Intramolecular C−H Insertion Reactions of (η^5-Cyclopentadienyl)dicarbonyliron Carbene Complexes: Scope of the Reactions and Application to the Synthesis of (±)-Sterpurene and (±)-Pentalenene

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(η^5-Cyclopentadienyl)dicarbonyliron carbene complexes, $[(\eta^5\text{-}C_5H_5)(CO)_2Fe{=}CHR]^+BF_4^-$, are generated as reactive intermediates from thioether derivatives, $(\eta^5\text{-}C_5H_5)(CO)_2FeCH(R)SPh$, by *S*-alkylation with trimethyloxonium tetrafluoroborate and loss of thioanisole. The carbene complexes undergo intramolecular C−H insertion into appropriately situated side chains to form cyclopentane derivatives. The reaction has been developed into a general procedure employing cycloalkanones as scaffolds bearing the iron carbene moieties and the side chains at C(2) and C(3), respectively. The products of the intramolecular insertion reactions are substituted bicyclo[*n*.3.0]alkanones. The scope and limitations of the reaction are described. The reaction is applied to a total synthesis of sterpurene and to a formal synthesis of pentalenene. Overall, this approach to cyclopentane annulation complements the related metal-catalyzed insertion reactions of diazocarbonyl compounds, which are also believed to occur via metal carbene complexes.

Introduction

Carbenes, carbenoids, and metal carbene complexes have been heavily investigated as reactive intermediates.[2] These species may be generated by numerous methods, and once they are obtained, they are commonly seen to undergo either addition reactions to alkenes to give cyclopropanes or insertions into various covalent bonds. The insertions occur either intermolecularly or intramolecularly and are seen most frequently for C−H, O−H, and N−H bonds. The intramolecular variants of these insertion reactions are especially useful in synthetic chemistry and lead to the formation of carbocyclic or heterocyclic products. These intramolecular reactions are usually regioselective for bonds located four atoms away from the carbene center, and therefore these reactions are particularly useful for the formation of five-membered rings, although there are also many cases of other ring sizes being produced.

Our work in this area had its origins in a key observation by Pettit and Jolly in 1966.[3] They found that when a cyclopentadienyl(dicarbonyl)iron (or Fp) ether derivative **1** was treated with acid in the presence of cyclohexene, norcarane was produced (Scheme 1). This outcome was explained by the proposed intermediacy of the cationic carbene complex **2** formed by protolytic loss of methanol from the ether. Addition of the methylene group from the carbene complex to the alkene then accounted for cyclopropane formation. The proposed carbene complex could not be observed directly as a result of its high reactivity, but instead it was generated *in situ* in the presence of the alkene.

Following this lead of Pettit and Jolly, other investigators began detailed experimental and calculational studies of the carbene complex **2** and several derivatives. Alternative methods were devised for the generation of these species. Much of this work has been reviewed.[4] Especially prominent are studies by Brookhart that have led to a mechanistic understanding of the iron-promoted cyclopropanation reaction and the development of synthetically useful procedures, including asymmetric iron reagents for enantioselective cyclopropane formation.[4a,5]

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(2) For reviews of carbenes and carbene complexes, see: (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75. (c) Carbene (Carbenoide). In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Regitz, M., Ed.; G. Thieme: Stuttgart, 1989; Vol. E19b. (d) Taber, D. F. Carbon−Carbon Bond Formation by C−H Insertion. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pattenden, G., Vol. Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 1045−1062. (e) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765−1808. (f) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385−5453. (g) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. (h) Doyle, M. P. Transition Metal Carbene Complexes: Diazodecomposition, Ylide, and Insertion. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Pergamon: Oxford, 1995; Vol 12, pp 421−468. (i) Doyle, M. P. *Aldrichimica Acta* **1996**, *29*, 3−11. (j) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*; Wiley: New York, 1998. (k) *Advances in Carbene Chemistry*; Brinker, U., Ed.; JAI Press: Stamford, CT, 1998; Vol. 2. (l) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145−3169.

(3) (a) Jolly, P. W.; Pettit, R. *J. Am. Chem. Soc.* **1966**, *88*, 5044−5045. (b) Riley, P. E.; Capshew, C. E.; Pettit, R.; Davis, R. E. *Inorg. Chem.* **1978**, *17*, 408−414.

(4) For reviews of the chemistry of these general types of iron carbene complexes, see: (a) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411−432. (b) Helquist, P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: London, 1991; Vol. 2, pp 143−194. (c) Fatiadi, A. J. *J. Res. Natl. Inst. Stand. Technol.* **1991**, *96*, 1−113. (d) Petz, W. *Iron-Carbene Complexes*; Springer-Verlag: Berlin, 1993. (e) Guerchais, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 803−811. (f) Ruck-Braun, K.; Mikulas, M.; Amrhein, P. *Synthesis* **1999**, 727−744. (g) Theys, R. D.; Vargas, R. M.; Wang, Q. W.; Hossain, M. M. *Organometallics* **1998**, *17*, 1333−1339.

(5) Brookhart, M.; Timmers, D.; Tucker, J. R.; Williams, G. D.; Husk, G. R.; Brunner, H.; Hammer, B. *J. Am. Chem. Soc.* **1983**, *105*, 6721−6723.

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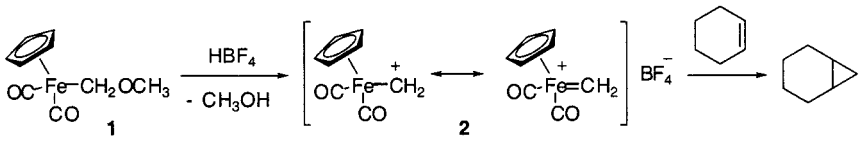
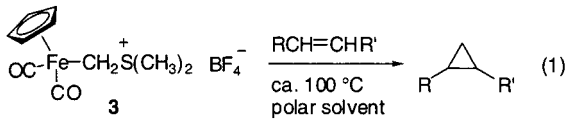
Scheme 1



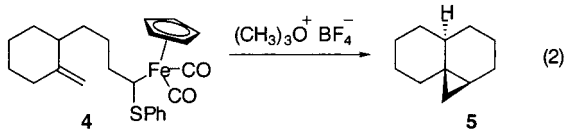
Among the most recent work is a method developed by Hossain for the conversion of aldehydes into iron carbene complexes.[4g]

Our first contribution to this area was the development of the sulfonium salt complex **3** as a truly practical, air- and water-stable reagent for cyclopropanation of alkenes (eq 1).[6] Thermal dissociation of dimethyl sulfide suppos-



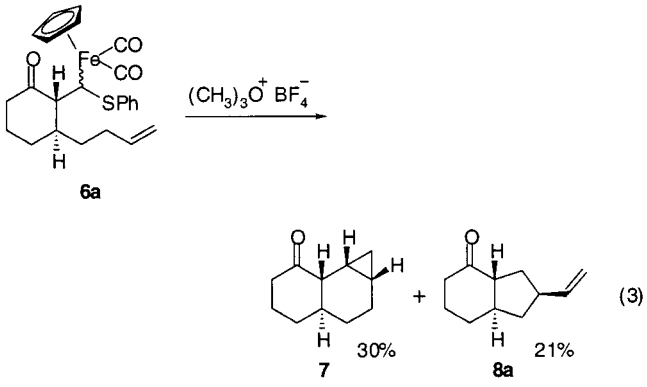
edly generates the carbene complex **2**. Upon development of a streamlined one-pot procedure for its preparation, reagent **3** became commercially available.

Over the years, we developed several extensions of this chemistry, including an intramolecular version of the cyclopropanation reaction (eq 2).[7] Methylation of the

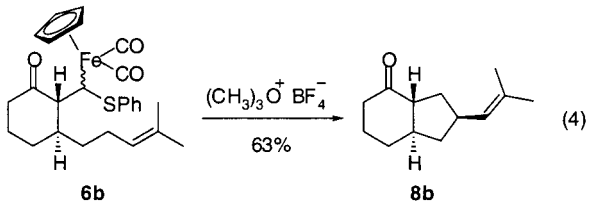


phenylthioalkyliron complex **4** presumably generated a transient sulfonium salt followed by dissociation of thioanisole and internal alkylidene delivery to the alkene.

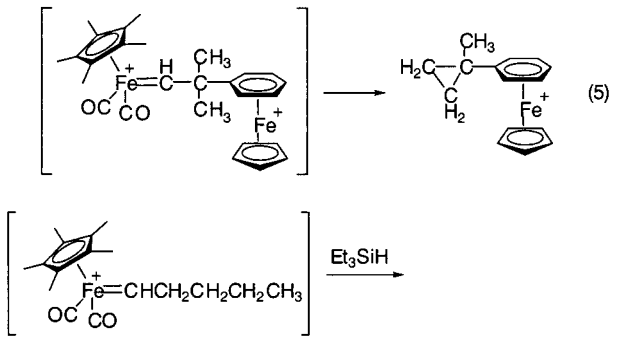
While exploring the scope of this reaction, we investigated substrate **6a** (eq 3). In addition to the expected



intramolecular cyclopropanation product **7**, a perhydroindanone **8a** was also produced. On the other hand, when the substrate **6b** bearing a more hindered alkene was employed, no cyclopropane was produced, but instead the perhydroindanone **8b** was obtained as the only cyclization product (eq 4).[8a]



The formation of cyclopentane-containing products **8a** and **8b** was suggestive of a carbene-like intramolecular C−H insertion reaction. Besides the well-known tendency of carbenes themselves to undergo this type of reaction, previous studies had also implicated transition metal carbene complexes in insertions.[2] A few cases of these reactions had been reported for discrete, stoichiometrically generated carbene complexes,[9] but more commonly, carbene complexes are believed to be formed as intermediates in the well-studied metal-catalyzed insertion reactions of diazo compounds.[2,10] We were therefore motivated to follow-up our preliminary observation of iron-based insertions in more detail.[8] Concurrent with our further studies, examples of C−H and Si−H insertion reactions of iron complexes were reported by Guerchais (eq 5)[11] and by Brookhart (eq 6),[12] respectively.



Results

Cyclic α,β-unsaturated ketones serve as scaffolds for assembling substrates for the iron-based intramolecular insertion reactions. The reaction sequence for preparation

(6) (a) Brandt, S.; Helquist, P. *J. Am. Chem. Soc.* **1979**, *101*, 6473−6475. (b) O'Connor, E. J.; Brandt, S.; Helquist, P. *J. Am. Chem. Soc.* **1987**, *109*, 3739−3747. (c) Mattson, M. N.; O'Connor, E. J.; Helquist, P. *Org. Synth.* **1991**, *70*, 177−194.

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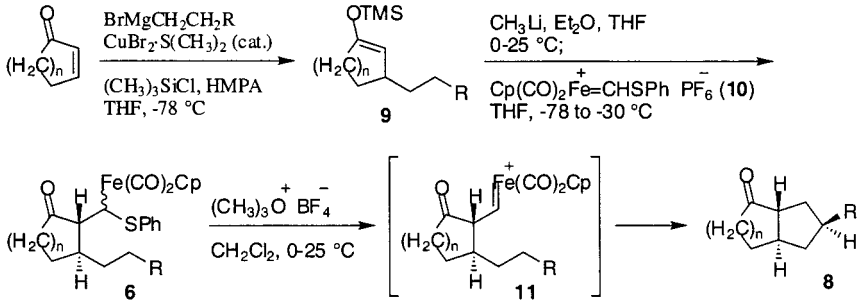
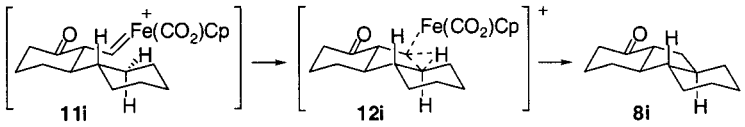
(9) (a) Fischer, H.; Schmid, J. *J. Mol. Catal.* **1988**, *46*, 277−285. (b) Wang, S. L. B.; Su, J.; Wulff, W. D.; Hoogsteen, K. *J. Am. Chem. Soc.* **1992**, *114*, 10665−10666. (c) Aumann, R.; Läge, M.; Krebs, B. *Chem. Ber.* **1994**, *127*, 731−738. (d) Barluenga, J.; Rodríguez, F.; Vadecard, J.; Bendix, M.; Fañanás, F. J.; López-Ortiz, F. *J. Am. Chem. Soc.* **1996**, *118*, 6090−6091. (e) Barluenga, J.; Aznar, F.; Fernandez, M. *Chem. Eur. J.* **1997**, *3*, 1629−1637. (f) Takeda, K.; Okamoto, Y.; Nakajima, A.; Yoshii, E.; Koizumi, T. *Synlett* **1997** 1181. (g) Barluenga, J.; Rodríguez, F.; Vadecard, J.; Bendix, M.; Fañanás, F. J.; López-Ortiz, F.; Rodríguez, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 8776−8782.

Scheme 2



Scheme 3



of the iron carbene precursors and their cyclization is shown in Scheme 2 (Cp = cyclopentadienyl).

Silyl enol ethers **9** are prepared by copper-promoted conjugate addition of Grignard reagents to cycloalkenones in the presence of trimethylsilyl chloride.[13] The silyl derivatives react with methyllithium to regenerate enolates. Addition to the thiocarbene complex $Cp(CO)_2Fe^{+}{=}CHSPh\ PF_6^{-}$ (**10**)[14] produces the substrates **6** as mixtures of diastereomers with respect to the iron-bearing carbon atom. For characterization purposes, these complexes may be purified by column chromatography under a nitrogen atmosphere[15] to give yellow-brown oils or solids. Separate diastereomers are not required for the following cyclization step, and the complexes may be used in crude form. Treatment with trimethyloxonium tetrafluoroborate[16] forms sulfonium salts. Spontaneous loss of thioanisole generates carbene complexes **11** which undergo C−H insertion to give the fused cyclopentanes **8**.

The results of several cyclizations are summarized in Table 1. A general observation is that C−H insertion occurs regioselectively at a carbon atom located four positions away from the carbene center, thus resulting in cyclopentane formation. Furthermore, the insertions occur with higher yields at positions bearing substituents that are regarded as being good cation stabilizing groups. Examples include insertions into benzylic (entries c−f, l, and o) and tertiary alkyl positions (entries j, k, and m). Secondary positions are not as effective (entries g, i, and n), although the β-effect of a silyl group[17] appears to provide a favorable influence at a secondary carbon (entry h). Allylic positions face the complication of competing cyclopropanation (entry a) and possibly allylic strain effects (entry b). Cyclohexanones, cycloheptanones, and cyclooctanones all function as good scaffolds for permitting appropriate proximity of the reactive carbene and C−H insertion sites.

High diastereoselectivity is seen in most cases whereby one major isomer is usually detected with respect to the substituent on the cyclopentane ring. Retention of configuration is observed when the site of C−H insertion is of defined configuration (entries e and f).[8c] Simple secondary cases show poor stereoselectivity (entries g and n). Insertion into a secondary position of a cyclohexyl ring presents special difficulties (entry i). A major product is obtained in a modest yield of 52% along with two minor components in 6% yield each. Although good characterization of them has not been possible, they appear to be isomers of the major product on the basis of their mass spectra. Because of poor ^{1}H NMR chemical shift dispersion even at high field strengths, measurement of coupling constants of the ring fusion protons has not been possible. The structure of the major product is postulated as being **8i**, on the basis of the favorable chair-chair-chair conformation depicted for transition state **12i** (Scheme 3; see also Discussion).

Stereochemical assignments for the cyclization products were generally made through use of ^{1}H NMR NOESY spectra. To corroborate these assignments, one

(10) (a) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686−7693. (b) Demonceau, A.; Noels, A. F.; Costa, J.-L.; Hubert, A. J. *J. Mol. Catal.* **1990**, *58*, 21−26. (c) Spero, D. M.; Adams, J. *Tetrahedron Lett.* **1992**, *33*, 1143−1146. (d) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958−964. (e) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296−3305. (f) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8991−9000. (g) Doyle, M. P.; Dyatkin, A. B.; Autry, C. I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 619−621. (h) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547−556. (i) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706−6712. (j) Clark, J. S.; Dossetter, A. G.; Russell, C. A.; Whittingham, W. G. *J. Org. Chem.* **1997**, *62*, 4910−4911. (k) Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998**, *63*, 1853−1862. (l) Wang, J.; Liang, F.; Chen, B. *J. Org. Chem.* **1998**, *63*, 8589−8594. (m) White, J. D.; Hrnciar, P. *J. Org. Chem.* **1999**, *64*, 7271−7273. (n) Sulikowski, G. A.; Lee, S. *Tetrahedron Lett.* **1999**, *40*, 8035−8038.

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(15) Kremer, K. A. M.; Helquist, P. *Organometallics* **1984**, *3*, 1743−1745.

(16) Trimethyloxonium tetrafluoroborate is commercially available (Aldrich), but we normally prepare it according to the procedure described in: Meerwein, H *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 1096−1098.

(17) Wierschke, S. G.; Chandrasekher, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496−1500. (b) Lambert, J. B.; Wang, G.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838−7845.

Table 1. Substrates and Results of Iron Carbene Cyclization Reactions

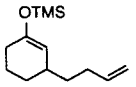
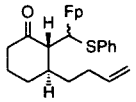
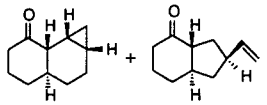
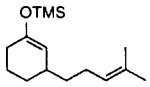
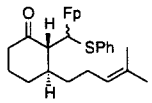
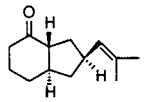
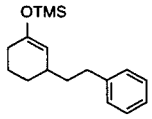
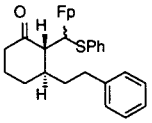
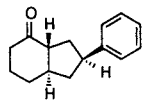
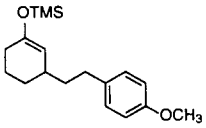
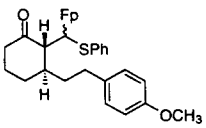
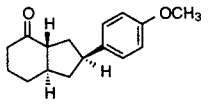
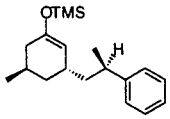
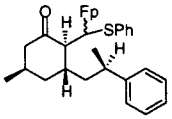
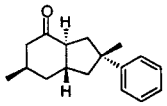
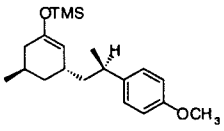
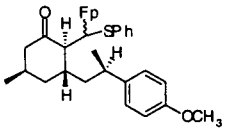
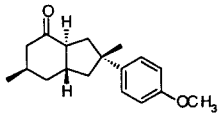
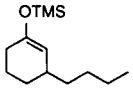
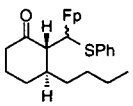
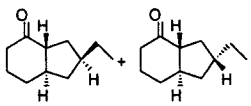
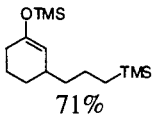
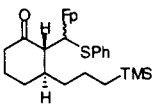
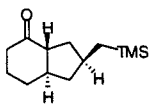
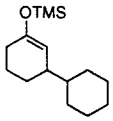
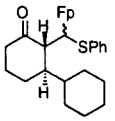
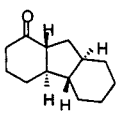
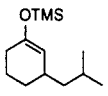
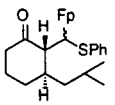
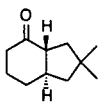
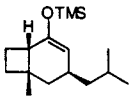
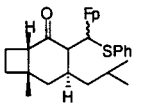
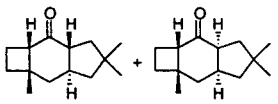
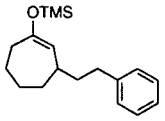
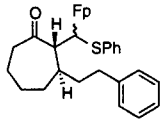
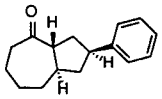
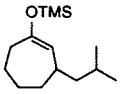
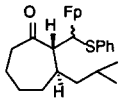
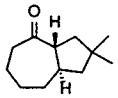
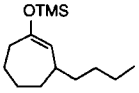
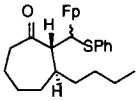
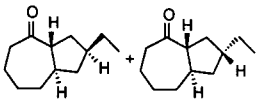
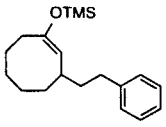
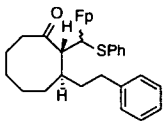
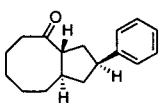
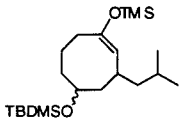
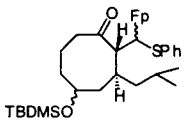
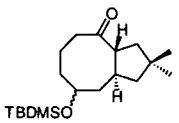
entry	enol ethers **9**[a]	iron complexes **6**[b]	cyclization products **8**[c]
a	 74%	 62% (2:1)	 30% (**7**)[d] 21% (**8a**)[d]
b	 90%	 69% (3:2)	 63%
c	 79%	 60% (2:1)	 90%
d	 86%	 45% (2:1)	 96%
e	 60%	 60% (3:2)	 70%
f	 58%	 30% (1:1)	 78%
g	 84%	 63% (2:1)	 31% (2:1)
h	 71%	 70% (2:1)	 86%
i	 54%	 61% (2:1)	 52%
j	 70%	 61% (2:1)	 72%

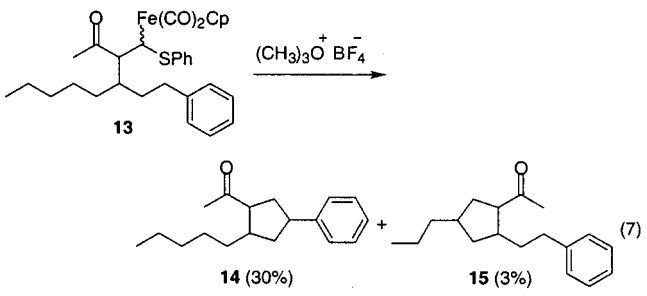
Table 1 (Continued)

entry	enol ethers **9**[a]	iron complexes **6**[b]	cyclization products **8**[c]
k	 88% (3:1)[e]	 70%[f]	 80-85% (1.3:1)
l	 72%	 67% (3:1)	 92%
m	 70%	 65% (4:1)	 77%
n	 77%	 68% (5:1)	 31% (1:1)
o	 68%	 65% (10:1)	 90%
p	 86% (1.3:1)		 37%[d]

[a] Yield from enone precursor (see Scheme 2). [b] Yields obtained from **9**; reported as mixtures of diastereomers. Fp = cyclopentadienyl-(dicarbonyl)iron. [c] Yield of pure, isolated product from iron complex **6** unless otherwise indicated. [d] Overall yield from enol ether precursor **9**. The yield from the iron complex **6b** is 63%. [e] 3:1 mixture of *cis*- and *trans*-isobutyl isomers obtained from addition to the enone; pure *cis*-isomer isolated and used in subsequent step. [f] Diastereomer ratio not determined; crude mixture used directly in the cyclization reaction.

of the products, **8d**, was studied by single-crystal X-ray diffraction. The resulting structure (see Supporting Information) is in full agreement with the spectroscopic assignment.

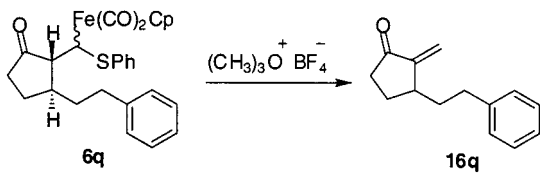
To test the conclusion that benzylic positions are more favorable sites of insertion than simple 2° positions, substrate **13** was prepared. Under the usual cyclization conditions, a mixture of cyclopentane derivatives **14** and **15** is obtained in a ratio of 10:1, respectively (eq 7); each



(7)

of these products is produced as a mixture of diastereomers. The regioselectivity seen in this case therefore serves to confirm the earlier inference concerning preferred sites of insertion.

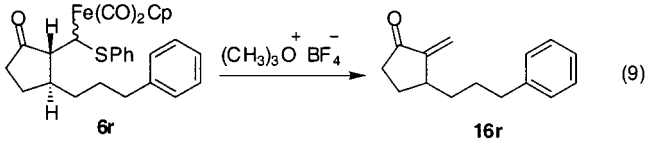
Some important limitations have been observed for these insertion reactions. Attempts to extend them to the use of a cyclopentanone scaffold were unsuccessful. Iron complex **6q** gives a complex mixture of products from which only the methylene ketone **16q** resulting from β-hydride elimination is isolated in very low yield (eq 8).



(8)

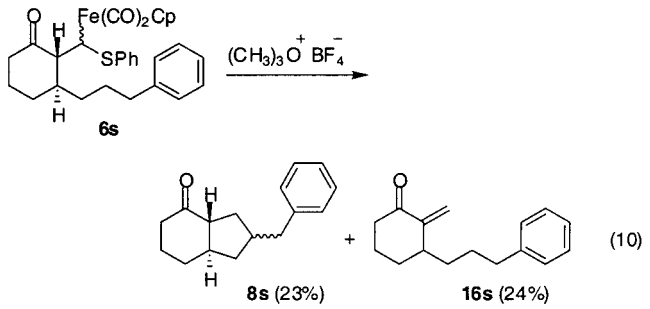
Increased ring strain in the transition state for formation of a *trans*-bicyclo[3.3.0]octanone derivative apparently prevents the intramolecular C−H reaction from occurring. Substrate **6r** was prepared to provide an alternative benzylic site for prospective C−H insertion leading to a

less strained, fused six-membered ring of a bicyclo[4.3.0]-nonanone system. However, an elimination product **16r** is again obtained in very low yield as the only characterized product (eq 9). This latter result may be regarded



(9)

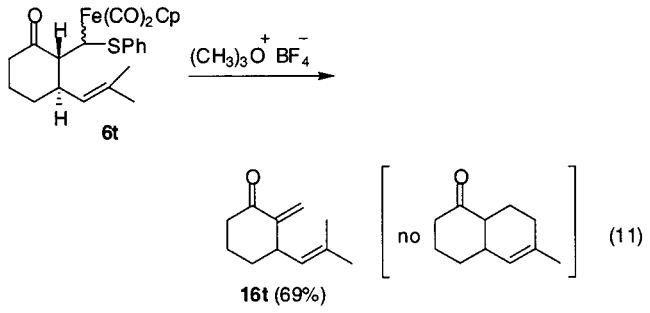
as yet another indication of the strong propensity of metal carbenes to undergo C−H insertions leading to five-membered rings, even when otherwise satisfactory sites for reaction are available for formation of other ring sizes. This point is reinforced by the reaction of iron complex **6s**, which again presents a benzylic site for six-membered ring formation. Instead, a five-membered ring product **8c** is formed in low yield as a mixture of diastereomers by insertion at a nonbenzylic 2° site together with a low yield of the elimination product **16s** (eq 10). Similar



(10)

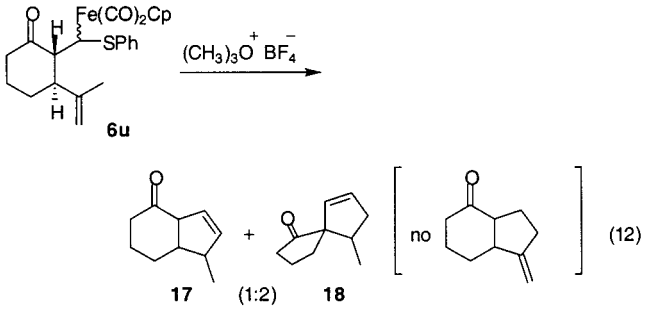
results are obtained with the 4-methoxyphenyl analogue of **6s** having presumably an even better benzylic activating group. For all practical purposes, substrate **6s** (and its methoxyphenyl analogue) behaves much like the 3-butylcyclohexanone derivative **6g**, which also provides a simple 2° site for insertion (Table 1, entry g).

In yet another attempt to promote six-membered ring formation, the isobutenylcyclohexanone derivative **6t** was prepared. However, the usual cyclization conditions lead to formation of the elimination product **16t** instead of a fused cyclohexene which would have resulted from allylic C−H insertion (eq 11).



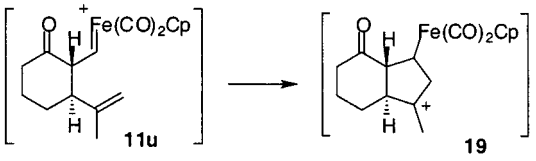
(11)

In a related system directed at the usual five-membered ring formation, isopropenylcyclohexanone derivative **6u** was employed. Under the standard conditions for iron carbene generation, none of the expected methylenecyclopentane annulation product is detected. Instead, very low yields of the methylcyclopentene products **17** and **18** are obtained (eq 12). This result can be explained on the basis of a difficult 5-endo-trig intramo-



(12)

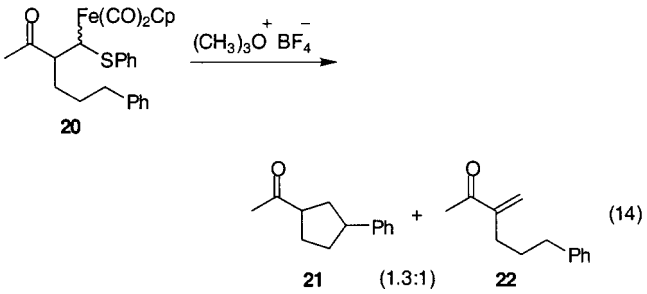
lecular alkene addition of the cationic intermediate **11u** to give carbocation **19** (eq 13). Subsequent 1,2-hydride



(13)

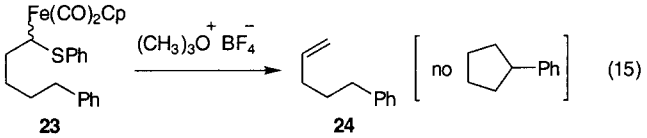
shifts followed by 1,2-acyl migration and iron elimination would account for the observed products. This behavior is consistent with other cationic cyclizations of iron carbene complexes that we have observed previously for alkene-containing substrates.[18] The higher degree of alkene substitution in substrate **6t** probably hinders an analogous cyclization from occurring in that case (see eq 11 above).

Another important limitation of these insertion reactions is that they appear to require a fairly rigid scaffold as exemplified by the several cycloalkanone substrates in Table 1. Less conformationally constrained substrates either give much lower yields of insertion products, or the insertion reactions fail entirely. For example, the substrate **13**, which was designed to probe regioselectivity issues (see eq 7 above), gives low yields of the cyclization products **14** and **15**. The closely related substrate **20** affords very low yields (<25%) of the desired cyclization product **21** and the competing elimination product **22** (eq 14). The even more conformationally mobile substrate **23**



(14)

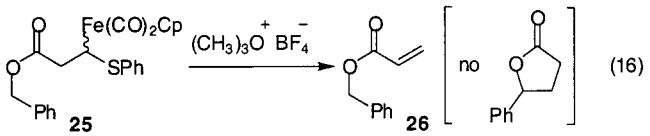
produces the elimination product **24** in very low yield as part of a complex mixture (eq 15); a cyclopentane product is not detected.



(15)

(18) (a) Seutet, P.; Helquist, P. *Tetrahedron Lett.* **1988**, *29*, 4921−4922. (b) Baker, C. T.; Mattson, M. N.; Helquist, P. *Tetrahedron Lett.* **1995**, *36*, 7015−7018.

Likewise, the ester substrate **25** undergoes elimination to give a complex mixture containing a small amount of benzyl acrylate as the only identifiable product with no evidence of intramolecular insertion adjacent to the ester oxygen tether (eq 16).



(16)

Applications

Sterpurene (**27**) was reported by Ayer as a metabolite of *Stereum purpureum*, a fungus that is responsible for silver leaf disease of a variety of trees and scrubs.[19] Syntheses of racemic and nonracemic sterpurene have been reported by several investigators.[20] We recognized this compound as a possible synthetic target for the application of our insertion reaction.

A necessary focus of any total synthesis of sterpurene is the construction of the 4/6/5 tricyclic carbon skeleton (Scheme 4). We anticipated that the tricyclic ketone **28** could be obtained by an insertion reaction employing complex **29**. In turn, our usual route to cyclization precursors would utilize bicyclic enone **30**, itself available by photochemical cycloaddition of ethylene and a cyclohexenone followed by reintroduction of unsaturation.[21]

This strategy was implemented successfully (Scheme 5). Commercially available 3-methyl-2-cyclohexenone undergoes photochemical cycloaddition of ethylene, and α-bromination of the resulting bicyclic ketone **31** followed by dehydrobromination generates enone **30**.[21] Copper(I)-catalyzed conjugate addition[13] of isobutylmagnesium bromide provides ketone **32** as a 3:1 to 4:1 mixture of β and α isomers favoring the former. After chromatographic separation, the β isomer is converted to enol silyl ether **33**. Enolate regeneration and trapping with thiocarbene complex **10** affords iron complex **29**. Treatment with trimethyloxonium tetrafluoroborate leads to the desired tricyclic ketone **28** as an inconsequential mixture of *trans*- and *cis*-fused isomers. This key step occurs in yields ranging from 80% to 90% from precursor **29**. However, the overall cyclopentane annulation is operationally simpler when iron complex **29** is not isolated or purified, in which case the overall yield of tricyclic ketone **28** is 48% from silyl enol ether **33**. The main limitation on the overall yield for this ring construction appears to be incomplete reaction of the enolate derived from **33** in that 20−30% of ketone **32** is recovered after exposure of the enolate to thiocarbene complex **10**. The synthesis is completed as in Little's route[20b] by addition of methyllithium to tricyclic ketone **28** and dehydration of the resulting alcohol. The (±)-sterpurene thus obtained is identical to previously obtained material by direct comparison of ^{1}H and ^{13}C NMR spectra.[19,20d]

Pentalenene (**34**), an angular triquinane, is the parent hydrocarbon of the pentalenolactone family of antibiotic metabolites. It was first synthesized by Ohfune, Shirahama, and Matsumoto in 1976 as part of a study of biosynthetic cyclizations,[22] but it was not actually reported as a naturally occurring compound until 1980 when it was isolated from *Streptomyces griseochromogenes*.[23] Numerous syntheses of pentalenene have subsequently been published.[24] As another application of our insertion reaction, we have accomplished a formal synthesis of (±)-pentalenene that merges with a late intermediate in Pattenden's earlier synthesis.[24f]

The basic strategy (Scheme 6) follows from a biomimetic, acid-catalyzed, transannular cyclization of fused 1,5-cyclooctadiene **35**. This intermediate, which was employed by Pattenden,[24f] is available from unsaturated ketone **36**. This ketone is the focus of our formal synthesis, featuring the formation of bicyclic ketone **37** from complex **38**. This carbene precursor is, in turn, prepared by the usual sequence from enone **39**.

The synthesis commences with commercially available 1,5-cyclooctanediol (**40**, Scheme 7), which is oxidized with Jones reagent to give 5-hydroxycyclooctanone in the form of bicyclic hemiketal **41**.[25] Protection with *tert*-butyldimethylsilyl chloride[26] gives monocyclic siloxy ketone **42**. The corresponding enone **39** is obtained by reaction of the ketone with benzeneselenenyl chloride followed by oxidative elimination of the selenide with hydrogen peroxide[27] or alternatively by conversion of the ketone to the silyl enol ether and use of the Saegusa procedure

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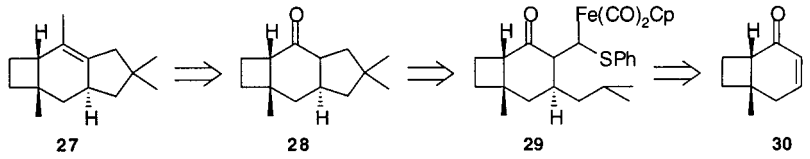
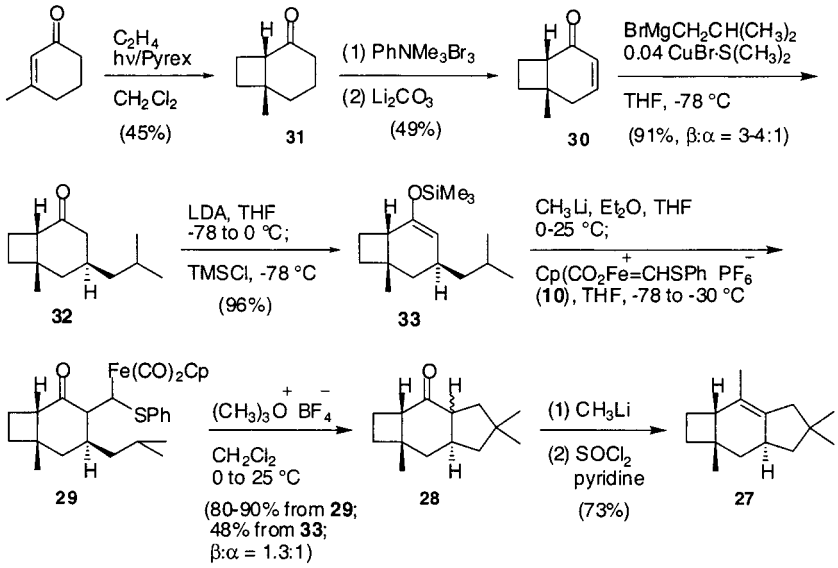
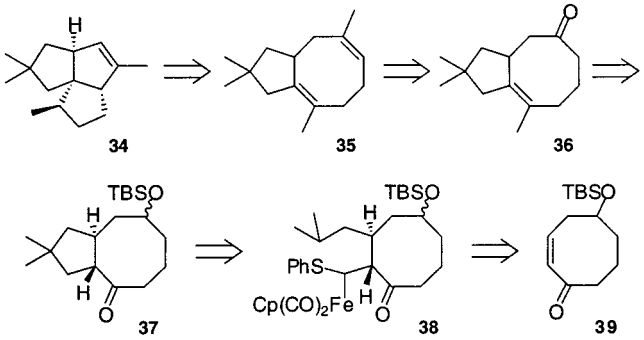
Scheme 4



Scheme 5



Scheme 6



for palladium-promoted oxidative elimination[28] (95% yield). Conjugate addition of isobutylmagnesium bromide to the enone provides silyl enol ether **43** as a 57:43 mixture of two diastereomers. Regeneration of the enolate with methyllithium and alkylation with thiocarbene complex **10** gives iron complex **38**, which is immediately treated with trimethyloxonium tetrafluoroborate to afford fused ketone **37**. Addition of methyllithium and dehydration of tertiary alcohol **44** with thionyl chloride and pyridine produces alkene **45**. Treatment with Jones reagent results in hydrolysis of the silyl enol ether and oxidation of the intermediate alcohol to give the desired unsaturated ketone **36**. Alternatively, the silyl ether group in **45** can be cleaved with tetra-*n*-butylammonium fluoride followed by Jones oxidation, but the overall yield for the two steps is somewhat lower (35% vs 44%). At this point, a formal synthesis of pentalenene is achieved in that **36** has been converted into pentalenene by Pattenden[24f] and others[22,24] through use, for example, of a Wittig reaction, $RhCl_3$-catalyzed alkene isomerization, and boron trifluoride promoted transannular cyclization. We have not repeated this reaction sequence, but the ^1H and ^{13}C NMR spectra of our synthetic **36** match the corresponding data kindly provided by Professor Pattenden.[29]

Discussion

We have developed a general procedure for cyclopentane annulation based upon intramolecular C−H insertion of cationic iron carbene complexes as reactive intermediates. The substrates are prepared from α,β-unsaturated ketones by copper-catalyzed conjugate addition of a side chain that provides a site for C−H insertion and enolate alkylation with a thiocarbene complex that provides the reactive center for the cyclization reaction. The key ring-forming step occurs in modest to high yields and with high diastereoselectivity for a wide range of substrates. The most effective sites of insertion are tertiary alkyl and benzylic C−H bonds. Depending upon the degree of substitution, an alkene side chain can serve as the site of either carbene addition to give fused cyclopropanes or of allylic C−H insertion to give fused alkenylcyclopentanes.

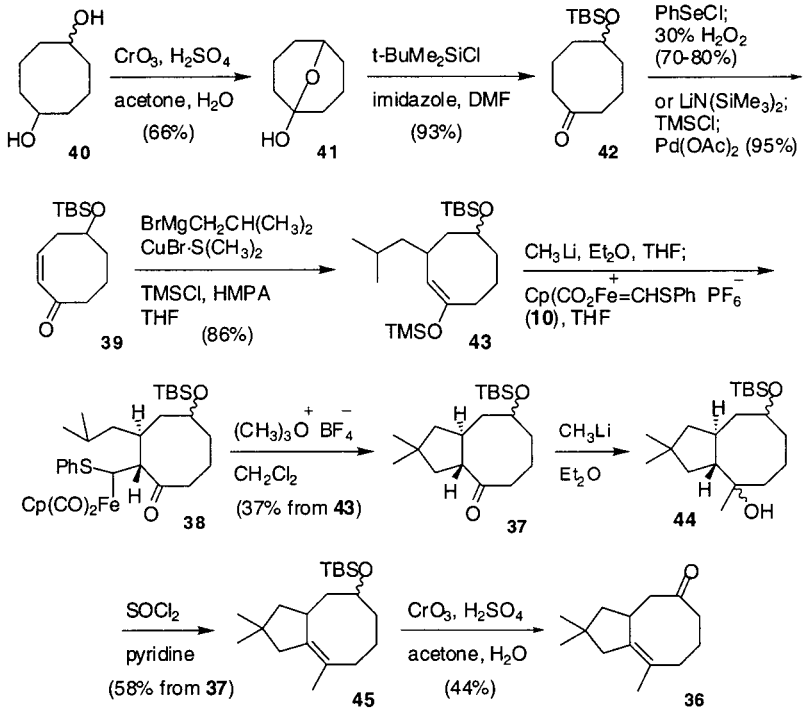
The stereoselectivity seen in these reactions can be accommodated by assuming a favorable chairlike conformation for the C−H insertion transition state **12c** as depicted for entry c from Table 1 as a representative case (Scheme 8). This pathway is supported by a separate study of several deuterium-labeled substrates.[8c]

There are some important limitations on the scope of this reaction. Most importantly, the carbene center and the side chain site of C−H insertion must be somewhat constrained to conformations that favor approach of the respective centers for bond formation. This need is met

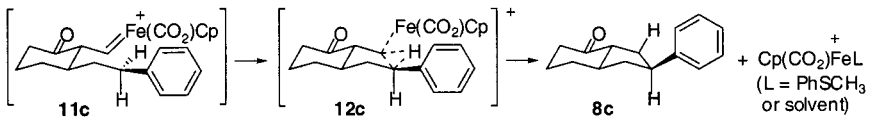
(28) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.

(29) Pattenden, G., personal correspondence.

Scheme 7



Scheme 8



by using at least somewhat rigid cyclic compounds as scaffolds, which in turn result in the formation of fused ring systems. When attempts are made to employ more conformationally mobile, open-chain substrates, competing elimination reactions of the intermediate carbene complexes predominate over the ring-forming, intramolecular insertion reactions. Another limitation is that simple secondary alkyl C−H bonds are much less effective sites of insertion compared to tertiary alkyl and benzylic positions. Simple primary alkyl sites do not appear to participate to any significant extent in these reactions.

The most heavily developed of the synthetically useful methods for intramolecular carbene insertion reactions are the metal-catalyzed reactions of α-diazocarbonyl compounds. Rhodium catalysts are especially effective in these reactions.[1,10] To a certain extent, these diazocarbonyl reactions and the present iron carbene insertions complement each other with respect to synthetic applications and strategies. Whereas the rhodium-catalyzed reactions generally show a preference for C−H insertion in the relative order of 3° > 2° > 1°, allylic, benzylic sites,[10] the order of preference for the iron carbene insertions falls in the order of 3°, benzylic, allylic > 2° > 1°. Also, whereas the use of diazocarbonyl compounds provides products having carbonyl groups α to the site of ring formation, the cycloalkanone scaffolds that we have employed for the iron-based reactions generate products having carbonyl groups *β* to the site of ring closure. These differences in the two approaches allow for flexibility in the choice of methods to meet the needs of desired synthetic applications.

Conclusions

Iron carbene complexes have previously been found to be useful intermediates in a number of reactions. Prior work had placed emphasis on the role of these intermediates in cyclopropanation reactions. Now they can also be recognized for their utility in intramolecular C−H insertion reactions to afford cyclopentane derivatives. These reactions add noteworthy flexibility to the choices that are available for synthetic applications requiring cyclopentane formation.

Substantial further work is required to develop these reactions to satisfy additional needs. Although iron is the least expensive of all metals and certainly more readily available than metals such as rhodium, the presently reported reactions would be even more attractive if they were to employ iron in a catalytic rather than stoichiometric fashion. Also, the use of chiral forms of the iron moiety may be attractive in permitting enantioselective C−H insertion reactions.

Experimental Section

General Procedure for the Preparation of Silyl Enol Ethers (9) via Conjugate Addition to Enones. Copper(I) bromide−dimethyl sulfide complex[30] (0.063 g, 0.3 mmol) was placed under nitrogen in a 100-mL round-bottom flask fitted with a septum. A Grignard reagent (9.0 mmol) in THF (15 mL) was added, and the suspension immediately turned blue. HMPA (2.6 mL, 15 mmol) was then added, and the suspension was cooled to −78 °C with stirring. Into the flask was added

(30) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460−1469.

a solution of 2-cycloalkenone (7.5 mmol) and $(CH_3)_3SiCl$ (1.9 mL, 15 mmol) in THF (5.0 mL) over a 5-min period. After the mixture was stirred for 3 h at −78 °C, triethylamine (2.0 mL) was added followed by hexanes (40 mL). The mixture was transferred to a separatory funnel, and the organic layer was washed with H_2O (3 × 20 mL) and saturated aqueous NH_4Cl (30 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The product was partially purified by Kugelrohr distillation or medium-pressure liquid chromatography and was used shortly thereafter in the next step.

General Procedure for Preparation of Thioalkyliron Complexes (6) by Reaction of Enolates with (η^5-Cyclopentadienyl)dicarbonyl[(phenylthio)carbenium]iron Hexafluorophosphate (10). A silyl enol ether **9** (1 mmol) in THF (5 mL) was placed in a 10-mL pear-shaped flask and cooled to 0 °C under nitrogen. Methyllithium (0.72 mL, 1 mmol, 1.4 M solution in diethyl ether) was added dropwise with stirring over a 2-min period. After 0.5 h, the ice bath was removed, and the solution was allowed to warm to 25 °C and stirred for 0.5 h. This enolate solution was cooled to −78 °C. Iron carbene complex **10** (0.444 g, 1.0 mmol) was placed in a Schlenk apparatus, consisting of two reaction vessels connected to each other by a filter tube and connected to a nitrogen manifold, and cooled to −78 °C prior to the addition of precooled THF (4 mL, −78 °C). Into the brown suspension was cannulated the freshly prepared enolate all at once. After the addition was complete, the mixture was stirred until all of the solid carbene complex was consumed (ca. 5−10 min). The mixture was stirred an additional 1 h and slowly warmed to ca. −30 °C. Precooled hexanes (20 mL, −78 °C) were cannulated by vacuum into the dark brown, homogeneous mixture. After 5 min, stirring was stopped, and the mixture was filtered by inverting the apparatus, thus removing the insoluble salts. Removal of the solvent from the filtrate under oil pump vacuum left an orange or red oil that was purified by column chromatography under a nitrogen atmosphere.[15]

General Procedure for Generation of Iron Alkylidene Complexes (11) and Their Cyclization Reactions to Produce Cyclopentanes (8). Into the reaction vessel containing the thioalkyliron complex **6** (0.5 mmol) was added methylene chloride (20 mL), and the solution was cannulated into a flask containing trimethyloxonium tetrafluoroborate (1.5 mmol) at 0 °C under nitrogen. The mixture was warmed to 25 °C over a 1-h period and was stirred for 2 h. The dark red solution was diluted with hexanes (25 mL) and stirred for 5 min to precipitate metal-containing material. The mixture was filtered through a pad of Celite, and the pad was washed with hexanes (30 mL). The solvent was removed by rotary evaporation, and the residue was purified by flash or medium-pressure liquid chromatography.

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Supporting Information Available: Experimental details and characterization data are provided for the compounds reported in this paper. Details are also provided for the single-crystal X-ray structure determination of compound **8d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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