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Bidentate carbenoid ester coordination in ruthenium(II) Schiff-base complexes leading to excellent levels of diastereo- and enantioselectivity in catalytic alkene cyclopropanation†

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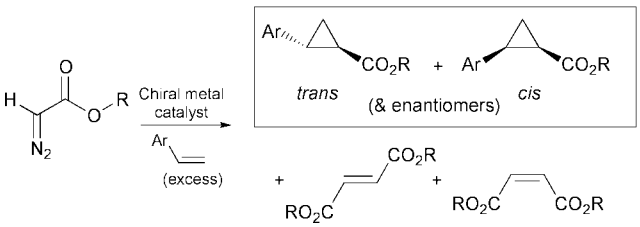
Exceptionally high stereoselectivity (ee ⩽ 98%, dr ⩽ 99 : 1) in the cyclopropanation of alkenes with ethyl diazoacetate using a non-planar ruthenium(II) Schiff-base precatalyst is a result of η^2*C,O* binding of the carbenoid ester intermediate, according to DFT calculations.

The design of selective methods for the catalytic enantioselective synthesis of cyclopropanes remains of great interest to organic chemists, not least because of the importance of the compounds in biological and medicinal chemistry.[1] The asymmetric addition of carbenes to electron rich alkenes[2] (alkene cyclopropanation) represents a conceptually simple approach,[3] but typical reactions, such as that of styrenes with α–diazoacetates in the presence of a chiral metal catalyst, give a total of six organic products (Scheme 1).

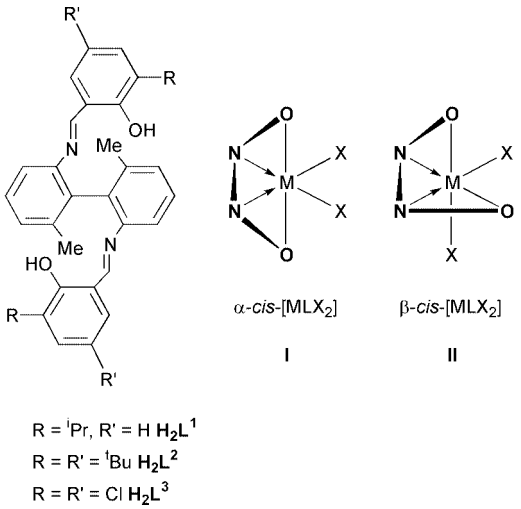
Chemoselectivity for cyclopropanes over carbene dimerisation products (diethyl malonate and fumarate) is achieved through use of an excess of alkene and slow addition of the carbene source *e.g.* ethyl diazoacetate (EDA) to the reaction mixture.[4,5] For *trans*-selective catalysts, excellent enantiomeric excesses have been obtained,[6] but most exhibit only moderate *trans*/*cis*- *i.e.* diastereoselectivity. For example, Evans' bis(oxazoline) copper system gave 99% ee in the *trans* product which was formed with a dr of 73 : 27.[6] This and other results are consistent with Pfaltz's analysis that the *cis/trans* selectivity for a given metal depends almost exclusively on the structure of the alkene and diazo compound; the effect of the ligand is relatively unimportant.[7] Correspondingly, the use of bulkier diazo ester substituents such as *tert*-butyl and 2,6-di-*tert*-butyl-4-methylphenol leads to much higher diastereoselectivities.[6,8,9] An exception here is found in Che's D_4-symmetric Ru porphyrin system (dr 97 : 3, ee 98% at −40 °C) where the four sterically-demanding chiral substituents strongly orient alkene approach.[10] Highly *cis* selective catalysts based on Co and Ru using *tert*-butyl diazoacetate have recently been reported (*e.g.* dr 7 : 93 and ee 99%).[11]

We have been interested in the use of biaryldiimine complexes in enantioselective catalysis,[12] and have discovered



Scheme 1 Products typically formed in metal catalysed cyclopropanation *via* intermolecular carbene transfer to alkene.

† Electronic supplementary information (ESI) available: experimental and theoretical details, structures of [RuL^1(CH$_3$CN)$_2$] and [RuL^1(η^2-CHCO$_2$Et)] (.pdb). CCDC 167600. See http://www.rsc.org/suppdata/cc/b1/b104964j/



R = ^{i}Pr, R' = H **H_2L^1**
R = R' = ^{t}Bu **H_2L^2**
R = R' = Cl **H_2L^3**

that unlike salen-derived ligands, the system L in its early transition metal complexes gives the α-*cis* topology **I** or occasionally the β-*cis* structure **II**;[13] both arrangements dictate that the co-ligands X are placed in mutually *cis* coordination sites. This has important consequences for alkene cyclopropanation by the complexes M = Ru as described herein.

The reaction of Na_2L^n with [{RuCl(μ-Cl)(η-C$_6$H$_6$)}$_2$] in acetonitrile gave the Ru^{II} complexes of ligands L^n in high yield.

The molecular structure of one example β-*cis*-[RuL^1(CH$_3$CN)$_2$] is shown in Fig. 1.† This, and analogous complexes of L^2 and L^3 retain the β-*cis* structure **II** in solution as evidenced by NMR spectroscopy.

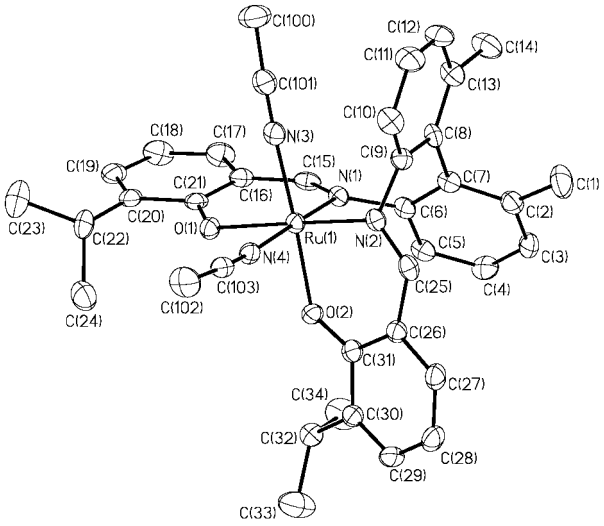


Fig. 1 Molecular structure of the precatalyst β-*cis*-[RuL^1(CH$_3$CN)$_2$].

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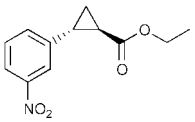
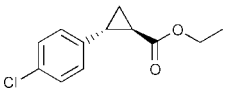
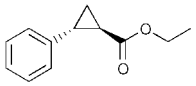
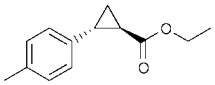
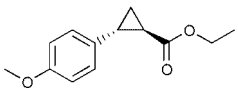
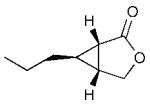
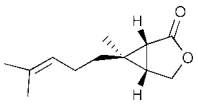
Table 1 Enantioselective cyclopropanation catalysed by (*R*)-β-*cis*-[RuL^1(CH$_3$CN)$_2$][a]

Entry	Product	Yield/(%)[b]	dr/(%)	ee/(%)[c]
1		92	99:1	98
2		88	99:1	97
3		94	98:2	95
4		90	96:4	86
5		89	96:4	86
6		80	—	91
7		98	—	85

[a] Entries 1–5; 5 mol% of (*R*)-β-*cis*-[RuL^n(CH$_3$CN)$_2$] in toluene, 4/5 equiv. of styrene, 2 h at rt. [b] Isolated yield after flash chromatography (yield based on EDA for entries 1–5). [c] Absolute configuration of *trans* isomer (1*R*,2*R*) by comparison of optical rotations with literature values (ref. 15) for entries 1–5.

The results of addition of EDA over 2 h to solutions of styrenes at rt in the presence of pure precatalyst (*R*)-β-*cis*-[RuL^1(CH$_3$CN)$_2$] are summarised in Table 1 (entries 1–5).‡ The chemoselectivity (yield), *trans*:*cis* ratios (dr) and ee are arguably the best yet attained.[10,11] The ligand L^1 appears to be close to optimal for the cyclopropanation of styrenes; preliminary experiments with the bulky system L^2 and the electron withdrawing L^3 gave significantly lower selectivities. Mechanistic details for the catalytic reaction are currently under investigation.§

The selectivity determining step in alkene cyclopropanation involves the transfer of a metal bound carbene to the substrate,[14] and we set out to investigate this crucial step for the current system using Density Functional Theory (DFT) calculations. A fully optimised DFT structure of the precatalyst β-*cis*-[RuL^1(CH$_3$CN)$_2$] was found to be virtually superimposable on the molecular structure shown in Fig. 1. Minimisation of a structure arising from the removal of the CH$_3$CN groups and addition of the carbene derived from EDA (*i.e.* :CH-CO$_2$Et) led spontaneously to formation of a chelate, reminiscent of η^2-carboxylate, with both carbene C atom and carbonyl oxygen atom bound to Ru (Fig. 2). This structure with the carbene C atom *trans* to phenolate is *ca.* 30 kJ mol^{-1} more stable than that with the carbene *trans* to imine; an observation in accord with the expected order of *trans* influence of the two groups (N > O).

Hence the electronically controlled placement of the carbene *trans* to phenolate and the subsequent ester binding determines which diastereomeric face of the carbenoid is presented to the incoming alkene. The sense of asymmetric induction is as predicted by this model.¶ Also as a result of tight binding of the carbenoid ester, the orientation of approach of the alkene toward the reaction centre is exceptionally well directed by the chiral biaryldiimine ligand (Fig. 2); this leads to the high diastereoselectivity observed.

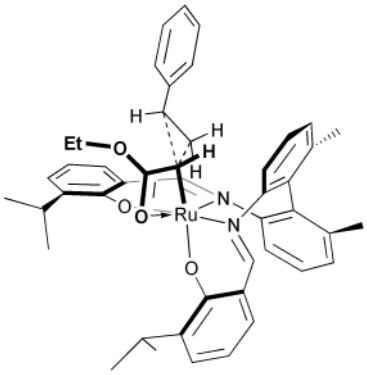


Fig. 2 Calculated structure of the carbene catalyst [RuL^1(η^2-CHCO$_2$Et)] showing the preferred orientation of approach of styrene.

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Notes and references

‡ This complex also efficiently catalyses the intramolecular cyclopropanation/cylisation of a range of allylic diazoacetates. For example, *trans*-hex-2-enyl and geranyl diazoacetates were converted to the corresponding oxabicyclohexanones (entries 6 and 7) in a similar manner to Doyle *et al.*,[3] with the exception that *slow addition of substrate was not required* and the reaction proceeded at rt in under 2 h.

§ Attenuated selectivity in polar solvents, particularly for more electron rich alkenes, suggests significant polarity in the transition state. This will be investigated by Hammett methods. Preliminary kinetic experiments have indicated that the reaction is first order in catalyst.

¶ The (*S*)-catalyst shown in Fig. 2 gives rise to 1*S*-2*S* cyclopropanes, hence (*S*)-β-*cis*-[RuL^1(CH$_3$CN)$_2$] used in the experimental study is predicted to yield 1*R*-2*R* isomers (Table 1).

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