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Review

Asymmetric catalytic cyclopropanation reactions in water

Irène Nicolas, Paul Le Maux, Gérard Simonneaux *

Ingénierie Chimique et Molécules pour le Vivant, UMR 6226, Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France

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Contents

Abstract

The development of environmentally benign reactions is an important goal in synthetic organic chemistry and chemical engineering. However, catalytic enantioselective reactions using transition-metal complexes in protic or aqueous solvents are limited. The current applications of asymmetric cyclopropanation will be herein reported. Distinct methodologies have been developed for carbene transfer such as the use of water-soluble catalysts or micelles in water. Carbene insertion to O–H bonds in water or alcohols catalyzed by transition-metal will also be presented since the competitive reaction with the solvent is possible. Comparison between hydrophobic and hydrophilic solvents will be discussed from an asymmetric point of view. The possibility of carbene transfer catalyzed by metalloporphyrins and heme proteins such as cytochrome P450 in water will also be discussed.

Keywords: Asymmetric cyclopropanation; Water; Alcohol; Carbene; Metal complex; Metalloporphyrin

1. Introduction

Water is an inexpensive and environmentally benign solvent that can be advantageously used in organic syntheses [1]. Thus the unique solvating properties of water have been shown in some cases to have beneficial effects on several types of organic reactions both in terms of rate and selectivity [2]. This topic has recently been reviewed by Lindström [1] and Li [3].

Historically, this effect was first underlined by Breslow [4] who mentioned the possibility of using water as a solvent to improve classical reactions. They discovered the special effect of water on Diels–Alder reactions [5]. Spectacular enhancement in the reaction rates was reported for the addition of cyclopentadiene with butenone when water was used as a solvent rather than classical organic solvents for these reactions [5]. Salt effects in water on Diels–Alder reactions have been reviewed by Kumar [6] and asymmetric organometallic reactions have been reviewed by Sinou [7]. The precise mechanism of hydrophobic interactions is still not well understood but consistent interpretations have recently been proposed [8–10].

* Corresponding author.
E-mail address: gerard.simonneaux@univ-rennes1.fr (G. Simonneaux).

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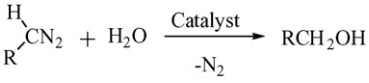
However the large extension of these organic reactions to carbene transfer processes in water catalyzed by transition-metal is far from having been demonstrated. One of the main advantages is to prevent the potential hazardous nature of the diazo derivatives, allowing an alternative method for their manipulation [11]. The use of water as the only supporting medium when the organic reactants are insoluble has other advantages such as the ease of product isolation. Generation of carbenes using transition metals in water may be also relevant to carbene reactions within living systems which were suggested for the metabolism of drugs or toxic substances by cytochrome P450 [12]. The main purpose of this review is to record the preliminary results in this area, underlying possible applications in organic synthesis. As the use of protic solvents could lead to possible O–H insertion reactions, a process that can compete with the cyclopropanation, these insertion reactions will be first summarized. Then, C–H insertion and asymmetric cyclopropanation in protic solvents will be highlighted; the last parts being devoted to carbene transfer by metalloporphyrins and possibly heme proteins.

2. Metal–carbene stability and reactivity in water or protic solvents

Carbenes are highly reactive, deficient carbon-containing species that have found widespread use in synthetic organic chemistry [13]. There may also be some application in surface modification and in polymerization methodologies [14]. The insertion of "free" carbenes photochemically generated into O–H bonds, leading to ethers has been reviewed many times [15–17]. For synthetic applications, alcohols have been generally used as ether precursors, but there are also some examples of O–H insertions with water, leading alcohols [17]. For simplicity, only recent catalytic metal–carbene reactions will be described herein. Since water is quite different from alcoholic solvents, the metal–carbene reactivity will be first presented.

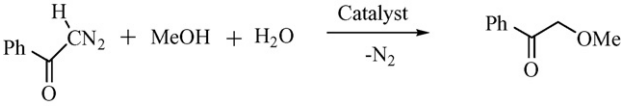
2.1. Metal–carbene stability in water

The stability of 'free' unsubstituted carbenes is generally low in water [18]. In contrast, carbenes can be stabilized by complexation with transition metals and, in some cases, the physicochemical properties of such metal–carbene complexes have been carefully studied. Thus, the pK_a values of many Fisher carbene complexes have been determined by Bernasconi et al. [19,20]. Actually, it has been known for many years that (methoxymethyl-carbene)pentacarbonylchromium(0), a protype Fischer carbene complex, is a rather strong acid [21]. This was first reported by Kreiter with the observation of a rapid conversion of CH_3 group to CD_3 group of (methoxymethyl-carbene)pentacarbonyl chromium(0) in dilute $NaOCH_3/CH_3OD$ solution [22]. Its thermodynamic acidity has been estimated of having a pK_a of 12.3 in water [23]:



(1)

In contrast, the O–H insertion reaction of rhodium–carbene complexes is so facile that there are several reports of reactions with water to give alcohols from synthetic viewpoint (Eq. (1)) [24,25] or as side reactions, due to traces of water inside the system [17]. Copper derivatives also catalyze decomposition of diazo derivatives in water [26,27] but in aqueous alcohols, insertion into the alcohol to give an ether (Eq. (2)) is generally preferred versus water in all cases, except *tert*-butanol O–H [28]:



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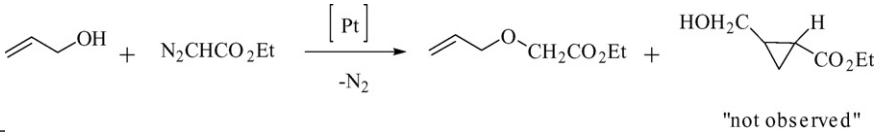
2.2. Metal–carbene reactions in alcohols

Since the pioneering work of Teyssie and coworkers [24], transition-metal catalyzed insertions of carbenes and carbenoids into the hydroxylic bonds of alcohols to give ethers (Eq. (2)) have been largely investigated [17,29] and only recent examples of carbenoid O–H insertions will be selected. The reactions will be sub-divided according to the metal.

Due to their high activity, many rhodium complexes have been used to catalyze insertion reactions of α-diazocarbonyl in polar O–H, S–H, Si–H, N–H bonds and C–H bonds [30–32]. In the particular case of O–H insertion processes, stereoselective insertions have been recently proposed [32]. The mechanism of O–H insertion has been discussed [32]. Two pathways for this insertion are possible: either a direct concerted insertion in the O–H bond or formation of an ylide intermediate followed by 1,2-hydrogen shift. In the later pathway, free ylide or metal-associated ylide has been proposed. The chiral catalyst enhancement of diastereocontrol for O–H insertion reactions [32] favours metal-associated ylides whereas the data obtained from kinetic analysis of rhodium carbene O–H insertion in alcohols [33] are in favour of a concerted insertion process. Further experimental evidence is needed to propose a definitive mechanism with rhodium complexes.

The addition of diazoesters to alcohols in presence of a catalytic amount of platinum complexes provides the corresponding O–H insertion products in good yields [34]. This is quite interesting since it provides a new carbon–oxygen bond and thus the conversion of an alcohol into an ether. Using allyl alcohol (Eq. (3)), the reaction was regioselective, since olefin cyclopropanation did not occur:



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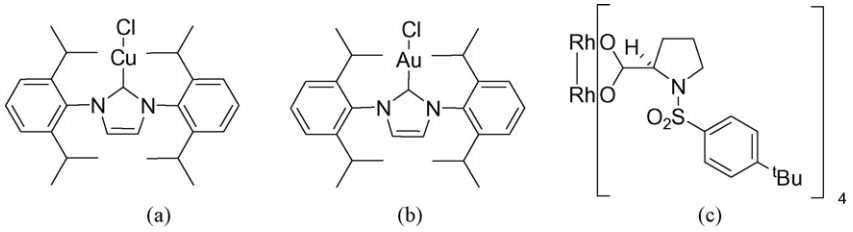


Fig. 1. Structure of catalysts (a) (IPr)CuCl [37], (b) (IPr)AuCl (IPr: 1,3-bis(diisopropyl-phenyl)imidazole-2-ylidene) [40] and (c) [1-[(4-*tert*-butylphenyl)-sulfonyl]-(2*S*)pyrrolidinecarboxylate]dirhodium(II) [44].

Although generally expected to be less reactive than rhodium complexes, ruthenium complexes with *N*-(*p*-toluenesulfonyl)diamine ligands are also efficient for insertion of carbenes generated from diazo compounds into O–H bonds of alcohols [35]. Using allylic alcohol as a model, the reaction was quite selective towards O–H insertion since less than 10% of cyclopropanation was observed.

Copper complexes containing homoscorpiate ligands efficiently catalyze the insertion of carbene fragments generated from ethyl diazoacetate into the O–H bond of saturated alcohols [36]. With unsaturated alcohols, the reaction proceeds selectively towards the O–H insertion product without formation of the cyclopropane compound (Eq. (3)). Recently, complete control of the chemoselectivity in catalytic carbene transfer reactions from ethyl diazoacetate was reported using an *N*-heterocyclic carbene–Cu catalytic system (Fig. 1a) [37]. In this case, only O–H insertion was obtained without any diazo compound dimerization reaction. Thus, the system is also inactive towards the formation of diethyl maleate and fumarate in the absence of the substrate.

An interesting aspect of metal-stabilized vinyl carbenoids is that the vinylcarbenoid can display electrophilic reactivity at either the carbenoid site or the vinyl terminus, in particular with rhodium complexes [38]. Remarkably, using vinyldiazoacetates as reagents, vinyl terminus O–H insertion was preferentially observed when the reaction was catalyzed by molybdenum complexes in methanol [39]. The results obtained with rhodium and molybdenium complexes are summarized in Fig. 2.

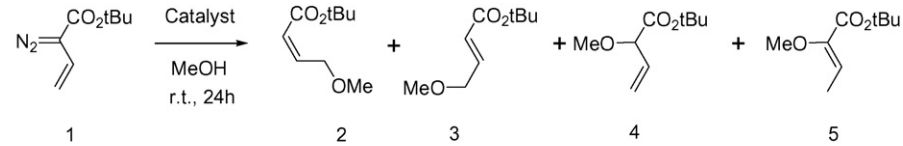
The first example of a gold-based catalyst (Fig. 1b) for the decomposition of ethyl diazoacetate and the subsequent transfer of the carbenoid unit to saturated and unsaturated substrates has recently been reported by Nolan and coworkers [40]. Thus the insertion in N–H and O–H bonds was studied and the corresponding amino acid derivatives and ethers were obtained quantitatively. The gold catalytic system was found to be very chemoselective since no diazo derived dimers were observed.

Other metal complexes (Ni, Pb) have also been used to catalyze O–H insertion but their application is less developed. Some results are summarized in a review [17].

3. C–H insertion in water

Generally, cyclopropanation and C–H insertion reactions employing diazo substrates are performed under anhydrous conditions due to the competiting O–H insertion reaction (vide supra). For the same reasons alcoholic solvents are precluded. However, these insertion reactions can be suppressed if the reaction occurs under micellar conditions [11]. Two examples of recent intermolecular [41] and intramolecular C–H [42,43] insertion reactions catalyzed by rhodium complexes have been recently reported. These reactions, which differ from the well-known reactions of rhodium carbenes, will be described herein.

Preferential Rh(II) carbenoid intramolecular C–H versus O–H insertion was reported by Afonso and coworkers [43] in 2006. Using α-diazo-acetamides and $Rh_2(OAc)_4$, the C–H insertion can be achieved to give β- and γ-lactams (Fig. 3) without competitive O–H insertion. This behaviour was explained by the presence of a larger hydrophobic environment around the reactive carbene center. The selectivity of the C–H insertion depends on the structure of the catalyst and the hydrophobic nature of the amide substituents. It was also suggested that the organized hydrophobic aggregate around the rhodium reaction center is comparable to the one assumed for the efficient Diels–Alder reaction observed in water for hydrophobic substrates [1]. Due to the high solubility and stability of the rhodium complex in water, the catalyst can be efficiently reused. A chiral version of this reaction, using enantiopure ligands on the rhodium, may



Catalyst	Total yield, %	Ratio 2: 3: 4: 5
$Mo(CO)_6$/s-TBSP-H	57	70: 30: 0: 0
Rh_2(S-TBSP)$_4$	81	16: 29: 29: 26

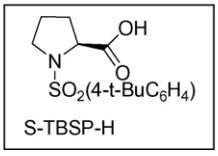


Fig. 2. Comparative study of the reaction of the vinyldiazoacetate **1** with methanol [39].

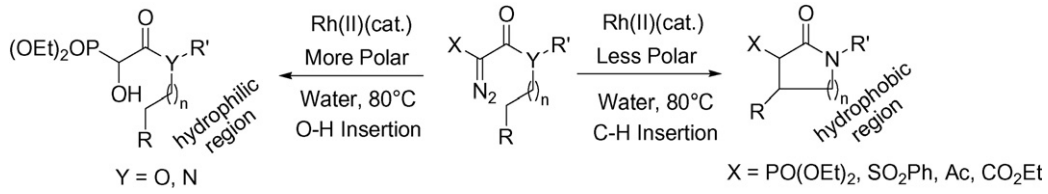


Fig. 3. Intramolecular C–H insertion catalyzed by $Rh_2(OAc)_4$ in water [43].

open new opportunities for asymmetric synthesis with a new adapted system.

The intermolecular C–H insertion on tryptophan residues of myoglobin and subtilisin with α-diazoacetate catalyzed by rhodium complexes ($Rh_2(OAc)_4$) has recently been reported in water (Fig. 4) [41]. The site selectivity was demonstrated by digesting the protein with trypsin and then analyzed by mass spectrometry. In light of the relatively low abundance of tryptophan residues on protein surfaces, this carbene transfer reaction in water offers new opportunities for selective bioconjugation that complements the classical used of cysteine and lysine modifications.

4. Asymmetric cyclopropanations in water or protic solvents

The choice of solvent can have a dramatic effect not only on the rate of the reaction but also on the enantioselectivity of asymmetric homogeneous catalysis. The role of solvents in determining these stereochemical outcomes cannot yet be clearly understood, but a thorough study reported by Jessop and coworkers [44] on cyclopropanation catalyzed by chiral rhodium complexes (Fig. 1c) reveals a decrease of the enantioselectivity in water for cyclopropanation. The authors tested the effect of controlled amounts of water on the enantioselectivity in methanol and found that the enantiomeric excess dropped drastically [44]. The presence of water in ionic liquids was also found to decrease the enantioselectivity for asymmetric cyclopropanation catalyzed by chiral copper complexes [45].

Thus, it is not surprising that there are few examples in the literature that study the cyclopropanation reaction in water as solvent, and even less under chiral conditions. It was however recognized by Nishiyama [46,47] that, for copper catalyzed cyclopropanations [48], the existence of free hydroxyl groups on chiral ligands does not interfere with the cyclopropanation.

Evidence was first presented in 2001 for a positive effect on the enantioselectivity for cyclopropanation with ruthenium [46] and cobalt [49] chiral catalysts in alcohol or aqueous alcohol. More recent studies with chiral rhodium complexes confirm a possible extension to other chiral systems [11,50]. All these results will be discussed herein.

Two possibilities can exist to perform carbene transfer in water: either a water-soluble chiral complex can be used but the metallocarbene should be stable enough in water or the reaction should be realized under micellar conditions. Obviously, the stability of the carbene intermediate depends strongly on the nature of the metal center.

Although there are many examples of cyclopropanation reactions, the first cyclopropanation effective in aqueous media or protic solvents was realized with bis(hydroxymethyldihydrooxazolyl)pyridine–ruthenium catalysts (Fig. 5) [51]. Thus catalytic asymmetric intermolecular cyclopropanation of terminal alkenes with diazoesters in the presence of hydrophilic chiral pybox complexes proceeded in protic or biphasic to give the corresponding cyclopropanation products in high enantiomeric excesses (90–97%) and *trans*/*cis* stereoselectivity to 97/3 [46,47]. Remarkably, the enantiomeric excess (8%) of the *trans* isomer in pure THF increases to 78% in a THF/H_2O (2/1) mixture for the cyclopropanation of styrene and menthyl diazoesters with these chiral ruthenium pybox. In these biphasic systems, most of the catalyst was dissolved in the aqueous phase and addition of phase-transfer reagents such as (n-Bu_4N)(HSO_4) into the system resulted in no improvement in the reaction and selectivities [47]. As the active species remained in the aqueous phase, the reuse of the water phase was tested for several runs with encouraging results but, however, with a large decrease of the yield and selectivity in the fourth run. The authors suggested that appropriate solvation of water molecules around the hydroxyl groups causes a more favourable chiral environment around the active site for the cyclopropanation.

In the same year, 2001, highly enantioselective cyclopropanation in alcoholic and aqueous solvents catalyzed by optically active β-ketoiminato cobalt(II) complex was reported by Yamada and coworkers [49] (Fig. 6a). The reaction proceeded very slowly in non-polar solvents without addition of external ligand such as *N*-methylimidazole. Similar effects were observed in various alcohols, and a strong coordination of the alcohol to the cobalt atom was suggested to explain the positive

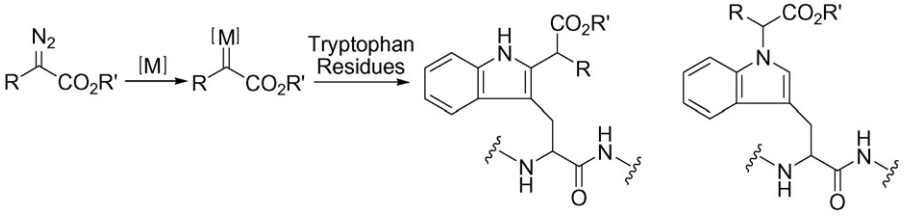


Fig. 4. Reaction of 3-methylindole with metallocarbenes in aqueous media [41].

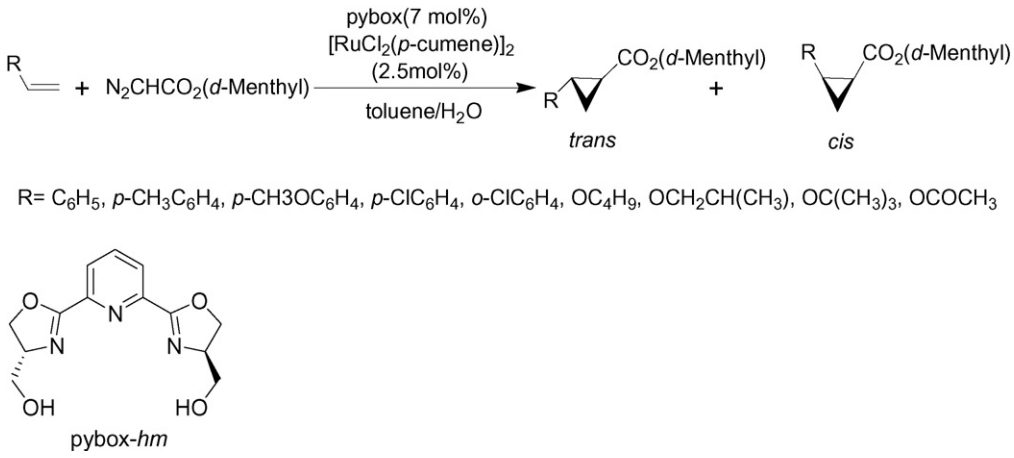


Fig. 5. Catalytic asymmetric cyclopropanation of various electron rich terminal alkenes and D-menthyl diazoacetate with chiral pybox-hm and $[RuCl_2(p\text{-cumene})]_2$ in the presence of water [94].

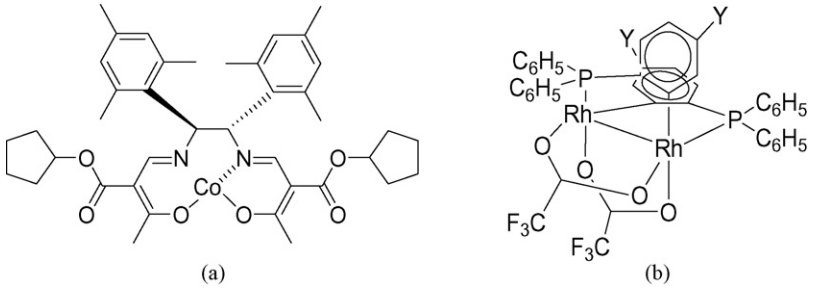


Fig. 6. Structure of chiral catalysts: (a) Ref. [49] and (b) Ref. [50].

effects, both on the rates and the enantioselectivity. In contrast, to the previous work, the cobalt complex was not soluble in water.

These results were somehow rationalized by Wurtz and Charette [11]. In an attempt to improve the viability of large-scale diazo-mediated cyclopropanation reaction, they also decided to use water as a reaction solvent. Their idea was to use hydrophobic catalysts and non-water-soluble alkenes that would lead to small alkene micelles in water. To illustrate their idea, a number of rhodium carboxylate catalysts were screened for cyclopropanation reactions with styrene in water. It was concluded that low yields were obtained with water-soluble catalysts while high yields were obtained with hydrophobic catalysts. This procedure also allows the *in situ* generation of the diazo compound from sodium nitrite and amino derivatives in water.

Enantiomerically pure dirhodium(II) complexes with *ortho*-metallated *para*-substituted aryl phosphines (Fig. 6b) have recently been shown to lead to the enantioselective cyclopropanation of styrene with ethyl diazoacetate (Fig. 7) [50]. Diastereoselectivities (up to 90%) and enantioselectivities (up to 90%) are comparable to those obtained in pentane. They are reached when, in the presence of chiral rhodium as catalyst, the catalytic reaction is performed in aqueous micellar conditions. As suggested by Wurtz and Charette [11], the hydrophobic catalyst is in the styrene layer, and at the same time, the ethyl diazoacetate, relatively soluble in water, slowly diffuses in the organic layer. Thus the catalytic reaction occurs in the organic layer. This micellar effect is quite thoughtfully discussed in the two previous examples [11,50].

5. Carbene transfer with metalloporphyrins in water

The use of metalloporphyrins as cyclopropanation catalysts originated with Callot et al. [52] who reported that (TPP)RhI (TPP = tetraphenyl porphyrin) provided a *cis* selective cyclopropanation of styrene with ethyl diazoacetate (Fig. 7) [53]. Examples involving osmium [54], ruthenium [55], cobalt [56] and iron [57–59] porphyrins as catalysts have been also reported but the catalysts mainly provided a *trans* product. However, to our knowledge, there is no report on cyclopropanation of

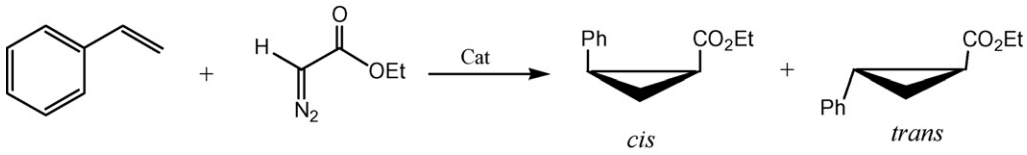


Fig. 7. Cyclopropanation of styrene with ethyl diazoacetate catalyzed by a metal complex.

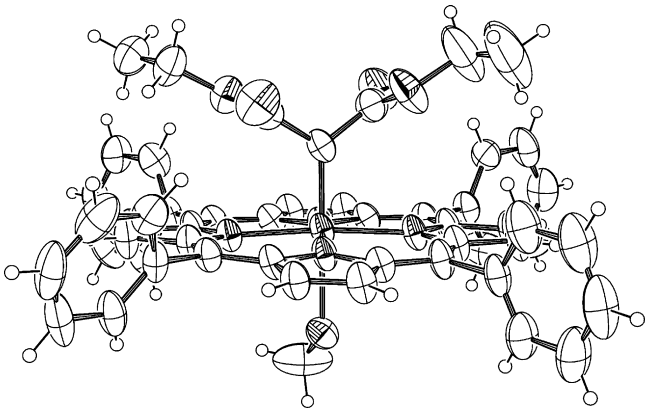


Fig. 8. Molecular structure of (TPP)Ru[(C(CO$_2$Et)$_2$)(MeOH)] [62].

olefins catalyzed by metal porphyrins in presence of water or hydrophilic solvents. This is not surprising for rhodium since it is known that rhodium porphyrins also efficiently catalyze carbene insertion into O–H bonds leading to ethers, by use of ethyl diazoacetate under mild condition (40 °C) [60,61]. In contrast, we reported the crystal structure of tetraphenylporphyrinatoruthenium(II)(diethoxycarbonyl)carbene complex bearing a methanol molecule in axial position (Fig. 8) [62] and the absence of O–H insertion with tetramesitylrutheniumporphyrin carbon monoxide [63]. Since the ruthenium carbene bond was found stable in presence of hydrophilic solvent, such as methanol, we became interested in exploring the possibility that ruthenium porphyrins may also catalyze cyclopropanation in water and alcohols. We reveal herein [64] that not only ruthenium porphyrins but also iron porphyrins are indeed efficient and general catalysts for diastereoselective and asymmetric cyclopropanation of styrenes in hydrophilic solvents.

The results obtained in cyclopropanation catalysis with ruthenium- and iron-porphyrins are summarized in Tables 1 and 2. The reaction of styrene with ethyl diazoacetate in the presence of TPPRuCO or TpMePPFeCl gave a mixture (*trans*/*cis* ~ 9/1) of cyclopropane derivatives, e.g. *trans*- and *cis*-2-phenylcyclopropane carboxylic esters. The catalytic cyclopropanations were run in three different solvents, EtOH and H_2O and CH_2Cl_2 for comparison. If we detect a small decrease of the yield with TPPRuCO, surprisingly, the yields were slightly higher in water with the iron-porphyrin

Table 1
Cyclopropanation of styrene with ethyl diazoacetate by complexes (P)RuCO and (P)FeCl

Entry	Catalyst	Solvents	Yield (%)	Ratio *trans*/*cis*
1	TPPRuCO[a]	CH_2Cl_2	78	93:7
2	TPPRuCO[a]	EtOH	68	97:3
3	TPPRuCO[a]	H_2O	53	92:8
4	TpMePPFeCl[b]	CH_2Cl_2	81	91:9
5	TpMePPFeCl[b]	EtOH	73	92:8
6	TpMePPFeCl[b]	H_2O	88	90:10

[a] Carbonyl-{tetraphenyl porphyrinato}ruthenium(II).
[b] Chloro-{tetrakis[*p*-methyl phenyl] porphyrinato}iron(III).

Table 2
Asymmetric cyclopropanation of styrene with ethyl diazoacetate by chiral complexes (P*)RuCO and (P*)FeCl (see Fig. 9)

Entry	Catalyst	Solvents	Yield (%)	Ratio *trans*/*cis*	ee (*trans*) (%)	ee (*cis*) (%)
1	HaltRuCO[a]	CH_2Cl_2	77	95:5	83	8.8
2	HaltRuCO[a]	EtOH	98	98:2	92	20
3	HaltRuCO[a]	H_2O	79	94:6	88.7	32
4	HaltFeCl[b]	CH_2Cl_2	72	95:5	74.5	3.1
5	HaltFeCl[b]	EtOH	85	89:11	53	5.4
6	HaltFeCl[b]	H_2O	70	96:4	85	9.6

[a] Carbonyl-{5,10,15,20-tetrakis[(1*S*,4*R*,5*R*,8*S*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene-9-yl]porphyrinato}ruthenium(II).
[b] Chloro-{5,10,15,20-tetrakis[(1*S*,4*R*,5*R*,8*S*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene-9-yl]porphyrinato}iron(III).

complex (see Table 1). The asymmetric version was also tested using Halterman porphyrin as chiral ligand (Fig. 9). As can be seen from Table 2, the use of water or ethanol is not detrimental to the enantiomeric excess and the yield with the iron or the ruthenium complex. Development of other chiral metalloporphyrin systems in water may also offer rich opportunities to improve the enantioselectivity and chemoselectivity of other catalytic reactions such as oxidation reactions.

6. Carbene transfer with heme proteins

Although carbenes are not natural substrates in biological systems, their formation (interactions) with heme proteins has been extensively studied. Initial experiments were carried out in the 1970s–1980s, and several short reviews on carbene formations during interactions of heme proteins with xenobiotics are available [65–68]. This review will discuss only possible intramolecular transfer from iron carbene intermediates to the porphyrin ring in heme proteins. In contrast, to our knowledge, there is no report on intermolecular carbene addition to olefins catalyzed by heme proteins in water. Consequently, this perspective will only be suggested.

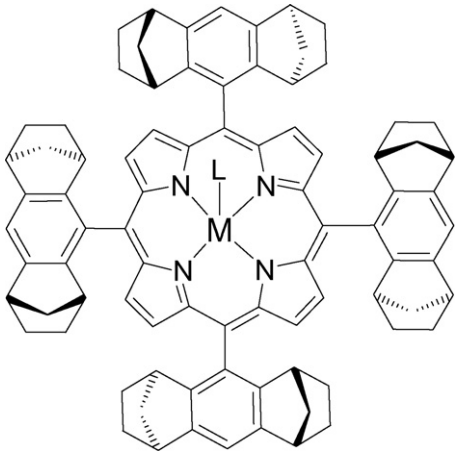
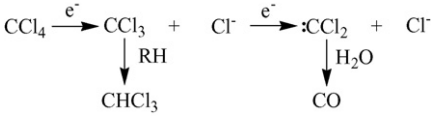


Fig. 9. Chiral metalloporphyrin complex (M–L: RuCO, FeCl) [95].

6.1. Formation and intramolecular transfer of carbene

It has long been recognized that cytochrome P450 can catalyze the reduction of polyhalogenated compounds. Carbon tetrachloride, for example, produced a relatively stable carbene complex in water (vide infra) via a reductive dehalogenation [69]. This discovery was the starting point of the bioorganometallic chemistry of heme proteins.

Evidence was first presented, by Ullrich and coworkers, in 1974 and then in 1977 for microsomal cytochrome P450 carbene complexes [12,69]. Carbon monoxide and chloroform, two other metabolites that result from the reduction of CCl_4, were detected in incubations that contained P450 and dithionite or in complete systems (P450 and reductase) (Eq. (4)) [69,70]. Since halothane ($CF_3CHClBr$) is one of the most widely used polyhalogenated anaesthetics, a possible formation of carbene species during the interaction of halothane and cytochrome P450 was also proposed by analogy with the results obtained with CCl_4. This hypothesis was first tested but the presence of σ-bonded alkyl derivatives was finally demonstrated [71]. Bacterial cytochrome P450 has been used as an excellent model to better understand bacterial reductive dehalogenation biochemistry [72]. In this study, it was found that the enzyme catalyzed a single turnover stoichiometric reduction of $CFCl_3$ to carbon monoxide, suggesting a carbene intermediate in the reaction pathway [72]. In the previous examples, the metallocarbene reacts with water and cannot be transferred. Accordingly, it was reported by Susslick, that such an iron-porphyrin carbene can be added to a double bond, only by a photochemical reaction [73]:



(4)

The 1,3-benzodioxole derivatives are oxidatively metabolized by cytochrome P450 monooxygenases with formation of very stable complexes of this cytochrome in the ferrous state, characterized by a Soret peak at 455 nm [74,75]. Indirect evidence for the presence of 1,3-benzodioxol-2-carbene complexes of cytochrome P450 came from model studies [76]. Structure–activity relationships in the interaction of alkoxymethylenedioxybenzene derivatives with microsomal mixed-function oxidase *in vivo* have been reported [77] and the mechanism of this reaction has also been discussed in a review by Ortiz de Montellano and Reich (Fig. 10) [78]. The metabolism of aryldioxymethylene compounds to catechol and carbon monoxide is consistent with hydroxylation of the carbene complex (Fig. 11) [78]. As previous examples with CCl_4, the metallocarbene seems to react with water without any intermolecular transfer.

Intramolecular transfer of metallocarbene in heme proteins is however possible. Thus the metabolites of sydnones (Fig. 12), which are a pharmacologically interesting class of drugs, have been shown to be a mechanism-based inactivator of microsomal P450 [79]. Enzymatic destruction is accompanied by the formation of *N*-vinylprotoporphyrin IX. It was first suggested

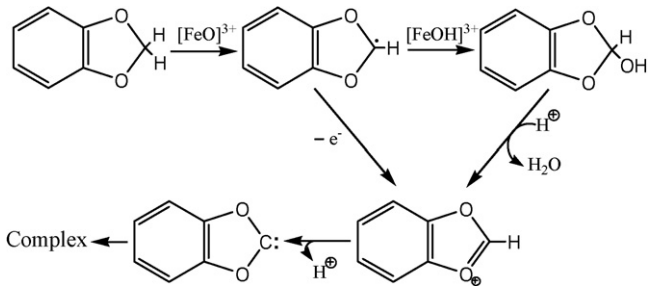


Fig. 10. Mechanism of 1,3-benzodioxole metabolism by cytochrome P450 monooxygenases [78].

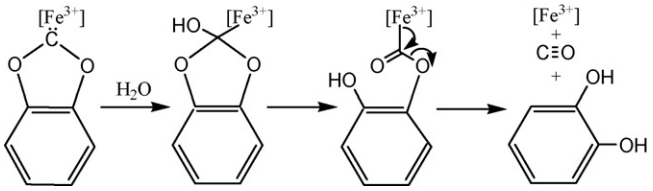


Fig. 11. The metabolism of aryldioxymethylene compounds with hydroxylation of the carbene complex [78].

that intermediate formation of diazo compounds (Fig. 13) [80] from sydnone metabolism gives bridged Fe–C–N iron carbene complexes [78]. To more define the mechanism of these reactions, other sydnone substrates that do not have a leaving group were also examined in order to explain the formation of *N*-alkyl heme adduct [81]. Reaction of the same diazoalkane with iron-porphyrin models confirms the formation of the carbene complexes as precursors of the *N*-alkyl porphyrins [82].

There are few reports of interactions of diazo derivatives with cytochrome P450 [12,83] but without real conclusive information. With trifluoro diazomethane, the suggested carbene complex [12] was found to be a σ-alkyl–iron complex [71]. The reaction of liver microsomes with diazoacetophenone seems to yield *N*-alkylporphyrin as was previously reported for the reaction with phenyl acetylene [83]. However, in both cases, the presence of a metallocarbene complex was not confirmed.

6.2. Bioorganometallic catalysis with heme proteins

Significant results discussed earlier in this chapter are summarized below: (i) carbene transfer can be efficiently catalyzed by metal complexes in water, (ii) metalloporphyrins and, in particular ruthenium porphyrins are excellent catalysts for carbene transfer reactions [84,85], including water as solvent and (iii) evidence for cytochrome P450 carbene complexes is now largely

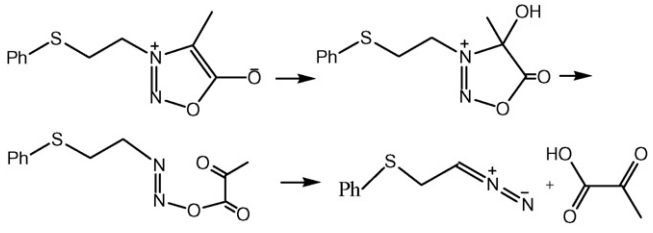


Fig. 12. Generation of diazo compounds from sydnone metabolism [79].

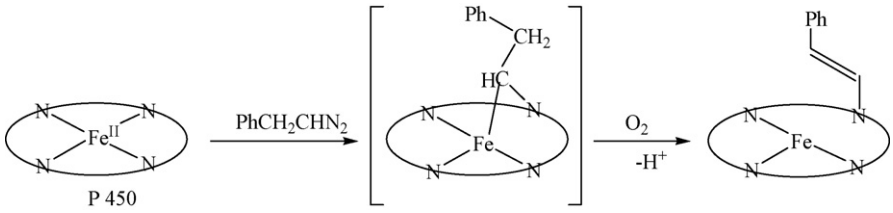


Fig. 13. Formation of *N*-vinylprotoporphyrin IX [82].

recognized [86]. In view of these results, it is tempting to suggest a combination of heme proteins with carbene precursors, such as diazo derivatives to set up a viable organometallic system for asymmetric synthesis. If native heme proteins can be possible candidates for organometallic reactions, one would also expect ruthenium reconstituted heme proteins also to be good candidates for catalyzing asymmetric cyclopropanations. The ruthenium juxtaposition in the periodic table makes ruthenium an ideal candidate for organometallic reactions with artificial heme proteins. Such hybrid hemeproteins have been previously reported, such as ruthenium myoglobin [87,88], ruthenium hemoglobin [89] and ruthenium peroxidases [90]. Thus the next stage in this area will be the engineering of new organometallic functions inside the heme proteins [91–93]. Although many examples have been described an effective system with metalloporphyrins, that utilizes heme proteins as catalysts for carbene transfer reactions, has not yet been forthcoming. However, it is probable that the availability of new artificial metalloproteins will solve this problem in the future.

7. Conclusion

Part of the results presented herein indicates that the asymmetric carbene transfer using chiral metal complexes as catalysts and water or hydrophobic solvents is possible, with good results. Diastereo- and enantioselectivities comparable to those obtained in "classical" organic solvents are obtained whether in micellar conditions or with water-soluble complexes. Although the number of efficient systems is still low, their development will be considerably widened in the future, with possible application in asymmetric catalysis.

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