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Ambifunctional cooperative catalysts

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Contents

1. Introduction

Synthesis by means of catalytic processes is one of the most rapidly evolving areas of preparative chemistry.[1] The incentives for such strategies are manifold, since they can be highly economical, potentially more environmentally benign and often require less tedious purification. The present goals are the development of more efficient and selective reagents for a greater variety of organic transformations. It is clear that far superior catalysts exist in nature than those which have been developed by chemists, regardless of the significant achievements that have been made.[2] The mechanism of action of many enzymes involves the cooperation of two or more reactive centres, yet man-made catalysts rarely exploit this approach, predominantly utilising just one centre.[3,4] It is considered that by imitating nature, the principle of *multifunctional* catalysis could offer many advantages over existing strategies.[5,6]

The majority of catalysts function in one of two ways. The first is to bind to a reactant, thus both activating it and inducing a chiral environment, which allows a second reagent to attack in a selective fashion.[7] Alternatively, two reactants simultaneously bind to the catalyst thus '*intramolecularising*' the reaction, which due to their proximity allows the substrates to react quickly and selectively.[8] Whilst both strategies have been exploited very successfully, multifunctional catalysts could offer a number of possible advantages. Catalysts that contain both Lewis acidic and basic sites could activate both reagent and substrate in a controlled environment or, alternatively, one reactive centre could be used to bind to the substrate whilst the second active site performs the chemical transformation. The presence of two metal centres, with their individual characteristics, would increase the scope of reactions that could be performed. Such synergistic cooperation between two functionalities would be analogous to enzymatic reactions if carried out on a chiral template.

In organising this review an attempt has been made to classify the catalysts according to the mode of cooperation

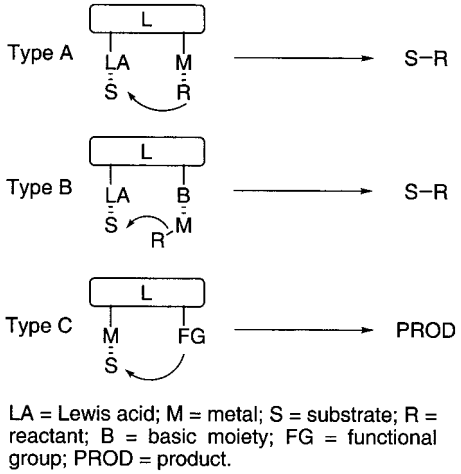

Figure 1. Three types of multifunctional catalysts.

Keywords: asymmetric reactions; catalysis; catalysts.

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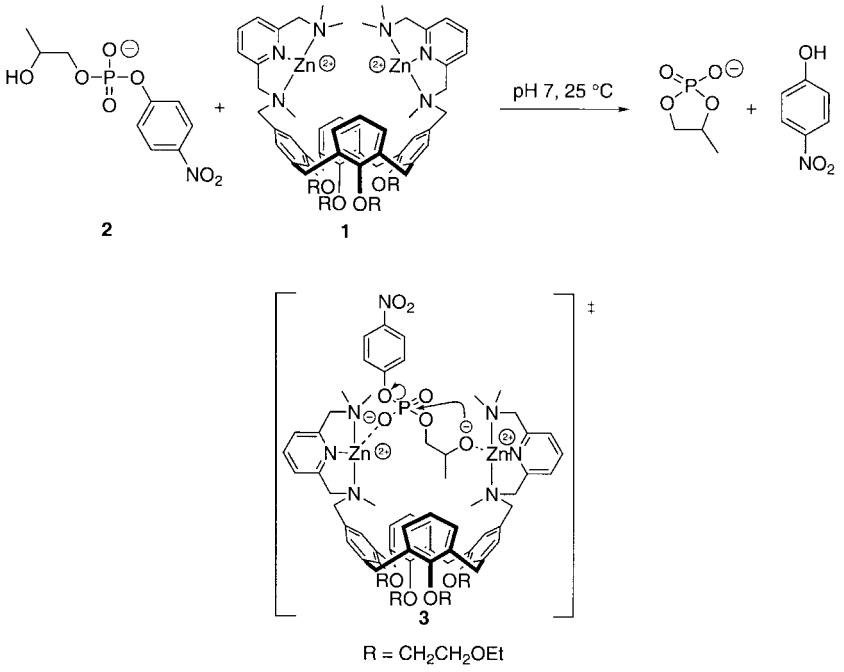
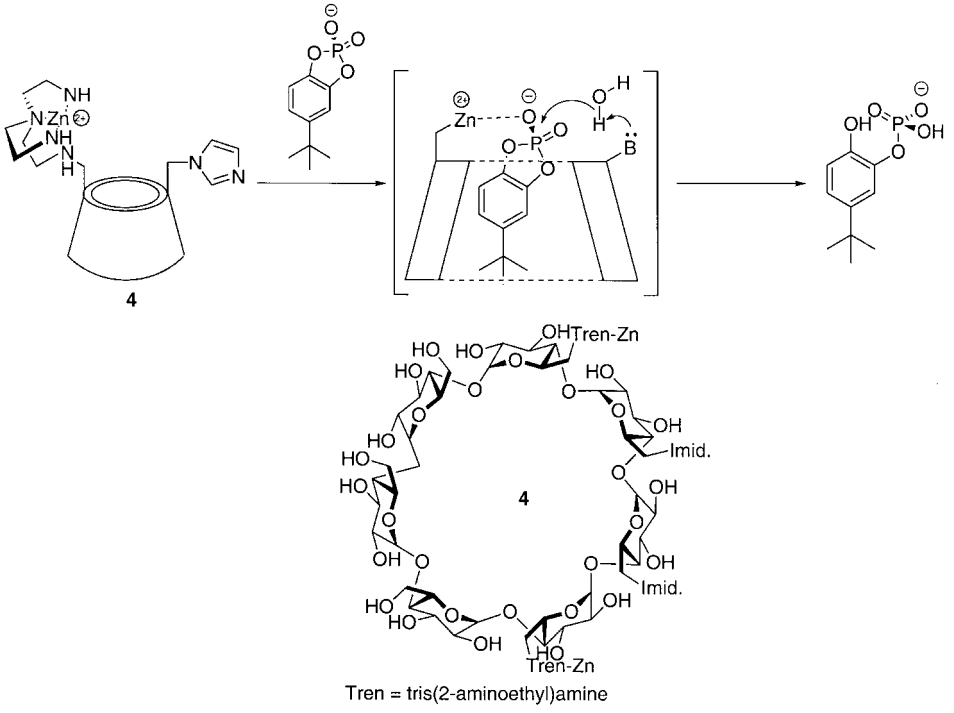


Scheme 1. Calix[4]arene-based dinuclear phosphoesterase mimic.

between the various reactive sites. Such classifications are only intended as guidelines and in many cases are open to a number of possible interpretations. Three reactivity patterns have been tentatively defined (Fig. 1).[9]

In the first (Type A), two metals (**LA** and **M**) are coordinated to the same ligand and in turn are available to bind to both the substrate (**S**) and the reactant (**R**) during the catalytic process. The metals can either be the same, *homobimetallic* compounds, as found in many hydrolase mimetics[4,10] or different, *heterobimetallic* compounds, as pioneered by Shibasaki.[5,11] The second class of catalysts contains a Lewis acidic centre (**LA**) and a basic site (**B**) in the same catalyst complex (Type B). Typically the substrate binds to the Lewis acid and a stoichiometric amount of a second metal reagent (**MR**) is required to bind to the base and deliver the reagent in a selective manner. The third class requires the substrate to bind to the complex prior to



Scheme 2. Bifunctional phosphohydrolase mimic.

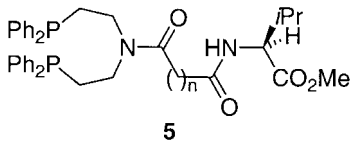


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Figure 2. Kumada's first generation bifunctional catalysts.

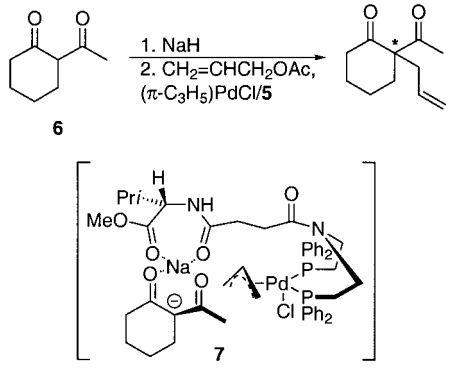
interaction with a functionality (**FG**) on the ligand (Type C). Although Type C catalysts could readily be incorporated into the previous two catalyst types in many cases, they deserve special mention due to the publication of some rational approaches and the great potential they offer.

This review will concentrate on small molecule catalysts that perform synthetically useful or hard to achieve transformations. Enzyme mimics (and supramolecular catalysts) will be briefly introduced to illustrate the evolution of this strategy. An in-depth discussion of such topics is beyond the scope of this review as they have been comprehensively covered in a number of articles.[3,4,12]

2. Bifunctional metalloenzyme mimics

In nature many enzymes possess a number of functional groups at the active site. These groups perform many important roles including substrate recognition, activation and stabilisation of transition states. Many enzymes such as RNA phosphohydrolases employ two metals in close proximity that operate in unison. The metal ions act as both a Lewis acid in activating the substrate and as a base in activating the nucleophile and, as such, they could be considered to be Type A multifunctional catalysts. In trying to mimic metalloenzymes it is possible to see the advent of multifunctional catalysis. A recent representative example by Reinhoudt is shown in Scheme 1.[13]

It was shown that **1** catalysed the cyclisation of the RNA model substrate 2-(hydroxypropyl)-*p*-nitrophenyl phosphate **2** with a 23,000-fold rate increase at pH 7, 25°C. The likely mode of action involves the synergistic operation of the two zinc centres **3**. One zinc atom acts as a Lewis acid activating the phosphate group whilst the second activates the nucleophilic hydroxyl group. The calix[4]arene also plays an important role as a molecular scaffold that organises the spatial arrangement of the two zinc groups, thereby facilitating the substrate binding and the 'push-pull' effect.



Scheme 3. Palladium-catalysed asymmetric allylic alkylation.

Multifunctional metalloenzyme mimics can alternatively be prepared that have only one metal centre and a second reactive organic moiety. Such a metalloenzyme could be classed as a Type C multifunctional catalyst. Breslow has shown that the correct spatial orientation of a zinc species with respect to an imidazole base generates a phosphohydrolase catalyst **4** with increased reactivity (Scheme 2). It was again shown that an appropriate molecular scaffold was required to pre-organise the functional groups to allow optimum catalytic activity.[14] The cyclodextrin not only orientates the functional sites, but also serves as a hydrophobic recognition domain, further improving the activity of such enzyme mimics.

The development of enzyme mimics to catalyse simple reactions can be considered to have initiated the evolution of multifunctional catalysts. By applying one of the principles of enzyme chemistry, the symbiotic cooperation of a number of functional groups, chemists have started to recognise many of the important tenets required for the design of efficient catalysts. Obviously, the choice of functionality is important but equally so is the design of the supporting ligand. The functional sites must have the correct positioning so that they can recognise the substrates and act in concert. The spatial organisation is also important to achieve selectivity as is the separation of the functionality. If the groups are too far apart they cannot cooperate, whereas if they are too close together they may interact in an intramolecular fashion and thus prevent the association of the substrate.

3. Small molecule multifunctional catalysis

3.1. Type A catalysts

A key feature of enzymes is their ability to perform enantioselective reactions by appropriately positioning substrates in proximity to each other whilst activating the reacting partners. The goal of Type A multifunctional catalysts is to mimic this action through the synergistic cooperation of functional groups (normally two metals) on a chiral template. One of the earliest attempts at such a strategy was the work of Kumada.[15]

The alkylation of π-allylpalladium species by stabilised nucleophiles has been extensively studied.[16] With few exceptions the nucleophile is symmetrical and no new stereocentre is formed on the incoming moiety.[17] The reason for this is that the reaction proceeds via attack of the nucleophile onto the face opposite the palladium species. Accordingly, any chiral ligand present on the palladium is far removed from the attacking nucleophile and has only a limited effect on the orientation of the incoming nucleophile. Kumada designed a new type of ligand **5** to address this problem (Fig. 2).[15]

A chiral group, capable of coordinating to the incoming nucleophile **6** was attached to a diphosphine ligand by a linker of suitable length. It was proposed that the ligand was complexed to the π-allyl system via the palladium species and that the nucleophile was then directed by chelation to the Lewis basic dicarbonyl species **7** (Scheme 3). The

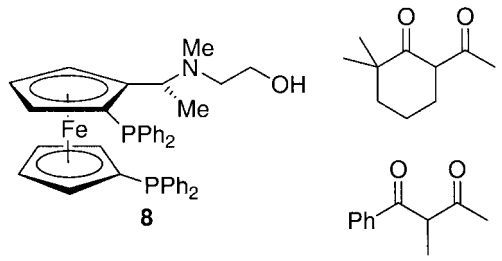
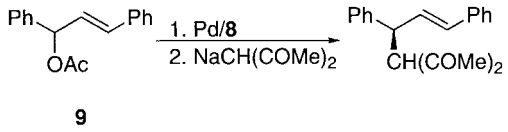


Figure 3. Ferrocenylphosphine ligand and substrates.



Scheme 4. Asymmetric allylic alkylation.

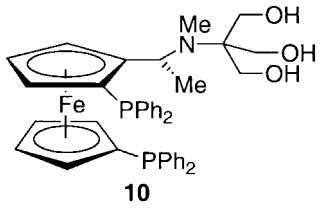


Figure 4. Optimised ligand for allylic alkylation.

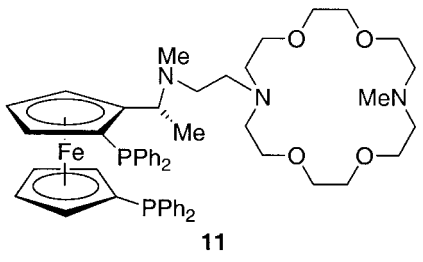


Figure 5. Crown ether-substituted ferrocenylphosphine ligand.

chirality in the Lewis basic functionality controlled the stereoselectivity (up to 52% ee). This hypothesis was supported by the lack of selectivity when the chelating groups were removed. Like metalloenzyme mimics, the spatial organisation of the catalyst was also very important. If the linker was too long the stereoselectivity rapidly decreased.

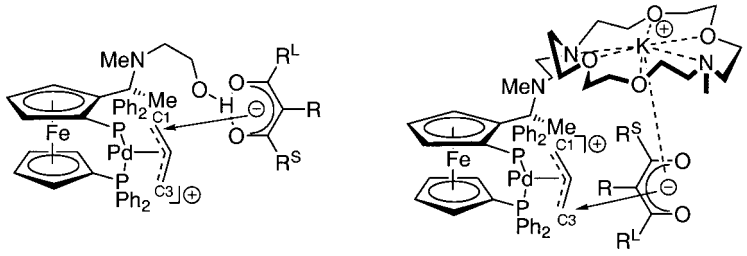
It is interesting to note that catalysts resulting in a higher enantioselectivity were more reactive. Again, it is thought that the spatial organisation brings the nucleophile into close proximity with the π-allyl species and thus accelerates the reaction whilst imparting selectivity. These ligands have now been improved upon.[18] Attaching a hydroxyl group via a chiral linker to a ferrocenylphosphine ligand **8** provides a catalyst which can furnish the desired products in 81% ee. These catalysts function well for a range of diketones (Fig. 3). The mechanism of the reaction is similar to that of the chelating ligands **5** but with hydrogen bonding being responsible for guiding the nucleophile.

Ferrocenylphosphine ligands have also been applied to the asymmetric substitution of 1,3-disubstituted allylic acetates **9** (Scheme 4).[19] In these reactions it was found that, by increasing the number of chelating groups on the ligand, the selectivity could be greatly improved. Consequently, the best ligand contained three hydroxyl groups **10** and resulted in up to 96% ee (Fig. 4).

Ito has developed a complementary ferrocenylphosphine ligand **11** (Fig. 5).[20] In this ligand the directing group has been replaced by a crown ether. The effects of the linker length and the size of the crown ether were again found to be critical. For optimum enantioselectivity (75% ee) and catalytic activity it was found that the size of the crown ether had to be complementary to the ionic radius of the guest cation. The length of the linker also played an important role. These findings again support the proposal that the second active site is delivering the nucleophile in an analogous fashion to an enzyme.

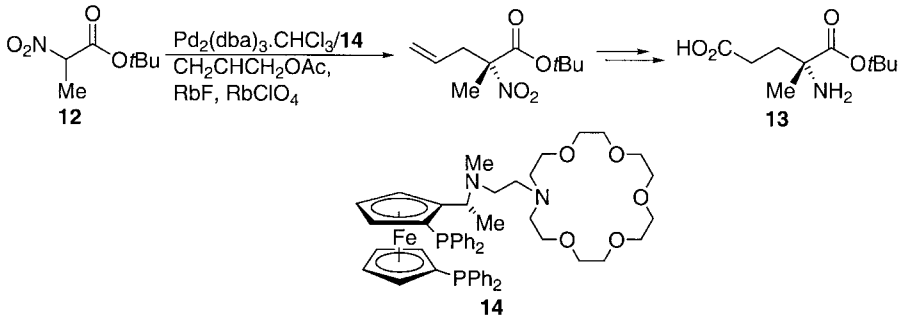
Surprisingly, the chiral sense of enantioselection for the crown ether catalyst **11** was opposite that found with the hydrogen bonding ligand **8**. It is believed that this is due to a reversal of the regiochemistry of attack on the allyl group (Fig. 6). The crown ether is considerably more sterically demanding and blocks the approach of the enolate to C1 and instead delivers it to C3.

Recently, the scope of these catalysts has been expanded to include the reaction of prochiral α-nitroketone- and α-nitroester-stabilised anions. The use of α-nitroesters such as **12** provides a facile route to the amino acids **13** (Scheme 5).[21] The best results (up to 80% ee) were achieved utilising **14** in the presence of RbF with $RbClO_4$ and a bulky ester.



R^S = sterically small substituent
R^L = sterically bulky substituent

Figure 6. Reversal of stereochemistry between hydroxyl- and crown ether-delivered nucleophiles.



Scheme 5. Allylation of α-nitroesters.

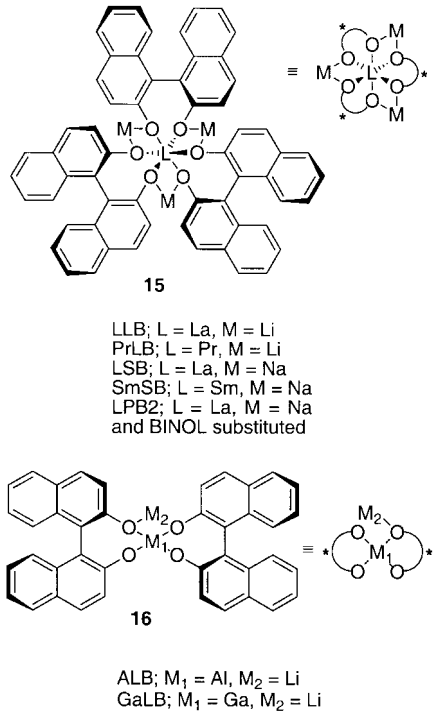
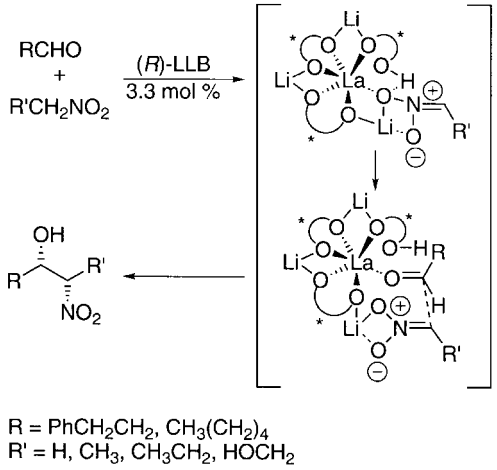


Figure 7. Shibasaki's heterobimetallic complexes.



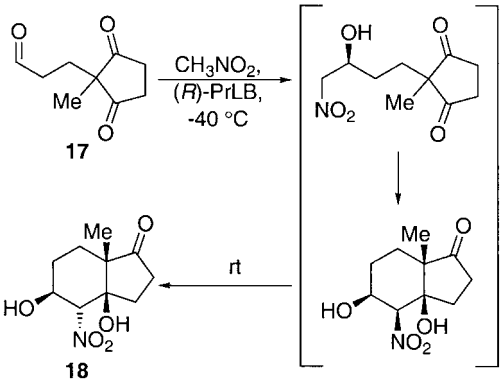
Scheme 6. Heterobimetallic catalysed Henry reaction.

The ferrocenylphosphine ligands described above demonstrate how bifunctional catalysts may be designed to overcome specific obstacles. By tuning the second active site, excellent yields and selectivity could be obtained. The heterobimetallic catalysts, which are next described, were initially discovered empirically. Their utility has been greatly expanded by investigating their mode of action and rationally designing novel variants.

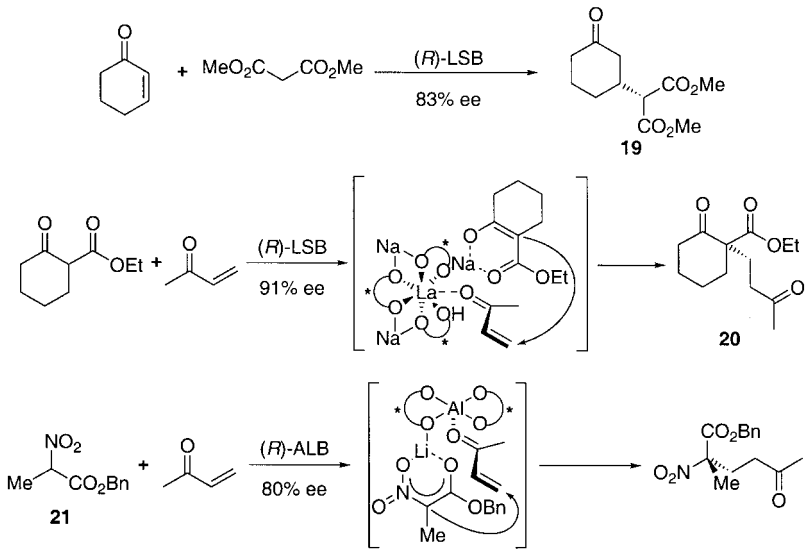
Probably the most extensively investigated Type A catalysts are the heterobimetallic catalysts reported by Shibasaki. The chemistry of these fascinating molecules has recently been reviewed[5,11,22]and therefore will only be briefly summarised here, along with recent developments. Two basic complexes have been developed, the tris-BINOL rare earth complexes **15** and the bis-BINOL Group 3 complexes **16** (Fig. 7). These complexes exhibit both Lewis acidic properties at the central metal atom and Brønsted basic properties at the outlying alkali metal centres. By careful choice of metal centres a wide variety of organic transformations can be achieved.

Initial studies began with the Henry (nitroaldol) reaction.[23] Surprisingly, this was the first report of an asymmetric variant on this useful reaction. It was shown that the reaction proceeds for a variety of aldehydes, including deactivated difluoroaldehydes (Scheme 6). The optimum yields and selectivities were obtained utilising a complex derived from a 6,6′-bis((trialkylsilyl)ethynyl)-substituted (*R*)-BINOL, which furnished the product in 97% yield and 97% ee.

A remarkable elaboration of this strategy was a tandem inter-intramolecular catalytic asymmetric cyclisation



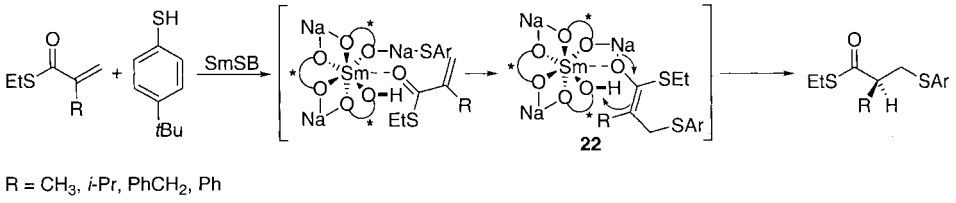
Scheme 7. Tandem inter-intramolecular nitroaldol sequence.



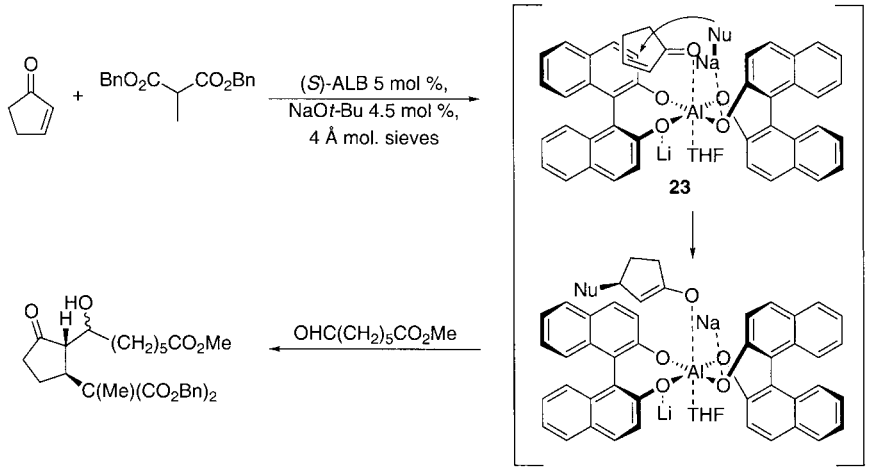
Scheme 8. Catalytic asymmetric Michael additions.

sequence that sets up four new stereocentres in 'one-pot' (Scheme 7).[24] Treatment of **17** with nitromethane and 5 mol% of a praseodymium complex ($PrLi_3$tris((*R*)-binaphthoxide) gave **18** in 65% ee crude (79% ee and 41% yield after recrystallisation). It is proposed that the Pr centre acts as a Lewis acid and activates the aldehyde **17**. The Li-naphthoxide portion then functions as a Brønsted base and deprotonates the nitromethane. Coordination of the aldehyde in the presence of a chiral template and delivery of the nucleophile by the bridging lithium complex results in intramolecularisation of the reaction and hence good enantioselectivity (vide supra). Transfer of a proton from the ligand to the new alkoxide regenerates the catalyst. Selective attack on the diketone moiety is thought to be controlled solely by the configuration at the new hydroxyl functionality.

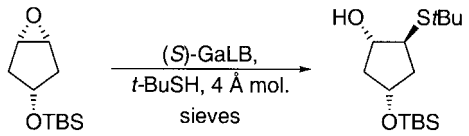
By varying the metal constituents of the complexes excellent catalysts for the asymmetric Michael reaction have been developed.[25] The optimum catalyst for the addition of malonates and thiols appears to be $LaNa_2$tris(binaphthoxide) (LSB) (Scheme 8). It is not clearly understood why the change of alkali metal is so important (lithium complexes proceed with no selectivity). It is postulated



Scheme 9. Catalytic asymmetric protonation.



Scheme 10. Michael-aldol addition cascade.



Scheme 11. Catalytic asymmetric ring opening of epoxides by thiols.

that the change in bond lengths and hence the bite angle of the BINOL moiety might affect the spatial arrangement of the substrates. The LSB complexes are, nevertheless, highly efficient and can be used to control the enantioselectivity on the Michael acceptor **19** or the donor **20**. Feringa has shown that the α-nitroesters **21** can also undergo asymmetric Michael addition to α,β-unsaturated ketones when treated with aluminium–lithium bis(binaphthoxide) (ALB).[26]

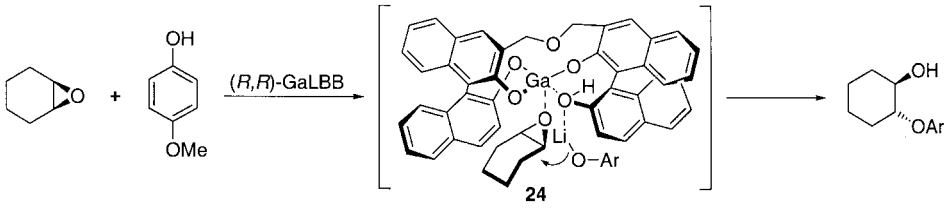
Recently the strategy has been extended to allow the Michael addition of thiols followed by asymmetric protonation of the resultant enolate **22** (Scheme 9).[27] Once again the optimum results were achieved by varying the constituents of the catalyst. In this example samarium was found to be the most effective lanthanide, giving the Michael adduct in 93% ee.

The elegance of these catalysts was highlighted by the synthesis of 11-deoxy-$PGF_{1\alpha}$ via a tandem Michael–aldol addition (Scheme 10).[28] The success of the tandem reaction relied on the development of a new catalyst. The initial lanthanide complexes formed highly reactive enolates that underwent rapid pseudo-intramolecular protonation, thus prohibiting reaction with an external electrophile. It was thought that an aluminium enolate would be more stable and undergo much slower protonation. The extended life of the enolate would permit the aldol reaction. To this end, the AlLibis(binaphthoxide)+NaOtBu complex (ALB-II) **23** was prepared. Gratifyingly, the reaction proceeds with excellent control at the two ring positions and considerable selectivity at the new hydroxyl group (addition judged to proceed in 84% yield and 92% ee).

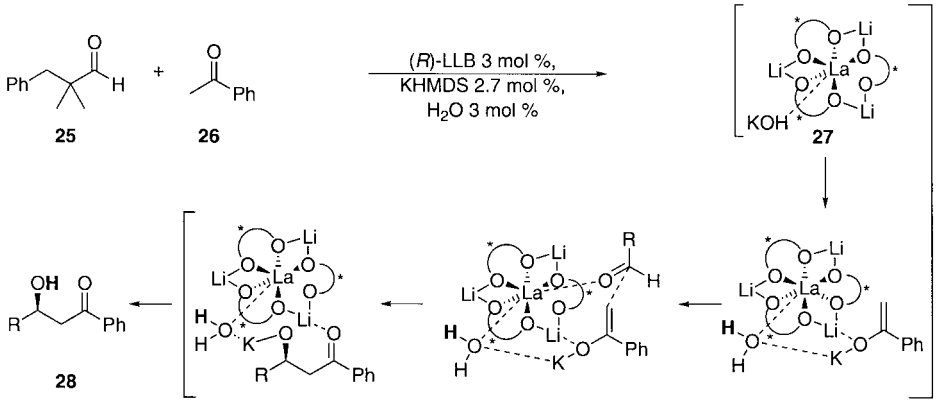
Shibasaki has applied these catalysts to other reactions that benefit from the complementary activation and positioning of the electrophile and the nucleophile, such as the catalytic asymmetric ring opening of epoxides with either thiols or phenols (Scheme 11).[29] Both the standard heterobimetallic catalysts, lanthanum·alkali metal·tris(binaphthoxide) and aluminium·lithium·bis(binaphthoxide) showed poor catalytic activity but promising selectivity (27–86% ee). Consequently, gallium was used to prepare a more reactive complex (GaLB) than its aluminium counterpart. GaLB proved to be very effective on a variety of cyclic epoxides. The use of less hindered thiols gave the poorest results due to competitive ligand exchange at the gallium centre whilst bulky thiols overcame this drawback and gave excellent results (98% ee).

The selective ring opening of epoxides with oxygen nucleophiles proved much more arduous to achieve.[30] High selectivity (94% ee) could be achieved with substituted GaLB (6,6′-bis((trialkylsilyl)ethynyl)-substituted (*R*)-BINOL) but with only modest yields (60%). Conversely, high yields (73%) could be achieved with modest selectivity (56% ee) if GaLibis((*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-BINOL) was used.[31] It was thought that the major problem was the competitive ligand exchange of the BINOL moiety by the phenol reagent. To limit the exchange the two BINOL units were linked **24**. The new catalysts proved more effective than their non-linked counterparts, resulting in yields of up to 72% and 91% ee (Scheme 12).[32]

Perhaps the most exciting application of Shibasaki's

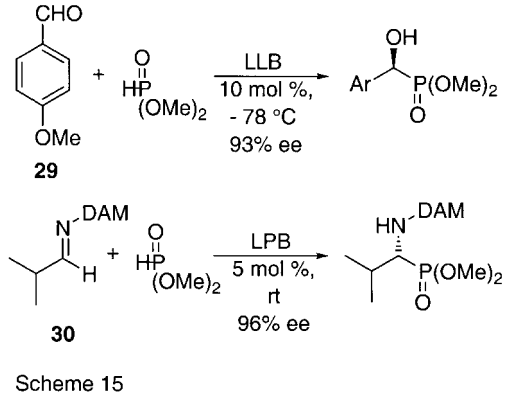


Scheme 12. Catalytic asymmetric ring opening of epoxides by phenols.



Scheme 13. Direct catalytic asymmetric aldol reaction.

Scheme 14. Direct catalytic asymmetric Mannich reaction.



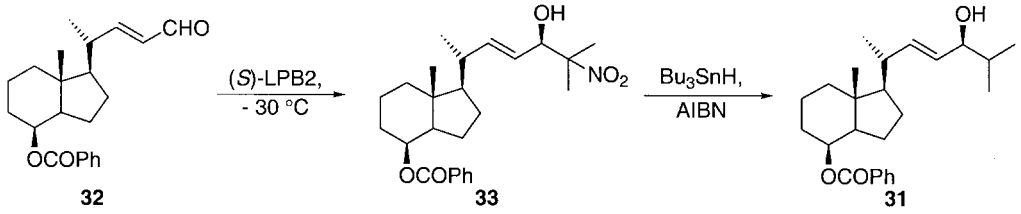
Scheme 15

Scheme 15. Catalytic asymmetric hydrophosphonylation.

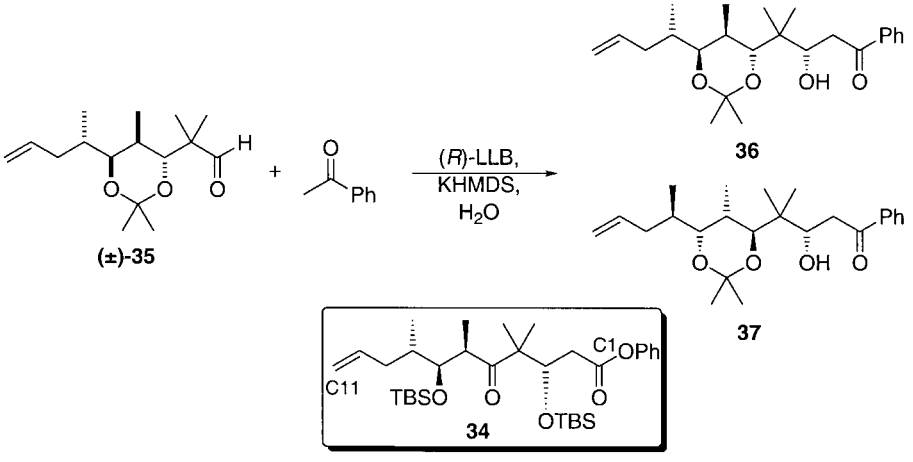
heterobimetallic catalysts is in the direct catalytic asymmetric aldol reaction. The aldol reaction has long been regarded as one of the most powerful carbon–carbon bond-forming reactions and, as a result, many catalytic asymmetric variants have been devised.[33] In all of these strategies, however, the ketone moiety is first converted into a more reactive species. Enzymes are known to be able to utilise unmodified ketones in aldol reactions by multifunctional catalysis.[34] At the active site, a Lewis acidic metal activates the carbonyl component whilst a basic functional group deprotonates the ketone. As has been shown (vide supra), the heterobimetallic catalysts act in a similar cooperative manner.

Initial studies, utilising $LaLi_3$tris(binaphthoxide) as the catalyst, validated this concept but had a number of drawbacks. A considerable excess of ketone was required, large amounts of catalyst (20 mol%) were used, the reaction times were exceedingly long and the enantioselectivities were only modest. The best results were obtained by the use of a heteropolymetallic catalyst prepared from LLB, KHMDS and H_2O. In the presence of 3 mol % of this new catalyst **27**, the reaction of **25** and **26** gave **28** in 71% yield and 85% ee (Scheme 13).[35]

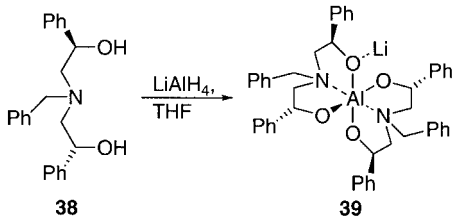
The use of unmodified ketones in the direct catalytic asymmetric Mannich reaction was the next logical progression.[36] An additional obstacle to this already taxing reaction was the in situ formation of the iminium species from a suitable precursor. Initial studies with LLB proved disappointing with both low yields and selectivity. It was believed that the complex was not sufficiently Lewis acidic to generate the iminium species. Addition of an external lanthanide triflate Lewis acid led to an improvement in the yield but a loss of enantioselectivity, presumably due to catalysis of the reaction independently of the BINOL moiety. To provide an asymmetric environment it was necessary to allow association between the heterobimetallic catalyst and the external Lewis acid. This was not possible with three bulky BINOL units present. ALB, with only two BINOL units, was therefore investigated. The most successful conditions utilised $La(OTf)_3$ in the presence of ALB



Scheme 16. Synthetic utility of a heterobimetallic catalyst.



Scheme 17. Synthesis of the C1–C11 fragment of epothilone A.



Scheme 18. Aminodiol-derived heterobimetallic catalyst.

(Scheme 14). Although the reaction proceeded with only moderate yield (69%) and selectivity (44% ee), it highlights the potential of a trimetallic system.

Since the introduction of heterobimetallic catalysts by Shibasaki a number of other groups have utilised them. Shibuya[37] and Spilling[38] have used LLB in the hydrophosphonylation of aldehydes, e.g. **29**. Although their initial results showed only a modest enantioselectivity (33–82% ee), Shibasaki has since optimised the reaction and expanded its utility to both cyclic and acyclic imines such as **30** (Scheme 15).[39]

The synthetic utility of the heterobimetallic catalysts has been illustrated extensively by Shibasaki and others. Okamoto has prepared an intermediate **31** towards the total synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 (Scheme 16).[40] Henry reaction of 2-nitropropane with the aldehyde **32** catalysed by LaK_3tris((S)-6,6′-bis((triethylsilyl)ethynyl)-BINOL) gave the desired alcohol **33** in 70% yield and 88% ee. Radical denitration with tributyltin hydride furnished the previously reported intermediate **31**.

Shibasaki has reported the enantioselective total synthesis of epothilone A utilising two different multifunctional catalysts in the key steps.[41] Synthesis of the C1–C11 unit **34** was achieved via the resolution of (±)-**35** by direct catalytic asymmetric aldol reaction which gave **36** in 30% yield, 89% ee, **37** in 29% yield, 88% ee and 30% recovery of the starting material (Scheme 17). The second fragment of epothilone was prepared via a catalytic asymmetric cyanosilylation using a Type B bifunctional catalyst (vide infra).

Following on from the catalysts developed by Shibasaki, a number of novel heterobimetallic complexes have been

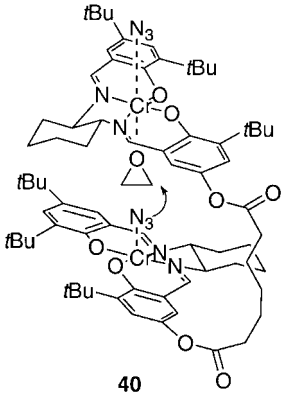
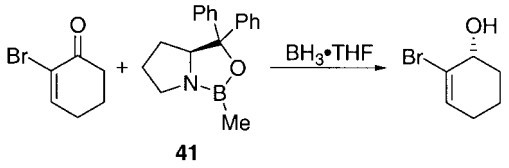


Figure 8. Dimeric (salen)Cr complexes.



Scheme 19. CBS reduction of a prochiral ketone.

developed.[42] The reaction of two equivalents of the C_2-symmetric amino diol **38** with $LiAlH_4$ was believed to give the complex **39** (Scheme 18).[42a] As yet, the structure has only been inferred from spectroscopic data as the complex has eluded crystallisation. This disadvantage notwithstanding (the Shibasaki catalysts are crystalline, air stable solids), the new catalyst has proved to be more efficient. It promotes the Michael addition of a variety of malonates to enones in good yields more rapidly and with comparable or better enantioselectivities than the BINOL complexes. The complex **39** also promoted the Michael addition of thiols with reaction times of <1 min, but with only moderate enantioselectivities. Treatment of (3*S*,4*S*)-1-benzylpyrrolidine-3,4-diol with $LiAlH_4$ has also been utilised to prepare a heterobimetallic catalyst for the Michael addition.[42b] Excellent conversions were achieved (100%) with a number of substrates but the enantioselectivity was poor (best example 32% ee).

Jacobsen has reported an intriguing example of a Type A bifunctional catalysis.[43] Earlier work had shown that asymmetric ring opening of epoxides with TMS-N_3 catalysed by a (salen)Cr complex exhibited second-order kinetic dependence on the catalyst, indicating that the reaction proceeded via simultaneous activation of both the epoxide and the azide by two individual molecules of catalyst. In order to encourage the cooperative mechanism a number of covalently-linked dimeric molecules were synthesised. It was found that the novel bifunctional catalysts **40** were one- to two-fold more reactive than their monomeric counterparts whilst still maintaining the same levels of enantioselectivity (Fig. 8), thus confirming the benefits of dual activation.

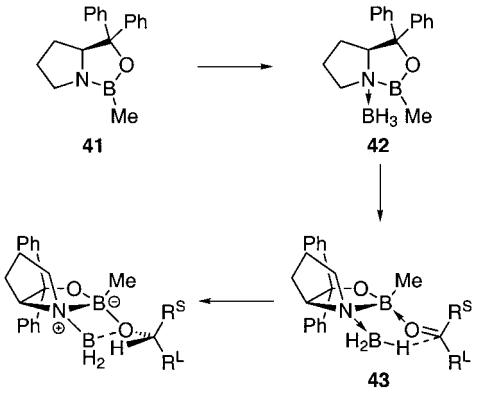
At the present time Type A catalysts have shown great versatility and promote a wide range of transformations, the majority of which have been found serendipitously. With a greater understanding of their mode of action it should be possible to rationally design better and more multifaceted catalysts.

3.2. Type B catalysts

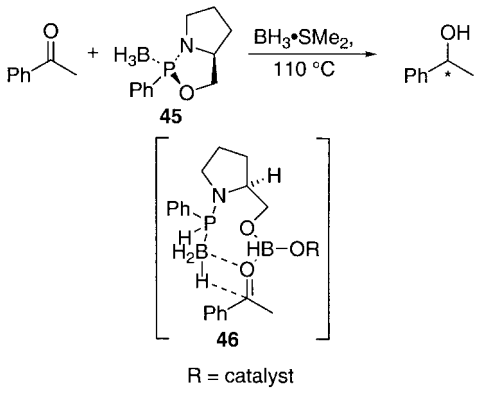
Type B multifunctional catalysts normally contain one Lewis acidic centre to bind the substrate and a Lewis basic centre to selectively deliver a stoichiometric reagent via coordination.

One of the most well-established examples of Type B catalysis is the chiral oxazaborolide-mediated reduction of ketones introduced by Corey, Bakshi and Shibata (CBS reduction) (Scheme 19).[44]

Treatment of 2-bromo-2-cyclohexen-1-one with a catalytic amount of the proline-derived oxazaborolide **41** (5–10 mol%)



Scheme 20. Proposed mechanism for the CBS reduction.

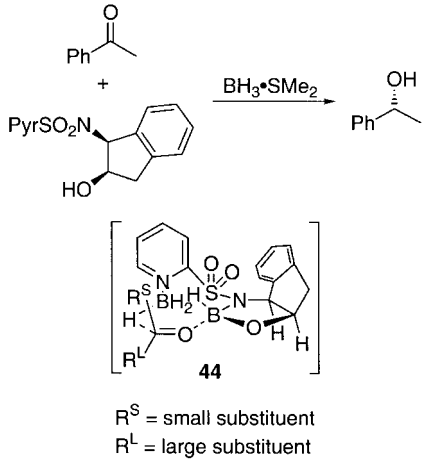


Scheme 22. A catalytic phosphorous reducing reagent.

in the presence of a stoichiometric quantity of a borane source (BH_3·THF or BH_3·Me_2S) results in a rapid and highly enantioselective reduction (>95% ee). In terms of multifunctional catalysis the Lewis acidic centre is provided by the boron atom whilst the nitrogen atom is the Lewis basic component and spatially organises the stoichiometric reductant.

The mechanism proceeds via the rapid coordination of BH_3 to the Lewis basic nitrogen from the α-face to give **42** (Scheme 20). Coordination results in activation of the borane with simultaneous intensification of the Lewis acidity of the endocyclic boron atom and ultimately activation of the ketone. Such synergy explains the impressive rate enhancement obtained by these catalysts. The increased electrophilicity of the endocyclic boron atom facilitates the coordination of the ketone substrate at the least-sterically-demanding lone pair. The resultant spatial arrangement minimises the steric interactions between the oxazaborolide and the ketone and aligns the electron deficient carbonyl moiety with the electronically activated boron-hydrogen bond to allow hydride transfer via a favourable six-membered transition state **43**.

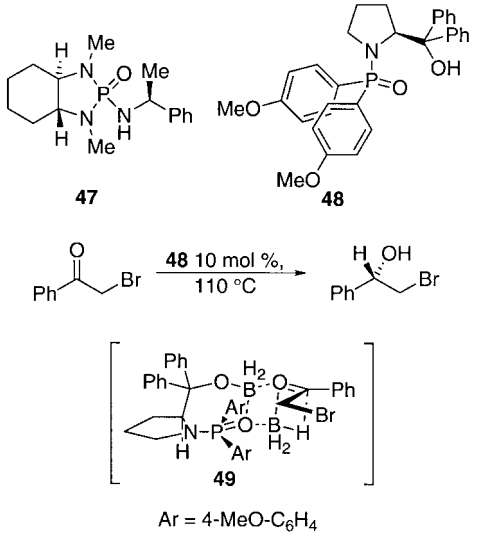
The CBS reduction is an excellent example of a small molecule multifunctional catalyst. The two active sites not only position the substrate and reagent to give an enantioselective reaction but also cooperate to activate both reactants. The considerable utility of the oxazaborolidine class of catalysts has led to the development of many structural variants.[45]



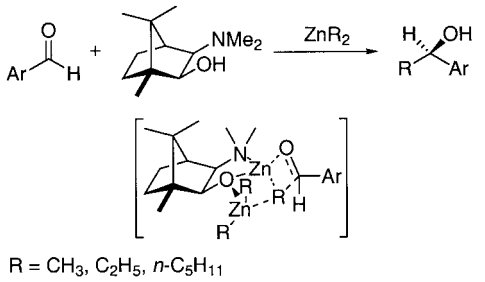
Scheme 21. Tethered directing groups.

As preliminary studies towards more complex reactions, Sibi and Cook have investigated oxazaborolidine-mediated reductions.[46] They designed a bifunctional catalyst incorporating an oxazaborolidine moiety as a Lewis acid and a sulfonamide-tethered Lewis base as a directing group (Scheme 21). The results suggest that the reaction proceeds via the intermediate **44**, in which the 2-pyridylsulfonyl group delivers the borane (80% ee). The use of a non-heterocyclic aromatic sulfone led to a dramatic loss of selectivity, as did altering the position of the Lewis base. It would appear that the nitrogen was necessary for reaction and that there is an optimal separation of the Lewis acid and Lewis basic functionality. Interestingly, the parent aminoindanol gave the best results of all the catalysts studied (94% ee), indicating that the CBS catalyst (vide supra) probably results in an optimal arrangement of all components necessary for the reduction.

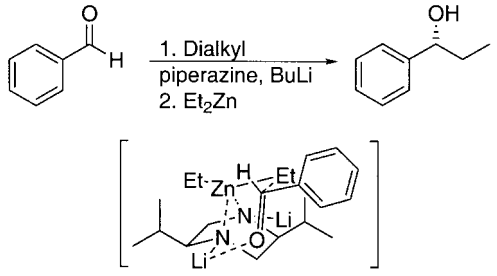
Buono has reported an oxazaphospholidine-borane complex



Scheme 23. Phosphinamide-based ketone reduction.



Scheme 24. Aminoalcohol catalysed addition of dialkylzinc reagents.



Scheme 25. Use of the dilithium salts of chiral piperazines.

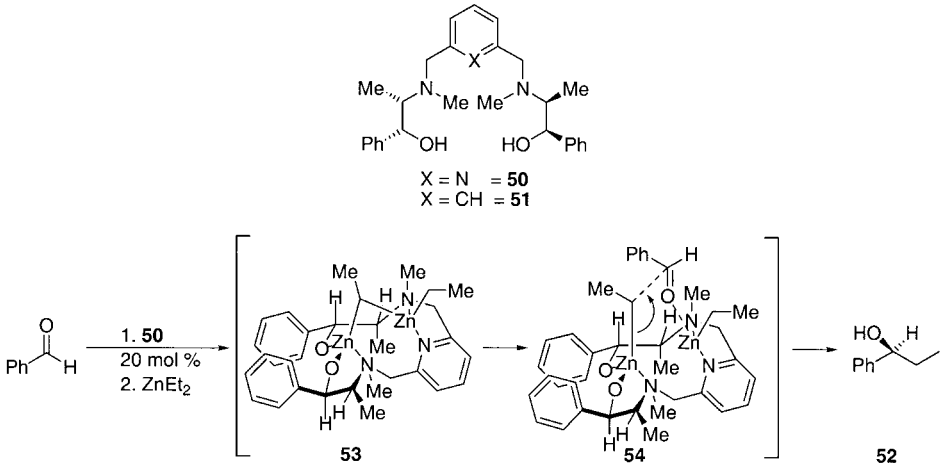
capable of enantioselective reductions (Scheme 22).[47] Interestingly, the catalyst **45** showed increased selectivity at elevated temperatures. It was believed that **45** was only a pro-catalyst and that, under the reaction conditions employed it was converted to the ring opened **46**. The two borane moieties are in different electronic environments. The dialkoxyborane is more electron deficient and behaves as a Lewis acid, activating the ketone. The phosphorous atom positions and activates the hydride donor. A modest selectivity has been obtained with this catalyst (65% ee with 16 mol% catalyst and >99% ee with 100 mol% catalyst).

Wills has investigated the use of phosphinamides as catalysts for the same reaction.[48] The premise for the reaction was the known electron donor character of the oxygen atom. Interaction of borane with the oxygen should result in an increase in electron density on the former, with a concomitant increase in reactivity. The initial assumption proved correct and considerable rate enhancements for the reduction could be achieved with the simple chiral phosphinamide **47** (Scheme 23). Unfortunately, only modest selectivity (46% ee) was achieved and it proved necessary to introduce a second functional group that could be used to attach a Lewis acid and thus position the ketones correctly to achieve good enantioselectivity (93% ee) (transition state **49**; Scheme 23). The advantage of the phosphinamide catalyst **48** is its robustness. Unlike oxazaborolidine-derived catalysts, it is stable to small amounts of moisture and can be readily recovered from the reaction mixture and reused.

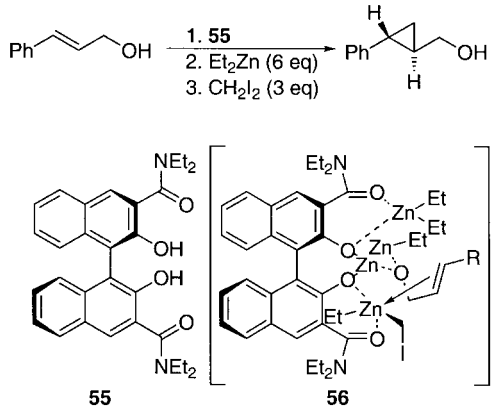
The asymmetric alkylation of the carbonyl moiety by organozinc complexes is conceptually related to catalytic CBS reductions. Dialkylzinc species are linear and non-reactive but on coordination to a bidentate donor ligand they form pseudo-tetrahedral complexes with considerably increased nucleophilicity. Noyori has shown that the use of aminoalcohols as ligands allows the addition to proceed with excellent enantioselectivities (99% ee) (Scheme 24).[49] With direct analogy to the CBS reduction, one metal atom is required for the catalytic cycle and behaves as a Lewis acid. The second stoichiometric zinc reagent coordinates to the Lewis basic oxygen atom, which both activates and directs the addition.

As with the oxazaborolidine catalysts, the catalytic addition of dialkylzinc species has attracted much interest and many novel templates have been developed. Most are believed to operate by a similar mechanism to that suggested by Noyori (vide supra).[50] One example that possibly proceeds via a heterobimetallic intermediate is the use of the dilithium salts of chiral piperazines. It has been proposed that the cyclic diamine acts as a bidentate ligand activating the dialkylzinc reagent, whilst the lithium metal activates and positions the aldehyde to allow addition to proceed with yields of up to 81% and 92% ee (Scheme 25).[51]

An interesting example reported by Williams shows how the selectivity of the addition can be reversed by a minor change in the coordination properties of the ligand (Scheme 26).[52] The pyridine ligand **50** was shown to be both more reactive and more selective (90% ee) than the simple aryl ligand **51** (76% ee). More surprisingly, **50** gave the



Scheme 26. Ligand effects on enantioselectivity.

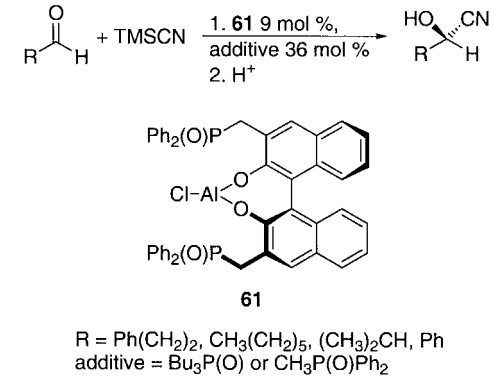


Scheme 27. Asymmetric Simmons–Smith cyclopropanation.

(*S*)-1-aryl-1-propanols **52** whilst **51** gave the corresponding (*R*)-1-aryl-1-propanols. It was speculated that the pyridine ligand formed a bridged chelate **53**, which gave rise to internal reagent delivery via **54**. With ligand **51** a more conventional approach, via a less controlled transition state, was believed to be active.

An analogous mechanism has been proposed for an asymmetric Simmons–Smith reaction (Scheme 27).[53] Evidence suggests that diethylzinc and the BINOL derivative **55** form a tetrametallic species **56**. The central zinc metal acts as a Lewis acid, coordinating the allyl alcohol, whilst one of the amide carbonyl groups behaves as a Lewis base and chelates the ethyl(iodomethyl)zinc. The spatial organisation results in highly selective methylene transfer (92% ee). Once again, the cooperation between two functionalities results in an excellent selectivity. An analogous ligand has been shown to be a highly effective template for the enantioselective addition of diethylzinc to aldehydes.[54]

A Type B catalytic system has been proposed for the asymmetric synthesis of isoxazolines.[55] In the only asymmetric metal-catalysed 1,3-dipolar cycloaddition of nitrile oxides with alkenes reported to date, allyl alcohol is treated with diethylzinc, (*R*,*R*)-diisopropyl tartrate and a substituted benzoximoyl chloride. The initial intermediate **57** is apparently much less reactive than the zinc–tartrate complex **58** (Scheme 28). An enantioselective 1,3-dipolar cycloaddition occurs, resulting in the formation of the

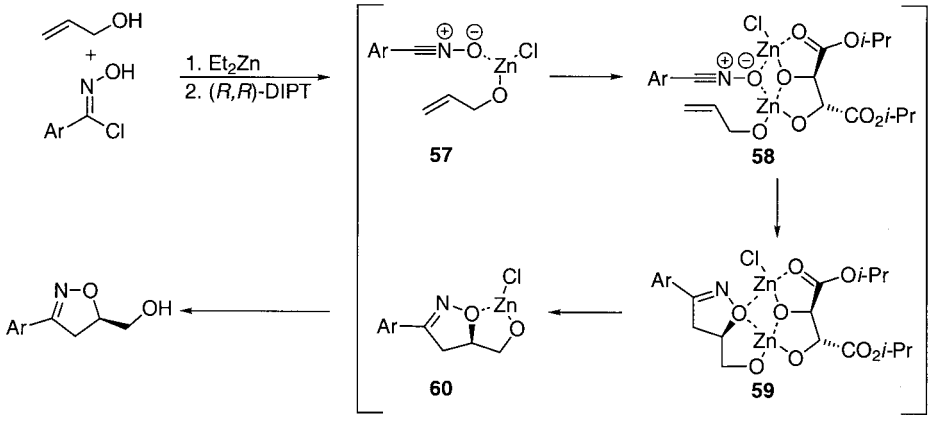


Scheme 29. Catalytic asymmetric cyanosilylation.

isoxazoline **59**. The zinc-tartrate complex returns to the catalytic cycle and **60** is hydrolysed on work-up to give the isoxazoline in up to 98% ee. The strategy has been extended to the cycloaddition of nitrones to give isoxazolidines. In both examples, the two zinc centres are used to position the dipole and the dipolarophile.

Shibasaki has designed an excellent Type B bifunctional catalyst for the asymmetric cyanosilylation of aldehydes (Scheme 29).[56] Utilising a substituted BINOL moiety **61** as the chiral template, the catalyst consisted of an aluminium atom as a Lewis acid and a phosphine oxide moiety to provide a Lewis basic oxygen atom. Once again, the purpose of the bifunctional catalyst was to activate both the substrate and the reagent.

Shibasaki's catalytic system highlights many of the issues that need to be addressed when designing an efficient Type B catalyst. Firstly, the distance between the two functionalities is important. Too much flexibility within the system would allow internal complexation of the Lewis acid and Lewis base moieties with a resulting deactivation of the catalyst. Tuning the strength of both interactions was also shown to be important. If the Lewis acid was too strong, the resulting activation of the carbonyl resulted in non-selective nucleophilic addition. This problem was overcome by use the of a donor additive which not only reduced the activity of the aluminium but also altered the catalyst's geometry to allow the internal phosphine oxide to exist in a more favourable position (Fig. 9).



Scheme 28. Catalytic asymmetric 1,3-dipolar cycloaddition.

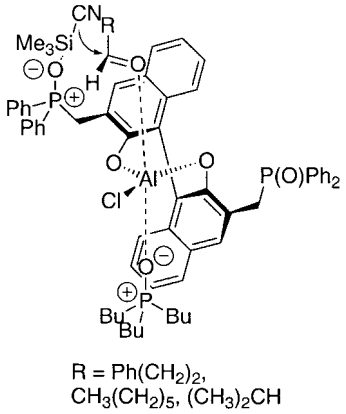


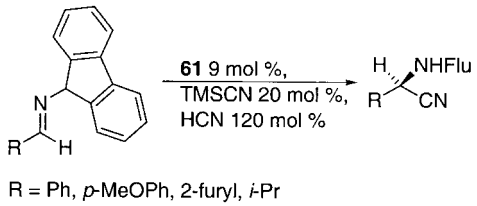
Figure 9. Proposed transition state for the asymmetric cyanosilylation.

Shibasaki has utilised the bifunctional catalyst **61** in the synthesis of the C12–C21 fragment **62** of epothilone A (Scheme 30).[41] The aldehyde **63** was converted to the enantiopure (99% ee) cyanohydrin **64** in an excellent (97%) yield.

Recently, the catalyst **61** has been used to develop an asymmetric variant of the Strecker reaction (Scheme 31).[57] Protic additives were shown to have a beneficial effect on the reaction rate and this led to the formulation of a catalytic system utilising only 9 mol% **61**, 20 mol% TMSCN and a stoichiometric amount of hydrogen cyanide. The nature of the nitrogen protecting group was found to exhibit a dramatic effect on the reaction. The best results were achieved with the fluorenyl group (up to 95% ee).

Attempts to improve the generality and reactivity of the bifunctional catalyst **61** have been reported.[58] A series of carbohydrates were used as chiral scaffolds to present the antithetic reactive centres (Fig. 10). The most effective catalyst was found to be **65** in which the number of possible conformations was constrained by the presence of the phenyl group at C6 (carbohydrate numbering). Although the novel catalyst was less enantioselective (80% ee) than **61** it offered a greater practicality since it was found to be more catalytically active and did not require additives or the slow addition of TMSCN.

Maruoka has developed an alternative bifunctional aluminium reagent.[59] Although not catalytic, it illustrates the same principles outlined above. Surprisingly, no effective procedure has been developed for the conjugate allylation of α,β-unsaturated aldehydes. Most reagents, including cuprates, result in mixtures of 1,2- and 1,4-addition products. Lewis acids are known to activate enones to both forms of nucleophilic addition. Initially a bulky Lewis acid, aluminium tris(2,6-diphenylphenoxide) (ATPH), was developed. It was hoped that ATPH would activate the enone whilst simultaneously shielding the



Scheme 31. Catalytic asymmetric Strecker-type reaction.

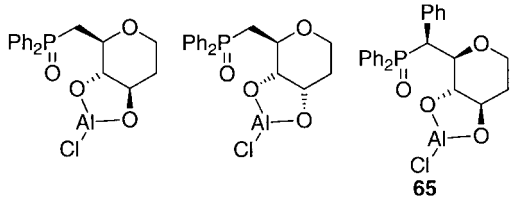
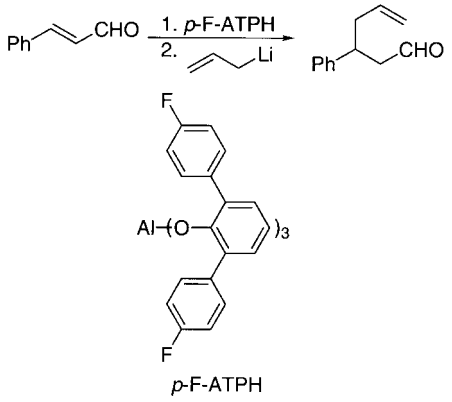


Figure 10. Carbohydrate-based cyanosilylation catalysts.

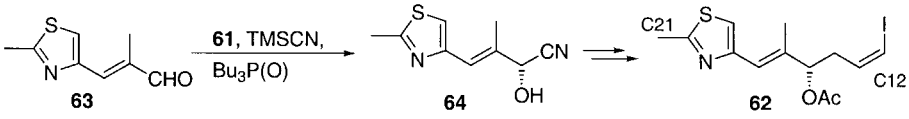


Scheme 32. Conjugate allylation of α,β-unsaturated aldehydes.

carbonyl moiety. Although ATPH was proficient for many Michael additions it proved to be ineffective for the desired reaction. In order to overcome this shortcoming, a novel reagent was designed that incorporated a second functional group, which could direct the allylmetal reagent (Scheme 32).

The novel reagent retained the aluminium Lewis acid to complex the aldehyde but had additional fluorine atoms attached to the phenyl ring. The fluorine coordinated to the lithium of the nucleophile directing the desired conjugate addition (Fig. 11). This methodology was expanded to allow the conjugate addition of a number of different alkyllithium reagents and it was found that increasing the number of fluorine atoms present on the receptor increased the selectivity.

As with the Type A catalysts, the original Type B



Scheme 30. Synthesis of the C21–C21 fragment of epothilone A.

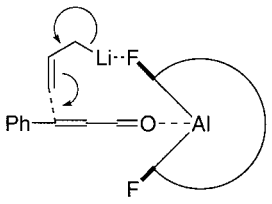
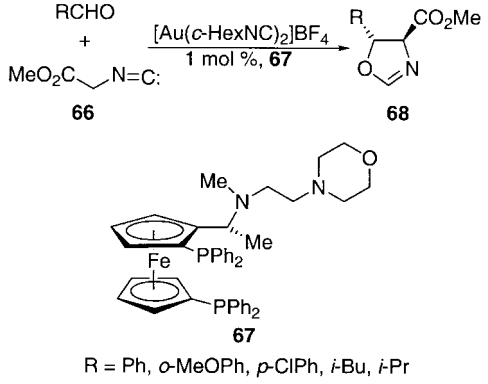


Figure 11. Proposed directing effect of fluorine.



Scheme 33. Gold catalysed asymmetric aldol reaction.

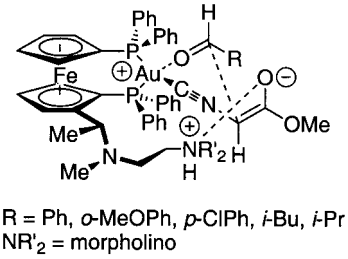
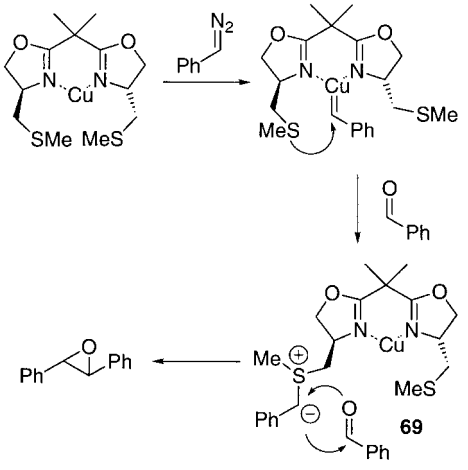


Figure 12. Proposed transition state for aldol reaction catalysed by Type C catalyst.



Scheme 34. Bifunctional catalyst for the asymmetric sulfur ylide epoxidation of aldehydes.

compounds were discovered empirically, but once the mechanism had been elucidated, a number of examples have been designed to overcome specific obstacles.

3.3. Type C catalysts

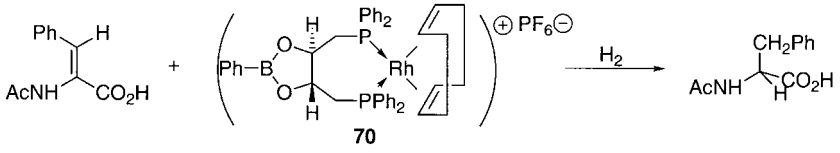
Type C catalysts, in which a metallic active site interacts with a substrate before a second site on the ligand performs a chemical reaction, are by far the rarest class of multifunctional catalysts. This is complicated by a possible ambiguity with Type A catalysts if the second active site is also a metal.

Possibly the earliest example of a reaction catalysed by a Type C, small molecule catalyst, was the aldol-type reaction of the isocyanocarboxylate **66** (Scheme 33).[60]

Addition of the isocyanate **66** to a variety of aldehydes in the presence of 1 mol% of the cationic gold(I) complex of **67** gave the oxazoline **68** in almost quantitative yield and excellent selectivity (96% ee). The isocyanate coordinates to the gold centre and the terminal tertiary amino group then abstracts a proton to form the enolate (Fig. 12). An attractive interaction between the ammonium cation and the enolate anion controls the approach of the complexed aldehyde. Evidence for the attractive intermediate comes from the observation that the length of the amine tether and the structure of the tertiary amine both have an effect on the selectivity whilst the steric bulk of the enolate has very little effect (such an effect would be associated with repulsive interactions). Interestingly, this example of a direct aldol-like reaction pre-dates the work of Shibasaki (vide supra).

Aggarwal has developed a highly efficient catalytic asymmetric variant of the Corey-Chaykovsky epoxidation.[61] Unfortunately, although sub-stoichiometric quantities of the chiral sulfur reagent are used there is a lower limit of 20 mol%. In order to improve the loading, a means of increasing the rate of reaction between the sulfur and the carbenoid species compared to the rate of dimerisation of the carbenoid was required. The ingenious solution to this problem was to develop a Type C catalyst in which the generation of the carbenoid and its reaction with the sulfur moiety were achieved in an intramolecular fashion. To this end, a series of copper bis-oxazoline complexes bearing a pendant sulfide were synthesised.[62]

Copper is well known to promote the decomposition of diazo compounds to the corresponding carbenoid species (Scheme 34). The rapid intramolecular attack of the sulfide forms the desired ylide **69** which can then undergo addition to an aldehyde, the rate enhancement allowing as little as 5 mol% of the sulfur compound to be used. Unfortunately the enantioselectivity of the reaction was very poor. It is



Scheme 35. Asymmetric hydrogenation with the bimetallic catalyst **70**.

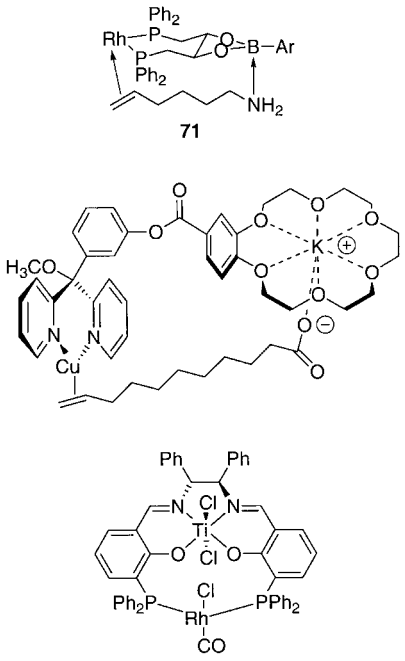


Figure 13. Potential Type C catalysts.

believed that the chiral centre is too remote from the ylide to have much effect.

A number of catalysts containing both hard and soft Lewis acids have been designed to perform catalytic asymmetric reactions. The groups of Kagan[63] and Jacobsen[64] have concurrently synthesised the catalysts **70** and **71** (Scheme 35 and Fig. 13). They proposed that such catalysts would utilise the hard borate ester to coordinate to a Lewis base, thus positioning the soft rhodium catalyst in proximity to the reactive functional group.

Kagan investigated the asymmetric hydrogenation of alkenes and ketones, as well as asymmetric hydrosilylations. Although the catalyst was active, the selectivity was found to be worse than the analogous monometallic catalyst derived from DIOP. It is possible that the separation between the two metal centres was not complementary to the substrates investigated. Jacobsen reported investigations of the binding of such catalysts to amines but not the chemical reactivity.

A number of potential catalysts based upon the same principle have been synthesised (Fig. 13),[65,66] some of which have been shown to possess catalytic activity and even moderate selectivity. As yet, the full potential of such catalysts has not been realised.

4. Conclusions

The last few years have seen great advances in the use of small molecule multifunctional catalysts in organic synthesis. The research of Shibasaki in particular shows the potential for such catalysts, but much work still needs to be undertaken. Many organic transformations can still only be achieved effectively with stoichiometric reagents. The use of multifunctional catalysts offers a great opportunity to overcome these limitations. The use of Type C catalysts, as highlighted by Ito and Aggarwal, has yet to be fully investigated. The more that is learnt about the mode of cooperation in such systems the more likely it is that new catalytic systems will be rationally designed.

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Biographical Sketch

Gareth John Rowlands was born in Horsham, England in 1972. He received his first degree [B.Sc.(Hons.)] from Imperial College, London and remained there to work on the synthesis of 2,5-disubstituted pyrrolidines via a 5-*endo*-trig cyclisation under the supervision of Donald Craig. After completing his Ph.D. degree in 1996 he moved to the University of Cambridge as a 1851 Research Fellow where he worked with Professor Steven V. Ley, FRS, towards the synthesis of altohyrtin A. In 1999 he started his own research at the University of Sussex, England. His research interests are focused on the development of new methods for the synthesis of alkaloids utilising many different aspects of organic chemistry.