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Study of the origin of enantioselectivity in cyclopropanation reactions using the chiral iron carbene complex $[(\eta^5\text{-}C_5H_5)(CO)_2Fe{=}CH[(\eta^6\text{-}o\text{-}MeOC_6H_4)Cr(CO)_3]]^+$

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Abstract

During our low temperature NMR studies we observed two rotational isomers of the carbene complex $[(\eta^5\text{-}C_5H_5)(CO)_2Fe{=}CH[(\eta^6\text{-}o\text{-}MeOC_6H_4)Cr(CO)_3]]+$ (**3**) with the O–Me group either *anti* or *anti* to the Fp moiety. While the $Cr(CO)_3$ group very effectively shields one face of the carbene complex from attack by the olefin, the presence of *anti* and *anti* isomers allows for the formation of both *R* and *S* configuration on C-1 of the cyclopropane through a backside or a frontside ring closure mechanism. The reaction of olefin with *anti R*-3 can result in *R*-configuration of the cyclopropane carbon C-1 through a frontside closure mechanism, or in *S*-configuration if backside closure takes place. In a similar manner, *anti R*-3 may produce *S*-configuration through frontside closure or *R*-configuration through backside closure. We previously have shown by crystallography that reaction the *R*-isomer of **3** with 2-methyl-propene induces predominantly a *R*-configuration at C-1 of the resulting cyclopropane (*RR*-(−)-2,2 dimethyl-1-*o*-methoxyphenyl(tricarbonyl chromium)cyclopropane, whereas the *S*-carbene results in the corresponding *SS* isomer. These findings are consistent with cyclopropane formation from the *syn* isomer through a frontside closure mechanism or from *anti* isomer through a backside closure mechanism. In the case of $[(\eta^5\text{-}C_5H_5)(CO)_2Fe{=}CH[(\eta^6\text{-}o\text{-}MeC_6H_4)Cr(CO)_3]]+$ (**4**), only *anti* isomer is observed and optical rotation data indicate that the methylcarbene exhibits the same asymmetric induction (i.e., *R*-carbene yields *R*-cyclopropane C-1 and *S*-carbene yields *S*-cyclopropane C-1) as the methoxy analogue, and the assumption of the *anti* isomer being the reactive one then implies that the reaction proceeds through a backside closure mechanism rather a frontside mechanism. It is very likely that this preference is also valid for the methoxy substituted complex **4**. Our results on **4** indicate that the enantioselectivity of the cyclopropanation reaction is not determined by the relative abundance of the isomers. As the *syn* isomer is the more abundant one, the *anti* isomer has to be the more reactive one compared to the *syn* isomer. Interchange of *syn* and *anti* isomers occurs fast compared to the rate of reaction of the carbene with olefin. The fast rate of interchange of *syn* and *anti* isomers relative to the rate of reaction with olefin precludes the direct observation of any differential reactivity form a change in the *syn* to *anti* ratio in the NMR spectrum. However, the in general lower ee values observed for **3** compared with **4** are consistent with the fact that the reactive isomer is less abundant in this case. Our data thus show that enantioselectivity of cyclopropanation with "chiral at carbene" complexes is controlled by the higher reactivity of the *anti* isomer and occurs through a backside ring closure mechanism.

Keywords: Chiral iron carbene; Asymmetric cyclopropantion; Enantioselectivity; *syn*/*anti* Isomers; Backside and frontside ring closure

1. Introduction

The cyclopropane group is an important structural component in many natural and unnatural products like cilastatin, the antibiotic W-7783 or 19-epicuracin A, to name just a few. Many cyclopropane syntheses involving metal carbene complexes have been described, both at a catalytic and stoichiometric scale. One important stoichiometric carbene transfer reagent used for asymmetric cyclopropanation is the iron carbene complex $Cp(CO)\text{-}PR'_3Fe{=}CHR$, which employs a chiral center on the iron

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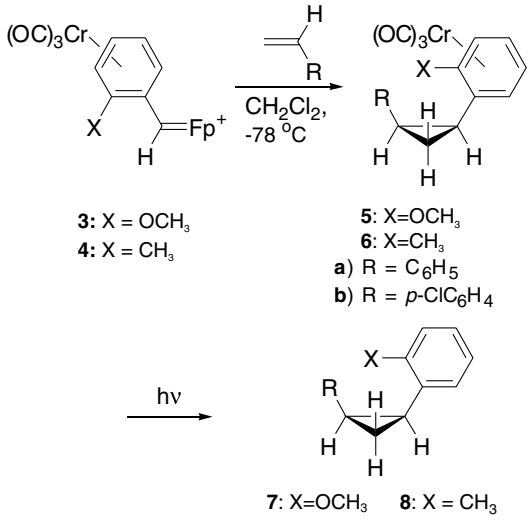
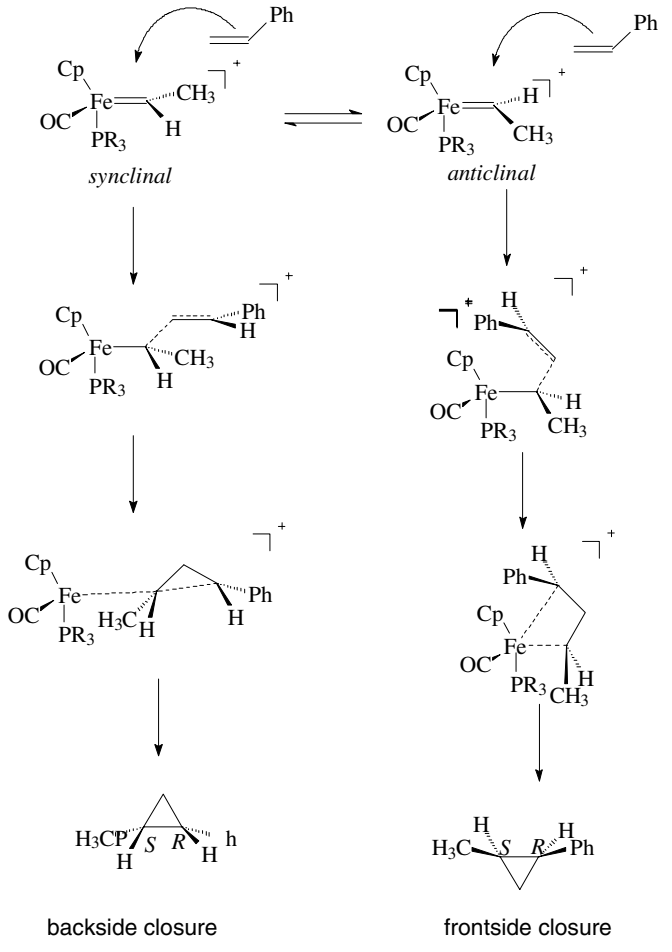
to induce enantioselective carbene transfer [1–4]. Investigation into the mechanisms of this reaction reveals that enantioselectivity is potentially controlled by two factors: first, initial attack of the olefin can occur on either the synclinal and anticlinal isomer, which are related to each other by rotation around the Fe=C bond, and are commonly in rapid exchange with each other. Second, formation of the three membered ring can occur either through a frontside closure process preserving the configuration at C, or through a backside closure involving inversion at C_α. Two important pieces of information emerging from Brookhart's studies [5] are that the synclinal isomers appear to be the more reactive ones and that the cyclopropane ring forms through a back side closure process [2] (Scheme 1).

In an attempt to avoid the problem of isomerization around the Fe=C_α bond, we developed cyclopropanation reactions employing the carbene complex $Cp(CO)_2$-Fe=CH[η^6-(*o*-$MeOC_6H_4$)$Cr(CO)_3$]$^+$ (**3**) in which the chiral center is moved from the metal center to the carbene ligand [6] (Scheme 2). This carbene complex is prepared in situ from the precursor $Cp(CO)_2Fe$=CH($OSiMe_3$)[η^6-(*o*-$MeOC_6H_4$)$Cr(CO)_3$] by addition of $Me_3SiSO_3CF_3$ (trimethylsilyl triflate) at −78 °C. Reaction with disubstituted olefins resulted in ee values as high as 95% [7]. While reaction with monosubstituted olefins like styrene yielded mainly *cis*-cyclopropanes, the ee values were considerably lower (46–60%) [8] (Table 1). In order to improve the selectivity of the reaction, we embarked on a study of the mechanism of cyclopropanation to identify the driving force for asymmetric induction in the case of chiral-at-carbene complexes. With this new carbene complex, rotation around the C_α–C_{ipso} bond rather than the Fe=C_α bond becomes important in determining the enantioselectivity of the reaction. We recently communicated preliminary results indicating that in the case of the methoxy substituted carbene complex **3**, two isomers related by rotation around the C_α-C_{ipso} bond are observed [9]. This led us to the design of methyl carbene complex **4**, in which only the sterically more stable *anti* isomer is observed, and cyclopropane formation is highly stereoselective (ee > 95%). In this paper we will present a closer analysis of the relationship between enantioselectivity of cyclopropane formation and



Scheme 2. Cyclopropane formation from "chiral at carbene" complexes.



Scheme 1. Possible mechanisms for cyclopropane formation from "chiral at iron" carbene complexes.

Table 1
Summary of ee, *cis*:*trans* ratio and overall yields (%) for cyclpropane formation

Carbene	CH_2=CHRR′	Yield	*cis*:*trans*	ee (*cis*)
R-**4**	R = Ph, R′ = H	80%	*cis* only	>95[a]
S-**4**	R = Ph, R′ = H	80%	*cis* only	>95[a]
R-**4**	R = *p*-ClC_6H_5, R′ = H	70%	6:1	>95[a]
S-**4**	R = *p*-ClC_6H_5, R′ = H	70%	6:1	>95[a]
R-**3**	R = CH_3, R′ = CH_3	90%	–	>95[b]
S-**3**	R = CH_3, R′ = CH_3	89%	–	>95[b]
R-**3**	R = Ph, R′ = Ph	85%	–	92[b]
S-**3**	R = Ph, R′ = Ph	86%	–	92[b]
R-**3**	R = Ph, R′ = H	93%	10:1	60[b]
S-**3**	R = Ph, R′ = H	89%	10:1	60[b]
R-**3**	R = *p*-Cl–Ph, R′ = H	60%	6:1	46, 53[b]
R-**3**	R = *p*-CF_3Ph, R′ = H	45%	3:1	30, 72

[a] Ref. [9].
[b] Ref. [7].

conformational interchange and reactivity of the carbene intermediate.

2. Results

2.1. Low temperature NMR

The carbene complex $[(\eta^5\text{-}C_5H_5)(CO)_2Fe{=}CH[(\eta^6\text{-}o\text{-}MeOC_6H_4)Cr(CO)_3]]^+$ (**3**) was prepared in situ in an NMR tube by combining the precursor **2** with TMSOTf and condensing CD_2Cl_2 at liquid nitrogen temperature into the mixture. After thawing at −78 °C the samples were introduced into the precooled NMR probe. Two sets of signals indicative of two isomers of carbene complex **3** were observed in the ^1H NMR spectrum at 193 K. The =C–H (H^α) signals appeared well separated at 13.7 and 13.3 ppm, with relative intensities of 1.8 to 1. A $^1H\{^{13}C\}$-HMQC spectrum revealed C-13 chemical shifts of 276.5 and 259.7 ppm for the corresponding carbon atoms, as expected for a terminal carbene complex [10]. Also two sets of signals were observed for all other C–H groups in the molecule with the exception of the Cp group. Each species exhibited a distinguished NOE pattern in the two dimensional NOESY spectrum (Fig. 1). In the case of the species with $\delta(H^\alpha)$ at 13.7 ppm a strong interaction of =C–H with H-6 in the aromatic ring is observed, while the isomer with $\delta(H^\alpha)$ at 13.2 ppm exhibits a characteristic carbene/OCH_3 cross peak. These different patterns are consistent with the presence of two conformers of **3**, which are related to each other by rotation around the C_α–C_{ipso} single bond, with the phenyl ring coplanar with the Fe–C_α–C_{ipso} plane as has been suggested before in similar carbene complexes [11]. In one of the two isomers, the methoxy group is *syn* to the Fp moiety, in the other case it is in an *anti* position. The NOE data indicates that the *syn* isomer is represented by the set of signals with $\delta(H) = 13.7$ ppm, which is thus the more abundant one (Fig. 1). Using the NOESY data, we were able to assign all proton resonances for the *syn* and *anti* isomers. In the case of the chiral on iron complex described by Brookhart et al. [2] rotation around the Fe=C_α bond resulted in the observation of two isomers, *synclinal* and *anticlinal*, which differed in the relative orientation of the C_α substituent and the $Cp(CO)(PR_3)Fe$ moiety. No indication of isomerism around the Fe=C_α bond was observed in our study, even at the lowest temperature (−90 °C). This is consistent with findings for other carbene complexes of the general formula $CpFe(CO)_2{=}CH(C_6H_4R)^+$ [11]. This indicates that either interchange of the isomers occurs too quickly on the NMR time scale, only one isomer is present, or the chemical shifts of H_α do not differ for the different isomers. However, our data indicates a weak NOE between H_α and the Cp ring, but no NOE between the aromatic ring and the Cp ring. This is consistent with the preferred geometry expected of this type of carbene complex, with the H_α–C_α–C_{ipso} plane bisecting the CO–Fe–CO angle, with H_α oriented towards the Cp ring and the phenyl group in the opposite direction [5,12,13] (Scheme 3). As asymmetric induction is governed by the $Cr(CO)_3$ moiety, in the case of our chiral at carbene complexes the isomerism around the Fe=C_α bond was irrelevant in terms of the stereochemistry of cyclopropanation reactions and was not further investigated.

The relative intensities of *syn* and *anti* isomers of **3** are changing with temperature. In the temperature range of 233–263 K the temperature dependence of the equilibrium constant of the equilibrium *syn* ⇌ *anti* (K_{sa}) shows the expected exponential behavior $\ln K_{sa} = -\Delta G_{anti\text{–}anti}/(RT)$ and from a fit of $\ln K_{sa}$ vs. $1/T$ the reaction enthalpy of $\Delta H_{sa} = 2.4(2)$ kJ mol^{-1} and -entropy $\Delta S_{sa} = -6(1)$ J K^{-1} mol^{-1} are obtained. It should be noted that the 1.8:1 *syn*:*anti* ratio observed at 193 K does not lie on the exponential curve and was excluded from the analysis. As shown below, *syn* to *anti* interchange is slow enough at that temperature that the observed value may not reflect the true equilibrium ratio, but the ratio of the rate of formation of the two carbene isomers from the precursor. The interaction of the methoxy oxygen lone pair with the positive iron mentioned above would also kinetically favor formation of *syn* isomer from the precursor.

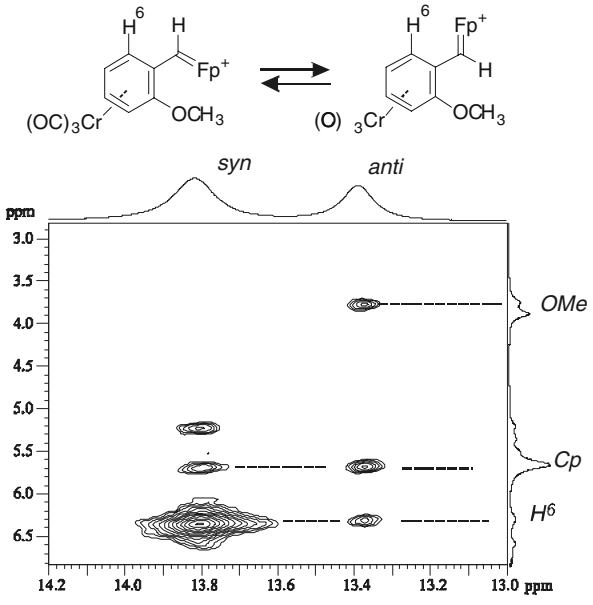
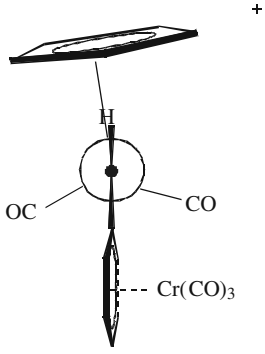


Fig. 1. NOESY spectrum of mixture of *syn* and *anti* isomers of **3**. (CD_2Cl_2, $T = 183$ K, $\tau = 300$ ms).



Scheme 3. Conformation around Fe=C bond in carbene complexes.

One could expect the *anti* isomer to be the preferred one as it exhibits less steric interaction between the methoxy and $CpFe(CO)_2$ groups. The higher abundance of the *syn* isomer indicates that there might be an electrostatic interaction of a lone pair on the methoxy oxygen with the positive charge of the Fp group. In order to test that reasoning we designed chiral carbene complex **4**, in which the methoxy group is replaced by a methyl group.

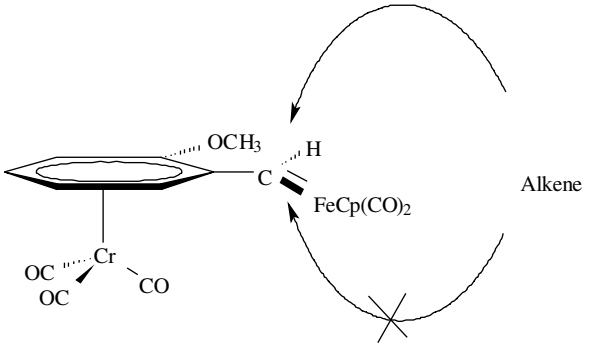
In the case of **4** only one set of signals is observed in both ^1H and ^{13}C NMR spectra [9], with an H^{α} proton NMR chemical shift of 13.85 ppm and the C^{α}C-13 NMR chemical shift of 269.9 ppm. Given the large separation of the ^{13}C chemical shifts of the =C–H carbons of *syn* and *anti* **3**, it is very unlikely that accidental overlap of signals occurs. The NOE data of **4** exhibits an NOE cross peak between H^{α} and the CH_3 group, but not between H^{α} and H-6. We can therefore determine that **4** exists almost exclusively as the sterically favored *anti* isomer and that $\Delta G_{anti-syn}$ is larger than 12 kJ mol^{-1} in this case [14].

2.2. syn/anti Interchange

Asymmetric induction in cyclopropanation reactions of the "chiral at carbene" complexes is governed by the shielding of the bulky $Cr(CO)_3$ group. This moiety completely shields the bottom face of the carbene from alkene attack (Scheme 4). However, the presence of two orientational isomers of the carbene complex in which the substituent on the aryl ring is either *syn* or *anti* to the Fp moiety, has the potential to destroy this asymmetry, allowing both *R* and *S* configuration to be produced on C-1 of the cyclopropane. It is tempting to directly relate the preferred presence of *syn* or *anti* isomer of the carbene complex to the enantioselectivity of cyclopropane formation. It is very likely that the strong preference for the *anti* isomer in the case of **4** plays a leading role in the high enantioselectivity observed for this carbene complex, as the formation of only one cyclopropane enantiomer (ee > 95%) correlates well with the presence of only the *anti* isomer [9]. However, in the case of **3**, the obtained ee values clearly do not reflect the initial *syn*/*anti* ratio which would induce only an ee of only 29%, independent of the nature of the olefin employed. The experimentally determined ee values are considerably higher, namely 46–65% for monosubstituted olefins and up to 95% for disubstituted olefins [7,9]. This is a clear indication that it is not only the abundance of *syn* and *anti* carbene isomers, but also other factors like their relative reactivities, that determine the selectivity of the reaction. As Brookhart and coworkers [5] described previously for the "chiral at iron" complex $CpFe(CO)(R_3P)$=CHMe interchange of the two carbene species may be taking place, and *syn* and *anti* isomers can react at different rates, with the reaction following a Curtin–Hammet–Winstein–Holness kinetics [15]. According to this equation, the ratio of reaction products (i.e., ee) will only represent the ratio of carbene isomers if the exchange rate between *syn* and *anti* isomer is small in comparison to the rate of reaction with olefins or nucleophiles in general; that is, if $k_{sa} + k_{as} \ll k_s$ [Nu], k_a [Nu], where k_{sa} and k_{as} are the *syn* to *anti* and *anti* to *syn* interconversion rates, and k_s and k_a are the reaction rates of the *syn* and *anti* isomers with a nucleophile.

Indeed, if the solution of the carbene complex **3** is allowed to warm above 253 K, the lines in the ^1H NMR spectrum broaden. Between 283 and 293 K coalescence of the methoxy and carbene protons of *syn* and *anti* is observed, indicative of exchange. At the same time a general broadening of all signals is observed, presumably due to onset of decomposition near room temperature, precluding a quantitative analysis of the line shape.

In order to quantify the rate of exchange between *syn* and *anti* isomer one dimensional inversion transfer NMR experiments were performed [16–19] in the temperature range of 233–263 K. For each temperature, the data was analyzed by non-linear curve fits to obtain the rate constants of *syn* to *anti* exchange at the respective temperature. A representative plot of experimental data taken at 263 K with the carbene resonance of the *syn* isomer selectively inverted shows bi exponential recovery of the magnetization of the *syn* signal and change in magnetization of the *anti*



Scheme 4. Attack of olefin on top face of carbene complex.

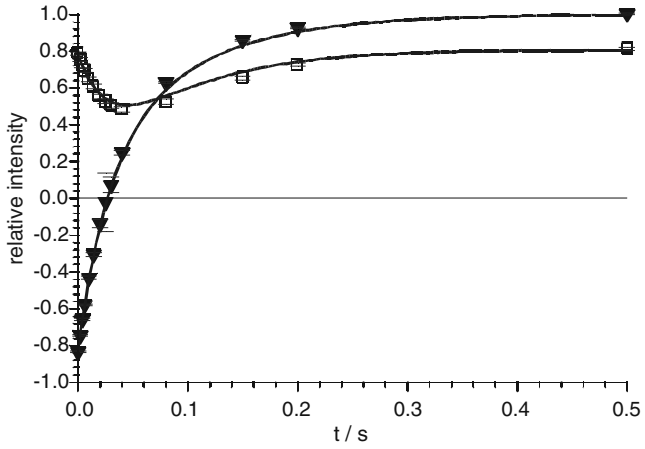


Fig. 2. Selective inversion transfer recovery of H^{α} proton NMR signals of *syn* carbene complex *syn*-**3** (263 K). (▼) *syn* protons inverted, (□) *anti*protons inverted, (—) least square fit of Bloch equations, $k_{SA} = 10.4\ s^{-1}$.

isomer. From the non-linear curve fits, a rate constant of exchange $k_{sa} = 10.1(4)\ s^{-1}$ was obtained (Fig. 2). Using the same procedure, rate constants were determined at 233, 243, 248, 253 and 258 K. The temperature dependence of the determined rate constants was fitted against the Eyring equation obtaining an enthalpy of activation of $\Delta H^{\ddagger}_{sa} = 58(3)$ kJ mol^{-1} and an activation entropy of around zero within experimental error ($\Delta S^{\ddagger}_{sa} = 2.4 \pm 11$ JK^{-1} mol^{-1}). This is the same order of magnitude as the values of 39.3–56.5 kJ mol^{-1} found for C_{α}–C_{ipso} rotation in $CpFe(CO)_2{=}\ CH(p\text{-}C_6H_4R)$ (R = H, F, CH_3, OCH_3) [11]. It appears that the $Cr(CO)_3$ moiety does only cause a slight increase in the barrier of rotation. In Brookhart's study, the barrier of rotation increased with the more electron donating capacities of the aromatic substituents ($\Delta G^{\ddagger}_{H} < \Delta G^{\ddagger}_{F} < \Delta G^{\ddagger}_{Me} < \Delta G^{\ddagger}_{OMe}$). Possibly the electron withdrawing effect of the $Cr(CO)_3$ moiety compensates the steric effects of the $Cr(CO)_3$ and *o*-methoxy groups. The barrier to C_{α}–C_{ipso} rotation is an order of magnitude higher than the difference in energy between the *syn* and *anti* isomers. Furthermore, the barrier of reorientation about the C_{α}–C_{ipso} bond is almost two times higher than the rotation around the Fe=C_{α} bond in the case of chiral on iron complexes ($\Delta G^{\ddagger} = 32.2$–$36.8$ kJ mol^{-1}) [2]. In order to evaluate the significance of the C_{α}–C_{ipso} rotation on the enantioselectivity of the reaction, we used the activation enthalpies and entropies to extrapolate *syn*/*anti* isomerization rates for temperatures where reaction rates for olefins could be measured (below). For a temperature of −78 °C (195 K), a value of $4 \times 10^{-4}\ s^{-1}$ is obtained (Fig. 3). That is equivalent to a life time of *syn* and *anti* isomer of 40 min at that temperature. At 213 K, a value of 10^{-3} s (15 min lifetime) is obtained. As mentioned above, at 195 K *syn* to *anti* exchange is slow enough that the *syn* to *anti* ratio observed at that temperature may not reflect an equilibrium value.

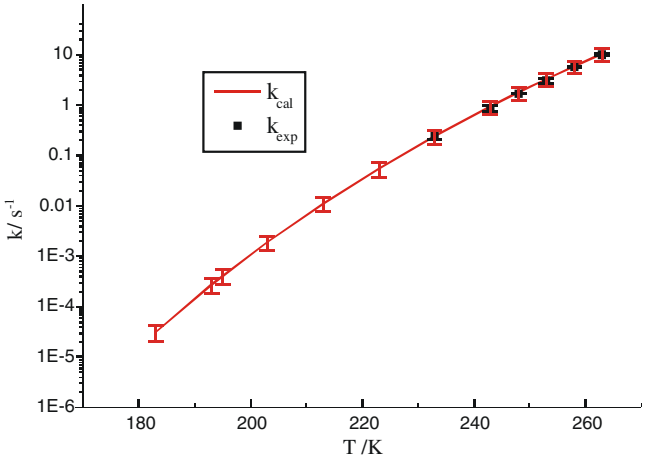


Fig. 3. Experimental values of k_{SA} (■) of **3** and extrapolated values according to the Eyring equation using values of $\Delta H^{\ddagger} = 58$ kJ mol^{-1} and $\Delta S^{\ddagger} = 2.4$ J K^{-1} mol^{-1}.

2.3. Kinetics of reaction with olefins

In order to compare the rates of *syn* to *anti* interconversion with the rate of reaction with olefins we used NMR to follow the reaction of the carbene complex **3** prepared in situ in the presence of 1,1-diphenylethylene at low temperature. A 10-fold excess of olefin was used in order to ensure a pseudo first order kinetics.

As shown in Fig. 4 at 213 K one observes a decrease in carbene proton signals, while at the same time, a new set of signals is observed. In particular, the appearance of signals with chemical shifts of 3.02, 1.93 and 1.64 ppm are indicative of the formation of 2,2-diphenyl-1-*o*-methoxyphenyl[chromiumtricarbonyl]-cyclopropane (**5**). Consistent with the high enantioselectivity observed for the cyclopropane formation from diphenylethylene, only one set of signals is observed. After 4 h about one third of all initial carbene complex had disappeared, and assuming a pseudo first order process, an effective rate constant of $3.5 \times 10^{-5}\ s^{-1}$ could be determined. This rate is still considerably lower than the rate of interchange of *syn* and *anti* isomers of **3** (k_{SA}) extrapolated for this temperature. Consistent with that finding, no change in the *syn* to *anti* ratio could be detected, but the ratio remained constant throughout the course of the reaction (Fig. 5). A similar picture is observed at 223 K, where a rate of $9 \times 10^{-5}\ s^{-1}$ is found for the reaction. As the synthesis of cyclopropanes is usually carried out with equimolar amounts of carbene and olefin, rather than a 10-fold excess, one can safely consider *syn* and *anti* isomers at equilibrium at all times during the reaction with olefin. Warming to 273 K results in completion of the reaction, with all carbene complex gone within minutes.

Reaction with styrene proceeded at a much lower rate of reaction, with no visible change in carbene concentration over several hours at temperatures up to 0 °C. Only upon warming to room temperature (20 °C) is an appreciable reduction in the intensity of the carbene signal observed. The slower reaction rate of styrene indicates that the *syn* and *anti* isomers are also in equilibrium during the reaction at all times. The fact that reaction takes place only after warming to room temperature might be responsible for the lower enantioselectivity in the case of styrene, when compared with diphenylethylene, because both the *syn* and *anti* isomers may be reacting at appreciable rates at higher temperatures.

3. Discussion and summary

Our studies establish that two rotational isomers of the carbene complex **3** are present at low temperature, with the O–Me group either *syn* or *anti* to the Fp moiety. While the $Cr(CO)_3$ group very effectively shields one face of the carbene complex from attack by the olefin (Scheme 4), the presence of *syn* and *anti* isomers allows for the formation of both *R* and *S* configuration on C-1 of the cyclopropane. Another factor governing enantioselectivity is the mechanism of ring closure, which can occur

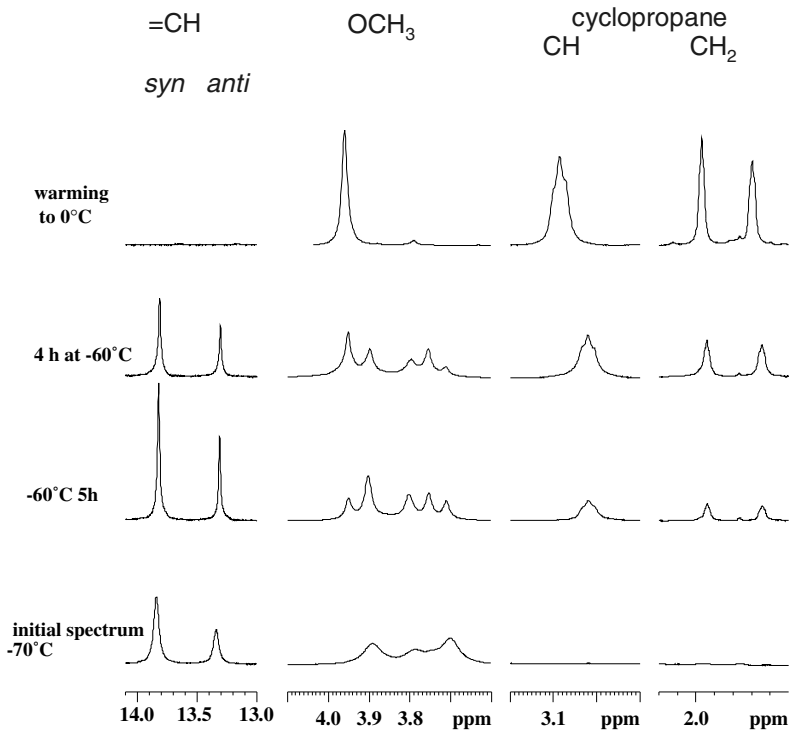


Fig. 4. Monitoring the formation of cyclopropane formation from carbene complex **3** reacted with 1,1-diphenylethylene at 213 K by NMR spectroscopy.

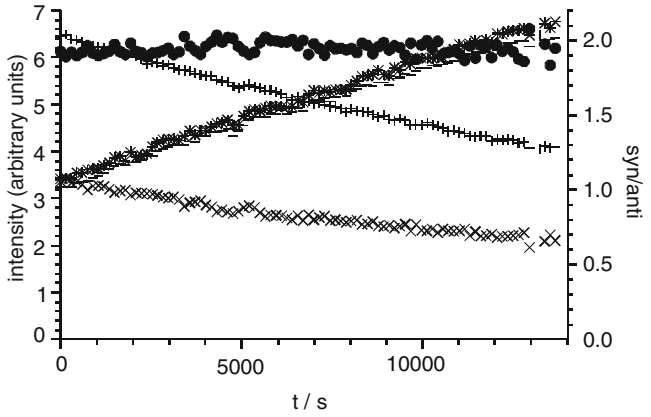
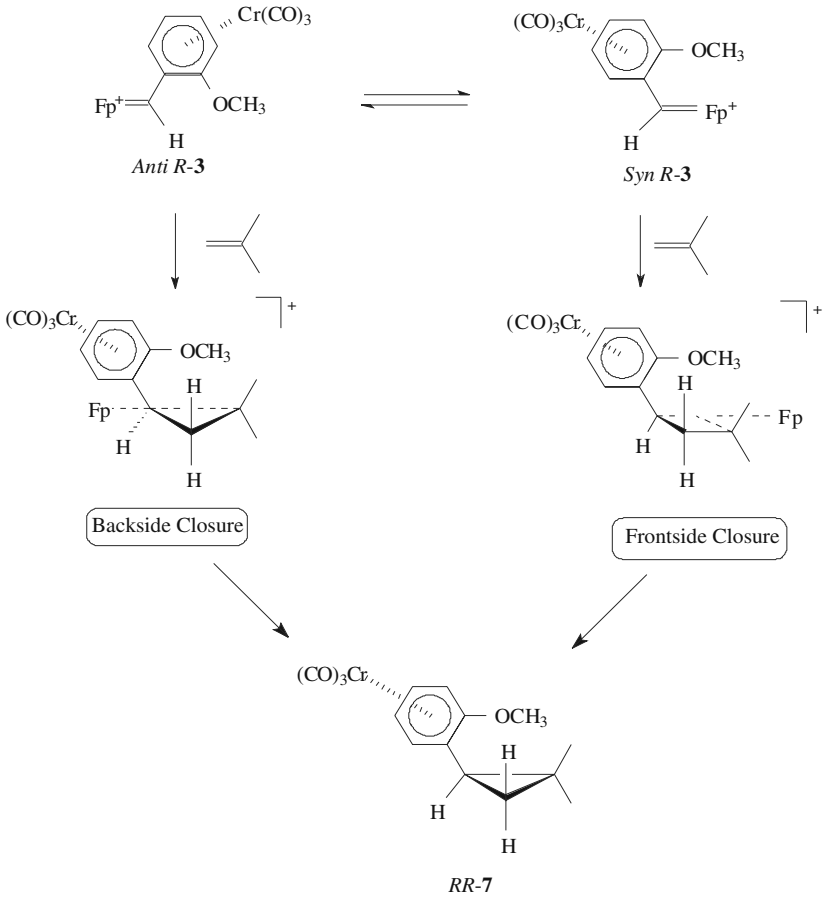


Fig. 5. Kinetics of reaction of carbene complex **3** with 1,1-diphenylethylene at 213 K. (+) *syn*-**3** H^{α}, (×) *anti*-**3** H^{α}, (∗) cyclopropane **5** $C^{1}H$, (−) cyclopropane **5** $C^{2}H_2$, (•) *syn*-**3**/*anti*-**3** ratio.

through a backside or a frontside closure. Considering both possibilities, reaction of olefin with *syn R*-**3** can result in *R*-configuration of the cyclopropane carbon C-1 through a frontside closure mechanism, or in *S*-configuration if backside closure takes place. In a similar manner, *anti R*-**3** may induce *S*-configuration through frontside closure or *R*-configuration through backside closure (Scheme 5). We previously have shown by crystallography that reaction of the *R*-isomer of **3** with 2-methyl-propene induces predominantly an *R*-configuration at C-1 of the resulting cyclopropane (*RR*-(−)-2,2 dimethyl-1-*o*-methoxyphenyl(tricarbonyl chromium)cyclopropane; whereas the *S*-carbene results in the corresponding *SS* isomer [7,8].

These findings are consistent with cyclopropane formation from the *syn* isomer through a frontside closure mechanism or from the *anti* isomer through a backside closure mechanism as shown in Scheme 5. In the case of **4**, only the *anti* isomer is observed and it appears to be reasonable to assume that the exclusively observed *anti* isomer is also the more reactive one in this case. Optical rotation data indicates that the methylcarbene exhibits the same asymmetric induction (i.e., *R*-carbene yields *R*-cyclopropane C-1 and *S*-carbene yields *S*-cyclopropane C-1) as the methoxy analog, and the assumption of the *anti* isomer being the reactive one then implies that the reaction proceeds through a backside closure mechanism, rather than a frontside mechanism (in agreement with Brookhart's findings). It is very likely that this preference is also valid for the methoxy substituted complex **3**. If the *syn* isomer was the more reactive one, a different ring closure mechanism would have to be present, which is highly unlikely. Our results with **3** indicate that the enantioselectivity of the cyclopropanation reaction is not determined by the relative abundance of the isomers. As the *syn* isomer is the more abundant one, *anti*-**3** has to be more reactive than *syn*-**3**. Interchange of *syn* and *anti* isomers occurs quickly, compared to the rate of reaction of the carbene with olefin. The fast rate of interchange of *syn* and *anti* isomers relative to the rate of reaction with olefin precludes the direct observation of any differential reactivity from a change in the *syn* to *anti* ratio in the NMR spectrum. However, the in general, lower ee values observed for **3** compared with **4** are consistent with the fact that the more reactive isomer is less abundant in this case. Our data thus shows that enantio-



Scheme 5. Possible mechanisms for cyclopropane formation from "chiral at carbene" complexes.

selectivity of cyclopropanation with "chiral at carbene" complexes is controlled by the higher reactivity of the *anti* isomer and can be further improved in carbene complexes which favor the *anti* isomer over the *syn* isomer. Ring closure then occurs through a backside closure mechanism, similar to cyclopropanation with "chiral at iron" complexes.

4. Experimental

4.1. General methods

All reactions of transition metal complexes were performed under a dry nitrogen atmosphere using standard Schlenk line and/or dry box techniques. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Dichloromethane was distilled from phosphorus pentoxide and pentane was purified by stirring overnight with concentrated sulphuric acid, washing with $NaHCO_3$ and water, drying over anhydrous Na_2SO_4 and distilling over sodium.

4.2. Analytical methods

Infrared spectra were recorded using a Nicolet FT-IR spectrometer. The CHN analyses were carried out with a Perkin–Elmer 240C analyzer. Optical rotations were determined on a Jasco DIP-370 digital polarimeter at 25 °C. Mass spectra were obtained on a Hewlett–Packard 5985B (H/P), GC/MS system, operated in DIP (direct insertion probe) CI or EI-70 eV.

All standard NMR experiments were performed at 298 K on a Bruker DPX-300 NMR spectrometer equipped with a Broadband *z*-gradient probe. All variable temperature experiments were performed on a Bruker DRX-500 spectrometer with a broadband probe and a BVT-3000 variable temperature unit. 2D NOESY and HMQC experiments were performed using standard pulse sequences. Selective inversion transfer experiments were performed at 233, 243, 248, 253, 258 and 263 K using the method of Robinson et al. [16,17] employing a $90°(x) - \Delta - 90°(x) - \tau - 90°(x)$ with the frequence offset centered between on either of the two carbene signals and $\Delta = 1/[2\Delta\delta] = 2$ ms. For each temperature two sets of experiments were performed employing inversion of either of the two carbene signals, and 14–16 experiments with the mixing time (τ) varied between 3 μs and 5 s were obtained for each set.

Data was analyzed using the integrated Bloch equations including chemical exchange [20] employing a three parameter fit using the Microcal Origin™ Software Package. Initial values for the longitudinal relaxation rates were taken from non selective inversion recovery experiments.

5. Syntheses

5.1. Synthesis of iron carbene precursors SS-(−) and RR-(+)-(η^5-C_5H_5)(CO)$_2$FeCH(OSiMe$_3$)[(η^6-o-$CH_3OC_6H_4$)-Cr(CO)$_3$)] (RR-1 and SS-1)

The methoxy substituted iron carbene complex **1** was synthesized as described previously [8].

5.2. Synthesis of iron carbene precursor SR-(+)-(η^5-C_5H_5)-(CO)$_2$FeCH(OSiMe$_3$)[(η^6-o-$CH_3C_6H_4$)Cr(CO)$_3$)]-SR(+)-2

A 3.6 −4.2 mmol (1.2 equiv.) sample of FpK was dissolved in 40–45 ml of THF and cooled to −78 °C. A 3.0–3.5 mmol (1 equiv.) sample of (−)-*o*-tolualdehyde-chromium-tricarbonyl complex was dissolved in 20 ml of freshly distilled THF and degassed three times by freeze–pump–thaw cycles. This aldehyde solution was then transferred to the flask containing FpK via a cannula under nitrogen at −78 °C. After the reaction mixture was stirred for 4–4.5 h at −78 °C, 3.6–4.2 mmol (1.2 equiv.) of chlorotrimethylsilane was added dropwise. Stirring was continued for an additional 4 h at −78 °C. After warming the reaction mixture for 20 min to ambient temperature, the solvent was removed under reduced pressure. The crude product was separated with a water-jacked column on silica gel (40–140 mesh) using 5–20% dichloromethane in pentane as solvent. The *SR*-(+) chiral iron carbene precursor was obtained as a golden-yellow solid in 78% yield (the second bright yellow band is the desired precursor, followed by red band of iron dimmer). ^{1}H NMR (CD_2Cl_2 300 MHz): 6.26 (s, 1H, CH), 5.75 (d, $J = 6.3$ Hz, 1H, Ph), 5.39 (t, $J = 6.1$ Hz, 1H, Ph), 5.32 (t, $J = 6.1$ Hz, 1H, Ph), 5.21 (d, $J = 6.0$ Hz, 1H, Ph), 4.89 (s, 5H, C_5H_5), 2.08 (s, 3H, CH_3), 0.32 (s, 9H, Si(CH_3)$_3$). ^{13}C NMR (CD_2Cl_2, 300 MHz): 235.1 (Cr(CO)$_3$), 215.5, 215.3 (Fe(CO)$_2$), 129.5 (C_{ipso}), 101.5 (*C*CH_3), 93.8, 92.9, 91.3, 88.2 (Ph), 86.1 (C_5H_5), 63.5 (FeCH), 18.5 (CH_3), 0.24 (Si(CH_3)$_3$). IR (CH_2Cl_2) $_{CO}$: 2013, 1946, 1871 cm^{-1}. $[\alpha]_D = +232°$ (*c*, 0.36, CH_2Cl_2). Anal. Calc. for $C_{21}H_{22}$O6CrFeSi: C, 49.81; H, 4.38. Found: C, 49.96; H, 4.36%.

5.3. Synthesis of iron carbene precursor RS(−)-2

Following the same procedure described above, the precursor *RS*-**2** was obtained from (+)-*o*-tolualdehyde-chromium-tricarbonyl complex with the same results. ^{1}H NMR and ^{13}C NMR are identical with *SR*(+)-**2**. $[\alpha]_D = -233°$ (*c*, 0.20, CH_2Cl_2).

5.4. In situ preparation of carbene complexes 3 and 4 for NMR spectroscopy

30 mg of the precursor *RR*-**1** (0.064 mmol) was added to an NMR tube under nitrogen atmosphere and dissolved in 0.75 ml CD_2Cl_2. The solution was degassed by a couple of freeze–pump–thaw cycles. After the addition of 1.2 equiv. trimethylsilyl triflate at liquid nitrogen temperature, the NMR tube was evacuated and sealed. The frozen solution was then thawed at −78 °C and mixed thoroughly, resulting in a rapid formation of purple solution of the carbene complex *R*-**3**. Subsequently the sample was introduced into the precooled NMR probe.

Carbene *R*-**4** was prepared in a similar manner from its precursor *SR*-**2**.

Spectral data for R-3. ^{1}H NMR ($CDCl_2$, 243 K): 13.69 (s, Fe=CH_α, *syn*), 13.21 (s, Fe=CH_α, *anti*), 6.74 (H-4, *anti*), 6.57 (H-4, *syn*), 6.33 (H-6, *syn*), 6.30 (H-6, *anti*), 5.62 (H-5, *anti*), 5.56 (H-3, *syn*), 5.37 (H-3, *anti*), 5.24 (H-5, *syn*/*anti*) (Ph), 5.68 (Cp-CH, *syn*), 5.65 (Cp-CH, *anti*), 3.92 (s, OCH_3, *syn*), 3.80 (s, OCH_3, *anti*). ^{13}C NMR ($CDCl_2$, 223 K): 275.8 (Fe=*C*H, *syn*), 258.8 (Fe=*C*H, *anti*), 229.5, 229.0 (Cr(CO)$_3$, *syn*/*anti*), 209.9, 208.4, 208.0, 207.7 (Fe(CO)2 *syn*/*anti*), 147.1, 146.1 (C_{ipso} *syn*/*anti*), 108.4, 106.0 (**C**OMe, *syn*/*anti*), 104.8 (C-6, *syn*), 98.5 (C-6, *anti*), 95.3 (C-4, *anti*), 94.8 (C-4, *syn*), 91.2 (C-5, *anti*), 87.9 (C-5, *syn*), 74.6 (C-3, *syn*), 73.8(C-3, *anti*), 90.9, 90.7 (Cp-CH, *syn*/*anti*), 56.7 (O–CH_3, *anti*), 55.8 (O*C*H$_3$, *syn*).

Spectral data for R-4. ^{1}H NMR (CD_2Cl_2, 233 K) 13.6 (Fe=*C*H_α), 6.63 (H-4), 6.34 (H-6), 5.91 (H-5), 5.52 (H-3), 5.79 (Cp), 2.45 (CH_3). ^{13}C NMR (from HMQC) 269.9 (Fe=*C*H_α), 96.8 (C-4), 101.2 (C-6), 94.7 (C-5), 94.9 (C-3), 91.7 (Cp), 20.1 (Me).

5.5. Monitoring of the reaction of 3 with diphenylethylene by NMR

Sample preparation was the same as for the in situ generation of the carbene complexes **3** and **4** but a tenfold excess of diphenylethelene was combined with the precursor *RR*-**3** prior to the addition of the trimethylsilyl triflate.

5.6. General procedure for enantiospecific cyclopropanation reactions using chiral iron carbene complexes S-4 and R-4

A 2.5–3.0 mmol (1 equiv.) sample of the diastereomerically pure precursor *S*(+)-**4** or *R*(−)-**4** was dissolved in 25 ml of CH_2Cl_2 and then cooled to −78 °C. A 5.0–6.0 mmol (2 equiv.) of alkene and a few drops of Et_3N were added. After adding 2.7–3.3 mmol (1.1 equiv.) of TMSOTf, the solution was stirred for 20 min at −78 °C. The color of the reaction mixture changed to purple after several minutes of stirring. The reaction mixture was then warmed to −30 °C and stirred overnight. If the purple color persisted, the reaction mixture was warmed to room temperature and stirred until the purple color faded. Passing the reaction mixture through a short column of neutral alumina (activity IV) followed by removal of the solvent under reduced pressure gave a yellow-brown residue. The extra alkene was washed away by pentane using stick filtration. To remove the Cr(CO)$_3$ moiety, the crude product was dissolved in pentane and ether (1:1) and stirred under a sun lamp or natural sunlight for 3 days with the solution open to air.

When the solution became colorless, it was subjected to a gravity filtration. The solvent was removed under reduced pressure and a colorless liquid was obtained. This mixture was directly analyzed by ^{1}H NMR to determine the *cis*/*trans* ratio. Otherwise, the mixture was separated by column chromatography on silica or alumina (activity III) and all cyclopropanes were collected to determine the *cis*/*trans* ratio and ee by ^{1}H NMR. Further purification by column chromatography or preparative TLC provided the *cis*-cyclopropanes.

5.7. Synthesis of (+)-1-o-methylphenyl-2-phenylcyclopropane (+)-8a

Using the procedure described above, 1-*o*-methylphenyl-2-phenylcyclopropane (+)**8a** was obtained from the reaction of precursor *S*(+)-**5** with styrene. Only *cis*-cyclopropane was detected by ^{1}H NMR and isolated as a colorless liquid. The ee was measured by ^{1}H NMR shift experiment using Yb(hfc)$_3$ and Ag-fod (method II). Only one enantiomer of cyclopropane (*RS*-**8a**) was observed. By comparison, the corresponding racemic cyclopropane was used for the same measurement and a 1:1 baseline separation of the methyl singlet was observed. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.19–6.86 (m, 9H, Ph), 2.50 (m, 2H, 2CH), 2.20 (s, 3H, CH_3), 1.54 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75.4 MHz) 139.0, 138.7, 135.8, 129.3, 129.0, 128.4, 127.3 (2C), 127.2 (2C), 126.1, 125.2, 24.5 (CH), 23.3 (CH), 19.6 (CH_3), 11.4 (CH_2). Anal. Calc. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.00; H, 7.79%. *m*/*z*: 208 (100%, M^+). $[\alpha]_D^{25} = +5.2^\circ$ (*c*, 0.59, $CHCl_3$).

5.8. Synthesis of (−)1-o-methylphenyl-2-phenylcyclopropane (−)-8a

Using the procedure described above, 1-*o*-methylphenyl-2-phenylcyclopropane (−)-**8a** was obtained from the reaction of precursor *R*-(−)-5 with styrene. Only *cis*-cyclopropane was detected by ^{1}H NMR and isolated as a colorless liquid. The ee was measured by ^{1}H NMR using Yb(hfc)$_3$ and Ag-fod as chiral shift reagents. Only one enantiomer of cyclopropane *SR*-**8a** was observed. The ^{1}H NMR and ^{13}C NMR are identical with its (+) isomer. $[\alpha]_D^{25} = -4.8^\circ$ (*c*, 0.38, $CHCl_3$).

5.9. Synthesis of (+)1-o-methylphenyl-2-p-chlorophenylcyclopropane (+)-8b

Using the procedure described above, *RS*-**8b** was obtained from the reaction of precursor *SR*-**5** with *p*-chlorostyrene. The *cis*/*trans* ratio was determined by ^{1}H NMR and GC–MS to be 6/1. Only *cis*-cyclopropane *RS*-**8b** was isolated as a colorless liquid. The ee was measured by ^{1}H NMR shift experiment using Yb(hfc)$_3$ and Ag-fod (method II). Only one enantiomer of *cis*-cyclopropane *RS*-**173** was observed. By comparison, the racemic cyclopropane was used for the same measurement and a 1:1 baseline separation of the methyl singlet was observed. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.12–6.93 (m, 8 H, Ph), 2.42 (dt, $J = 8.7$ Hz, $J = 6.4$ Hz, 2H, 2CH), 2.10 (s, 3H, CH_3), 1.48 (m, 1H, CH_2), 1.37 (dt, $J = 12.1$ Hz, $J = 6.3$ Hz, 1H, CH_2). ^{13}C NMR ($CDCl_3$, 75.4 MHz) 138.6, 137.6, 135.3, 130.8, 129.4, 128.9, 128.4 (2C), 127.4 (2C), 126.3, 125.3, 24.6 (CH), 22.7 (CH), 19.5 (CH_3), 11.6 (CH_2). Anal. Calc. for $C_{16}H_{15}Cl$: C, 79.17; H,6.23. Found: C, 79.13; H, 6.21%. *m*/*z*: 242 (100%, M^+). $[\alpha]_D^{25} = 18.9^\circ$ (*c*, 0.36, $CHCl_3$).

5.10. Synthesis of (SR)-1-o-methylphenyl-2-p-chlorophenylcyclopropane (−)-8b

Using the procedure described above, *SR*-**173** was obtained from the reaction of the precursor *RS*-**171** with *p*-chlorostyrene. The *cis*/*trans* ratio was determined by ^{1}H NMR and GC–MS to be 6/1. Only *cis* cyclopropane *SR*-**173** was isolated as a colorless liquid. The ee was measured by ^{1}H NMR shift experiment using Yb(hfc)$_3$ and Ag-fod (method II). Only one enantiomer of *cis*-cyclopropane *SR*-**173** was observed. The ^{1}H NMR and ^{13}C NMR are identical with *RS*-**173**. $[\alpha]_D^{25} = -17.2^\circ$ (*c*, 0.38, $CHCl_3$).

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