

Iron-Catalyzed Doyle–Kirmse Reaction of Allyl Sulfides with (Trimethylsilyl)diazomethane

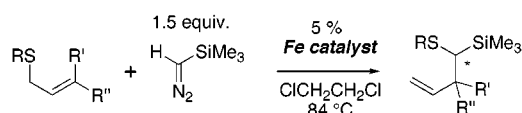
David S. Carter and David L. Van Vranken*

Department of Chemistry, University of California, Irvine, California 92697-2025

dlvanvra@uci.edu

Received February 29, 2000

ABSTRACT



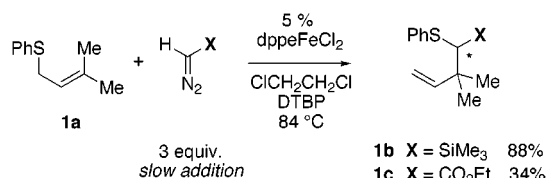
Iron salts efficiently catalyze the Doyle–Kirmse reaction of allyl sulfides with (trimethylsilyl)diazomethane and ethyl diazoacetate in dichloroethane at 83 °C. Competitive dimerization is less of a problem with (trimethylsilyl)diazomethane than with ethyl diazoacetate. Good results are obtained using only 1.5 equiv of (trimethylsilyl)diazomethane, even without slow addition. Phosphine ligands affect the kinetics, but not the diastereoselectivity. Dppe and BINAP lead to higher yields than dppp, but no enantioselection was detected with *R*(+)-BINAP.

Iron is one of the premier transition metals for biological catalysis, but in organic synthesis iron plays a diminutive role relative to metals such as palladium, rhodium, and ruthenium, especially for carbon–carbon bond forming reactions. The most common homogeneous iron catalysts have undesirable properties. For example, iron porphyrins¹ are difficult to modify, while cyclopentadienyl iron complexes² are often unstable when exposed to air. Recently, simple iron catalyst precursors have found application in carbon–carbon bond forming reactions, for example, the Fe(acac)₃-catalyzed coupling of Grignard reagents and vinyl halides.³

The Doyle–Kirmse reaction of allyl sulfides and diazo compounds is a powerful method for C–C bond formation, presumably involving metal carbenoid intermediates.⁴ A variety of metals catalyze the Doyle–Kirmse reaction, notably rhodium, copper, and cobalt, but the corresponding

iron-catalyzed process is unknown. The recently reported iron-catalyzed nitrene transfer to sulfides and sulfoxides is an essential precedent for the corresponding Doyle–Kirmse reaction.⁵ The following work demonstrates the efficacy of simple iron complexes as catalyst precursors for the Doyle–Kirmse reaction of allyl sulfides. When the Doyle–Kirmse

Scheme 1



reaction was carried out using commercially available dppeFeCl₂, the reaction was found to proceed efficiently with (trimethylsilyl)diazomethane (TMSD) but not with ethyl diazoacetate (Scheme 1). This is the first example of iron catalysis of the Doyle–Kirmse reaction.

(1) Wolf, J. R.; Hamaker, C. G.; Djukic, J. P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

(2) Mahmood, S. J.; Saha, A. K.; Hossain, M. M. *Tetrahedron* **1998**, *54*, 349.

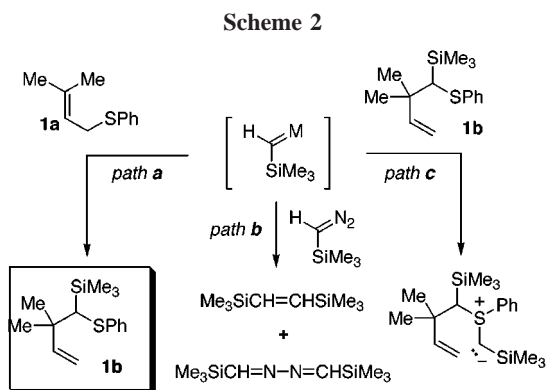
(3) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.

(4) (a) Kirmse, W.; Kapps, M. *Chem. Ber.* **1968**, *101*, 994. (b) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons: New York, 1998. (d) Aggarwal, V. K.; Ferrara, M.; Hainz, R.; Spey, S. E. *Tetrahedron Lett.* **1999**, *40*, 8923. (e) Carter, D.

S.; Van Vranken, D. L. *Tetrahedron Lett.* **1999**, *40*, 1617. (f) Cagle, P. C.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1994**, *117*, 11730. (g) Meyer, O.; Cagle, P. C.; Weickhardt, K.; Vichard, D.; Gladysz, J. A. *Pure Appl. Chem.* **1996**, *68*, 79.

(5) Bach, T.; Korber, C. *Tetrahedron Lett.* **1998**, *39*, 5015.

Traditionally, the Doyle–Kirmse reaction is run with an excess of sulfide and slow addition of the diazo compound to favor path a over path b (Scheme 2), but in a recent



advance Aggarwal and co-workers have shown that slow addition is unnecessary for efficient rhodium-catalyzed Doyle–Kirmse reaction with (trimethylsilyl)diazomethane.^{4d} These conditions are possible with TMSD for two reasons: first, the rhodium (trimethylsilyl)carbenoid is less electrophilic than the corresponding carboxyethylcarbenoid, second, the bulkier trimethylsilyl group slows addition of TMSD to the carbenoid.

Following this precedent, the Doyle–Kirmse reaction was carried out with dppeFeCl₂ by stirring 4.5 equiv of TMSD with the allyl sulfide **1** in refluxing dichloroethane for 2 h. The yield for this reaction (85%) was comparable to the yield obtained with slow addition (Scheme 1). Further studies of reaction stoichiometry demonstrated that the large excess of TMSD is unnecessary. Even better results (90% yield) were obtained with 1.5 equiv of the diazo compound.

A variety of Fe(II) and Fe(III) salts were explored as catalyst precursors. While 2,6-di-*tert*-butylpyridine has a beneficial effect on the CuOTf-catalyzed Doyle–Kirmse reaction, it was found to be unnecessary for the iron-catalyzed process. Ferrous chloride, ferrous bromide, and ferrous iodide all catalyzed the Doyle–Kirmse reaction (Table 1, entries 1–3). The reaction appears to be slower with ferrous iodide, but when the reaction time is extended from 2 to 5 h the yield of [2,3] product **1b** goes up to 77% and the amount of recovered starting material drops to 17%. The insolubility of ferrous chloride in dichloroethane makes it difficult to assess the effect of halide because the ferrous salt did not dissolve until the TMSD was added and the reaction was heated. Halide ligands seem to be important for the Fe(II)-catalyzed process, since with ferrous iodide catalyst the reaction was still incomplete after 8 h (77% product, 17% starting material). Both Fe(OAc)₂ and [(H₂O)₆Fe]²⁺·2BF₄⁻ gave no product, even with 4.5 equiv of TMSD.

Fe(III) salts were also effective catalyst precursors (Table 1). The requirement for halides seemed to be required by the failure of Fe(acac)₃ to catalyze the reaction, but surprisingly Fe(acac)₃ gave an 83% yield of homoallyl sulfide **1b** when the stoichiometry of TMSD was raised to 4.5 equiv.

Table 1. Catalysis of the Doyle–Kirmse Reaction by Fe Salts

entry	catalyst	product, %	start. mtrl, %
1	FeCl ₂ ^a	11	79
2	FeBr ₂	84	0
3	FeI ₂	65	23
4	Fe(OAc) ₂	0	nd
5	FeCl ₃	82	0
6	FeBr ₃	74	0
7	Fe(acac) ₃	0	nd
8	Fe(acac) ₃ ^a	83	0

^a 4.5 equiv of TMSD.

While it is possible that the reactions in Table 1 proceed via Fe(III) intermediates, a more likely scenario is that the ferric salts are reduced to catalytically active ferrous species.

For the cinnamyl substrates **3a** and **4a**, diastereoselection was modest.⁶ However, diastereoselection offers the opportunity to address the role of ligand and metal in the [2,3] rearrangement process. If the ligand affects the rate of the reaction, then it is probably involved in the catalytic cycle; if the ligand affects the diastereoselectivity, then it is probably involved in the rearrangement step of the catalytic cycle.

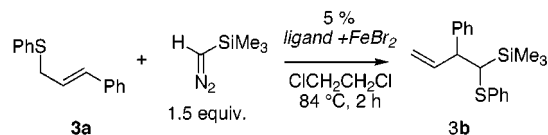
As the phosphine ligand is varied, or even omitted, the diastereoselection does not change markedly (Table 3). Thus,

Table 2. Substituent Effects on Reactivity

Substrate	Yield	S.M.	diast.
1a	89%	not detd.	-
2a	67%	not detd.	-
3a	94%	0%	87 : 13
4a	57%	11%	83 : 17

it seems unlikely that the phosphine ligand is involved in the step that determines diastereoselection. This result is surprising because Aggarwal has shown convincingly that the diastereomeric ratio observed in the Doyle–Kirmse reaction of substrate **4a** using rhodium dimer catalysts is ligand dependent. Rh₂(OAc)₄ leads to 90:10 diastereomeric ratio whereas Rh₂(5*S*-MEPY)₄ leads to a 49:51 diastereo-

Table 3. Effects of Ligands on the Fe-Catalyzed Doyle–Kirmse Reaction



entry	ligand	product, %	dr ^a
1	dppe	93	80:20
2	Ph ₃ P	88	85:15
3	(<i>R</i>)-BINAP	92	83:17
4	dppp	37	80:20
5	none	87	80:20

^a dr = diastereomeric ratio.

meric ratio.^{4d} There are two plausible explanations for the insensitivity of diastereomeric ratio (Table 3) with phosphine ligand. Either iron is bound to sulfide substrate in preference to the phosphine or the iron is not bound to sulfide or phosphine. The former explanation seems plausible since

(6) To a flame dried round-bottom flask equipped with a magnetic stir-bar was added FeCl₂dppe (0.018 g, 0.03 mmol) under argon. Sulfide **3a** (0.152 g, 0.67 mmol) was dissolved in 6.7 mL of 1,2-dichloroethane and introduced via syringe. The mixture was allowed to stir 10 min. (Trimethylsilyl)diazomethane (0.50 mL, 2.0 M in hexanes, 1.01 mmol) was introduced via syringe. The mixture was warmed to reflux. After 2 h the solution was cooled, filtered through Celite, and concentrated in vacuo to give a brown oil. The crude mixture was purified via preparative thin-layer chromatography (hexanes) to afford **3b** (0.196 g, 94%, dr: 83:17) as a clear oil. **3b**: ¹H NMR, major diastereomer (500 MHz, CDCl₃) δ 7.27–7.24 (m, 2H), 7.21–7.17 (m, 2H), 7.14–7.09 (m, 1H), 7.09–7.05 (m, 2H), 7.04–7.00 (m, 1H), 6.98–6.96 (m, 2H), 6.31 (ddd, *J* = 17.0, 10.2, 9.1 Hz, 1H), 5.15–5.09 (m, 2H), 3.79 (dd, *J* = 9.1, 5.1 Hz, 1H), 2.74 (d, *J* = 5.1 Hz, 1H), 0.07 (s, 9H); ¹³C NMR, major diastereomer (125 MHz, CDCl₃) δ 144.0, 139.8, 138.8, 129.4, 128.3, 128.2, 128.1, 126.5, 125.4, 116.3, 51.6, 43.2, –1.6; HRMS(EI) Calcd for C₁₉H₂₄SSi [M]⁺ 312.1368, Found: 312.1362. Anal. Calcd for C₁₉H₂₄SSi: C, 73.02; H, 7.74. Found: C, 73.27; H, 7.74.

other transition metals such as Pd(+2) and Ru(+2) are known to bind to dialkyl sulfides with high affinity.⁷

Some ligands can diminish the catalyst efficiency. For example, when dppp is added to the reaction, 33% starting material remains after 2 h. When the Woerpel–Evans bis-oxazoline (BOX) ligand is added, the reaction is completely shut down and no reaction is observed. These results suggest that dppp and bis-oxazolines bind to and deactivate the catalyst.

When ferrous bromide was premixed with dppe, the Doyle–Kirmse reaction continuously generated product over about 90 min following higher order kinetics. In contrast, when the reaction was carried out with FeBr₂ in the absence of phosphine there was an induction period of about 30 min during which time virtually no product was formed. After this induction period, a rapid reaction began and the starting material was fully consumed within the next 30 min. Thus, a highly reactive catalyst species is involved in the absence of phosphine ligands.

In conclusion, this work represents the first example of a Doyle–Kirmse reaction catalyzed by iron salts. The reaction proceeds in refluxing dichloroethane with 1.5 equiv of (trimethylsilyl)diazomethane without slow addition of the diazo compound. The halide ligand has little influence on the reaction, and the diastereoselectivity is relatively insensitive to the presence of phosphine ligands. Currently, the role of phosphine ligands, if any, is uncertain.

Acknowledgment. This work is supported by the National Science Foundation (CHE-9623903) with additional support from the Glaxo-Wellcome Chemistry Scholars program, Eli Lilly, and Dupont.

OL005740R

(7) (a) Albéniz, A. C.; Casado, A. L.; Espinet, P. *Inorg. Chem.* **1999**, 38, 2510. (b) Kuehn, C. G.; Taube, H. *J. Am. Chem. Soc.* **1976**, 98, 689.