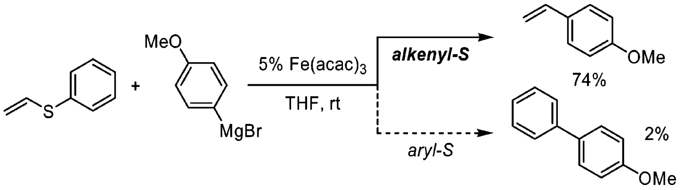
ABSTRACT



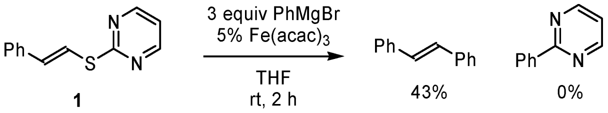
The iron-catalyzed cross-coupling reaction of alkenyl sulfides with Grignard reagents is described. While the cross-coupling proceeds efficiently at alkenyl–S bonds, almost no cross-coupling takes place at aryl–S bonds, attesting to a unique selectivity of iron catalysis. The beneficial effect of potentially coordinating 2-pyrimidyl group on sulfur is also described.

The transition-metal-catalyzed cross-coupling reactions are undoubtedly one of the most versatile and efficacious carbon−carbon bond-forming reactions, and the development of improved catalysts and reagents continues to evolve at a rapid pace.[1] During the past three decades of extensive worldwide research, palladium or nickel has emerged as a favorite among transition metals. While recently discovered active Pd and Ni catalysts have substantially broadened the scope of coupling components (both donors and acceptors),[2] we felt that the search for alternative transition metals that effect these useful processes would be also important from both scientific and practical (environmental) points of view.

Iron is extremely interesting in this regard because it is the most abundant metal after aluminum in the earth's crust (5%) and, hence, much cheaper than palladium and nickel. In 1971, Kochi and Tamura reported iron-catalyzed effective substitution reaction of alkenyl halides with Grignard reagents as a first example of effective cross-coupling of an sp^2 carbon electrophile.[3] Since this pioneering work, reports on iron-catalyzed cross-coupling have appeared in the literature,[4] including extensive studies by the Fürstner group where aryl chloride and tosylate can be coupled with Grignard reagents.[4v,w,y] Moreover, Nakamura, Hayashi, and Fürstner discovered very recently that iron salts can serve as efficient catalysts for the "hard-to-achieve" cross-coupling reaction using alkyl halides, which represents an important advance in cross-coupling chemistry.[5]

During the course of our investigation using alkenyl 2-pyrimidyl sulfides in multisubstituted olefin synthesis,[6,7] we found that the cross-coupling between styryl 2-pyrimidyl sulfide (**1**) and PhMgBr proceeded smoothly under the influence of Fe(acac)$_3$ catalyst at room temperature to give *trans*-stilbene in 43% yield (Scheme 1). The cross-coupling did not take place at the 2-pyrimidyl−S bond.[8] Nevertheless, this is the first example of iron-catalyzed cross-coupling reaction using alkenyl sulfides. In view of the apparent significance of iron catalysis, we set out to investigate the

Scheme 1



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(1) (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) *Cross-Coupling Reactions*; Miyaura, N., Ed.; Topics in Current Chemistry Vol. 219; Springer: New York, 2002.

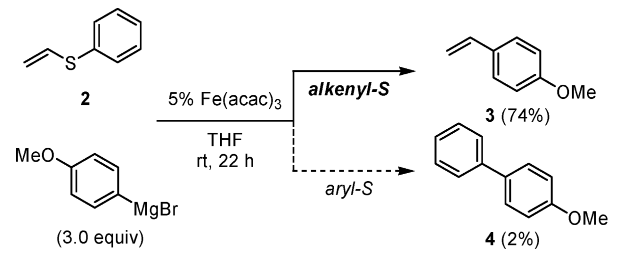
(2) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (b) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384.

10.1021/ol047504c CCC: $30.25

iron-catalyzed cross-coupling using alkenyl sulfides as coupling components.[9]

To examine whether the 2-pyrimidyl group is essential or not in this cross-coupling, phenyl vinyl sulfide (**2**) was treated with *p*-$MeOC_6H_4MgBr$ (3.0 equiv) in the presence of $Fe(acac)_3$ (5 mol %) in THF at room temperature (Scheme 2). After usual workup, we found that *p*-methoxystyrene **3** is exclusively produced in this reaction (74% yield). 4-Methoxybiphenyl **4** (product derived from the cross-coupling at the phenyl−S bond) was obtained only in 2% yield as judged by GC and NMR analysis.

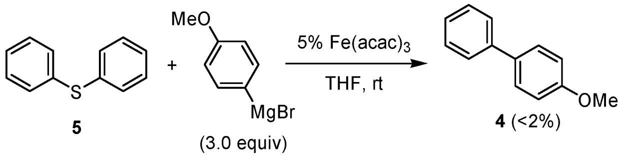
Scheme 2



As for catalyst precursor, $FeCl_3$, $FeCl_2$, and $Fe(OAc)_2$ can also be used in this cross-coupling, albeit in somewhat lower yields. In all cases examined, **3** was exclusively produced. The organozinc reagents were found not to be applicable in this cross-coupling. The addition of coordinating additives such as TMEDA (*N*,*N*,*N′*,*N′*-tetramethylethylenediamine), 2,2′-bipyridyl, and 1-methyl-2-pyrrolidinone (NMP), which exert beneficial effects in the reported iron catalysis only had detrimental effects in this cross-coupling.

The control experiment using diphenyl sulfide (**5**) undoubtedly corroborated that the iron-catalyzed cross-coupling at aryl−S bond is extremely sluggish (Scheme 3). This is in a sharp contrast to the usual Pd− or Ni-catalyzed processes where both alkenyl and aryl compoments can participate in cross-coupling. The emergence of such bond selectivity (alkenyl-S ≫ aryl-S) is extremely intriguing not only from a mechanistic point of view but also from a synthetic point of view.

Scheme 3



Next, we examined the cross-coupling of **2** with several Grignard reagents to roughly grasp the scope of this new cross-coupling procedure (Table 1).[10] As already mentioned, the reaction with *p*-$MeOC_6H_4MgBr$ proceeded smoothly to give *p*-methoxystyrene in 74% yield (entry 1). On the other hand, the reactions using *m*-$MeOC_6H_4MgBr$ and *o*-$MeOC_6H_4MgBr$ furnished the cross-coupling products in much lower yields (entries 2 and 3). Unfortunately, alkynyl Grignard reagents were not applicable in this cross-coupling (entry 4). However, the use of alkyl Grignard reagent ($C_{12}H_{25}MgBr$)

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(3) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Tamura, M.; Kochi, J. K. *Synthesis* **1971**, 303. (c) Tamura, M.; Kochi, J. *J. Organomet. Chem.* **1971**, *31*, 289. (d) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (e) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502. (f) Kwan, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 4903. (g) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351.

(4) Alkenyl halides/Grignard reagents: (a) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449. (b) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199. (c) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901. (d) Fakhfakh, M. A.; Franck, X.; Hocquemiller, R.; Figadère, B. *J. Organomet. Chem.* **2001**, *624*, 131. (e) Hölzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732. Alkenyl halides/organolithium reagents: (f) Walborsky, H. M.; Banks, R. B. *J. Org. Chem.* **1981**, *46*, 5074. Alkenyl halides/organomanganese reagents: (g) Cahiez, G.; Marquais, S. *Tetrahedron Lett.* **1996**, *37*, 1773. (h) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53. (i) Fürstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009. Alkenyl sulfones/Grignard reagents: (j) Fabre, J. L.; Julia, M.; Verpeaux, J. N. *Tetrahedron Lett.* **1982**, *23*, 2469. (k) Alvarez, E.; Cuvigny, T.; du Penhoat, C. H.; Julia, M. *Tetrahedron* **1988**, *44*, 111. (l) Alvarez, E.; Cuvigny, T.; du Penhoat, C. H.; Julia, M. *Tetrahedron* **1988**, *44*, 119. Acyl halides/Grignard reagents: (m) Percival, W. C.; Wagner, R. B.; Cook, N. C. *J. Am. Chem. Soc.* **1953**, *75*, 3731. (n) Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. *Tetrahedron Lett.* **1984**, *25*, 4805. (o) Ritter, K.; Hanack, M. *Tetrahedron Lett.* **1985**, *26*, 1285. (p) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053. (q) Dell′Anna, M. M.; Mastrorilli, P.; Nobile, C. F.; Marchese, G.; Taurino, M. R. *J. Mol. Catal. A: Chem.* **2000**, *161*, 239. (r) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700. Thioesters/Grignard reagents: (s) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 3595. Allylic phosphates/Grignard reagents: (t) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 513. (u) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017. Aryl halides (triflates)/Grignard reagents: (v) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (w) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (x) Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 3547. (y) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (z) Hocek, M.; Hocková, D.; Dvřáková, H. *Synthesis* **2004**, 889.

(5) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (b) Nagao, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. (c) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. See also: (d) Brinker, U. H.; König, L. *Chem. Ber.* **1983**, *116*, 882. (e) Nishii, Y.; Wakasugi, K.; Tanabe, Y. *Synlett* **1998**, 67. (f) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822.

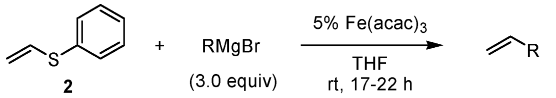
(6) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778.

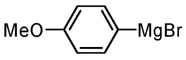
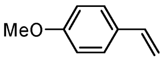
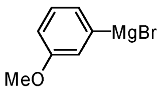
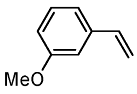
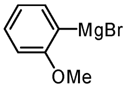
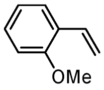
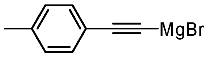
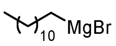
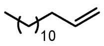
(7) For our related works on multisubstituted olefin synthesis, see: (a) Itami, K.; Mitsudo, K.; Kamei, T.; Koike, T.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 12013. (b) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600. (c) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577. (d) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (e) Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3695. (f) Itami, K.; Tonogaki, K.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 4093.

(8) This observation is in line with the finding of Fürstner that cross-coupling took place at the pyrimidyl−Cl bond rather than pyrimidyl−S bond when 4-chloro-2-methylthiopyrimidine was treated with Grignard reagent in the presence of $Fe(acac)_3$ catalyst.[4w]

(9) There are many reports on nickel- or palladium-catalyzed cross-coupling reaction using sulfides. For early works, see: (a) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. (b) Wenkert, E.; Ferreira, T. W.; Michelotti, *J. Chem. Soc., Chem. Commun.* **1979**, 637. (c) Takei, H.; Miura, M.; Sugimura, H.; Okamura, H. *Tetrahedron Lett.* **1979**, 1447. (d) Okamura, H.; Takei, H. *Tetrahedron Lett.* **1979**, 3425. For a review, see: (e) Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1990**, 89. For recent examples, see: (f) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189. (g) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449. (h) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (i) Savarin, C.; Srogl, J. Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229. (j) Angiolelli, M. E.; Casalnuovo, A. L.; Selby, T. P. *Synlett* **2000**, 905. (k) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2002**, *43*, 1039. (l) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (m) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Synlett* **2002**, 447. (n) Reference 6.

Table 1. Iron-Catalyzed Cross-Coupling of **2** with Various Grignard Reagents



entry	RMgBr	product	yield (%)[a]
1			74 (66)
2			40
3			11
4		-	0
5			65

[a] Determined by GC and NMR analysis using an internal standard. The number in parentheses is the isolated yield.

resulted in the production of 1-tetradecene in 65% yield (entry 5). Overall, the efficiency of this newly developed cross-coupling reaction was found to be highly dependent on Grignard reagents employed.

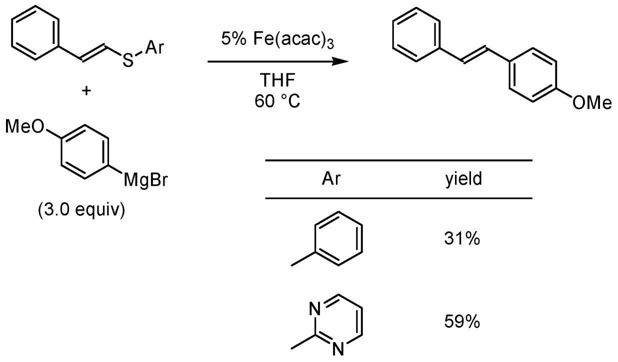
Although detailed study has not been conducted at present, the mechanism of this newly developed iron-catalyzed cross-coupling using alkenyl sulfides is of great interest. In the related cross-coupling using alkenyl halides, Kochi has proposed a mechanism based on oxidative addition of alkenyl halide to Fe(I) followed by transmetalation with Grignard reagent and reductive elimination.[3e] Very recently, Fürstner has proposed an alternative mechanism based on Fe(II)/Fe(0) cycle for iron-catalyzed cross-coupling of aryl halides with Grignard reagents.[4w] Although it might be possible to assume that the cross-coupling described herein proceeds through a mechanism similar to either of these mechanisms, we feel that it is not necessarily easy to explain the observed bond selectivity (alkenyl−S ≫ aryl−S) with such mechanisms. In nickel- and palladium-catalysis, cross-coupling reactions are known to take place at both alkenyl−S and aryl−S bonds.

As an alternative to these mechanisms, we surmise that an addition/elimination mechanism might be also possible. Thus, organoiron species generated by the reaction between iron salts and Grignard reagents undergoes carbometalation across C═C bond of alkenyl sulfides to give β-phenylthio-substituted organoiron species, which undergoes 1,2-elimination of PhS−[Fe] species to afford the cross-coupling products (olefins). The transmetalation of PhS−[Fe] species with Grignard reagents regenerates organoiron species to complete a catalytic cycle.[11,12]

This addition/elimination mechanism explains the aforementioned alkenyl-S bond selectivity easier than those described above. However, we must stress that these discussions are purely speculative with no evidence. Clearly, more experimental data must be accumulated to elucidate the mechanism.

In addition to the Grignard reagents employed (Table 1), it was found that the structure of alkenyl sulfides also affect the efficiency of the present iron-catalyzed cross-coupling (Scheme 4). For example, the use of styryl phenyl sulfide in place of vinyl phenyl sulfide as coupling partner resulted in the substantial decline in cross-coupling efficiency (74% → 31%; Schemes 2 and 4). However, the yield was substantially increased when the phenyl group of styryl phenyl sulfide was replaced with the 2-pyrimidyl group (31% → 59%; Scheme 4).[13] Although the beneficial effect of 2-pyrimidyl group on sulfur has not been clearly understood yet, we presume that the 2-pyrimidyl group might be acting as a directing group to a certain iron species to help the reacting C═C bond to coordinate to iron through complex-induced proximity effect.[14]

Scheme 4



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(10) **Typical Procedure.** To a mixture of Fe(acac)$_3$ (17.7 mg, 0.05 mmol) and phenyl vinyl sulfide (**2**; 135.5 mg, 1.0 mmol) in dry THF (1.0 mL) was slowly added a solution of *p*-MeOC$_6$H$_4$MgBr (3.0 mmol, 0.5 M) in THF at −78 °C under argon. The resultant mixture was further stirred at room temperature for 21 h. The yield of *p*-methoxystyrene was determined to be 74% as judged by GC analysis using *n*-pentadecane as an internal standard. Usual aqueous workup followed by purification by gel permeation chromatography (CHCl$_3$) afforded *p*-methoxystyrene (88.2 mg, 66%) as a pale yellow oil. All products listed in Table 1 exhibited spectral data in agreement with literature values.

(11) Such an addition/elimination sequence has been proposed for the reaction of organocopper reagents with β-alkylthio-substituted α,β-unsaturated carbonyl compounds. (a) Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 1027. (b) Posner, G. H.; Brunelle, D. J. *J. Org. Chem.* **1973**, *38*, 2747. (c) Posner, G. H.; Brunelle, D. J. *J. Chem. Soc., Chem. Commun.* **1973**, 907. (d) Gammill, R. B.; Bryson, T. A. *Tetrahedron Lett.* **1975**, 3793.

(12) There are some reports on the iron-catalyzed addition reactions (carbometalation) of organometallic reagents across alkenes and alkynes. (a) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (b) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373. (c) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621.

(13) Styryl 2-pyrimidyl sulfide was prepared by the Mizoroki-Heck-type arylation of vinyl 2-pyrimidyl sulfide with iodobenzene under the influence of Pd[P(t-Bu)$_3$]$_2$ catalyst and triethylamine (99% yield).[6]

In summary, we found the iron-catalyzed cross-coupling of alkenyl sulfides with Grignard reagents. Aryl and alkyl Grignard reagents are applicable in this cross-coupling. While the cross-coupling proceeds efficiently at alkenyl−S bonds, almost no cross-coupling takes place at aryl−S bonds, attesting to a unique selectivity of iron catalysis. In connection with these results, an addition/elimination mechanism has been proposed as a possible alternative to the generally accepted cross-coupling mechanism.

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Note Added after ASAP Publication. The journal title in ref 4z was incorrectly listed as *Synlett*, not *Synthesis*, in the version published ASAP March 8, 2005; the correct version was published March 9, 2005.

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(14) For reviews on directed chemical reactions: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (d) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (e) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.