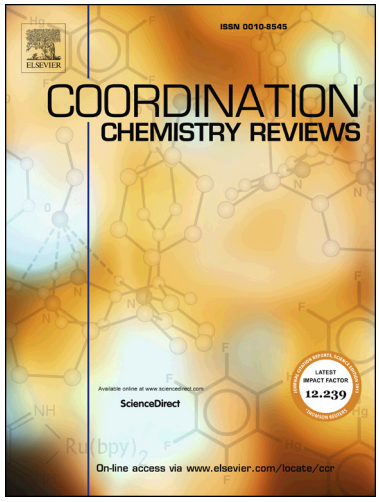

Enantioselective Main Group Catalysis: Modern Catalysts for Organic Transformations

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Enantioselective Main Group Catalysis: Modern Catalysts for Organic Transformations.

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Contents

This review highlights a number of recent developments in the field of main group enantioselective catalysis. Many essential transformations can be effected catalytically such as hydrosilylation, hydroamination and hydrogenation reactions, amongst others, in an asymmetric fashion using earth abundant *s*- and *p*-block elements such as calcium, strontium, boron and aluminum. Recent work in this area has shown that these systems are not only active in catalysis but may also have the potential to compete with transition metal based systems with the reduced cost and toxicity often associated with main group chemistry.
Keywords: · enantioselective · main group · catalysis · chiral · asymmetric

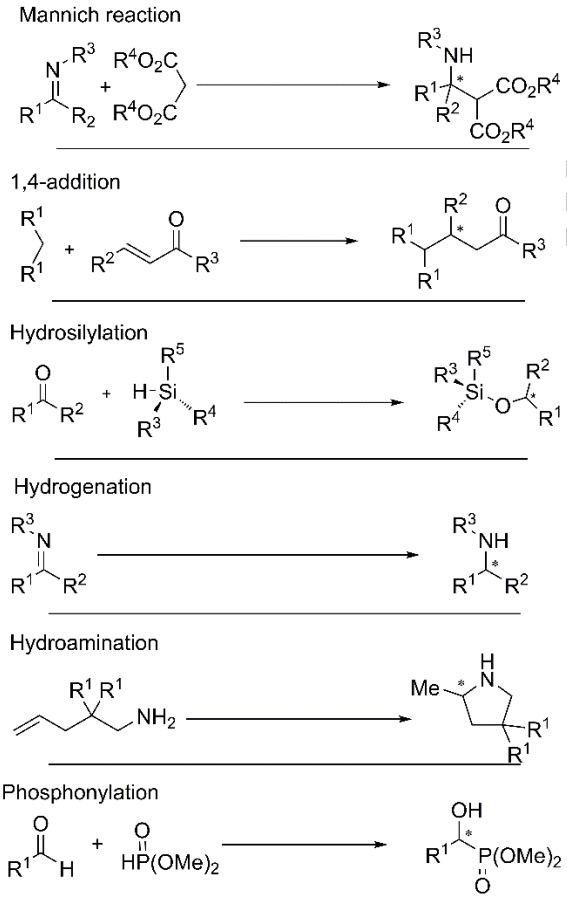
1. Introduction

Molecules that include stereocenters are ubiquitous in chemistry as some of the most important molecules essential to life are chiral. While nature has developed intricate ways of synthesizing these non-racemic molecules with astoundingly high selectivity, artificial mimics were not able to reach the same level of enantiomeric excess (ee) for many decades [1,2]. Pioneering work into chiral induction was carried out by William S. Knowles, Ryōji Noyori and K. Barry Sharpless [1-5]. Transition metals have traditionally been considered key to the function of a good catalysts with their variable oxidation states, *d*-orbital availability, vacant coordination sites and complex stability, providing the basis for the modular development of stereospecific catalysts capable of effecting a broad range of transformations with an extensive substrate scope. However, this approach has inherent obstacles to overcome, some of which include toxicity and low relative abundances which in turn relates to catalyst cost. Many effective transition metal catalysts for chiral induction are based on rare low abundance metals such as platinum, palladium, iridium, rhodium and ruthenium, all of which are inherently expensive due to their scarce natural abundance [6-9]. The application of heavy-metal transition metal catalysts may also pose issues with certain applications in the pharmaceutical sector due to restrictions on their use, coupled with rigorous purification techniques to ensure their full removal from the final target drug [10,11]. This has stimulated the development of alternative catalytic systems that could give comparable results with lower costs and incorporating less toxic materials particularly within industrial or pharmacological settings.

Of the approaches to challenge the predominance of these *d*- and *f*-block catalysts, organocatalysis and more recently main group catalysis have been of particular importance due to their (usually) higher abundance and potentially lower toxicity. The tunability of main group catalysts is not as comprehensive as that of transition metals as they rely on the chemistry of *s*- and *p*-orbitals which are not as chemically versatile as their *d*-block counterparts. However, a recent review by Power highlights how heavier main group elements can mimic transition metals in certain instances in synthetically indispensable reactions such as the activation of H_2 in alkene, alkyne and arene hydrogenation as well as hydroformylation [12]. In particular, the potential, particularly for the heavier *p*-block metals, to exhibit multiple

oxidation states and versatile coordination geometries based upon multi-center bonding, coupled with tunable Lewis acidity, is now beginning to make them attractive alternatives to conventional transition metal based catalysis.

While asymmetric organocatalysis is now an established field [13-16], enantioselective main group catalysis is still in its infancy. In 2007, List reported that the view of conventional catalysis is "built on three rather than two pillars, namely biocatalysis, metal catalysis, and organocatalysis" [17]. We propose another dimension (or pillar) to this list, namely "main group catalysis". However, the question is how do we differentiate between main group catalysis and organocatalysis or indeed between main group metal and classical metal catalysis? Organocatalysts are often defined as small organic molecules that can catalyze a chemical reaction, which are typically composed of carbon, hydrogen, oxygen, nitrogen, sulfur or phosphorus where "an inorganic element is not part of the active principle" [17]. However, the definition of an "inorganic element" gets a bit ambiguous when looking at the *p*-block elements. Therefore, for the purpose of this review we have limited this to catalysis using the *s*-block elements and the *p*-block elements which are not typically considered as organocatalysts.



Scheme 1. Example reactions covered in this review.

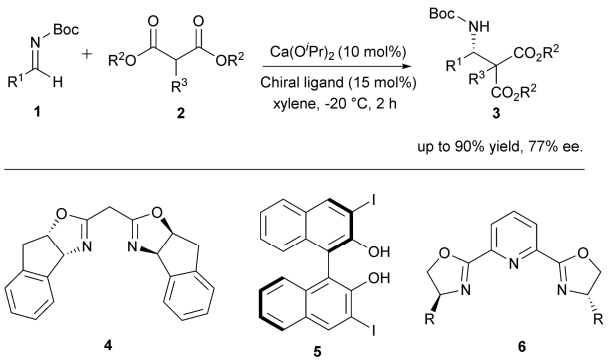
There has been a resurgence in main group chemistry in the past decade, with many *s*- and *p*-block centered systems acting as efficient catalysts in a vast multitude of reactions such as cyclizations, hydrogenations and annulations amongst many others [18-35]. Whilst many of these have been shown to be very effective, routinely obtaining quantitative conversions, any control of enantioselectivity has either been minimal or an incidental by-product. There has been a concerted effort by many eminent researchers in this area to champion the use of main group centered catalysts to compete with traditional transition metal catalysts, with many now having a strong foothold in common synthetic procedures. With this field now becoming widely established, the opportunity for these novel catalysts to effect enantioselective transformations is being realized with new insights into mechanistic details which in turn aids in catalysts and ligand design. Some of the topics described within concern the use of group 2 metals such as magnesium, calcium and strontium as catalytic centers with the utilization of several ligand systems such as BINOL, PyBOX, BOX and BOPA. The adaptation of these ligands combats the Schlenk equilibrium that is so often the cause of a lack of enantioselectivity due to ligand redistribution. Additionally, group 2 metals also have a large ionic radius compared to their heavier congeners progressing across the period, giving rise to the ability to bind substrates in a number of coordination sites in a fashion reminiscent of transition metals. However, the ionic radius is not the only property that lends to the ability to act as an effective catalyst, another consideration is the highly electropositive nature of the alkaline-earth metals and, in turn, the relative Lewis

acidity. In addition, electron deficient group 13 elements also play a critical role in many emerging catalytic systems [36]. Whilst the ability of lighter group 13 metalloids such as boron is limited in terms of coordination sites, as the reactivity is predominated by the vacant p_z orbital, the newly established field of frustrated Lewis pairs (FLPs) has utilized the electron deficiency of group 13 elements to great effect. The concept of frustrated Lewis pairs arises through the formation of bulky strongly Lewis acidic boranes [21-23,37,38] and borocations [39], and to a lesser extent phosphonium [40] and silylium cations [41-43], in conjunction with sterically crowded Lewis bases such as phosphines, amines or imine reactants, amongst others. This steric obstruction precludes adduct formation allowing interesting and unique transformations to take place as a result of the unquenched reactivity of these donor/acceptor moieties. The combined effort of these approaches has led to amazing progress being made in the last two decades in this rapidly expanding field. We shall describe how a new generation of catalysts based on main group elements now exhibit competitive reactivity in terms of yield and enantioselectivity when compared to transition metals specifically in the formation of C-C, C-H, C-N, C-O, and C-P bonds *inter alia* (Scheme 1). These new catalysts, if exploited, would undoubtedly lead to a revolution in the synthesis of fine chemicals and pharmaceutical agents building on the premise of an alternative to coinage metal catalysts and may change current perceptions of the chemical dominance of transition metals in catalysis.

2. Group 2-catalyzed Mannich reactions

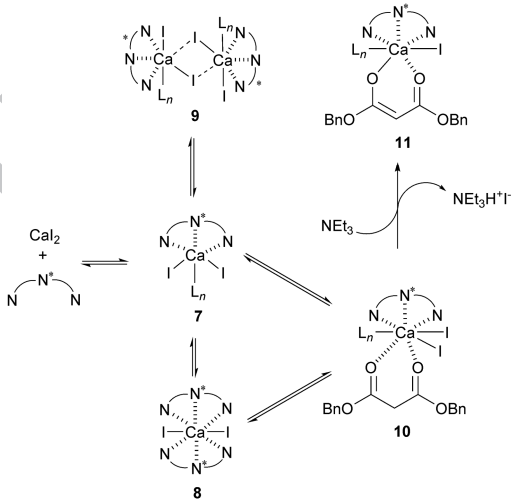
The Mannich condensation reaction is one of the best known synthetic routes for the formation of *β*-aminocarbonyl units through the addition of an enolizable aldehyde or malonate to a Schiff base *via* a nucleophilic addition reaction. These have been employed as useful precursors in medicinal chemistry and are the basis for many natural product synthetic pathways such as the preparation of β-lactams and β-amino acids [44,45]. When there are no stereochemical restraints employed, a mixture of *anti* and *syn* products are observed however, in certain cases preferential product formation has been shown albeit with some temperature dependence [46]. This is illustrated in the diastereotopic selectivity of the phenolic Mannich reaction reported by Rondot and co-workers in which thermodynamic control can be exploited to discern between products using a metal catalyst. Conducting the reaction at higher temperatures of 60 °C yielded the *syn* adduct, whereas decreasing the temperature to -10 °C led to the converse *anti* form [46]. The Mannich reaction can also be performed using group 2 metals with little alteration of the reaction conditions. However, the labile nature of many alkaline-earth complexes has hampered progress in this area through their tendency to undergo rapid ligand redistribution processes which may render the catalytic species inactive or unable to control the stereoselectivity [47,48]. Thus, the development of chiral Group 2 metal catalysts requires the development of appropriate ligands which bind strongly to the metal center whilst imparting significant stereo- and/or regio-control. Under ambient conditions, chiral alkaline-earth catalysts gave moderate to high enantioselectivities and yields in these types of Mannich reactions [33,49,50]. In recent years, the application of chiral calcium, strontium, and barium catalysts have been explored further, gaining remarkably good stereoselectivity (~70% ee) with little modification to the reaction conditions, with better selectivity observed at lower temperatures [51].

The formation of the asymmetric catalysts from the complexation of chiral ligands **4**–**6** and the calcium isopropoxide precatalyst (Scheme 2) are examples of successful enantioselective catalysts, whereby the chirality of the metal complex is imposed on the transition state leading to the products (**3**). One promising chiral ligand for use in conjunction with group 2 metals is the PyBOX ligand (**6**, Scheme 2) giving rise to excellent conversion (>79%), however with only moderate control over enantioselectivity at 40% ee. Substitution of the R-groups on the oxazoline backbone of **6** results in varying enhancements to ee values with the benzyl derivative giving the most promising results with a reported ee of 47% [51]. Modification of the reaction conditions adjust the product distribution, with lower temperatures interestingly giving a more racemic mixture in certain cases, whereas reaction at more ambient temperatures provides superior enantioselectivities. Further reducing the temperature, partial decomplexation of the calcium and ligand occurred, therefore free calcium-alkoxide allowed racemic background reactions to take place without the chiral influence [51]. Attempts to combat decomplexation processes by increasing the ligand:metal ratio resulted in higher enantioselectivities, *e.g.* using a 1:1.5 metal to ligand combination. By saturating the metal with ligand, it ensures that a chiral influence is present at the catalytic center for much of the catalysts lifetime. Further optimizations including solvent variation, such as reacting in xylene, while using a dibenzyl malonate substrate gave much improved selectivities (90% yield, 77% ee). This is comparable to transition metal catalyzed Mannich reactions [52,53] setting an interesting precedent for the future of this type of main group enantioselective catalysis [54].



Scheme 2. Ligand design for calcium-catalyzed Mannich reactions [51].

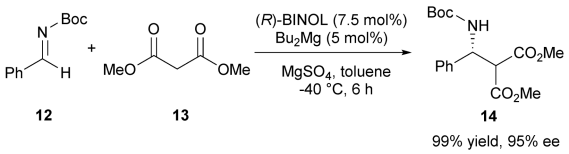
Furthermore, studies by the Kobayashi group built upon this body of work using the same PyBOX ligand **6** (R = Bn) in similar reactions between phenyl/butyl imines and benzyl malonate at -78 °C, however, CaI_2 was selected as the precatalyst instead of the commonly seen calcium isopropoxide [55]. Favorable conversions were noted at 89% with equally good enantioselectivities of 92% ee also being seen. Expanding the substrate scope to various aryl imines was then carried out using 5 mol% of catalyst loading with a wide variety of electron-donating and -withdrawing groups being used. Indeed, this system was tolerant to a vast array of functional groups, such as halogens, CF_3, OMe, furyl and thienyl *inter alia*, all giving good to excellent yields (66–99%) and enantioselectivities (81–96% ee). As before, a slight excess of PyBOX ligand was necessary (1:1.5 metal:ligand) to ensure decomplexation to the precatalyst is to be disfavored. In an interesting turn, applying this same system to aliphatic imines (R^1 = Et, ^{n}Pr, ^{i}Bu, ^{n}Pentyl, Scheme 2) also garnered excellent enantioselectivities of *ca.* 90% ee. To date, only a handful of catalysts, more often organocatalysts, could effect this reaction using aliphatic imines, moreover they would often require high catalyst loadings to generate enantiomerically enriched products [56]. The formation of the active catalyst was shown *via* NMR spectroscopy in a series of addition steps following the addition of the PyBOX ligand to CaI_2 which exists in equilibrium with the heteroleptic (**7**) and homoleptic (**8**) species (Scheme 3), with indications that the dinuclear species (**9**) was also being formed [57]. Both the hetero- and homoleptic system can undergo coordination of the malonate to give **10** with subsequent addition of excess NEt_3 to abstract one iodide equivalent giving the enolate complex **11** (Scheme 3). This activated complex could then undergo the Michael addition as expected, whilst being under the chiral influence of the PyBOX scaffold coordinated to calcium. Incidentally, these systems were effective under aerobic conditions, therefore the need for specialist equipment to strictly preclude oxygen and moisture was not necessarily requisite.



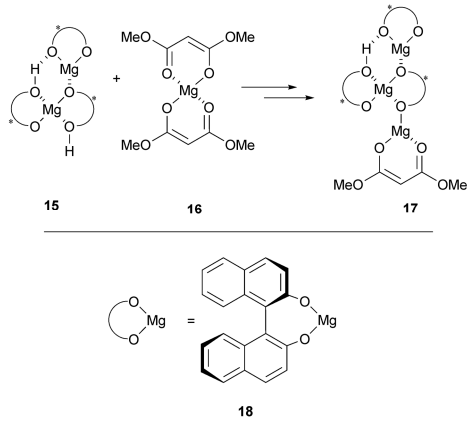
Scheme 3. Complexation and equilibria of CaI_2 PyBOX ligand system [55].

In a deviation away from calcium centered catalysts, Ishihara et al. showcased a series of transformations, such as hetero-Diels-Alder reactions, phosphonylations and Mannich addition reactions using a magnesium BINOL system [58]. Much the same as other group 2 chemistry, facile ligand redistribution occurred with potential problems lying in unwanted oligomerization/polymerization. Previous work within the same group saw that the addition of highly coordinative molecules such as water or alcohols functioned as a co-catalyst [59], thus precluding such oligomerization. In this study, however, water was not needed and in fact, decreased catalytic turnover. Again, a common motif of these alkaline-earth metal systems was necessary to control molar ratios of ligand to metal. Whilst carrying out the reaction between the aldimine **12** and methyl malonate **13** (Scheme 4) in a stoichiometric ratio gave very favorable returns (97% yield, 92% ee), whilst

increasing to a 2:3 metal:ligand ratio improved these results to 99% yield and 95% ee. In contrast, the inverse ratio hindered the selectivity as expected giving a good insight into the potential reaction coordinate and geometry of these active magnesium centers.



Scheme 4. Mg-catalyzed Mannich reaction of malonate to aldimine [58].



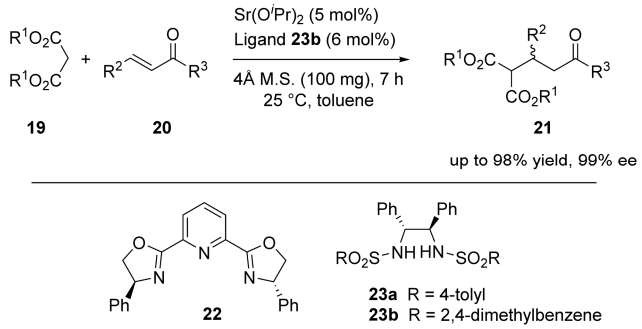
Scheme 5. Formation of supramolecular catalyst **17** [58].

The concept of the 2:3 supramolecular complex observed here has been noted previously in other reactivity, particularly in the phosphonylation of α,β-unsaturated ketones, however were hitherto unknown for the Mannich reaction [60]. It was this structure **17** that controlled the absolute stereochemistry of the reaction through a series of steps initiated by the Brønsted basic naphthoxide moiety activating the malonate followed by activation of the aldimine by the Brønsted acidic naphthol unit. When combined, the active center is flanked by the enantiomerically pure BINOL ligands thus conferring the chirality upon the final product. Indeed, further studies into the mechanism were carried out by looking at the relationship between (*R*)-BINOL and the absolute stereochemistry of the product. Through these studies, a negative non-linear relationship emerged thus lending credence to the hypothesized 2:3 supramolecular structure [58].

Such advances in calcium and magnesium catalysis truly consolidates the position of main group elements in catalysis, and challenges the traditional notion that the chemical flexibility provided by *d*-orbitals are necessary to undergo complex reaction pathways, especially in asymmetric induction.

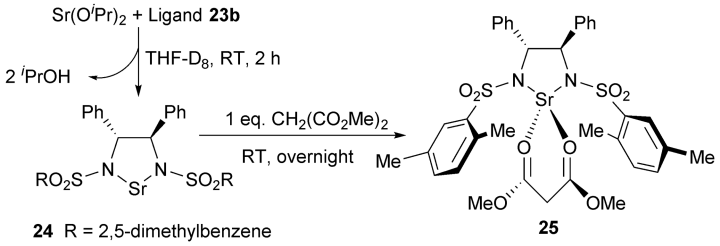
3. Group 2-catalyzed 1,4-addition reactions

The Michael reaction is one of the most powerful carbon-carbon bond forming reactions proceeding *via* the conjugate addition of a carbanion or other nucleophile to an α,β-unsaturated carbonyl compound [61], hence this pathway enables the construction of a diverse array of various products from relatively simple starting materials. The use of group 2 metals in these types of transformations has been established with ongoing research into further broadening the applications to a wider variety of substrates [62,63]. Indeed, calcium catalysts have been utilized for 1,4-addition reactions, yet improvements to the selectivity were observed with heavier group 2 elements with recent studies showing promise whilst using the PyBOX ligand system **22** derived from that mentioned earlier (see **6**, Scheme 2). Further enhancements were made by using the sulfonamide ligands **23a,b** displaying central chirality on the ethylene bridge of the bidentate ligand backbone (Scheme 6).



Scheme 6. Conjugate addition between a malonate and α,β-unsaturated ketone using various asymmetric group 2 metal complexes [63].

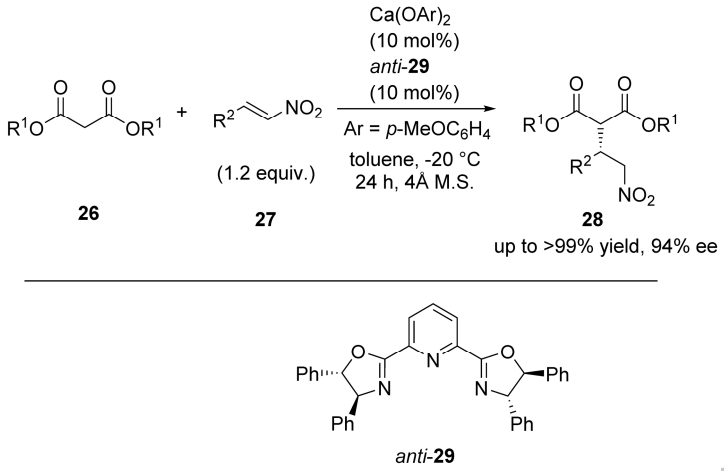
The substitution of calcium for strontium as the active metal center gave far superior enantioselectivities. While calcium has been the focus of vast amounts of research [35,64], strontium catalysts are not as well established in spite of their relatively high abundance in the earth's crust [65]. This catalytic setup was applicable to a number of differing substrates including electron-withdrawing and -donating groups on both the malonate and α,β-unsaturated ketones, all of which leading to excellent enantioselectivity (>94% ee) [63]. The strontium catalyst **24** was generated by the addition of a chiral ligand **23b** to Sr(O^{i}Pr)$_2$ in the same way as the active calcium species earlier (Scheme 2). As the ligand displaced the isopropoxide group to form isopropyl alcohol, the concomitant formation of the active strontium species **24** occurred giving the chiral backbone needed for the effective enantioselective Michael addition (Scheme 7).



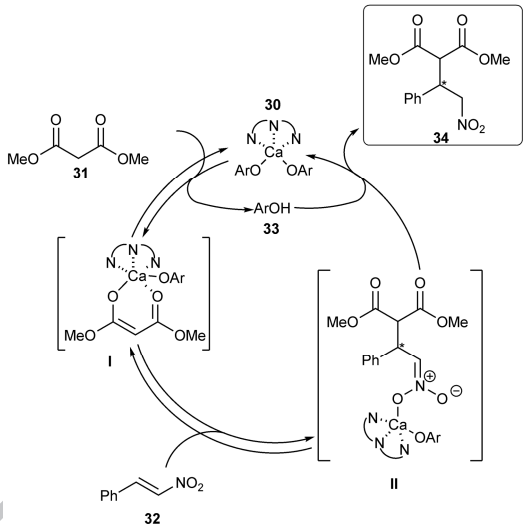
Scheme 7. Active strontium catalyst formation and malonate coordination [63].

Other 1,4-addition reactions have been observed, such as the reaction of 1,3-dicarbonyl with nitroalkenes (Scheme 8) [66]. This pathway is incredibly useful in the preparation of chiral γ-nitro carbonyl species **28**, leading to asymmetric amines through subsequent reduction reactions. The reactivity of the metal center was screened in these 1,4-additions, finding that calcium, once again, was the metal of choice over strontium [66]. The chiral PyBOX ligand could be fine-tuned to give the best enantioselectivity with good examples being seen in the employment of the *anti*-5,4-diphenyl PyBOX ligand **29**.

In a deviation from the previously established Ca(O^{i}Pr)$_2$ precatalyst, Kobayashi et al. found that using Ca(OC$_6$H$_4$Me)$_2$ led to greater selectivity with subsequent catalyst formation with the chiral PyBOX ligand **29** [66]. A wide range of substrates were suitable in this catalytic cycle from aliphatic chains to substituted aryl components with all but a few showing excellent enantioselectivities typically above 85% ee. The exceptions being *ortho*-substituted aryl derivatives and bulky ^{t}Bu groups. The lack of enantiospecificity in these cases is suggested to result from steric constraints affording unfavorable high energy transition states when compared to the other less hindered derivatives [66]. In the same study, the catalytic cycle was posited to proceed *via* dissociation of an ArO$^-$ ligand followed by enolization of the malonate by deprotonation of the α-carbon and subsequent coordination to the calcium center (**I**, Scheme 9). This is then set up for the 1,4-addition of the β-nitrostyrene leading to the nitro-calcium adduct (**II**, Scheme 9) followed by protonation to give the final chiral addition product **34** and regenerated catalyst agreeing with other work using carboxylic acid moieties such as those derived from amino acids [62,67].

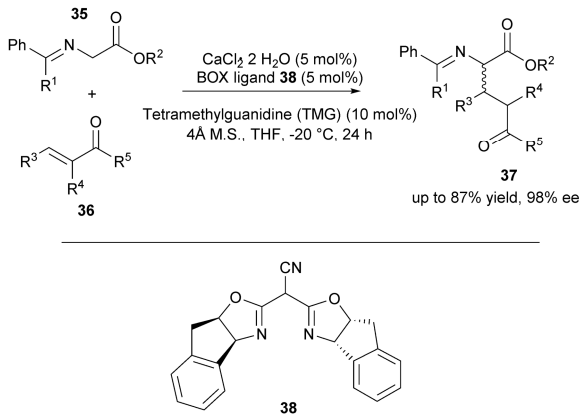


Scheme 8. Catalytic malonate addition reaction using calcium PyBOX complex [66].



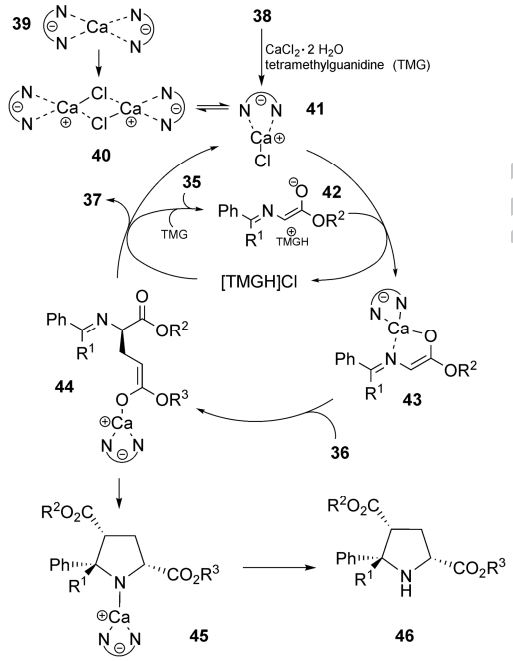
Scheme 9. Proposed catalytic cycle of calcium-catalyzed addition reaction to nitro-styrene [66].

More recent work from the Kobayashi group has led to some truly remarkable enantioselectivity in the comparable 1,4-addition reactions between azomethine precursors (**35**) and α,β-unsaturated compounds (**36**). This furnished glutamic acid derivatives such as **37** through the employment of a $CaCl_2$ or $Ca(OTf)_2$ precatalyst in conjunction with various chiral bisoxazoline ligands (Scheme 10).



Scheme 10. 1,4-addition between azomethine and α,β-unsaturated ester [62].

Very good yields as well as excellent enantioselectivities were recorded, 87% and 98% ee respectively, when using optimized conditions involving the indane functionalized BOX ligand (**38**, Schemes 10 and 11) [68]. Further to this, a tandem 1,4-addition/[3+2] cycloaddition could occur depending on the enolate that was employed. The less nucleophilic enolate proceeded through the proposed addition process followed by protonation to yield the Schiff base functionalized glutamic acid **37**, whereas in the case where a more nucleophilic enolate was used, the intermediate could undergo a [3+2] cycloaddition followed by protonation to give the functionalized pyrrolidine **46** (Scheme 11) with enantioselectivities routinely exceeding 90% ee [68]. Supplementary organic transformations have been effected by similar Ca-BOX systems such as the installation of chiral tertiary and quaternary centers on 3-tetrasubstituted oxindoles further displaying the increased versatility of these calcium catalysts in contrast to previous assertions that such systems were incapable of effecting a wide selection of reactions in such good enantioselectivity [69,70].



Scheme 11. Proposed 1,4-addition mechanism using BOX ligand and $CaCl_2$ precatalyst [68].

The incorporation of an alkaline-earth metal in this transformation demonstrates the ability for these main group elements to effect complex transformations due in part to their Lewis acidity and large ionic radius. With effective tuning of the steric constraints and electronic properties of the ligand systems that are used, the boundaries of calcium and strontium catalyzed enantioselective 1,4-addition reactions are being extended, with outstanding progress being made with some very promising yields and enantioselectivities being reported covering a broad substrate scope and application.

4. Silylation of ketones and imines

Whilst many elegant methods for hydrosilylation exist, most employ transition metal catalysts such as iridium, platinum, rhodium and ruthenium to gain enantioselectivity [71-73]. Recent reports show that Group 2 metals also have a role in hydrosilylation and hydrogenation as mimetic models for organo-lanthanide catalysts [74], with calcium and strontium being used as the active metal center [75,76]. These main group catalysts can provide stark improvements over conventional transition metal catalysts as they provide the clean synthesis of the siloxy product with good regio-control with a distinct lack of alkene isomerization in opposition to the Speier and Karstedt transition metal catalysts [76]. By using 1,1-diphenylethylene (DPE), an alkene that is unable to polymerize, and calcium catalysts (**47** and **48**, Figure 1) hydrosilylation occurs to give the corresponding 1,2-addition product. Whilst both the homoleptic and heteroleptic calcium and strontium catalysts are effective at forming the silane product with good regio-control, the stereo-selectivity is not controlled and is therefore unselective. This is attributed to the fact that the heteroleptic species exists in Schlenk equilibria with the homoleptic catalysts in a ratio of approximately 4:1:1 (Scheme 12).

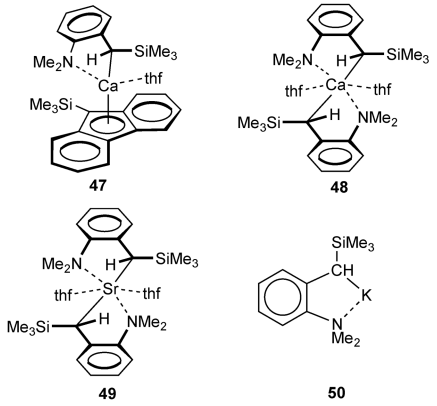
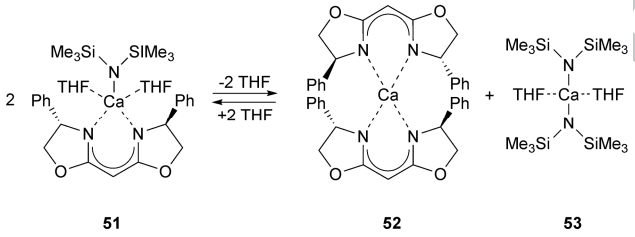


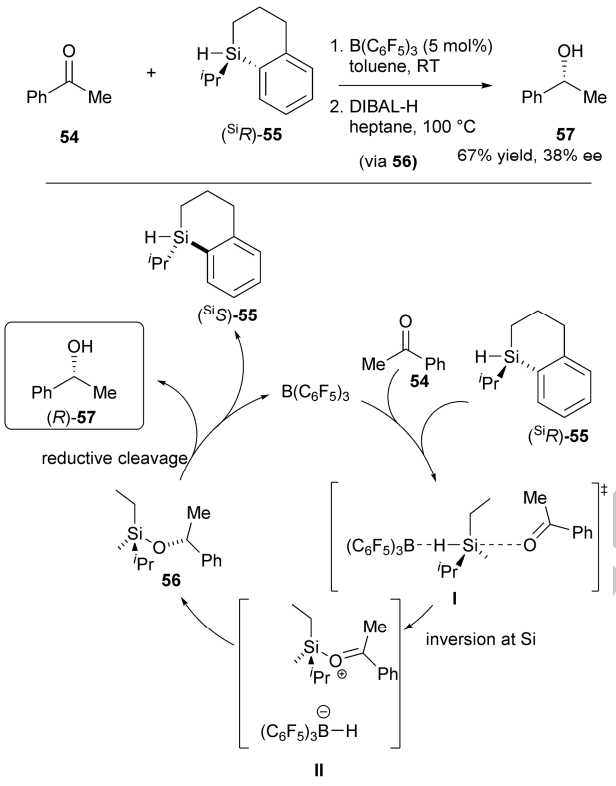
Figure 1. Range of group 2 homoleptic and heteroleptic catalysts [76].



Scheme 12. Schlenk equilibrium between homoleptic and heteroleptic catalysts [77].

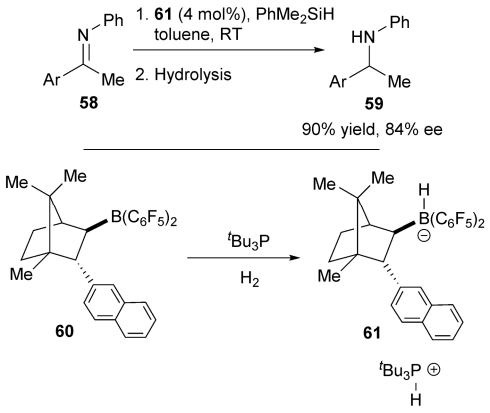
The observed poor selectivity is a result of this equilibrium with **52** being inactive as a catalyst, conversely the homoleptic species **53** is active leading to increased racemization. This equilibrium can be directed through the addition of the inactive species **53** driving the equilibrium toward **51** (Scheme 12) [77]. This shift in equilibrium gives the heteroleptic species **51** in greater quantities, leading to more effective asymmetric induction. As the use of group 2 metals in this field is still in development, only poor enantiomeric excess values have been reported to date (*ca.* 10%), although better results have been noted using different catalytic systems [77].

Other more recent discoveries have been made by using strongly Lewis acidic group 13 elements, namely boranes. Early reports by Piers outline the use of the strongly Lewis acidic borane $B(C_6F_5)_3$ along with various silanes (*e.g.* Ph_3SiH, Et_3SiH and $PhMe_2SiH$) in metal-free catalytic hydrosilylation of imines, aldehydes, ketones, and esters. However, these reactions had no control over the enantioselectivity and hence gave racemic mixtures [78-81]. This concept was expanded in further mechanistic studies outlined by Oestreich et al. whereby the simple activation of the carbonyl moiety by the tertiary silane followed by hydride abstraction by the strong Lewis acid $B(C_6F_5)_3$ led to the ion pair being formed (**II**, Scheme 13). Hydride transfer to the carbonyl then afforded the final silyl ether species **56** and the regenerated Lewis acid catalyst. This study utilized an enantiomerically enriched silane precursor to dictate the chirality of the alcohol product with this transformation leading to some moderate enantioselectivities (38% ee) without any optimization providing a good basis for further development. The Oestreich group showed that the reaction proceeded *via* an S_N2 mechanism as complete inversion was seen at silicon (**I**, Scheme 13). The silylated product **56** was then subjected to reductive cleavage using diisobutylaluminum hydride (DIBAL-H) to yield the alcohol **57** retaining the stereochemistry inferred by the silane to give the observed *R*-configuration [82,83].



Scheme 13. Catalytic hydrosilylation of ketones using $B(C_6F_5)_3$ proposed by Oestreich [82].

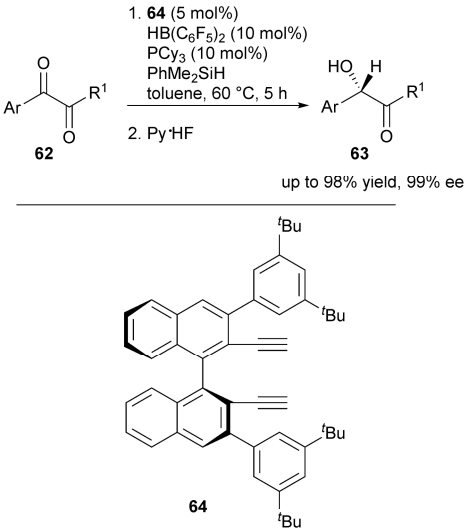
Other advances have been made within this field by Klankermayer when introducing camphor-derived boranes and phosphonium borates similar to those observed in hydrogenation reactions (see Section 5). Indeed these systems constitute frustrated Lewis pairs (FLPs), whereby the combination of sterically hindered Lewis acids, the archetypal example being $B(C_6F_5)_3$, and equally bulky Lewis bases such as $^tBu_3P$ leads to the inability to form the classic Lewis adduct [37]. This reactivity, made famous by Stephan et al. primarily in the heterolytic cleavage of H_2, has found prominence in many other aspects of main group catalysis, more recently in enantioselective hydrosilylation. When using the naphthyl-functionalized camphorylborane (**60**, Scheme 14) in the absence of a bulky Lewis base, high yields were reported in the hydrosilylation of 1-diphenylethan-1-imine (**58**) but afforded an almost racemic mixture. Incorporation of a sterically demanding Lewis base ($^tBu_3P$) unfortunately reduced the recovered yield to 50%, but markedly improved the ratio of enantiomerically enriched products (83%). This was however overcome by equipping the imine substrate with electron-donating 4-methoxyphenyl groups at either the C or N position in order to give one of the best conversions at 90% with an ee of 84% [84].



Scheme 14. Hydrosilylation and subsequent hydrolysis of imines using camphoryl borane [84].

In a similar vein, recent studies by Du et al. have focused on the use of the BINOL-derived axially chiral diboranes similar to those developed by the Klankermayer group for use in hydrogenation reactions (see Section 5, Figure 3). 1,2-Hydroboration of the diyne

functionalized BINOL system **64** using Piers' borane yields, as expected, the active diborane catalyst (Scheme 15). When benzil (**62**) was subjected to the diborane alone, moderate enantioselectivities were garnered at 22% ee. However, when sterically encumbered phosphines were employed, in particular PCy_3 this enantiomeric excess was vastly increased to 98%. An expansive number of benzil derivatives were tested including various halogenated, electron-donating and -withdrawing aryl groups with nearly all being very high yielding, whilst being equally exceptional at generating enantiomerically enriched products with the majority offering enantioselectivities in the range 95 – 99% ee [85]. The success of this methodology spawned a new generation of catalyst from Oestreich and co-workers whereby transmetallation of an axially chiral BINAP Sn^{IV} species with $(C_6F_5)BCl_2$ gave the mononuclear chiral boron catalyst similar in nature to those championed by Du. These systems also proved to be very successful in hydrosilylation of ketones, giving full conversion in almost all cases with generally impressive ees that reached up to 99%, with the majority achieving a minimum of 80%. A slight drawback of this approach was the long reaction times, nevertheless the transformations were carried out at ambient temperatures and appeared to be generally tolerant of various electronic effect, however, the slightly more bulky substrates, such as mesitylacetophenone, were isolated in only 12% yield and 17% ee indicating steric crowding could inhibit some reactivity [86].



Scheme 15. Hydrosilylation and subsequent hydrolysis of benzyl using BINOL framework [85].

Other variations of silylation reactions exist such as cyanohydrin synthesis from aldehydes using TMSCN in the presence of a lithium binaphtholate complex [87], or related cyanosilylation reactions as reported by Corey and co-workers with a novel methodology to install both trimethylsilyl and nitrile functionalities using an oxazoborolidinium catalyst (**65**, Figure 2) [88,89]. In previous studies, this transformation was more often conducted using heavier metals such as titanium [90], lanthanide [91] or systems derived from more biologically inspired routes including the use of aluminum co-catalysts [92,93]. However, work by the Corey group in this area showed effective enantioselective formation of cyanohydrin derivatives from aldehydes with isolated yields of 94% and enantioselectivities as high as 95% ee [88]. With this premise set, this chemistry was poised to be extended to a wider variation of substrates namely various methyl ketones. Contrary to the classic cyanohydrin addition reactions that utilize trimethylsilyl cyanide as the cyanide donor, the combination of TMSCN with diphenylmethylphosphine oxide gave the corresponding activated attacking isocyanide group as $Ph_2MeP(OTMS)(N{\equiv}C{:})$. Once complexation of the Lewis basic ketone to the Lewis acidic boron of the catalyst occurs, *si*-face attack of the cyanide takes place preferentially as the *re*-face is blocked by the aryl rings of the catalyst periphery (Figure 2). Condition optimization saw that catalyst **65** was the most effective when reacted in toluene under ambient to mild conditions [89].

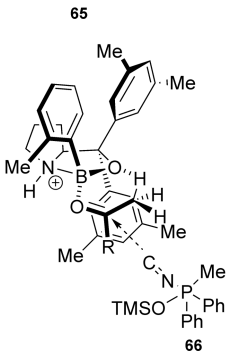


Figure 2. Transition state of oxazoborolidinium-catalyzed cyanosilylation [89].

Substitution at the *para* position of acetophenone moiety strongly affects the conversion and asymmetric transformation *e.g.* *p*-OMe (45%, 32% ee) and *p*-NO_2 (83%, 96% ee). The addition of an electron-withdrawing group in the *para* position decreases the basicity of the carbonyl functionality, leading to reduced catalyst activity due to weaker complexation. However, the cyanosilylation step would occur sooner in comparison to the acetophenones with enhanced basicity, in addition there would be enhanced attractive forces between the coordinated methyl ketone carbonyl and the adjacent electron-rich π-system of the aryl group of **65**. The basis for this catalyst has also been extended to further reactions such as in the Diels-Alder step in the formation of giberellic acid giving the corresponding addition product in 99% ee [94].

5. Hydrogenation reactions using group 13 Lewis acids and frustrated Lewis pairs

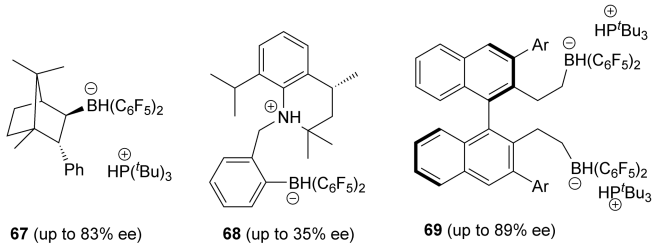
Asymmetric hydrogenation, as with most enantioselective techniques, routinely uses transition metals to gain the desired chiral product [95-99]. In light of recent breakthroughs in the field of frustrated Lewis pairs, new catalysts have been introduced that can reversibly activate hydrogen (amongst other small molecules) to add across unsaturated double bonds such as alkenes, alkynes, allenes and imines *inter alia* [21,100,101]. The ability to activate, in a reversible manner, traditionally inert small molecules comes from the unique reactivity displayed by these FLP systems. This unquenched reactivity readily furnishes the heterolytic cleavage of H_2, resulting in protic and hydridic moieties which can easily facilitate addition reactions across unsaturated frameworks [37].

Preliminary studies into enantioselective FLP hydrogenation by Klankermayer et al. using an electrophilic borane derived from pinene produced only moderate enantioselectivities (13% ee) when used in the hydrogenation of imines [102]. However, when using the borylated camphor derivative, combined with a sterically hindered phosphine (**67**) in the same transformation, marked improvements were achieved by furnishing the hydrogenated product in 83% ee [103]. Indeed, an advantage of such derivatives, such as the pinene and camphor motif is that they could be readily obtained from the chiral pool, and could subsequently induce asymmetry when located proximal to the boron center to obtain chiral carbon centers [102,104]. Further work by Stephan et al. probed the use of chiral phosphines in FLP hydrogenations to induce stereocenters in the reduction of the model imine, Ph(Me)C=NPh. However, this was met with limited success with the best system being the combination of $B(C_6F_5)_3$/(*S,S*)-diop being used in 20 mol% whilst being heated to 100 °C. This returned modest enantioselectivities at only 25% ee, however, almost complete conversion was obtained. This low stereoselectivity was due to the mechanistic aspects of the FLP proton/hydride delivery. As the process of hydrogen delivery is thought to be initiated by protonation of the imine by the phosphonium followed by hydride transfer from hydridoborate, it was not surprising that the chiral influence of the phosphine was not present upon hydride delivery as any NH···P hydrogen bonding would be very weak [105].

In light of this, new catalyst designs from Repo et al. incorporated the idea of *ansa*-amino-boranes (**68**) in which the Lewis basic and Lewis acidic functionalities are in close vicinity to one another on the same scaffold yet bulky substituents prevent effective orbital overlap [106,107]. However, this catalyst displayed a reduced proclivity to hydrogenate imine substrates with only moderate enantioselectivities were achieved (< 35% ee), although were an improvement on intermolecular FLP systems seen above. Work by Du et al. showed very good preliminary results with enantioselectivities exceeding 80% ee using bifunctionalized diborane catalysts (**69**) derived from BINAP structures which displayed much better promise of the same imine hydrogenation [108]. Optimizing these conditions produced greatly enhanced results giving a conversion of >90% with enantioselectivities also exceeding the 80% ee mark [108,109]. Indeed, the successful activation of a wider substrate scope using this catalyst was also possible including hydrogenation of silyl enol ethers, pyridines and 2,3-substituted quinoxalines to give highly *cis* selective products in up to 96% ee in the latter case [109-112].

Further to this body of work, the Repo group set to amalgamate ideas set forth by Klankermayer and Du, with an elegant catalyst design being proposed which constituted both intramolecular FLPs and axially chiral BINAP ligands offering outstanding results in the

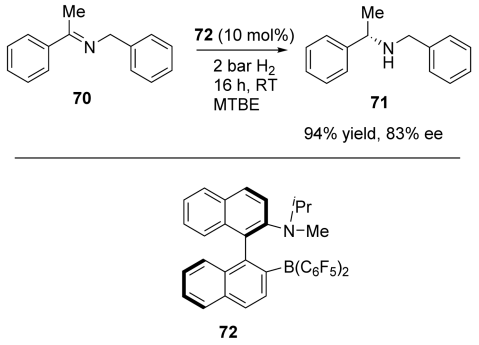
hydrogenation of imines [113]. The addition of H_2 at 2 bar at ambient temperature to the intramolecular FLP **72** gave rapid cleavage of elemental hydrogen to give the active ammonium borate catalyst. When this was introduced to the unsaturated substrate **70**, only poor conversion was seen initially when reacted in toluene with a 10 mol% loading, however optimization led to a tremendous increase in both ee (83%) and conversion (94%). Expansion of this reaction led to a range of acetophenone based substrates which underwent hydrogenation in a varying array of enantioselectivities (32 – 83% ee), as well as enamines which displayed marked improvement in conversion (99% by ^{1}H NMR spectroscopy) and enantiomeric excess (47 – 99%) [113].



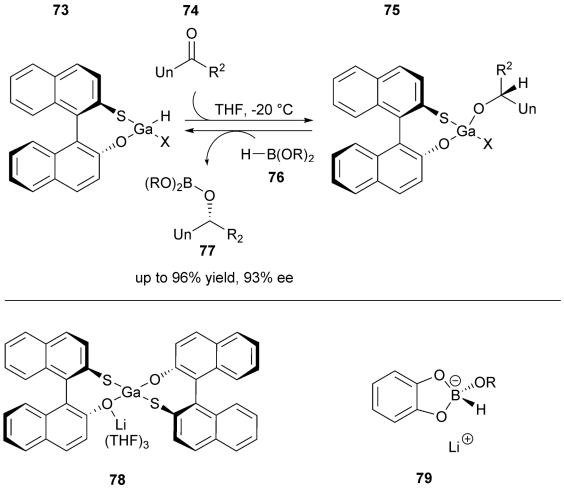
67 (up to 83% ee) **68** (up to 35% ee) **69** (up to 89% ee)

Figure 3. Recent FLP catalysts for hydrogenation reactions [113].

Other interesting methodologies exploiting the ubiquitous BINAP framework have been reported and include the work of Woodward and co-workers in the transfer hydrogenation of ketones using gallium catalysts (**73** and **78,** Scheme 17) in the presence of catecholborane. Excellent yields and enantioselectivities were reported gaining up to 96% conversion in excess of 90% ee [114]. These systems were similar in nature to the aluminum Shibasaki catalysts used in the phosphonylation of ketones (see section 7).



Scheme 16. Hydrogenation using asymmetric FLP based catalyst to form **71** [113]. MTBE = methyl ^{t}butyl ether



Scheme 17. Ga-catalyzed transfer hydrogenation of unsaturated ketones. (Un = unsaturated functionality) [114].

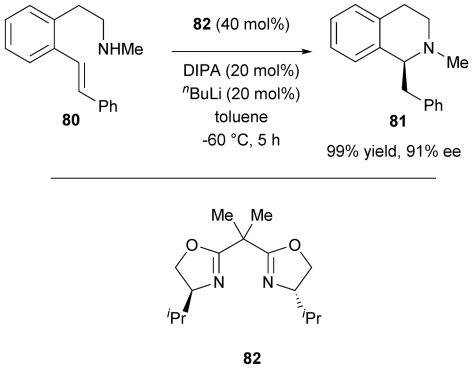
In addition to these Lewis acidic boranes, borocations have recently emerged as an effective substitute for the Lewis acidic component in FLP chemistry [115-118]. The inclusion of a formal positive charge on boron aids in the modularity of the reactive center resulting in the

necessity for strongly electron-withdrawing groups (such as C_6F_5-groups) now becoming more optional. Nearly all studies to date focus mainly on the hydrogenation of carbon-heteroatom unsaturated frameworks such as imines in an analogous fashion as mentioned earlier in this section. However, without any chiral information being present, the products are garnered as a racemate. To this end, work by Stephan, Crudden and Melen et al. utilized chiral carbene-stabilized borenium Lewis acids in enantioselective FLP hydrogenation of imines [119]. In this work borenium cations are formed through the coordination of various N-heterocyclic carbene (NHC) units, including those derived from camphoric acid precursors, to 9-borabicyclo(3.3.1)nonane (9-BBN), diisopinocamphyl borane (Ipc_2BH) or Piers' borane ($HB(C_6F_5)_2$) followed by hydride abstraction with $[Ph_3C][B(C_6F_5)_4]$. Some of these novel systems indeed prove to be very active catalysts in hydrogenation reactions with quantitative yields being observed *via* NMR spectroscopy. However, enantioselectivities have been far more modest with the greatest being recorded at 20% ee, with most examples presenting at *ca*. 10%. This does however provide excellent groundwork to build upon, with further catalyst designs being proposed by this collaborative effort.

The inception of FLP chemistry has proved to be instrumental in order to effect enantioselective hydrogenation reactions as the ability of main group metals of cleanly cleave dihydrogen was hitherto unknown in main group catalysis. The incorporation of common chiral motifs such as BINOL as well as structures derived from the chiral pool allow this unique reactivity to be exploited to gain asymmetric products in excellent yields with very good to excellent enantioselectivities also being noted. As this field of main group catalysis is still in its infancy, there is an abundance of exciting avenues still left to explore, thus confirming FLP chemistry as an integral component in chiral induction reactions.

6. Hydroamination reactions with *s*-block elements

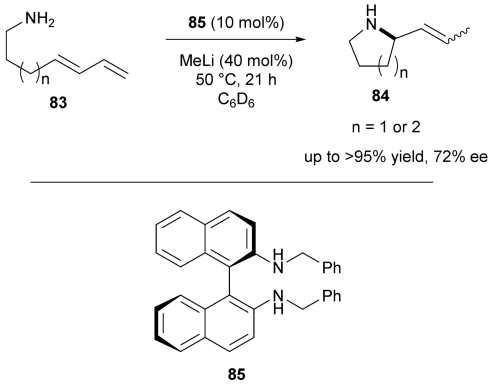
Rare transition metals, such as iridium and palladium, dominate the field of catalyzed hydroamination reactions [8,120-123], as is the case with most modern catalytic pathways, but new studies show that this process can be carried out using alkaline earth metals, such as magnesium, calcium and lithium, to give enantiomerically enriched products [33,124]. Avenues that have been investigated in the hydroamination of alkenes involve the lithium centered bisoxazoline complexes, analogous to that investigated by Ward et al. seen later in this section. Early work by Tomioka et al. used the chiral bisoxazoline ligand **82** in conjunction with ^{n}BuLi and the secondary amine precursor **80** to effect a 6-*exo*-trig cyclization to yield the tetrahydroisoquinoline **81** (Scheme 18) [125]. At -60 °C, the resulting conversion was poor at 6% however moderate enantiomeric excess was gained (54%). This was improved upon through reducing the loading of ligand **82** and ^{n}BuLi to 40 and 20 mol% respectively. While the reaction at -60 °C displayed both an improvement in yield and ee, further enhancements could be made. Attempting the reaction under the same conditions but at ambient temperature now gave essentially quantitative conversion, however the ee was slightly reduced as a result. The addition of diisopropylamine (DIPA) was then trialled as an external protonating agent and indeed in the presence of 20 mol% diisopropylamine the reaction proceeded quantitatively with a reasonably good enantiomeric excess of 91%. The bisoxazoline ligand was then altered with a series of aliphatic groups in place of the ^{i}Pr units, however in most cases the ee did not improve significantly above 75-85% regardless of the steric bulk added to the ligand (other than ^{t}Bu where ee = 19%).



Scheme 18. Hydroamination using Li-BOX catalyst *via exo*-cyclization [125].

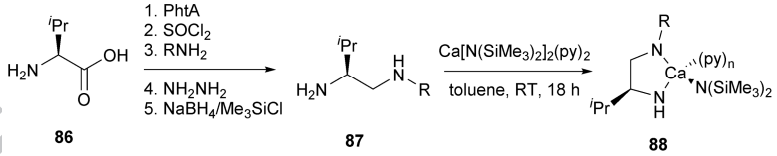
Another approach by Collin et al. pursued the application of diaminobinaphthyl frameworks in a similar fashion described by Tomioka previously whereby the diaminobinaphthyl ligand **85** was treated with MeLi in a 1:4 ratio to give the active catalyst *in situ* which was then applied to the cyclohydroamination of amino-1,3-dienes **83** (Scheme 19) [126]. Using 10 mol% of catalyst Li-**85** in ethereal solvent resulted in the clean *exo*-cyclization in as little as 20 minutes and 51% ee. Changing from THF to diethyl ether conferred a slight increase in activity, however the enantioselectivity was slightly diminished as a result. Additionally, reducing catalyst loading from 10 mol% to 2 mol% only had a slight deleterious effect on the enantioselectivity. Altering the chiral ligand **85** to include mesityl, pyridyl, cyclopentyl or ^{t}Bu functionalities instead of the phenyl moiety did not lead to any enhancements in terms of selectivity or reactivity, hence was concluded that steric

obstruction of the active site through N bound groups was not conditional to infer chirality. This methodology was later applied to form the six-membered functionalized piperidine structures with relatively good enantioselectivities at 72% ee.



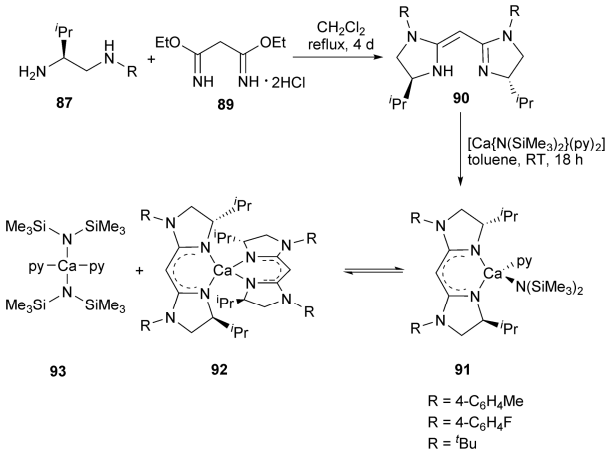
Scheme 19. Hydroamination using amine functionalized Li-BINOL system [126].

Recent attempts to use the chiral calcium-BOX system observed in hydrosilylation reactions (see Scheme 12, section 4) have shown promise at inducing stereogenic centers in hydroamination reactions producing almost complete conversion, however, the scope of the reaction was limited to intramolecular cyclization as before, with poor enantioselectivities being reported (*ca* 10% ee). It can be hypothesized that similarly poor enantiomeric excess is seen for the same reasons as observed in hydrosilylation reactions [127-129]. As stated previously, one of the issues that sometimes opposes the widespread utilization of group 2 centered catalysts, in particular calcium, is their propensity for rapid ligand redistribution. There have been many attempts to create group 2 catalysts that inhibit such redistributions, such as the work by Ward et al. This group were indeed successful in synthesizing a heteroleptic calcium catalyst *via* the coordination of a bidentate ethylene diamine ligand **87** generated from enantiomerically pure L-valine starting material **86** (Scheme 20) [127]. Whilst the idea is novel, with the utilization of relatively low cost commercially available starting materials and comparative ease of synthesis, the propensity to form stereochemically enriched products is still modest with these systems. Examinations into the lepticity of the active species showed similar trends as with previous catalysts, the heteroleptic species **88** was the active species while the homoleptic compound produced no conversion or a racemate. A range of these catalysts were tested in hydroamination reactions *via* intramolecular cyclization of amino-olefin substrates containing either methyl or phenyl groups in the 2-position. Varying results were obtained ranging from 0 – >99% conversion, with the most noteworthy outcome being a conversion of 80% with a relatively good ee of 26% when compared to the work Kobayashi et al. [33]. The minutia of why this unexpectedly high selectivity has yet to be detailed, however, it is expected that π-π stacking of the phenyl rings on the diamine catalyst and substrate may have a stabilizing effect through the intermediate steps of the catalytic cycle.

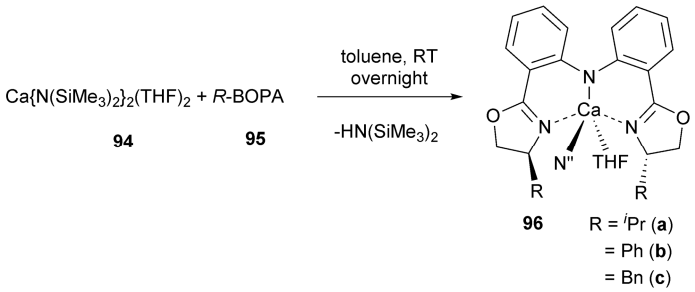


Scheme 20. Synthesis of chiral calcium catalyst from L-valine (PhtA = phthalimide) [127].

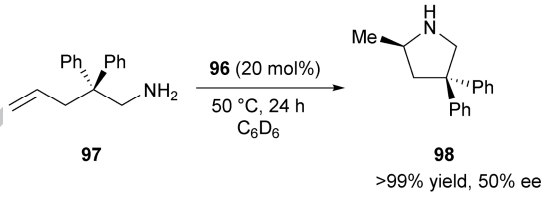
Further work by this group looked at the adaptation of these ethylene diamine ligands to form bisimidazoline ligands through the condensation reaction of the diamine **87** and Pinner salt **89** (Scheme 21) [128]. This adaptation proved detrimental to the function of the catalysts with selectivity of the cyclic hydroamination product being reduced to *ca* 10%. In this case the metal/ligand redistribution is more complex than a simple Schlenk-type equilibrium, indicating that the equilibrium position is of little consequence to the selectivity. Additional studies by the Ward group shifted focus to bis(oxazolinylphenyl) amine (BOPA) ligand systems (**96**) in an attempt to address the rate of ligand redistribution rather than the equilibrium of ligand transfer itself. To this end, BOPA ligands were developed in a bid to increase the steric influence about the calcium center by functionalizing the oxazoline moieties with ^{i}Pr, Ph and Bn groups.



Scheme 21. Formation of bisimidazoline calcium catalyst [128].



Scheme 22. Formation of heteroleptic Ca-BOPA system **96** [129].



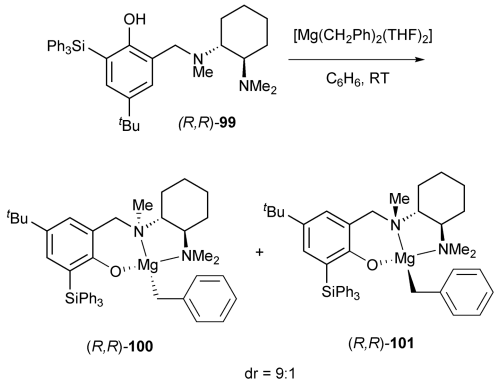
Scheme 23. Hydroamination of aminoalkene using Ca-BOPA system **96b** [129].

The incorporation of the more sterically crowded groups (specifically Ph, **96b**) retarded formation of the undesired Schlenk-type equilibrium. Promising results from the cyclohydroamination of 2,2-diphenylpent-4-en-1-amine (**97**) gave near quantitative yields of the corresponding pyrrolidine (**98**) with enantiomeric excesses reaching as high as 50%, a threshold that has yet to be broken by similar calcium-based catalysts for this reaction (Scheme 22 and 23) [129].

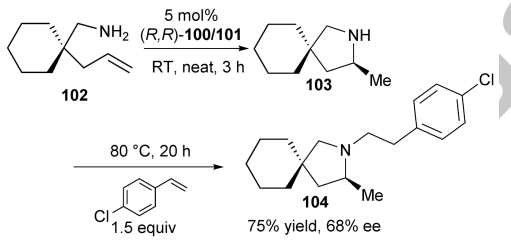
Work by Hultzsch et al. has focused on the synthesis of ligand systems that do not participate in this Schlenk-type rearrangement in attempts to improve on their previous generation catalysts which gave enantioselectivities of *ca* 25-35% ee [124]. To this end, the achiral phenoxyamine magnesium catalysts are immune to the facile ligand redistribution and, as a consequence, yield far superior results in terms of stereo-specificity with the reaction being conducted under milder conditions. The chiral magnesium catalyst (*R,R*)-**100/101** consists of a chelating cyclohexyldiamine linker to tether the magnesium center to the asymmetric backbone (Scheme 24). This backbone includes a triphenylsilyl group that acts to prevent ligand exchange due to the steric demand, leading to enhanced stereoselectivity over the previous generation catalysts [127,130,131]. This system was capable of activating a range of aminoalkene substrates to give cyclic amines in high yields and enantioselectivities even at reduced temperatures (typically greater than 80% ee).

Further applications showed that this catalyst could be used in tandem intramolecular/intermolecular hydroamination reactions of **102** to give the corresponding tertiary pyrrolidine **104** *via* **103** in good yields while maintaining a moderately high degree of enantioselectivity

(Scheme 25). It is postulated that the heavier group 2 alkaline earth metals will show enhanced catalytic activity for the reasons stated previously (see section 2) and are the focus of ongoing research.



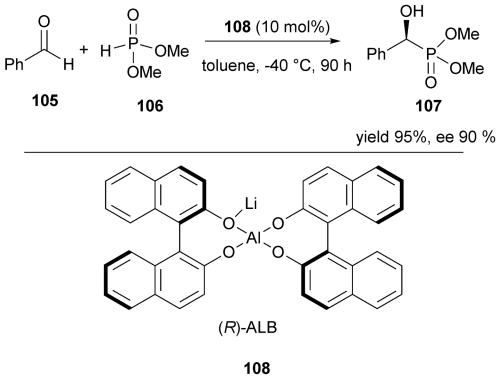
Scheme 24. Formation of active chiral magnesium catalyst [124].



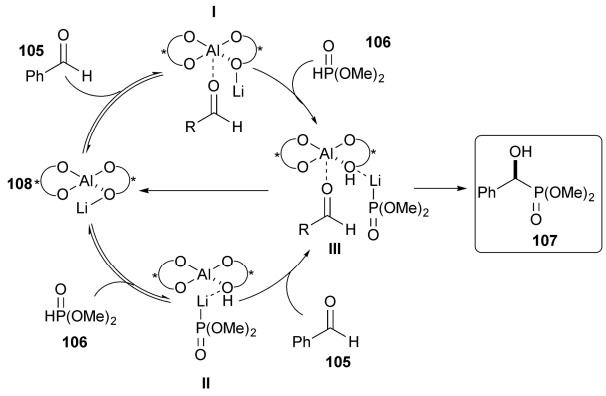
Scheme 25. Hydroamination using chiral magnesium catalyst **100/101** [124].

7. Aluminum-centered catalysts in phosphonylation reactions

While aluminum catalysts have been well documented as being effective for a broad spectrum of Lewis acid catalyzed reactions, such as Friedel-Crafts acylations, Alder-ene reactions, and polymerization reactions amongst others, they have also been used since the 1990's as an effective basis for asymmetric catalysis. Initial reports by Shibasaki et al. built on previous lanthanum-based catalysts to develop their aluminum counterparts which provided astounding reactivity and selectivity for first generation catalysts [132]. Indeed, aluminum catalysts play an important part in hydrophosphonylation of imines and aldehydes amongst others to form α-amino and α-hydroxy phosphonic acids respectively. The Al–Li–BINOL (ALB) catalyst **108** is certainly effective, owing in part to its bifunctionality with the aluminum metal center acting as a Lewis acid and the lithium BINOL system as a Lewis base (Scheme 26). A mechanistic pathway has been proposed illustrating this bifunctionality and how it is utilized during asymmetric transformations. The Lewis acidic aluminum coordinates the aldehyde (**I**, Scheme 27) followed by protonation of the lithiated BINOL and coordination of the remaining phosphonate moiety (**III**, Scheme 27). Once both the phosphonate and aldehyde are proximal to one another at the metal center, stereoselective addition of the phosphonate with concomitant protonation of the carbonyl generate the product **107** thus regenerating the ALB catalyst. It is mechanistically feasible that the addition of the phosphonate and aldehyde occurs reversibly *via* **I** and **II** respectively (Scheme 27), and thus are in equilibrium at the active center.



Scheme 26. Shibasaki 1st generation lithium aluminum BINOL catalyst **108** [132].



Scheme 27. Catalytic hydrophosphonylation cycle using **108** [132].

Further work in this field during the 2000's focused on optimizing the chiral backbone, deviating away from the bimetallic lithium BINOL system in favor of the Al-salen systems (**109** and **110**, Figure 4) [133-136]. Preliminary work into the functionality and application of aluminum salen systems by Kee et al. set ambitious aims to synthesize a metal catalyst that gives enantioselective products in the phospho-aldol reaction that is tunable, air and water stable, tolerant to varying substrates without the need for drying or special purification all while being recoverable and reusable [134]. To this end a catalyst that did indeed fit these strict criterion giving quantitative yields of a wide range of substrates was found, all while being carried out in aerobic, ambient conditions, however only modest ees (10-49%) were observed. Consequently, two pathways to phosphonylation were put forward, one whereby the tervalent phosphito moiety phosphonylates the aldehyde *via* a closed (Pathway 1, Scheme 28) or an open (Pathway 2, Scheme 28) transition state. Pathway 1 only concerns one active metal center whereby a sigmatropic rearrangement takes place breaking the carbonyl double bond (**I**, Scheme 28) and forming the more stable phosphorus oxygen double bond (**II**, Scheme 28) giving a chelating phosphonate and newly introduced chiral center at carbon. The second envisaged mechanism proceeding *via* a two metal center transition state whereby dual activation of both carbonyl and phosphate takes place (**III** and **IV**, Scheme 28) with subsequent rearrangement as before yielding the newly formed chiral phosphonylated product.

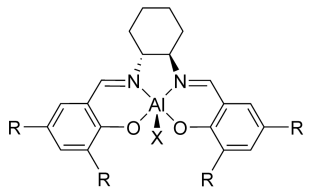
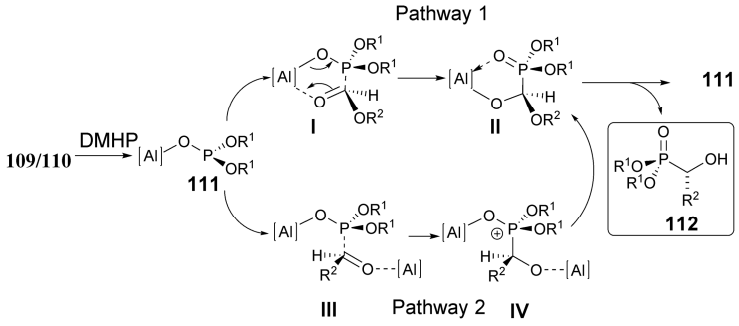


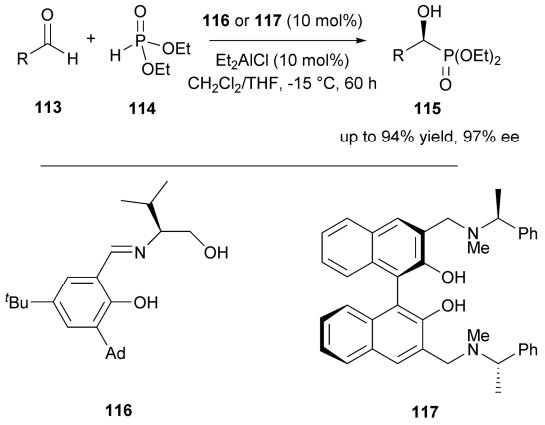
Figure 4. Al-Salen complex used in phosphonylation [134].



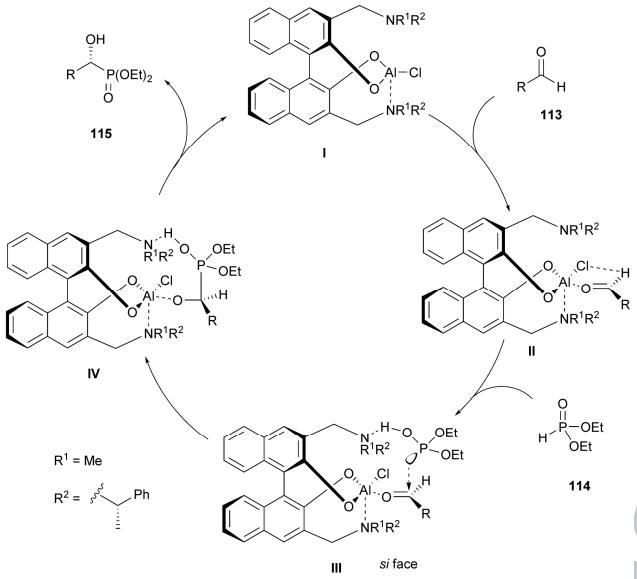
Scheme 28. Proposed catalytic cycles of phosphonylation by aluminum catalyst [134].

Of course a third route may occur whereby the metal plays no part in the carbonyl activation step, however this will be relatively slow, yet may contribute to the lowered enantioselectivities observed. Another point of note is that while **110a** did catalyze the addition reaction it proceeded at a slower rate, and with lower selectivity. In contrast to many contemporary catalysts which employ bulky ^{t}Bu groups to discern between which face is attacked, the use of these sterically demanding moieties actually switches off selectivity, presumably as access to the active aluminum site would be restricted [135]. As a result of this, the closed transition state is less favorable leading to the less stereo-differentiating pathway being adopted. Further research by Saito and co-workers investigated the application of these aluminum catalysts to other unsaturated frameworks such as aldimines with increasingly positive results leading to very good enantioselectivities reaching up to 95% ee with near quantitative conversion [137].

More recent advances have been made by Feng et al. utilizing tridentate chiral Schiff base derivatives, with **116** proving superior, in place of the salen-type ligands reported earlier [138]. For the reaction between aldehydes and diethyl phosphite (comparable to that seen in Scheme 26), the use of ligand at -15 °C garnered some truly impressive initial observations, producing the phosphonylated product **115** in yield of 80% with excellent enantioselectivities of 96% ee. With the optimized conditions in hand (10 mol% catalyst, -15 °C, CH_2Cl_2/THF) an expansive substrate scope was tested. Generally, all gave good to excellent yields with enantiomeric excesses approaching 95% regardless of the aldehyde in question, be it aliphatic or electron rich/poor aryls with the best results giving enantioselectivities of 97% ee in 94% yield (Scheme 29). This group also went on to incorporate aminobinaphthol systems **117** to effect the same reaction, however this was met with more limited success with yields limited to 70-90% and enantioselectivities generally around 70% ee [139]. However, a plausible mechanism was proposed for the catalytic cycle whereby the transition states **I**–**IV** are stabilized by a series of coordinative hydrogen bonds to orientate the incoming phosphite to attack the *si* face of the carbonyl (Scheme 30).

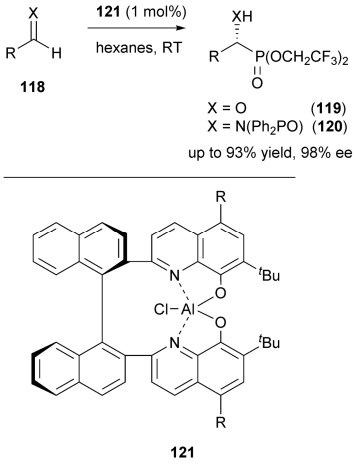


Scheme 29. Al-catalyzed phosphonylation of aldehydes using Schiff base or BINOL system [138].



Scheme 30. Proposed catalytic cycle for the phosphonylation of aldehydes [139].

In 2008, Yamamoto and co-workers introduced a novel Al^{III} catalyst incorporating a blend of both salen and BINOL-type functionalities in the form of the tethered bis(8-quinolato) complex **121** (Scheme 31) [140]. Initial screening showed that electron-withdrawing ester moieties (OCH_2CF_3) on the phosphite were essential for increased enantioselectivity. Whilst the mechanism has not been elucidated fully, it is thought to undergo initial deprotonation of the phosphite to generate a more nucleophilic species, thus the relative acidity of the proton is strongly linked to the basicity of the central phosphorus. Other parameters that were trialled were temperature and solvent variance with the outcome showing that conducting the reaction at ambient temperatures in hexanes gave the most promising results (94% yield, 78% ee). The catalyst **121** was then targeted for optimization with the induction of chirality proving to be strongly correlated to the steric obstruction brought about by substitution of the 5,5'-position. By increasing the bulk about this position using 2,4,6-trimethylphenyl (R = Mes, Scheme 31) moieties the yield and ee had risen dramatically to 95% and 96% respectively. Applying this system to both a range of aldehydes and aldimines including aliphatic and electron poor/rich aromatics produced a bevy of high yielding reactions with impressive enantiospecificity (82–98% ee), all using only 1 mol% catalyst loading (Scheme 31).

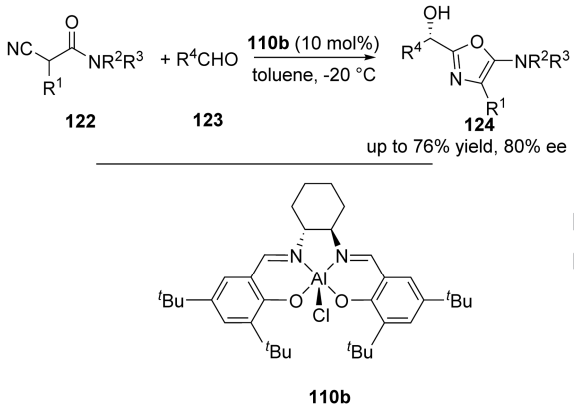


Scheme 31. Phosphonylation using tethered bis(8-quinolinato) aluminum complex [140].

Indeed aluminum compounds have long been established as effective Lewis acid catalysts and co-catalysts however recent pioneering work by Shibasaki, Feng, and Yamamoto et al. have shown how careful ligand selection can lead to a very effective catalyst capable of undergoing phosphonylation reactions with a very high degree of selectivity in addition to being high yielding. Whilst optimizations such as reducing catalyst loading are the focus of ongoing work in order to become truly competitive, the very broad substrate scope outlined in this section is truly impressive and indeed further consolidates the use of main group elements as potential alternatives to transition metals.

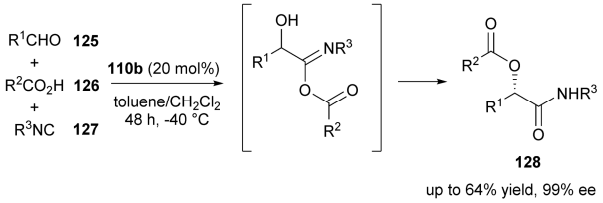
8. Domino reactions

Domino reactions hold a prominent place in modern synthetic methodology through the atom economic formation of complex compounds, and more recently with high enantioselective control over chiral centers. In some cases multiple asymmetric centers are created with extremely good enantioselectivities reaching as high as 99% ee in many cases [141-148]. A broad range of products result from this type of reactivity such as (hydroxyalkyl)tetrazoles, (hydroxyalkyl)oxazoles and diamino acids, which are discussed here, amongst others. Early reports by Zhu in this area were based on the same Al-catalyst employed in hydrophosphonylation (see section 7, **110b**, Figure 4). This catalyst was selected due in part to the fact that only one coordination site is preferential for aldehyde binding. In the case where two or more sites are available, other potential side reactions may occur such as aldol reactions or ligand chelation. In these initial reactions this Al^{III} catalyst **110b** was employed in the reaction between α-isocyanoacetamides and aldehydes to give the corresponding 5-aminooxazoles **124** in good yields of 76%, and more crucially, a very good handle on enantioselectivity (80% ee) (Scheme 32) [149]. Optimization of the reaction conditions using 10 mol% of the catalyst at -20 °C in toluene were determined for effective transformation, which was then applied to various substrates providing various yields and enantioselectivities (35–90% yield, 50–80% ee).



Scheme 32. Al-salen- catalyzed cascade reaction to form oxazole **124** [149].

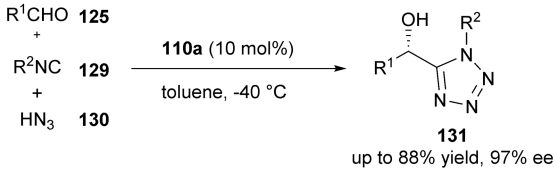
Building from this, the same group moved to employ the same Al^{III} catalyst in the Passerini three-component reaction which looked at the condensation of an aldehyde, carboxylic acid, and isocyanide to produce an α-acyloxyamide **128** [150]. As was the case previously, the choice of catalyst was paramount as the propensity for unwanted side reactions must be removed. This was especially prominent in these three-component reactions where all three substrates contain Lewis basic sites which may coordinate to the metal center thus inhibiting or deactivating the catalyst. To this end, **110b** indeed fits this remit with the initial screening reaction as seen in Scheme 33 giving relatively good yields and enantioselectivities of the product **128** (26% yield, 80% ee). Upon optimization (10 mol% catalyst, toluene, 48 h, -40 °C) a pronounced increase in both yield and enantioselectivity was seen giving the product in up to 63% yield and 84% ee. This increase in ee was seen when changing the aliphatic isocyanide for the less reactive aromatic cyanide which was presumed to inhibit the unwanted side-reactions mentioned earlier. Further adaptations to the substrates increased the reported conversion to 64% and a resoundingly excellent enantioselectivity of >99% ee when using 2-chloroethanoic acid and 2-methylpropanal in the presence of *para*-methoxybenzylisocyanide. With this methodology, altering the isocyanide and aldehyde generally gave yields at *ca.* 60% with enantioselectivities reaching between 71–93% ee.



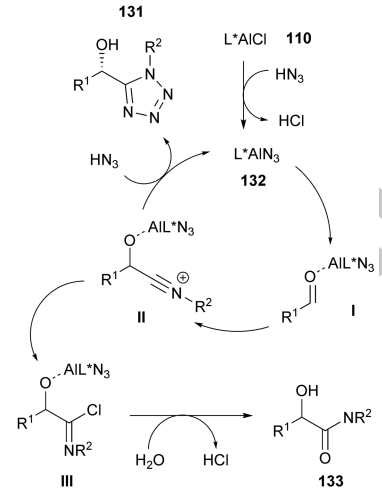
Scheme 33. Al-salen- catalyzed multi-component reaction [150].

Other eminent work by Zhu and co-workers extend this reactivity to form (hydroxyalkyl)tetrazoles, being one of the first methods to synthesize such molecules in an enantioselective fashion (Scheme 34) [151]. In this study, aldehydes **125** were combined with isocyanides **129** and hydrazoic acid **130** catalyzed by a series of salen-based aluminum catalysts, with **110a** displaying the best catalytic activity. Using this catalyst at 20 mol% gave the chiral product **131** in 95% yield and 85% ee, whilst reducing the catalyst loading to 5 mol% gave equally good enantioselectivities of 86% ee, however, the conversion was negatively affected with yields reaching only 69%. This procedure was effective for a range of various branched and linear aliphatic aldehydes in conjunction with differing isocyanides including electron-rich and –poor aromatic substituents. In general, yields and enantioselectivities remained in the region of 80–90% ee regardless of the substrates used with the best being reported with enantioselectivities of 97% ee in 88% yield. However, whilst this reaction shows the versatility of these

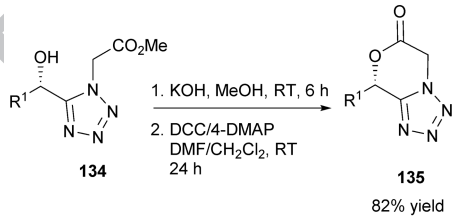
aluminum catalysts for various multi-component reactions, one of the drawbacks is more evident with this reactivity, that being unwanted side-reactions. Regardless of the conditions and substrates used, the production of **133** could not be fully suppressed as this was specifically linked to the function of the catalyst itself, or the presence of adventitious water (Scheme 35). Interestingly, when using methyl 4-isocyanobut-2-ynoate ($CNCH_2CCO_2Me$) the resulting tetrazole could then undergo lactonization to give the corresponding bicyclic product **135** in 82% yield (Scheme 36).



Scheme 34. Al-catalyzed formation of (hydroxyalkyl)tetrazoles [151].



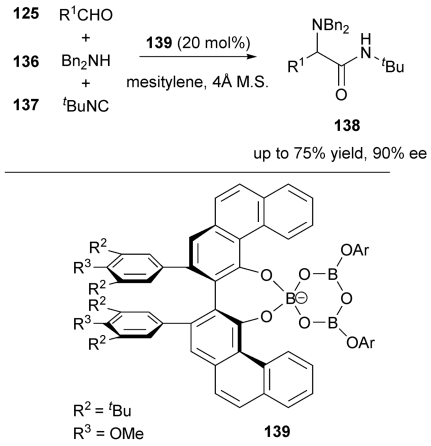
Scheme 35. Proposed mechanism for the formation of (hydroxyaryl)tetrazole and side product **133** [151].



Scheme 36. Formation of cyclic lactone from tetrazole methyl ester [151]. DCC = dicyclohexylcarbodiimide, 4-DMAP = 4-dimethylamino pyridine.

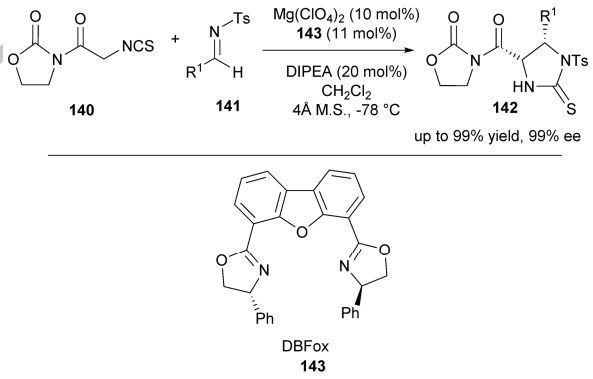
A new approach to this type of three-component reactions is to produce α-aminoamides, similar to that made famous by Ugi [152], by incorporating secondary amines alongside isocyanides and aldehydes using the recently developed [153,154] BOROX catalyst (**139**) from various VAPOL building blocks (Scheme 37) [155]. Preliminary studies using this methodology gave the resultant α-aminoamide in 37% yield, however enantioselectivities were poor at 10% ee using catalyst **139** without functionalization of the tethered phenyl moieties. The choice of amine was essential as primary amines resulted exclusively in the corresponding imine. In contrast, the secondary amine, dibenzylamine, gave the most promising results. The next stage of optimizations led to the elucidation of compound **139** as the optimal catalyst with substitution of the tethered phenyl groups of the VAPOL backbone for 3,5-dimethyl-4-methoxybenzene moieties. Indeed, these modifications to the catalyst increased the enantioselectivity of the reaction giving the product in 71% ee and 94% yield. Solvent screening also showed that coordinating solvents were detrimental to asymmetric induction with THF and acetonitrile reducing the enantioselectivities to 9% and 28% ee respectively. Mesitylene was screened as the optimal solvent which produced some of the most favorable results, when reacted in the presence of 4-methoxy-2,6-dimethylphenol, of up to 90% ee in 75% yield (Scheme 37). This has been further exploited by the Wulff group in the formation of asymmetric aziridines from aldehydes in a novel multicomponent system using the aforementioned BOROX catalyst **139**. Applying the same methodology as seen before, using aldehydes, protected primary amines and diazoesters, yields the corresponding protected aziridines in extremely high enantioselectivities, routinely achieving >95% ee in relatively good isolated yield [156].

Extensions of this work regarded the synthesis of sphinganine derivatives using the same approach, again in extremely high yields and enantiomeric excesses (96–98% ee) [157].



Scheme 37. Use of the BOROX catalyst **139** in multi-component reaction [154].

Whilst these previous group 13 elements have proven to be successful in these multi-component reactions, alkaline-earth metals have also been offered as successful alternatives in these types of reactions. Specifically recent work by Willis as well as Zhu used chiral magnesium catalysts formed from the reaction between $Mg(ClO_4)_2$ and various L-donor ligands based on PyBox, BOX and DBFox scaffolds [158,159]. Ligand **143** offered the best enantioselectivities seen in the initial reaction of an isothiocyanate **140** with *N*-tosyl imine **141** garnering the final rearrangement product **142** in 94% yield and 96% ee (Scheme 38). Varying the imine that was used had little effect on the enantioselectivity of the reaction with yields predominantly above 90% and enantioselectivities commonly reaching 99% ee regardless of the electronic contribution of the appended functionality. Additionally, when an indole functionalized imine was used, a β-amino-tryptophan derivative prevailed displaying the synthetic use of such methodologies in potential therapeutic agents. The observed *anti*-symmetry was hypothesized to arise through the *syn* coordination of the Lewis acid to the *E*-imine, controlling the diastereoselectivity throughout the reaction, with this being backed by control reactions confirming the diastereomer ratios throughout the reaction. Further to this, magnesium centered catalysts have been used in many other cascade reactions such as the work by Shibasaki et al. in the formation of oxazolinedinethione [160].



Scheme 38. Mg-catalyzed formation of α,β-diamino acids [158].

These reactions further consolidate the use of main group catalysts in progressively more complex one-pot reactions, in particular the installation of several chiral centers in a one-pot reaction in an extremely atom-efficient manner. Indeed, these rearrangements can be carried out by many different catalysts from group 2 metals such as magnesium and to a lesser extent calcium, whilst there has also been a great deal of success with group 13 metals and metalloids routinely obtaining complex organic products with yields in excess of 90% with equally as impressive enantiomeric excesses.

9. Conclusions

Recent developments in the use of main group catalysts have exhibited great efficiency in a range of organic one-pot reactions for the installation of C-C, C-H and C-N bonds *inter alia*. This is all conducted whilst also retaining the ability to generate stereoselective products in generally high yields and enantiomeric excesses under ambient conditions through reaction condition optimization and ligand design. The

potential advantages of using main group based catalysts have clear precedence in the developing field of green chemistry with reduced environmental impacts coupled with the lower toxicity showing promise toward applications in both the pharmacological and medicinal fields. Indeed, main group chemistry provides new opportunities in catalysis, a field previously reserved for the heavier transition metals. With an increasing body of work in this area and a paradigm shift in thinking of the role of the metal ions in catalytic processes, new and emerging uses of main group reagents continue to further this field, establishing main group elements as another pillar in the critical discipline of catalysis.

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Enantioselective Main Group Catalysis: Modern Catalysts for Organic Transformations.

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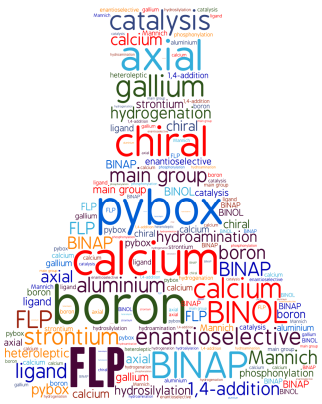

The current field of synthetic enantioselective catalysis is dominated by transition metals such as ruthenium, palladium and copper, launched through the success of pioneering work by Knowles, Noyori and Sharpless, however, there are inherent problems with using heavy rare earth transition metals, namely their prohibitive costs and potential toxicity. To combat this an alternative has been found in the form of main group centred catalysts. Indeed the recent application of main group elements in catalysis has expanded to encompass enantioselective transformations. As main group elements, for example calcium, magnesium, boron and aluminium have become more preeminent as active catalysts, their applications in enantioselective catalysis has also made great strides in recent years. In this review we highlight the importance of earth abundant main group *s*- and *p*-block catalysts as candidates for effective asymmetric induction in a range of organic transformations such as 1,4-additions, hydrosilylation, hydrogenation and phosphonylation as well as dispelling common myths surrounding early *s*- and *p*-block elements with regard to their catalytic applications.

Highlights for:

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- An overview of emerging main group catalysts used in chiral induction is outlined.
- Mechanistic aspects of various enantioselective catalytic cycles are described.
- Solutions to common limitations of main group systems are offered.
- Main group alternatives to traditional transition metal complexes are presented.