Intramolecular C-H Insertion Reactions of Iron Carbene Complexes as a General Method for Synthesis of Bicyclo[n.3.0]alkanones

Shingo Ishii, Paul Helquist*

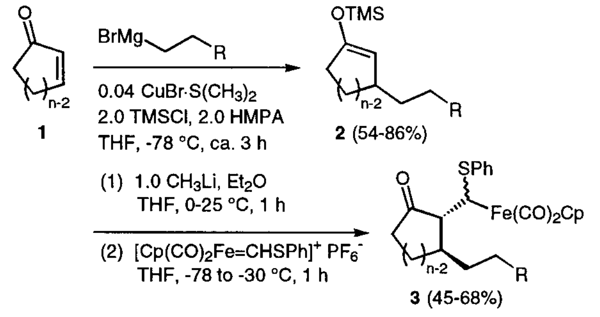
Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556 U.S.A.

Received 10 October 1996

This paper is dedicated to Professor E. J. Corey in recognition of the great service, commitment, and inspiration that he has provided to the world of organic chemistry during the past five decades

Abstract: Iron carbene complexes tethered to substituted cycloalkanones undergo intramolecular C-H insertion reactions with alkyl side chains to produce a variety of substituted bicyclo[n.3.0]alkanone derivatives.

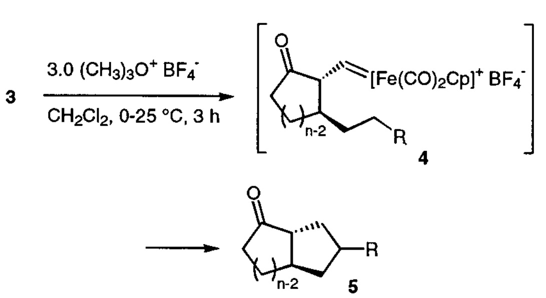
Transition metal carbene complexes have taken a key place among organometallic species having important applications in synthetic organic chemistry.[1] Carbene complexes are frequently generated as reactive intermediates under metal-catalyzed conditions, but many also function as useful stoichiometric reagents. In the former category are the well-known reactions of diazocarbonyl compounds catalyzed by rhodium, copper, and other metal complexes. Among the stoichiometric complexes, the Fischer carbene complexes, $(CO)_5M{=}C(R)OR'$ (M = Cr, Mo, or W), and the iron complexes, $[Cp(L)_2Fe{=}CRR']^+ X^-$ (Cp = cyclopentadienyl; L = CO or phosphine ligand; X^- = BF_4^- or other non-coordinating anion), have seen especially widespread applications. The iron complexes in particular have proven to be very useful for the conversion of alkenes into cyclopropanes.[2] However, in a few isolated cases, these complexes have also been seen to undergo intramolecular C-H insertion reactions to give cyclopentane derivatives.[3] Insertion reactions are much more fully developed for the rhodium-catalyzed reactions of diazocarbonyl compounds.[4] Therefore, we perceived the need to perform a preliminary assessment of the scope of the intramolecular insertion reactions of the iron complexes. In this work, we have placed emphasis on the construction of cyclopentane derivatives fused to other rings of various sizes. The resulting bicyclo[n.3.0] systems are ubiquitous among natural products and many other carbocyclic compounds of widespread interest.



Scheme 1

The substrates for these studies are obtained straightforwardly from 2-cycloalkenones (Scheme 1). Copper-catalyzed conjugate additions of Grignard reagents in the presence of trimethylsilyl chloride[5] provide the enol silyl ethers **2**. Enolate regeneration and alkylation with a stabilized iron phenylthiocarbene complex[6] afford the desired substrates **3** as mixtures of diastereomers which are normally used directly in the subsequent cyclizations without further purification.

S-Methylation of the substrates **3** and loss of thioanisole generate the iron carbene complexes **4** as reactive intermediates.[2] Intramolecular insertions into C-H bonds of the side chains then produce the bicyclo[n.3.0]alkan-2-ones **5** (Scheme 2). The results are summarized in Table 1. The indicated stereochemical assignments are based upon high-field ^1H and ^{13}C NMR studies.



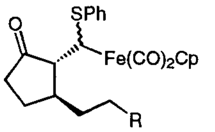
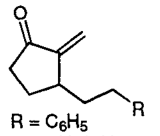
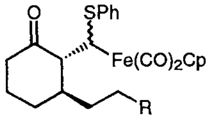
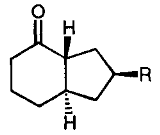
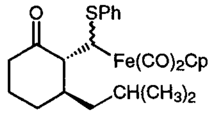
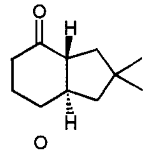
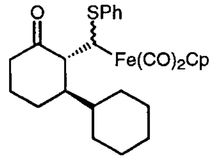
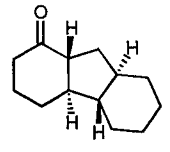
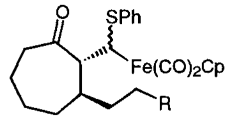
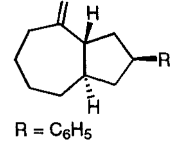
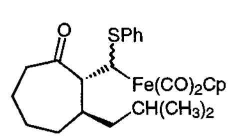
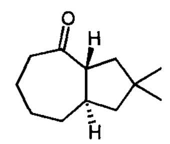
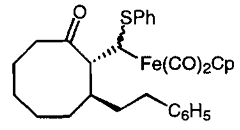
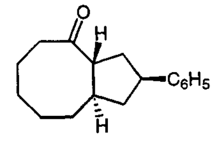
Scheme 2

A number of conclusions can be drawn from these results. First of all, the method is useful for cyclopentane annulation onto pre-existing six-, seven-, and eight-membered rings to give bicyclo[n.3.0]alkan-2-ones where n = 4, 5, and 6 (see entries 3-12). On the other hand, the method is not useful for the *trans*-substituted five-membered ring substrates that have been studied to date (entries 1 and 2). This limitation is likely to arise in these cases from the strain that would be inherent in the transition state for formation of a *trans*-bicyclo[3.3.0]octanone. Consequently, the intermediate carbene complexes instead undergo elimination to the corresponding unsaturated ketones. Although the possible dependence of this reaction on ring fusion stereochemistry has not been tested, it is conceivable that the failure to form bicyclo[3.3.0]octanones by this approach may be restricted to the *trans*-fused series; appropriate studies of the formation of *cis*-fused products have yet to be performed. Entry 2 also demonstrates the lack of propensity to form six-membered rings, even though a favorable site for insertion is available for this alternative pathway.

Another observation is the greater efficiency of insertion into benzylic (entries 3, 4, 9, and 12), tertiary (entries 7 and 11), and allylic positions (entry 5) compared to secondary positions (entries 6, 8, and 10). Furthermore, the reactions at allylic and benzylic positions occur with high stereoselectivity whereby only single diastereomers are detected in these cases (entries 3, 4, 5, 9, and 12). In contrast, insertions into secondary positions show low or no stereoselectivity (entries 6 and 10). We have yet to observe an insertion into a primary C-H bond. Although we have not performed a rigorous competition study of preferred sites of insertion, the above results appear to be in partial contrast with rhodium-catalyzed insertion reactions of diazocarbonyl compounds for which the order of site preference in some related cases is tertiary > secondary > allylic and benzylic based upon internal competition studies.[7] Another contrast that can be drawn between the rhodium-catalyzed reactions and the present iron-based results is that the reactive carbene center undergoing the insertion reaction is α to a carbonyl group in the former but β to a carbonyl group in the latter. Both of these points pertaining to sites of reaction are of relevance in planning possible applications of these insertions, and also illustrate some of the complementary features of the rhodium- and iron-based methods.

In summary, the intramolecular C-H insertion reactions of iron carbene complexes provide a general pathway for the construction of fused ring systems. Furthermore, the iron- and the rhodium-based reactions appear to complement each other with respect to their potential synthetic applications. However, much work remains to be done to develop the full potential of the iron-based method, including further investigation of the scope of the reaction, the effects of employing other ligands on the lifetime and the reactivity of the iron carbene intermediates, and the possibility of developing catalytic and asymmetric versions of these reactions.

Table 1. Intramolecular C-H Insertion of Iron Carbene Complexes

Entry	Substrate	Product	Yield (%)
1 2		 R = C_6H_5 R = $CH_2C_6H_5$	8 12
3 4 5 6		 R = C_6H_5 R = $4\text{-}C_6H_4OCH_3$ R = $CH{=}C(CH_3)_2$ R = Et, (β-Et:α-Et = 2:1)	90 96 63 31
7			72
8			52
9 10		 R = C_6H_5 R = Et, (β-Et:α-Et = 1:1)	92 31
11			77
12			90

Representative Procedure: 8-Phenylbicyclo[4.3.0]nonan-2-one(**5**, n = 4, R = Ph). 1-Trimethylsilyloxy-3-(2-phenylethyl)-1-cyclohexene (**2**, n = 4, R = Ph) was obtained by a well-established procedure employing 2-cyclohexenone, 2-phenylethylmagnesium bromide, catalytic CuBr·SMe$_2$, trimethylsilyl chloride, and HMPA.[5] To this silyl enol ether (0.274 g, 1.00 mmol) in THF (5 mL) at 0 °C under nitrogen was added methyllithium in ether (1.4 *M*, 0.72 mL, 1.0 mmol) over a 2-min period. The solution was stirred at 0 °C for 0.5h, then warmed to 25 °C for 0.5 h, cooled to -78 °C, and transferred by cannula into a solution of $Cp(CO)_2Fe^+{=}CHSPh\ PF_6^-$ (0.444 g, 1.00 mmol) in THF (4 mL) at -78 °C. The mixture was stirred for 1 h, slowly warmed to ca. -30 °C, and diluted with pre-cooled hexanes (20 mL, -78 °C). After 5 min, the mixture was filtered, and the filtrate was concentrated under vacuum to give **3** (n = 4, R = Ph) as a red oil which could be purified by column chromatography or used directly in the next step. A solution of this compound (0.250 g, 0.500 mmol) and methylene chloride (20 mL) was added to trimethyl-oxonium tetrafluoroborate[8] (0.222 g, 1.5 mmol) at 0 °C under nitrogen. After slowly being warmed to 25 °C over a 1 h period and then stirred for 2 h, the dark red solution was diluted with hexanes (25 mL) and stirred for ca. 5 min to precipitate the inorganic material. The solution 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 column chromatography (silica gel, 1:5 methylene chloride/hexanes) to give 0.096 g (90%) of **5** (n = 4, R = Ph) as a colorless crystalline solid: mp 46-46.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (m, 5 H, Ar<u>H</u>), 3.19 (tdd, *J* = 11.1, 6.8, 4.6 Hz, H-2), 2.58 (tdd, *J* = 10.9, 8.9, 0.6 Hz, H-3a), 2.47 (dt, *J* = 13.6, 10.9 Hz, H-3α), 2.38 (bd, *J* = 13.8 Hz, H-5α), 2.33 (ddd, *J* = 12.1, 7.2, 5.1 Hz, H-1α), 2.31 (tdd, *J* = 13.5, 7.0, 0.9 Hz, H-5β), 2.15 (dddt, *J* = 13.4, 6.6, 4.6, 2.3 Hz, H-6β), 2.07 (bdd, *J* = 12.8, 3.0 Hz, H-7α), 1.80 (qdd, *J* = 11.9, 5.2, 3.2 Hz, H-7a), 1.75 (ddd, *J* = 13.5, 8.1, 5.1 Hz, H-3β), 1.71 (qdd, *J* = 13.3, 4.9, 4.5 Hz, H-6α), 1.52 (qd, *J* = 12.2, 4.3 Hz, H-7β), 1.51 (td, *J* = 11.8, 10.7 Hz, H-1β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.60 (C-4), 147.08 (*ipso*-Ph), 128.36 (Ph), 126.89 (Ph), 125.76 (Ph), 57.93 (C-3a), 50.00 (C-7a), 42.67 (C-1), 42.13 (C-2), 41.31 (C-5), 30.86 (C-3), 30.50 (C-7) 27.65 (C-6); IR (CH_2Cl_2) 3030 (Ar), 2930 (CH), 1702 (CO) cm^{-1}; MS (EI), *m/e* (rel intensity) 214 (100, M$^+$), 171 (61), 160 (22), 143 (30), 128 (20), 115 (17), 110 (29), 97 (50, M - $C_6H_5C_3H_4$), 91 (50). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.94; H, 8.58.

Acknowledgment. We are grateful to Dr. Shikai Zhao and Dr. Christopher Knors for their contributions to the earlier stages of this work. We also acknowledge generous support provided by the National Science Foundation, the National Institutes of Health, the Petroleum Research Fund, administered by the American Chemical Society, and the University of Notre Dame.

References and Notes

1. (a) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Weinheim, 1983. (b) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Paquette, L. A., Vol. Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1065-1113. (c) Padwa, A.; Austin, D. J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1797. (d) Simpson, S. J. *Organometal. Chem.* **1994**, *24*, 316 and the earlier volumes of this series.
2. (a) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411. (b) Helquist, P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: London, 1991; Vol. 2, pp 143-194. (c) Petz, W. *Iron-Carbene Complexes*; Springer-Verlag: Berlin, 1993.
3. (a) Zhao, S.-K.; Knors, C.; Helquist, P. *J. Am. Chem. Soc.* **1989**, *111*, 8527. (b) Zhao, S.-K.; Helquist, P. *J. Org. Chem.* **1990**, *55*, 5820. (c) Zhao, S.; Mehta, G.; Helquist, P. *Tetrahedron Lett.* **1991**, *32*, 5753. (d) Zhao, S. Ph.D. Dissertation, University of Notre Dame, 1991. (e) Ishii, S. Ph.D. Dissertation, University of Notre Dame, 1996.
4. (a) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pattenden, G., Vol. Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 1045-1062. (b) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (c) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (d) Doyle, M. P. *Aldrichim. Acta* **1996**, *29*, 3. (e) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837. (f) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706.
5. (a) Bourgain-Commerçon, M.; Foulon, J.-P.; Normant, J. F. *J. Organomet. Chem.* **1982**, *228*, 321. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Ibid.* **1986**, *27*, 1047. (d) Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087. (e) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575. (f) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1988**, *44*, 2055.
6. (a) Knors, C.; Kuo, G.-H.; Lauher, J. W.; Eigenbrot, C.; Helquist, P. *Organometallics* **1987**, *6*, 988. (b) Knors, C.; Helquist, P. *Organomet. Synth.* **1988**, *4*, 205.
7. (a) Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 7686. For contrasting cases, see: (b) Ceccherelli, P.; Curini, M.;

Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 7065. (c) 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. (d) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296.

8. Meerwein, H. *Organic Syntheses Coll. Vol. V*; Baumgarten, H. E., Ed.; Wiley: New York, 1973; pp 1096-1103.