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Bifunctional Binols: Chiral 3,3′-Bis(aminomethyl)-1,1′-bi-2-naphthols (Binolams) in Asymmetric Catalysis

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Dedicated to Prof. Andreas Pfaltz on the occasion of his 60th birthday

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3,3′-Bis(dialkylaminomethyl)-1,1′-binaphth-2-ols (Binolams) have emerged during the last five years as very efficient chiral ligands in many enantioselective processes. Enantiomerically pure Binolams are easily accessible by means of a variety of methods, the most widely used being the so-called chiral Binol route. In most cases, Binolam-metal complexes behave as bifunctional catalysts: that is, they are characterized by their dual action on the reagents, being able to activate both the nucleophilic and the electrophilic species involved in the reaction. The most successful transformations carried out with complexes of this type include cyanation of aldehydes and ketones and enantioselective nucleophilic additions of enolate derivatives and organometallic compounds to C=O or C=N double bonds. As a final bonus, the basic natures of these ligands allow their recovery in high yields in numerous transformations.

1. Introduction

The widespread demand for enantiomerically pure compounds ultimately comes from the central roles that enantiomer recognition and differential reactivities of enantiomers play in biological activity. There are many examples of pharmaceutical drugs, agrochemicals, flavors, and fragrances in which the desired property is related to absolute configuration.[1] This pervasive need for chiral compounds has stimulated intensive research in the development of improved methods for accessing them.[2] Non-enzymatic strategies directed towards the preparation of enantiomerically pure compounds fall into three main categories: a) resolution of a racemic mixture, either spontaneous or with the aid of an enantiopure reagent, b) structural modification of an enantiomerically pure substrate (in most cases of natural origin), which undergoes highly diastereoselective transformations, and c) conversion of an achiral precursor into a chiral product (asymmetric synthesis) performed with the aid of chiral auxiliaries, reagents, or catalysts (asymmetric catalysis).

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The design of new catalysts for common – and also less common – reactions is actively pursued in the field of asymmetric catalysis, and usually involves the design of feasible ligands. The invention of the earliest ligands for asymmetric hydrogenations catalyzed by transition metal complexes occurred in the early 1970s, and their number is nowadays continually expanding.[3] In recognition of the achievements made with the so-called artificial enzymes, Knowles, Noyori, and Sharpless shared the 2001 Nobel Prize in chemistry.

Since those early days, a myriad of chiral catalysts have been employed in the generation of stereogenic centers mainly through C–O, C–N, and C–C bond-forming reactions.[3] The chiral ligands are crucial parts in these active organometallic catalysts.[4] Such a ligand should not only increase the reactivity, but it should also provide a kinetic bias in such a way that one of the two possible enantiomeric products is formed preferentially. The design of suitable chiral ligands for a particular application, however, remains a formidable task. The complexity of most catalytic processes precludes a purely rational approach based on mechanistic and structural criteria, so most new chiral catalysts are still identified by empirical means, for which combinations of chance, intuition, and systematic screening, all playing important roles, are required.

Bifunctional catalysts[5] merit special comment because their dual function (activation of both nucleophile and electrophile in a ternary complex) leads to further lowering of the energies of the transition structures and thus to further

acceleration. In recent years we have been devoting our efforts to exploration of the use of bifunctional Binol derivatives in the asymmetric catalysis area. In particular, C_2-symmetric[6] 3,3′-bis(dialkylaminomethyl)-1,1′-binaphth-2-ols (Binolam ligands) of general structure **I** (Figure 1, a), and – to a lesser extent – the C_1-symmetric, single-armed ligands **II** (Figure 1, b), have emerged as highly valuable scaffolds for the possible generation of bifunctional chiral Lewis acids and/or organocatalysts. Moreover, according to the X-ray diffraction structure of 3,3′-bis(diethylaminomethyl)-1,1'-binaphth-2-ol, Binolams appear to be ideally suited to form octahedral complexes with appropriate metals (Figure 1, c).[7] Unlike in unsubstituted Binol ligands,[8,9] the key feature of the resulting bifunctional Lewis acids is the different electronic domains present in the metal cation and in the aminomethyl arms, which facilitate their dual action as shown in **III**: the metal cation acting as a chiral Lewis acid in activating the electrophilic species, whereas the aminomethyl arm facilitates suitable approach of the nucleophile (Figure 1, d).

Several applications of Binolams **I** or **II** other than in asymmetric synthesis have been reported in the areas of host–guest complexation and molecular recognition,[10–12] as well as in the development of macromolecular architectures[13] and in the construction of artificial enzymes and membranes.[14] In addition, two further important properties of these structures **I** should also be highlighted: a) Binolams are potent DNA intercalating agents, a property that makes them promising molecules for anticancer therapies,[15,16] and b) the fluorescent properties of Binolams are highly useful for chiral recognition.[16]

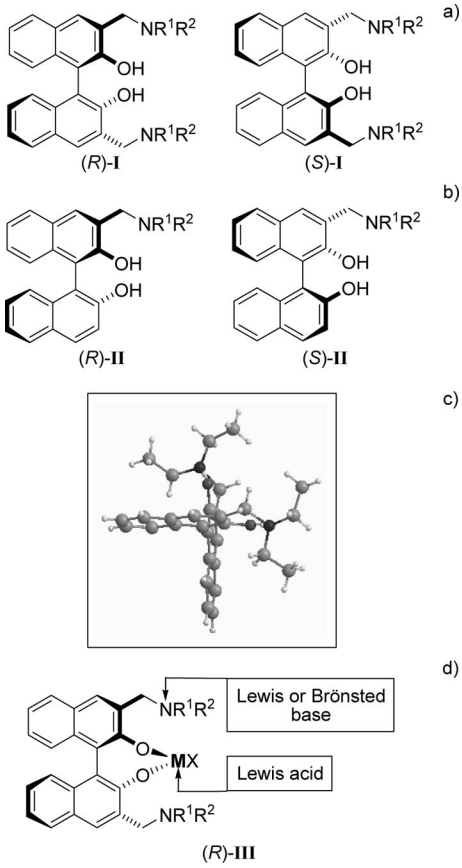

Figure 1. a) General structure of Binolams with C_2 symmetry; b) general structure of Binolams with C_1 symmetry; c) X-ray diffraction analysis of (*S*)-**I** ($R^1 = R^2 = Et$); d) bifunctional character of chiral Binolam-metal complexes.

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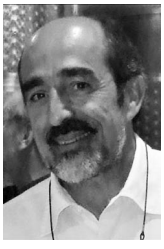


José M. Saá was born in Lugo (Spain) in 1948, studied Chemistry at the University of Santiago de Compostela, and did his Ph.D. under the direction of Prof. Ignacio Ribas and Luis Castedo. After postdoctoral research with Prof. M. P. Cava at the University of Pennsylvania (Philadelphia) he first joined the faculty of the University of Santiago de Compostela (Spain) in 1978, and then moved in 1982 to the University of the Balearic Islands (UIB), where since 1986 he has been Full Professor.

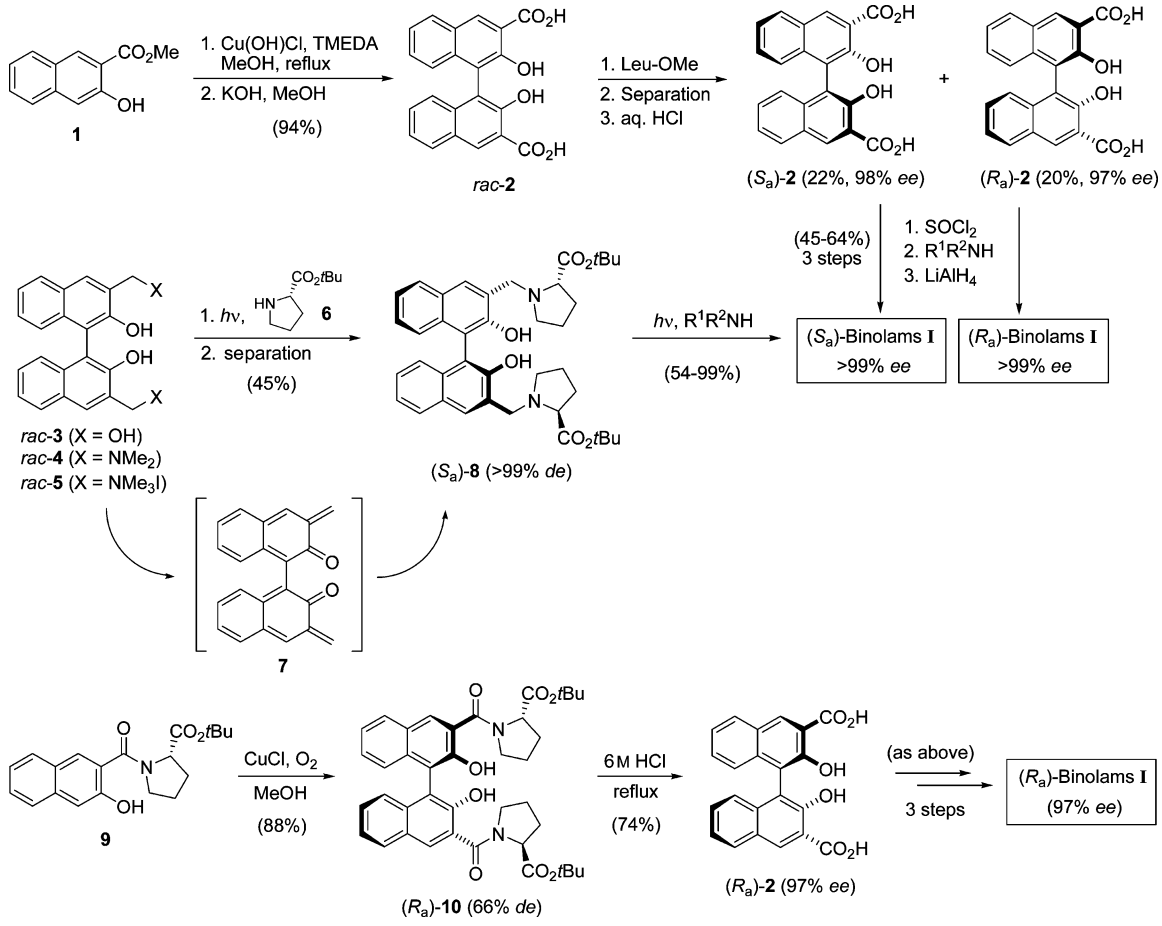
Because of our interest in asymmetric catalysis, in this review we center the discussion on two issues. Firstly, we examine the preparation of Binolams **I**, and secondly the focus switches to the results achieved in asymmetric catalysis with Binolams and their derivatives. In particular, we examine chiral 3,3′-bis(dialkylaminomethyl)-1,1′-binaphth-2-ols **I** either as organocatalysts or as metal catalysts (typically generated in situ by treatment with the appropriate metal derivative), capable of mediating enantioselective processes in which C–O and C–C bond-forming reactions occur.

2. Synthesis of Chiral Binolam Ligands of Types I and II

The syntheses of Binolam ligands **I** and their derivatives have in general been inspired by the numerous strategies developed for the preparation of chiral Binol-type systems.[8,9] In fact, the most useful methodologies by which to obtain them variously involve: a) the separation of diastereomeric mixtures of appropriate Binol derivatives mediated by chiral α-amino acid surrogates, b) dynamic kinetic transformations (DYKATs), c) transition-metal-catalyzed enantioselective or diastereoselective Csp^2–Csp^2 coupling between two identical or two different binaphth-2-ol units, or d) appropriate functionalization of enantiomerically enriched Binols.

Cram and co-workers were the first to report the optical resolution of the Binol acid *rac*-**2** (Scheme 1) – itself synthesized by a standard copper-catalyzed Csp^2–Csp^2 homocoupling of the methyl ester **1** and subsequent hydrolysis[17] – with the aid of L-leucine methyl ester, leading to the enantiomerically pure compounds (R_a)-**2** and (S_a)-**2** (Scheme 1).[10] However, this tedious separation sequence requires long reaction times (a week), and its efficiency is rather poor (the final yields of the enantiomerically pure compounds **2** achieved were around to 35%). The enantiomerically enriched dicarboxylic acids **2** thus obtained are direct precursors of Binolams **I** through a sequence involving the formation of the corresponding bis-acyl chlorides, followed by amide formation and complete reduction of the amide carbonyl group with $LiAlH_4$ in THF at reflux. A large number of enantiopure Binolams prepared by this protocol have been described.[7]

Photolysis of the *ortho*-substituted Binols **3** (Scheme 1, X = OH), Binolams **4** (X = NR_2), or of the corresponding ammonium salts **5** (X = NR_3^+), gives rise to reactive *ortho*-quinone methides, which can be quenched by available nucleophiles. Freccero et al. recently reported a highly efficient



Scheme 1. Synthesis of Binolams **I** through optical resolution or by a diastereoselective strategy.

DYKAT process[18] in which photolysis of racemic **3**, **4**, or **5** was carried out in the presence of enantiomerically pure proline *tert*-butyl ester **6**, thereby giving rise to diastereomerically enriched bisproline **8** (>99% *de* after separation). A second photochemically induced transformation, carried out upon enantiomerically enriched **8** in the presence of secondary amines, yielded enantiomerically enriched (>99% *ee*) Binolams **I** (Scheme 1).[14]

On the other hand, copper-catalyzed homocoupling of the enantiomerically pure naphthol carboxamide **9** took place diastereoselectively, thereby leading to **10** (66% *de*) (Scheme 1). Fortunately, chromatographic purification allowed compound **10** to be isolated in 97% *de* and 65% yield; subsequent hydrolysis afforded the dicarboxylic acid (R_a)-**2** in 97% *ee* and, eventually, the desired Binolams **I**.[19]

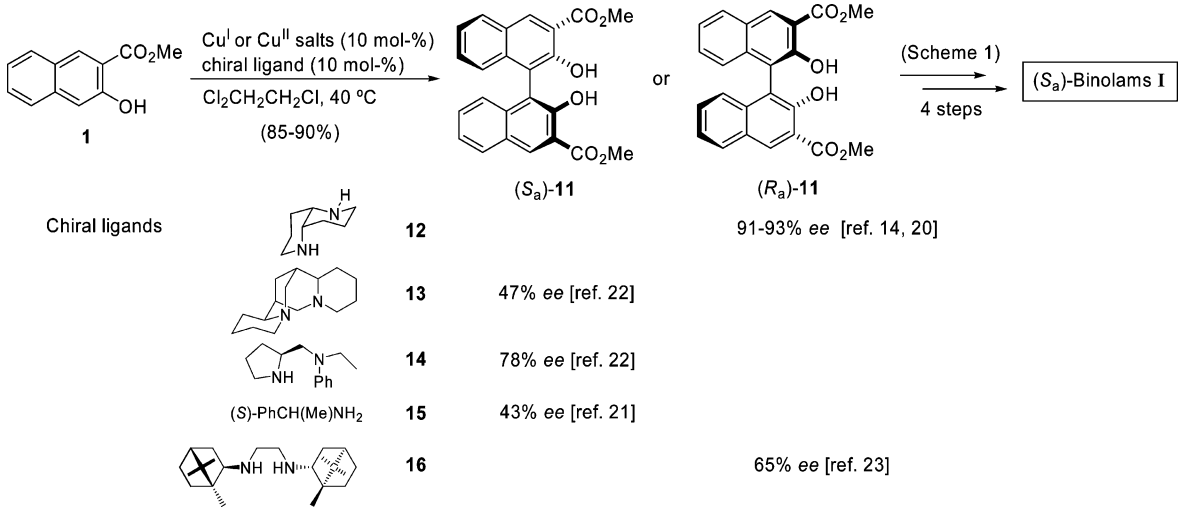
The design of a versatile catalytic system capable of performing enantioselective Csp^2–Csp^2 coupling between two identical or different binaphth-2-ol units has proven to be a difficult task. A number of diamines (10 mol-% loadings) have been evaluated in the enantioselective, copper-catalyzed homocoupling of **1**, the most efficient ligand so far being (*S*,*S*)-1,5-diaza-*cis*-decalin (**12**), which led to compound (R_a)-**11** in 91–93% *ee* (Scheme 2).[15,20] Chiral (*S*)-α-methylbenzylamine (**15**) afforded only a 43% *ee* of product (S_a)-**2**,[21] but the complex formed by diamine **14** and copper(II) salts gave better enantioselection than other ligands such as (–)-sparteine (**13**)[22] or the (1*R*)-(+)-camphor-derived diamine **16**[23] (Scheme 2). The catalytic complexes **12**·CuX have been also tested in the synthesis of chiral binaphthyl polymers by this type of oxidative coupling or by a domino reaction incorporating a Glaser–Hay coupling as terminating step.[20a]

The fourth synthetic plan calls for the direct functionalization of chiral enantiomerically pure (R_a)- or (S_a)-Binol **17** (Scheme 3), or of their bis-*O*-methoxymethylated derivatives **18**. Thus, selective double deprotonation at the C3- and C3′-positions, followed with quenching with carbon dioxide or DMF, gives rise to enantiomerically pure dicarboxylic acid **2**[24] or dicarbaldehyde **19**,[25] respectively, in very good yields and without loss of enantiomeric purity (Scheme 3). Subsequent functional group transformations upon the reactive formyl groups (reductive amination) or the easily available dihalide derivatives **20** (S_N2 displacement), led to enantiomerically pure Binolams **I**.

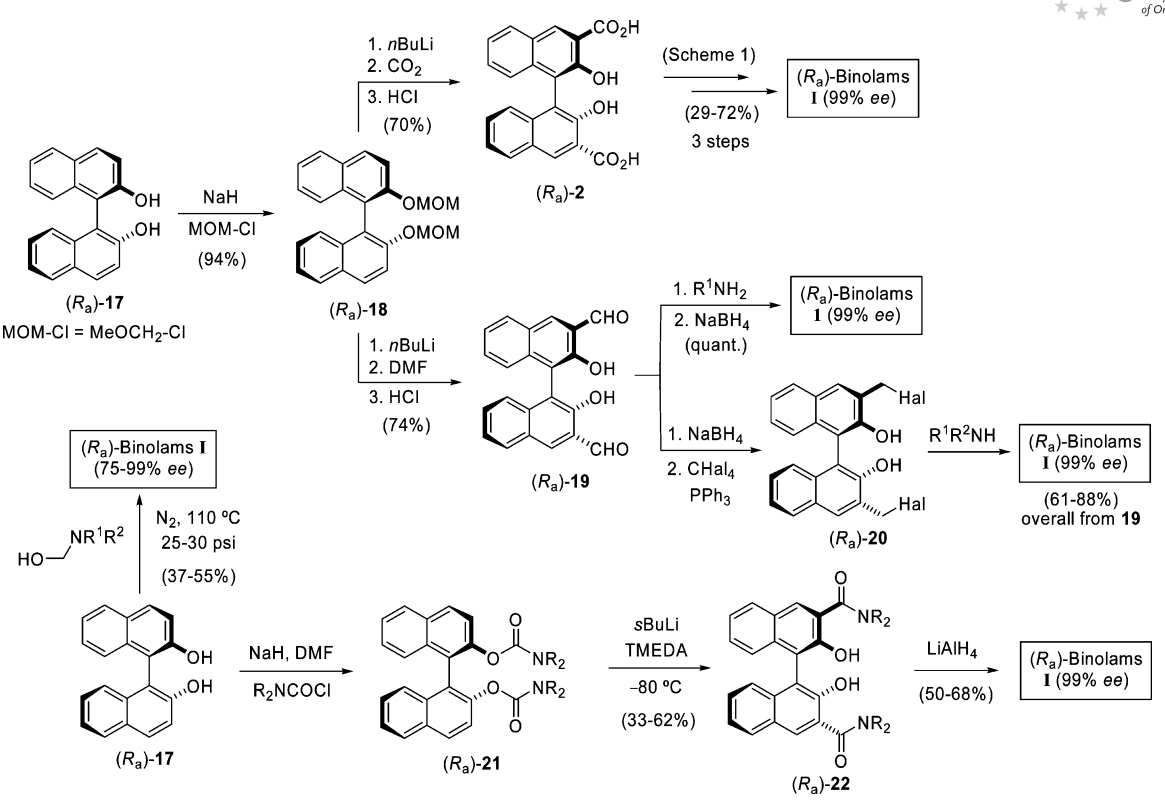
The dicarboxylic acid **2** is also an appropriate starting point for the synthesis of *N*,*N*-disubstituted Binolams **I**. For the preparation of *N*-monosubstituted Binolams, however, the reductive amination route from dicarbaldehyde **19** is desirable. The use of bis(halomethylarenes) **20** is strongly recommended when a bis(tetraalkylammonium salt) derived from a Binolam **I** is required. On the other hand, direct functionalization of enantiomerically pure Binol by use of Mannich reactions with *N*-hydroxymethyl dialkylamines at 110 °C under pressure (25–30 psi) furnished mixtures of C3-monosubstituted Binolam **II** (30% yield) and Binolam **I** (55% yield, 75% *ee*). Final recrystallization led to Binolam **I** in 37% yield and >99% *ee*[26] (Scheme 3).

A further attempt at direct functionalization of enantiopure Binol was based on the anionic Fries rearrangement undergone by dicarbamate (R_a)-**21** on treatment with *s*BuLi/TMEDA at very low temperatures. The resulting diamide (R_a)-**22**, obtained in moderate to good chemical yields, was eventually reduced with $LiAlH_4$, thereby giving rise to the titled Binolams **I** with excellent *ee* values (Scheme 3).[27] Partially hydrogenated Binolams are easily available by means of direct Mannich reactions with the corresponding H_8-Binols. Indeed, H_8-Binolams are obtained under mild conditions from commercially available H_8-Binol and mixtures of formaldehyde/dialkylamine or, instead, by routes analogous to those described for the titled Binolam ligands of type **I**.[28,29]

In summary, on assessing the advantages and disadvantages of the protocols for accessing enantiopure Binolams described above, it is safe to conclude that those based on the direct functionalization of enantiomerically pure Binol are the most valuable in terms of chemical yield, enantiomeric excess, reaction time, and reaction scaling.



Scheme 2. Enantioselective synthesis of Binolams **I** through the use of chiral copper(I) complexes and Csp^2–Csp^2 homocoupling.

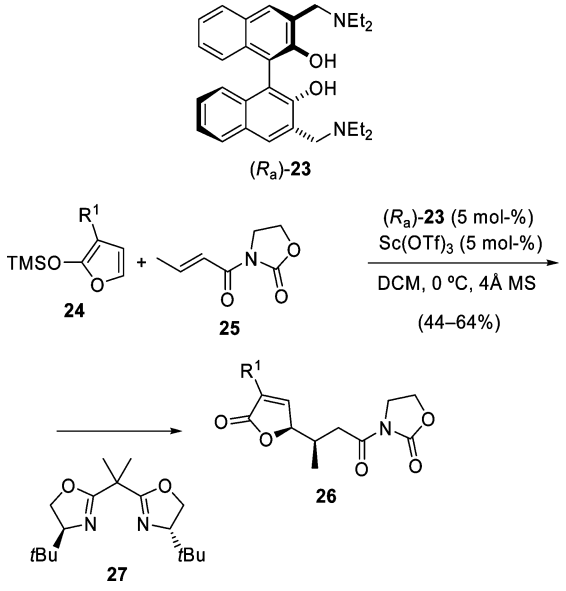


Scheme 3. Synthesis of Binolams **I** from chiral (R_a)- or (S_a)-Binol **17**.

3. Applications in Asymmetric Synthesis

3.1. Catalytic Enantioselective Michael-Type Addition Reactions

The Lewis-acid-promoted Michael-type addition of the 2-(trimethylsilyloxy)furans **24** (Scheme 4) to 3-[(*E*)-but-2-enoyl]-1,3-oxazolidin-2-one (**25**) was examined. In this reaction, a complex mixture generated by $Sc(OTf)_3$ and (R_a)-Binolam **23**, both in 5 mol-% loadings (no evidence has been provided as to the nature of the mixture) was employed as catalyst.[30,31] The reaction afforded **26** (44–64% yield) with high diastereoselection (>50:1 *dr*), but with only moderate enantioselection (up to 73% *ee*). The absolute configuration of the major product was determined both by X-ray diffraction analysis and by chemical derivatization to a known structure. In many examples, the introduction of hexafluoroisopropyl alcohol (HFIP), which is more acidic and has poor coordinating ability, as additive accelerated the reaction, increasing the chemical yields. The enantioselectivity of this process was eventually improved (up to 92% *ee*, Scheme 4) by use of the complex mixture resulting from Cu(OTf) and *t*BuBox **27**.[30,31]



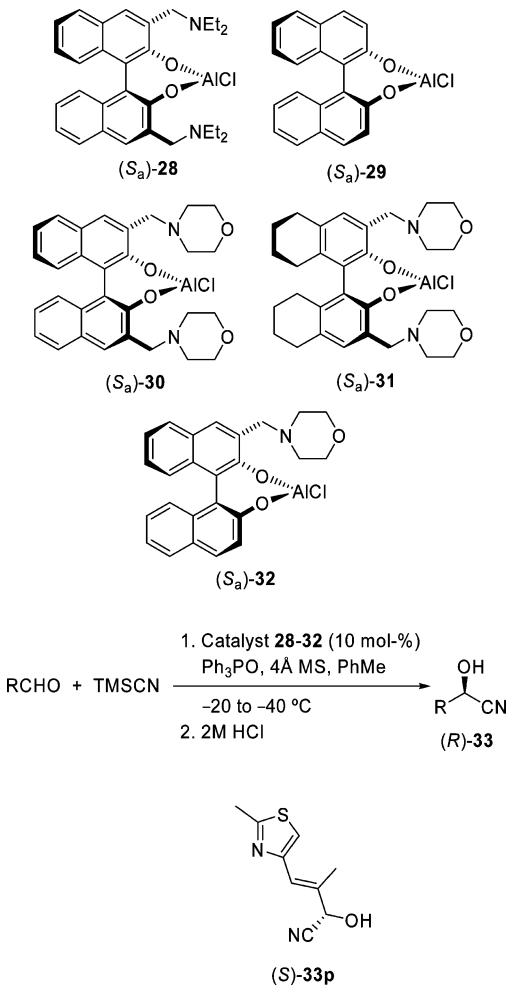
Scheme 4. Enantioselective Michael-type addition promoted by Binolam (R_a)-**23**/$Sc(OTf)_3$.

3.2. Catalytic Enantioselective Cyanide Additions

The preparation of nonracemic cyanohydrins is an important goal for current asymmetric organic synthesis,[32] because the resulting enantiopure cyanohydrins and their derivatives are valuable chiral building blocks for organic synthesis.

As illustrated in Scheme 5, a number of chiral aluminium complexes derived from Binolams **28**–**32** have been tested as catalysts in the cyanosilylation of aldehydes with trimethylsilylcyanide (TMSCN). It is worth mentioning that although the complexes shown are written as monomeric species, the exact natures of these compounds, either in solid

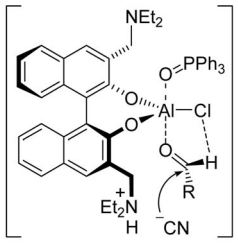
or in solution phase, are in most cases unknown. Moreover, it is also worth commenting that, in general, aluminium complexes gave better enantioselection than the analogous titanium or zinc complexes, as shown below.



Scheme 5. Binolam·AlCl complexes tested for the cyanosilylation of aldehydes.

Specifically, the chiral complexes (R_a)- or (S_a)-**28**, formed by mixing equimolar amounts of Me_2AlCl and (S_a)-Binolam **23**, were successfully employed as catalysts for the overall cyanosilylation of aliphatic, aromatic, heteroaromatic, and α,β-unsaturated aldehydes. After hydrolysis, cyanohydrins (*R*)-**33** were obtained with good yields (45–99%) and enantioselectivities (85–99% *ee* values). This system showed the following advantages over Shibasaki's catalyst:[33] the operational temperature (–20 or –40 °C) was conveniently higher,[34,35] and at the end of the reaction a simple extractive workup was sufficient for the recovery of the valuable Binolam ligand, which could be reused without loss in efficiency. By this protocol it was possible to obtain (*S*)-**33p** – a key intermediate in the synthesis of epothilone A – in excellent yield (>98%) and with high enantioselection (92% *ee*).[33] As a general rule, the (S_a) chiral complex gave rise to the (*R*)-configured cyanohydrins **33**, and contrariwise, the (R_a) chiral complex yielded the (*S*)-configured cyanohydrins **33** (Scheme 5).

In an attempt to define the bifunctional nature of the catalyst **28**, the activity of the monofunctional (S_a)-Binol·AlCl complex **29** (Scheme 5) was studied for purposes of comparison. The efficiency of the former catalyst was found to be much higher than that of the analogous Binol-derived catalyst, thereby suggesting, but not proving, the bifunctional nature of the former. In a key experiment that accounts for the specific role played by the amino group in **28** (either as a Lewis or a Brønsted base) it was found that operating in the presence of triethylamine led to mostly racemized material. These observations, together with the absence of nonlinear effects, and the pentacoordinate nature of the aluminium atom, as suggested by the ^{27}Al NMR spectra, support the assumption of the bifunctional character of complex **28** for this particular reaction, with the aluminium atom acting as a Lewis acid center and the amino group playing the role of a Brønsted or Lewis base.[35] The roles of the required additives – triphenylphosphane oxide and molecular sieves (4 Å) – were also explored. The action of triphenylphosphane oxide appears to be the conversion of catalyst aggregates into the active monomeric species, as suggested by the fact that nonlinear effects were observed in its absence, whereas nonlinear effects were absent in its presence. On the other hand, we have learned that the role played by the molecular sieves (4 Å) is through their incorporation of a small amount of water (a 7% weight loss was determined by thermogravimetric analysis at 400 °C), which is capable of generating HCN by hydrolysis of TMSCN. Accordingly, the working mechanism for this reaction calls for HCN being captured by the diethylaminomethyl arm, while the Al–Cl unit would serve the role of a Lewis acid to fix the incoming aldehyde through a strong Al···O=C interaction and a weak one of the Cl···H–C=O type, as suggested by Corey.[36] The aldehyde in this ternary complex **A** is ideally suited to undergo attack by the nearby cyanide unit. The optical yield of the reaction dropped dramatically when an ethyl or a cyano group was directly bonded to the aluminium atom.[35] The final reaction with incoming TMSCN leads to *O*-silylation and liberates HCN for a subsequent cycle. Accordingly, the appropriate definition for the overall cyanosilylation observed is that of an enantioselective hydrocyanation followed by *O*-silylation.

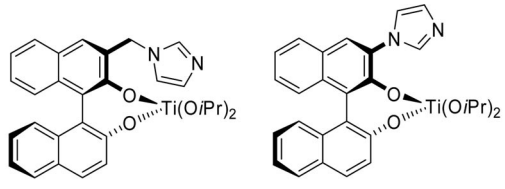


A

Aluminium complexes **30**–**32** (Scheme 5) have also been examined as catalysts for the enantioselective cyanosilylation of aldehydes under very similar conditions, with the highest conversions and enantioselectivities being achieved by the chiral catalytic complex (S_a)-**30**. Interestingly (S_a)-**30** gave excellent enantioselection (99 to 94% *ee*) with aliphatic aldehydes (twelve examples), improving on the results seen with (S_a)-**28**.[28] The catalytic capacity of **30** can thus be considered complementary to that of **28**, as this is somewhat more efficient for aromatic and heteroaromatic aldehydes.

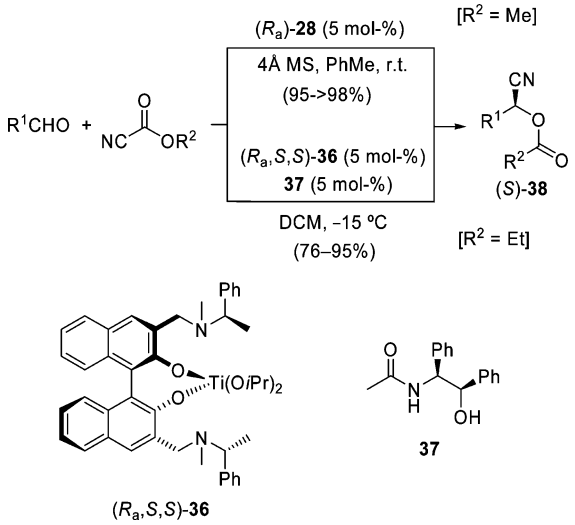
Complexes **30**–**32** have also been explored as catalysts for the enantioselective cyanosilylation of acetophenone under reaction conditions otherwise similar to those described in Scheme 5 but with the introduction of some additives such as HMPA or *N*-methylmorpholine oxide. Unfortunately, low yields of the racemic *O*-silylated cyanohydrins were obtained at the end of the reactions.[28]

Binolam-derived titanium(IV) complexes have also been explored as catalysts for enantioselective cyanosilylation. As in the case of aluminium complexes, the titanium(IV) complexes are written as monomeric species, but the exact natures of these compounds, either in solid or in solution phase, are in most cases unknown. In particular, the C_1-symmetric titanium(IV) complex **34** showed catalytic activity.[37] Unfortunately, the cyanosilylation of benzaldehyde at –40 °C, either in the presence or in the absence of triphenylphosphane oxide, took place in low chemical yields (21 or 44%, respectively) and with only moderate identical enantioselection in both cases (51% *ee*).[37] As described previously, the authors were able to demonstrate the presence of HCN by ^{1}H NMR experiments.[35] Accordingly, the authors had also found support for a dual activation mechanism, with the imidazole moiety acting as a Brønsted base to catch HCN and a titanium atom acting as Lewis acid. It might be suggested that this hypothetical ternary complex should have serious problems in promoting enantioselective cyanations. Fortunately, the closely related complex **35** afforded excellent enantioselection in the cyanosilylation of all type of aldehydes (98–91% *ee* values for aromatic aldehydes, 98–91% *ee* values for aliphatic aldehydes, and 90% *ee* values for α,β-unsaturated aldehydes).[37]



34 **35**

The Binolam·AlCl complexes (R_a)- or (S_a)-**28** were also effective in promoting the enantioselective synthesis of cyanocarbonates **38** (Scheme 6) from aldehydes and methyl cyanoformate (ethyl cyanoformate reacted rather poorly) under very mild conditions (addition of reagents in one portion, at room temperature). The best results were obtained in toluene in the presence of MS (4 Å). Both the chemical yields and enantioselectivities were good (up to 81% *ee* values), but lower than those obtained for the cyanosilylation reactions. Aromatic, heteroaromatic, aliphatic, and α,β-unsaturated aldehydes exhibited similar chemical behavior, and analogous enantioselectivities were obtained in all cases.[38,39] All of the results are in accordance with the bifunctional mechanism described previously for the cyanosilylation reactions. In other words, the overall cyanocarbonylation process is in fact the result of an initial enantioselective hydrocyanation followed by *O*-methoxycarbonylation, a process that liberates the required HCN for a subsequent cycle.



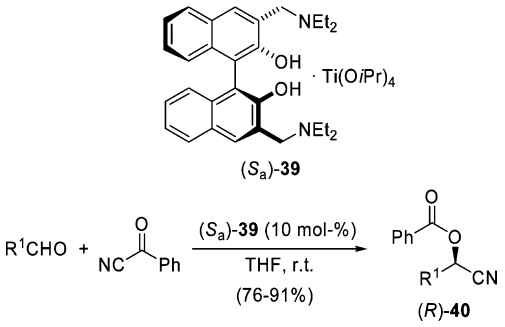
Scheme 6. Binolam complexes tested in cyanoformylation of aldehydes.

Binolam-derived titanium(IV) complexes have also been employed for enantioselective cyanocarbonylations of aldehydes. The structures of the actual catalysts are again uncertain, due to the fact that they result from mixing, at –15 °C, equimolar amounts of Binolam, Ti(O*i*Pr)$_4$, and the amido alcohol **37**.[40] Cyanocarbonylations of aldehydes under these conditions were quite efficient (up to 92% *ee* values) for all kinds of aldehydes (Scheme 6). The proposed mechanism, which postulates the possible implication of a monomeric self-assembled catalyst of 1:1:1 stoichiometry, calls for a dual role of the catalyst to activate both the aldehyde and the cyanoethoxycarboxylation reagent employed. In spite of this proposal we tentatively suggest that the reaction conditions employed would likely produce a certain amount of HCN. Accordingly, the overall cyanoethoxycarboxylation could well be the result of an enantioselective hydrocyanation followed by *O*-functionalization. This alternative mechanism should not therefore be discounted.[40]

These cyanohydrin derivatives are useful building blocks for the preparation of other enantiomerically pure compounds.[33h] Actually, under acidic hydrolysis conditions, these cyanohydrin derivatives can be converted into the corresponding enantiopure hydroxyacids by chemoselective hydrolysis of (*S*)-**38** (R^2 = Me). *O*-Methoxycarbonyl ethyl esters were obtained in very good yields by alcoholysis of (*S*)-

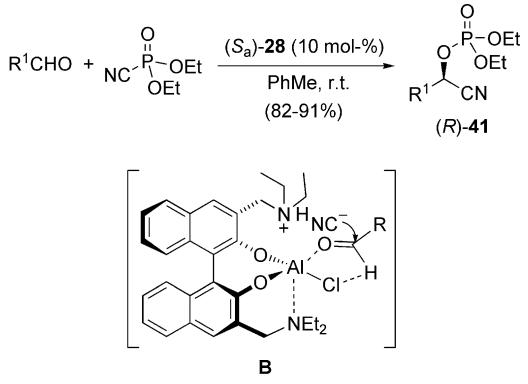
38 with HCl (2 M)/EtOH, whereas *O*-methoxycarbonyl carboxylic acids were generated by treatment with HCl (12 M) at room temperature. Complete hydrolysis in HCl (12 M) at reflux led to α-hydroxy acids in good yields, but again, partial hydrolysis (*O*-protected amides result upon treatment with aqueous TMSCl) could be achieved by using the appropriate reagents.[39] Enantiomerically pure β-amino alcohols could be obtained by reduction with $LiAlH_4$.[39]

Much effort has been put into the development of simple methods for enantioselective cyanoacylations with acyl cyanides. The chiral aggregate (S_a)-**39** (Scheme 7) resulting from mixing of equimolar amounts of Binolam **23** and $Ti(OiPr)_4$ was found to be a suitable catalyst for the enantioselective synthesis of *O*-benzoyl cyanohydrins **40** with commercial benzoylcyanide as reagent, for which purpose the use of aluminium complex (S_a)-**28** gave much poorer results. Unfortunately, the enantioselection was only modest with all type of aldehydes (56–68% *ee* values) in spite of numerous attempts to improve it. Because HCN can be detected in the reaction mixture, the suggested mechanism calls for an enantioselective hydrocyanation followed by a fast *O*-benzoylation by benzoyl cyanide.[41] For this transformation higher catalyst loadings (10 mol-%) were required, in accordance with the lower reactivity of acyl cyanides.



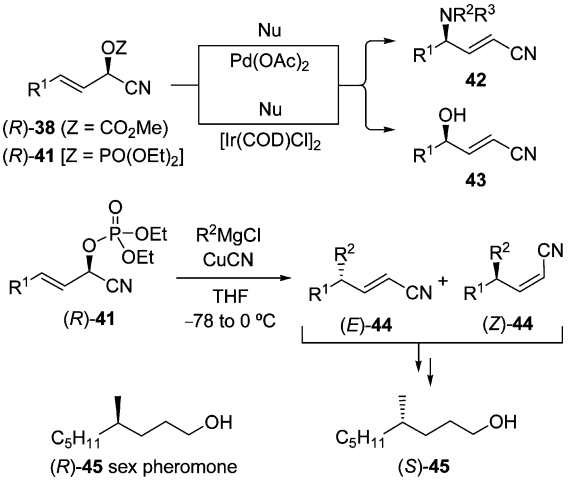
Scheme 7. Binolam·Ti^{IV} aggregate (S_a)-**39** tested in the cyanobenzoylation of aldehydes.

The only reported route to enantiopure cyanohydrin *O*-phosphates (*R*)-**41** (Scheme 8) involves the use of Binolam·AlCl (S_a)-**28** as chiral catalyst. This is quite remarkable, because cyanohydrin *O*-phosphates (*R*)-**41** are very difficult to obtain in optically pure form by direct phosphorylation of enantio-enriched cyanohydrins in the presence of a base, partial racemization being the main drawback.[42,43] A large series of aldehydes reacted with commercial diethyl cyanophosphonate in the presence of the chiral complex (S_a)-**28** (10 mol-%) in toluene at room temperature, no additives being required to facilitate the reaction, as had been the case in previous examples involving cyanosilylations or cyanoformylations promoted by the same catalyst (Scheme 8).[42,43] Chemical yields and enantioselectivities were very high, and the chiral ligand could be recovered almost quantitatively at the end of the reaction after an extractive acidic/basic workup. A thorough study of the mechanism of this reaction was carried out. The existence of a strongly positive NLE suggested that the catalytically active complex could be a monomeric catalytic species, in equilibrium with inactive, or more slowly acting, dimeric or oligomeric species (the so called "reservoir effect"). In addition, computations at the HF/6–31G* level served to delineate the relative importance of the direct cyanophosphorylation route versus the indirect route involving hydrocyanation followed by *O*-phosphorylation. The data clearly supported the most likely involvement of the indirect route, for which both HCN and HNC modes of addition were found to be active routes to be considered. Eventually, it was found that the lowest energy barrier corresponded to the addition of HCN to the *Si* face of the aldehyde, as shown in transition state **B** (Scheme 8).[39] More importantly, the results of these computations are consistent with the experimental observations.



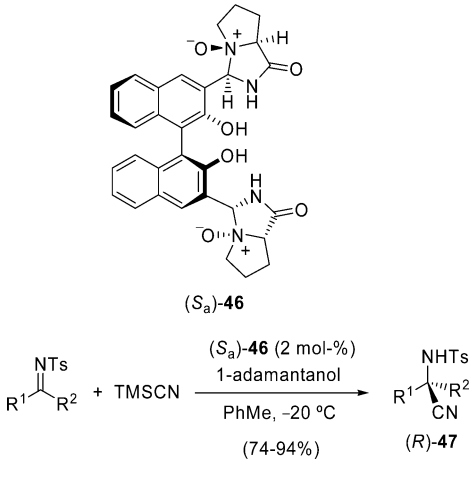
Scheme 8. Binolam (S_a)-**28** tested in the cyanophosphorylation of aldehydes.

Cyanophosphates **41** were found to be stereochemically stable upon standing at room temperature for months. Their utility in organic synthesis was surveyed and contrasted with that of the cyanocarbonate analogues. Although in both cases racemization occurred in basic or acidic media, treatment of (*R*)-**41** (R^1 = Ph) with anhydrous HCl/EtOH at 0 °C yielded highly enantio-enriched (*R*)-*O*-phosphorylmandelate (with less than 3% loss of enantiomeric purity). Cyanohydrin derivatives, obtained from α,β-unsaturated aldehydes, underwent iridium- or palladium-catalyzed S_N2' substitution reactions with carbo- or heteronucleophiles.[44] Dialkyl cuprates, generated in situ, also give rise to S_N2' substitution processes.[45] The final α,β-unsaturated nitriles – **42**, **43**, and **44** – thus obtained were found to be very attractive intermediates in organic synthesis. Compound **42** is as a direct precursor of γ-amino acids,[44] compound **43** ($R^1 = C_5H_{11}$) is an intermediate in the synthesis of coriolic acid,[46] and the enantiomerically enriched products **44** ($R^1 = C_5H_{11}$, R^2 = Me) were the precursors of compound (*R*)-**45**, which is the pheromone of the yellow mealworm *Tenebrio molitor* L., and its enantiomer (*S*)-**45**[45] (Scheme 9). An important drawback of these allylic substitutions is the control of the final configurations of the alkenes, due to the small stereoelectronic hindrance of the cyano substituent.[44,45]



Scheme 9. Synthetic utility of the unsaturated cyanohydrin derivatives **38** and **41**.

All attempts at extending the use of Binolam·AlCl **28** as an enantioselective catalyst for Strecker additions of cyanide derivatives to imines led to racemic compounds.[47] Recently, though, a Strecker-type reaction using ligand **46** as organocatalyst has been reported (Scheme 10).[48] This product was prepared from the chiral dialdehyde (S_a)-**19** and prolinamide, followed by oxidation with MCPBA at very low temperature. The addition of TMSCN to ketoimines catalyzed by **46** afforded *N*-tosylamino nitriles (*R*)-**47** in very good yields and with excellent enantioselection (90–99% *ee* values). It is worth mentioning that a large amount of adamantan-1-ol was required as additive in order to reach high levels of enantioselection (Scheme 10). Presumably, this addition induces the formation of HCN,[48] as shown for previous cases.

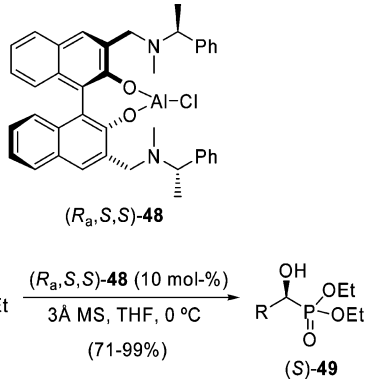


Scheme 10. Strecker-type additions onto ketimines mediated by the organocatalyst **46**.

In summary, metal-based catalysts derived from bifunctional Binolam ligands appear to be ideally suited for one-pot syntheses of enantiomerically enriched cyanohydrin derivatives. Worthy of note is the fact that the Binolam ligand can be recovered and reused without any significant loss of activity. Traces of HCN are either present in the commercial cyanide source employed, or are formed in situ by hydrolysis or alcoholysis. This, together with other relevant factors, supports the proposal that bifunctional Binolam-metal catalysts work as Lewis acid-Brønsted base (LABB) catalysts, and that this is followed by an *O*-functionalization (silylation, phosphorylation, alkoxycarbonylation or acylation) step, which liberates HCN for a subsequent cycle.

3.3. Enantioselective Hydrophosphonylation of Aldehydes

The hydrophosphonylation of aldehydes (Pudovic reaction, Scheme 11) involves the addition of diethyl phosphate, which exists in tautomeric equilibrium with hydrogen diethylphosphonate [H(OEt)$_2$P=O]. The chiral Binolam-derived aluminium complex (R_a,*S*,*S*)-**48** (10 mol-%) has been shown to be an appropriate catalyst for the enantioselective hydrophosphonylation of aldehydes, with enriched α-hydroxyphosphonates (*S*)-**49** being obtained in high yields and with good enantioselectivities (up to 84% *ee* values). The reaction, which is of wide scope, because aromatic, heteroaromatic, and aliphatic aldehydes all gave similar results (Scheme 11),[49] has been proposed to involve a bifunctional LABB mechanism similar to that illustrated above for the addition of HCN.

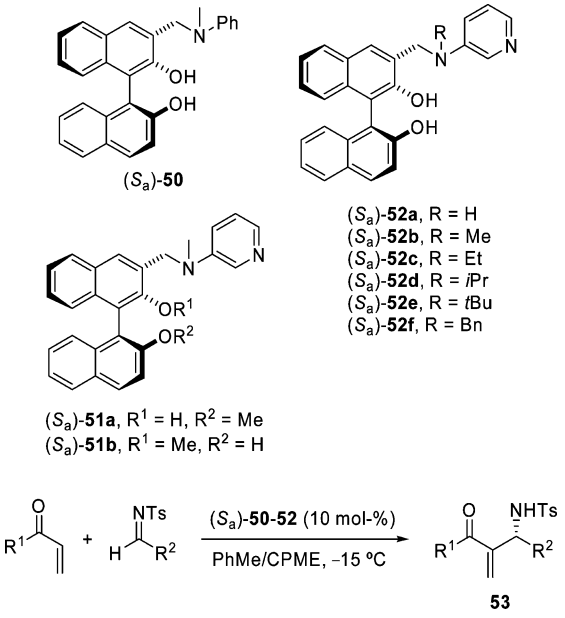


Scheme 11. Enantioselective hydrophosphonylation of aldehydes.

3.4. Enantioselective Aza-Morita–Baylis–Hillman Reaction

The aza-Morita–Baylis–Hillman (aza-MBH) reaction can be defined as a condensation of an electron-poor alkene and an aldimine, catalyzed by a tertiary amine or phosphane.[50] Usually, this reaction is very slow and the enantioselective approach has proven to be a difficult task to achieve. Capriciously, Binolam **I** derivatives were unable to catalyze the reaction, whereas Binolam **II** derivatives were applicable. The singly aminomethyl-armed structures **50**–**52** thus gave satisfactory yields of the final product **53** (Scheme 12) with very high enantioselection.[51–53] Under the optimized reaction conditions at –15 °C, with a catalyst loading of 10 mol-%, in a mixture of toluene and CPME (cyclopentyl methyl ether) as solvent, the best enantioselection (88–95% *ee*) was achieved with chiral organocatalyst

(S_a)-**52d** (Scheme 12 and Table 1). Compounds (S_a)-**51b**, (S_a)-**52c**, (S_a)-**52e**, and (S_a)-**52f** also promoted this reaction with very good conversions and high enantioselection, but their scope was quite limited.



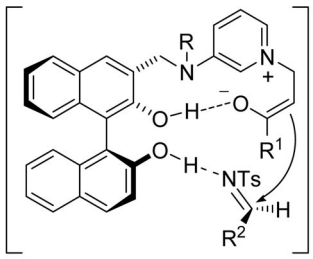
Scheme 12. Aza-MBH reactions promoted by organocatalysts (S_a)-**50**–**52**.

Table 1. Enantioselective aza-MBH catalyzed by **50**–**52**.

Entry	(S_a)-Ligand	Yield (%)[a] of **53**	*ee* of **53**
1	**50**	n.d.[b]	n.d.[b]
2	**51a**	5	24
3	**51b**	85	79
4	**52a**	62	87
5	**52b**	97	90
6	**52c**	90	91
7	**52d**	88 (quant.)	88–95
8	**52e**	72	83
9	**52f**	99	93

[a] Reaction run with methyl vinyl ketone and *N*-tosylimine with R^2 = *p*-ClC_6H_4. [b] n.d.: not detected.

The catalyst action appears to involve the dual activation of both nucleophile and electrophile, as suggested by several pieces of indirect evidence. If both Brønsted acid and Lewis base units were conveniently positioned, the acid unit could activate a carbonyl group of the α,β-unsaturated system and, consequently, the Lewis base unit would react at the β-position of the substrate in transition state **C**. A subsequent Mannich-type addition, followed by a retro-Michael-type step, would finally give the desired product **53**. This bifunctional mechanism was also supported by several experiments, such as the fact that the reaction performed with organocatalyst (S_a)-**50** was unsuccessful due to the lack of the heteroaromatic nitrogen, again reinforcing its crucial role in a dual mechanism.[50–53]

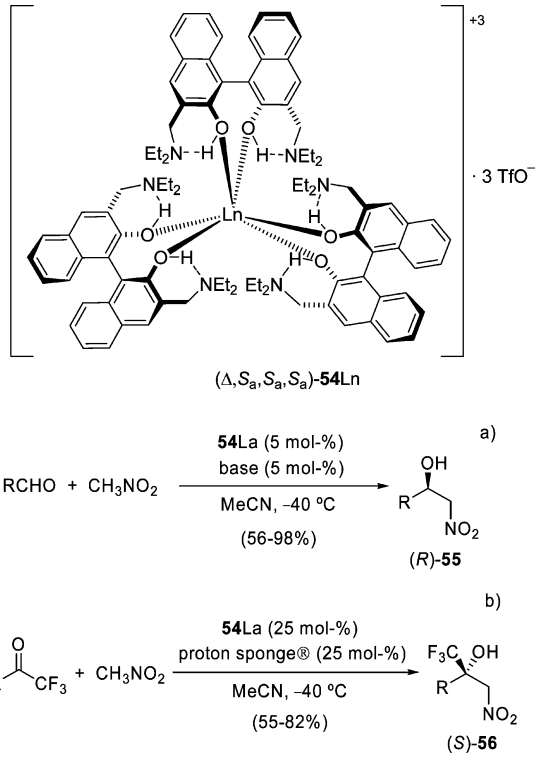


C

3.5. Enantioselective Nitroaldol Reaction

The nitroaldol (Henry) reaction[54] has been the goal of many enantioselective strategies as a result of the high functional density present on the product structures at the end of the reaction. Binolam **I** compounds, thanks to the topological disposition of their ligating arms [according to the X-ray diffraction data for Binolam (R = Et), the C2–C1–C1′–C2′ dihedral angle is 90.3°], are ideally suited for forming octahedral complexes. Accordingly, Binolams have been reported to form 3:1 lanthanide(III) triflate complexes **54** (Scheme 13, a) quantitatively,[55] simply on mixing of ligand **23** (3 equiv.) with lanthanide(III) triflate (1 equiv.) in dry acetonitrile. The resulting hexacoordinate complexes **54** were found to be shelf-stable solids, though nevertheless kinetically labile, characterized by having an additional stereogenic element at the lanthanide atom and an extended array of acid and basic sites.[56] Among the lanthanide complexes (**54Ln**) studied, the lanthanum complex **54La** was the most suitable for the enantioselective addition of nitromethane to aromatic, aliphatic, and α,β-unsaturated aldehydes. The reaction took place at –40 °C in dry acetonitrile in the presence of **54La** (5 mol-%) and an equimolar amount (5 mol-%) of an amine such as DBU, or proton sponge® [1,8-bis(dimethylamino)naphthalene], slightly better with the latter base (Scheme 13, a). The absence of nonlinear effects is consistent with the involvement of kinetically labile, monomeric 3:1 complexes. The proposed hypothetical mechanism calls for a prior deprotonation step upon precatalyst **54**, thereby giving rise to the actual catalyst, presumably incorporating a Lewis acid/Lewis base/Brønsted base-arrayed network, in which the lanthanum Lewis acid should ligate nitromethane and be deprotonated by the amine Brønsted base site. Final coordination of the aldehyde should then be followed by carbon-carbon bond formation and the eventual recovery of the catalytic active complex.[55]

More interestingly, complex **54La** (25 mol-%) was also effective in catalyzing nitroaldol reactions between α-trifluoromethyl ketones and nitromethane (Scheme 13, b) in an enantioselective manner, a previously unachieved goal.[57] Alkyl, alkynyl, benzyl, and aryl trifluoromethyl ketones were allowed to react in acetonitrile at –40 °C for 4 d in the presence of proton sponge® (25 mol-%), furnishing tertiary nitroaldols (*S*)-**56** in good yields and high enantioselectivities (67–98% *ee* values, Scheme 13, b). Reduction of the nitro groups with "nickel boride" yielded the corresponding amino alcohols, each containing a chiral

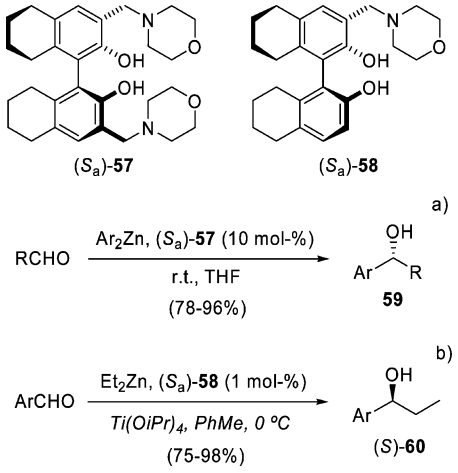


Scheme 13. Enantioselective nitroaldol (Henry) reaction promoted by complex **54**La.

quaternary carbon with no loss of enantiomeric purity. The absolute configuration of these amino alcohols (*R*)-**55** (R = Ph) and (*S*)-**56** (R = Ph) were assigned from the sign of the Flack parameter from the X-ray diffraction structure. The hypothetical mechanism for this nitroaldol condensation calls for an specific chelating ability of the $–COCF_3$ unit opposite to that of an aldehyde –CHO, in accordance with the opposite configurations of the final adducts (*R*)-**55** and (*S*)-**56**.[57]

3.6. Enantioselective Organozinc Compound Additions

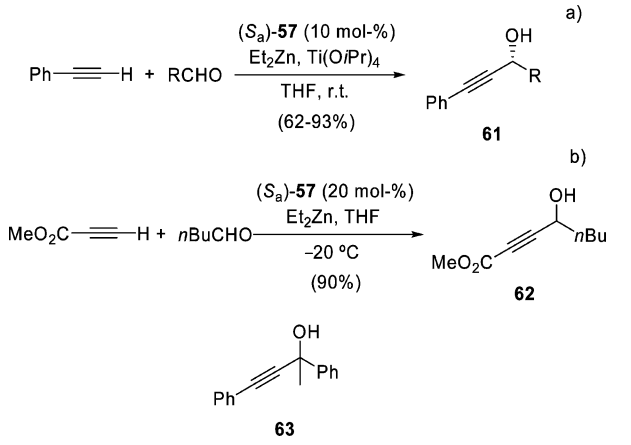
The addition of organozinc compounds onto C=O or C=N double bonds is a currently used practice for evaluating the efficiency of a chiral ligand. Binolam ligands **I** and **II** have been studied with regard to the addition of diphenyl- or diethylzinc and zinc phenylacetylide onto carbonyl compounds, mainly aldehydes. Binolams of type **I**, the precursor amides **22**, and the partially hydrogenated ligands (S_a)-**57** and (S_a)-**58** were examined for catalytic capacity. The highest catalytic activity on the enantioselective diphenylzinc addition onto aldehydes was found for (S_a)-**57**.[28,29] Both aromatic and aliphatic aldehydes gave good yields of alcohols **59** with excellent enantioselectivities (90–97% *ee* values and 92–99% *ee* values, respectively), even for linear aliphatic aldehydes (Scheme 14, a).[28,29] NMR spectroscopic studies revealed the presence of different zinc alkoxides (oligomers or clusters) originating from the reaction between ligand and organozinc reagent, thus suggesting that the catalytically active species could even possess three or four metallic centers.[25,26] The reaction has been successfully extended to functionalized arylzinc reagents, prepared in situ from the corresponding aryl iodides (such as *m*-iodoanisole, methyl *p*-iodobenzoate, and *m*-iodobenzonitrile) and diethylzinc. Both chemical yields and enantioselectivities were very high when the reaction was carried out at 0 °C either with aliphatic or aromatic aldehydes (Scheme 14, a).[58]



Scheme 14. Enantioselective addition of organozinc compounds onto aldehydes.

Diethylzinc, however, added to aldehydes with poor enantioselectivity. Eventually, the authors found that the presence of $Ti(OiPr)_4$ (1.2 equiv.) was required, together with the Binolam ligand (S_a)-**58** (10 mol-%), for efficiency in additions to aromatic aldehydes, thereby furnishing chiral alcohols (*S*)-**60** in good yields and with high enantioselectivities (64–98% *ee* values, Scheme 14, b).[59] Other Binol-derived compounds were eventually found to be more efficient than Binolams.

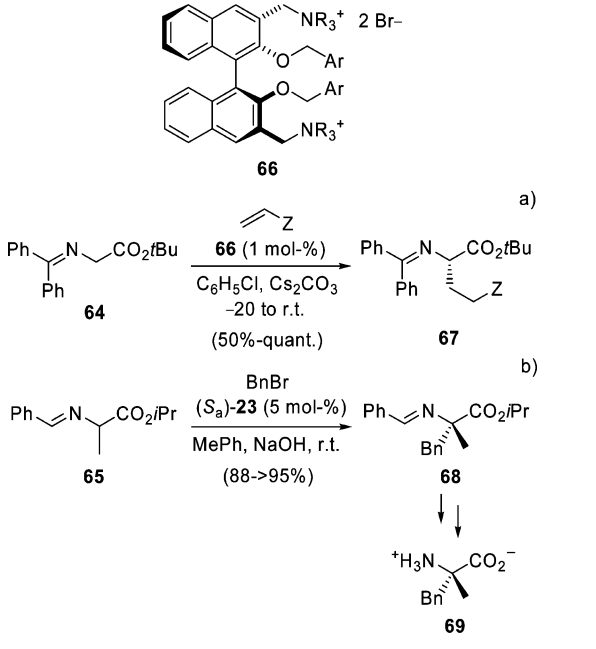
Bifunctional ligand (S_a)-**57** was employed to catalyze enantioselective alkynylzinc additions onto aldehydes (Scheme 15), thereby leading to chiral propargylic alcohols **61**, which are of great utility in organic synthesis. The reactions were carried out at room temperature by mixing the ligand (S_a)-**57** (20 mol-%), diethylzinc (4 equiv.), $Ti(OiPr)_4$ (1 equiv.), and phenylacetylene (4 equiv.) in THF. Aromatic aldehydes reacted in good yields and with high selectivities (67–98% *ee* values; Scheme 15, a), but linear aliphatic aldehydes gave lower enantioselectivities (67% *ee* from *n*-octanal). On the other hand, addition to ketones required the use of $Ti(OiPr)_4$ (40 mol-%) in 1,4-dioxane as solvent in order to provide the enantiomerically enriched tertiary alcohol **63**, which contains a quaternary carbon, in 69% *ee* (Scheme 15).[28] Use of (S_a)-**57** (20 mol-%) allowed the preparation of polyfunctionalized **62** in 69% enantiomeric purity (Scheme 15, b).[28]



Scheme 15. Enantioselective addition of alkynylzinc compounds onto aldehydes.

3.7. Enantioselective α-Alkylation of Iminoesters

Activated enolates derived from ketimino glycinate **64** or aldimino alaninate **65** (Scheme 16) have been employed for the asymmetric synthesis of α-amino acids, for which purpose enantioselective alkylations with electrophilic reagents and Michael-type addition reactions onto electrophilic alkenes were explored with chiral PTC agents.[60] The versatility of this strategy allows α-substituted α-amino acids to be obtained from the starting ketimine **64**, or instead for α,α-disubstituted α-amino acids to be obtained from aldimine **65**. The capacity of Binolam and Binolam derivatives to catalyze these processes has been explored on several occasions. In particular, Binolam **23** was examined as a pre-catalyst for the direct alkylation of iminoglycinate **64** in the expectation that quaternization of the α-carbon would occur in situ, thereby generating the actual PTC catalyst. The best results obtained involved the use of KOH (40%) in a two-phase system.[61] Enantiomerically pure bis-ammonium salt **66**, prepared in two steps from the corresponding Binaphthol **I**, was assayed as a chiral PTC agent (1 mol-%, Ar = 4-$CF_3C_6H_4$, NR_3 = NEt_3) in 1,4-addition reactions between *tert*-butyl iminoglycinate **64** and methyl acrylate, *N*,*N*-diphenyl acrylamide, acrylonitrile, phenyl vinyl ketone, and phenyl vinyl sulfone, in chlorobenzene as solvent and with Cs_2CO_3 (2 equiv.) as solid base. Although the obtained yields of the α-alkylated products **67** were moderate to high (50–100%), enantioselectivities were found to be unsatisfactory (32–75% *ee* values; Scheme 16, a).[25]

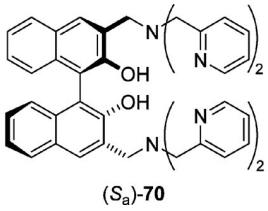


Scheme 16. Enantioselective PTC additions and alkylations promoted by Binolam **I** derivatives.

The preparation of the non-proteinogenic quaternary α-methyl-α-amino acid (*S*)-**69**, an artificial sweetener, could be achieved by starting from iminoester **68**. The best reaction conditions for obtaining the α-benzylalanine (68% *ee*) are shown in part b of Scheme 16. The most suitable chiral PTC agent was found to be Binolam derivative **66**, employed in a 5 mol-% loading in toluene, the selected base being NaOH (2 equiv.).[61]

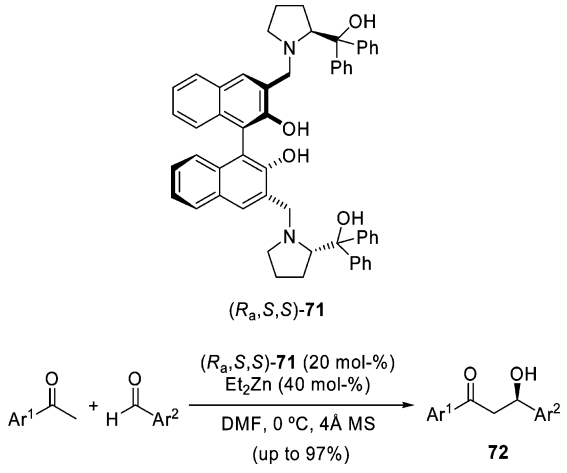
3.8. Enantioselective Alkane Oxidations

The enantioselective C–H oxidation of alkanes is a field of great prospect and usefulness in which the application of enzyme-like catalysts is being explored. Complexation of ligand (S_a)-**70** with iron(III) salts yielded a dinuclear complex that was tested as a catalyst for the enantioselective oxidation of alkanes to yield alcohols. The authors employed *m*-chloroperbenzoic acid (*m*CPBA) or *N*-methylmorpholine oxide (NMO) as stoichiometric oxidants. Unfortunately, the enantioselectivity under these conditions was extremely low, in favor of the (*R*) isomer (≤10%) of the corresponding alcohol.[62]



3.9. Enantioselective Aldol Reactions

The first direct asymmetric aldol reactions between aryl ketones and aryl aldehydes reported to date were catalyzed by the chiral metal complex generated by treatment of semicrown chiral ligand **71** (20 mol-%) with diethylzinc (40 mol-%) (Scheme 17). Although the reactions took approximately 5 days to go to completion, both the chemical yields (36–97%) of **72** and the enantioselectivities were good. Indeed, an 80% *ee* was obtained for the reaction between acetophenone and furfural. The proposed mechanism calls for a dinuclear zinc complex in which the zincate enol of the ketone attacks the aldehyde (Scheme 17).[63]



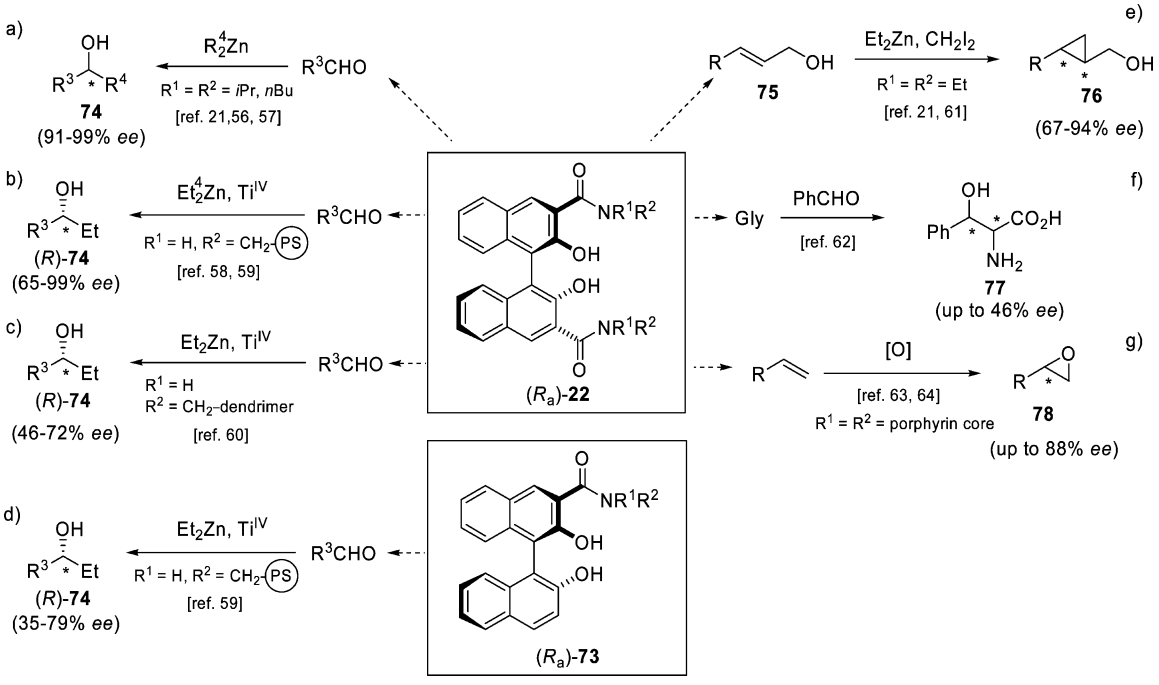
Scheme 17. Enantioselective aldol-type addition promoted by Binolam (R_a,*S*,*S*)-**71**/Sc(OTf)$_3$.

3.10. Enantioselective Transformations Promoted by Binolam Precursors 22 and 73

The Binolam precursory amides **22** and **73** have also been tested as catalysts for several enantioselective transformations. Here we briefly describe their most relevant applications as enantioselective catalysts for additions of dialkyl- or diphenylzinc to carbonyl compounds,[24,64,65,66–68] for Simmons–Smith cyclopropanations,[24,69] for aldol reactions,[70] and for epoxidation reactions (Scheme 18).[71,72]

The enantioselective diethylzinc additions onto aldehydes were performed directly at 0 °C by use of bisamide (R_a)-**22** (R^1 = R^2 = *n*Bu, 10 mol-%) to provide, after hydrolysis, alcohols (*R*)-**74** in good yields and with very high enantioselectivities (91–99% *ee* values) (Scheme 18, a).[24,64] An identical range of enantioselection was determined in the analogous reactions with diphenylzinc as reagent. In these reactions the selected ligand was (S_a)-**22** (R^1 = R^2 = *i*Pr) rather than the other *N*-substituted Binolams.[65] In both sets of examples the ethyl and the phenyl groups were efficiently transferred to aromatic, heteroaromatic, and aliphatic aldehydes.[24,64,65] To facilitate recovery of the chiral ligands from the reaction mixtures, the use of polystyrene-supported amides (R_a)-**22**[66,67] and (R_a)-**73**[67] for catalysis was explored. In both cases the presence of catalytic amounts of Ti(O*i*Pr)$_4$ was necessary for the diethylzinc addition to be carried out at 0 °C, with the ligand (R_a)-**22** being the more effective (see parts b and d in Scheme 18). Moreover, alcohols (*R*)-**74** were also obtained when a dendrimeric skeleton was attached to the nitrogen atom of ligand (R_a)-**22** under otherwise identical reaction conditions. Moderate enantioselectivities (46–72% *ee* values, Scheme 18, c) were obtained in this case. Obviously, the advantage of using polystyrene- or dendrimer-supported (R_a)-**22** as catalysts is that they could be satisfactorily separated by filtration and further reused for another batch.

Amide (R_a)-**22** (R^1 = R^2 = Et) has also been explored as a catalyst for the asymmetric Simmons–Smith reaction with the (*E*) allylic alcohol **75** (cinnamyl alcohol), to afford cyclopropanes **76**. The absolute configurations of the final products are not given here because they strongly depend



Scheme 18. Most relevant applications of the chiral ligands **22** and **73**.

on the geometries and substituents of the alkenes. For illustrative purposes, however, one case is given: cyclopropane (1*R*,2*R*)-**76** was obtained in 94% *ee* when cinnamyl alcohol was used as starting material (Scheme 18, e).[24,69]

The enantioselective aldol reaction between glycine and benzaldehyde could be mediated by supramolecular assemblies composed of lipidic species, a hydrophobic pyridoxal, and copper(II) ions. Unfortunately, the enantioselection achieved for aldol **77** was very low when (S_a)-**22** was the central chiral part of the supramolecular entity (46% *ee*). The absolute configurations of the stereogenic centers were also difficult to generalize. The stereochemical microenvironment around the copper ion involved in the intermediate Schiff-base complex, which allowed either *Si* or *Re* attack onto benzaldehyde (Scheme 18, f), is extremely complex.

Finally, the C_2-symmetric diamide (R_a)-**22** was inserted into two "handles" around a porphyrin core, imitating the model of the natural proteins. The resulting chiral iron(III) complexes exhibited moderate enantioselection in the epoxidation of alkenes with iodosylbenzene as oxidant (Scheme 18, g).[71,72] Styrene derivatives were found to be the ideal substrates for this epoxidation reaction, which afforded chiral epoxides **78** in good yields.

4. Conclusions

Jacobsen coined the term "privileged" catalysts for those capable of promoting a large variety of different enantioselective transformations.[73] As illustrated above, Binolams[74] and Binolam complexes have been shown to catalyze numerous enantioselective additions involving enolate derivatives, such as the aza-Morita–Baylis–Hillman (aza-MBH) reaction, the nitroaldol (Henry) reaction, Michael-type additions, and α-alkylation reactions, as well as additions of organozinc reagents to carbonyls and imine derivatives. In addition, they have been found to be highly valuable for the enantioselective cyanation of aldehydes. In our view, the bifunctional structures of Binolams and of their metal complexes allow these species to promote dual catalytic action in activating both nucleophilic and the electrophilic species. In our opinion, it is this capacity that elevates Binolams to the category of privileged catalysts (or ligands). Accordingly, the future of Binolams in enantioselective catalysis is still very promising.

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