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The carbonyl ene reaction

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Contents

1. Introduction

This review aims to provide synthetic chemists with an analysis of the research carried out on carbonyl ene reactions. It does not attempt to be comprehensive and, in particular, early research that has previously been reviewed[1–6] is only discussed briefly or described where it serves to exemplify a class of ene reaction. An ene reaction can be broadly classified as the reaction of an alkene bearing an allylic hydrogen (the ene) with a double or triple bond, known as the enophile. These reactions are accompanied by migration of the double bond and a 1,5-hydrogen shift. The reaction can be represented generically as shown in Scheme 1. It can be seen that potentially the ene reaction can be used to build up a wide range of functionalised products, although there are some limitations that are also discussed here. A particularly appealing feature of the ene reaction is that it is potentially 100% atom efficient: all of the atoms in the starting material end up in the product. C–C bond-forming reactions between carbonyl compounds and nucleophilic reagents most frequently employ a metal-based nucleophile and require removal of metal waste. Atom-efficient C–C bond-forming reactions are now rising in importance due to the demand for developing reactions that do not generate waste. This review does not

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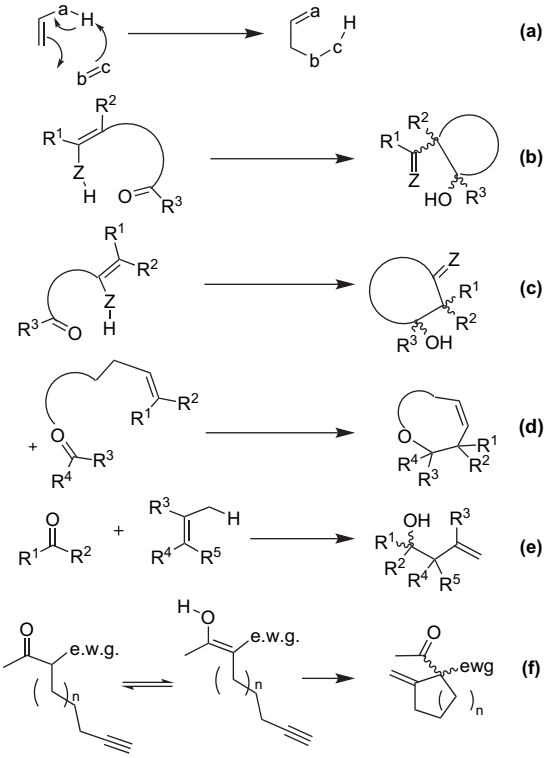
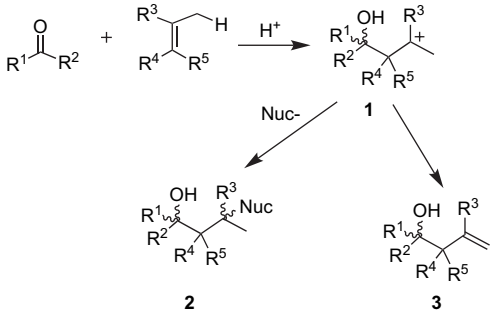
seek to analyse these reactions from a green chemistry perspective (indeed, many of the earlier studies utilise stoichiometric aluminium salts to promote the reaction), but does aim to provide a guide for synthetic chemists that allows an assessment of the viability of various types of ene reactions for synthesis and describes some of the best catalyst systems for promoting the reactions.



Scheme 1. (a) General scheme representing ene reactions; (b) intramolecular type I ene cyclisation; (c) intramolecular type II ene cyclisation; (d) intramolecular type III ene cyclisation; (e) intermolecular carbonyl ene reaction; (f) Conia ene reaction of activated carbonyl compounds.

The ene component is an alkene (or enol), which can react with a quite broad range of enophiles. These include alkenes, alkynes, allenes, carbonyls, imines and main-group double bonds. This review is exclusively focussed on reactions that make use of a carbonyl compound either as the enophile or as the ene in its enol tautomer. We have excluded ene components derived from enamines (Z=N) and metallo-ene reactions where a metal undergoes the 1,5-shift in place of hydrogen, since these are mechanistically distinct reactions. Readers are directed to several excellent reviews and monographs that describe ene reactions of other classes of substrate.[6–9] From a mechanistic perspective, ene reactions often proceed in a concerted manner through a cyclic transition state but can also proceed through stepwise mechanisms involving carbocation intermediates. Acid- or Lewis acid-catalysed carbonyl ene reactions between alkenes and aldehydes or ketones that proceed via a carbocation intermediate (e.g., **1**) are considered to be a subset of the Prins reaction (Scheme 2).[5] In the Prins reaction, the carbocation intermediate is either quenched by another nucleophile to give **2** or loses the allylic proton to form an ene-type product, **3**. This review only seeks to describe research on Prins reactions that give ene-type products.

For many ene reactions, the exact mechanism is either not defined or has been shown to proceed by both concerted and ionic pathways, depending on the reaction conditions. If Lewis acid catalysts are employed, there can be a continuum between these two mechanisms, with an earlier transition state representing



Scheme 2. Prins reaction between alkene and carbonyl under acid catalysis.

increased carbocation character during the C–C bond-forming reaction. In organising this review, we have elected to not make any distinction between these mechanistic pathways and have described any reaction that provides products that could arise by a concerted reaction between the two components. The ene component can be considered to act either as a nucleophile or as a 4-electron-coupling partner in the concerted process, akin to the diene component in a Diels–Alder reaction. Consequently, electron-rich alkenes are more reactive than electron-deficient ones by several orders of magnitude. In general, 1,1-disubstituted alkenes are the preferred ene components, followed by trisubstituted alkenes, both of which are significantly more reactive than tetrasubstituted, monosubstituted and 1,2-disubstituted alkenes. The enophile component is preferably electron deficient. In the higher-energy intermolecular reactions, it is frequently only the most reactive 1,1-alkenes combined with electron-deficient aldehydes that undergo reactions under relatively mild conditions. Intramolecular reactions have greater scope and can represent a particularly simple and efficient cyclisation reaction.

1.1. Catalysts and promoters for the ene reaction

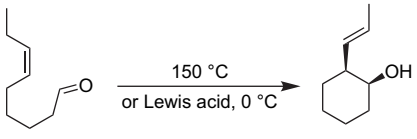
Ene reactions can proceed without any catalysts or promoters, but due to the relatively high activation barrier require moderate to very high temperatures to proceed. Ene reactions that proceed via the Prins reaction mechanism classically use Brønsted acids to promote the C–C bond-forming step, with the acid regenerated in the elimination step. A major development from about 40 years ago has been the use of Lewis acid promoters or catalysts to enable the ene reactions to proceed at room temperature or below. The most commonly employed promoters have been aluminium salts. Lewis acids such as $AlMe_2Cl$ promote the ene reactions at low temperatures (often preferably $-78\,^{\circ}C$). These are promoters rather than catalysts, since in many reactions the methyl ligands are subjected to alcoholysis by the ene product. Indeed, it has been proposed that this is a useful feature in preventing side reactions such as elimination, since the initial product is an aluminium alkoxide that is then cleaved during work up. However, there are other Lewis acids that act as classical catalysts, accelerating the rate of reaction without being consumed, and consequently these are used in substoichiometric amounts. The simplest of these are compounds such as $SnCl_4$, $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$ and $Yb(OTf)_3$. In general, detailed studies of optimising reaction conditions with regard to low catalyst loadings have not been carried out for the more complex substrates, since the reactions have predominantly been employed in small-scale reactions utilised in natural product synthesis. However, more detailed research on optimising catalysts has been carried out on the more commercially important citronellal cyclisation and, in particular, the glyoxylate ene reaction. It is likely that more practical conditions could be found for some of the other cyclisations if further studies are made.

The catalytic asymmetric carbonyl ene reaction has been practised since 1980s, with the first genuine catalyst being derived from titanium(IV) complexes and enantiomerically pure diols such as binaphthol (see Scheme 9 for the first example discussed here). The exact structure of such catalysts was difficult to pin down for many years and depends on the ligands used, but in many cases it is likely to be dimeric in nature. The titanium catalysts have in general been used at high catalyst loadings, but there is now one example where incremental modification of the diol ligands led to a reaction operating with just 0.01% catalyst (see Table 3). Late transition-metal catalysts derived from chiral ligands have also been employed with success in the glyoxylate ene reactions, with the copper(II) complexes of chiral nitrogen ligands worthy of special mention. These have extended the scope to some less-reactive enophiles and allowed less nucleophilic alkenes to be employed, suggesting that for many ene reactions a determined effort on catalyst development should lead to improved reactivity and stereocontrol. The more recent generation of catalysts has not been studied to any great extent in cyclisation reactions. Hopefully, further studies will also see ene cyclisations being promoted with diastereo- and enantioselectivity under convenient and practical conditions, and these are awaited with interest.

The examples discussed throughout this review have been chosen to show the reaction scope, since this is one of the major issues with the ene reaction, but where possible they also serve to indicate the types of catalysts that have been studied thus far. Intramolecular reactions are discussed first, since these reactions were more extensively used from an early stage, due to their lower activation barrier and their synthetic potential. The latter part of the review describes some of the new ene catalysts that have emerged recently, primarily for use in the glyoxylate ene reaction.

2. Intramolecular carbonyl ene reactions

The intramolecular carbonyl ene reaction is more entropically favoured than the intermolecular reaction, and hence the carbonyl functionality does not need to be so highly activated, and the reaction will proceed under milder conditions. For example, the completely unactivated unsaturated aldehyde **4** will react thermally at 150 °C or at 0 °C in the presence of a Lewis acid to give the *syn* isomer **5** in 75% yield (Scheme 3).[10] The corresponding intermolecular reaction between an alkyl aldehyde and an internal alkene does not proceed.

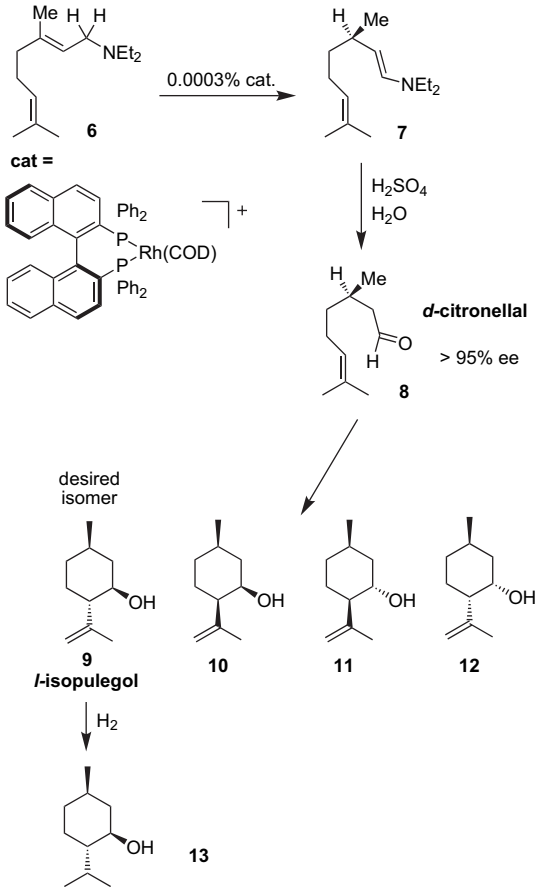


Scheme 3.

Intramolecular carbonyl ene reactions are often further classified into three main variants, depending on the connectivity of the enophile (carbonyl) group to the ene.[1] The reaction shown above is often described as a type I ene cyclisation. The type I carbonyl ene reaction involves the C–C bond being formed at the internal carbon of the C=C bond in the starting material. This can be represented in general form as in Scheme 1b. The type II carbonyl ene reaction involves the C–C bond being formed at the terminal carbon of the C=C bond in the starting material. This is shown generically in Scheme 1c. Type III cyclisations (Scheme 1d) are not normally observed in carbonyl ene reactions, since these require an oxonium ion to represent the enophile, yet some intriguing examples have been reported.

2.1. Type I carbonyl ene cyclisations

The type I ene cyclisation, represented in Scheme 1b, is a very useful method for producing cyclohexanols. The most extensive studies in this area have been in the industrially important type I cyclisation of citronellal derivatives, **8** to isopulegol isomer **9**, the penultimate intermediate en route to menthol, **13**. Citronellal can be synthesised in enantiomerically pure form using the Rh/BINAP-catalysed enamine isomerisation (**6**→**7**) developed by Takesago Perfumery Co. A very wide range of catalysts have been investigated towards cyclising this precursor with high chemical yield and diastereoselectivity (Scheme 4). As far as one can tell, the initial industrial process used stoichiometric amounts of $ZnBr_2$ as catalyst for the ene cyclisation. This catalyst gives higher selectivity for the desired *anti* isomer than $ZnCl_2$, $FeCl_3$, $TiCl_4$ and $SnCl_4$.[11] The *anti* isomer (**9** or **11**) is normally favoured in all these types of ene cyclisation, but some Lewis acids such as $[Mo(CO)_4ClBr_2]NEt_3(Bn)$ reverse this stereoselectivity towards the *syn* products (**10** or **12**) with ratios up to 4/1.[12]

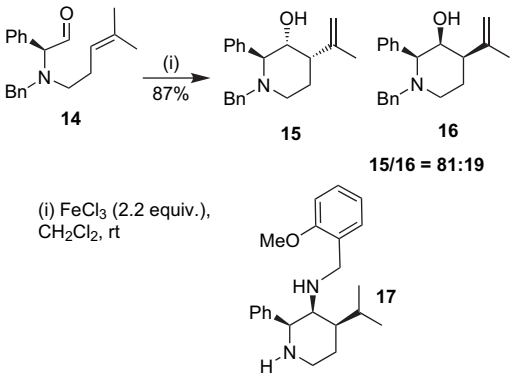


Scheme 4. Synthesis of isopulegol in industrial menthol synthesis.

Scandium triflate has been found to be highly selective towards the desired isopulegol at 5 mol % catalyst loadings, but requires low temperatures to achieve good chemo- and diastereoselectivity.[13] Bismuth triflate has been found to be a highly active catalyst for this reaction with 0.1 mol % catalyst, allowing complete consumption of the starting materials within 5 min. However, the low isolated yields reported suggest the problems with chemoselectivity of this reaction that are combined with modest diastereoselectivity (~4/1).[14] A recent patent from Takesago Perfumery Co. reports very bulky tris(2,6-diarylphenoxy)aluminium catalysts that give high yields of the desired isomer in an ~200/1 ratio at −15 °C.[15] This seems to be the most selective catalyst thus far.

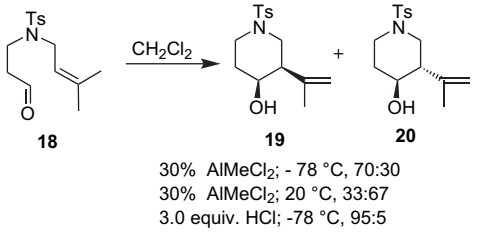
Several recent papers have dealt with the use of heterogeneous catalysts that are able to catalyse both the diastereoselective ene cyclisation and the subsequent hydrogenation of the C=C double bond to give menthol directly. For example, Ir-impregnated ^{1}H-β zeolites can catalyse the formation of citronellal directly to menthol with high conversions and selectivity towards the isomers of menthol (desired isomer in up to 75% yield).[16] More recently, Ni/Zr β catalysts have improved this tandem reaction to give around 90% of the desired menthol isomer.[17]

The type I ene cyclisation of amino-aldehyde **14** in the presence of 2.2 equiv of $FeCl_3$ was found to give exclusively a *syn* relationship (as shown in **15** and **16**), either side of the new C–C bond being formed, but with only ~4/1 diastereoselectivity with respect to the existing chiral centre α to the aldehyde (Scheme 5). Nevertheless, the desired diastereomer was separated in good yield and subsequently converted into a non-peptidic substance P antagonist **17** in enantiomerially pure form.[18]



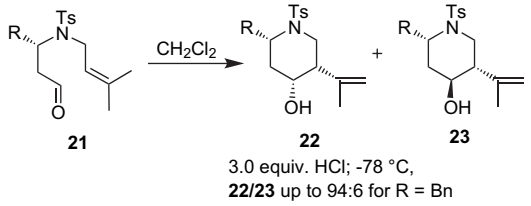
Scheme 5.

Snaith and co-workers have recently explored the use of type I ene cyclisation of **18** to deliver substituted piperidines, **19** and **20** (Scheme 6).[19] Using between 30 and 100 mol % $AlMeCl_2$ as catalyst at −78 °C, reasonable selectivity towards the *syn* isomer **19** was observed.



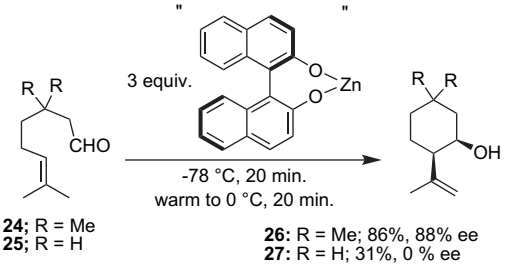
Scheme 6.

Reactions carried out at room temperature or above resulted in the opposite *anti* diastereomer being formed in higher selectivity (up to 8/92 at 61 °C). If concentrated HCl was used at −78 °C, very good *syn* diastereoselectivity was observed (95/5), along with high yields. These observations prompted the authors to propose that the *syn* piperidine was the kinetic product of this type of cyclisation, with equilibration being the cause of the *anti* selectivity at higher temperature. When using a Brønsted acid as promoter, it is likely that these cyclisations have at least some ionic character. Calculations suggest that the *syn* carbocation intermediate and the concerted transition state for the *syn* product are both more stable than the *anti* pathway, thus providing some mechanistic basis for the observed results.[20] However, this mechanistic work was unable to fully account for the more modest *syn* diastereoselectivity observed in an HCl-promoted citronellal cyclisation. Nonetheless, it seems likely that a non-concerted mechanism delivers these cyclisation products and that other cyclisations may also selectively form kinetically favoured products under low temperature Brønsted acid catalysis. A more recent paper by the same group demonstrates that 2,4,5-trisubstituted piperidines **22** and **23** are also available by the same strategy from cyclisation precursor **21** (Scheme 7).[21]



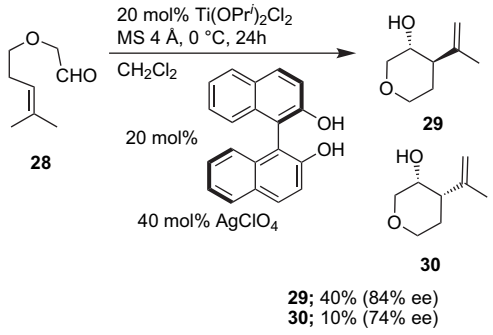
Scheme 7.

There has been relatively little progress on catalytic asymmetric ene cyclisation of prochiral substrates. An initial early report by Yamamoto and co-workers described an enantioselective carbonyl ene cyclisation of **24** and **25** mediated by 3 equiv of Zn–BINOL reagent (Scheme 8). Good yields of the expected *anti* alcohol were observed in the cyclisation of **24** to **26** with up to 88% ee. The less substituted substrate **25**, on the other hand, was less reactive and gave the racemic product **27**.[22]



Scheme 8.

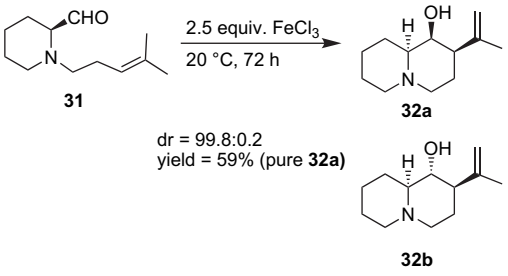
The Mikami group have utilised their excellent Ti(IV)/BINOL catalysts to realise the first catalytic asymmetric ene cyclisations using substrate **28** (Scheme 9). For a more in-depth discussion of the Ti(IV)/BINOL system, see Section 3.3. Catalysts prepared from $Ti(O^{i}Pr)_2Cl_2$, (*R*)-BINOL and $AgClO_4$ gave modest yields of the desired cyclic ethers **29** and **30** with good enantioselectivity and diastereoselectivity.[23] However, further improvements in catalytic asymmetric type I ene cyclisations are required.



Scheme 9.

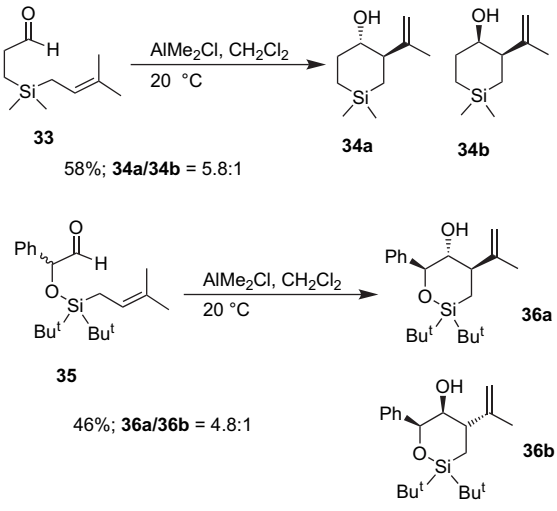
Laschat and Grehl have made use of imino–ene-type cyclisations for the synthesis of α-amino-substituted indolizines and quinolizidines. In these reactions, changing the Lewis acid catalyst

from $TiCl_4$ to $FeCl_3$ gives a reversal of diastereoselectivity from *syn* (Ti) to *anti* (Fe). In the course of these studies, the carbonyl ene reaction of **31** was studied. In this case, excellent diastereoselectivity towards the *syn* product **32a** (over **32b**) was observed regardless of the Lewis acid employed (Scheme 10).[24]



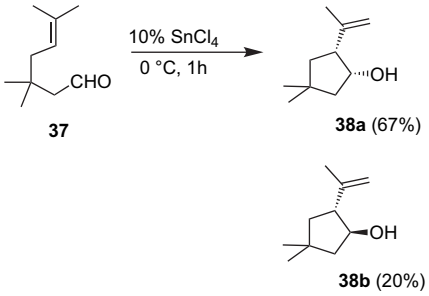
Scheme 10.

A silicon-tethered ene substrate **33** has been found to cyclise in an analogous manner to citronellal, giving predominantly the *anti* isomer **34a** in a 5.8/1 ratio. Unfortunately, when a range of vinyl silane precursors with shorter tethers were subjected to the ene cyclisation conditions, no five-membered ring products could be isolated. This difficulty in five-membered ring formation could be attributed either to problems arising from the presence of the silicon (Si–C cleaved side products were detected) or to the greater difficulty in forming five-membered rings by type I ene cyclisation.[25] An interesting extension to this methodology is to make use of substrates in which the ene component is tethered to the enophile by an Si–O linkage. This strategy should thus provide greater synthetic utility, since the ene products should be readily cleaved to polyols. In practise, substrate **35** was readily available in two steps from phenylethane-1,2-diol and could be cyclised in the presence of $AlMe_2Cl$ to predominantly give the *anti*,*anti* isomer **36a** in moderate yield and selectivity (Scheme 11). Unfortunately, **36a** could not be oxidatively cleaved to give the triol product. Changing the substituents on silicon did allow triols to be prepared using this procedure, but only in low yield.[26]



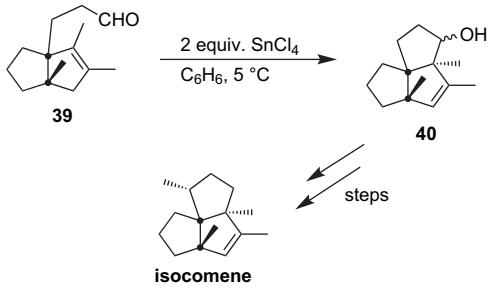
Scheme 11.

The failure of the five-membered cyclisation described above is not unique. Type 1 ene reactions do generally seem to be difficult reactions for cyclopentanol synthesis. The reactions are a higher-energy process than cyclohexanol formations and, for this reason, they have not been heavily utilised. In an early paper by Andersen, ene reactions to produce five- and six-membered rings were compared. The ene cyclisations that produce cyclopentanols were more prone to side reactions and low yields, depending on the reaction conditions employed. However, if the correct conditions were employed, cyclisation does occur. Aldehyde **37** did cyclise after some optimisation. $AlEt_2Cl$ promoters cause addition of the ethyl group to the carbonyl and stoichiometric $AlMe_2Cl$ can only be effective if the temperature is maintained below −60 °C. The optimum conditions for the formation of **38a** require 10 mol % $SnCl_4$ at 0 °C for 1 h and give modest diastereoselectivity of **38a** over **38b** (Scheme 12).[27]



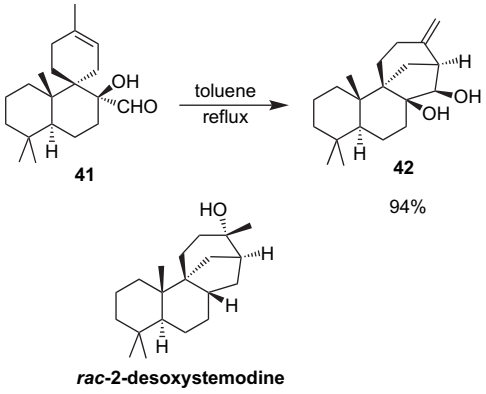
Scheme 12.

Other examples of type I ene cyclisations to five-membered rings that proceed very effectively have taken advantage of the lower entropy loss incurred when the alkene and aldehyde are held in close proximity to each other by a cyclic framework. A nice example is that found in the synthesis of *rac*-isocomene (Scheme 13). Treatment of **39** with excess $SnCl_4$ gave an excellent yield of **40**. The stereochemistry was not confirmed, since it was directly oxidised to the ketone after isolation. However, it is noted that this reaction was completely regioselective for the internal double-bond isomers **40**.[28]



Scheme 13.

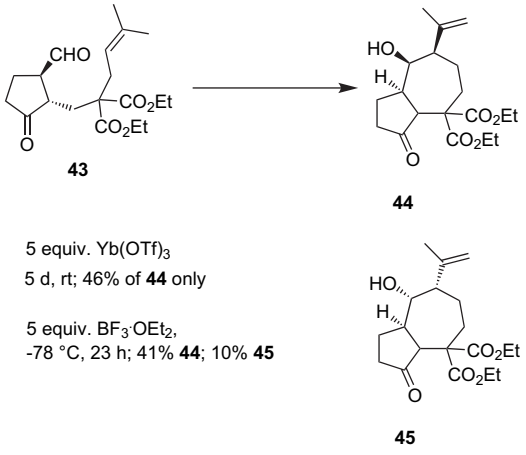
A straightforward thermal ene cyclisation at just 105 °C has been reported to take place on a tricyclic substrate **41** (Scheme 14). This was utilised as the key step in the synthesis of *rac*-2-desoxystemodine. Structural analysis of substrate **41** shows an intramolecular hydrogen bond between the alcohol and the aldehyde. This interaction may well facilitate this cyclisation either by further rigidifying the reactants or by withdrawing electron density from the carbonyl group. In this example, the thermal ene cyclisation of **41** to **42** was far more effective than attempts made using Lewis acid promoters, since these gave a mixture of products. Studies carried out on the deoxy analogue of **41** show that this does not undergo ene reactions, consistent with the proposed pivotal role of the hydroxyl group.[29] In recent years, type I ene reactions have barely been used for cyclopentanol synthesis. However, these earlier studies certainly suggest they are a viable strategy for products that have bicyclic five-membered ring systems.



Scheme 14.

Andersen and co-workers have noted that the rate sequence for type I ene cyclisations is 6>5≫7- membered rings.[27] However, there are examples of type I ene cyclisations of larger ring systems, particularly when the alkene and aldehyde are held by a cyclic framework.

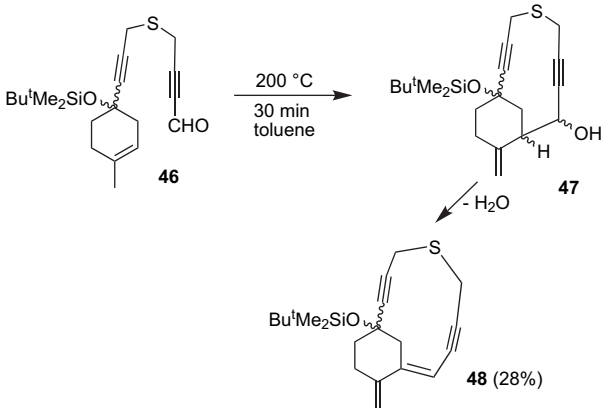
A type I ene cyclisation to deliver a seven-membered ring has been reported as a potential approach towards the guaianolide family of natural products. If $Yb(OTf)_3$ is used as the Lewis acid catalyst, then a moderate yield of the diastereomer **44** with an *anti*-fused ring junction was obtained from precursor **43** (Scheme 15). Boron trifluoride etherate-promoted reactions were less diastereoselective and also produced the other *syn*-epimer, **45**.[30]



Scheme 15.

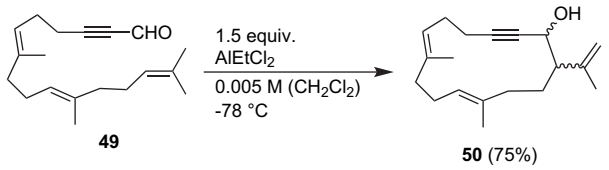
The Mikami group have demonstrated that 11-membered rings can be formed using type I ene reactions (Scheme 16). In the case described below, cyclisation of **46** was studied as an approach to the bicyclic core of dynemicin, calichemicin and esperamicin. Heating this substrate in a sealed tube promoted ene cyclisation and elimination of water to give **48** in fairly low yield, although the only other material present was unreacted **46**. Lewis acid catalysis could not improve this yield or allow the isolation of compound **47**. The stereochemistry of the ene reaction is thus unknown.[31]

Marshall and Andersen reported the synthesis of a 12-membered ring system by $AlEtCl_2$-promoted cyclisation of **49** (Scheme 17). Good yields were observed, but no diastereoselectivity. The use of stoichiometric boron trifluoride etherate did promote the cyclisation with reasonable diastereoselectivity, but in this case the yields were reduced to below 50%. The aluminium-promoted reaction was therefore used to prepare **50** as a mixture of diastereomers. Product **50** was subsequently oxidised and hence the lack of diastereoselectivity in this step was not significant in transforming **50** into the macrocyclic product, *rac*-mukolol.[32] This



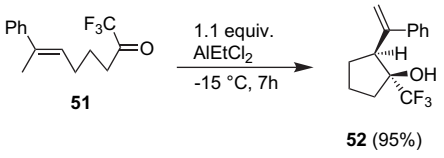
Scheme 16.

paper additionally shows how 14-membered rings can also be formed (without diastereoselectivity) using similar conditions. It is probably significant that both these examples of large-ring syntheses utilise substrates that possess relatively few degrees of freedom, thus placing aldehyde and ene in close proximity to each other.



Scheme 17.

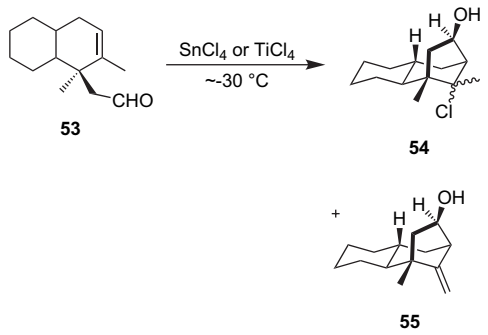
Type I ene cyclisations of ketones have rarely been reported.[33] Ketones are much poorer enophiles in these reactions and need to be highly activated to undergo cyclisation. Introducing electron-withdrawing substituents in close proximity to the carbonyl group can improve the enophilic character of a carbonyl group significantly and, thus, trifluoromethyl ketones will undergo cyclisation reactions (Scheme 18). An example is cyclisation of **51** to give **52** in essentially quantitative yield and complete diastereoselectivity using $AlEtCl_2$ as the Lewis acid.[34,35]



Scheme 18.

2.2. Type II carbonyl ene cyclisations

Type II ene cyclisations are also a useful method for the synthesis of various carbocycles. In these reactions, it is generally thought that seven-membered rings are more readily prepared than six-membered rings. Type II ene cyclisations have rarely been used for cyclopentanol synthesis and, in cases where such products are formed, they are proposed to occur via stepwise reaction mechanisms. For example, cyclisation of **53** in the presence of $SnCl_4$ or $TiCl_4$ delivers varying amounts of both chlorohydrin **54** and ene product **55** as a single diastereomer. During chromatography, **54** was found to eliminate to produce the ene-type product. All the available evidence strongly points towards a two-step, Prins-type mechanism, and one cannot completely rule out the formation of

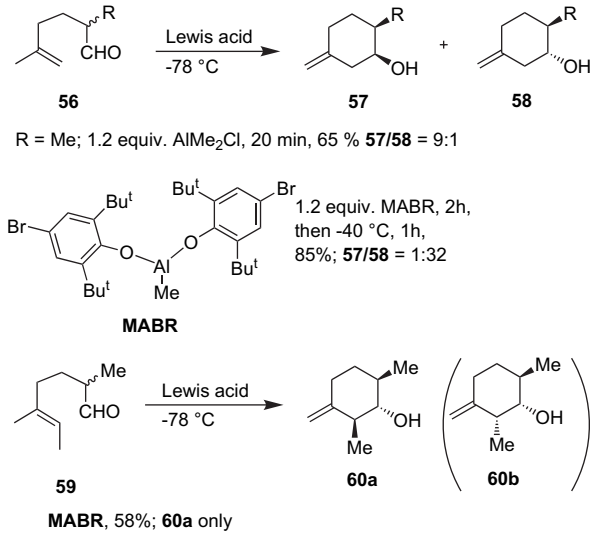


Scheme 19.

the ene product always being from rapid elimination of HCl from **54**. Regardless of the mechanism, treatment of **53** with $TiCl_4$ followed by treatment with NaOMe gives an 86% yield of **55** (Scheme 19).[27]

The majority of more recent applications of type II ene cyclisations have been in cyclohexanol synthesis, and illustrative examples are discussed in the following pages.

In type II cyclisations of α-substituted aldehydes of type **56**, Snider and co-workers originally reported very good diastereoselectivity in favour of the *syn* isomer **57** when the cyclisation was promoted by $AlMe_2Cl$ (Scheme 20).[36] More recently, Yamamoto utilised the very bulky Lewis acid MABR to promote the same cyclisation with very high selectivity towards the *anti* diastereomer. This selectivity was demonstrated to be fairly general for a range of aldehydes of type **56**. Reaction of the more highly substituted substrates **59** gave the diastereomerically pure alcohol **60a**.[37,38]



Scheme 20.

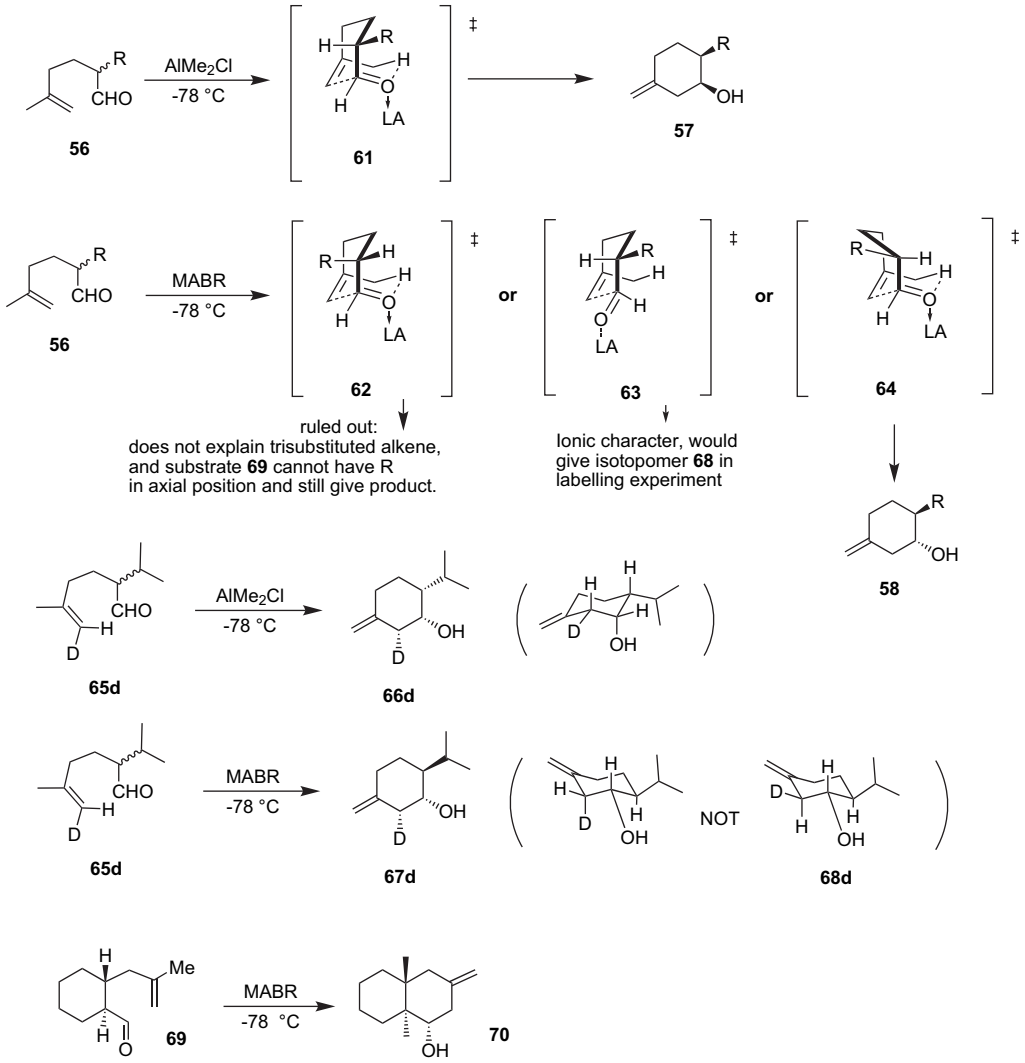
These experimental results presented something of mechanistic quandary. The accepted transition state for these ene cyclisations invoked a chair transition state (TS) with product **57** or **58** arising from transition state **61** or **62**, respectively, as proposed by Snider and co-workers (Scheme 21).[36] Thus, the unusual diastereoselectivity observed by Yamamoto in the cyclisation of simple aldehydes **56** can potentially be explained by reactions proceeding via TS **62** to cyclohexanol **58**. However, the diastereoselectivity observed with the more highly substituted alkenes such as **59** (giving isomer **60a**) is not predicted from transition state **62** (which would predict isomer **60b**). In addition, the synthesis of *anti*-decalin product **70** (Scheme 21) could not have proceeded via a transition state akin to **62** since enforcing this transition state does not allow the cyclohexane ring of **69** to adopt a stable conformation. Further work by Yamamoto and co-workers led them to propose an open transition state **63** and, therefore, some ionic character to these ene cyclisations.

This mechanistic debate has been reconciled by elegant labelling studies by Brown and co-workers.[39] These researchers were uncomfortable with the non-concerted mechanism for this reaction, since Marshall and co-workers' own labelling experiments had shown H and D transfers were stereospecific during cyclisation of a labelled variant of alkene **56**.[40] Their alternative transition-state model invoked a closed transition state with a boat configuration (**64**) when *anti* products are observed. This model fits all the confirmed experimental data for *anti*-selective cyclisations. Deuterated aldehyde **65d** cyclised with $AlMe_2Cl$ to give the expected *syn* product **66d** with equatorial deuteration. This is fully consistent with the original Snider model of a closed-chair transition state. Cyclisation using MABR delivered the expected *anti* product. The relative position of the deuteron in this product will indicate the structure of the transition state for this cyclisation. Labelled **65d**, if it were to cyclise via the Yamamoto open transition state, would give the *anti* alcohol with equatorial deuteration (**68d**), whereas the boat transition state would result in axial deuteration (**67d**). The latter is indeed observed. For concerted type II ene cyclisation reactions, anyway, *syn* products, obtained when using most Lewis acids, form through a closed-chair transition state, whereas bulky Lewis acids change the reaction pathway to the boat transition state and *anti* selectivity. However, it should be noted that open and non-concerted ene cyclisations do still take place with some promoters.

The highly *anti*-selective cyclisation discovered by Yamamoto would be more synthetically valuable if the custom-made and, consequently, relatively expensive Lewis acid could be used in catalytic quantities. However, further studies using MABR by Brown and Braddock have shown that a Meerwein–Ponndorf–Verley (MPV) reduction of the aldehyde starting material **65** occurs. The product acts as a hydride donor, giving products **71** and **72** (Scheme 22). The same problem occurred with *syn*-selective cyclisations catalysed by $AlMe_2Cl$. The hydride-transfer reactions must proceed from an aluminium complex in which the methyl ligand has been exchanged for the product alkoxide (with methane formation). Since aluminium complexes with phenol and chloride ligands (CABR) should be incapable of deprotonation of the product, these were examined and found to act catalytically without MPV reduction side products. However, in this case, the reactions were no longer *anti* selective, giving the *syn* product with more modest selectivity.[41] It seems most likely that the catalyst is not stable under the reaction conditions and forms a less sterically hindered species that proceeds predominantly through the *anti*-selective chair transition state of Snider. Attempts have been made to realise the intriguing concept of dynamic kinetic resolution of racemic **65** to give enantiomerically pure **67**. However, these were complicated by side reactions.[42]

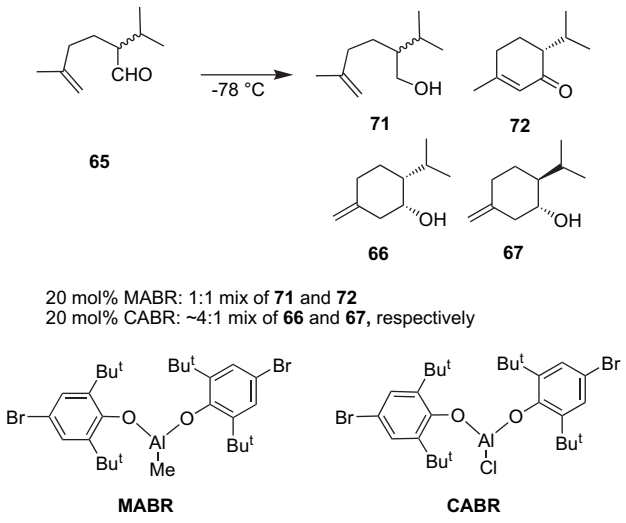
An interesting type II carbonyl ene cyclisation of silicon-tethered unsaturated aldehydes **73** and **75** has been developed. These reactions were found to be more sluggish than their all-carbon analogues, but they deliver very good yields of cyclohexanols, **74** and **76**/**77**, and in the case of α-substituted aldehydes, good selectivity to the expected *syn* isomer **76** on cyclisation (Scheme 23).[43]

When β-substituted aldehydes are employed, the analogous lowest-energy transition state **82** for cyclisation places the β-substituent in the equatorial position, and thus gives *anti* products (**78**→**79a** and **80**→**81a**). These are shown for both the simple[36] and silicon-substituted aldehydes **78** and **80** in Scheme 24. Quantum mechanical investigations into type II ene reactions show that alkyl groups will always adopt an equatorial position in a six-membered chair transition state, although it was suggested that alkoxy substituents may give alternative transition states and stereochemistry.[44]

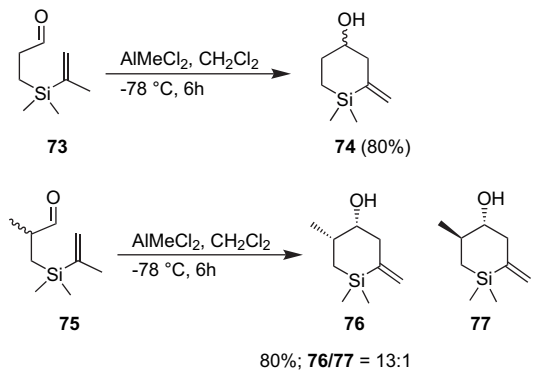


Scheme 21.

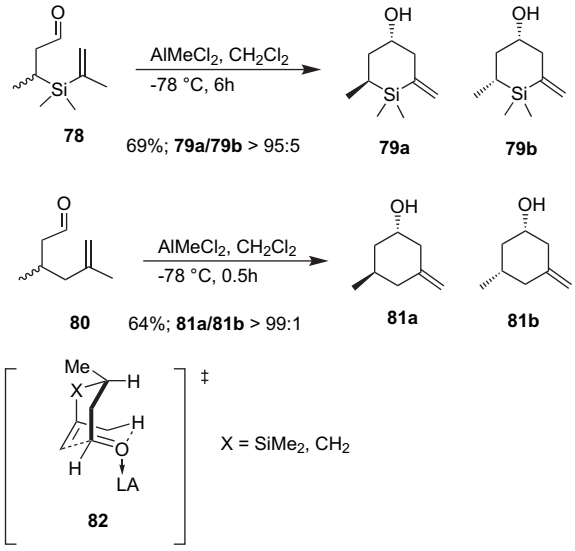
Despite early reports suggesting that seven-membered rings are formed most readily by type II ene cylisations,[27] there have been relatively few recent applications. An excellent early example of a type II ene cyclisation that gives a seven-membered ring is shown in Scheme 25. The cyclisation is a stereospecific method to construct cycloheptanols under mild conditions. Reaction of aldehyde **83** with a catalytic quantity of $SnCl_4$ induces a clean cyclisation that is entirely diastereoselective to give **84**. A crystal structure of a derivative of the product firmly established the relative stereochemistry to be that shown in Scheme 25.[45] This type of ene cyclisation was utilised by Andersen and Golec in the total synthesis of 8-epikessanol.[46]



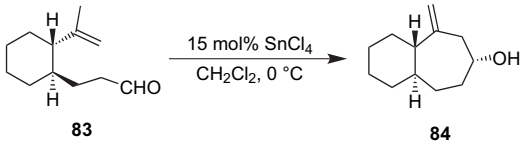
Scheme 22. MABR Lewis acids cannot be used catalytically due to competing MPV reduction.



Scheme 23.

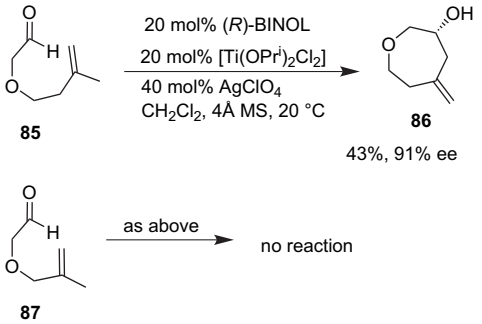


Scheme 24.



Scheme 25.

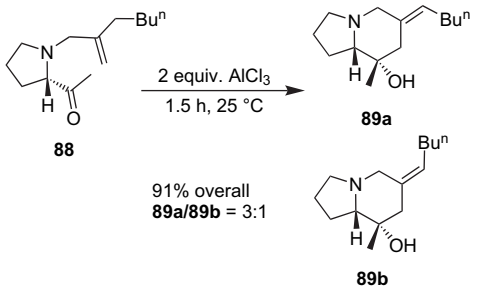
Mikami's chiral Ti/BINOL catalyst system has also been employed for type II cyclisations (Scheme 26). In these examples, cyclisation of allylic ether **87** to give the six-membered ring product was not possible. However, cyclisation of the homoallylic ether **85** to give the seven-membered ring compound **86** could be achieved with reasonable yields and very good enantioselectivity.[47]



Scheme 26.

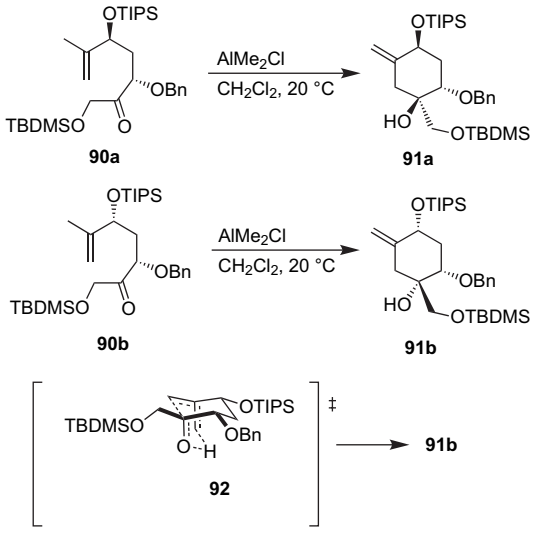
As has already been discussed, ene reactions of ketones are extremely challenging and, consequently, type II ene cyclisations of ketones are relatively rare. A good example in which such a reaction has been used is Overman's synthesis of of pumiliotoxin alkaloid analogues.[48] The cyclisation of **88** was particularly efficient, provided that stoichiometric $AlCl_3$ was employed, with other Lewis acids giving mixtures of products (Scheme 27). Although two double-bond isomers (**89a** and **b**) were observed, the reaction was selective for the relative stereochemistry shown, consistent with the Snider transition-state model and concerted mechanism discussed in Scheme 21. Analogues of **88** with different double-bond substituents gave side products.

More recently, Craig and co-workers explored a type II ketone ene cyclisation as one possible route to the six-membered ring system in the paclitaxel family (Scheme 28). Cyclisation of both **90a**



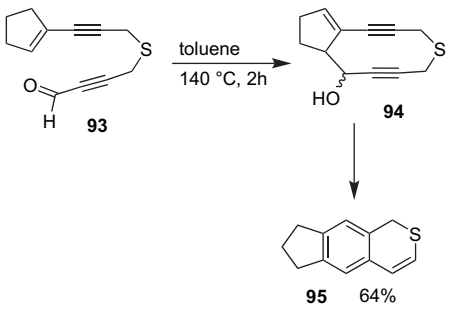
Scheme 27.

and **90b** was quantitative and completely diastereoselective in forming the diastereomers **91a** and **91b** with *syn* relationships between OTIPS and OH groups. The diastereoselectivity is, once again, readily explained by the preference of the substituents to adopt equatorial positions in the chair-like transition state, **92**.[49]



Scheme 28.

The type II cyclisation of an aldehyde **93** was studied during the course of an attempt to synthesise the core of the neocarzinostatin antitumour antibiotics. Lewis acid catalysis was not successful in promoting these reactions. However, if **93** was heated at 140 °C, a clean reaction to produce the unexpected aromatic product **95** took place (Scheme 29). The most likely mechanism for the formation of such a product invokes the desired ene cyclisation to give the intermediate **94**, followed by a dehydration–aromatisation sequence.[50] Although the tandem reaction observed ultimately prevented the desired synthesis, the reaction is of interest, since it established that even 10-membered rings can be formed by a type II cyclisation. Marshall and Andersen have shown that 12- to

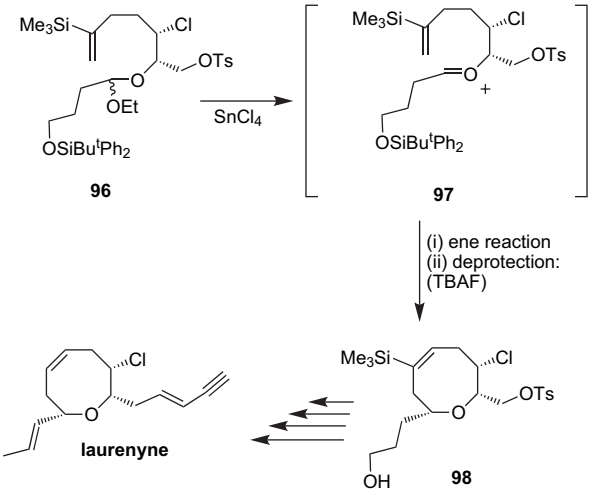


Scheme 29.

16-membered ring systems are also available by type II ene cyclisations.[32]

2.3. Type III carbonyl ene cyclisations

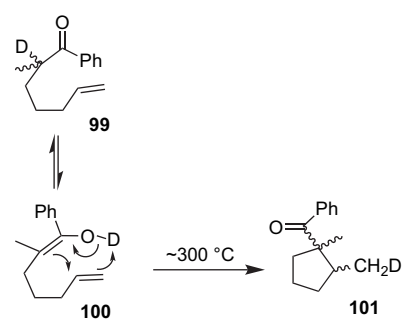
Type III carbonyl ene cyclisations require an oxonium ion as enophile. This type of ene cyclisation is, perhaps, more esoteric, yet it has been used in an elegant synthesis of (−)-laurenyne.[51] Isotope effect studies, along with competition experiments on model compounds, have provided strong evidence for a type III ene cyclisation mechanism.[52] The key step in the cyclisation to form oxocene **98** from acetal **96** via oxonium ion **97** is shown in Scheme 30.



Scheme 30.

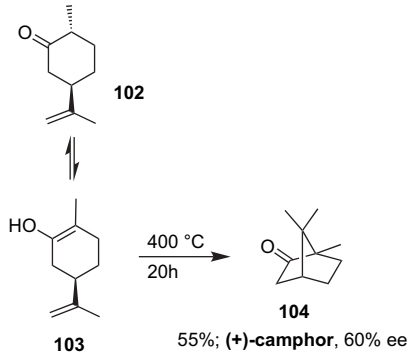
2.4. Conia ene reactions

The Conia ene reaction is a carbon–carbon bond-forming reaction in which the enol tautomer of an activated carbonyl compound undergoes an ene-type reaction with an alkene or alkyne enophile. The reactions are named after J. M. Conia, who carried out many studies on the thermal cyclisation of unsaturated ketones at very high temperatures (typically 300–400 °C).[53] An example of such a reaction is the cyclisation of ketone **99** shown in Scheme 31, and processes such as these, carried out under neutral conditions, may indeed be concerted ene-type reactions and are therefore briefly reviewed here. The transfer of deuterium into the position shown in compound **101** is certainly consistent with the enol **100** being the reactive tautomer.[54] When the Conia ene reaction is carried out using transition-metal catalysts, it seems less likely that a pericyclic reaction mechanism can occur. There are also analogous reactions in which preformed enolates add to alkynes or alkenes in an intramolecular fashion, followed by quenching with a suitable electrophile or acid. For the purposes of this section, we have, somewhat arbitrarily, only selected examples where products could *potentially* have arisen from a classical ene-type mechanism.



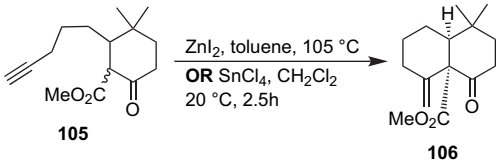
Scheme 31.

Another interesting example from Conia's work is the thermolysis of (+)-dihydrocarvone (Scheme 32).[55] The dihydrocarvone used was a 3/1 mixture of diastereomers, due to epimers at the α-carbon only. Thus, the very small amount of enol present in the equilibrium was a single enantiomer. On heating at 400 °C, a moderate yield of enantio-enriched (+)-camphor **104** was obtained. Given that (+)-camphor was configurationally stable under the reaction conditions, partial racemisation of **102**/**103** must have occurred prior to cyclisation. The majority of Conia's work on high-temperature cyclisations has been summarised in a review.[53]



Scheme 32.

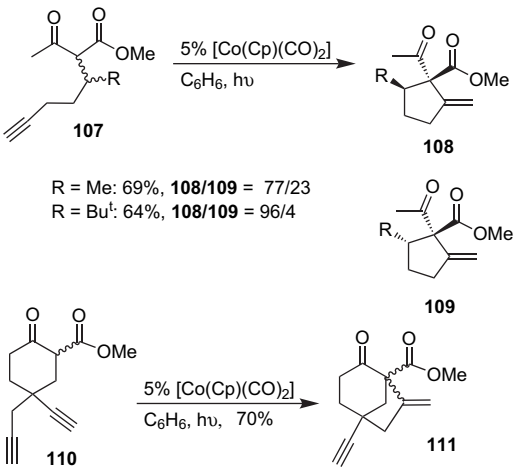
An early example of a Conia ene cyclisation that was carried out using either thermal conditions or Lewis acid catalysis is shown in Scheme 33.[56] The ene cyclisation of **105** to give **106** under thermolysis conditions was perfectly satisfactory, but such extreme temperatures are not desirable. There are many functional groups that are not compatible with such conditions and, as with most procedures, the cyclisations would be preferable if they could be run below the boiling points of common solvents. Reactions run in the presence of a catalytic amount of zinc iodide in boiling toluene or tin tetrachloride at room temperature allow essentially quantitative yields. Given that neither zinc nor tin complexes tend to coordinate to alkynes, it seems most likely that these Lewis acids serve to increase the concentration of an enol-type tautomer.



Scheme 33.

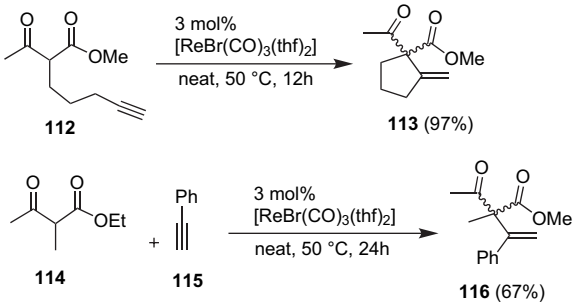
[Co(Cp)(CO)$_2$] catalyses the Conia ene cyclisation under neutral conditions at moderate temperatures under UV irradiation. The diastereoselectivity of this cyclisation is highly dependent on the R substituent in **107**. The starting material was a 1/1 mixture of diastereomers and, when the R group in **107** was phenyl, no diastereoselectivity was observed. Bulky alkyl groups result in large improvements in the diastereomeric ratio (**108**/**109**) up to 92% de (Scheme 34).[57] The reaction of the cyclic β-keto-ester **110** gave a good yield of the bicyclic compound **111** with complete chemoselectivity.[58]

There have been several very interesting reports of both inter- and intramolecular 'hydroalkylation' of alkenes and alkynes in the presence of transition-metal catalysts.[59–62] An example that gives Conia ene-type products is the rhenium-catalysed hydroalkylation of alkynes. This reaction occurs in both an inter- and intramolecular sense and is proposed to involve attack of the enol tautomer on



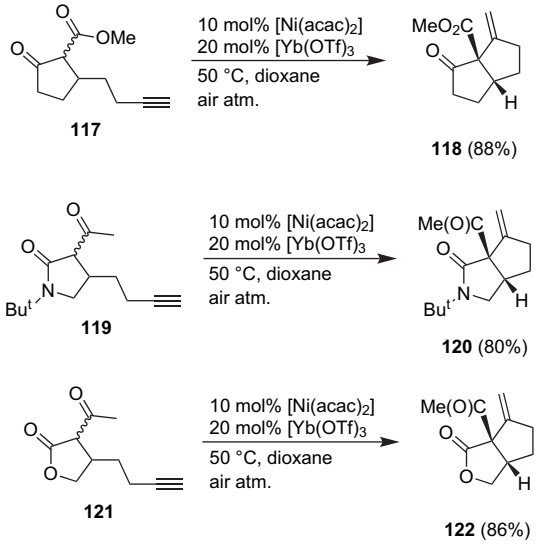
Scheme 34.

a rhenium complexed alkyne. A couple of selected examples of intramolecular (**112**<**113**) and intermolecular reactions (**114**+**115**>**116**) are shown in Scheme 35.[59]



Scheme 35.

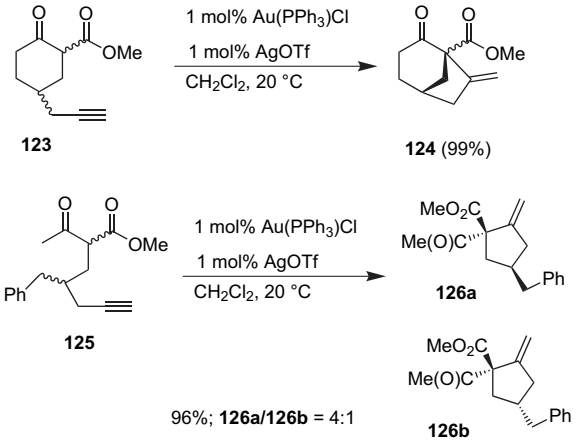
A combination of [Ni(acac)$_2$] and [Yb(OTf)$_3$] allows the cyclisation of **112** to take place at 50 °C (not shown).[63] This dual catalyst system was employed to cyclise a range of acetylenic 1,3-dicarbonyl substrates. Selected examples are substrates **117**, **119** and **121** that cyclise to give **118**, **120** and **122**, respectively (Scheme 36). The role of the Yb(OTf)$_3$ is not completely understood. If no Yb(OTf)$_3$ is present, the reaction proceeds, but more slowly. However, the use of excess co-catalyst also reduces the reaction rate considerably.



Scheme 36.

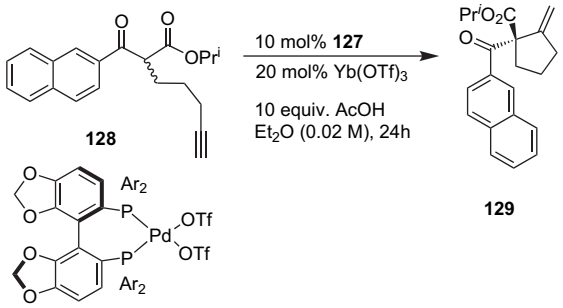
One possibility is that the Yb(OTf)$_3$ merely forms Ni(OTf)$_2$ from Ni(acac)$_2$. A full study identifying the catalytic species has not been reported.

Gold catalysts were, until recently, rarely employed in organic synthesis. However, the last 5 years have seen a remarkable renaissance in gold catalysis, mainly based upon the realisation that an extremely soft metal like gold can selectivity bind and activate alkynes in the presence of other harder donor groups in the reactants. A good example of the utility of gold catalysis is Toste's gold-catalysed Conia ene reaction in which 1 mol % of gold(I) triphenylphosphine triflate, prepared in situ from [Au(PPh$_3$)Cl] and AgOTf, catalyses the cyclisation of **112** to **113** in high yield within 15 min at room temperature under air atmosphere. Two other high-yielding examples are the cyclisation of **123**>**124** and **125**>**126** as shown in Scheme 37.[64]



Scheme 37.

Attempts to render the gold-catalysed process highly enantioselective have not been successful. However, the use of [Pd(DTBM-SEGPHOS)(OTf)$_2$] as catalyst in combination with [Yb(OTf)$_3$] and 10 equiv of acetic acid did allow a highly enantioselective catalytic Conia ene reaction of **128** to yield **129** (Scheme 38).[65] The exact role of each catalyst and the acetic acid is somewhat unclear at present. Further developments in enantioselective Conia ene reactions would be desirable.



127: Ar = 3,5-di-(*tert*-butyl)-4-methoxyphenyl
[Pd(DTBM-SEGPHOS)(OTf)$_2$]

Scheme 38.

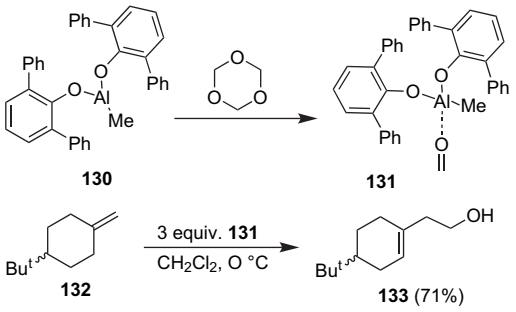
3. Intermolecular carbonyl ene reactions

The intermolecular carbonyl ene reaction proceeds far less readily than the cyclisation reactions. Most reactions will only take place on highly activated substrates in the presence of Lewis acid catalysts. However, despite these limitations, these reactions have

found use in synthesis. Some of the most useful examples of intermolecular carbonyl ene reactions are, therefore, described here.

3.1. Intermolecular ene reactions of unactivated aldehydes

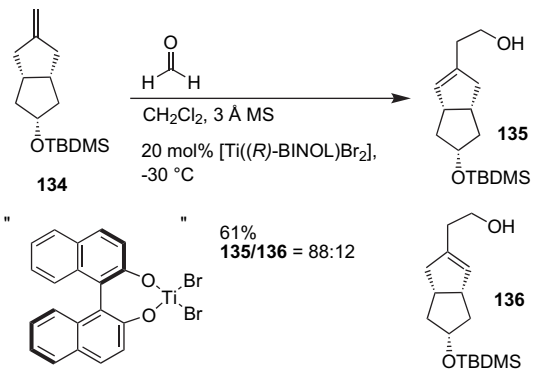
The ene reaction between aldehydes and alkenes is accelerated significantly by the presence of electron-withdrawing groups on the carbonyl compound, making ene reactions of unactivated aldehydes rather rare. However, if highly activated ene substrates are employed in combination with catalysts, then some synthetically useful reactions do proceed. Early studies demonstrated that heating alkenes and formaldehyde in acetic acid/acetic anhydride mixtures at >150 °C allows the ene reaction and acetylation to take place.[66] If the reactions are run in the presence of stoichiometric $AlMe_2Cl$ as promoter, then improved yields are observed at room temperature.[67] Yamamoto has shown that reacting trioxane or gaseous formaldehyde with the bulky aluminium reagent **130** gives a formaldehyde–aluminium complex, **131** that will undergo ene reactions with a range of alkenes.[68,69] The Yamamoto group note that this formaldehyde reagent gives better chemoselectivity and regioselectivity than simple stoichiometric Al promoters. An example is the reaction of **131** and **132** to yield **133** as shown in Scheme 39.



Scheme 39.

1,1′-Disubstituted alkenes such as α-methylstyrene derivatives react with formaldehyde at 80 °C using Zr^{4+} montmorillonite clays as heterogeneous catalysts to give the desired homoallylic alcohols in moderate yield.[70] Other simple aldehydes did not give appreciable amounts of the ene products, suggesting that the formaldehyde undergoes ene reactions more readily than other simple aldehydes.

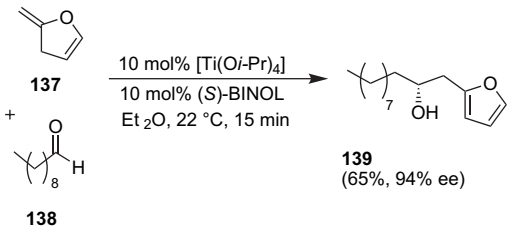
An interesting desymmetrisation of the alkene **134** by an ene reaction with formaldehyde can be accomplished in the presence of catalytic amounts of a catalyst, then formulated as $Ti(BINOL)Br_2$ (Scheme 40). The symmetric bicyclic alkene is pro-chiral: selective regio- and stereoselective abstraction of a specific proton during



Scheme 40.

the ene process is required in order to achieve stereoselective reaction. The titanium-based catalyst was found to be quite effective at achieving this challenging task, and an 88/12 ratio of stereoisomers **135**/**136** was obtained in 61% yield if the reactions were carried out at −30 °C. This type of reaction was then successfully employed to synthesise isocarbacyclin analogues.[71]

Intermolecular ene reactions between alkenes and simple aryl and alkyl aldehydes are challenging. They do not occur cleanly with thermal heating, although nucleophilic alkenes will react with unactivated aldehydes by a Prins mechanism promoted by excess $AlMe_2Cl$.[67,72] Catalytic ene reactions are currently only possible if highly activated alkenes such as enol ethers are employed as the ene component. For example, Miles and co-workers have found that 2-methylene-2,3-dihydrofuran **137** is an extremely reactive ene component. Reactions with benzaldehyde or decanal **138** take place at room temperature using Lewis acid catalysts with high yield. If Ti/(*S*)-BINOL catalysts are employed, (*R*)-1-(2-furyl)undecan-2-ol **139** could be isolated in 65% yield and 94% ee (Scheme 41).[73]



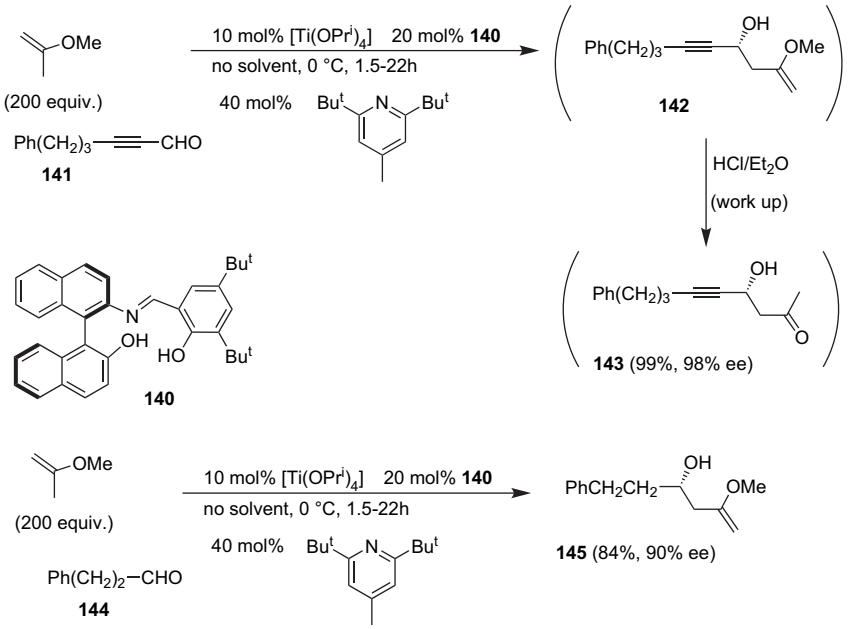
Scheme 41.

Carreira and co-workers have shown that titanium complexes of tridentate O^N^O ligands such as **140** can act as catalysts for the ene reaction of 2-methoxypropene with unactivated aldehydes such as **141** (Scheme 42). The reaction is noteworthy for working effectively on alkyl aldehydes, which can be more problematic substrates in some asymmetric catalytic reactions. The ene products such as **142** were in general directly converted into acetone aldol addition products, **143**, by an acidic work up. However, the authors do demonstrate that the ene-type products can also be isolated in high yield. For example, ene reaction of **144** with 2-methoxypropene gave an 84% yield of **145**, which could then be converted into other functionalised products. The catalyst was less effective for benzaldehyde (and, presumably, other aryl aldehydes).[74]

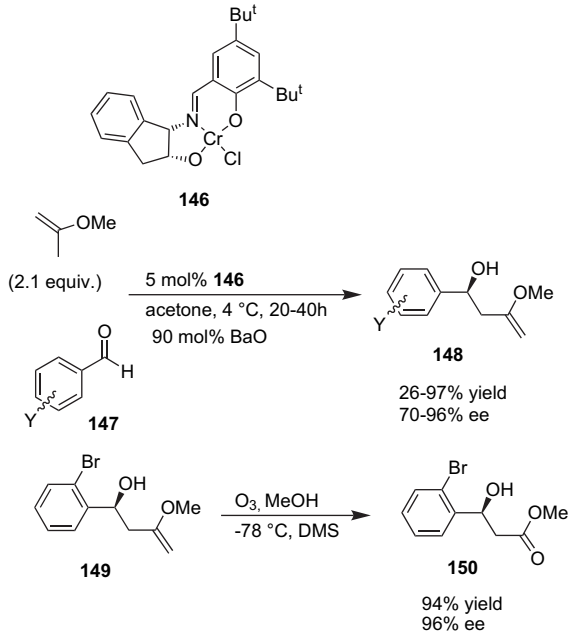
Jacobsen and Ruck have reported that a Cr(III) complex, **146**, derived from a chiral tridentate ligand promotes the reaction of 2-methoxypropene with aldehydes of type **147** (Scheme 43). A range of aryl-aldehydes react to give products of type **148** in high yield and enantioselectivity if BaO is employed as a desiccant. The products are potentially useful synthons, as demonstrated by the high-yielding conversion of **149** into 1,3-hydroxyketones (by acid-catalysed hydrolysis of the enol ether) or, as shown in Scheme 43, into 1,3-hydroxy ester, **150** (by ozonolysis), with no loss of enantioselectivity.[75]

The reaction could be extended to silyl-enol ethers such as 2-trimethylsilyloxypropene, **152** (Scheme 44). Remarkably, using catalyst **151** there were no traces of the Mukayama aldol products that might be expected from this nucleophile, and β-hydroxy silyl-enol ethers **155** and **156** were isolated in good yields and very good enantioselectivities from reactions of aldehydes **153** and **154**. These reactions also required the presence of additives, in this case 4 Å molecular sieves and Hunig's base to suppress side reactions and an unselective background reaction.[76]

A potentially very attractive approach to chiral β-amino-alcohols is the ene reaction of an α-amino-aldehyde. Reaction of the readily available enantiopure *N*,*N*′-dibenzylated derivative **157** with

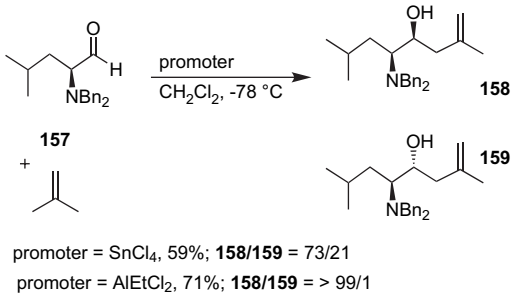


Scheme 42.



Scheme 43.

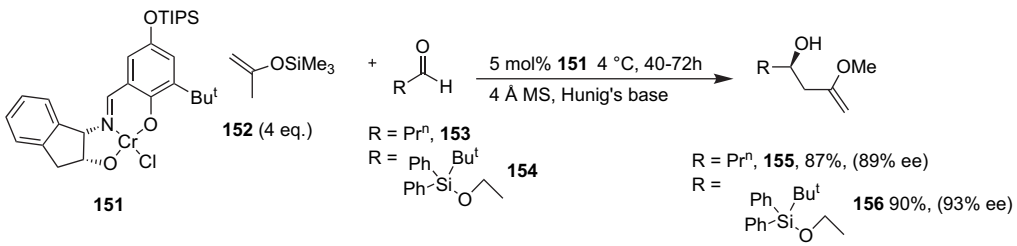
reacted with a ketene silyl acetal using aluminium catalysts. This change in selectivity is not easily accounted for unless one invokes the major species as a poorly reactive monodentate Al-aldehyde complex that can only react with stronger nucleophiles such as ketene silyl acetals to give *anti* products. A bidentate Al–aldehyde cation could be present in very small amounts, but represent the only complex sufficiently reactive to undergo the C–C bond-forming reaction with the alkenes. Using this chelation-control model predicts the observed stereoselectivity. This is potentially very useful chemistry, but we do note that only two of the most nucleophilic alkenes were employed in this paper, and the scope of this reaction has not been fully described.[77]



Scheme 45.

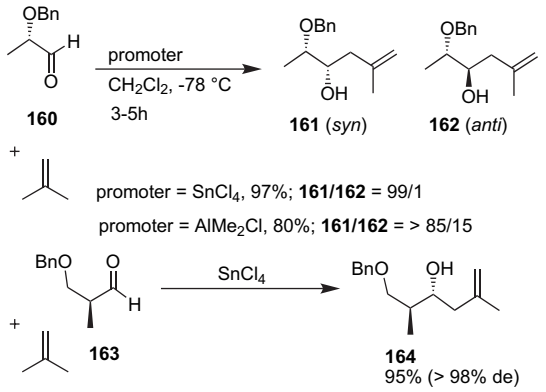
isobutylene in the presence of $AlEtCl_2$ gives essentially perfect *syn* selectivity for **158** over **159** and good yield (Scheme 45). The *syn* selectivity of this reaction is opposite to that observed when **157** is

Another potentially useful intermolecular ene reaction is that of alkoxy aldehyde **160** and alkenes (Scheme 46). In these reactions,



Scheme 44.

$SnCl_4$ is the catalyst of choice, giving the *syn* product **161** exclusively. Other Lewis acids were less effective giving lower yields and some of isomer **162**. This stereochemistry agrees with a chelation-control model. $SnCl_4$ was also effective in promoting the reaction with the chiral β-benzyloxy aldehyde **163** to give *anti* **164** in excellent yield (the *anti* preference merely reflects the structure of the chiral starting material). The authors describe how this type of ene reaction can be applied in the preparation of a diol side chain in a synthesis of a natural product derivative. We would also add that there does not seem to be a report describing the results obtained with some less nucleophilic alkenes, so it is likely that this methodology is specific for 1,1- and other highly activated alkenes.[78]



Scheme 46.

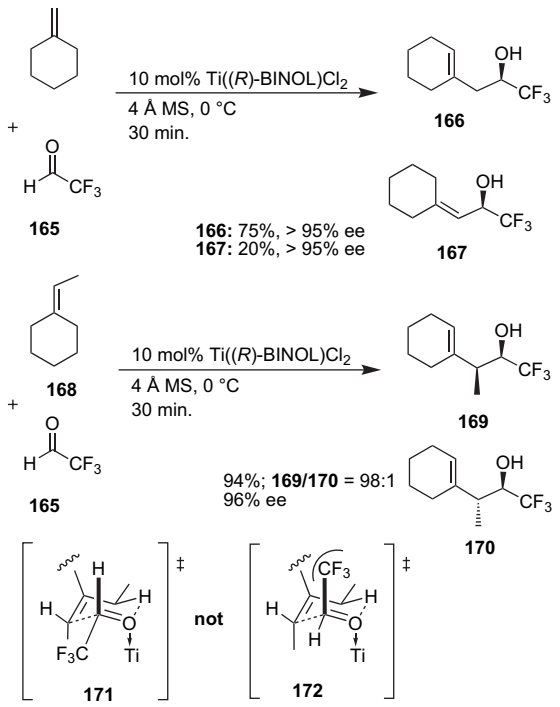
3.2. Intermolecular ene reactions of activated aldehydes

The highly activated enophile fluoral (**165**) has been found to undergo highly enantioselective ene reactions in the presence of Ti/BINOL catalysts (Scheme 47). However, the reaction of methylenecyclohexane was complicated by the formation of significant quantities of the double-bond isomer **167**, presumably formed by a cationic stepwise pathway analogous to a Friedel–Crafts reaction (Scheme 47). This latter pathway was even more significant when chloral (Cl_3CCHO) was employed as the enophile, with approximately 45% of the reaction mixture being the Freidel–Crafts-type product, also in lower ee. Calculations demonstrated that fluoral has a lower energy LUMO for the ene-type reaction than chloral. Chloral bears a higher partial positive charge on the carbonyl carbon, thus rationalising the reactivity observed.

The fluoral ene reaction was most effective when a trisubstituted alkene was employed. High yields, excellent *syn* diastereoselectivity and high ees were observed. The *syn* diastereoselectivity is consistent with monodentate coordination of the fluoral to Ti and a cyclic transition state with the CF_3 substituent in the equatorial position (i.e., **171**).[79]

The Ti/BINOL catalyst system can be used to promote the ene reactions of 1,1-disubstituted alkenes with substrates **173** and **175**. Good yields and reasonably good ees for products **174** and **176** were observed. An interesting extension of this methodology is shown in Scheme 48. A prochiral symmetric precursor **134** (see Scheme 40) reacted with **173** under the control of the catalyst to preferentially form the diastereomer and the double-bond regioisomer **177** in good ee. The Ti/BINOL catalyst therefore exerts both regiocontrol to favour **177** over **178** in the desymmetrisation and enantioface control.[80]

The previous examples hopefully give the reader the clear picture that enophiles need to be activated by the close proximity of electron-withdrawing groups. The only examples of non-activated aldehydes undergoing reaction use stoichiometric aluminium salts



Scheme 47.

and are also limited in scope, although this can be partially overcome if reactive enol ether enes are employed. Due to their ready availability at low cost and the synthetic utility of hydroxyl esters, probably the most intensively researched ene reactions have been those making use of glyoxylates, and the more recent of these studies are described in some detail below. It is in the glyoxylate ene and related reactions that the most significant developments in catalyst design have been made and, consequently, these are discussed here. It is likely that the catalysts described below could have other applications in the more complex intramolecular reactions already discussed, but a major effort towards developing reactive, recyclable and more selective catalysts for these reactions has not yet been made.

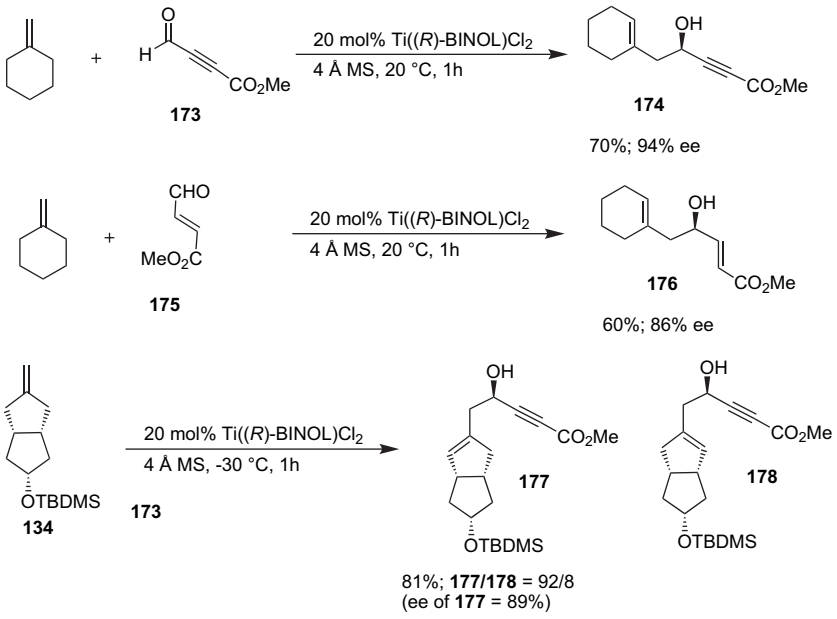
3.3. Glyoxylate ene reaction

The glyoxylate ene reaction (Eq. 1) is an important carbon–carbon bond-forming reaction, providing a source of synthetically useful homoallylic alcohols. This reaction provides a more atom-economical route into the same class of compounds that would be obtained by the addition of a substituted allyllithium or allyl Grignard reagent to the glyoxylate. The reaction was first described by Klimova and Arbuzov,[81,82] and the first asymmetric example appeared in 1982 when Whitesell described a method utilising 8-phenylmenthyl glyoxylate as a chiral auxiliary in $SnCl_4$-catalysed ene reactions.[83–85] The glyoxylate ene reaction remains a particularly active area of research. Since earlier work has been reviewed previously,[86–92] the focus of this discussion is on the literature from 2000 onwards.

(1)

3.3.1. Titanium catalysts

Mikami and co-workers reported the first example of the catalytic asymmetric ene reaction with glyoxylate.[93,94] A chiral titanium



Scheme 48.

complex was prepared in situ by the reaction of $Ti(O^iPr)_2X_2$ (X=Cl, Br) (**179a**,**b**) with optically pure BINOL in the presence of 4 Å molecular sieves. Mikami originally reported the catalyst structure as **179a**,**b**, although this is not the active species. High yields and enantioselectivities were obtained for the reaction of methyl glyoxylate with a variety of 1,1-disubstituted olefins (Table 1). The dichloride complex gave a lower reactivity, but higher enantioselectivities than the dibromide complex for reactions involving abstraction of a methyl hydrogen (entries 1–4). However, the dibromide complex is better for abstraction of a methylene hydrogen, with improved enantioselectivity and reactivity (entries 5–8). While these complexes give good results with 1,1-disubstituted olefins (entries 9–12), the results are less satisfactory with trisubstituted olefins, giving only low-to-moderate enantioselectivities, although high *syn* selectivities are observed.[95] No ene product was obtained with mono- or 1,2-disubstituted olefins.[94] This titanium BINOL system has been used by Roche on a multi 100-kg scale in a pilot process (Fig. 1).[96]

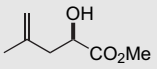
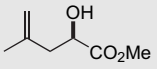
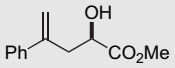
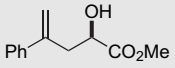
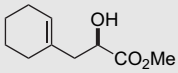
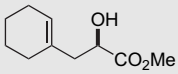
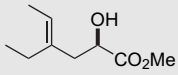
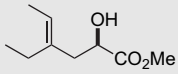
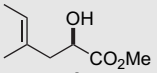
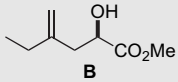
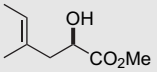
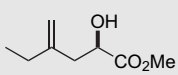
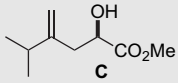
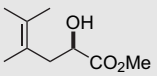
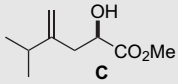
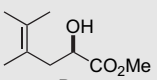
The presence of 4 Å molecular sieves during catalyst formation is important for high enantioselectivities. The use of commercial *unactivated* 4 Å molecular sieves serves to catalyse the ligand exchange reaction of $Ti(O^iPr)_2Cl_2$ with BINOL to make the active titanium–BINOL species, which is primarily composed of a μ_3-oxotitanium species.[97] The sieves serve as a water donor to hydrolyse the titanium pre-catalyst and act as a base to trap HCl during the formation of the active titanium–BINOL catalytic species. The catalytic activity of this species is dependent on the type of zeolite used in its preparation.

A number of variations on this titanium system have been reported over the years. In addition to **179a**,**b**, these also include complexes **179c**,**d**, prepared by addition of the appropriate silver complex to **179b**,[98,99] the μ-oxo dimeric species **180**, isolated both upon azeotropic removal of isopropanol from a solution of BINOL and $Ti(O^iPr)_2Cl_2$ after filtration of 4 Å molecular sieves[100] or upon hydrolysis and azeotropic removal of isopropanol from **179e**,[101] brominated derivatives **181** and **182**,[102,95] and derivatives such as **183**, prepared by the reaction of $[Ti(BINOL)(O^iPr)_2]$ (**179e**) with various activators.[103–107] An excellent summary of the work on these titanium systems up to 2000 can be found in a review by Dias[88] and is not repeated here except where necessary to put more recent work into context.

As the exact nature of the active species is unknown, it is possible that more than one of the abovementioned systems might, in fact, involve the same active species. In any case, it is certainly clear that higher order and multiple titanium species can form,[108–111] and ligand accelerated catalysis might allow for a relatively small amount of a highly catalytically active species to be responsible for the observed chemistry.[104] Mikami and co-workers have recently proposed a structure for the μ^3-oxo-titanium complex, Ti_4(BINOLato)$(O^iPr)_4(\mu\text{-}O)_4$, obtained during preparation of the active titanium–BINOL catalyst via partial hydrolysis of **179e**.[105] While **183** has been proposed to be the precursor to the active species, it is unstable and X-ray quality crystals could not be obtained. A more stable analogue of this ladder structure has been prepared using the more bulky alkoxo ligand, 2,4-dimethyl-3-pentyloxo, and shown crystallographically to have a structure in good agreement with that proposed above.[105] Indeed, catalysts prepared with several bulky alkoxo ligands all showed catalytic activity, albeit at a lower level than the original isopropoxy system. This decreased activity is presumably due to the increased stability of these more sterically hindered systems and thus a slower formation of the active species. Lower activity was also attributed to a more hindered approach of the substrate to the complex.

When the catalyst precursor **179a**,**b** was prepared from partially resolved (*R*)-BINOL and $Ti(O^iPr)_2X_2$, a positive nonlinear effect was observed.[108,109] The ene reaction between α-methylstyrene and methyl glyoxylate using complex **179a** prepared from (*R*)-BINOL with only 33% ee gives the desired product with 91.4% ee in 92% yield. Similarly, when using complex **179b**, 35–40% ee BINOL is good enough to get the same levels of enantiomeric induction as obtained with **179b** prepared from enantiomerically pure BINOL. For a given enantiomeric purity of the catalyst precursors **179a**,**b**, the degree of asymmetric amplification increases with decreasing molar concentration of the complex. Based on the dimeric structure known to exist for the analogous diphenoxytitanium dichloride ($Ti(OPh)_2Cl_2$), Mikami and co-workers attribute the nonlinear effect to the isostructural dinuclear chelate complex **184** (Fig. 2).[109] They suggest that there is a big difference in catalytic activity between the homochiral dimer ((*R*,*R*) or (*S*,*S*)) and the heterochiral *meso* dimer ((*R*,*S*)). The less-reactive *meso* isomer is formed preferentially, leaving the excess (*R*)-BINOL to form the enantiomerically pure (*R*,*R*) dimer after the (*S*)-BINOL supply is exhausted. The observed ene product thus derives only from this more reactive (*R*,*R*)-homochiral dimer.[108,109] The existence of tri- and tetranuclear

Table 1
Ene reaction of 1,1-disubstituted olefins with methyl glyoxylate[93,94]

Entry	Ene	Catalyst (mol %)	Time (h)	Product	Yield (%)(*E*/*Z*)	ee (%)
1		**179a** (10)	3		87	83
2		**179b** (10)	8		72	95
3		**179a** (1)	3		98	94
4		**179b** (1)	8		97	97
5		**179a** (5)	3		89	98
6		**179b** (10)	8		82	83
7		**179a** (5)	3		73 (91/9)	*E* 98, Z>90
8		**179b** (10)	3		68 (89/11)	*E* 94, *Z*>90
9		**179a** (5)	3	 **A**  **B**	93 (overall) 61 (A) (57/4) 39 (B)	*E*>98, *Z*>90 91
10		**179b** (10)	3	 **A**  **B**	68 (overall) 58 (A) (54/4) 42 (B)	n.d
11		**179a** (5)	3	 **C**  **D**	91 (overall) 83 (C) 17 (D)	92 >98
12		**179b** (10)	3	 **C**  **D**	73 (overall) 87 (C) (57/4) 13 (D)	n.d

n.d.=not determined.

species has also been demonstrated.[110,111] However, more recently, Mikami and Matsumoto reported the detailed kinetic analysis of the nonlinear effect simulated for monomeric, dimeric, trimeric and tetrameric species, which they compared to the experimental results.[112] The best match was obtained for the dimeric case.

One of the inconveniences of the glyoxylate ene reaction is that commercial ethyl glyoxylate exists primarily in a polymeric form, which must be cracked by distillation immediately prior to use. Nadeau and co-workers have shown that $MgCl_2$ and $ZnCl_2$ can be used as additives in titanium–BINOL-catalysed ene reactions to catalyse the depolymerisation of ethyl glyoxylate without having any adverse effects on the ene reaction.[113] $ZnCl_2$ was identified as the best additive, retaining the enantioselectivity of the original system.

Yudin and co-workers have described the preparation of a system in which one of the BINOL enantiomers is replaced by the partially fluorinated (*R*)-F_8BINOL (*R*)-**185** (Fig. 3).[107] It was expected that the formation of the pseudo-*meso* aggregate would be favoured by the same factors that favour *meso* formation with BINOL alone. When $Ti(O^iPr)_4$ was treated with 2 equiv of (*S*)-**185**, the resulting complex catalysed the ene reaction of α-methylstyrene

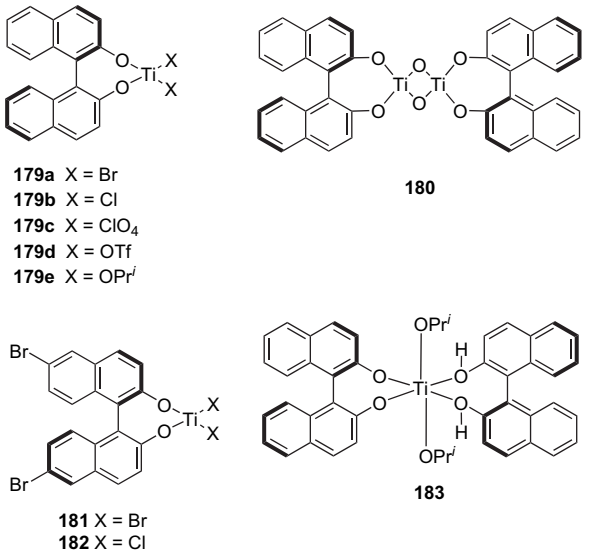


Figure 1. Some of the titanium catalysts derived from binol ligands.

with ethyl glyoxylate to give the same sense of asymmetric induction as that obtained with (*S*)-BINOL, but at a slower rate (92% ee, 53% yield). Unexpectedly, however, the complex formed from the pseudoracemic mixture of (*R*)-**185** and (*S*)-BINOL showed *higher* catalytic activity than complexes prepared with either ligand alone, giving 99% ee and improved yields. In addition, this complex could also catalyse the reaction between ethyl glyoxylate and 1,1-disubstituted aliphatic alkenes with 99% ee, a reaction that did not proceed with catalysts prepared from either ligand used alone. These results are indicative of a synergistic relationship between the two pseudoenantiomeric ligands, a relationship further supported by a crystal structure, which showed a pseudocrystallographic inversion symmetry broken by the fluorine substitution. The structure showed a central core of six oxo-bridged titanium centres surrounded by BINOL and F_8BINOL halves. This species does not exhibit any catalytic properties, presumably due to the fact that all titanium centres are coordinatively saturated and cannot function as Lewis acids.

Mikami and co-workers have shown that effective catalysts can also be derived from titanium complexes coordinated to two diol ligands, only one of which needs to be chiral.[103,104,106] The authors attribute these results to the formation of a monomeric hexacoordinate titanium complex of the type **182**. For example, Mikami has studied the activation of racemic Ti(BINOL)(O^iPr)$_2$ (**179e**), prepared from racemic BINOL and Ti(O^iPr)$_4$ in a 1/1 ratio in toluene.[103] Various additives (0.25–1 equiv) were used, and the ene reaction of α-methylstyrene and *n*-butyl glyoxylate was carried out in situ (Table 2). High enantioselectivities were obtained with 0.5 equiv of acidic (*R*)-5-Cl-BIPOL (**186**) (80.8% ee) or (*R*)-BINOL (89.8% ee) (entries 2 and 3). However, yields were only low to moderate. The reverse process, in which chiral Ti((*R*)-BINOL)(O^iPr)$_2$ is activated with racemic BINOL, gave 69.2% yield and 95.7% ee (entry 4). Improved yields and enantioselectivities were obtained upon activation of chiral Ti((*R*)-BINOL)(O^iPr)$_2$ with a second equivalent of (*R*)-BINOL (82.1% yield and 96.8% ee) (entry 5). In this case, the ene

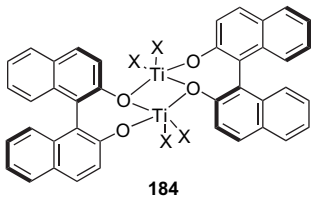


Figure 2.

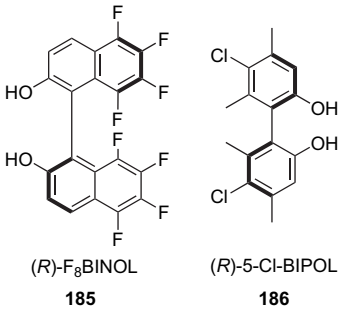


Figure 3.

reaction catalysed by the resulting complex **186** is 26-fold faster than the reaction in the absence of additive.[103] The reaction activated by (*S*)-BINOL is not as good, leading to only 48% yield and 86% ee (entry 6). In the absence of additive, high ee (94.5%) was obtained, but the yield was only 19.8% (entry 1).

Mikami and co-workers have also reported the selective self-assembly of similar chiral titanium catalysts from the achiral precursor Ti(O^iPr)$_4$ and two different chiral diols, one more acidic and one more basic.[104] The same species is formed, regardless of the order of addition of the diols or with the simultaneous introduction of the diols. A similar approach was used by Vallée and co-workers, who activated Ti((*R*)-BINOL)(O^iPr)$_2$ with conformationally flexible biphenols to give complexes analogous to **182**.[106] These species again give high enantioselectivities for the reaction of glyoxylates with α-methylstyrene. In contrast to Mikami's systems, a lower enantioselectivity was obtained if the ligands are added simultaneously to Ti(O^iPr)$_4$ or if the addition order is reversed. This difference was attributed to small amounts of contaminants formed under the different reaction conditions (for example, the achiral species formed from two biphenol ligands).

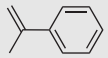
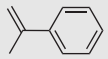
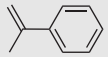
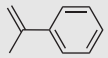
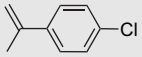
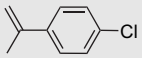
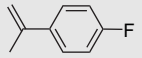
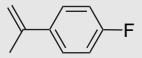
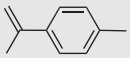
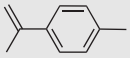
A *quasi* solvent-free enantioselective carbonyl ene reaction was reported by Ding and co-workers (Table 3).[114] They used Mikami-type catalysts prepared by the reaction of (*R*)-BINOL with Ti(O^iPr)$_4$ in a 2/1 ratio in dichloromethane/toluene. The ene reaction of α-methylstyrene with ethyl glyoxylate using catalyst loadings of 0.1 mol %, with a solvent volume of only about 13% of the total system, ran quantitatively at room temperature to give ene products with 90% ee. High-throughput screening of BINOL derivatives demonstrated that both electronic and steric effects have significant effects on the catalytic activity of the resulting titanium–BINOL systems. Steric hindrance at the 3,3′-position (**187**) had negative effects, while electron-withdrawing groups at the 6,6′-position (**188**) proved advantageous for both enantioselectivity and reactivity (Fig. 4). Presumably, the improved results with these latter systems were due to the enhanced Lewis acidity of the titanium complexes prepared from these ligands. These systems allowed a reduction of catalyst loading to 0.01 mol %, with a simultaneous reduction of the solvent volume to only 1.3% of the system. Moderate-to-high yields and high enantiomeric excesses were obtained. A variety of 2-arylpropenes, including those with electron-donating

Table 2
Reaction of α-methylstyrene with *n*-butyl glyoxylate[103,104,a]

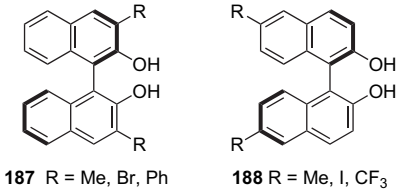
Entry	First diol	Second diol	Yield (%)	ee (%)
1	(±)-BINOL	None	19.8	94.5
2	(±)-BINOL	(*R*)-BINOL	52.0	89.8
3	(±)-BINOL	(*R*)-5-Cl–BIPOL	38.0	80.8
4	(*R*)-BINOL	(±)-BINOL	69.2	95.7
5	(*R*)-BINOL	(*R*)-BINOL	82.1	96.8
6	(*R*)-BINOL	(*S*)-BINOL	48.0	86.0
7	(*R*)-BINOL	(*R*)-5-Cl–BIPOL	66.0	97.2
8	(*R*)-5-Cl–BIPOL	(*R*)-BINOL	66	97

[a] Ti(first diol)(O^iPr)$_2$ (10 mol %), second diol (5 mol %), toluene, 0 °C, 60 min.

Table 3
Ene reaction with ethyl glyoxylate using ligands **188** under nearly solvent-free conditions[114, a]

Entry	Ene	First ligand **188** R=	Second ligand **188** R=	Time (h)	Yield (%)	ee (%)
1[b]		I	I	48	98	98.2
2[b]		I	CF_3	48	85	97.6
3[c]		I	I	72	76	97.2
4[c]		I	CF_3	72	49	97.9
5[b]		I	I	48	89	99.4
6[b]		I	CF_3	36	96	98.2
7[b]		I	I	48	83	98.4
8[b]		I	CF_3	48	96	98.4
9[b]		I	I	36	>99	97.1
10[b]		I	CF_3	24	>99	97.0
11[c]		I	CF_3	42	42	91.8

[a] Ligands and $Ti(O^iPr)_4$ (1/1/1) were stirred in toluene at rt for 2 h; ene reaction carried out at 0 °C.
[b] Catalyst loadings 0.1 mol %.
[c] Catalyst loadings 0.01 mol %.



187 R = Me, Br, Ph **188** R = Me, I, CF_3

Figure 4.

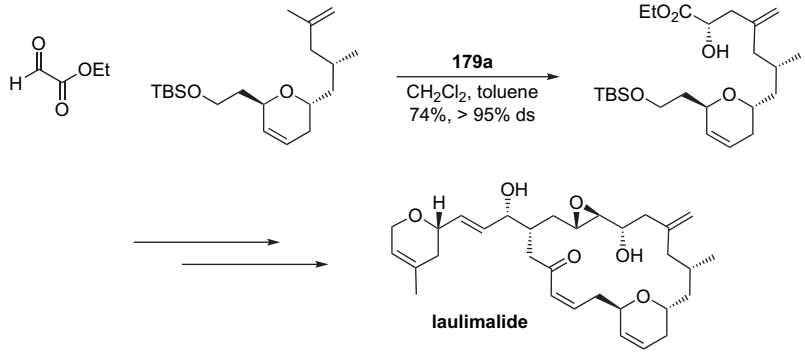
and withdrawing groups (entries 1–10), and cyclic olefins such as methylenecyclohexane could be utilised as the ene component (entry 11).

The enantioselective glyoxylate ene reaction has seen applications in total synthesis. For example, Pitts and Mulzer used the intermolecular ene reaction between a 1,1-disubstituted alkene and ethyl glyoxylate catalysed by Ti((*S*)-BINOL)Br_2 (**179a**) as a key step in the synthesis of the antitumour agent, laulimalide (Scheme 49).[115]

3.3.2. Copper catalysts

Although the exact nature of the active species in the Mikami system is unclear, its behaviour is consistent with a non-chelating interaction of the glyoxylate and the titanium.[116] On the other hand, Evans and co-workers have described bidentate bis(oxazoline)copper(II) complexes **189a–d**, **190a–d**, **191** and **192** (Fig. 5), which are capable of a chelating activation of α-dicarbonyl compounds.[117,118] Such cationic complexes are expected to be more Lewis acidic than the titanium(IV)-based catalysts and, consequently, more reactive. In fact, some of these species not only catalyse the ene reaction of ethyl glyoxylate with less-reactive enes than can be used with the titanium catalysts, but **190a** even promotes the addition of methylenecyclohexane to methyl pyruvate, which cannot be used as the enophile in the titanium system. The best results were obtained with catalysts **189c** and **190a**, which give excellent yields and enantiomeric excesses in the glyoxylate ene reaction. Interestingly, **189c** gives the opposite selectivity to **190a**, so either enantiomer of the product can be obtained from one enantiomer of the ligand family.[119] Evans attributed this reversal to the intermediacy of a distorted square planar bis(oxazoline)copper(II)–substrate complex.[119] Support for this suggestion was provided by X-ray crystallographic studies, which showed that the water molecules in the *tert*-butyl-substituted bis(aquo) complex **192** are distorted from square planar away from the oxazoline, while the water molecules in the phenyl-substituted bis(aquo) analogue show distortion from square planar towards the oxazoline. While Evans and co-workers ruled out an explanation invoking a tetrahedral geometry for **189c**,[119] Singh and co-workers suggested that differences in the metal-centre geometry might explain the similar reversal in the sense of enantioselection they observed in ene reactions utilising copper(I) and copper(II) complexes of bis(oxazoline) ligands **193** and **194**.[120] In the case of ligand **193**, they suggest that the driving force for the formation of a tetrahedral geometry is the π–π stacking of one of the phenyl groups and the carbonyl moiety of the glyoxylate. Hillier and co-workers have suggested that copper complexes such as these only serve to activate the enophile and that the ene reaction proceeds by a stepwise mechanism.[121]

Representative results of the glyoxylate ene reaction utilising complexes **189**–**192** are shown in Table 4. The bis(aquo) complex **192** is bench-stable and is therefore easier to handle with only a slight decrease in the reaction rate, compared to **190a**. Lower enantioselectivities are observed in coordinating solvents such as acetonitrile, compared to dichloromethane, THF, toluene and ether.[117,118] While the catalyst loading can be as low as 0.2%, a loading of 1% has been used for most studies. Both symmetric and unsymmetric 1,1-disubstituted olefins are excellent enes in the



Scheme 49.

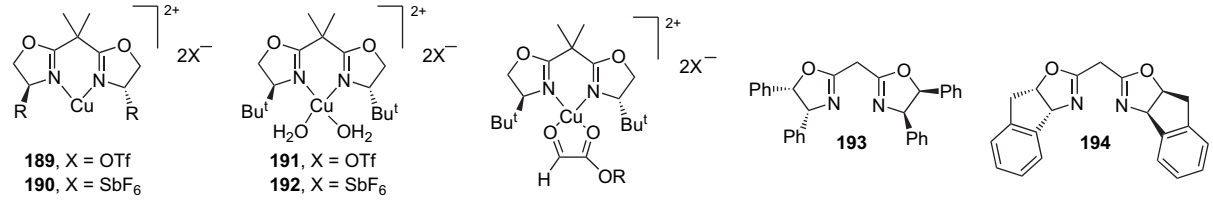
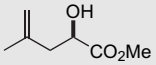
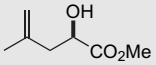
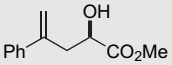
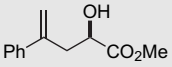
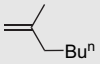
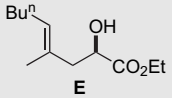
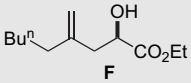
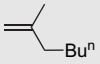
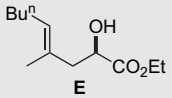
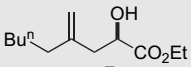
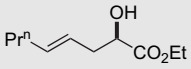
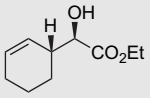
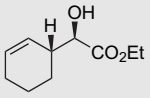
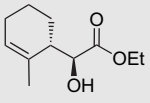
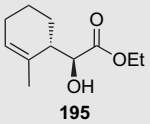


Figure 5.

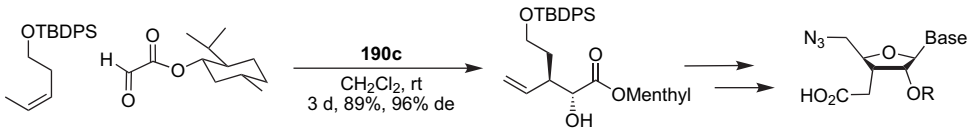
Table 4
Ene reaction with ethyl glyoxylate[117,118]

Entry	Ene	Catalyst (mol %)	Temp (°C)	Product	Yield (%) (*E*/*Z*)	ee (%)
1		**189c** (10)	0		92	92 (*R*)
2		**192** (1)	0		83	96 (*S*)
3		**189c** (1)	0		99	89 (*R*)
4		**192** (1)	0		97	93 (*S*)
5		**189c** (10)	25	 **E**	81	
				 **F**	10 (E) (57/4)	
6		**192** (1)	25	 **E**	90 (F) 68	91 (*R*)
				 **F**	26 (E) (54/4)	
7		**190a** (10)	15		74 (F) 96 (91/9)	96 (*S*) E 98, Z>90
8		**189c** (10)	0		70 (95/5)[a]	*endo* 94 (*R*)
9		**190a** (5)	0		95 (86/14)[a]	*endo* 98 (*S*)
10		**189c** (10)	25	 **195**	86 (89/11)[a]	*endo* 92 (*R*)
11		**192** (1)	25	 **195**	86 (78/22)[a]	*endo* 98 (*S*)

[a] *endo*/*exo*.

reaction with ethyl glyoxylate, although mixtures of products are generally observed with unsymmetric alkenes (entries 1–6). Improved regioselectivities are obtained with catalyst **189c**. With both catalysts, the regioselectivity favours removal of a methyl proton over a methylene (entries 5 and 6).

Although the catalyst loading had to be increased to 10 mol %, these bis(oxazoline) copper(II) complexes were effective catalysts for the ene reaction using some more difficult olefin substrates.[117,118] For example, some 1,2-disubstituted olefins could be used as the ene with ethyl glyoxylate using catalysts **189c** and **190a** (entries 8 and 9).

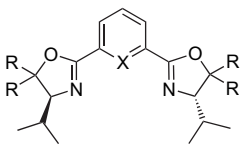


Scheme 50.

These reactions represent the first reported examples of catalytic, enantioselective ene reactions with these substrates. The degree of *endo* diastereoselectivity depends on the ligand and is better for **189c** than that for **190a**. Several less-reactive substrates required the use of the more reactive **190c** or did not undergo the ene reaction with these catalysts. For the reaction with ethyl glyoxylate catalysed by **189c** or **192**, the trisubstituted cyclic olefin, 1-methylcyclohexene, also gave excellent enantioselectivity, modest *endo* diastereoselectivity, and complete regioselectivity in favour of product **195** (entries 10 and 11). Catalyst **190a** was effective for the first catalytic, enantioselective ene reaction of a less nucleophilic monosubstituted alkene, 1-hexene, which reacted with ethyl glyoxylate to give the ene product with 98% ee and high *E* olefin selectivity (entry 7). Evans and co-workers have demonstrated that complexes **189c** and **192** can catalyse the depolymerisation of ethyl glyoxylate.[118] By using increased reaction times, they could obtain comparable yields and enantiomeric excesses using the polymeric solutions directly rather than needing to utilise freshly distilled ethyl glyoxylate.

The Evans catalyst has been used to catalyse the reaction between isobutylene and ethyl glyoxylate to prepare a starting material for the synthesis of a fragment of amphidinolide B1.[122] Rozners and Liu have reported the synthesis of several nucleoside 5′-azido 3′-carboxylic acids as monomers for the preparation of chemically modified RNA utilising the glyoxylate ene reaction with the Evans catalyst (Scheme 50).[123,124] In this case, they found it necessary to either purify the product by crystallisation or make use of double asymmetric induction utilising the chiral auxiliary methodology of Whitesell.[83–85] In the interest of large-scale production, these authors chose to use the less expensive menthyl glyoxlate rather than 8-phenylmenthyl glyoxylate, despite the potential for a greater level of asymmetric induction from the latter.

The copper complexes of pybox and related ligands (Fig. 6, **196a–c**) have also been investigated in the reaction of α-methylstyrene with ethyl glyoxylate. However, while such species do catalyse the reaction, no enantioselectivity (≤2% ee) has been observed.[120] Slightly better success was obtained with copper(II) complexes of chiral spiro-bis(oxazoline) ligands **197** and **198**, which give low-to-moderate yields and enantioselectivities in this reaction.[125,126] Fluorinated bis(oxazoline) ligands **199–202** have also been studied in the glyoxylate ene reaction.[127,128] The use of complexes of these ligands should improve the catalyst recycling and product isolation, as such reactions can be run as fluorous biphasic systems, with the perfluorinated species remaining in the fluorous solvent. In fact, catalyst **200** was recycled and re-used, to give results comparable to those obtained in the initial run. The C_1-symmetric ligands **200** and **202** (Fig. 7) gave better enantioselectivities than the C_2-symmetric ligands **199** and **201**. These two ligands catalysed the reaction of α-methylstyrene with ethyl glyoxylate to



196a X = N, R = Ph
196b X = N, R = H
196c X = CH, R = H

Figure 6.

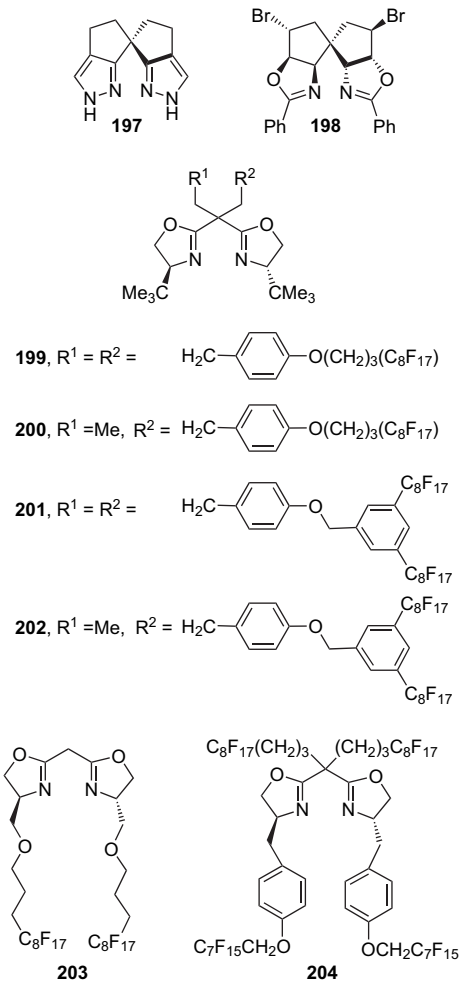


Figure 7.

give the ene products in 74% ee (65% yield) and 67% ee (99% yield), respectively. In the best case, the enantiomeric excess was 15% lower than that for the best results reported with Evans' ligands. This selectivity difference was attributed to a negative effect of the perfluorinated side chains. The authors suggested that this might be due to steric effects, since substituents at the bridge might reduce the bite angle and make it more difficult for the ligand to bind the copper ions. The better ligands are less sterically demanding, so the authors suggest that the ligand–copper cation complexation should be similar to that of Evans' system. The use of fluorinated ligands **203** and **204** has also been reported, but these ligands gave essentially no enantioselectivity.[129]

3.3.3. *Palladium, platinum and nickel catalysts*

Much recent attention has been focused on the development of palladium, platinum and nickel catalysts for the ene reaction (Fig. 8). Representative examples are shown in Tables 5 and 6. Mikami and co-workers became interested in investigating the use of chiral palladium catalysts in the ene reaction, due to the limitation in the scope of the titanium–BINOL catalyst systems to 1,1-disubstituted olefins.[130] Upon investigation of a variety of

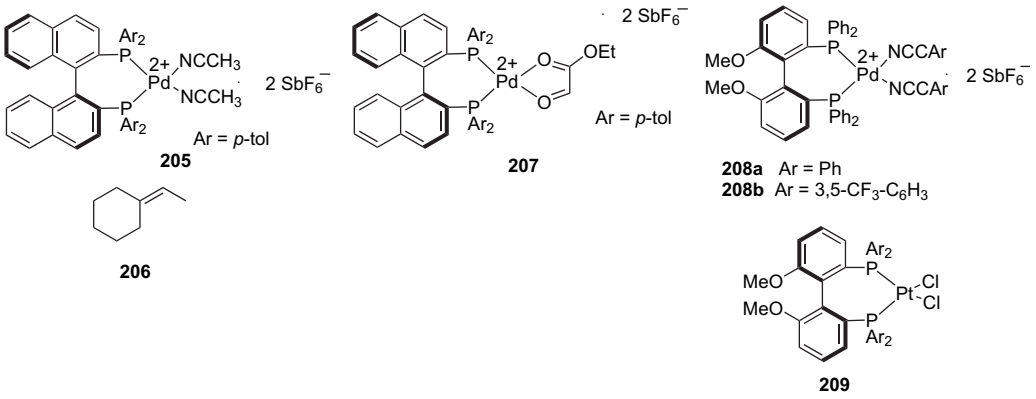


Figure 8.

Table 5
Reaction of methylenecyclohexene with ethyl glyoxylate

Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Solvent[h]	Yield (%)	ee (%)
1	**205** (10)	60	4	DCE	97	88
2	**208a** (2)	0	5	DCM	50	81
3	**208b** (2)	0	5	DCM	70	81
4	**209**,[a] Ar=Ph (2)	−50	5	DCM	36	74
5	**209**,[b] Ar=Ph (2)	−50	5	DCM	67	77
6	**209**,[a,c] Ar=Ph (2)	−50	5	DCM	77	77
7	**209**,[a,c] Ar=*p*-^{t}Bu–C_6H_4 (2)	−50	5	DCM	79	85
8	**209**,[a,c] Ar=*p*-MeOC_6H_4 (2)	−50	5	DCM	78	83
9	**210b**[d] (2)	0	5	DCM	62	71
10	**210c**[e] (5)	rt	5	DCM	25	10
11	**210c**[f] (5)	rt	5	DCM	52	76
12	**210b**[g] (5)	rt	5	DCM	88	70
13	[((*S*)-biphep)-Pd((*S*)-DABN)] (5)	rt	24	DCM	78	69
14	**212** N^N=DABN (2.5)	rt	24	DCM	86	81
15	**213a** N^N=(*R*)-DABN, (5.5)	rt	24	DCM	91	92
16	**214a**[a] (5)	rt	2	DCM	50	6
17	**214b**[a] (5)	rt	2	DCM	79	2
18	**214c**[a] (5)	rt	2	DCM	73	61
19	**214a**[a] (5)	rt	2	**215a**	73	67
20	**214b**[a] (5)	rt	2	**215a**	82	30
21	**214c**[a] (5)	rt	2	**215a**	74	70

[a] Activated with AgOTf.
[b] Activated with $AgSbF_6$.
[c] C_6F_5–OH as additive.
[d] Prepared from **210a** with $AgSbF_6$.
[e] Prepared from λ-[Pt(biphep)((*S*)-BINOL)] with HOTf.
[f] Prepared from λ-[Pt(biphep)((*S*)-BINOL)] with AgOTf.
[g] Prepared from λ-[Pt(biphep)((*S*)-BINOL)] with $AgSbF_6$.
[h] DCE=1,2-dichloroethane; DCM=dichloromethane.

Table 6
Reaction of α-methylstyrene with ethyl glyoxylate in CH_2Cl_2[a]

Entry	Catalyst (mol %)	Yield (%)	ee (%)
1	**213a**, N^N=(*R*)-DABN (5.5)	84	90
2	**213a**, N^N=(*R*)-DM-DABN (5.5)	43	45
3	**213b**, N^N=(*R*)-DABN (5.5)	92	27
4	**213c** N^N=(*R*)-DABN (5.5)	96	7
5	**213b** N^N=(*R*)-DM-DABN, (5.5)	80	44

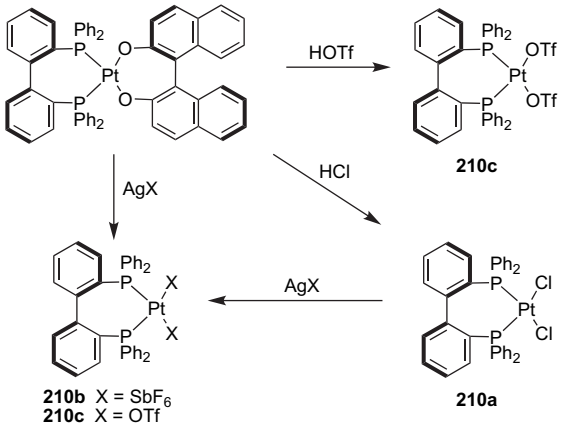
[a] Reaction time: 24 h at room temperature.

palladium(II) complexes and counterions, they determined that the combination of a palladium(II) dicationic species with a weakly coordinating anion such as BF_4^- or SbF_6^- led to good catalysts for the asymmetric glyoxylate ene reaction. The most effective complex was the chiral Tol-BINAP-coordinated palladium(II) diantimonate complex **205**, which proved more effective than complexes of either the less hindered BINAP or the more sterically bulky Xyl-BINAP. With optimised reaction conditions and reaction temperatures of 60 °C, catalyst **205** is useful not only for the glyoxylate ene reaction of 1,1-disubstituted olefins with enantioselectivities up to 88% (Table 5, entry 1), but also for the reaction of ethyl glyoxylate with the trisubstituted olefin, ethylidenecyclohexane **206**, to give the homoallylic alcohol product with up to 81% ee and low-to-moderate diastereoselectivity (up to 70% de, depending on the reaction conditions). These catalysts are not effective with monosubstituted olefins. The authors suggest that the dicationic palladium complex coordinates to both glyoxylate carbonyl oxygens to give the bidentate intermediate **207**. The structurally similar complexes **208a**,**b** also catalyse the reaction of methylenecyclohexane with ethyl glyoxylate, giving products with low-to-moderate yields and moderate enantioselectivities (Table 5, entries 2 and 3).[131]

Gagné and co-workers looked at the MeOBiphep platinum complexes **209** (Table 5, entries 4–8).[132] Ligands with aryl groups containing electron-donating substituents were superior to those containing electron-withdrawing groups. The most effective was the complex with Ar=*p*-^{t}Bu–C_6H_4 (entry 7). Similar to Mikami's palladium system, improved reactivity was observed upon activation with $AgSbF_6$, rather than activation with $AgBF_4$ or AgOTf (entries 4 and 5). However, the authors chose to optimise the reaction with triflate anion, citing concerns about the cost and molecular weight. Using the reaction of methylenecyclohexane with ethyl glyoxylate, they found that adding acidic phenols such as *m*-CF_3–C_6H_4–OH or C_6F_5–OH increased the rate and enantioselectivity of the triflate-based catalysts to a level higher than that of the hexafluoroantimonate-based catalysts while having no effect on reactions using the hexafluoroantimonate catalysts (entries 6–8). The effect of the additive was attributed either to a kinetic role, by catalysing the rate of product and/or counterion substitution at the metal centre, or to a thermodynamic role, by reducing the coordinating ability of the counterion by stabilisation of the solvent-separated ion pair. In either case, the effect would be expected to be less dramatic with hexafluoroantimonate as it is both kinetically more labile and has a lower propensity to hydrogen bond than triflate. Furthermore, water is a competitive inhibitor of catalysis, and the acidic phenols lower its effects by sequestering traces of water in a hydrogen-bonded network, thereby increasing reproducibility of the reactions.

Gagné and co-workers also investigated complexes **210a–c**, prepared from the conformationally unstable (*tropos*) biphep ligand.[133] Although the enantiomers of the biphep ligand interconvert rapidly at room temperature, coordination to a substitutionally inert platinum(II) centre slows this process. Thus, they were able to use enantiomerically pure BINOL (which is conformationally stable or *atropos*) to resolve Pt(biphep)((*S*)-BINOL) complexes in high diastereomeric purity. The separated diastereomers could be activated with HOTf to give **210c** as a single enantiomer (Scheme 51). Alternatively the BINOL complexes could be treated with HCl to obtain the corresponding enantiopure

Pt(biphep)Cl_2 complexes (**210a**) with retention of configuration. These species could then be activated with silver salts to generate the dicationic species **210b** or **210c**. Compound **210b** was shown to be an active catalyst for the ene reaction. Addition of methylenecyclohexane to ethyl glyoxylate catalysed by this compound gave the desired product in high conversion and moderate enantiomeric excess at room temperature (Table 5, entry 9). Luo and Schumann have shown that direct activation of the λ-[Pt(biphep)(*S*)-BINOL] complex with HOTf to give the dicationic λ-[Pt(biphep)$(OTf)_2$] **210c** resulted in only a low yield (25%) and enantioselectivity (10%) for this same ene reaction (Table 5, entry 10).[134] However, direct activation of the λ-[Pt(biphep)((*S*)-BINOL)] complex with AgOTf or $AgSbF_6$ allowed for increased yields and enantioselectivities (entries 11 and 12). The authors attribute the difficulties with HOTf activation to incomplete reaction and complications due to unreacted HOTf. This system, activated by silver salts, was also useful for the ene reaction using phenyl glyoxal as the enophile.



Scheme 51.

Mikami has used the enantiodiscriminating agent DABNTf (Fig. 9, DABN=diaminobinaphthyl, **211**) to prepare a variety of palladium complexes such as [Pd((*S*)-biphep)((*S*)-DABN)] or [Pd((*P*,*S*,*S*)-tetraphos)((*S*)-DABN)] (**212**), which could be used directly as catalysts in the asymmetric ene reaction of

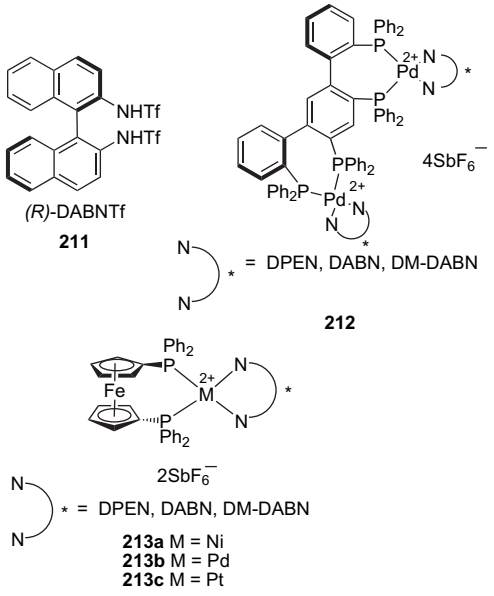


Figure 9.

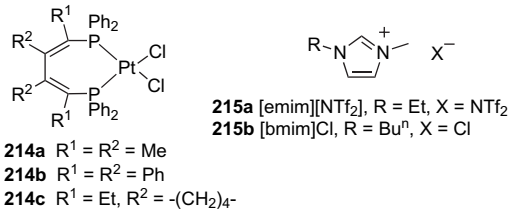


Figure 10.

methylenecyclohexane with ethyl glyoxylate to give the ene products in moderate yields and enantioselectivities (Table 5, entries 13 and 14).[135]

This type of methodology was also used with chirally dynamic DPPF (diphenylphosphinoferrocene) ligands.[136] Enantio- and diastereomerically pure nickel, palladium and platinum complexes **213** were obtained by coordination of enantiopure DABN to M(DPPF)$(SbF_6)_2$ to control axial chirality. For the reaction of ethyl glyoxylate with α-methylstyrene, complexes **213b**,**c** (N^N=DABN) gave nearly quantitative yields but low enantiomeric excesses, while 3,3-dimethyldiaminobinaphthyl (DM-DABN) gave improved enantioselectivities but lower yields (Table 6, entries 3–5). The more Lewis acidic nickel complexes were more effective in terms of both enantioselectivity and catalytic efficiency. For example, the DABN–nickel complex **213a** gave 84% yield and 90% ee in this reaction, while DM-DABN gave inferior results in this case (Table 6, entries 1 and 2). Unlike the biphep complexes **210**,[133,137] the palladium and platinum DPPF complexes do not retain conformational stability upon decomplexation of the chiral diamine ligand. Reactions of DABN–nickel complexes without the DPPF ligand gave lower enantioselectivities.

The platinum complexes **214a**–**c** of *tropos* ligand NUPHOS (Fig. 10) can also be obtained by resolution with BINOL.[138] λ- or δ-[Pt(NUPHOS)((*S*)-BINOL)] complexes can be cleaved with either HCl to generate the dichloride, which can be activated with silver salts, or with HOTf to generate the triflate complex directly. The performance of these catalysts in dichloromethane is comparable to that observed with BINAP complexes (Table 5, entries 16–18). The catalyst precursor and the method of generating the active species had an effect on the glyoxylate ene reactions carried out in dichloromethane. Lower yields and enantioselectivities were obtained for the catalysts prepared by reaction of the BINOL complex with HOTf, possibly due to the presence of liberated BINOL. The ene reactions could also be carried out in the ionic liquids shown in Figure 10. The reaction of methylenecyclohexane with ethyl glyoxylate or phenyl glyoxal gave significantly higher enantioselectivities in [emim][NTf_2] (1-ethyl-3-methylimidazolium trifluorosulfonylimide) (**215a**), compared to dichloromethane and, in general, higher yields were observed (Table 5, entries 19–21). This effect was attributed to both a slower rate of racemisation of the catalyst in the ionic liquid, compared to dichloromethane, and a faster rate of the carbonyl ene reaction.[138] The active catalyst was again proposed to involve two-point binding of the dicarbonyl substrate to give a square planar complex similar to that proposed by Evans and co-workers in the copper systems.[117]

3.3.4. Lanthanide catalysts

Complexes of several lanthanides (Lns), prepared from pybox ligands **216** (Fig. 11) and $Ln(OTf)_3$, have been shown to catalyse the glyoxylate ene reaction with moderate yields and enantiomeric excesses of up to 54%.[139] The best results were obtained with $Yb(OTf)_3$. While 2-arylalkenes as the ene component gave only low-to-moderate enantioselectivities and yields, 1,1-dialkyl-olefins failed to react with these catalysts. The reactions were faster without the ligand, a phenomenon also observed in our own

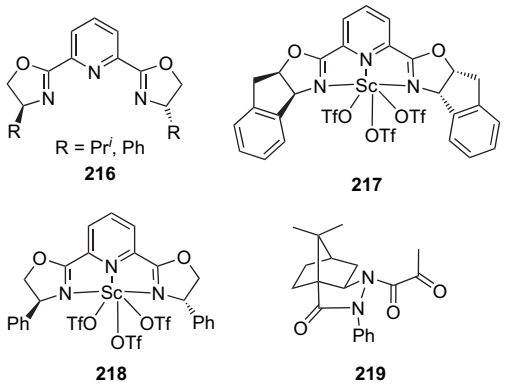


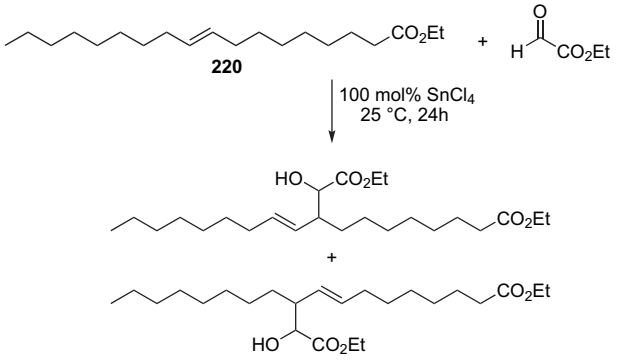
Figure 11.

laboratory for lanthanide-catalysed ene reactions using both pyridyl alcohol and diol ligands.[140] It is likely that coordination of the ligand lowers the Lewis acidity of the metal complex.[139] For α-methylstyrene, the pybox–Yb complex (R=Ph) gave better results with ethyl glyoxylate than with either methyl or butyl glyoxylate. Double asymmetric induction using menthyl glyoxylate gave a comparable yield to ethyl glyoxylate, with a diastereomeric excess of 81%.

3.3.5. Other metal catalysts

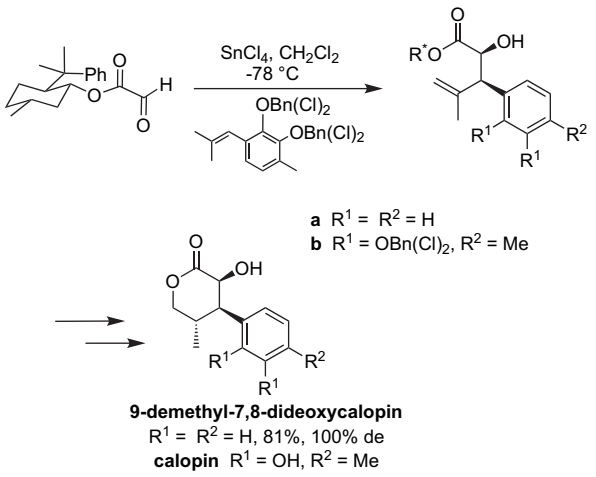
Chiral scandium complexes **217** and **218** (Fig. 11) are also active catalysts for the ethyl glyoxylate and *N*-phenyl glyoxamide ene reactions, although no details for the glyoxylate reaction were reported.[141] The glyoxamide ene reaction proceeded with excellent enantioselectivity. The use of *N*-glyoxyloyl camphorpyrazolidinone **219** as an enophile containing a chiral auxiliary in the $Sc(OTf)_3$-catalysed ene reaction has been reported,[142] and the yields and diastereoselectivities were moderate to good. For example, the reaction with α-methylstyrene proceeded in 87% yield with 94% de.

Stoichiometric quantities of $SnCl_4$ have been used to catalyse the ene reaction of ethyl oleate (**220**) with ethyl glyoxylate in 67% yield (Scheme 52).[143] A mixture of regioisomers was obtained. The need for high concentrations of the Lewis acid was attributed to the fact that the carbonyl group of **220** also complexes to the Lewis acid.



Scheme 52.

Several of the reported synthetic applications of the ene reaction have relied on the Whitesell methodology,[83–85] utilising achiral $SnCl_4$ to catalyse the reactions of alkenes with 8-phenylmenthyl glyoxylate. For example, Steglich and co-workers have reported syntheses of the model fungal metabolite, (+)-9-demethyl-7,8-dideoxycalopin[144] and the mushroom metabolite (+)-calopin (Scheme 53).[145]



Scheme 53.

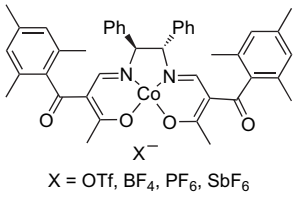


Figure 12.

Chiral β-ketoiminato-cobalt(III) complexes **221** and their derivatives catalyse the reaction of 1,1-substituted alkenes with benzyl glyoxylate and phenyl glyoxal (Fig. 12).[146,147] Neutral cobalt(II) and cobalt(III) complexes did not catalyse the reaction. As with other metal catalysts (see above), the counterion had a large effect on the yield and enantioselectivity, with the best results obtained with the less-coordinating hexafluoroantimonate ion. Enantiomeric excesses as high as 85% (91% yield) were obtained for the reaction of α-methylstyrene with benzyl glyoxylate catalysed by 5 mol% **221**, slightly lower than the results for the analogous reaction with phenyl glyoxal (94% ee, 95% yield). The results were highly dependent on both the solvent and the temperature, with donor solvents such as acetonitrile and ether giving decreased catalytic activity, due to their ability to coordinate to the copper centre. The best solvent was chloroform.

The Lewis acidic ionic liquid, [bmim]Cl (1-butyl-3-methylimidazolium chloride) **215b**, composed of $AlCl_3$ and 1-butyl-3-methylimidazolium chloride, can be used as both the solvent and the catalyst in the ene reaction of α-methylstyrene and ethyl glyoxylate. The reaction proceeds in 95% yield and the solvent can be re-used several times.[148]

The highly reactive ene, 2-methylene-2,3-dihydrofuran **137**, can undergo reaction with ethyl glyoxylate at 0 °C in dichloromethane in the absence of any catalyst (89% yield). This reactive species can also react with a variety of aldehydes, although a Lewis acid catalyst is required for these enophiles.[149]

3.3.6. Polymer-supported reactions

A polymer-supported Ti–BINOL catalyst **222**, based on the Mikami and Nakai titanium BINAP catalysts, catalyses the ene reaction of α-methylstyrene and methyl glyoxylate to give the desired homoallylic alcohol product in 53% yield and 95% ee. In the presence of 4 Å molecular sieves (MS), the yields increased to quantitative, while maintaining the high enantiomeric excesses (Fig. 13). The catalyst was recovered and recycled twice without substantial

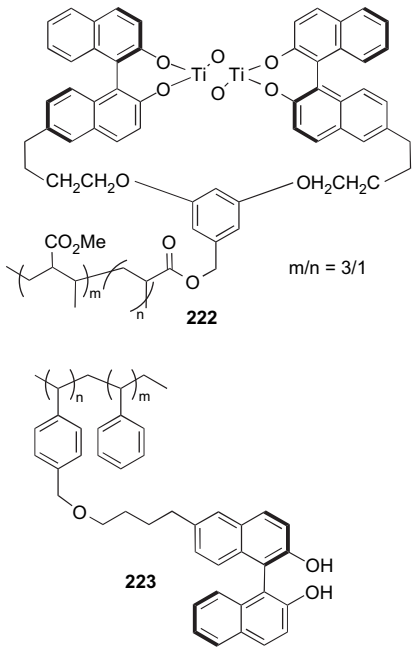


Figure 13.

loss of enantioselectivity, but with slightly reduced yield by the third use.[150] Polymer-bound versions of these types of titanium catalysts have also been prepared by self-assembly of non-cross-linked polystyrene polymers **223**, containing BINOL groups, with $Ti(O^iPr)_4$ and H_2O.[151] In this case, formation of the μ-oxo-titanium complexes would cross-link the chains. Only moderate yields and enantioselectivities were obtained for the reaction of α-methylstyrene and ethyl glyoxylate. The best results (68% yield and 84% ee) were obtained in ether with n/m=1/6. These catalysts could be recycled and re-used repeatedly, with little change in either yield or enantioselectivity.

A different approach to supported μ-oxo-titanium catalysts involved the preparation of insoluble titanium catalysts prepared by the reaction of multidentate ligands such as **224**–**227** with $Ti(O^iPr)_4$, reported independently by both Sasai[152] and Ding (Fig. 14).[153,154] Sasai reported that the reaction of ethyl glyoxylate with α-methylstyrene catalysed by a polymer prepared by the self-assembly of the enantiomer of **224**, $Ti(O^iPr)_4$ and water (1/2/4) proceeded in 81% yield with 90% ee.[152] This polymer could be recycled and re-used with no deterioration of enantioselectivity, although the yields decreased with each successive use. Ding and co-workers prepared polymers **228**, based upon Mikami's titanium–BINOL complexes **182**, by mixing BINOL ligands **224**–**227** with $Ti(O^iPr)_4$ in a 1/1 ratio in dichloromethane at room temperature.[153–155] The linker had a large effect on the glyoxylate ene reaction, which was attributed to a change in the supramolecular structure of the assembly upon changing the spacer, causing a change in the selectivity and activity. The best results were obtained with the ligands **224** and **226**, containing an electron-withdrawing bromo substituent. Polymers of these ligands gave >99% yield and 96% and 95% ee, respectively, in the ene reaction of α-methylstyrene with ethyl glyoxylate. Polymers of ligand **227**, on the other hand, showed poor catalytic activity and enantioselectivity. Addition of 4 Å MS had no significant effect on the reaction, which could also be carried out under solvent-free conditions. The catalyst could be recycled and re-used, although both the catalytic activity and enantioselectivity dropped off with each subsequent use. This deterioration was attributed to partial decomposition of the assemblies during catalysis.

Bis(oxazoline)-modified CuH zeolite Y catalysts have been demonstrated to be efficient catalysts for ene reactions of various alkenes with ethyl glyoxylate, giving moderate yields and moderate-to-high enantioselectivities, although long reaction times were required for some substrates.[156] These catalysts, which are prepared by the addition of bis(oxazoline) ligands **229**–**231** (Fig. 15) to Cu-exchanged zeolite Y, could also be used successfully to catalyse the reaction of α-methylstyrene with less-reactive enophiles, such as methyl pyruvate and imine compounds. The catalysts can be recovered and re-used without loss of activity if the catalyst is washed with ethyl acetate prior to re-use.

Another approach to recyclable catalysts has involved nano-sized gold particles with two alkyl chains, one terminating with alkyl sulfides and the other terminating with alkyl sulfides attached to copper(II) complexes of bisoxazolines **232**.[157] Although these gold particles are dispersed in dichloromethane, they aggregate in hexane, allowing for removal by filtration. Ene reactions of α-methylstyrene with ethyl glyoxylate gave 99% yield and 86% ee. These catalysts were recycled up to four times with retention of ee and only slight loss of yield with each re-use.

Insoluble polymer-bound bis(oxazoline) ligand **233** (Fig. 15), when complexed with $Cu(OTf)_2$, has been investigated as a catalyst for the glyoxylate ene reaction, along with complexes of the soluble model ligand **234**.[158] Under conditions analogous to those used for the monomeric parent (Evans' **189c**), less sterically hindered alkenes gave similar reaction rates and enantioselectivities with **233** and **234** as they did with **189c**. Enantioselectivities were lower with

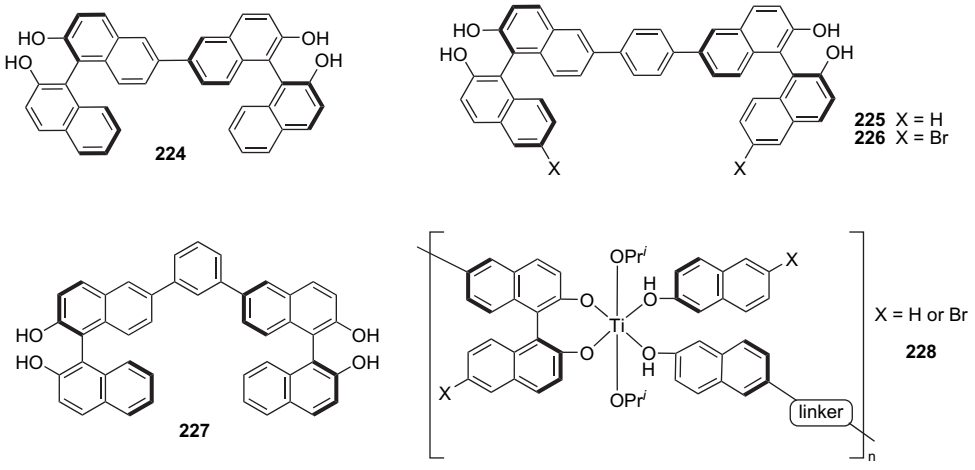


Figure 14.

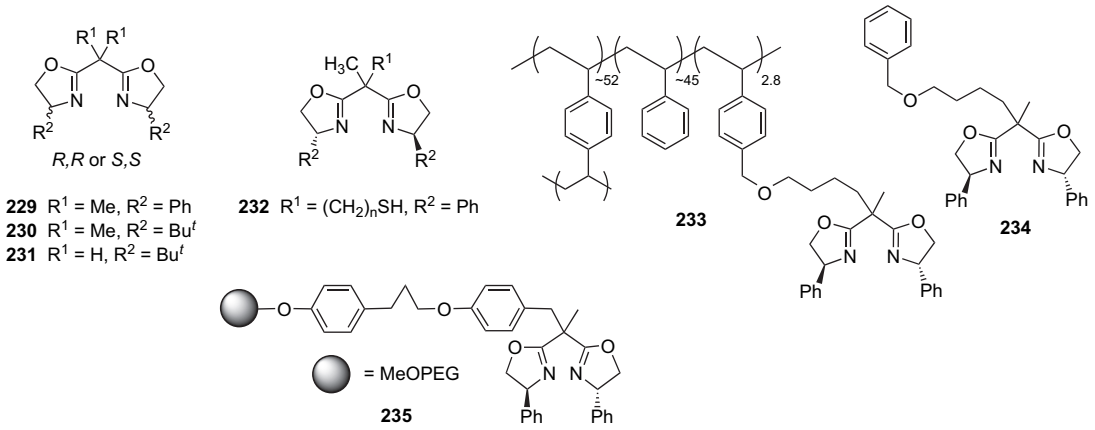


Figure 15.

more sterically hindered olefins. Catalysts derived from **233** could be recycled and re-used multiple times in either batch-mode or continuous-flow conditions, with some loss of catalytic activity but not enantioselectivity. Functionalised 1,1-disubstituted olefins and the trisubstituted 1-methylcyclohexene could also be used as the ene component with this catalyst, although longer reaction times were required. In many cases for smaller olefins, the degree and sense of asymmetric induction were similar to that obtained with **189c**.

Modified poly(ethylene glycols) MeOPEGs (monomethyl ethers of PEG_{5000}) with immobilised bis(oxazoline) ligands (Fig. 15, **235**) have also been prepared. When complexed to copper(II), these species catalysed the ene reaction of ethyl glyoxylate with α-methylstyrene (96% yield, 95% ee) and methylenecyclohexane (90% yield, 87% ee). Under the same reaction conditions, the unsupported Evans catalyst gave 99% yield for both substrates, with 89 and 87% ee, respectively.[159] The catalyst could be recovered and re-used, although slightly lower yields and enantioselectivity were obtained. Merrifield polymer-supported bis(oxazoline)-copper(II)-catalysed ene reactions have also been reported, although only low enantiomeric excesses and moderate yields were obtained.[160]

Gagné and co-workers have prepared molecularly imprinted polymers prepared by the polymerisation of Pt((*S*)-MeOBiphep)X_2 species **209** and **236** containing *p*-styryl groups on the aryl substituents (Fig. 16). Pt((*S*)-MeOBiphep)Cl_2 polymers can be obtained by removal of the BINOL with HCl from polymers of **236**. The resulting polymer can be activated by $AgSbF_6$ in much the same way as the monomeric versions of these species.[161] These species show lower activity and lower enantioselectivity than the analogous catalyst in solution. Studies aimed at poisoning the most open and less selective sites revealed that while the cavity shape controls binding and poisoning, it is the chiral diphosphine that controls the reaction enantioselectivity.

Kobayashi and co-workers have approached the difficulties of working with glyoxylates by utilising polymer-supported analogues.[162] They have prepared polymer-supported glyoxylate on tartrate resin, although the supported glyoxylate could only be isolated in its monohydrated form **237**, rather than the aldehyde form (Fig. 17).

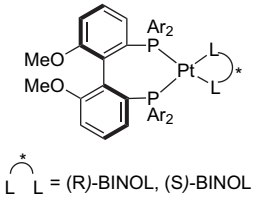


Figure 16.

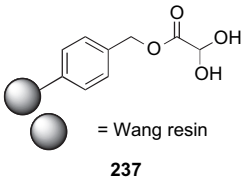


Figure 17.

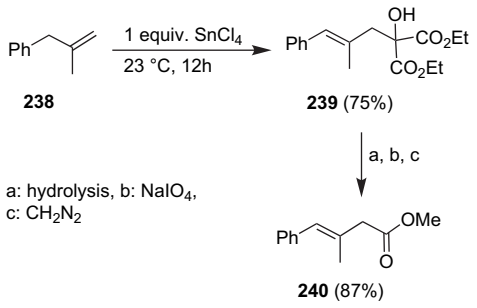
This polymer was tested in the ene reaction with α-methylstyrene using several catalysts. $Yb(OTf)_3$ gave higher yields than $Sc(OTf)_3$, but a catalyst loading of 50% was required in order to get a good yield (81%) upon reductive cleavage of the ene product from the polymer support, and $SnCl_4$ and $TiCl_4$ failed to give any ene product. The trisubstituted olefin 1-methylcyclohexene could also be used as the ene with the supported glyoxylate, but stoichiometric $Yb(OTf)_3$ was required and the product was obtained in only 59% yield.

3.4. Intermolecular ene reactions of activated ketones

Intermolecular ene reactions of ketones are rare, despite the considerable potential of this method as an atom-efficient tertiary alcohol synthesis. Some time ago, Snider demonstrated that even unactivated ketones such as cyclohexanone can take part in these reactions in the presence of stoichiometric amounts of an $AlEtCl_2$ promoter. However, yields were generally below 50%, and the reactions were extremely sensitive to the substrates employed. These important early results have, therefore, not been transformed into a useful methodology for intermolecular ene reactions.[163]

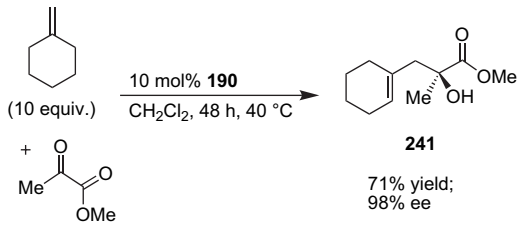
If the ketone possesses two electron-withdrawing groups, however, useful results can be obtained both thermally and under Lewis acid catalysis. For example, Salomon and co-workers have shown that a wide range of alkenes (including less nucleophilic alkenes) will undergo thermal reaction with diethyl oxomalonate after several days at 180 °C. The use of stoichiometric $SnCl_4$ was investigated in some examples where the thermal reactions were less satisfactory and found to promote the reactions at room temperature or below as shown in the transformation of **238** to **239**. This is quite a useful methodology, since a subsequent oxidative decarboxylation reaction converts the ene products into allyl carboxylic acids.[164] An example is the formation of compound **240** from **238** (Scheme 54).

Evans reported the first example of a catalytic asymmetric ketone ene reaction. The reaction of 1,1-alkenes with ethyl pyruvate was much more difficult to catalyse than the gyloxylate ene reactions studied with the same catalysts. Thus, catalyst loadings need to be higher and it is also important that the 1,1-disubstituted

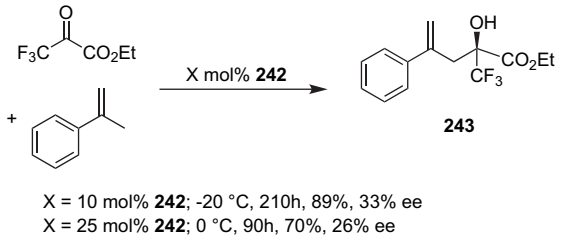


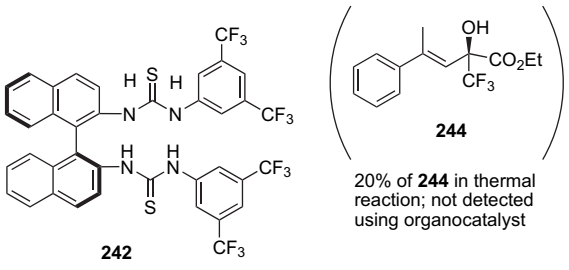
Scheme 54.

alkene is used in excess. However, using 10 mol % of the Cu catalyst **190** and 10 equiv of methylenecyclohexane, good yields of essentially enantiopure **241** could be obtained (Scheme 55). Similarly, excellent ees and high yields could be realised using several other 1,1-alkenes, but none of the less-reactive alkenes were reported.[165]



Scheme 55.





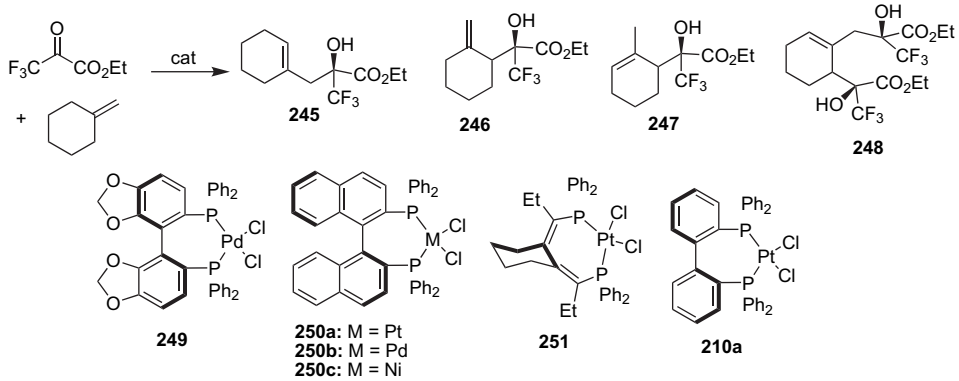
Scheme 56.

We have screened a number of highly Lewis acidic catalysts in the ene reaction of other ketone substrates with no success. A step change in the catalyst performance is required, even for partially activated electron-deficient ketones to co-operate in intermolecular asymmetric ene reactions. An exception is the highly activated trifluoropyruvate. Our own experiments show that this ketone reacts with α-methylstyrene at a significantly faster rate than ethyl glyoxylate. Indeed, the trifluoropyruvate ene reaction takes place slowly at room temperature without a catalyst or more rapidly in catalyst-free reactions using microwave heating. The double-bond isomer **244** is sometimes observed in significant quantities using thermal activation. The use of the very mildly Lewis acidic organocatalyst **242** allowed the first organocatalytic carbonyl ene reaction to be observed, albeit that **243** is formed with modest enantioselectivity and low turnover frequencies (Scheme 56). In the organocatalytic procedure, none of the double-bond isomer was detected.[166]

More satisfactory asymmetric ene reactions to trifluoropyruvate have been accomplished using dicationic Pd complexes (Scheme 57). The dicationic Pd(II)–SEGPHOS complex **249**, in combination with silver salts of weakly coordinating anions, has proved to be effective for the reaction of 1,1- and 1,2-disubstituted, trisubstituted and monosubstituted olefins with ethyl trifluoropyruvate (Table 7, entries 1 and 6–9).[167] High yields and enantioselectivities were obtained, along with high *E* selectivity and high *anti* diastereoselectivity. In the reaction of 1,1-alkenes such as methylenecyclohexane with trifluoropyruvate, Pt and Ni/BINAP complexes **250a** and **250c** were found to be highly enantioselective, but several side products were also detected. In the case of the methylenecyclohexane ene reaction, **246**–**248** were observed in very significant amounts alongside the expected product **245**, reducing the applicability of these catalysts. The palladium system **250b**, on the other hand, gave much higher selectivity and, in the case of methylenecyclohexane, only produced the desired isomer in 93% ee (Table 7, entries 2–4). The unusual enantiopure NUPHOS–Pt complexes **251**, when used in combination with $AgSbF_6$, promoted the ene reactions of several alkenes with excellent ees, although in some cases (Table 7, entry 5) several double-bond isomers could be detected in a similar manner to the Pt/BINAP catalysts.[168]

Mikami and co-workers have used the resolved Pt catalyst **210b** in the ethyl trifluoropyruvate ene reaction with monosubstituted alkenes to give products in high yields with both high enantio- and high *E* selectivity (Table 7, entries 10 and 11). The resolution of the complex derived from the *tropos* ligand was accomplished using enantiodiscriminating agent **211** to obtain configurationally stable biphep–Pt complexes **210a**, which, upon activation with $AgSbF_6$, could be used in the ene reactions.

It can be seen that intermolecular ene reactions of ketones remain a challenge. However, the reactions will proceed in high yield and enantioselectivity for some of the more highly activated



Scheme 57.

Table 7
Reaction of various enes with ethyl trifluoropyruvate in CH_2Cl_2

Entry	Catalyst (mol %)[a]	ene	Temp (°C)	Time (h)	Yield (%)	ee (%) (% *E*)
1	**249** (5)		rt	0.25	100	96
2	**250a** (5)		rt	0.5	38[b]	77
3	**250b** (5)		rt	0.5	100[c]	93
4	**250c** (5)		rt	0.5	57	74
5	**251**		rt	0.15	43[d]	70
6	**249** (5)		rt	0.5	100	96 (100)
7	**249**(5)		rt	0.5	79	97 (100)
8	**249** (5)	**206**	rt	0.5	80	84 (98/2)[e]
9	**249** (5)		rt	1	64	92 (91/9)[e]
10	**210b** (5)		−20	1	83	98 (100)
11	**210b** (5)		−20	1	92	98 (100)

[a] Catalyst used in combination with $AgSbF_6$.
[b] Conversion: 100% with a ratio of **245**/**246**/**247**/**248** of 38/47/10/5, ee referring to the ene product.
[c] Conversion: 100% with a ratio of **245**/**246**/**247**/**248** of 57/40/2/1, ee referring to the ene product.
[d] Conversion: 100% with a ratio of **245**/**246**/**247**/**248** of 43/55/1/1, ee referring to the ene product.
[e] *anti*/*syn* ratio.

substrates. If significant progress could be made in the intermolecular ene reactions of ketones, this would be an immensely valuable route to (enantioenriched) tertiary alcohols. It remains to be seen if such developments will materialise.

4. Summary

This report has aimed to give the synthetic chemist an appreciation of the relative reactivity of enophiles and alkenes such that an informed decision regarding the viability of their use in a synthesis can be made. The examples chosen do not represent comprehensive coverage of the area, but, hopefully, do serve to cover most types of carbonyl ene reactions that might be used in synthesis. Some fascinating and elegant syntheses have already been accomplished using ene methodology, and it is envisaged that the coming years will see further interesting applications and, hopefully, progress on some of the more challenging reactions. The main problem with ene reactions is the high activation barrier of many of the reactions, which often limits the scope to specific enes and enophiles. In addition to guiding chemists towards reactions that proceed effectively, we hope this review has also highlighted some of the challenges that lie ahead.

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Biographical sketch

Matthew L. Clarke carried out his Ph.D. (1999) at the University of Bath, under the supervision of Professor Jonathan Williams. From 1999–2001, Clarke worked as a research fellow in homogeneous catalysis in collaboration with Professors J. Derek Woollins and David Cole-Hamilton, before being appointed to a fixed term lectureship at the University of Bristol in 2001. In 2003, Clarke moved back to the University of St. Andrews taking up a permanent independent post as a Lecturer in Chemistry (and as Reader since Summer 2008). The Clarke group's recent research is diverse, but a main theme has been trying to develop highly efficient, environmentally benign, catalytic synthetic methodology. The research projects therefore incorporate catalysis, organometallic, organophosphorus, coordination, asymmetric, physical organic and synthetic organic chemistries. In 2006, Clarke was awarded the 2005 Royal Society of Chemistry's Meldola medal, is one of the 2008 recipients of the Thieme Journals award for promising Organic Chemists and most recently has been awarded the Royal Society of Edinburgh/Scottish Government 'Supports Research' Fellowship for 2008/9.

Marcia B. France graduated from MIT in 1988, where she did undergraduate research on asymmetric epoxidation and asymmetric osmylation in the laboratory of Dr. K. Barry Sharpless. She was an NSF Predoctoral Fellow at Yale University, where she received her M.S. in 1990 and at Caltech, where she received her Ph.D. in 1995. Her doctoral work under the direction of Dr. Robert H. Grubbs involved the development of ruthenium carbene catalysts for applications in olefin metathesis. She joined the Faculty at Washington and Lee University in 1994, where she is currently Professor of Chemistry. She has been a Visiting Associate Professor at Stanford University and a Visiting Research Scientist at the University of St. Andrews, doing collaborative research with Dr. Matthew L. Clarke. Her current research interests include asymmetric cyclopropanation, olefin metathesis and the design of novel *N,N* and *P,N* ligands for asymmetric catalysis.