Alkene cyclopropanation catalyzed by Halterman iron porphyrin: participation of organic bases as axial ligands

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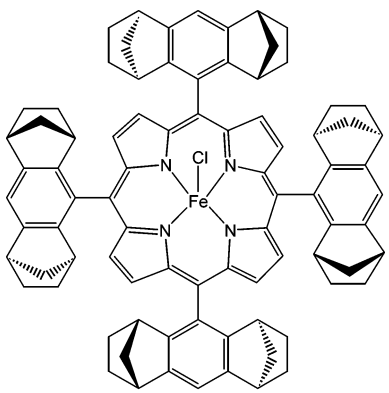
With the iron(III) complex of the Halterman iron porphyrin [P*Fe(Cl)] and ethyl diazoacetate (EDA) as catalyst and carbene source, respectively, styrene-type substrates were converted to cyclopropyl esters with high *trans*/*cis* ratio (not less than 12) and high enantioselectivity for the *trans*-isomers (74–86% ee). The isomeric distribution of the cyclopropyl esters so obtained is akin to that obtained from the previously reported Ru(II) counterpart [P*Ru(CO)]. A linear Hammett correlation $\log(k_X/k_H) = \sigma^+\rho$ was observed with $\rho = -0.57$ suggesting the involvement of an electrophilic cyclopropanating species derived from the iron(II) center as the reactive intermediate in the catalytic cycle. This is further supported by a dramatic decrease in the enantioselectivity and *trans*/*cis* ratio observed in an experiment of styrene cyclopropanation when the reaction mixture was deliberately exposed to air. Axial ligand effects on the selectivities was also investigated. Substantial improvement in *trans*/*cis* ratios could be achieved by addition of organic bases such as pyridine (py) and 1-methylimidazole (MeIm) to the catalytic reaction. The existence of axially ligated iron carbene moieties, [P*Fe(CHCO$_2$Et)(py)] and [P*Fe(CHCO$_2$Et)(MeIm)], was established by electrospray mass spectrometry. Study of secondary kinetic isotope effect indicated that a more product-like transition state was generated by addition of MeIm.

Introduction

Iron and ruthenium porphyrins have been an important class of catalyst for group and atom transfer reactions such as alkene cyclopropanation,[1] aziridination[2] and aldehyde olefination.[3] Compared to other excellent transition metal catalysts,[4] ruthenium porphyrins feature high catalytic turnovers and enticingly high diastereoselectivity for the preferential formation of *trans*-cyclopropyl ester in alkene cyclopropanation using diazo esters as carbene sources.[1p] In fact, unrelenting efforts have been directed to carbene transfer reactions mediated by metalloporhyrins.[1,5] This may be one of the reasons that *trans*-cyclopropyl esters are of high synthetic utility as they are important organic intermediates for drug production, as in the case of tranylcypromine (an antidepressant)[6] and a melantolin agonist for the treatment of sleep disorders.[7] Despite the periodic relationship between iron and ruthenium, asymmetric versions of iron-catalyzed alkene cyclopropanation are unexpectedly sporadic. In fact, chiral iron carbene complexes were shown to be efficient stoichiometric cyclopropanating reagents.[1r,s]

In a report of comparing iron and ruthenium metal centers with the same chiral D_2-symmetrical porphyrin ligand in styrene cyclopropanation by Gross *et al.*,[1n] the same level of *trans*/*cis* ratio for the cyclopropyl esters were obtained but the enantiomeric excess for the *trans*-isomer obtained with the chiral iron porphyrin was significantly lower than that in the case of Ru(II) counterpart. The highest enantioselectivity of alkene cyclopropanation using chiral iron porphyrin as catalyst was reported by Woo and co-workers, and the enantiomeric excess of the *trans*-cyclopropyl ester from styrene was up to 42% with ethyl diazoacetate (EDA) as carbene source.[1r]

This report describes the competent catalytic performance of Halterman iron porphyrin [P*Fe(Cl)][8] (Fig. 1) in enantioselective alkene cyclopropanation without adding one-electron reductant although the addition of reductant for converting iron(III) to iron(II) or directly employing the iron(II) complex is generally necessary to turn on the efficient catalysis. Axial ligand effect was



P*Fe(Cl) **1**

Fig. 1 Structure of **1**.

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also examined because of the *trans*-relationship to the transferable carbene moiety and the common phenomenon that participation of axial ligand can fundamentally determine or alter the reactivity and selectivity of various similar catalytic systems including alkene epoxidation[9] and aziridination[2] and cyclopropanation.[1]

Results

Catalytic cyclopropanation catalyzed by P*Fe(Cl)

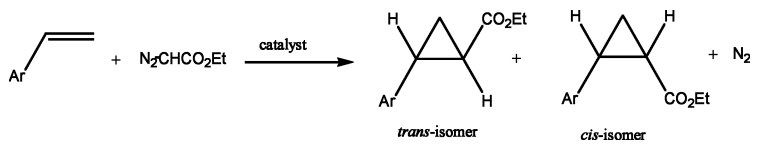
According to the shape preference for terminal alkene substrates in cyclopropanation with achiral iron porphyrin as catalyst reported by Woo and co-workers, styrene, *p*-substituted styrenes, α-methylstyrene and 1,1-diphenylethylene were chosen as the substrate spectrum in this study. Ethyl diazoacetate (EDA) was the limiting reactant for the purpose of suppressing the formation of diethyl furmurate and diethyl maleate and 0.2% catalyst was used. Under an inert atmosphere, monosubstituted aromatic alkenes were smoothly converted to cyclopropyl esters and the product yields range from 56 to 72% (Table 1). GC analyses indicated very clean product profiles and only trace diethyl fumarate and maleate were detected in all cases. For styrene, the addition of cobaltocene gave almost the same enantiomeric excess (*ca.* 80% ee) (entry 3) but a moderate increase in *trans*/*cis* ratio when compared to the case without the one-electron reductant (entry 1). So, iron(II) porphyrin could be generated *in situ* with EDA, which could be a reductant, to account for the high % ee of the *trans*-isomer and the high *trans*/*cis* ratio. In fact, *trans*/*cis* higher than 8 could be considered as an indication of the involvement of an Fe(II) intermediate for sterically unhindered tetraarylporphyrin systems. This suggestion of involving Fe(II) intermediacy was further supported by the dramatic decreases in both the % ee of the *trans*-isomer and *trans*/*cis* ratio (entry 2) when the reaction mixture was exposed to air. The negative effects were attributed to that Fe(III) porphyrin became the major catalytic species in aerobic conditions.

Lowering the catalyst loading to 0.02% lead to a product turnover over 1000 and improvements in both *trans*/*cis* ratio and percentage enantiomeric excess of the *trans*-isomer were observed. It is speculated that the improvements in the selectivities may be due to a structural modification of the porphyrin ligand in the high turnover condition.[10] In an experiment of *0.002*% catalyst loading, 10^4 turnovers were attained and also no detrimental effects on the selectivities were observed! Similarly, *p*-chlorostyrene, *p*-methylstyrene and *p*-methoxystyrene were cyclopropanated affording similar product isomeric distribution (high *trans*/*cis* ratio, high % ee for the *trans*-isomer) which is akin to those obtained with the ruthenium(II) analogue [P*Ru(CO)] previously reported by our laboratory.[11] Satisfactory enantioselectivity (not less than 80% ee) was also obtained with 1,1-disubstituted alkenes including α-methylstyrene and 1,1-diphenylethylene (entries 8 and 9).

Hammett kinetic study

The cyclopropanation rates of *para*-substituted styrenes *p*-$XC_6H_4CH{=}CH_2$ (X = OCH_3, CH_3, Cl, NO_2) relative to that of styrene were determined through competition experiments for EDA cyclopropanation in dichloromethane by employing equimolar amounts of styrene and the *para*-substituted derivatives. The relative rates k_X/k_H, defined as the molar ratio of resultant cyclopropyl esters derived from *p*-$XC_6H_4CH{=}CH_2$ to that derived

Table 1 Enantioselective cyclopropanation of alkenes with EDA using Fe(P*)(Cl) as catalyst[a]



Entry	Substrate	Product	Isolated[e] yield (%)	*trans*/*cis*	*trans* ee (%)	*cis* ee (%)	TON[g]
1	Styrene	Ethyl 2-phenylcyclopropane carboxylic acid ester	71	12 : 1[f]	80[f]	1.1[f]	368
2	Styrene[c]	Ethyl 2-phenylcyclopropane carboxylic acid ester	64	4 : 1[f]	43[f]	1.6[f]	200
3	Styrene[d]	Ethyl 2-phenylcyclopropane carboxylic acid ester	60	18 : 1[f]	81[f]	3.4[f]	405
4	Styrene[b]	Ethyl 2-phenylcyclopropane carboxylic acid ester	70	23 : 1[f]	86[f]	6[f]	1218
5	4-Chlorostyrene	Ethyl 2-(4-chlorophenyl)cyclopropane carboxylic acid ester	57	18 : 1[g]	75[g]	32[g]	284
6	4-Methylstyrene	Ethyl 2-(4-methylphenyl)cyclopropane carboxylate	56	12 : 1[g]	79[g]	Not determined	424
7	4-Methoxystrene	2-(4-Methoxyphenyl)cyclopropane carboxylic acid ester	65	13 : 1[g]	74[g]	43[g]	416
8	α-Methylstyrene	Ethyl 2-methyl-2-phenylcyclopropane carboxylic acid ester	68	3 : 1[f]	81[f]	16[f]	390
9	1,1-Diphenylethene	Ethyl 2,2-diphenylcyclopropane carboxylic acid ester	72	—		83[h]	410

[a] *Reaction conditions*: catalyst : EDA : alkene = 1 : 500 : 1500, CH_2Cl_2, room temperature, stirring during 4 h addition time followed by 1 h stirring under N_2. [b] *Reaction conditions*: catalyst : EDA : alkene = 1 : 2000 : 6000, CH_2Cl_2, room temperature, stirring during 4 h addition time followed by 1 h stirring under N_2. [c] Under air. [d] Adding cobaltocene. [e] Isolated product yields based on EDA. [f] Determined by chiral GC-FID (column: Varian cyclodex B, length 25 m). [g] Determined by GC-MS after conversion to the L-menthyl ester. [h] Determined by chiral HPLC (Daicel OJ). [i] Calculated as the amount of cyclopropyl esters divided by the amount of catalyst.

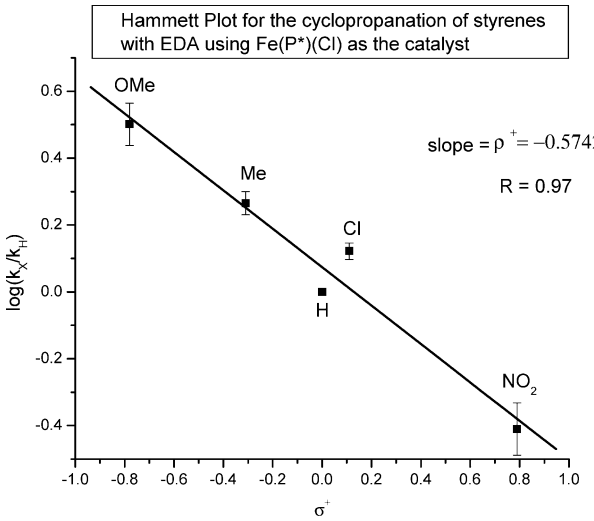


Fig. 2 Hammett plot for the cyclopropanation of *para*-substituted styrenes with EDA using Fe(P*)(Cl) as the catalyst.

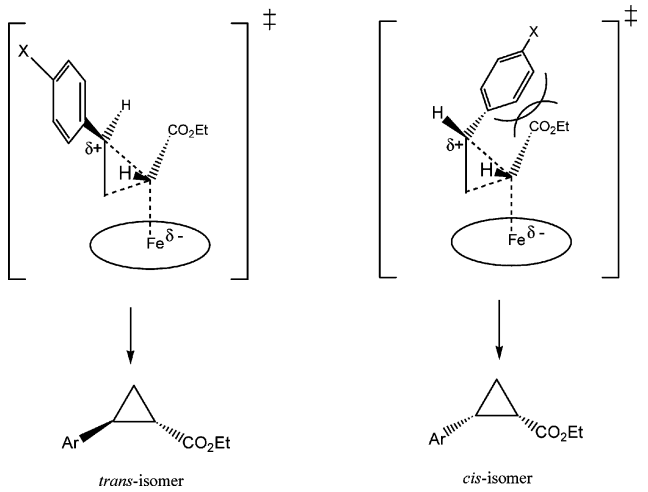


Fig. 3 The side view of diastereoselectivity of intermolecular cyclopropanation.

from *p*-$HC_6H_4CH{=}CH_2$, styrene. The corresponding Hammett plot [$\log(k_H/k_X)$ *vs.* σ^+] is shown in Fig. 2 with $\rho = -0.57$. This value is comparable to that obtained with Fe(TTP) (−0.68)[1i] and P*Ru(CO) (−0.44).[10] The negative slope is consistent with the proposal of an electrophilic iron carbene intermediate and suggests an accumulation of positive charge of some degree on the benzylic carbon of the styrenes. It is the trend that the rate of cyclopropanation is accelerated with electron-donating groups on the *para* position. *p*-Nitrostyrene being the most electrodeficient alkene gave the slowest reaction rate among the four substrates. *p*-Chlorostyrene, however, reacted somewhat faster than styrene and this may indicate that the rate-limiting transition state, of which the benzylic carbon carrying some cationic character, was stabilized by the chloro substituent *via* mesomeric interaction. Together with the high *trans*-selectivity, it may also indicate a more product-like transition state when compared with rhodium(III) porphyrin catalysts.[1e] The transition state previously proposed by Woo and co-workers to account for the high *trans*-selectivity and positive charge accumulation on the substrate part is depicted in Fig. 3.[1i]

Effect of axial ligand on styrene cyclopropanation

The use of donor solvents such as tetrahydrofuran (THF) and diethyl ether was found to enhance the *trans*-selectivity for both iron[1i] and ruthenium[1p] porphyrin-catalyzed styrene cyclopropanation. Apart from solvation effect for stabilizing polar diastereomeric intermediates to different degrees, axial ligation of the donor solvent onto the metallo-carbene moiety could be another plausible explanation for the enhancement. In this work, various organic bases were screened for seeking an alternative way to improve the *trans*-selectivity and to verify the involvement of axially ligated monocarbene as the active cyclopropanating agent in the catalytic cycle. Results of styrene cyclopropanation with P*Fe(Cl) in the presence of various nitrogen-containing heterocycles, 4-phenylpyridine *N*-oxide and dimethyl sulfoxide (DMSO) are collected in Table 2. Obviously, substantial increases in *trans*/*cis* ratio were observed in all cases of adding the axial ligand and the best result (*trans*/*cis* = 33) was obtained with pyridine (entry 2). The use of 4-dimethylaminopyridine (DMAP) and MeIm, both of which possess high π-electron density, gave *trans*/*cis* ratios (*ca.* 25) lower than that in the case of using pyridine. The *trans*-selectivity obtained with *N*-methylpyrrolidine, being a sp^3 nitrogen donor, produced no further improvement when compared with DMAP and MeIm. Using heteroatom oxides, 4-phenylpyridine *N*-oxide and DMSO could also afford significant enhancement in *trans*-selectivity.

Secondary kinetic isotope effect

Woo and co-workers probed the nature of transition state of iron-mediated alkene cyclopropanation[1i] by investigating the secondary

Table 2 Cyclopropanation of styrene with various organic bases as axial ligands[a]

Entry	Organic base	*trans*/*cis*[b]	*trans* ee (%)[b]	*cis* ee (%)[b]	TON[c]
1	Cl	12	80	1.1	368
2	Pyridine (py)	33	82	6.8	307
3	DMAP	24	81	13.0	321
4	1-Methylimidazole (MeIm)	26	83	2.3	275
5	1-Methylpyrrolidine	27	86	13.0	293
6	4-Phenylpyridine *N*-oxide	23	83	1.2	209
7	DMSO	17	82	3.6	385

[a] *Reaction conditions*: catalyst : organic base : EDA : alkene = 1 : 20 : 500 : 1500, CH_2Cl_2, room temperature, stirring during 4 h addition time followed by 1 h stirring under N_2. [b] Determined by chiral GC-FID (column: Varian cyclodex B, length 25 m). [c] Calculated as the amount of cyclopropyl esters divided by the amount of catalyst.

kinetic isotope effect (SKIE) in a competition experiment between styrene and d_8-styrene and made an important comparison to the case of a rhodium porphyrin.[1e] This provided information of rehybridization in the rate-limiting transition state. With this methodology, the effect of axial ligand on the nature of transition state could therefore be probed by examining the k_H/k_D values obtained with and without axial ligand in styrene cyclopropanation catalyzed by P*Fe(II). An inverse SKIE (k_H/k_D) of 0.87 (±0.01) was observed in the absence of axial ligand. Interestingly, the SKIE value was lowered to 0.81 (±0.01) in presence of MeIm. This indicated that a higher degree of rehybridization from sp^2 to sp^3 of styrene in the transition state occurred in the case of adding axial ligand. Since SKIE is a kinetic phenomenon not involving the cleavage of C–H bond, the change in the magnitude in the case of no fundamental mechanistic change for a particular reaction is therefore bound to be small. In our case the difference between −0.87 and −0.81 is significant enough to indicate the direction of the shift of transition state towards product side. In other words, a more-product like transition is developed in the presence of axial ligand. This mechanistically explains the improvements of *trans*/*cis* ratio in cyclopropanation of styrenes upon adding axial ligands.

Six-coordinate iron monocarbene as the active intermediate for alkene cyclopropanation

Electrospray ionization as a very soft ionization method in mass spectrometry was employed to detect the target molecular ions generated from [P*Fe($CHCO_2Et$)(py)] and [P*Fe($CHCO_2Et$)(MeIm)]. EDA, P*Fe(Cl) and pyridine or imidazole were mixed in dichloromethane in a small reaction vial equipped with a rubber septum. The mixtures were then subjected to ESMS analyses. The mass spectra of the molecular ion targets $(M + H)^+$ are shown in Fig. 4(a) and 5(a). The declustering voltage was lowered to 10.0 V in order to observe the axially ligated iron monocarbene moiety. Simulations of isotopic distributions for the target ions $C_{93}H_{87}N_5O_2Fe$ [P*Fe($CHCO_2Et$)(py)] (Fig. 4(b)) and $C_{92}H_{88}FeN_6O_2$ [P*Fe($CHCO_2Et$)(MeIm)] (Fig. 5(b)) were performed for confirming the identity, and good agreements between the simulation and experimental results were obtained. ESMS detection of [P*Fe($CHCO_2Et$)(py)] and [P*Fe($CHCO_2Et$)(MeIm)] and the improvements in *trans*-selectivity upon addition of the organic bases could therefore be ascribed to the formation of axially ligated iron monocarbene in the catalytic cycle for cyclopropanating alkenes.

Discussion

With reference to the previous report of using (+)-P*Ru(CO),[1p,11] the same antipode of the D_4-symmetrical porphyrin [(+)-P*H_2] was used in this work. Because of the preference of producing *trans*-isomer and that the absolute configuration of major stereoisomer of cyclopropyl ester derived from styrene is (1*S*,2*S*), the asymmetric induction model for styrene cyclopropanation mediated by (+)-P*Ru($CHCO_2Et$)[1p,11] could be used to explain the stereochemical outcome obtained with (+)-P*Fe($CHCO_2Et$) as the reactive species. It is also a logical extension of the mechanistic aspect that Ru^{2+} and Fe^{2+} should be capable of generating transition states of similar geometry for interacting

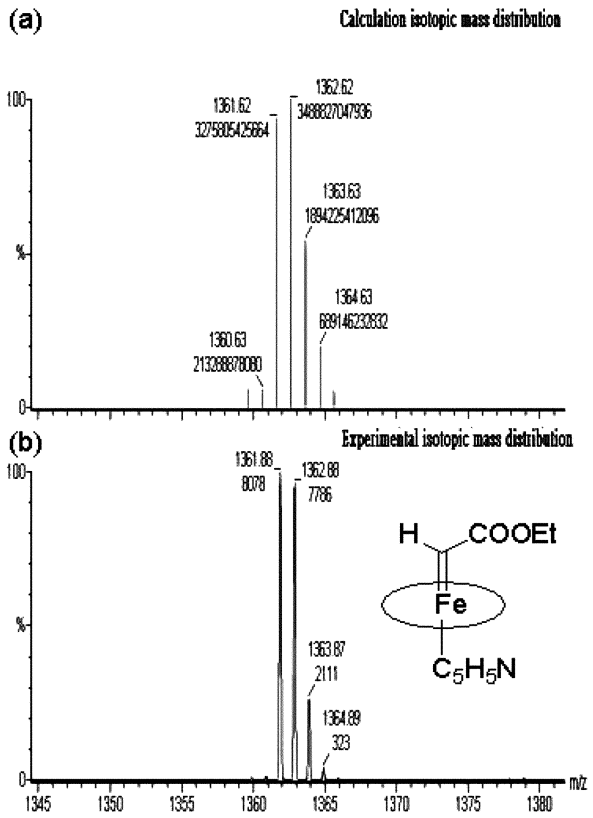


Fig. 4 (a) The simulated spectra of Fe^{III}(P*)(C_5H_5N); (b) the most abundant ions in the ES mass spectra of Fe^{III}(P*)(C_5H_5N).

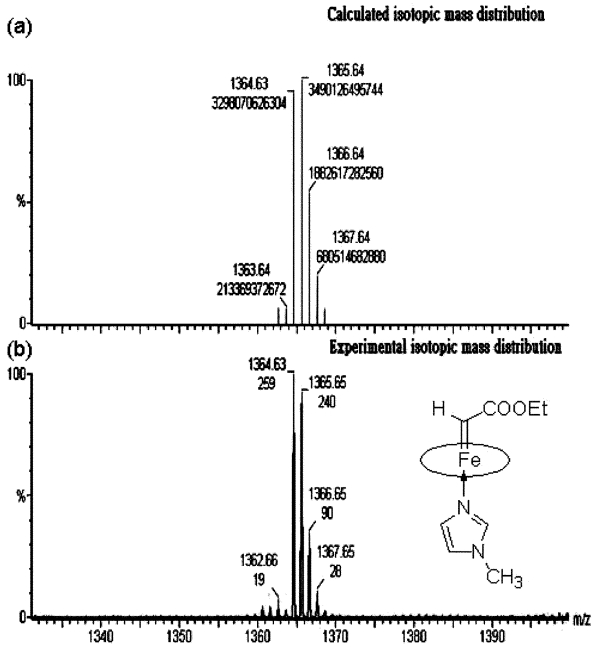


Fig. 5 (a) The simulated spectra of Fe^{III}(P*)($C_4H_6N_2$); (b) the most abundant ions in the ES mass spectra of Fe^{III}(P*)($C_4H_6N_2$).

with the same chiral environment to produce the characteristic distribution set of stereoisomers. Again, the subtle steric difference between the methano and ethano bridges on the chiral wings

operates with high enantiocontrol in cyclopropanation of aromatic terminal alkenes (Fig. 6).

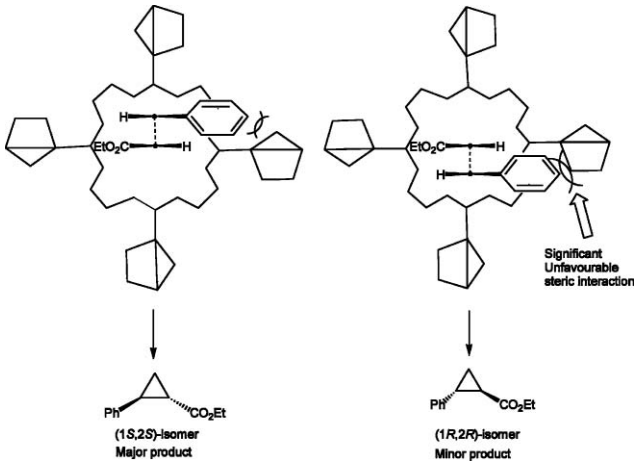
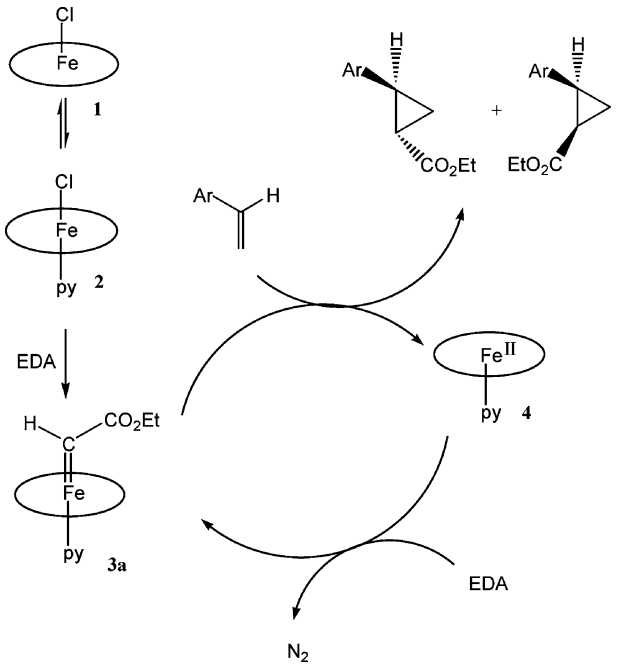


Fig. 6 The enantioselectivity of the intermolecular alkene cyclopropanation.

There are some fully characterized stable monocarbene complexes of iron,[12] ruthenium[1p,13] and osmium[1f,h,q,r,14] supported by porphyrin ligands in the literature. They are, however, disubstituted carbenes such as M=CPh$_2$, M=CPh(CO$_2$Et), M=C(CO$_2$Et)$_2$, whose stability may be attributed to the steric nature around the electrophilic carbene and the C=C double bond of the alkene substrates are so hindered that a significantly higher activation energy barrier has to be overcome for the formation of a product-like transition state in the course of carbene transfer. In fact, the ligated disubstituted carbene moiety of the stable metal complexes can, in general, be rendered transferable to organic substrates by employing relatively high reaction temperature in the presence of axial ligands (*e.g.* in refluxing toluene and in the presence of triphenylphosphine for (TPP)Ru=C(CO$_2$Et)$_2$). On the other hand, metalloporphyrins ligated with monosubstituted carbene (:CHR), such as (TPP)Os(CHCO$_2$Et),[14] (TPP)Fe=CH(mesityl)[1r] and (TPP)Fe=CH(TMS)[1r] could be isolated as impure forms and characterized by ^{1}H NMR and undergo stoichiometric alkene cyclopropanation. It should be pointed out that lengthening of Ru=CPh$_2$ and Fe=CPh$_2$ bonds in porphyrin environments with the sixth vacancy occupied by axial ligands was reported previously by Che and co-workers.[15]

Based on the aforementioned past findings, P*Fe(CHCO$_2$Et)(py) (**3a**) is thought to be the active cyclopropanating agent when using pyridine as additive. As the participation of pyridine in the sixth coordination of the monocarbene entity [P*Fe(CHCO$_2$Et)(py)] was revealed by the substantial enhancement in *trans*/*cis* ratio and by electrospray mass spectrometry, P*Fe(CHCO$_2$Et)(py) (**3a**) is unambiguously assigned to be the cyclopropanating agent, while P*Fe(py) (**4**) is regarded as the resting state of the catalyst ready for another catalytic turnover (Scheme 1). Moreover, the proposal that donor solvents such as THF and diethyl ether play a role of axial ligand in promoting the *trans*-selectivity claimed in the previous reports of iron and ruthenium porphyrin-catalyzed styrene cyclopropanation, is further consolidated.



Scheme 1 The proposed catalytic cycle of alkene cyclopropanation and participation of organic base.

In the examples of iron disubstituted carbene (Fe=CPh$_2$)[16] and (Fe=CCl$_2$)[13a] supported by porphyrin ligands, the iron(IV) state was assigned for the iron monocarbene moieties based on Mössbauer spectroscopic studies.[12] A high 'aminophilicity' can therefore be anticipated for the high valent metal center. The improvements in *trans*/*cis* ratio upon addition of axial ligands suggest a more product-like transition state is generated for the catalytic reaction. This is supported by the effect of axial ligand on the inverse secondary kinetic isotope effect. Attempts were made to establish the Hammett plots in the presence of axial ligands and this would directly give clues of the effect of axial ligation on the electrophilicity of the iron monocarbene moiety. Unfortunately, the data points obtained in duplicate runs were obviously scattered and rather irreproducible rendering the study inconclusive. With *N*-methylimidazole as axial ligand, the log(k_X/k_H) values for various *para*-substituted styrenes were 0.25 ± 0.02 (*p*-MeO), 0.16 ± 0.03 (*p*-Me), 0.31 ± 0.08 and 0.0063 ± 0.005 (*p*-NO$_2$).

Conclusion

Despite the inferior results of asymmetric cyclopropanation with chiral iron porphyrins so far documented, P*Fe(Cl) was demonstrated as a competent catalyst for alkene cyclopropanation in terms of not only catalytic turnovers but also enantio- and diastereo-controls in this work. Moreover, a prominent axial ligand effect on *trans*/*cis* ratio for styrene cyclopropanation was described and axially ligated iron monocarbene complexes supported by the chiral porphyrin were observed with ESMS. This is the first experimentally based mechanistic proposal of hexacoordinate iron monocarbene as a catalytically active species. This provides a useful insight for the development of iron-based catalysts for alkene cyclopropanation and other synthetically useful carbene transfer reactions. In addition, the future of using iron complexes as catalysts is particularly important because

the use of cheaper, non-toxic and environmentally benign metal centers has been a trend in catalyst development for industrial synthesis of organic compounds.

Experimental

Materials

Styrene, 4-methylstyrene, 4-chlorostyrene, 4-methoxystyrene, 4-nitrostyrene, 1,1-diphenylethene, α-methylstyrene, ethyl diazoacetate, cobaltocene, 4-dimethylaminopyridine and 1-methylpyrrolidine were purchased from Aldrich. 1-Methylimidazole (99%), 4-phenylpyridine *N*-oxide (99%), dimethyl sulfoxide (99%) and pyridine (99%) were purchased from Acros. d_8-Styrene was purchased from Cambridge Isotope Laboratories. (P* = 5,10,15,20-tetrakis(1,2,3,4,5,6,7,8,-octahydro-1,4:5,8-imethanoanthracen-9-yl) and $Rh_2(OAc)_4$ were synthesized by literature reported methods.[1p] Dichloromethane (A.R., ACROS) was first washed with conc. H_2SO_4 (aq.), neutralized and then distilled from CaH. Styrene and 4-methoxystyrene were distilled under vacuum immediately before use. Other alkenes were passed through a short column of silica gel immediately before use. All reactions with Fe(P*)(Cl) were carried out under a nitrogen atmosphere.

General procedure of catalytic alkene cyclopropanation

Under an inert atmosphere, complex **1** (4 mg, 3.25 μmol) and pyridine (65 μmol) were dissolved in dichloromethane (2.4 mL). To this solution was added a solution of ethyl diazoacetate (0.185 g, 1.6×10^{-3} mol) in dichloromethane (5 mL) over a period of 4 h at room temperature with the aid of a syringe pump. The reaction mixture was stirred for 1 h and then evaporated to dryness *in vacuo*. The crude cyclopropyl esters were purified by chromatography on a silica gel column with ethyl acetate–hexane (1 : 15, v/v) as eluent.

Competitive cyclopropanation of styrene and *para*-substituted styrene

In a typical experiment, equimolar amounts of each alkene (1.5 mmol each) and complex **1** (0.5 mg) were dissolved in dichloromethane (2 mL) at room temperature. A solution of EDA (0.3 mmol) in dichloromethane (1 mL) was added over a period of 6 h. The ratio of cyclopropyl esters derived from styrene and *para*-substituted styrene was determined by GC-MS analysis.

Determination of secondary kinetic isotope effect

Complex **1** (0.4 mg) and cobaltocene were added into a 10 mL round-bottom flask containing 2 mL dichloromethane and then was stirred at ambient temperature for 30 min under a nitrogen atmosphere. Equimolar amounts of styrene and styrene-d_8 (4.86×10^{-3} mol each) and EDA (1.62×10^{-4} mol) were added. The reaction mixture was stirred for an additional 24 h. The ratio of cyclopropyl esters derived from styrene and d^8-styrene was analyzed by GC-MS in selected ion monitoring mode (detecting masses 190 and 198), and the peak areas were integrated and corrected for the k_H/k_D of ionization. The experiment was repeated twice to obtain an average based on at least three GC-MS runs for each of the three experiments. The SKIE in the presence of axial ligand for the same reaction was similarly determined by adding MeIm to the mixture of complex **1** and cobaltocene.

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