TUTORIAL REVIEW

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Ruthenium-catalysed carbenoid cyclopropanation reactions with diazo compounds

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The transition-metal catalysed cyclopropanation of olefinic bonds using diazo compounds as a carbene source is among the best developed and most useful transformations available to the synthetic organic chemist. Nevertheless, the quest for new catalyst/ligand systems continues in order to further extend the scope of this method and to identify more economical catalytic systems. In this *tutorial review*, several different ruthenium complexes are presented which have recently emerged as suitable catalysts for carbenoid cyclopropanation. For the model reaction – cyclopropanation of styrene(s) with diazoacetates – and also for some intramolecular cyclopropanation reactions highly remarkable results in terms of catalyst efficiency, product yields, dia- and enantioselectivity have been reported.

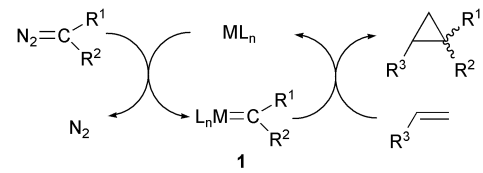
1 Introduction

Cyclopropanes are attractive and often sought synthetic targets, because the specific reactivity of this carbocyclic ring system renders them useful as synthetic building blocks and because incorporation of a three-membered ring serves to impose conformational constraints on otherwise flexible acyclic chains. Cyclopropane rings are also found in a variety of natural products and biologically active compounds. The synthesis of cyclopropanes by transition-metal mediated carbene transfer from aliphatic diazo compounds to carbon–carbon double bonds is not only a major method for the preparation of cyclopropanes but is also among the best developed and most general methods available to the synthetic organic chemist.[1]

Highly effective and stereocontrolled syntheses of functionalised cyclopropanes are achieved in particular with catalysts based on copper and rhodium. Palladium-based catalysts have advantages in special cases, and catalysts based on other late transition-metals (*e.g.*, iron and osmium) have been reported only occasionally. Outstanding levels of enantioselectivity have been achieved with some chiral catalysts: copper(I) complexes with C_2-symmetric bis(oxazoline) ligands and dinuclear rhodium(II) complexes of the type $Rh_2L^*_4$, where L* is a chiral bidentate carboxylate, amidate or phosphate ligand, must be named here in the first place.[1,2] On the other hand, diastereocontrol of the intermolecular cyclopropanation reaction is more difficult to handle, because the *cis*/*trans* or *syn*/*anti* selective formation of cyclopropanes is most often controlled by the particular olefin/diazo compound combination. Nevertheless, catalysts with cleverly designed ligands have been developed which do allow highly selective *trans*- or *cis*-cyclopropanation in particular cases.

Ruthenium complexes are newcomers in the field of catalytic cyclopropanation. Most results on this topic have been published only in the last decade. It is perhaps not wrong to say that the attention given to ruthenium was not only curiosity-driven but had two other major reasons. Firstly, the smashing success of rhodium complexes catalysing carbene transfer reactions is somewhat spoiled by the high price of the catalyst metal. Although it is true that the price of many powerful chiral catalysts is dictated by the cost of the ligands rather than by the transition-metal, the cost of the latter may become an issue when a catalytic reaction is scaled up from the typical mmol scale of a research laboratory to a molar or multi-molar scale in an industrial process unit. (Contrary to general belief, diazoacetates are occasionally applied on such scales; for an example, see Section 2.5.) In this respect, ruthenium, a direct neighbour of rhodium in the periodic table, offers an advantage because it currently costs roughly one tenth the price of rhodium. The second reason for paying attention to ruthenium is given by the greater diversity of complexes to be evaluated, due to the larger number of oxidation states and the richer coordination chemistry[3] as compared to rhodium.

The catalytic cycle of a carbenoid cyclopropanation reaction is outlined in Scheme 1. It is seen that a metal–carbene complex **1**, in this case ruthenium–carbene complex, is the central reaction intermediate. Such intermediates have been indeed observed spectroscopically in ruthenium-catalysed reactions. In other cases, stable ruthenium–carbene complexes have been isolated from the stoichiometric reaction between a ruthenium complex and a diazo compound and were shown to catalyse the carbene transfer reaction between an olefin and a diazo compound at elevated temperature.



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Scheme 1

Looking at a ruthenium–carbene complex (**1**, M = Ru), one is reminded immediately of certain ruthenium complexes of the type

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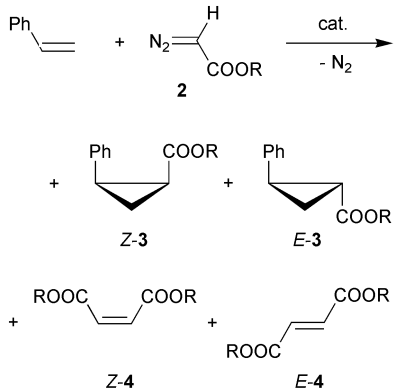
$Cl_2(L_2)Ru{=}CHR$ which are nowadays widely used for olefin and olefin/alkyne metathesis reactions, and one may wonder about the eventual competition between alkene cyclopropanation and alkene metathesis. In anticipation of Sections 2 and 3, it may just be said here that the borderline is indeed encountered in some cases. These introductory remarks may suffice to illustrate that ruthenium-catalysed cyclopropanation reactions are of interest for several reasons. This review will show that, after the first scattered reports of successful ruthenium-catalysed cyclopropanation reactions, this topic has recently found the attention of several research groups from all over the world and remarkable results have been obtained.

2 Structural diversity and effectiveness of ruthenium catalysts

2.1 General remarks; early exploratory studies

The cyclopropanation of styrene with methyl diazoacetate (MDA) or ethyl diazoacetate (EDA) (**2**, R = Me or Et) serves as the benchmarking reaction for the evaluation of almost any new catalyst (Scheme 2). Typically, it yields a diastereomeric mixture of



Scheme 2

cyclopropanes *Z*-**3** and *E*-**3**, accompanied by the formal carbene dimers *Z*- and *E*-**4**. The relative amounts of the latter increase when the cyclopropanation becomes sluggish.

In 1980, Hubert and Noels[4] published the results of the first systematic search for new cyclopropanation catalysts and reported that the dinuclear Ru(II)/Ru(III) complex $Ru_2(OAc)_4Cl$ gave cyclopropanes **3** (R = Et) in 38% yield and with an *E*/*Z* ratio of 1.8. One year later, Doyle[5] identified the Ru(0) cluster $Ru_3(CO)_{12}$ as an effective catalyst for the cyclopropanation of butyl vinyl ether (65% yield at 60 °C). Nevertheless, these results were not very exiting compared to several other catalysts such as $Rh_2(OAc)_4$, $Cu(acac)_2$, and $Pd(OAc)_2$.

The first encouraging results were not published before 1992: ruthenacarborane **5** (Fig. 1), with the composition

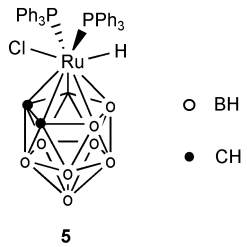


Fig. 1

$[Cl(PPh_3)_2RuH(C_2B_9H_{11})]$, and a structural isomer which probably rearranges into **5** under the reaction conditions, are very efficient and effective catalysts for olefin cyclopropanation with EDA.[6] Good to excellent cyclopropane yields were obtained with terminal alkenes (styrene, 4-substituted styrenes, butyl vinyl ether, vinyl acetate, 1-hexene; 87–96% yield, *Z*/*E* ratios ranging from 0.59 to 0.78), α-methylstyrene (87%, *Z*/*E* = 1.03), cycloalkenes (C_nH_{2n}, *n* = 5–8, 53–88%) and 1,3-dienes (1,3-cyclohexadiene, isoprene, 2,5-dimethyl-2,4-hexadiene, 75–97%). With isoprene, the methyl-substituted double bond is cyclopropanated preferentially (74.4 *vs.* 12.6% yield), and styrene reacts 7.9 times faster than 1-hexene. All reactions were run in excess alkene at up to 60 °C using only 0.5 mol% of catalyst relative to EDA.

The mechanistic picture of the cyclopropanation reaction suggests (see Section 3) that the transition metal must provide at least one free coordination site or an easily displaceable ligand. In the latter case, it is by no means clear if and how the diazo group/catalyst interaction is involved in a displacement reaction or which of two or more different ancillary ligands around the transition metal is actually replaced by the diazo or carbene moiety. It is therefore not surprising that different coordination motifs of ruthenium have been probed. The most important results are presented in the following sections.

2.2 Dinuclear ruthenium(I) and ruthenium(II) carboxylate complexes

The dinuclear ruthenium(II) carboxylate complexes **6** (Fig. 2) represent the immediate structural analogues of dirhodium(II)

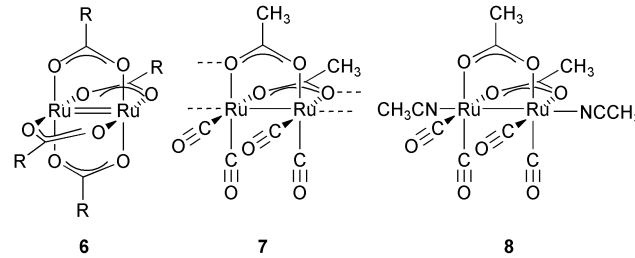
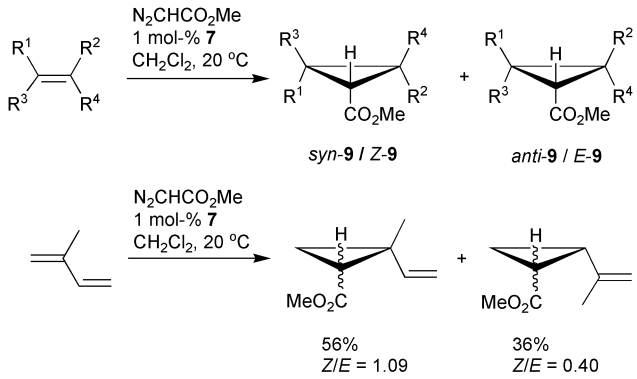


Fig. 2

tetracarboxylates which are currently the most versatile catalysts for carbenoid reactions with diazo compounds. However, due to their different electron configuration, complexes **6** have a metal–metal bond order of two and two unpaired electrons. These complexes promote both cyclopropanation and olefin metathesis reactions.[7,8] Unfortunately, only a few data on cyclopropanation are available: The trifluoroacetate complex (**6**, R = CF_3) catalyses cyclopropanation of cyclooctene with EDA in quantitative yield (99% based on EDA, at 60 °C; *endo*/*exo* = 1.65) while $Rh_2(OAc)_4$ is less well suited (treatment of a mixture of styrene and norbornene with EDA at 60 °C yields mainly products of cross-metathesis of the alkenes, yields of cyclopropanated styrene and norbornene are 35–40 and 2%, respectively). The metathesis reactions require activation of **6** by the diazoacetate, and the metathetical activity is attributed to the kinetic lability of the acetato bridges in the complex.

Maas and coworkers have identified the ruthenium(I) complexes $[Ru_2(CO)_4(\mu\text{-}OAc)_2]_n$ (**7**) and $[Ru_2(CO)_4(\mu\text{-}OAc)_2(CH_3CN)_2]$ (**8**) as versatile cyclopropanation catalysts.[9] Complex **7** is a coordination polymer which is not soluble in common non-donor organic solvents nor in alkenes, but it dissolves during the course of the reaction. In contrast, the bis(acetonitrile) complex **8** is soluble in the reaction mixtures. It is assumed that the coordination polymer of **7** is broken up by interaction with the diazo compound while in **8**, the axial acetonitrile ligands must be replaced by the diazo or carbene moiety. Cyclopropanation of a variety of alkenes with MDA occurs in good to high yield when catalysed by **7** at 20 °C (Scheme 3 and Table 1).[9,10] With complex **8**, virtually the same yields are obtained when the reactions are performed at 60 °C (except 2,3-dimethyl-2-butene). The yields of cyclopropanes **9** resulting from mono-substituted or 1,1-disubstituted alkenes and isoprene are rather similar to the reactions catalysed by $Rh_2(OAc)_4$, but are somewhat lower for 1,2-disubstituted, tri- and tetrasubstituted alkenes. This



Scheme 3

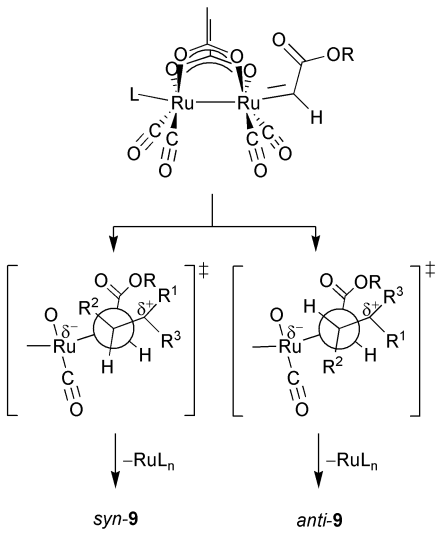
indicates that for the reactivity towards the presumed ruthenium–carbene intermediates, steric hindrance at the olefinic bond can override the nucleophilicity of the alkene.

Table 1 Cyclopropanation of alkenes with MDA and catalyst **7** (Scheme 3)

R^1	R^2	R^3	R^4	Yield of **9** (%)	*Z*-**9**:*E*-**9**[a]
Ph	H	H	H	95	38:62
Bu	H	H	H	67	33:67
EtO	H	H	H	89	18:82
Ph	H	Me	H	91	60:40
–$(CH_2)_4$–		H	H	68	21:79
–$(CH_2)_3O$–		H	H	62	only *E*
Me	Me	Me	H	61	86:14
Me	CH_2CCl_3	Me	H	55	84:16
Me	Cl	Me	H	20	91:9
Me	CH=CMe_2	Me	H	91	90:10
Me	CH=CCl_2	Me	H	30	83:17
Me	Me	Me	Me	47	

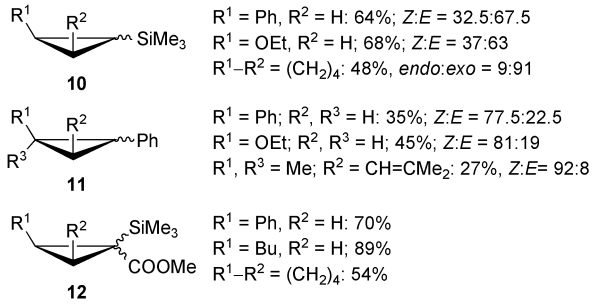
[a] Or *syn*:*anti*, *endo*:*exo*.

The diastereomer ratios *Z*-**9**/*E*-**9** obtained for styrene, 1-hexene, and cyclohexene are similar to those with $Rh_2(OAc)_4$. For trisubstituted alkenes, however, an unprecedented *syn*-selectivity, yielding the thermodynamically less favoured cyclopropane, is found.[10] This diastereoselectivity may be attributed to the known sawhorse configuration of the dimeric dicarbonylruthenium carboxylate complexes which controls both the configuration at the Ru=C bond of the metal–carbene intermediate and the approach of the alkene (Scheme 4).



Scheme 4

Complex **7** can also be applied to catalyse alkene cyclopropanation with (trimethylsilyl)diazomethane and phenyldiazomethane to give cyclopropanes **10** and **11**, respectively (Scheme 5).[11] With *ca*. 3 mol% of catalyst, the yields compare well with those obtained with $Rh_2(OAc)_4$ or CuCl as catalysts, and the consistent *Z*- (*syn*-)



Scheme 5

selective formation of phenylcyclopropanes **11** is also observed with these catalysts. While **7** does not seem to decompose dimethyl diazomalonate, it induces carbenoid reactions with methyl (trialkylsilyl)diazoacetates at elevated temperature (Scheme 5).[9,12] Terminal alkenes and cyclohexene are effectively transformed into cyclopropanes **12**. The cyclopropanation of 1-hexene is accompanied by a small amount of the metathesis product BuCH=C(SiMe_3)COOMe, and it has been reported elsewhere[8] that the system **8**/diazoacetate initiates ring-opening metathetical polymerisation (ROMP) of cyclooctene and norbornene at 100 °C.

2.3 Five- and six-coordinate ruthenium–phosphane complexes

The commercially available complex $RuCl_2(PPh_3)_3$, the same complex activated in boiling benzene under air, and the hydrido and silyl complexes $RuH_3[Si(OEt)_3](PPh_3)_2$ and $Ru[Si(OEt)_3]_2(PPh_3)_2$ have been investigated.[13] For the cyclopropanation of styrene, *para*-substituted styrenes and α-methylstyrene, high yields were obtained with all catalysts when the reactions were run at 60 °C. The catalysts were, however, totally ineffective for cyclopropanation of non-activated terminal and internal alkenes as well as cycloalkenes. Yields obtained from isoprene did not surmount 26%. An interesting observation is the increase of the *Z*-**3**/*E*-**3** ratio at elevated temperature (for $RuCl_2(PPh_3)_3$: 0.48 at 20 °C, 0.79 at 60 °C).

As variations of $RuCl_2(PPh_3)_3$, several five-coordinate Ru(II) complexes with tridentate phosphane ligands were examined (Fig. 3) and were found to be poor cyclopropanation catalysts with EDA,

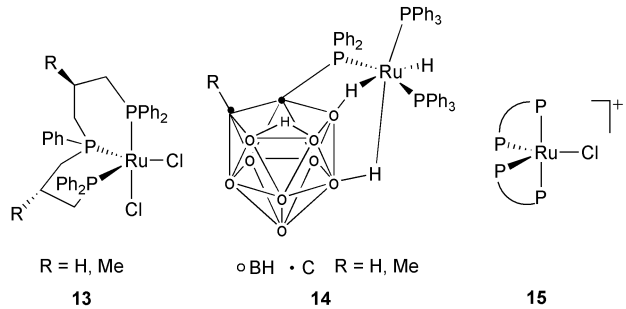


Fig. 3

giving rise to the carbene dimers instead.[14] However, when complex **13** was treated with AgOTf to remove a chloride ligand, the yield for the cyclopropanation of styrene with EDA rose from 21 to 84% (*Z*/*E* = 0.71).

The catalytic activity of ruthenacarboranes **5** has already been mentioned. The related Ru(II) complexes [$RuH(PPh_3)_2$(7-PPh_2-8-R-$C_2B_9H_{10}$] (**14**), in which the carborane moiety acts as a tridentate ligand through coordination at the PPh_2 group and two B–H–Ru agostic bonds, show similar characteristics, but reach their full performance in cyclopropanation of alkenes with EDA only at 100 °C.[15] It is assumed that one of the two PPh_3 ligands is displaced

in the catalytic process. Interestingly, the cyclopropane ratio *Z*-**3**/*E*-**3** can be changed in favour of the *Z*-isomer when a bulky diazo ester residue is used (methyl diazoacetate: 0.72, *tert*-butyl diazoacetate 1.99).

Five-coordinate bis(diphosphane)ruthenium(II) complexes of the type $[RuCl(P\cdots P)_2]PF_6$ (**15**, P···P is, *e.g.*, (*S*,*S*)-2,2-bis(diphenylphosphanyl)butane (chiraphos)) do not offer advantages as cyclopropanation catalysts.[16] For the styrene + EDA reaction, carried out at 20 °C and with 1 mol% of catalyst, conversion is slow and yields of cyclopropane **3** are moderate, and almost no diastereoselectivity is observed (*Z*:*E* ≈ 45:55).

2.4 Ruthenium–arene and cyclopentadienyl–ruthenium complexes

The ruthenium(II) cymene complex $[RuCl_2(PPh_3)(p\text{-cymene})]$ (**16a**, Fig. 4) was found to catalyse cyclopropanation of styrene and

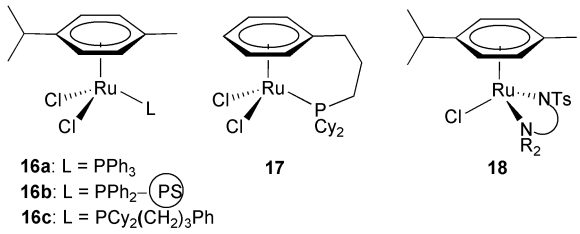


Fig. 4

α-methylstyrene (60 °C, 1 mol% of catalyst, 71 and 82% yield).[17] The polymer-supported version **16b** gave almost the same yields as the homogeneous catalyst and could be re-used several times and no leaching from the polystyrene support was observed.[17] Several by-products resulting from metathesis and olefin homologation were found with catalyst **16c** which did not show up when the phosphane and arene ligands were tethered as in **17**.[18] The difference appears to be due to the easier thermally induced loss of the arene ligand in the case of **16c**.

The diamine complexes **18** are also effective cylcopropanation catalysts for EDA and styrenes, α- and β-methylstyrene, 1-octene, and cyclooctene at 60–100 °C, while norbornene undergoes ROMP exclusively.[19] Several diamine ligands were tested of which the phenylenediamine derived ligand (TsN–*o*-C_6H_4–NH_2) emerged as the best one in terms of turnover frequency and cyclopropane yields.

Several 18-electron Ru(II) and Ru(IV) complexes with cyclopentadienyl ligands have been found to catalyse carbene transfer from diazo compounds to olefins (Fig. 5). Complexes of the type

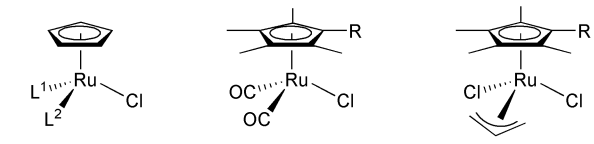
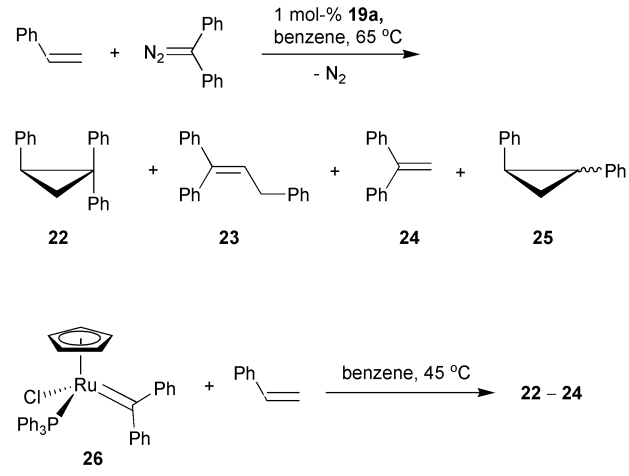


Fig. 5

$[(\eta^5\text{-}C_5H_5)RuClL^1L^2]$ (*e.g.*, **19a–d**) are effective catalysts for the terminal alkene + EDA reaction; in addition, complexes with bis(triarylphosphane) substitution, such as **19a,b**, yield an unusual *cis*-stereoselectivity (*e.g.* for styrene and **19a**: 0.5 mol% of catalyst, reaction at 45 °C/4 h, 95% of **3** (R = Et), *Z*/*E* = 2.1).[20] According to the necessary reaction temperature, the reactivity of the catalysts decreases in the order **19b** > **19a** > **19c** ≈ **19d** which may reflect the decreasing rate of dissociation of a phosphane ligand to form the catalytically active 16-electron ruthenium complex.

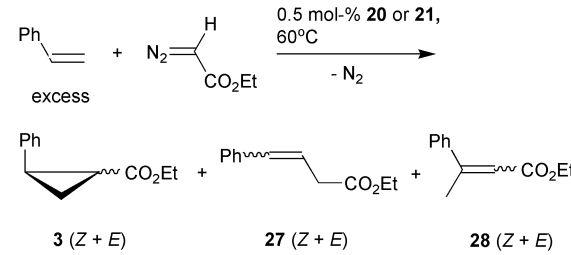
In contrast to EDA, the reaction of diphenyldiazomethane and styrene catalysed by **19a** yields only little of cyclopropanation product **22** (9%, probably formed in an uncatalysed thermal reaction), the other products being olefins **23** (58%) and **24** (17%) and 1,2-diphenylcyclopropane **25** (16%, *E* and *Z*) (Scheme 6).[20]



Scheme 6

The ruthenium–carbene complex **26**, observed NMR-spectroscopically during the reaction, could be prepared by a stoichiometric reaction of **19a** and N_2CPh_2; the stoichiometric reaction between **26** and styrene gave products **22–24** in similar yields as in the catalytic reaction. A mechanistic scheme based on these findings and including ruthenacyclobutane intermediates was proposed.

When complexes **20** and **21** (R = Me, CH(OH)Ph, COPh, 1,3-dioxolan-2-yl, CH=CH–COPh, *etc.*) are used to catalyse the reaction of diazoacetates with styrene, cyclopropanes **3** are still the major products, but in some cases significant amounts of olefin **27** and traces (< 3%) of olefin **28** are also found as are the formal carbene dimers, diethyl maleate and fumarate (Scheme 7).[21] The



Scheme 7

two olefinic homologation products are the formal products of carbene insertion in either of the vinylic C–H bonds of styrene, but the mechanistic picture, again with the possible participation of ruthenacyclobutane intermediates, remains speculative. Ru(IV) complexes **21** give rise to higher amounts of homologation products than complexes **20** or the cationic analogue of **20**, $[\eta^5\text{-}C_5Me_5)Ru(CO)_2(CH_3CN)]BF_4$, which appears to be an excellent cyclopropanation catalyst. For example, catalyst **20** (R = Me) gave 70% of cyclopropane **3** and 7.5% of olefin **27**; the corresponding figures for **21** (R = Me) were 69 and 16%. With **20** (R = COPh) and **21** (R = COPh), values of 75/1% *vs.* 60/32% were found.

2.5 Ruthenium(II) complexes with multidentate nitrogen ligands designed for enantioselective catalysis

Several ruthenium(II) complexes with multidentate chelating ligands have been prepared in the hope of controlling the diastereoselectivity and, in the case of chiral ligands, the enantioselectivity of carbenoid cyclopropanation reactions. Some chelating P,P and P,P,P ligands[14,16] which have already been mentioned in Section 2.3 (*e.g.*, **13**, R = Me) gave cyclopropanes **3** with only low levels of diastereomeric or enantiomeric excess. Much better results were obtained with various multidentate ligands that contain

nitrogen as donor atoms exclusively or in combination with O or P. Only the major developments will be discussed in the following.

Fig. 6 shows some tridentate N,N,N and N,N,P ligands and/or the related ruthenium complexes. Selected results for the cyclopropanation of styrene with diazoacetates (often the only reaction investigated) are collected in Table 2.

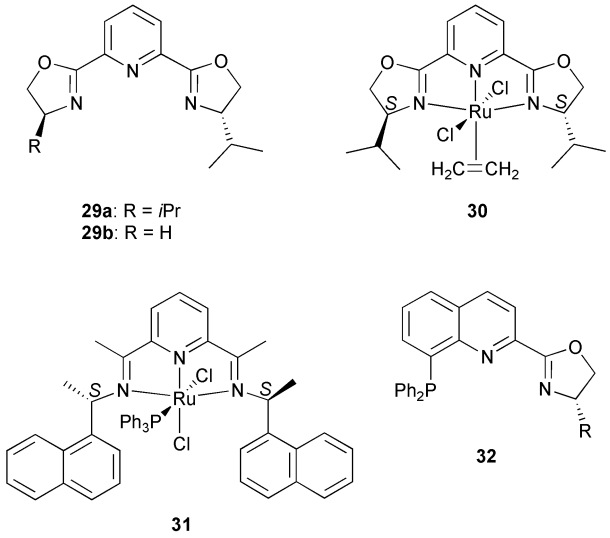


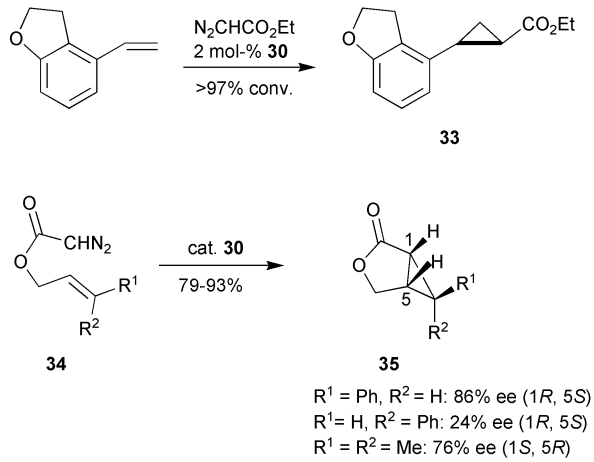
Fig. 6

Table 2 Asymmetric cyclopropanation of styrene with diazoacetates (Scheme 3) catalysed by ruthenium(II) complexes with tri- and tetradentate nitrogen-containing ligands

Entry	Catalyst or ligand	$N_2CHCOOR$, R =	Yield of **3** (%)	*Z*-**3**:*E*-**3**	ee (%), *Z*-**3**	ee (%), *E*-**3**	Ref.
1	**29a**[a]	Et	69	8:92	78[b]	89[c]	22
2	**29a**	*t*Bu	81	3:97	85[b]	94[c]	22
3	**29b**[d]	Et	93	11:89	66[b]	90[c]	24
4	**29b**[d]	*l*-menthyl	84	1:99	64[b]	94[c]	24
5	**30**	Et	73	9:91	79[b]	89[c]	22
6	**30**	*d*-menthyl	82	3:97	97[b]	87[c]	22
7	**31**	Et	65	14:86	76[b]		27
8	**37**	Et[e]	33	93:7	88[f]	35[g]	30
9	**37**	*t*Bu[h]	45	93:7	97[f]	15[g]	30
10	**40**[i]	Et	94	2:98		95	33

[a] *In-situ* preparation of catalyst from $[RuCl_2(p\text{-cymene})]_2$ and excess ligand **29a**; CH_2Cl_2, rt. [b] (1*R*,2*S*). [c] (1*R*,2*R*). [d] *In-situ* preparation of catalyst from $[RuCl_2(p\text{-cymene})]_2$ and excess ligand **29b**; CH_2Cl_2, 30–35 °C. [e] In THF–styrene (2:1). [f] (1*S*,2*R*). [g] (1*R*,2*R*). [h] In THF–styrene (1:1). [i] R^1 = *i*-Pr, R^2 = H.

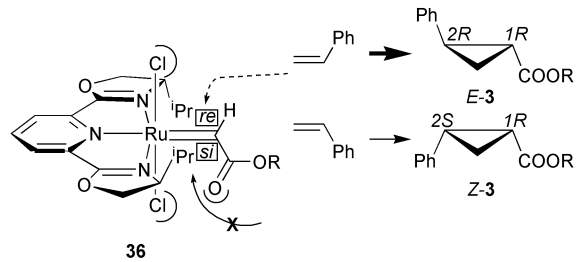
Nishiyama and coworkers found that in the presence of a catalyst prepared *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and the chiral C_2-symmetric ligand **29a** ((*S*,*S*)-ip-pybox), cyclopropanes **3** were obtained in good chemical yield, with excellent *E*-selectivity and with enantioselectivities up to 97% ee (Table 2, entries 1 and 2).[22] The isolated ruthenium(ip-pybox)(ethylene) complex **30**, which was prepared from the ruthenium(II) precursor and the ligand **29a** in an ethylene atmosphere, was found to exhibit the same catalytic activity.[22] With catalyst **30**, similarly high *E*-selectivities and ee values were also found for cyclopropanation of 3-phenyl-1-propene and 1-heptene, although the yields dropped to 45–54%; however, 1,2-disubstituted and trisubstituted alkenes did not react. In a large scale industrial process, catalyst **30** was used for the *trans*- and enantioselective cyclopropanation of 4-vinyl-2,3-dihydrobenzofuran (52 kg) with EDA (101 kg, 2.5 equivalents) *en route* to a melatonin agonist derived from (*R*,*R*)-cyclopropane **33** (Scheme 8).[23] Intramolecular cyclopropanation of allylic diazoacetates **34** catalysed by **30** also proceeded well and gave bicyclic lactones **35** partly with good enantioselectivity (Scheme 8).[22]



Scheme 8

Water-soluble analogues of the Ru–pybox catalyst (cf. **30**, CH_2OH or $(CH_3)CHOH$ instead of *i*Pr, *R*,*R* configuration) provided good yields for cyclopropanation of styrene with diazoacetates in a toluene–water mixture and hold promise as re-usable catalysts.[24] The high *trans*-selectivity and enantioselectivity (in particular with *d*- and *l*-menthyl diazoacetate) known from catalyst **30** is also found with these modified catalysts.

Models explaining the observed stereoselectivities of the inter- and intramolecular cyclopropanations have been proposed.[22] For the intermolecular case, this is shown in Scheme 9. Approach of the olefin to the presumed Ru–carbene intermediate **36** (analogues of **36** where R is a bulky aryl substituent have in fact been isolated[25]) is directed towards the *re*-face of the Ru-carbene center, because the *si*-face is well shielded. This defines the absolute configuration at the ester-substituted carbon atom of **3**, while the *Z*:*E* ratio appears to result from minimization of steric interaction between Ph and COOR in a late transition state. Interestingly, the high *E*-preference is an inherent property of the octahedral Ru–pybox complex since already the non-chiral pybox ligand (**30**, H instead of *i*Pr) gave a *Z*-**3**/*E*-**3** ratio of 11:89 with EDA. In a subsequent study, it was found that comparably high ee values as with the C_2-symmetric chiral ligand **29a** were obtained with the pybox ligand **29b** bearing only one chiral oxazoline ring (Table 2).[26]



Scheme 9

Several Ru complexes bearing non-chiral and chiral 2,6-bis(1-iminoethyl)pyridine ligands have been investigated.[27] Complex **31** gave fair yields of cyclopropanes **3**, with a strong preference for the *E*-isomer and an enantioselectivity distinctly higher than with the ligand derived from (*R*)-1-phenethylamine (Table 2, entry 7). Treatment of **31** with $AgPF_6$ enhanced the catalytic activity but was detrimental to the dia- and enantioselectivity. No enantioselectivity was obtained with catalysts prepared *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and tridentate chiral 2,2′:6′,2″-terpyridine ligands.[28]

Complexes obtained from $[RuCl_2(p\text{-cymene})]_2$ and chiral N,N,P-tridentate ligands **32** (R = *t*Bu, *i*Pr, Ph) catalyse the formation of cyclopropanes **3** in acceptable yields but with dia- and (modest) enantioselectivities that strongly depend on substituent R at the oxazoline ring and the ester group in the diazoacetate.[29] The same situation is encountered for the intramolecular cyclopropanation of unsaturated diazoketones and allyl diazoacetates.

Suitable cyclopropanation catalysts are also found among ruthenium(II) complexes with tetradentate ligands (Fig. 7). Katsuki

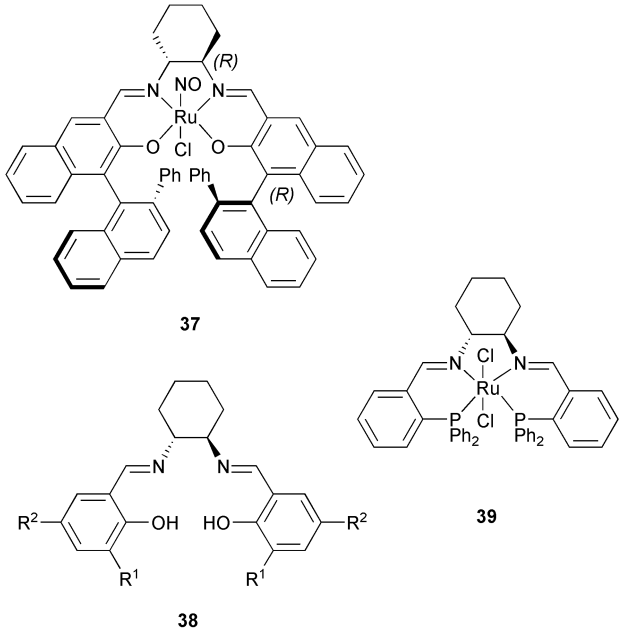


Fig. 7

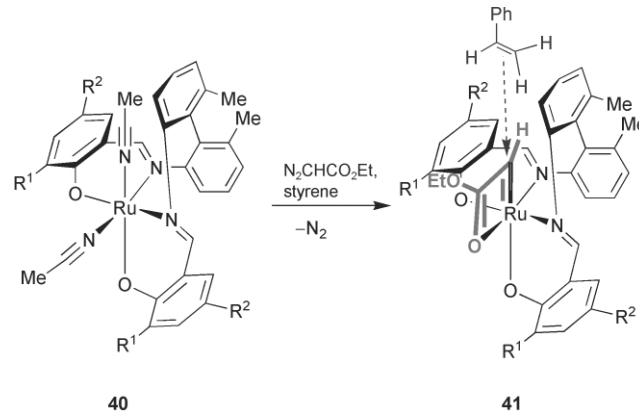
and co-workers have studied several (NO^+)(salen)ruthenium(II) complexes of which complex **37** was identified as a precatalyst which gives exceptional *Z* selectivity accompanied by high enantioselectivity for the cyclopropanation of styrene and its ring-substituted derivatives with diazoacetates (Table 2, entries 8 and 9).[30] Unfortunately, chemical yields are at best moderate and a relatively high catalyst load (5 mol%) is required. Complex **37** must be activated by irradiation to create a vacant coordination site; when this is done with 440 nm light or an incandescent light source, the photochemical generation of the free carbene from the diazoacetate causing non-enantioselective cyclopropanation is largely suppressed.

With catalysts prepared *in situ* from $[RuCl_2(p\text{-cymene})]_2$ or $RuCl_2(PPh_3)_3$ and various alkyl-, halogen- or nitro-substituted salen ligands **38**, cyclopropanation of styrene with EDA occurred in good to high chemical yield, with an unspectacular *E*-selectivity (*E*/*Z* ≈ 1.3–4.0) and with ee ≤ 80%.[31] With ruthenium complex **39** activated by AgOTf, the cyclopropane yield was high and a moderate *Z* selectivity was found.[32] The enantioselectivity was low but could be increased considerably by addition of N-donor molecules; in the best case, addition of collidine gave 90% ee for *Z*-**3** (R = Et) and 73% ee for *E*-**3**.

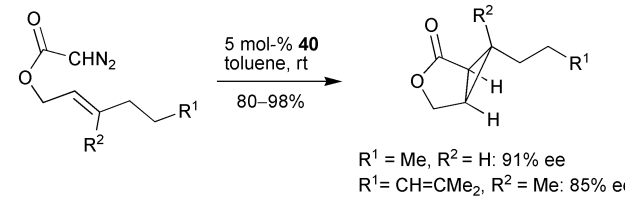
Ruthenium(II) complexes of the type $Ru(L)(CH_3CN)_2$ (**40**), where L is a tetradentate (O,N,N,O) chiral biaryldiimine ligand, represent a remarkable new development.[33] They catalyse both inter- and intramolecular cyclopropanation reactions (Table 2, entry 10, and Schemes 10 and 11) with high yield and good to high enantioselectivity. In addition, styrenes are cyclopropanated with high *E*-selectivity. DFT calculations suggest that in the intermediate metal–carbene complex **41** both acetonitrile ligands are replaced by the carbonyl carbene unit that maintains a η^2-coordination at the metal, with the Ru–C bond in the apical position. This model is in agreement with the observed dia- and enantioselectivity.

2.6 Ruthenium porphyrin complexes

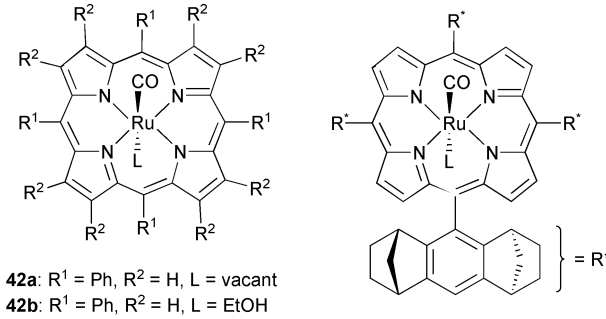
Similar to porphyrin complexes of rhodium, osmium and iron,[1] ruthenium(II) and ruthenium(VI) porphyrins were found to catalyse carbenoid reactions of diazo compounds. Cyclopropanation reactions of styrene, ring-substituted styrenes, α-substituted styrenes, 1,3-dienes, and some nucleophilic terminal alkenes with diazoacetates are catalysed by ruthenium porphyrins **42a**,[34,35] **42b**,[36] **43**,[36] **44a,b**[36–38] **45**,[34] dendritic Ru-porphyrins,[39] and others[34,36,40] (Fig. 8). While these reactions occur in some cases with exceptionally



Scheme 10



Scheme 11



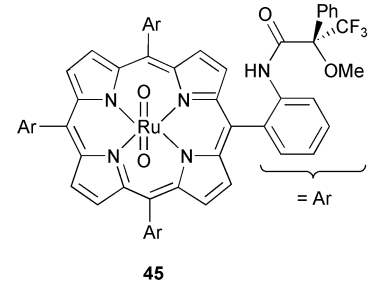


Fig. 8

high turnover numbers (up to 11000 for **44b**[38]), non-activated terminal alkenes as well as internal alkenes (*e.g.*,[35] 3-phenyl-1-propene, 4-vinylcyclohexene) do not react – in partial contrast to rhodium(III) porphyrins that are not effective only with tetra-substituted alkenes.

A characteristic feature of ruthenium porphyrins is the expressed *E* selectivity of the formed cyclopropanes. As an example, catalysis of the styrene + EDA reaction with **44a** (0.15 mol% of catalyst, 1,2-dichloroethane, 20 °C) gave cyclopropanes **3** in quantitative yield and with a *E*:*Z* ratio of 96:4[37] that even increased when the temperature was lowered to −40 °C.[38] Electron-withdrawing substituents on the phenyl ring of styrene also enhance the *E*:*Z*

ratio.[35] Ruthenium porphyrins share the *E*-selectivity with related osmium and iron porphyrins, while rhodium(III) porphyrins tend to give *Z*-2-phenylcyclopropanecarboxylic esters preferentially.

Asymmetric cyclopropanations have been tested with several chiral ruthenium porphyrins.[34,36–38,40] While only low ee values were obtained with catalyst **45**, complexes **44a** and **44b**, featuring a D_4-symmetric chiral ligand with bulky substituents, gave in some cases high levels of asymmetric induction. Thus, in the styrene + EDA reaction, up to 98% ee for *E*-**3** (R = Et) but only up to 16% for *Z*-**3** was achieved;[37,38] in the styrene + *d*- or *l*-menthyl diazoacetate reaction, de values of 64–67% for *E*-**3** and 90–95% for *Z*-**3** were obtained.[38] For intramolecular cyclopropanation of allyl diazoacetates, moderate ee values were typically obtained, *e.g.* **34** → **35** (R^1 = R^2 = Me, 65% yield) with 36% ee.[38]

The robustness of the ruthenium porphyrins and their remarkable selectivity in catalysing (not only) cyclopropanation reactions has stimulated efforts to recover and to re-use these catalysts. Attachment of 5,10,15,20-tetraarylporphyrin carbonylruthenium complexes to poly(ethyleneglycol) gave soluble polymer-supported catalysts that could be easily removed by addition of ether to the product mixture and cooling.[41] Encapsulation of the chiral complex **44a** in mesoporous silica supports gave a catalyst that performed well under heterogeneous conditions in an intramolecular cyclopropanation of an allyl diazoacetate; the ee value of the product decreased somewhat when the catalyst was re-used four times.[42]

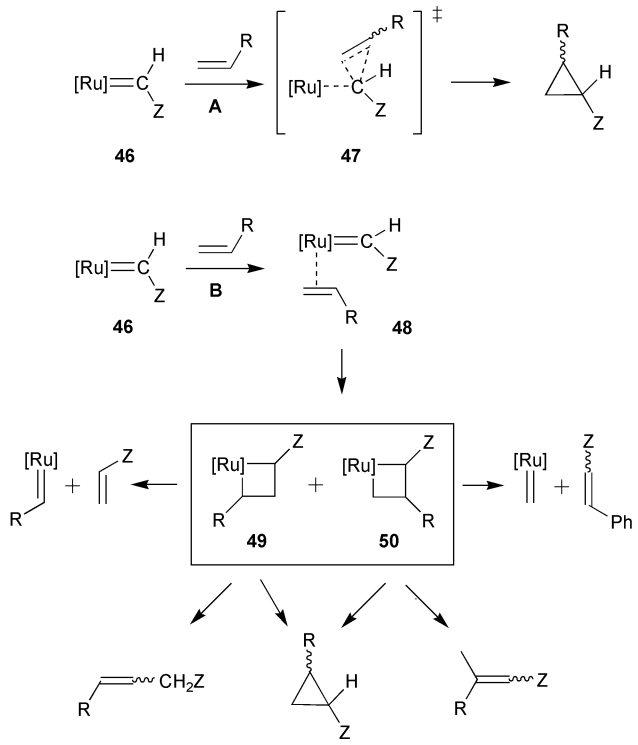
3 Mechanistic models

Scheme 1 postulates a metal–carbene complex **1** as the central intermediate in carbenoid cyclopropanation reactions. In fact, ruthenium differs from copper and rhodium in that a number of ruthenium–carbene complexes have been isolated from the stoichiometric reaction between a catalytically active ruthenium complex and a diazo compound, *e.g.* [$RuCl_2$(pybox)(=CH-$SiMe_3$)],[43] **36** (R = 2,6-di-*tert*-butyl-4-methylphenyl),[25] the diphenylcarbene complex derived from ruthenium porphyrin **44a** ([RuP*(=CPh_2)],[38] and complex [$RuCl_2$(ttp)(=$CHCO_2Et$)] derived from **13**.[14] These complexes transfer their carbene ligand to styrene at elevated temperature and catalyse cyclopropanation of alkenes with diazoacetates; dia- and enantioselectivity characteristics of the reactions using the original Ru catalysts are largely reproduced.[25,38] Furthermore, transient ruthenium–carbene complexes were observed spectroscopically.[14,34]

Like other carbene complexes of late transition metals, ruthenium carbene complexes are electrophilic, although in general less so than the more reactive and short-lived carbene complexes of copper and rhodium. The reaction of EDA with *para*-substituted styrenes is accelerated by electron-donating substituents and retarded by electron-withdrawing ones.[44] For the reactions catalysed by tetraphenylporphyrin complex **42a**, a linear Hammett plot ($\log(k_X/k_H) = \rho\cdot\sigma$) with $\rho = -1.29 \pm 0.08$ was found,[35] while porphyrin catalyst **44b** gave a linear correlation only when σ^+ values were used ($\rho^+ = -0.44 \pm 0.09$).[38] Similar electronic preferences were observed with EDA/porphyrin systems derived from Fe(TTP) and $Os_2(TTP)_2$ (TTP = tetra-(4-tolyl)porphyrin), but not with rhodium(III) porphyrins.[45]

Two principal pathways may be discussed for the carbene transfer from a carbene complex **46** to an alkene, a carbenoid and a coordination mechanism (Scheme 12, path A and B, respectively).[1,4,14]

Ruthenium carbene complexes that do not have an additional vacant coordination site at the metal are expected to react by the carbenoid pathway which also prevails for rhodium- and copper-catalysed reactions (for calculations on copper-catalysed cyclopropanations, see refs. 46,47). Cyclopropane formation is assumed to go through a late and rather unsymmetrical transition state **47** with build-up of some positive charge at the more distant C-atom of the alkene (for an illustration, see Scheme 4). This hypothesis explains



Scheme 12

why most ruthenium-catalysed reactions proceed well only with terminal alkenes bearing good cation-stabilizing substituents (*e.g.* aryl, OR, vinyl). In the case of 1,2-disubstituted, three- and tetrasubstituted alkenes, the considerable extent of bond-forming in the transition state is accompanied by unfavourable steric interactions of the substrate with the metal's ligand sphere and the substituent(s) at the carbene moiety. The distinction between an early transition state in the case of rhodium porphyrins[45] and a late transition state in the case of ruthenium porphyrins has been used to explain why the former catalysts generate cyclopropanes *cis*-selectively while the latter induce *trans*-selectivity.[35]

The coordination mechanism (path B in Scheme 12) implies the simultaneous coordination of the carbene and the olefin at the metal. In fact, complex **48** may be formed from **46** as shown in the Scheme, or after initial coordination of the intact diazo compound and the alkene at the metal. In any case, the original catalyst (or precatalyst) must provide two easily accessible coordination sites, *e.g.*, by the presence of two easily displacable ligands in a 18-valence electron complex. However, as the calculated structure of carbene complex **41** (Scheme 10) suggests, not every 14-electron complex fragment is ready to coordinate both the carbene moiety and the alkene. Complexes of type **48** may rearrange to ruthenacyclobutanes **49** and **50** (depending on the original alkene orientation), the chemistry of which is as yet poorly understood.[8,21] Several reaction channels are available, and examples have been given in this review. Thus, reductive elimination of the metal fragment would generate the desired cyclopropanes. Cleavage of one Ru–C bond followed by metal elimination and H shift would generate olefinic homologation products (see also Schemes 6 and 7). Finally, [2 + 2] cycloreversion of the ruthenacyclobutanes would give rise to metathesis products and, in the case of cycloalkenes as substrates, initiate ROMP. The factors favouring one or the other reaction pathway are not yet known in detail.[8]

4 Conclusion and outlook

Complexes of ruthenium in different oxidation states (+1, +2, +4, +6) and with various ligand types and coordination motifs have been found to catalyse the cyclopropanation of certain alkenes effectively. With ruthenium porphyrins in particular, exceptionally high turnover rates are observed. With the appropriate ligand

sphere, either high *cis*-selectivity or high *trans*-selective cyclopropanation of 1,1-disubstituted alkenes with diazoacetates can be achieved, and high levels of asymmetric induction can be realized. A significant drawback of ruthenium-catalysed cyclopropanation reactions is the rather low electrophilic character of the presumed ruthenium–carbene intermediates which often restricts the application to terminal activated alkenes such as styrene(s) and vinyl ethers, while simple alkenes and double bonds with a higher degree of alkyl substitution react sluggishly or not at all. Notable exceptions are so far the dinuclear ruthenium(I) carboxylates **7** and ruthenacarboranes such as **5** and **14**. Another limitation may be seen in the propensity of some ruthenium complexes to catalyse not only cyclopropanation but also alkene metathesis and alkene homologation reactions.

In those inter- and intramolecular cyclopropanation reactions where ruthenium catalysts work successfully, they often rival established rhodium catalysts in terms of effectiveness and relative as well as absolute stereochemistry. Furthermore, there is a steadily increasing number of literature reports on other carbenoid reactions of diazo compounds catalysed by ruthenium, *e.g.* X–H insertion reactions, intramolecular C–H insertion, carbonyl ylide formation, and carbene dimer formation. In little more than a decade, ruthenium has emerged as the third important catalyst metal for the carbenoid chemistry of diazo compounds, besides copper and rhodium.

Future developments should try to overcome some of the present limitations, *i.e*. to find catalysts that give ruthenium carbene intermediates electrophilic enough to react with a wide range of olefinic substrates and that at the same time give high levels of dia- and enantioselectivity. Intramolecular cyclopropanation has so far been limited to the transformation of unsaturated diazoacetates into bicyclic lactones and should be extended to the conversion of unsaturated diazoketones into bicyclo[*n*.1.0]alkanes; as it is still more difficult, with chiral copper and rhodium catalysts, to control the asymmetric induction in the intramolecular cyclopropanation of diazoketones as compared to diazoacetates,[1] identification of suitable chiral ruthenium catalysts is particularly attractive. A systematic evaluation of ruthenium catalysts for other carbene transfer reactions – those mentioned above and others including intermolecular C–H insertion reactions (where significant progress has recently been achieved in rhodium-catalysed reactions with aryl- and vinyldiazoacetates[48]), is also still ahead. The rich coordination chemistry of ruthenium appears to offer opportunities in all these directions.

Acknowledgements

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References

1 M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley & Sons, New York, 1998.
2 M. P. Doyle and M. Protopopova, *Tetrahedron*, 1998, **54**, 7919.
3 E. A. Seddon and K. R. Seddon, *The Chemistry of Ruthenium*, Elsevier, Amsterdam, 1984.
4 A. J. Anciaux, A. J. Hubert, A. F. Noels, N. Petiniot and P. Teyssié, *J. Org. Chem.*, 1980, **45**, 695.
5 W. H. Tamblyn, S. R. Hoffmann and M. P. Doyle, *J. Organomet. Chem.*, 1981, **216**, C64.
6 A. Demonceau, E. Saive, Y. de Froidmont, A. F. Noels, A. J. Hubert, I. T. Chizhevsky, I. A. Lobanova and V. I. Bregadze, *Tetrahedron Lett.*, 1992, **33**, 2009.
7 A. Demonceau, A. F. Noels, E. Saive and A. J. Hubert, *J. Mol. Catal.*, 1992, **76**, 123.
8 Short review: A. F. Noels and A. Demonceau, *J. Phys. Org. Chem.*, 1998, **11**, 602; A. F. Noels, A. Demonceau and D. Jan, *Russ. Chem. Bull.*, 1999, **48**, 1206.
9 G. Maas, T. Werle, M. Alt and D. Mayer, *Tetrahedron*, 1993, **49**, 881.
10 T. Werle and G. Maas, *Adv. Synth. Catal.*, 2001, **343**, 37.
11 G. Maas and J. Seitz, *Tetrahedron Lett.*, 2001, **42**, 6137.
12 G. Maas, M. Alt, D. Mayer, U. Bergsträsser, S. Sklenak, P. Xavier and Y. Apeloig, *Organometallics*, 2001, **20**, 4607.
13 A. Demonceau, E. Abreu Dias, C. A. Lemoine, A. W. Stumpf, A. F. Noels, C. Pietraszuk, J. Gulinski and B. Marciniec, *Tetrahedron Lett.*, 1995, **36**, 3519.
14 H. M. Lee, C. Bianchini, G. Jia and P. Barbaro, *Organometallics*, 1999, **18**, 1961.
15 A. Demonceau, F. Simal, A. F. Noels, C. Viñas, R. Nuñez and F. Teixidor, *Tetrahedron Lett.*, 1997, **38**, 4079.
16 R. M. Stoop, C. Bauer, P. Setz, M. Wörle, T. Y. H. Wong and A. Mezzetti, *Organometallics*, 1999, **18**, 5691.
17 N. E. Leadbeater, K. A. Scott and L. J. Scott, *J. Org. Chem.*, 2000, **65**, 3231.
18 F. Simal, D. Jan, A. Demonceau and A. F. Noels, *Tetrahedron Lett.*, 1999, **40**, 1653.
19 F. Simal, A. Demonceau and A. F. Noels, *Tetrahedron Lett.*, 1998, **39**, 3493.
20 W. Baratta, W. A. Herrmann, R. M. Kratzer and P. Rigi, *Organometallics*, 2000, **19**, 3664.
21 F. Simal, A. Demonceau, A. F. Noels, D. R. T. Knowles, S. O'Leary, P. M. Maitlis and O. Gusev, *J. Organomet. Chem.*, 1998, **558**, 163.
22 H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki and K. Itoh, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1247.
23 J. H. Simpson, J. Godfrey, R. Fox, A. Kotnis, D. Kacsur, J. Hamm, M. Totelben, V. Rosso, R. Mueller, E. Delaney and R. P. Deshpande, *Tetrahedron: Asymmetry*, 2003, **14**, 3569.
24 S. Iwasa, S. Tsushima, K. Nishiyama, Y. Tsuchiya, F. Takezawa and H. Nishiyama, *Tetrahedron: Asymmetry.*, 2003, **14**, 855.
25 S.-B. Park, M. Sakata and H. Nishiyama, *Chem. Eur. J.*, 1996, **2**, 303. For a crystal structure analysis of the related bis(methoxycarbonyl)carbene complex see: H. Nishiyama, K. Aoki, H. Itoh, T. Iwamura, N. Sakata, O. Kurihara and Y. Motoyama, *Chem. Lett.*, 1996, 1071.
26 H. Nishiyama, N. Soeda, T. Naito and Y. Motoyama, *Tetrahedron: Asymmetry*, 1998, **9**, 2865.
27 C. Bianchini and H. M. Lee, *Organometallics*, 2000, **19**, 1833.
28 G. Chelucci, A. Saba, D. Vignola and C. Solinas, *Tetrahedron*, 2001, **57**, 1099.
29 S.-W. Park, J.-H. Son, S.-G. Kim and K. H. Ahn, *Tetrahedron: Asymmetry*, 1999, **10**, 1903.
30 T. Ushida, R. Irie and T. Katsuki, *Tetrahedron*, 2000, **56**, 3501; T. Ushida, R. Irie and T. Katsuki, *Synlett*, 1999, 1793; T. Ushida, R. Irie and T. Katsuki, *Synlett*, 1999, 1163.
31 X. Yao, M. Qiu, W. Lü, H. Chen and Z. Zheng, *Tetrahedron: Asymmetry*, 2001, **12**, 197.
32 Z. Zheng, X. Yao, C. Li, H. Chen and X. Hu, *Tetrahedron Lett.*, 2001, **42**, 2847.
33 I. J. Munslow, K. M. Gillespie, R. J. Deeth and P. Scott, *Chem. Commun.*, 2001, 1638.
34 E. Galardon, P. Le Maux and G. Simonneaux, *Chem. Commun.*, 1997, 927.
35 E. Galardon, P. Le Maux and G. Simonneaux, *Tetrahedron*, 2000, **56**, 615.
36 W. C. Lo, C.-M. Che, K.-F. Cheng and T. C. W. Mak, *Chem. Commun.*, 1997, 1205.
37 M. Frauenkron and A. Berkessel, *Tetrahedron Lett.*, 1997, **38**, 7175.
38 C.-M. Che, J. S. Huang, F.-W. Lee, Y. Li, T.-S. Lai, H.-L. Kwong, P.-F. Teng, W.-S. Lee, W.-C. Lo, S. M. Peng and Z.-Y. Zhou, *J. Am. Chem. Soc.*, 2001, **123**, 4119.
39 J.-L. Zhang, H.-B. Zhou, J.-S. Huang and C.-M. Che, *Chem. Eur. J.*, 2002, **8**, 1554.
40 E. Galardon, S. Roué, P. Le Maux and G. Simonneaux, *Tetrahedron Lett.*, 1998, **39**, 2333.
41 J.-L. Zhang and C.-M. Che, *Org. Lett.*, 2002, **4**, 1911.
42 J.-L. Zhang, Y.-L. Liu and C.-M. Che, *Chem. Commun.*, 2002, 2906.
43 S.-B. Park, H. Nishiyama, Y. Itoh and K. Itoh, *J. Chem. Soc., Chem. Commun.*, 1994, 1315.
44 S. Bachmann and A. Mezzetti, *Helv. Chim. Acta*, 2001, **84**, 3063.
45 See, for example: J. R. Wolf, C. G. Hamaker, J.-P. Djukic, T. Kodadek and L. K. Woo, *J. Am. Chem. Soc.*, 1995, **117**, 9194.
46 J. M. Fraile, J. I. García, V. Martínez-Merino, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, 2001, **123**, 7616.
47 T. Rasmussen, J. F. Jensen, N. Østergaard, D. Tanner, T. Ziegler and P.-O. Norrby, *Chem. Eur, J.*, 2002, **8**, 177.
48 H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2903.