Stereochemical Probes of Intramolecular C−H Insertion Reactions of Iron-Carbene Complexes

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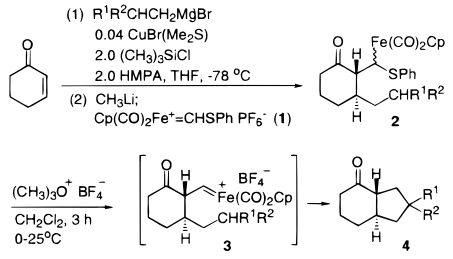
A common characteristic of carbenes and metal-carbene complexes is their propensity to undergo insertion reactions into O−H, N−H, and C−H bonds.[1] Several forms of intramolecular C−H insertions, including enantioselective versions, have been developed for the construction, most importantly, of cyclopentanes and five-membered heterocycles. The importance of these reactions is reflected by their widespread use in synthesis.

We have reported the use of (η^5-cyclopentadienyl)(dicarbonyl)-iron-carbene complexes, $[(C_5H_5)(CO)_2Fe{=}CHR]^+ X^-$, in intramolecular C−H insertion reactions,[2,3] and we have employed these reactions in natural product syntheses.[4] A few related reactions of iron complexes have been reported by other workers.[5] However, a detailed understanding of the stereochemistry of these reactions is needed before more elaborate applications are pursued. We now report our studies of key stereochemical features of iron-carbene insertions.

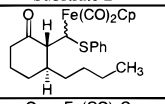
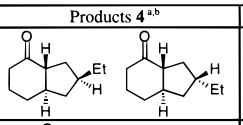
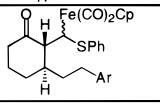
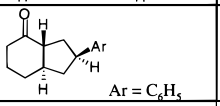
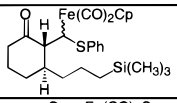
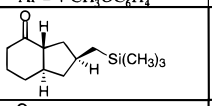
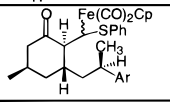
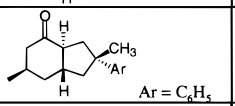
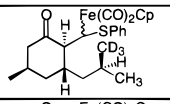
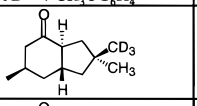
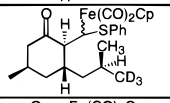
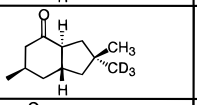
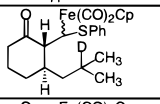
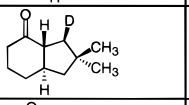
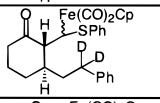
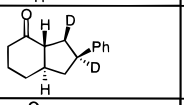
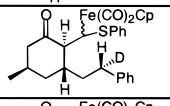
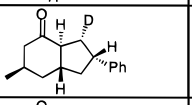
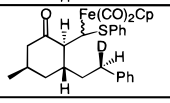
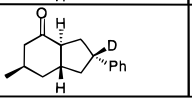
Useful scaffolds for these reactions are obtained by copper-promoted 1,4-addition of Grignard reagents to cyclohexenone followed by enolate alkylation with thiocarbene complex **1**[6] (Scheme 1).[2] *S*-Methylation of the thioalkyliron derivatives **2** with

Scheme 1



trimethyloxonium tetrafluoroborate[7] and loss of thioanisole generate carbene complexes **3**. Intramolecular C−H insertion produces fused cyclopentanes **4**. We have chosen several side chains (Table 1) to probe the stereochemical outcome of the cyclization.

Table 1. Stereochemical Probes of Intramolecular Iron-Carbene C−H Insertion Reactions

Entry	Substrate **2**[a]	Products **4**[a,b]	Yields
a			31% (2:1)
b			90%
c		Ar = 4-$CH_3OC_6H_4$	96%
d			86%
e[c]			70%
f[c]		Ar = 4-$CH_3OC_6H_4$	78%
g[c,d]			50%
h[c,d]			56%
i			70%
j			90%
k[c]			75%
l[c]			78

[a] Substrates and products were racemic unless otherwise indicated. [b] Products were formed as one major diastereomer (≥90%) unless otherwise indicated. [c] Substrate and product were obtained stereoselectively in the major enantiomeric form shown. [d] ∼5−10% of diastereomeric product detected by ^{13}C NMR; see footnote 8.

The observation that a simple alkyl side chain (entry a) results in the formation of a mixture of diastereomers, whereas more sterically demanding (and perhaps electronically perturbing) 2-arylethyl (entries b and c) and 3-(trimethylsilyl)propyl (entry d) side chains occur with high diastereoselectivity[8] is important in planning applications of this procedure, but this observation is

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(8) Stereoisomeric compositions were determined by ^1H and ^{13}C NMR having lower limits of detection of minor isomers of ∼5−10%. Several stereochemical assignments are based upon nOe studies. Details are in the Supporting Information. The structure of **4b** was confirmed by X-ray diffraction. In entries g and h of Table 1, small amounts (∼5−10%) of the diastereomeric products **4h** and **4g** were detected by ^{13}C NMR.; they were likely due to non-diastereomerically pure precursors rather than actual crossover during the insertion reactions. The locations of the isotopic labels in products **4i**−**l** were determined by comparison of ^1H and ^{13}C NMR spectra of these compounds and their separately prepared, non-deuterated counterparts.

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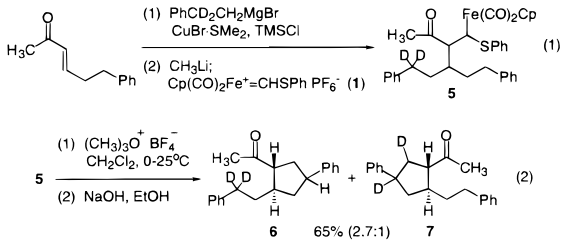
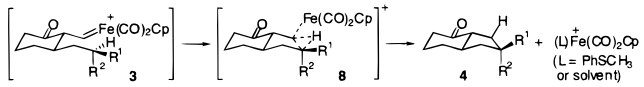
not particularly revealing with respect to more subtle, mechanistically related, stereochemical aspects of this reaction. More informative are the results obtained with substrates having two different substituents at the insertion sites. Substrates **2e** and **2f** were prepared with the depicted absolute configurations (entries e and f).[9] Subsequent insertion reactions gave stereoisomers **4e** and **4f** as the major cyclization products with ≥90% diastereoselectivity.[8] Entries g and h serve as especially sensitive probes of stereochemistry whereby the CH_3 and CD_3 groups have essentially identical steric requirements but yet the isotopically diastereomeric substrates **2g** and **2h** give the diastereomeric products **4g** and **4h**, respectively, with ∼90% stereoselectivity.[8] The deuterium-labeled substrates in entries i through l serve as probes of the origin of the participating hydrogen atom and its location in the insertion products.[8]

Deuterium-labeled **5** was prepared (eq 1) as a preliminary probe of primary kinetic isotope effects. Cyclization followed by base-catalyzed equilibration of *cis* and *trans* products gave **6** and **7** in a ratio of approximately 2.7:1 (eq 2).[10] This internal competition experiment suggests a primary isotope effect of this magnitude. This value must be regarded cautiously as a tentative estimate due to possible stereochemical complications of preparing a substrate **5** having three stereogenic centers without a good measure or good control of the actual diastereomeric composition.



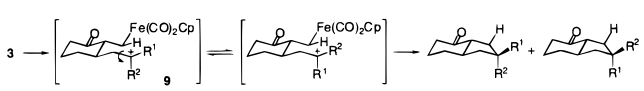
Previous studies of C−H insertion reactions of carbenes and metal-carbene complexes suggest that they often occur by concerted, one-step pathways, although stepwise mechanisms may apply in some cases whereby transfer of hydrogen produces charged or radical intermediates followed by separate radical or dipolar recombination.[1,11,12] The concerted pathway has commonly been invoked for metal-catalyzed cyclizations of diazocarbonyl compounds which most likely occur via metal-carbene complexes.[1,12] Taken as a set, our results can best be accommodated by a one-step, concerted insertion of an iron-carbene complex into a properly situated C−H bond via a chair-like, cyclic transition state **8** (Scheme 2).

Scheme 2



A stepwise pathway involving an internal hydride transfer to form a carbocation intermediate **9** appears to be untenable due to the expected rapid carbon−carbon single bond rotation that would produce a mixture of diastereomeric products (Scheme 3). In the

Scheme 3



cases of entries g and h, these rotations would have led to mixtures of products **4g** and **4h** having essentially equal stabilities, but these products were obtained with ∼90% diastereoselectivity in each case. In entry f, the *p*-methoxyphenyl substituent may have been anticipated to provide extra stabilization and therefore a longer lifetime for a carbocationic intermediate that again could have undergone bond rotation, leading to a mixture of diastereomeric products,[13] but the reaction was highly diastereoselective. In entry d, β-silicon stabilization of a carbocationic intermediate and subsequent elimination of the silyl group may have been expected to generate an alkene side product, which was not seen.

The tentative estimate of a primary kinetic isotope effect of approximately 2.7 is in good agreement with values that are most typically in the range 1.6−4.2 for related insertion reactions of carbenes[11a−c,d,f,g,i,j] and in the range 1.2−3.1 for metal-catalyzed insertions of diazo compounds or reactions of preformed metal-carbene complexes.[12c,h,u] In some cases of stepwise radical pathways, larger values have been reported for carbene insertions.[11g] The relatively small kinetic isotope effect seen in the present work suggests only a modest extent of net C−H bond breaking in the transition state. More rigorous studies will be necessary before drawing firmer conclusions.

Intramolecular C−H insertion reactions of iron-carbene complexes provide a highly stereoselective route to cyclopentanes. The results of this study will permit applications in synthesis for which a given stereochemical outcome can be planned with a high level of confidence. Attractive further goals are to develop more cost-effective catalytic reactions, even though iron is inexpensive, and to develop asymmetric versions of these reactions.

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Supporting Information Available: Experimental procedures and selected NMR spectra for precursors, cyclization substrates, and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Stereoselective syntheses of these substrates are described in the Supporting Information.

(10) This experiment was performed four times to give a product ratio of 2.7 ± 0.3.

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