Enantiospecific Cis-Cyclopropane Synthesis Using the Chiral Iron Carbene Complexes *S*- and *R*-(η^5-C_5H_5)$(CO)_2$Fe=CH[(η^6-*o*-$CH_3C_6H_4$)Cr$(CO)_3$]$^+$

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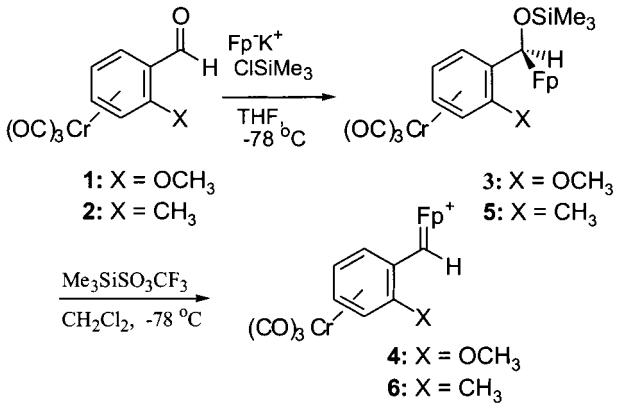
*Summary: The first enantiospecific cis-cyclopropanation reaction involving a chiral-at-carbene-ligand complex was developed by utilizing the carbene complex S- or R-Cp$(CO)_2$Fe=CH[η^6-(o-$CH_3C_6H_4$)Cr$(CO)_3$]$^+$ (**6**). Low-temperature NMR studies indicate that the ratio of syn to anti isomer of the carbene is related to the enantioselectivity of cyclopropanation and lead to the design of **6**, which occurs exclusively in the anti conformation.*

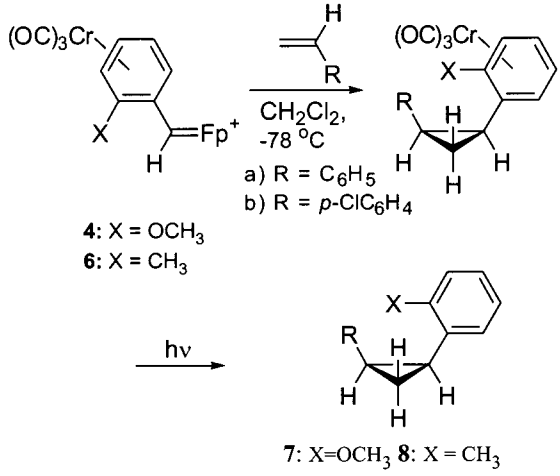
Iron carbene complexes have been widely used in the formation of cyclopropanes from olefins.[1,2] Considering the presence of cyclopropane rings in many biologically active compounds such as cilastatin and 19-epicuracin A the importance of enantioselective cyclopropane synthesis emerges. In the study of asymmetric cyclopropanation reactions, chiral-at-iron carbene complexes Cp(CO)(PR′$_3$)Fe=CHR$^+$ have been used to prepare the cyclopropanes in an enantioselective manner.[3−6] Due to the existence of anticlinal and synclinal isomers, and their interconversion caused by C=Fe double-bond rotation, the asymmetric induction varied depending on the experimental conditions.[5,6] To avoid this problem and to find a practical route for asymmetric synthesis, we decided to move the chiral center to the carbene ligand.[7] In this context we recently reported the synthesis of the chiral carbene complex Cp$(CO)_2$Fe=CH[η^6-(*o*-$CH_3OC_6H_4$)Cr$(CO)_3$]$^+$ (**4**), which was successfully used in the preparation of *S*-(+)-2,2-dimethylcyclopropanecarboxylic acid.[8] The precursor to this carbene is readily obtained as a yellow solid in 80% yield by reacting either (−)- or (+)-(*o*-anisolecarboxaldehyde)tricarbonylchromium (**1**) with Fp anion, followed by chlorotrimethylsilane trapping (Scheme 1).

When this new chiral carbene reacted with monosubstituted alkenes such as styrene, predominantly the cis-cyclopropane **7** was formed (Scheme 2), making **4** one of the few systems exhibiting such selectivity. However, the enantiomeric excess (ee) was considerably lower in comparison to the disubstituted alkenes.[9] It was proposed that this lower ee was caused by the possibility of two isomers of **4**, which differ by rotation of the (*o*-$CH_3OC_6H_4$)Cr$(CO)_3$ moiety about the C_α−C_{ipso} single bond. To verify this hypothesis, we prepared the carbene complex in situ in an NMR tube at low temperature and introduced the sample into the precooled NMR probe. As suspected, two sets of signals were observed in the ^{1}H NMR spectrum. With the help of a NOESY spectrum it was confirmed that both the syn and anti isomers were present with a relative ratio of 1.8/1 at 193 K (Figure 1), each of which gives rise to a distinguished

Scheme 1. Formation of Carbene Complexes 4 and 6 (Fp = CpFe$(CO)_2$)



Scheme 2. Cyclopropane Formation



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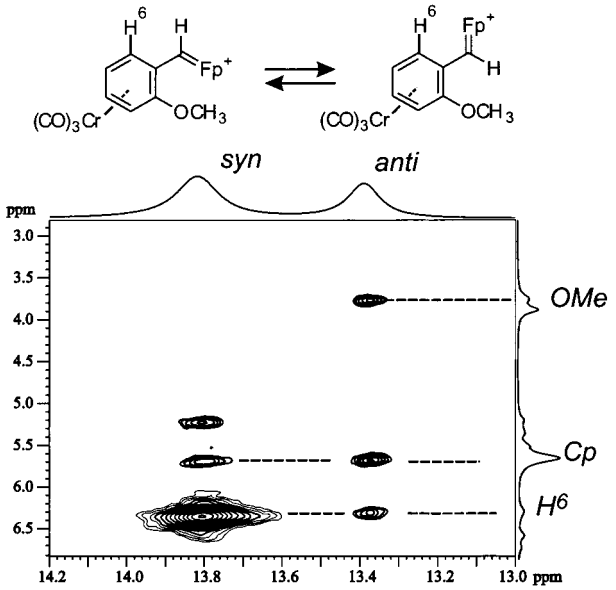

Figure 1. Carbene region of the NOESY spectrum of **4** (T = 183 K, τ_{mix} = 300 ms).

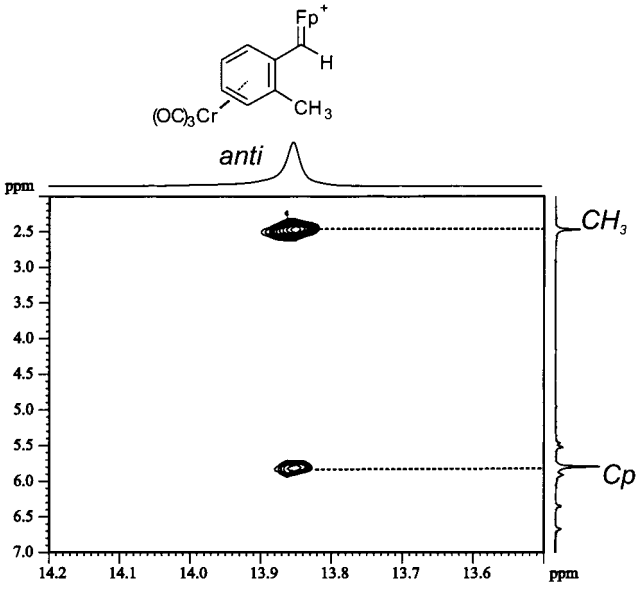

Figure 2. Carbene region of the NOESY spectrum of **6** (T = 233 K, τ_{mix} = 400 ms).

NOE pattern. In particular, in the case of the syn isomer a strong interaction with H-6 of the aromatic ring is observed, while only the anti isomer exhibits a carbene/OCH_3 cross-peak. Both isomers were further characterized using ^1H, ^{13}C, and $^1H\{^{13}C\}$-HMQC NMR experiments to confirm that assignment.

The presence of both the syn and anti isomers implies that there are two possibilities for olefins to react with the carbene **4** to give different enantiomers of the cyclopropane, thus reducing the enantioselectivity of the cyclopropane formation. Matters are complicated by slow interconversion of the syn and anti isomers, the details of which are currently under closer investigation. One apparent strategy to improve the enantioselectivity of cyclopropane formation is to improve the preference of one carbene isomer over the other. It may be rationalized that the electron lone pair of the methoxy group stabilizes the sterically more demanding syn isomer by electrostatic interaction. Following this line of argument, the conformation of the chiral carbene complex *S*- or *R*-$Cp(CO)_2Fe{=}CH[\eta^6$-(*o*-$CH_3C_6H_4$)$Cr(CO)_3]^+$ (**6**) should be determined by steric factors alone, since the aforementioned electrostatic interaction is eliminated and the anti isomer is expected to dominate. In the presence of only one rotamer enantiospecific cyclopropane synthesis is possible, especially for monosubstituted alkenes. Our study confirmed this point by both low-temperature NMR study and asymmetric synthesis of cyclopropanes. The carbene precursor **5** was prepared using the same procedure as described previously for the preparation of its 5-methoxy analogue **3**, employing either (−)- or (+)-*o*-toluenealdehyde(tricarbonyl)chromium (Scheme 1). Characterization by ^1H NMR and $^1H\{^{13}C\}$ HMQC experiments obtained at temperatures from −90 to +10 °C indicated the presence of only a single carbene species. A 2-D NOESY experiment performed at 233 K (Figure 2) shows for the carbene proton only strong interaction with the methyl protons, but no NOE cross-peak is observed with H-6 of the phenyl group. Thus, the single rotamer present for **6** is identified as the anti isomer.

Table 1. Summary of ee Values, Cis:Trans Ratios and Overall Yields (%) for Cyclopropane Formation

carbene	$CH_2{=}CHR$	yield, %	cis:trans	ee (cis)
***R*-6**	R = Ph	80	cis only	>95[a]
***S*-6**	R = Ph	80	cis only	>95[a]
***R*-6**	R = *p*-ClC_6H_5	70	6:1	>95[a]
***S*-6**	R = *p*-ClC_6H_5	70	6:1	>95[a]
***R*-4**	R = Ph	93	10:1	60[b]
***S*-4**	R = Ph	89	10:1	60[b]
***R*-4**	R = *p*-ClC_6H_5	60	6:1	46[b]

[a] This work. [b] Reference 9.

To carry out the asymmetric cyclopropanation reaction, the carbene precursor *SR*-**5** or *RS*-**5** was treated with 1 equiv of trimethylsilyl triflate at −78 °C in the presence of 4 equiv of styrene. After cleavage of the $Cr(CO)_3$ moiety the chiral cyclopropane **8** was obtained in good yield (Scheme 2). The ee of the *R*-cis cyclopropane was determined by proton NMR, utilizing a combination of D-Yb(hfc)$_3$ and Ag-fod in $CDCl_3$ as chiral shift reagents. It turned out that only one enantiomer could be detected, corresponding to an ee >95% and thus an enantiospecific formation of cyclopropane (+)-**8**. The same result was obtained when the opposite enantiomer (−)-**8** was prepared starting from the carbene complex *S*-**6**. As a control experiment, the racemic mixture of *R*/*S*-**6** gave two 1:1 sets of proton NMR signals in the presence of the chiral shift reagent. To demonstrate the general applicability of the method, the reaction was repeated with *p*-chlorostyrene, resulting in a similar selectivity. The results are summarized in Table 1 and compared to ones obtained previously with the methoxycarbene.

In conclusion, the first enantiospecific cis-cyclopropanation reaction involving a chiral-at-carbene-ligand complex was developed. Low-temperature NMR studies indicate that the ratio of syn to anti isomer of the carbene is related to the enantioselectivity of cyclopropanation and lead to the design of carbene complex **6**, which occurs exclusively in the anti conformation and as a result supports enantiospecific synthesis of cyclopropanes. The method can be applied to synthesize both

enantiomers of cyclopropanes from the corresponding aldehydes **2**. Further study is currently underway in order to investigate the mechanism and apply this novel method to the organic syntheses.

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Supporting Information Available: Text giving experimental details about the preparation of **4**, **6**, and **8** and ^{1}H and ^{13}C NMR data of **4**−**6** and **8** and figures giving ^{1}H NMR spectra of **8** in the presence of shift reagents, illustrating the measurement of ee. This material is available free of charge via the Internet at http://pubs.acs.org.

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