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ASYMMETRIC SYNTHESIS OF CYCLOPROPANE CARBOXYLATES: CATALYSIS OF DIAZOACETATE REACTIONS BY COPPER(II) SCHIFF BASE COMPLEXES DERIVED FROM α-AMINO ACIDS

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Summary

The asymmetric synthesis of cyclopropane carboxylates, which are intermediates in the synthesis of photostable pyrethroid insecticides, by catalysed reaction of ethyl diazoacetate with halo-olefins is described. Using chiral copper(II) Schiff base complexes derived from L-phenylalanine and aromatic aldehydes as catalysts, both the degree and direction of optical induction were found to depend upon the olefin. Unexpectedly, in several reactions there was marked stereoselectivity at C(3), rather than C(1), of the cyclopropanes. This novel pattern of selectivity is interpreted in terms of carbene transfer from a metal-carbene intermediate in which a chiral ligand controls the orientation of an approaching olefin.

Introduction

The transition metal catalysed reaction of diazoacetate esters with olefins provides a useful method of generating cyclopropane carboxylates [1] including precursors of pyrethroid insecticides [2]. Use of a substituted olefin gives rise to a mixture of four stereoisomeric cyclopropanes as products. These four stereoisomers comprise a pair of *cis* isomers which are enantiomers of each other and a pair of *trans* isomers which are also enantiomers of each other. The *R* configuration at C(1) of the cyclopropane ring is essential and *cis* geometry is preferable for the activity of the final insecticide. The ratio of the *cis* and *trans* isomers can often be controlled by the choice of transition metal used as catalyst and enantioselectivity may be induced by means of chiral ligands.

In the reaction of 2,5-dimethyl-1,4-hexadiene with alkyl diazoacetates employing chiral copper(II) Schiff base catalysts, Aratani et al. have formed chrysanthemates

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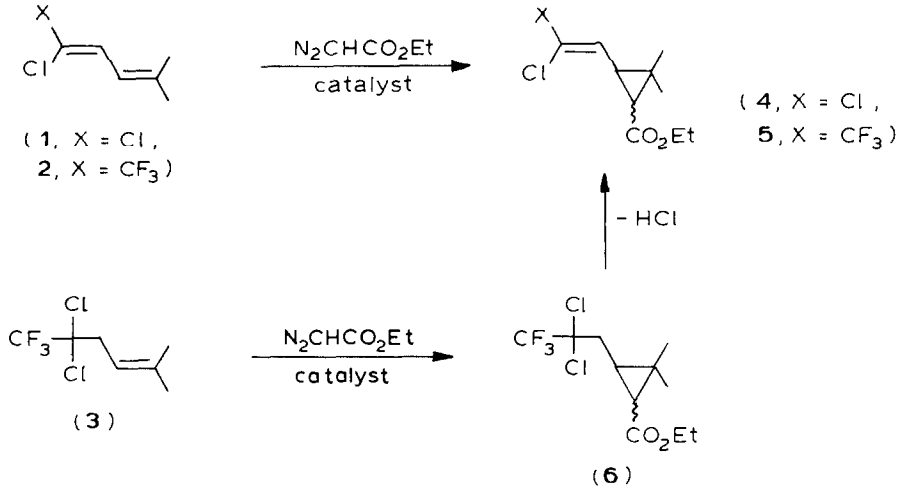
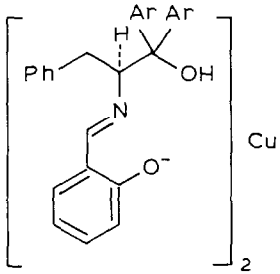
with optical yields of up to 90% [3–5]. The Schiff base ligands were prepared by condensation of optically active vicinal carbinol amines (derived from α-amino acids) with salicylaldehyde. It was found that these catalysts afforded ethyl chrysanthemate with *cis/trans* ratios of ca. 40/60, and with catalysts having the *R* configuration on the Schiff base ligands, enantioselectivity towards the insecticidally active 1*R*-cyclopropanes was noted. When complexes derived from natural L-α-amino acids having the *S* configuration on the Schiff base ligands were used, excesses of the insecticidally inactive 1*S*-cyclopropanes were obtained. Interestingly, and in contrast to the above observations, intramolecular cyclisation of 2,5-dimethyl-4-hexene-2-yl diazoacetate, which gave the *cis* isomer of dihydrochryanthemolactone exclusively, enantioselectivity (34%) in favour of the 1*S* enantiomer was found using Schiff base catalysts derived from D-α-amino acids [6]. Aratani et al. [7] have also described asymmetric synthesis of cyclopropane precursors of permethrin (NRDC 143) by the cycloaddition of ethyl diazoacetate to 1,1-dichloro-4-methyl-1,3-pentadiene (**1**) using α-amino acid derived binuclear copper(II) Schiff base complexes as catalysts. Surprisingly, and in contrast to their results in chrysanthemate synthesis, they obtained a modest enantiomeric differentiation in favour of the 1*S*-cyclopropanes when the catalysts were derived from D-α-amino acids.

Recently, we have described [8] the asymmetric synthesis of cyclopropane intermediates of permethrin and other photostable pyrethroids using novel chiral copper(II) Schiff base complexes which were obtained by condensing amino sugars with either salicylaldehyde or pyridine-2-carboxaldehyde. With **1**, catalysts derived from 2-amino-D-altropyranoside, having the *S* configuration at C(2) of the glycosidic ring, selectivity towards the 1*S* isomers of the cyclopropane were displayed, whereas catalysts prepared from 2-amino-D-glucopyranoside and 2-amino-D-allopyranoside – both having the *R* configuration at C(2) of the glycosidic rings – favoured formation of the 1*R* cyclopropanes.

This paper describes the cyclopropanation of the two halodienes 1,1-dichloro-4-methyl-penta-1,3-diene (**1**) [9] and 2-chloro-5-methyl-1,1,1-trifluoro-hexa-2,4-diene (**2**) [10] and the monoene 2,2-dichloro-4-methyl-1,1,1-trifluoro-hex-4-ene (**3**) [10] to give the cyclopropanes **4**–**6**, respectively, (Scheme 1) using the novel Schiff base



SCHEME 1. The preparation of cyclopropane carboxylates.



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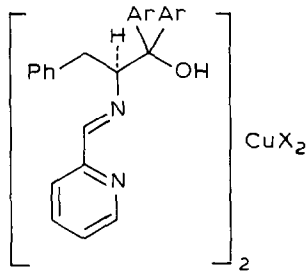
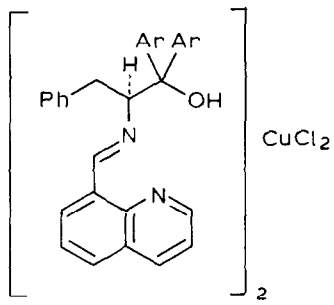


(8, X = Cl,
9, X = BF_4)



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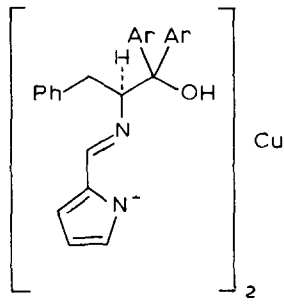

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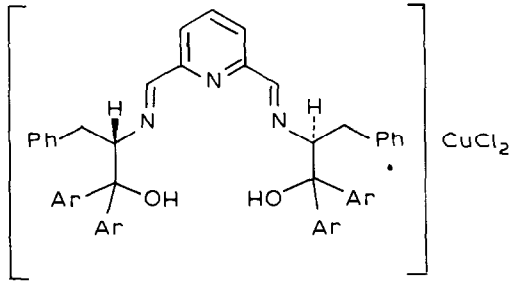

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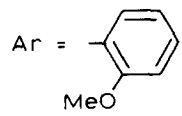

catalysts **7–12** in which chirality was derived from L-phenylalanine. The cyclopropane **6** is a precursor of the vinyl cyclopropane **5**.

Experimental

The preparation of the Schiff bases obtained by condenstion of (*S*)-2-amino-1,1-bis(2-methoxyphenyl)-3-phenylpropan-1-ol [4] with the corresponding aromatic aldehyde and their subsequent conversion into the copper(II) complexes **7–12** is described elsewhere [11]. The ability of each of the complexes to act as catalysts in the asymmetric cyclopropanation of the olefins **1–3** was tested and the cyclopropane products, after transesterification with *d*-octan-2-ol to generate four diastereoisomers

TABLE 1
REACTIONS OF THE OLEFINS **1**–**3** WITH ETHYL DIAZOACETATE (EDA) USING VARIOUS COPPER(II) SCHIFF BASE COMPLEXES AS CATALYSTS

Exp. No.	Olefin	Olefin conc. (mmol)	Catalyst	Catalyst conc. (mmol)	EDA conc. (mmol)	Solvent [a]	Temp. (°C)	Yield of cyclopropane [b] (%)	Isomer distribution (%)				
									cis/*trans*	*cis*-1*R*,3*S*	*cis*-1*S*,3*R*	*trans*-1*R*,3*R*	*trans*-1*S*,3*S*
1	**1**	14.6	Cu	4.7	4.0	DCE	96	45	43/57	21.5	21.5	28.5	28.5
2	**1**	120	**7**	0.4	15.0	PhMe	50	33	40/60	17	23	23.5	36.5
3	**1**	40	**8**	0.1	8.0	DCE	75	3	41/59	17	24	32	29
4	**1**	40	**10**	0.1	8.0	DCE	75	15	42/58	15	27	32	26
5	**1**	40	**11**	0.1	8.0	PhMe/DCE	70	16	43/57	21	22	33	24
6	**2** [c]	22	Cu	2.4	3.5	PhMe	90	17	51/49	25.5	25.5	24.5	24.5
7	**2** [c]	22	**7**	0.1	3.5	PhMe/DCE	70	9	51/49	25.5	25.5	24.5	24.5
8	**2** [c]	22	**12**	0.1	3.5	PhMe	80	4	51/49	25.5	25.5	24.5	24.5
9	**3**	18.1	Cu	0.6	3.5	PhMe	75	27	55/45	27.5	27.5	22.5	22.5
10	**3**	11.3	**7**	0.05	2.0	PhMe/DCE	75	12	62/38	39	23	24	14
11	**3**	12.5	**7**	1.3	250 [d]	DCE	110	12	59/41	34	25	23	28
12	**3**	22.6	**8**	0.1	7.5	PhMe/DCE	70	17	69/31	43	26	13	29
13	**3**	22.6	**8** [e]	0.1	7.5	PhMe/DCE	70	3	57/43	37	20	15.5	27.5
14	**3**	22.5	**9**	0.1	7.5	PhMe/DCE	70	12.5	63/37	40	23	12	25
15	**3**	18.1	**10**	0.05	3.5	PhMe/DCE	70	–	58/42	35	23	18	24
16	**3**	25	**11**	0.05	5.0	PhMe/DCE	70	14	54/46	29	25	20	26
17	**3**	11.3	**12**	0.04	2.0	PhMe	80	–	60/40	38	22	20	20
18	**3**	22.6	**12** [e]	0.1	3.9	PhMe/DCE	70	5	57/43	33	24	20	23

[a] DCE = 1,2-Dichloroethane. [b] Yield = 100(mol cyclopropane carboxylate formed)/(mol EDA decomposed). [c] Estimated to be a mixture of approximately 16/1 *Z*/*E* isomers by ^{1}H NMR. [d] EDA generated by diazotization of ethyl glycinate with nitrite, followed by phase transfer to the reaction medium. [e] Catalyst generated in situ by addition of Schiff base and copper(II) chloride dihydrate to the reaction.

were analysed by GLC [8]. The experimental procedure was essentially the same for each complex and a description of the experiment involving the cyclopropanation of the mixed halo-monoene **3** with the pyridyl chloride complex **8** as the catalyst serves to illustrate the method. Table 1 gives details of conditions used in the other experiments.

General procedure

A 100 ml three-necked flask was placed in a thermostatted oil bath at 70 °C and charged with the monoene **3** (2.5 g, 11.3 mmol), the catalyst **8** (0.104 g, 0.1 mmol) and a solvent mixture comprising toluene (3 ml) and 1,2-dichloroethane (10 ml) to give a homogeneous solution. The flask was purged with nitrogen and connected to a simple gas burette. The reaction mixture was stirred at 70 °C and a solution comprising the monoene **3** (2.5 g, 11.3 mmol), ethyl diazoacetate (0.885 g, 7.5 mmol), toluene (8 ml) and 1,2-dichloroethane (5 ml) was added dropwise at a constant rate (1.2 ml h^{-1}) via a peristaltic pump. After an initiation period of approximately 2 h the evolution of nitrogen was observed and the solution had turned from pale green to a red brown colour. After a total of 20 h the volume of nitrogen collected was approximately 170 ml (ca. 100% of theoretical for total decomposition of ethyl diazoacetate). The solution was analysed by GLC (3% silicone OV17 on Chromosorb WHP, 2.7 m column) for yield of cyclopropane (17%) and *cis/trans* isomer ratio (69/31). A further analysis was then carried out which permitted estimation of the relative yields of all four stereoisomers produced during the reaction. An aliquot (1 ml) of the crude reaction mixture was heated under reflux with an excess of *d*-octan-2-ol and tetra-n-butyl titanate under an atmosphere of nitrogen for 2 h. GLC analysis (5% LAC2R 446 on Chromosorb W, 3 m column) showed four peaks corresponding to the two *cis* and two *trans* diastereoisomeric *d*-octyl esters. The isomer composition was found to be *cis*-1*R*,3*S*,43%; *cis*-1*S*, 3*R*, 26%; *trans*-1*R*,3*R*, 13%; *trans*-1*S*,3*S*, 19%. The transesterification reaction was unaffected by the presence of the chiral copper catalyst and the reliability of the analytical method was confirmed by experiments with mixtures of known compostion. Assignment of the diastereoisomer peaks was made by comparison with samples with known absolute configurations.

Results and discussion

Table 1 summarises the results. For comparison, the results when copper bronze was used as a heterogeneous catalyst are included. With the other catalysts, homogeneous solutions were effected by suitable choice of solvent as indicated.

Yields of cyclopropanes were low, and although no attempts were made to optimise them, this may be due to the relatively low nucleophilicity of the olefins. Induction periods preceding the evolution of nitrogen and colour changes to red brown solutions were usually noted, and the catalysts could not be recovered after reaction. These observations indicate that the initial copper(II) complexes were not the active catalysts. Possibly the copper(II) species were reduced to copper(I) species as suggested by Salomon and Kochi [12] and these were the active catalysts.

The *cis/trans* ratios for **4** (exp. no. 1–5) fell between 40/60 and 43/57 in fair agreement with the observations of others [7]. All the chiral catalysts tested showed a selectivity towards the 1*R*,3*S* enantiomer of the *cis* pair of isomers and, with the

exception of the catalyst **7**, a selectivity towards the 1*S*,3*S* enantiomer of the *trans* pair. The cyclopropanation of the mixed halodiene **2** (exp. no. 6–8) occurred in low yield and without stereoselectivity. With the mixed halomonoene **3** (exp no. 9–18) the *cis/trans* ratios of the product cyclopropane (**6**) fell between 54/46 and 63/37 except with the pyridyl catalyst **8** which gave more of the *cis* isomers. All the catalysts examined favoured the 1*R*,3*S* enantiomer in the *cis* pair of isomers and, with the exception of catalyst **7**, the 1*S*,3*S* enantiomer was the preferred *trans* isomer. The exceptional behaviour of catalyst **7** was also noted in its influence upon the enantioselectivity of the *trans* isomers of the cyclopropane **4** and shows that the aldehyde component of the Schiff base plays a role in determining induction. Catalyst **7** was used both on a large (exp. no. 11) and a small scale (exp. no. 10). The large scale experiment involved two liquid phases in contact; the ethyl diazoacetate was generated in an aqueous medium and reacted with the olefin in 1,2-dichloroethane. This reaction was performed at a higher temperature and with faster addition of the reactants than the small scale reaction, and while the yield of the cyclopropane was not altered, lower optical induction resulted. Exp. no. 12 and 14 demonstrated little or no anion effect (Cl^- vs. BF_4^-) on enantioselectivity for the *cis*-1*R*,3*S*-cyclopropane but a noticeable difference in the enantioselectivity for the *trans*-1*S*,3*S* isomer, the less well coordinating BF_4^- anion gave rise to the greater selectivity. In general it was found that in the whole series of reactions the degree of enantioselectivity achieved follows the expected nucleophilicity of the olefins i.e. optical induction for **3** > **1** ≫ **2**.

Reaction mechanism

The mechanism of metal-catalysed reactions of a diazoacetate with olefins is not fully understood but it is thought [1] to proceed via an intermediate metal-carbene complex. Framework molecular models indicate that coordination of a carboethoxy carbene to a transition metal centre bearing an optically active ligand and transfer of the carbene to an olefin can be influenced by the metal's chiral environment. Investigations [4,14,15] of asymmetric cyclopropanation have generally shown that optical induction occurs at C(1) of the cyclopropane. Such selectivities have been interpretted by Nakamura [15,16] for cyclopropanation of olefins by diazoacetate using cobalt(II) catalysts, in terms of a metal-carbene intermediate in which there is a low barrier to rotation about the metal–carbene bond, thus giving rise to two stereoisomers. This model has also been applied to certain copper(II) catalysts where secondary interactions between the carboethoxy group on the carbene and a functional group on the chiral ligand coordinated to the metal may have been involved in orienting the carbene [8]. π-Approach of an olefin substrate such that the metal atom, the carbene atom and the two carbon atoms in the double bond are coplanar results in the formation of cyclopropane rings in which the stereochemistry at C(1) of the cyclopropane is dictated by its original orientation in the metal-carbene complex and on which side of the carbene the olefin attacks. The *cis/trans* ratio of the product as well as the stereochemistries at both C(2) and C(3) are dictated by the orientation of the approaching olefin. A simplified view of the model is presented in Fig. 1. On testing catalyst **7** with olefin **1** (exp. no. 2) *cis* and *trans* cyclopropanes which were enriched in the 1*S* enantiomers were formed. In contrast, the same catalyst gave an excess of isomers having the 1*R* configuration when the substrate was **3** (exp. no. 10 and 11). Both observations can be accommodated by the model.

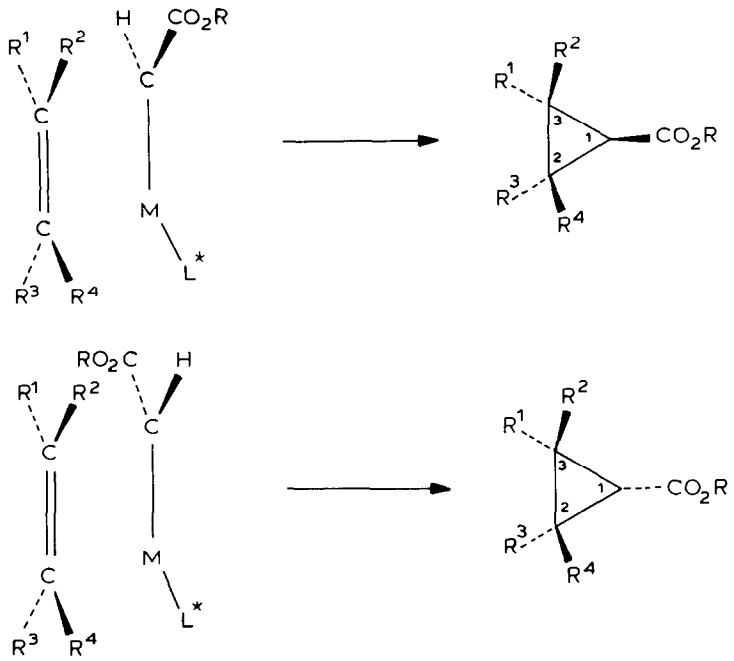

Fig. 1. Envisaged π-approach of a substituted olefin to a metal-carboalkoxycarbene complex leading to stereoisomeric cyclopropanes (L* represents a chiral ligand coordinated to the metal).

Clearly, the nature of the olefinic substrate, in addition to the chiral environment about the metal, has an influence upon the optical induction at C(1) in the cyclopropane products. In terms of the model, the two olefins preferred to attack from different sides of the carbenoid, but space filling molecular models do not allow reliable prediction of which side of the carbenoid would be attacked most easily by any given olefin.

The results of reactions of **1** and **3** in the presence of the novel catalysts **8–14** (exp. no. 3–5 and 12–18, respectively) were most unexpected and they are not consistent with Nakamura's mechanism. Optical induction occurred at C(3) rather than C(1) of the cyclopropanes. Again the direction of the optical induction depended upon the olefin; with **1** the 3*R* isomers were formed selectively whilst with **3** the preference was for the 3*S* isomers. One interpretation of these results is that the orientation of the approaching olefin was controlled by the ligand on the carbenoid intermediate but that rotation about the metal–carbene bond was possible. This situation is shown in Fig. 2. The difference in the sense of optical induction at C(3) of the cyclopropanes derived from **1** and **3** could result if **3** approached the carbenoid as shown in Fig. 2(a) but that either (i) **1** attacked the other side of the carbenoid (Fig. 2(b)) or (ii) the carbenoid was approached by the opposite face of **1** (Fig. 2(c)).

Callot and Piechocki [17] have recently obtained high *cis* selectivity in cyclopropanation reactions of substituted olefins by ethyl diazoacetate using rhodium(III) porphyrins as catalysts. They proposed a model in which the metal–carbene bond and the olefin's double bond are perpendicularly oriented to

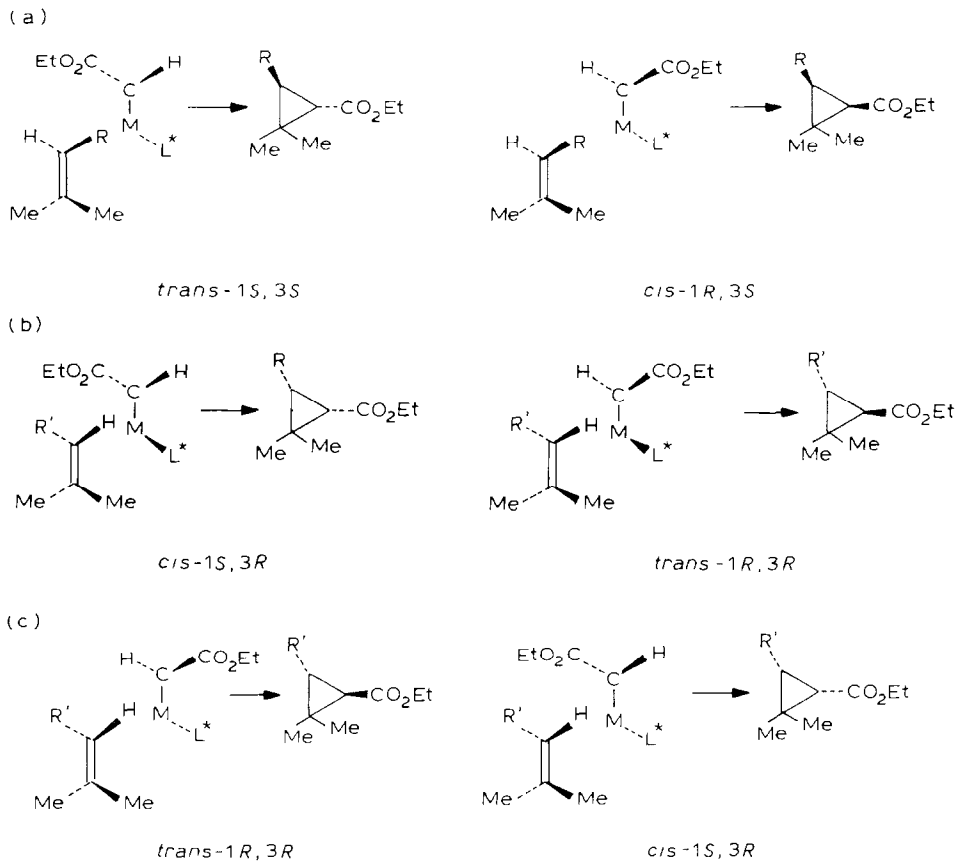

Fig. 2. Envisaged π-approach of (a) monoene **3** (R = 2,2-dichloro-3,3,3-trifluoropropyl) and (b) and (c) diene **1** (R′ = $\beta\beta$-dichlorovinyl) to metal-carbene complexes leading to diastereoisomeric cyclopropanes.

each other – rather than parallel as assumed in the mechanisms above. Such intermediates, in which the substituent groups on the olefin are directed away from the metal's planar ligands, are thought to account for the high *cis* selectivity. This model provides an alternative rationalisation of the control of geometry at C(3), rather than at C(1) of the incipient cyclopropane carboxylate. Imagine that the chiral ligand restricts rotation about the metal–carbene bond, permits approach of the olefin from only one side of the carbene, and influences the orientation of the olefin but does not determine whether the olefin approaches in a parallel or side-on manner. Parallel or π-approach, would lead to one cyclopropane isomer preferentially (e.g. *trans*-1*S*,3*S* Fig. 3(a)). If some olefin molecules approach side-on (Fig. 3(b)), then the cyclopropane would be formed with the same configuration at C(3) but the opposite configurations at C(1). Thus rotation of the olefin through 90° about its direction of approach could result in an inversion of stereochemistry at C(1) whilst retaining that at C(3).

Finally, the observed preference for the *trans*-1*S*,3*S* and *cis*-1*R*,3*S* isomers of **6** could be useful in preparing the insecticidally most desirable *cis*-1*R* form. Separation of *cis* and *trans* isomers is possible and the *trans*-1*S*,3*S* form can be epimerised into its *cis*-1*R*,3*S* isomer [18].

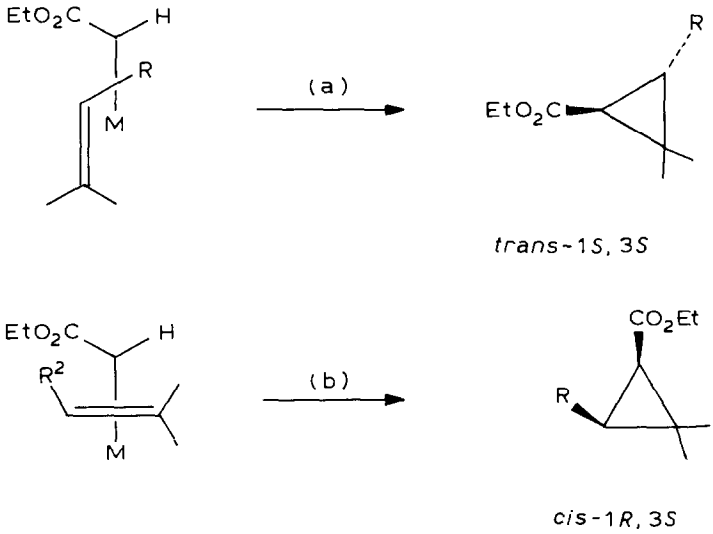

Fig. 3. Consequences of (a) parallel π-approach of the olefin and (b) side-on π-approach of the olefin to a metal-carbene complex.

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