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## The Direct Catalytic Asymmetric Aldol Reaction

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### Abstract

Asymmetric aldol reactions are a powerful method for the construction of carbon-carbon bonds in an enantioselective fashion. Historically this reaction has been performed in a stoichiometric fashion to control the various aspects of chemo-, diastereo-, regio- and enantioselectivity, however, a more atom economical approach would unite high selectivity with the use of only a catalytic amount of a chiral promoter. This *critical review* documents the development of direct catalytic asymmetric aldol methodologies, including organocatalytic and metal-based strategies. New methods have improved the reactivity, selectivity and substrate scope of the direct aldol reaction and enabled the synthesis of complex molecular targets

### 1. Introduction

The aldol reaction, first discovered by Wurtz in 1872,<sup>1</sup> is one of the most powerful transformations in organic chemistry. The process unites two carbonyl partners to give  $\beta$ -hydroxyketones with up to two new stereocenters (Scheme 1). The aldol reaction presents numerous challenges, including issues of chemo-, regio-, diastereo-, and enantioselectivity to the synthetic chemist, which has spurred the development of many powerful stoichiometric processes to address these issues.<sup>2</sup> Development of catalytic methods that avoid the production of stoichiometric by-products while maintaining the high levels of control available from such processes provides an atom-economical alternative for these important transformations.<sup>3</sup> Indeed, numerous catalytic methods have been reported in recent years, including enzymes,<sup>4</sup> catalytic antibodies<sup>5</sup> and small molecules.<sup>6–8</sup> The focus of this review will be on small molecule catalysts, including organocatalysts and metal complexes, with special emphasis on selectivity, substrate scope and current limitations.

In biological systems, the aldol reaction is accomplished by two types of aldolases, classified by their different mechanisms (Scheme 2).<sup>9</sup> Type I aldolases function *via* an enamine mechanism, in which an enzyme lysine residue reacts with the donor component **8** to generate an enamine (**B**) in the active site. This enamine (**C**) then attacks the acceptor electrophile (**9**) to give iminium adduct **D**. Hydrolysis frees the substrate from the enzyme and releases the aldol adduct **10**.

Type II aldolases catalyze the aldol reaction by activation of the donor substrate **8** with an active site histidine-bound zinc ion. This acidifies the  $\alpha$ -proton, allowing for facile generation of zinc enolate **F**. Activation of the carbonyl of the acceptor **11** through hydrogen-bonding is followed by attack of the zinc enolate to provide aldol adduct **G**. Protonation and decomplexation yields aldol adduct **10**.

These biological processes have provided a template for the development of small molecule catalysts. Indeed, most of the reported catalytic systems fall into these two mechanistic classes. Nature's aldolases inspire chemists to create small molecule mimics capable of both imitating the power of enzymes in terms of selectivity and efficiency, but also to develop systems capable of catalyzing aldol reactions for a wide array of substrates, which nature's enzymes will not tolerate.

## 2. Enamine-Catalyzed Aldol Reactions

Small molecule catalysts which take advantage of an enamine mechanism analogous to the type I aldolases comprise the vast majority of reported methods for carrying out direct catalytic asymmetric aldol reactions. As these approaches have been reviewed previously,<sup>10–24</sup> the goal of this review will be to highlight and compare the reactivity, scope and selectivity of a wide range of catalysts, rather than catalogue every example of their use. This review will not focus on design parameters such as catalyst immobilization,<sup>25–35</sup> attaching hydrophobic groups to the catalyst,<sup>30, 36–38</sup> reactions in micelles,<sup>39, 40</sup> host-guest catalytic systems,<sup>41, 42</sup> or the use of ionic liquids<sup>43–54</sup> or surfactants,<sup>55–60</sup> which can be found elsewhere.<sup>12, 13</sup> Instead, this review will highlight what is currently possible synthetically and what challenges remain unmet for enamine-based catalysts.

### 2.1 Proline-Catalyzed Aldol Reactions

The first report of a direct asymmetric aldol reaction catalyzed by a small molecule was the Hajos-Parrish-Eder-Sauer-Wiechert cyclization, disclosed in 1971 (Scheme 3).<sup>61, 62</sup> This intramolecular aldol cyclization proceeded with only 3 mol% proline (**13**) to give the cyclized product **14** in excellent yield and enantioselectivity. Unfortunately, both the yield and the enantioselectivity dropped for the 6-membered ring substrate **15**. Despite this reaction's utility, particularly for the synthesis of steroids, its mechanism was not determined, nor was proline appreciated as a broadly applicable catalyst, for many years. Amino acids such as proline are particularly appealing catalysts, due to their natural abundance and low cost.

The Hajos-Parrish-Eder-Sauer-Wiechert reaction is an enol-endo aldolization. Enol-exo cyclizations are also possible using proline catalysis. In 2003 List and coworkers reported the enol-exo cyclization of a variety of dialdehydes, such as **17**, yielding 6-membered rings (**18**) in high yields, diastereo- and enantioselectivities. Five-membered rings (**20**) were formed with reduced diastereo- and enantioselectivities (Scheme 4).<sup>63, 64</sup> List has also demonstrated that transannular intramolecular cyclizations are possible using catalytic proline, though the enantioselectivity was not high. Using modified catalyst **22** the enantioselectivity was greatly improved. The utility of this transannular cyclization was demonstrated in List's synthesis of (+)-hirsutene (**24**).

The first intermolecular proline-catalyzed direct aldol reaction was described by List and coworkers in 2000 (Table 1).<sup>65</sup> Using 20–30 mol% L-proline and a 4:1 solution of DMSO:acetone, the desired aldol adducts **27** were obtained. Aryl aldehydes were good substrates for this reaction, as were branched aliphatic substrates, which gave the highest yields and enantioselectivities.  $\alpha$ -Unbranched aldehydes were less successful substrates, giving low yields and moderate enantioselectivity after tuning of the reaction conditions to prevent aldehyde self-condensation.<sup>66</sup> Unfortunately, even under these optimized conditions (employing neat acetone or chloroform as cosolvent for 3–7 days), the cross-aldol condensation product **4** (Scheme 1) was a significant byproduct, resulting in low overall yield. Despite the low yield and modest enantioselection of this process, the simplicity and mildness of these reaction conditions is exceptional. This methodology was used by List and

coworkers to complete the synthesis of (*S*)-ipsenol (**28**), a sex pheromone of the bark beetle. The acetone aldol has also been used for the syntheses of 4-hydroxypipericolic acid derivative **29**<sup>67</sup> and carboxylic acid **30**, a building block for the synthesis of epothilone.<sup>68</sup>

A great deal of research has clarified the mechanism of the proline-catalyzed aldol reaction, which is essentially that of a class I aldolase (Scheme 5).<sup>24, 61, 69–105</sup> The accepted mechanism for the intermolecular process begins with rate-limiting enamine formation (**A**), followed by carbonyl addition, activated by the carboxylic acid of proline (**B**), followed by hydrolysis of iminium ion **C** to give aldol adduct **27**. The addition step has a similar energy barrier as the enamine formation, indicating that under different conditions or with different substrates, the rate-determining step may be the addition step. In fact, recent kinetic evidence obtained by Armstrong and Blackmond indicates that under the reaction conditions studied, the addition step is rate-determining.<sup>106</sup>

Several by-products have been observed in the proline-catalyzed acetone aldol reaction that lead to reduced yields, including aldol condensation (yielding enone **33**), and the aldol reaction and condensation of the aldehyde component, which generates adducts **34** and **35**, respectively (Scheme 6). Additionally, oxazolidinone **36** derived from the aldehyde component **31** has been observed. To achieve high yields of the desired adducts **32**, acetone is used in a large excess to prevent homodimerization of the aldehyde and catalyst kill events, such as the formation of oxazolidinone **36**.

A beneficial effect of water in small amounts was first reported by Pihko and coworkers.<sup>107, 108</sup> Armstrong and Blackmond have recently clarified the role of water in the reaction (Scheme 7).<sup>109</sup> They demonstrated that water in fact decreases the rate of the reaction, as it must be extruded before the rate-limiting step (Scheme 5), but off cycle processes are shut down significantly in the presence of water, thereby giving an overall positive effect on the yield of the desired aldol product **27**. By shifting the equilibrium between aldehyde **25** and iminium ion **A** toward aldehyde **25** with added water, the formation of byproducts can be avoided. Formation of oxazolidinone **37** and oxazole **38** (derived from decarboxylation of iminium ion **A**, followed by addition of ammonium ylide **B** to another equivalent of aldehyde **25**) is largely prevented in this way.

An alternative mechanism for proline catalyzed reactions was proposed in 2007 by Seebach and Eschenmoser (Scheme 8).<sup>110</sup> The authors propose that oxazolidinones, which are observable by NMR, are key players in the catalytic cycle, rather than mere catalytic sinks. Their proposed mechanism begins by formation of oxazolidinone **A** by condensation of proline with the donor component **39**. Regioselective formation of an enamine, either by E2 elimination or through a two-step iminium formation and intramolecular proton transfer sequence, then undergoes a *trans* addition to an electrophile (approach from the *re* face) to generate oxazolidinone **C**. Hydrolysis then gives the desired product **40**. This mechanistic proposal differs greatly from the *List-Houk* model in that the key step is triggered by a  $\eta$ -lactonization process and does not involve activation of the acceptor component by the catalyst. It is difficult to see how this model would predict high levels of enantioselectivity for the aldol reaction catalyzed by proline since the approach of the aldehyde to the enamine is not controlled through an H-bonding interaction. Also, this model can only be applied to catalysts bearing a free carboxylic acid group, which can participate in oxazolidinone formation.

The proline-catalyzed aldol reaction was extended to ketones other than acetone in 2001 (Table 2).<sup>22, 66</sup> Since the ketone was required in near solvent quantities, the reaction was limited to simple ketone substrates, such as cyclohexanone and cyclopentanone, for practical reasons. The *anti* aldol adducts **42** were favored over the *syn* configuration in most cases.

For cyclic ketones, only one enamine geometry is possible, the *E* enamine **A**. The orientation of the aldehyde when approaching this enamine, therefore, gives rise to the diastereoselectivity. The orientation depicted in **A** is generally favored, as it avoids steric clashes with the alkyl group on the other side of the enamine, as long as R<sub>S</sub> is smaller than this alkyl group. Cyclohexanone tends to give higher diastereoselectivities than cyclopentanone, as do aliphatic aldehydes when compared to aromatic aldehydes. These reactions are typically run for 3 days with 10–30 mol% catalyst, indicating that the reaction rate is rather slow. The original conditions reported by Barbas<sup>111</sup> for the synthesis of aldol adduct **42** were improved upon by using the solvent-free conditions reported by Hayashi to give the cyclohexanone adduct **42a** in 73% yield, 9:1 dr and in >99% ee favoring the *anti* isomer.<sup>112</sup> The cyclopentanone aldol catalyzed by proline has been used for the synthesis of adduct **42f**, which was used for the synthesis of the antimalarial (+)-(11*R*, 12*S*)-mefloquine hydrochloride.<sup>113</sup>

In 2001 Barbas and coworkers described the use of proline with 2-butanone, an unsymmetrical ketone.<sup>111</sup> Under the reaction conditions (20 mol% catalyst, 0.1M substrate in 1:4 ketone:DMSO, ambient temperature for 1–2 days) only the linear product was observed. The authors suggest that the formation of the kinetic enamine is rate-limiting, resulting in observation of only the linear product. Interestingly, employing *N*-ethyl-*N*-methylimidazolium trifluoromethanesulfonate ([emim][OTf]), an ionic liquid, rather than using DMSO as solvent led to isolation of the branched product, with a strong preference for the *anti* diastereomer.<sup>46, 114</sup>

Hydroxyacetone has also been used successfully as a donor for the proline-catalyzed direct aldol reaction, using similar reaction conditions (20–30 mol% catalyst, 0.1M substrate in 1:4 ketone:DMSO, ambient temperature for 1–3 days).<sup>115</sup> Formation of the branched products is observed, with high diastereoselectivity for  $\alpha$ -branched aldehydes, and lower diastereoselectivity observed for aryl aldehydes and  $\alpha$ -unbranched aldehydes. Low yields were observed for  $\alpha$ -unbranched aldehydes, similar to the acetone aldol. This reaction has been used for a formal synthesis of the steroidal plant-growth inhibitor brassinolide (Scheme 9).<sup>116</sup>

The dihydroxyacetone derivative 2,2-dimethyl-1,3-diox-5- one has also been used successfully as a donor in the proline-catalyzed aldol reaction.<sup>117–119</sup> In 2005 Enders and Grondal reported a highly *anti* selective aldol reaction that can be used to generate protected sugar derivatives in high enantioselectivity by selecting the appropriate aldehyde substrate. Aldol adduct **42m**, for example, is a protected L-ribose derivative. Gratifyingly, only one equivalent of the ketone donor was needed to obtain the desired adducts in good yields, employing 30 mol% proline as catalyst. Previous work by Barbas and coworkers demonstrated that unprotected dihydroxyacetone could be used and gave good diastereoselectivity, however, the aldol adducts obtained were racemic in this case.<sup>120</sup> Later in the same year as the Enders and Grondal report, Barbas and coworkers disclosed similar reaction conditions for the use of 2,2-dimethyl-1,3-diox-5- one, demonstrating that the reaction proceeded well with aliphatic, aromatic, and even protected phthalimide substrates using 20 mol% proline.<sup>121</sup> Aliphatic aldehydes gave higher diastereoselectivity than aromatic derivatives. It is notable that the  $\alpha$ -unbranched derivative **42o** was obtained in high yield, in contrast to the adduct derived from reaction of this aldehyde with acetone or cyclohexanone. The discovery of these simple reaction conditions for the use of a protected form of dihydroxyacetone in a direct catalytic aldol reaction has opened up new synthetic routes for the synthesis of various sugar derivatives.

A protected variant of hydroxyacetone have also been used to generate diols in which one of the alcohols is differentiated from the other with a protecting group. TBS-protected

hydroxyacetone undergoes *anti*-selective aldol addition with aromatic substrates.<sup>122</sup> Aldol adduct **42r** is obtained with 90% ee, however, the ee was lower for other aromatic aldehydes (for example, 40% ee was obtained when benzaldehyde was used).  $\alpha,\beta$ -Unsaturated aldehydes gave either no yield or gave predominantly the linear isomer, such as adduct **42t**. The ee in this case was also quite low.

Proline catalysis has also been used for reaction with highly activated ketone electrophiles **48** (Table 3). The self condensation of 2,2-dimethyl-1,3-diox-5-one was observed by Enders and Grondal, producing adduct **49a** in 94% ee.<sup>118</sup> Zhang and coworkers reported the use of  $\alpha$ -trifluoromethyl ketones for the synthesis of aldol adducts such as **49b** with only 10 mol% proline with excellent yields, though the best ee observed was 64%.<sup>123</sup> Maruoka demonstrated the feasibility of using  $\alpha$ -keto esters as electrophiles with cyclohexanone as donor in 2005.<sup>124</sup> Aldol adduct **49c** was obtained in excellent enantio- and diastereoselectivity, although 50 mol% catalyst was needed to achieve these excellent results. Adduct **49c** was taken on to complete the synthesis of a key intermediate for the synthesis of (*S*)-oxybutynin **50**. The research groups of Zhang and Shao reported the use of  $\alpha$ -keto esters as electrophiles for the acetone aldol catalyzed by proline in 2006 using 60 and 50 mol% proline, respectively.<sup>125, 126</sup>  $\alpha$ -Keto phosphonates have also been used as substrates for the proline-catalyzed acetone aldol, yielding the desired aldol adducts **49** in high yield and enantioselectivity when electron-deficient aldehydes are employed as the acceptors, using a catalyst loading of 20 mol%.<sup>127</sup> Electron-rich aromatic substrates, however, gave lower yields due to their lower reactivity. Adduct **49g** was obtained in only 32% yield using 50 mol% proline.

Aldehydes can also be used as donors for the proline-catalyzed aldol reaction. Barbas first noted the trimerization of acetaldehyde **51** in 10% yield and 90% ee (Scheme 10).<sup>128</sup> Dienal **53** was isolated together with the interesting trimer **52**. The first proline-catalyzed cross-aldol reaction of aldehyde donors was reported by Jørgensen (Table 4).<sup>129</sup> Using 50 mol% proline, aldehydes were coupled with non-enolizable  $\alpha$ -keto esters to give  $\alpha$ -chiral aldehydes **54**. While adducts **54a** and **54b** were isolated in good enantioselectivity, the phenyl substituted adduct **54c** was found to be racemic. The trifluoromethyl derivative **54d** was isolated in poor diastereoselectivity with moderate enantioselectivity.

MacMillan and coworkers reported a remarkable breakthrough for the cross-aldol reaction of aldehydes in 2002.<sup>130</sup> Using slow addition of the donor aldehyde (2 equivalents) to the desired acceptor aldehyde the desired cross-aldol products **54** could be obtained in excellent yields and enantioselectivities with only 10 mol% proline. The diastereoselectivity was moderate with  $\alpha$ -unbranched or aromatic acceptor aldehydes and excellent with  $\alpha$ -branched acceptor aldehydes. Even remarkably similar aldehydes gave exclusively the desired cross-aldol adduct, such as adduct **54f**. The acceptor substrate (in the case where the aldehydes are different) in each case is either non-enolizable or generates a less-reactive enamine. In this way the dimerization of the acceptor aldehyde is suppressed. Pihko and coworkers used this methodology for a short synthesis of prelactone B (Scheme 11).<sup>131</sup> MacMillan and coworkers also used this method for the synthesis of callipeltoside C.<sup>132</sup>

In 2004 MacMillan and coworkers extended this methodology to the dimerization of protected  $\alpha$ -hydroxy aldehydes to give highly functionalized aldehydes.<sup>133</sup> These substrates could themselves be used in a subsequent Mukaiyama aldol to give protected sugar derivatives.<sup>134</sup> MacMillan and Mangion used this methodology to complete the synthesis of (–)-littoralisone (Scheme 12).<sup>135</sup> Cross-aldol reactions with aliphatic aldehyde donors could also be used to give the desired aldol adducts, even with sterically-hindered donor aldehydes (adduct **54i** for example). When more hindered aldehydes, such as isobutyraldehyde, that do not readily participate in enamine formation, are employed, both triisopropylsilyl- and

benzyl-protected hydroxyacetaldehyde can be used as the donor component in the cross aldol reaction, albeit in rather low yields.

MacMillan reported the use of  $\alpha$ -thioacetal aldehydes as acceptors for the cross-aldol reaction of aldehydes in 2004.<sup>136</sup> The highly functionalized products **54o-q** were formed in moderate to excellent yields, and in excellent diastereo- and enantioselectivities with a variety of aldehyde donors. Tanaka and Barbas reported the use of a protected nitrogen-containing aldehyde for the production of adduct **54r,s** in 2004.<sup>137</sup> The nitrogen-containing aldehyde could also be used as the donor.

Aldehyde cross-trimerizations have also been reported for the synthesis of complex products in only one step from simple substrates. Barbas and coworkers reported the trimerization of alkyl aldehydes in 2002 using syringe-pump addition of two equivalents of propionaldehyde to one equivalent of the acceptor aldehyde (Table 5).<sup>138</sup> The trimers were isolated after oxidation to the corresponding lactones **69** (The proposed relative configuration was later corrected by Córdova<sup>139</sup> after a crystal structure was obtained, the corrected relative configuration is illustrated). The trimers were isolated in rather low yield (together with the C4 epimer) and disappointingly low ee, but given the simplicity of the reaction conditions and the amazing complexity generated in a single reaction, the transformation is exceptional. The authors note that the ee of the reaction degrades with time, for example **69a** was obtained in 47% ee after 10 h at 4 °C.

Córdova and coworkers reported a similar reaction with considerably higher enantioselectivity in 2005 (Table 6).<sup>139</sup> By altering the reaction conditions they were able to increase the enantioselectivity considerably, likely by shutting down the racemization observed under the conditions described by Barbas. Córdova observed that the ee was highly dependent on the reaction conditions and was best controlled by portion-wise addition of propionaldehyde. By separating the two sequential aldol steps, and using the opposite enantiomer for the second step, they were able to effectively shut down the retro-aldol for the first step, and thereby increase the enantioselectivity. This also allowed them to vary the three component aldehydes. The yields are rather low, but given the rapid assembly of complexity, the modest yield is easily compensated for.

Remarkably, this trimerization was expanded to the synthesis of sugars by Córdova and coworkers in 2005 (Scheme 14).<sup>140, 141</sup> For this class of aldehyde it appears that the retro-aldol is not problematic. Using only 10 mol% L-proline, 41% of protected hexose **73** was generated in excellent enantioselectivity, together with 51% of the dimer **54h**. A large nonlinear effect was observed for this reaction, with proline of only 40% ee generating the product hexose **73** in >99% ee. This observation led the authors to propose a model for the evolution of homochirality, in which simple amino acids with low levels of enantiomeric excess amplify this small imbalance of one enantiomer to homochirality through prebiotic gluconeogenesis.

The ability of such a simple molecule to generate such high levels of complexity is truly remarkable. Given the low cost and abundance of proline, as well as its wide scope, it is certainly the first choice for any enamine-catalyzed reaction, including the direct catalytic aldol reaction.

## 2.2 Catalyst Development

Despite the utility of proline for carrying out a wide array of aldol reactions, a great deal of effort has been exerted for the development of new catalysts. The long reaction times and poor results with certain substrates, such as  $\alpha$ -unbranched aldehydes, have led numerous researchers to develop more reactive catalysts, as well as design catalysts that will not

undergo oxazolidinone formation, which is the major catalyst deactivation pathway (Scheme 6 and 7). The need for high catalyst loadings, large excesses of ketone and long reaction times when using proline as catalyst has at times been imputed to its low solubility in the reaction media, and therefore many catalyst designs incorporate increased lipophilicity. New catalyst designs have also provided access to isomers not favored using reported proline-catalyzed conditions.

The initial screen of catalysts reported by List and coworkers in 2000 for the asymmetric aldol of acetone with *para*-nitrobenzaldehyde **74** illustrates the effect of a number of different modifications of the proline structure (Table 7).<sup>65, 66</sup> Primary amino acids histidine (**75**), tyrosine (**76**), phenylalanine (**77**), and valine (**78**) provide less than 10% yield of the desired adduct **27a**. Methylation of valine to produce an acyclic secondary amine (**79**) did not improve the yield. Both the azetidine (**80**) and piperidine (**81**) were inferior to the pyrrolidine structure of proline (**13**). Changing the carboxylic acid to an amide (**82**) also gave little reactivity. The thiazolidium carboxylate (**83**) gave similar, though slightly inferior results. Interestingly, proline derivative **84** gave a higher yield and enantioselectivity than proline itself. The *tert*-butyl ether derivative **85** gave lower yield and enantioselectivity, as did the acylated derivative **86**, though to a lesser extent. Diastereomer **87** provided the opposite enantiomer, with reduced yield and selectivity.

A number of other amino acids and small peptides have been evaluated as alternate catalysts for the direct catalytic asymmetric aldol reaction (Table 8).<sup>15, 142–150</sup> The reaction between acetone and *para*-nitrobenzaldehyde has been used in this field as a model system to evaluate catalyst activity and is a convenient way to compare the performance of the multitude of available catalysts. Among the amino acids and peptides screened, L-Pro-L-Pro-L-Asp-NH<sub>2</sub>, reported by Wennemers and coworkers, gave the best results.<sup>148</sup> The catalyst loading could be significantly decreased to 1 mol% to give the desired adduct *ent*-**27a** in 99% yield and 80% ee after 4 hour, using acetone as solvent. Compared to the other reported amino acids and small peptides, this is a significant increase in catalytic activity. Interestingly, this catalyst gives the opposite enantiomer than that obtained *via* proline-catalysis, an observation the authors trace to the secondary structure of this catalyst.

Many catalysts have been developed based on the structure of proline (Table 9). Some of the common modifications to the proline structure include increasing the hydrophobicity to improve solubility in organic solvents and modification of the carboxylic acid to a variety of other hydrogen-bonding groups. Other trends include adding steric bulk and stereocenters to enhance the enantioselectivity. Many of these catalysts require numerous steps for their synthesis, and this should be considered when choosing a catalyst. Proline, on the other hand, is abundant and inexpensive, and therefore new catalyst designs must provide significant improvements to surpass the utility of proline, both in terms of selectivity and reactivity.

One of the earliest designed catalysts was reported by Barbas in 2001.<sup>111</sup> Using 20 mol% of catalyst **88** over the course of 1–2 days, adduct **27a** was isolated in improved enantioselectivity when compared to proline, but the reactivity of this catalyst was rather low, reflected in the high catalyst loading, long reaction times and the need to use acetone as a co-solvent. Yamamoto reported the use of catalyst **89** for the direct catalytic aldol reaction in 2001.<sup>151, 152</sup> With only 3 mol% catalyst **89**, adduct **27a** was obtained in moderate yield and ee after 2 hours. Despite this improved reactivity, acetone was still used as solvent under the optimized conditions. In 2003, Gong and Wu reported the use of 20 mol% of catalyst **90** over the course of 1–2 days.<sup>153, 154</sup> The enantioselectivity obtained was quite good, though the reactivity was not high, and acetone was again needed as solvent. Arvidsson reported the use of tetrazole **91** for the direct catalytic aldol of acetone with aldehyde **74**,<sup>155, 156</sup> a

catalyst that was reported in the same year by Saito and Yamamoto for reaction with chloral and trifluoroacetaldehyde (vide infra).<sup>157</sup> A catalyst loading of 5 mol% and reaction time of 40 hours with acetone as a cosolvent gave the product **27a** in 82% yield and 79% ee. Sulfonylcarboxamide catalyst **92** was reported in 2004 by Berkessel and coworkers.<sup>158</sup> The catalyst was used in 30 mol% loading with acetone as a cosolvent over the course of 1 day to yield the desired adduct **27a** in excellent yield and enantioselectivity. Benzoimidazole catalyst **93**, reported by Landais and Vincent,<sup>159</sup> could be used with a catalyst loading as low as 2 mol%, together with trifluoroacetic acid, in neat acetone over the course of 1 day to give the desired adduct **27a** in 87% yield and 82% ee. In 2005 Gong reported an extremely enantioselective catalyst (**94**) possessing a chiral diester sidechain.<sup>160</sup> Using only 2 mol% **94** the aldol reaction yielded adduct **27a** in 62% yield and in 99% ee. The reaction was carried out in neat acetone over the course of 1–2 days, indicating that the reactivity was still rather low. Chimni and coworkers reported the use of proline derivative **95** in 2005.<sup>161, 162</sup> The reaction conditions required the use of 20 mol% **95** in wet acetone over the course of 40 hours. Unfortunately the enantioselectivity was lower than that obtained using proline alone. Thioamide **96**, reported by Gryko, delivered adduct **27a** in 62% yield and 84% ee using acetone as solvent and 20 mol% catalyst loading after 68 hours.<sup>163, 164</sup> Ley and coworkers reported sulfonylcarboxamide catalyst **97**, similar to catalyst **92**, which gave adduct **27a** in 100% yield and 92% ee, using acetone as solvent and 20 mol% catalyst loading over 1–2 days.<sup>165</sup>

Camphorsulfonyl-derivative **98** was disclosed by Kokotos and coworkers in 2005.<sup>166</sup> The catalyst could be used in 10 mol% loading with an equal molar amount of triethylamine with acetone as a cosolvent over 18–24 hours yielding adduct **27a** in 71% yield and 90% ee. Kokotos also reported sulfonylcarboxamide catalyst **99** in the same year, similar to catalysts **92** and **97**, which gave adduct **27a** in 63% yield and in 90% ee using 20 mol% catalyst and an equivalent amount of triethylamine, with acetone as a cosolvent over the course of 18–24 hours.<sup>167</sup> C<sub>2</sub>-Symmetric stilbene derivative **100** was disclosed by Zhao and coworkers in 2005.<sup>168</sup> The catalyst was used in 10 mol% loading in acetone over 12–24 hours, delivering adduct **27a** in 88% yield and 98% ee. Phosphonate catalyst **101** was reported in 2006 by Dinér and Amedjkouh to give the opposite enantiomer of adduct **27a** in 69% yield and 82% ee.<sup>169</sup> The catalyst was used in 20 mol% loading with acetone as cosolvent over the course of 1 day. Sun and Wu disclosed hydrazide catalyst **102** for the direct catalytic aldol in 2006.<sup>170</sup> With 20 mol% of catalyst **102** and an equal amount of trifluoroacetic acid, employing acetone as a cosolvent over 7 hours the desired adduct **27a** was obtained in 95% yield and in 96% ee. Zhao reported 4-disubstituted proline derivative **103** in 2006 for the direct catalytic aldol reaction.<sup>171</sup> Using 10 mol% of this catalyst with acetone as cosolvent over 2 days the adduct **27a** was obtained in 87% yield and 95% ee. C<sub>2</sub>-Symmetric proline derivative **104**, together with an equal amount of triethylamine, was employed by Wu and coworkers in 2006.<sup>172</sup> The catalyst was used in 30 mol% loading and the reaction was run in acetone as solvent over 30 hours to deliver the desired adduct **27a** in 91% yield but in only 65% ee. Singh reported the highly selective catalyst **105** in 2006.<sup>173</sup> Using 10 mol% catalyst in acetone for 1–2 days the product **27a** was obtained in 70% yield and 99% ee.

Catalyst **106** was reported for the asymmetric aldol reaction by Xiao and coworkers.<sup>174</sup> The catalyst was used in 20 mol% loading with 40 mol% acetic acid over 18 hours to give the adduct **27a** in 57% yield and 77% ee. Binaphthyl-derivative **107**, disclosed by Benaglia and coworkers, can be used in 10 mol% with acetone as solvent over 88 hours to deliver adduct **27a** in 92% yield and in 90% ee.<sup>175</sup> A C<sub>2</sub>-symmetric binaphthyl derivative **108** was disclosed by Nájera and coworkers, used in 10 mol% loading along with 20 mol% benzoic acid, with acetone as cosolvent over 36 hours. These conditions delivered the adduct **23a** in 92% yield and in 88% ee.<sup>176</sup> Zhou and Zhou reported the use of spiro-derivative **109**,



employing only 1 mol% catalyst over 4 hours in acetone.<sup>177</sup> This increased reactivity resulted in an 80% yield of adduct **27a**, but unfortunately only in 51% ee. Hayashi reported the utility of silylprotected 4-hydroxyproline **110** in 2006 for the direct catalytic asymmetric aldol reaction.<sup>178</sup> The catalyst loading used was 10 mol% with 5 equivalents of acetone in water over 18 hours. The adduct **27a** was obtained in 63% yield and 67% ee. Binaphthyl derivative **111** was reported in 2007 by Lattanzi.<sup>179, 180</sup> The catalyst was used in 5 mol% loading using only 3 equivalents of acetone over 10 hours to deliver the adduct in 99% yield and in 70% ee. Catalyst **112**, reported by Xiao in 2007, was used in 20 mol% loading with an equal amount of acetic acid.<sup>181</sup> The reaction was run in brine with 10 equivalents of acetone over 39 hours to yield adduct **27a** in 71% yield and 66% ee. He and Gong disclosed the use of 5 mol% catalyst **113** using acetone as solvent over 60 hours.<sup>182</sup> The adduct **27a** was obtained in 57% yield with 91% ee.

Iuliano and coworkers reported the synthesis and use of steroid-derived catalyst **114** containing a D-proline tethered to the 6-membered ring.<sup>183</sup> The catalyst was tested for reactivity in the direct catalytic aldol reaction with *para*-nitrobenzaldehyde **74**. The catalyst was used in 5 mol% loading with acetone as a cosolvent over the course of 2 days. The reaction yield was not given, but proceeded in complete conversion to give adduct **27a** in 80% ee. Phosphoramidate catalyst **115** was reported in 2008 by Li and coworkers.<sup>184</sup> With 10 mol% catalyst, an equal amount of *N*-methylmorpholine and 6 equivalents of acetone the product **27a** was obtained in 65% yield and 72% ee. Trinitroanilide catalyst **116** was reported by Shirai and coworkers in 2008.<sup>185</sup> The reaction was performed using HMPA as solvent with 30 equivalents of water and 20 equivalents of acetone to give the adduct **27a** in 90% yield and 85% ee after 4 days. Catalyst **117**, which is similar to catalyst **94**, was reported by Gong in 2008.<sup>186</sup> Using only 1 mol% catalyst loading and 2 equivalents of acetone the adduct was obtained in 85% yield and 71% ee after 14 hours. Cinchona alkaloid derivative **118** was reported by Xiao in 2008.<sup>187</sup> Similar conditions were reported by Liu and coworkers in 2009.<sup>188</sup> The reaction was carried out using 10 mol% catalyst **118** and 20 mol% acetic acid in acetone over the course of 1–3 days to deliver adduct **27a** in excellent yield and in 92% ee. Nájera and coworkers reported the use of prolinethioamide **119** for the direct catalytic asymmetric aldol reaction in 2008.<sup>189</sup> The reaction conditions consisted of using 5 mol% of catalyst **119** for 2 days, yielding adduct **27a** in 80% yield and 80% ee. In 2009, Da and coworkers reported the use of stilbene catalyst **120**.<sup>190</sup> Using only 1 mol% catalyst, together with an equal amount of 2,4-dinitrophenol, and 10 equivalents of acetone a 96% yield of adduct **27a** was obtained in 94% ee after 20 hours. Fu and coworkers reported the use of catalyst **121** in 2009. Adduct **27a** was obtained in 90% yield in 80% ee using 10 mol% catalyst loading and only two equivalents of acetone.<sup>191</sup>

Although many of these catalysts have successfully improved the enantioselectivity of the aldol reaction between acetone and *para*-nitrobenzaldehyde, reactivity remains a problem. Da's catalyst **120** gives perhaps the best combination of low catalyst loadings, good yield, and good enantioselectivity amongst the reported catalysts. The catalyst can be made in three steps with 76% overall yield. There is still a great deal of room for improvement in terms of reactivity, as the reaction times are almost uniformly very long (days). The need for huge excesses of the ketone component is also a huge drawback in cases in which the ketone is of more value than acetone.

A variety of catalysts have been reported that are not based on the structure of proline (Table 10). Maruoka reported binaphthyl catalyst **122** in 2005, which catalyzes the aldol reaction between *para*-nitrobenzaldehyde **74** and acetone using 5 mol% **122** with 27 equivalents of acetone in 82% yield and with 95% ee over the course of 1 day.<sup>192</sup> Later the same group reported the use of the highly substituted biphenyl catalyst **123** which could be used in as little as 0.5 mol% to give the desired adduct **27a** in 90% yield and 96% ee, although the

reaction took 2–3 days to complete and required the use of acetone as solvent to achieve these results.<sup>193</sup> In 2007 Teo reported the use of siloxy serine derivative **124** for the direct catalytic aldol reaction with cyclic ketones.<sup>194</sup> Unfortunately, the yield and selectivity were low when applied to acetone. Luo and coworkers reported the use of a primary amine catalyst **125** for the asymmetric aldol.<sup>195</sup> Using 10 mol% catalyst with 20 equivalents of acetone, adduct **27a** was obtained in 94% yield and 95% ee after 20–72 hours. Liu reported the use of cinchona alkaloid derivative **126** for use with cyclic ketones in 2007.<sup>196</sup> When applied to acetone, the catalyst **126** gave disappointingly low yield and enantioselectivity.

Binaphthyl catalyst **127** was reported by Liu and Luo in 2008.<sup>197</sup> The catalyst **127** was used in a 10 mol% loading with 20 mol% trifluoroacetic acid using acetone as solvent to deliver adduct **27a** in 43% yield and 94% ee. The rest of the material was almost entirely the aldol condensation product, rather than unreacted starting aldehyde **74**. Bispidine catalyst **128** was reported by Feng and Hu in 2008 and applied to the acetone aldol with *para*-nitrobenzaldehyde **74**.<sup>198</sup> Using 30 mol% catalyst **128** in acetone with 30 mol% 3,3',5,5'-tetrabromobiphenol as an additive adduct **27a** was obtained in 70% yield with 91% ee after 2 days. Binaphthyl derivative **129**, disclosed by Shao in 2008, was used in only 3.5 mol% catalyst loading with 20 equivalents of acetone.<sup>199</sup> The aldol adduct **27a** was obtained in 71% yield and 87% ee after 2 days. In 2009, Da reported the use of catalyst **130** for the asymmetric aldol.<sup>200</sup> When applied to *para*-nitrobenzaldehyde **74** and acetone, the reaction proceeded with 82% yield and 96% ee. The reaction conditions included the use of 20 mol% catalyst **130** and 20 mol% 2,4-dinitrophenol in acetone as solvent over the course of 26 hours. Triflamide catalyst **131** was reported in 2009 for use with cyclic ketones.<sup>201</sup> Unfortunately, when the reaction conditions were applied to acetone, both the yield and enantioselectivity were disappointingly low. Among the non-proline derived catalysts, the biphenyl catalyst **123** of Maruoka and the cyclohexanediamine catalyst **125** of Luo and Cheng stand out. Although the Maruoka catalyst **123** is the more active, the simplicity of Luo and Cheng's catalyst **125**, which can be synthesized in far fewer steps, make it an appealing choice.

Given the high reactivity of *para*-nitrobenzaldehyde **74** relative to typical aldehydes, it is an excellent substrate for finding reactivity initially, but it is less useful as a measure of the general applicability of a catalyst for less reactive (and more typical) substrates. For this reason the reactivity of various catalysts using benzaldehyde (**132**) as an acceptor have been compared (Table 11). Proline was found to catalyze this reaction in 62% yield and in 72% ee using 30–40 mol% catalyst loading with acetone as cosolvent for 2–8 hours (Table 1). Among the catalysts described, many do not surpass this level of reactivity and enantioselectivity.<sup>142, 151, 156, 161, 162, 170, 172, 177, 179, 185, 202, 203</sup> Among those that do are thiazole **88**,<sup>111</sup> stilbene derivative **90**,<sup>153</sup> diester **94**,<sup>160</sup> C<sub>2</sub>-symmetric catalyst **100**,<sup>163</sup> 4-disubstituted proline derivative **103**,<sup>171</sup> prolinamide **134**,<sup>173, 204</sup> binaphthyl derivative **107**,<sup>175</sup> diamine **125**,<sup>195</sup> cinchona alkaloid derivative **118**,<sup>187</sup> sulfonamide **135**,<sup>205</sup> and 4-hydroxy proline derivative **136**.<sup>206</sup> The reaction conditions for most of these catalysts have already been described (*vide supra*) and were not changed when using benzaldehyde **132** in place of *para*-nitrobenzaldehyde **74**. Singh's catalyst **134** was used in an analogous fashion to derivative **105** (Table 9). Sulfamide catalyst **135**, also developed by Singh,<sup>205</sup> was used in 5 mol% loading using 4 equivalents of acetone to give adduct **27b** in 75% yield with 89% ee after 20–52 hours. Among the catalysts reported with benzaldehyde **132**, the 4-hydroxyproline catalyst **136** of Nakano and Takeshita stands out for its high yield and enantioselectivity.<sup>206</sup> With only 5 mol% catalyst (using acetone as solvent) adduct **27b** was obtained in 99% yield and >99% ee in 36 hours. Interestingly, although the enantioselectivity of the catalytic system remained excellent, the yield of the reaction dropped to 48% when cyclohexanecarboxaldehyde was used. Notably, although Wennemers

catalyst L-Pro-L-Pro-L-Asp-NH<sub>2</sub> gave decreased enantioselectivity, the catalyst could be used in only 1 mol% loading.

When the even more electron-rich aromatic aldehyde *para*-methoxybenzaldehyde **137** was used, reactivity dropped off significantly for many of the catalysts (Table 12). Singh's prolinamide catalyst **134** and Nakano and Takeshita's catalyst **136**, using identical conditions as described above, retained their high activity and excellent enantioselectivity. These catalysts should make excellent choices for use with aromatic aldehydes when the enantioselectivity afforded by proline is deemed to be insufficient for one's purposes.

As noted in the case of catalyst **136**, the results obtained can vary widely with the substrate employed.  $\alpha$ -Branched aldehydes are among the best substrates for proline-catalysis, delivering adduct **27c** in 97% yield and 96% ee (Table 1). Although many alternate catalysts give good results, they cannot improve upon the high yield and enantioselectivity, coupled with the ready availability, of proline (Table 13).  $\alpha$ -Unbranched aldehydes are problematic in the proline-catalyzed aldol reaction. When isovaleraldehyde is used as a substrate, adduct **27d** is obtained in 34% yield and 73% ee (Table 1). Very few reports of  $\alpha$ -unbranched aldehyde substrates have been disclosed with alternate catalysts, and these show no significant improvement (Table 14).

Many catalysts have been evaluated for the reaction between cyclohexanone and *para*-nitrobenzaldehyde (Table 15). This reaction is highly successful using proline as catalyst delivering adduct **42a** in 73% yield, with a 9:1 *anti:syn* ratio and >99% ee (Table 2). Diastereoselectivity with cyclic ketones is not always high when employing proline, however, particularly with other aromatic aldehydes. Among the reported catalysts, stilbene derivative **100**,<sup>168</sup> pyrrolidine **142**,<sup>207</sup> binaphthyl catalyst **108**,<sup>176</sup> hydrazide **102**,<sup>208</sup> binaphthyl catalyst **107**,<sup>175</sup> silylated proline derivative **143**,<sup>178</sup> cyclohexanediamine **112**,<sup>174</sup> 4-disubstituted proline catalyst **103**,<sup>171</sup> aryl prolinamide **144**,<sup>209</sup> binaphthyl derivative **111**,<sup>180</sup> prolinamide **145**,<sup>146</sup> binaphthyl catalyst **147**,<sup>210</sup> prolinamide **148**,<sup>211, 212</sup> diester **117**,<sup>186</sup> phosphine oxide **151**,<sup>213</sup> prolinamide **121**<sup>191</sup> and thiourea **152**<sup>214</sup> gave particularly good results. Of these, pyrrolidine **145**, binaphthyl catalyst **147**, prolinamide **148**, diester **117** and thiourea **152** gave the best combination of high yield, diastereoselectivity and enantioselectivity. Phosphine oxide catalyst **151**<sup>215</sup> and oxazoline **149**,<sup>216</sup> two novel catalyst designs, did not give improved results.

The reaction conditions used by Zhao employing stilbene catalyst **100** were the same as used previously (10 mol% catalyst loading, *vide supra*).<sup>168</sup> Sun's pyrrolidine catalyst **117** was used in 20 mol% loading, using cyclohexanone as a cosolvent over the course of 4 hours.<sup>207</sup> Sun also reported the use of hydrazide catalyst **77** for use with cyclohexanone as the donor. These conditions employed 20 mol% catalyst with cyclohexanone as cosolvent for 1 hour.<sup>208</sup> Binaphthyl catalyst **82** was used in 10 mol% loading using cyclohexanone as solvent over 88 hours.<sup>175</sup> The silylated catalyst **118** was used in 10 mol% with 5 equivalents of cyclohexanone over 18 hours.<sup>178</sup> Xiao reported the use of 20 mol% of catalyst **112**, along with 20% acetic acid, with cyclohexanone as cosolvent over the course of 6–24 hours.<sup>174</sup> The 4-disubstituted proline catalyst **103** was used in 10 mol% catalyst loading, as before.<sup>171</sup> Aryl prolinamide catalyst **144**, reported by Sathapovajana and Vilaivan in 2007, was used in 10 mol% loading with 2 equivalents of cyclohexanone and a reaction time of 1 day. Lattanzi reported in 2007 that 10 mol% of binaphthyl catalyst **111** with 3 equivalents of cyclohexanone yielded adduct **42a** in 65 hours.<sup>180</sup> Prolinamide catalyst **145** was used in 20 mol% with 20 mol% acetic acid using cyclohexanone as a cosolvent with a reaction time of 24–72 hours.<sup>146</sup> Binaphthyl catalyst **147** was used by Ma and coworkers in 10 mol% loading with 5 equivalents of cyclohexanone in 72 hours.<sup>210</sup> Chimni's catalyst **148** was used in 20 mol% loading with 5 equivalents of cyclohexanone with a reaction time of 1 day.<sup>211, 212</sup>

Gong's catalyst **117** was used in only 1 mol% loading with 2 equivalents of cyclohexanone, over the course of 5 hours.<sup>186</sup> The phosphine oxide catalyst **151**, containing three proline units, was used in 2 mol% loading.<sup>213</sup> Despite this low catalyst loading, the reaction took 72–120 hours to complete. Thiourea catalyst **152** was used in 20 mol% loading with 2 equivalents of cyclohexanone over the course of 1.5 days.<sup>214</sup> Of these catalysts, Gong's diester catalyst **117** appears to be not only highly selective, but also the most reactive.

Although primary amino acids give poorer selectivity than proline for the aldol reaction in many cases, in certain instances they show improved results. In the Hajos-Parrish-Eder-Sauer-Wiechert of substrate **153** (*S*)-phenylalanine gave superior results for the aldol condensation (Scheme 14).<sup>217</sup> Ethyl ketone **155** also gave superior results with (*S*)-phenylalanine as catalyst.<sup>218</sup> These results suggest that with more hindered ketones, primary amines may have an advantage over secondary amines. This has led many investigators to evaluate primary amine catalysts for the reaction of cyclohexanone **141** with *para*-nitrobenzaldehyde **74** (Table 16). Among the catalysts examined, protected threonine catalyst **159**,<sup>219</sup> cinchona derivative **125**,<sup>196</sup> cyclohexyl catalyst **160**,<sup>220</sup> protected serine derivative **124**,<sup>194</sup> binaphthyl catalyst **129**,<sup>199</sup> triflamide catalyst **131**,<sup>201</sup> and stilbene catalyst **161**<sup>221</sup> gave good results. Unprotected amino acids tryptophan **158**<sup>222</sup> and histidine **75**,<sup>223</sup> and dipeptide **157**,<sup>224</sup> gave inferior results. The conditions used for the threonine catalyst **159**, as reported by Lu and coworkers, required only 2 mol% catalyst loading and 2 equivalents of cyclohexanone for 20 hours.<sup>219</sup> The cinchona derivative **126** was used in 10 mol% loading with 15 mol% triflic acid, using cyclohexanone as solvent over the course of 9 hours.<sup>196</sup> Maruoka's catalyst **160** was used in 5 mol%, though the reaction took 3–4 days.<sup>220</sup> Shao's catalyst **129** could be used in only 3.5 mol% with 3 equivalents of cyclohexanone over 10 hours.<sup>199</sup> Triflamide catalyst **131** was used in 10 mol% loading with 10 equivalents of cyclohexanone over the course of 2 days.<sup>201</sup> Lai's catalyst **161** was used in 10 mol% with 10 equivalents of cyclohexanone over the course of 12 hours.<sup>221</sup> Among these catalysts, the silylated threonine catalyst **159** gives perhaps the best combination of good reactivity, good selectivity, and ease of synthesis.

With less reactive aldehydes such as benzaldehyde **132** or *para*-methoxybenzaldehyde **137**, much poorer results were obtained with most of the catalysts (Table 17). Singh's catalyst **105** retained good reactivity, however, even with *para*-methoxybenzaldehyde **137**.<sup>173</sup> Armstrong's aryl ether catalyst **162** also showed good reactivity, and was needed in only 2 mol% loading with only one equivalent of cyclohexanone, though the reaction still took 2 days to complete.<sup>41</sup> The cyclohexyldiamine catalyst **112**,<sup>174</sup> anilide catalyst **144**,<sup>209</sup> protected threonine derivative **159**,<sup>219</sup> sulfamide **134**,<sup>205</sup> dipeptide catalyst **145**,<sup>146</sup> diester catalyst **117**,<sup>186</sup> 4-hydroxyproline derivative **150**,<sup>206</sup> and Fu's catalyst **121**<sup>191</sup> all gave fair results as well. The reaction conditions for these catalysts have been given above.

Proline is an excellent catalyst for aldol reactions of cyclohexanone with alkyl aldehydes, especially  $\alpha$ -branched aldehydes (Table 2). Use of more elaborate catalysts has been reported, but with generally worse results than using proline itself (Table 18). Silyl derivative **143** and binaphthyl catalyst **107** give high yields for cyclohexanecarboxaldehyde, but other aldehydes give poor yields, though with excellent selectivities. Proline also gives high diastereo- and enantioselectivity, however, and remains the preferred catalyst for such substrates, due to its ready availability.

When cyclopentanone is used as a donor in the proline-catalyzed asymmetric aldol reaction poor diastereoselectivity is observed. Many of the developed catalysts have been applied to this substrate, and fortunately, several catalysts were found with improved diastereoselectivity for the *anti* diastereomer (Table 19). Singh's sulfamide catalyst **135**,<sup>205</sup> Shirai's trinitrocatalyst **116**,<sup>185</sup> Shao's binaphthyl catalyst **129**,<sup>199</sup> Maruoka's cyclohexyl

catalyst **160**,<sup>220</sup> Miura and Imai's triflamide catalyst **131**<sup>201</sup> and Chen's thiourea catalyst **152**<sup>214</sup> all showed improved diastereoselectivity over the 1:1 selectivity observed for proline. Of these catalysts, Maruoka's gives the best balance of selectivity and yield. Interestingly, several catalysts showed selectivity for the *syn* adduct **42f**, including hydrazide **102**,<sup>170</sup> binaphthyl catalyst **108**,<sup>176</sup> anilide catalyst **144**,<sup>209</sup> cyclohexanediamine catalyst **125**<sup>195</sup> and Da's stilbene catalyst **130**.<sup>190</sup> Luo and Cheng's catalyst **125** is remarkable in its selectivity, and should prove quite useful for the synthesis of *syn* products.

When proline was used with 2-butanone **167** and *para*-nitrobenzaldehyde **74**, the linear adduct **42h** was obtained in 65% yield and 77% ee (Table 2). Many catalysts have been applied to this reaction enhancing both the yield and selectivity of the linear adduct **42h**, but also provided access to both diastereomers of the branched adduct **168** (Table 20). The linear product was favored by catalysts **88**,<sup>111</sup> **90**,<sup>154</sup> **99**,<sup>165</sup> **94**,<sup>160</sup> **107**,<sup>225</sup> **103**,<sup>171</sup> **108**,<sup>176, 226</sup> **148**,<sup>211</sup> **117**,<sup>186</sup> and **128**.<sup>198</sup> Among these catalysts, Nájera's binaphthyl amine **108** provided the linear adduct **42h** with the best yield and selectivity. Xiao's cyclohexanediamine catalyst **112**, on the other hand, gave the branched product **168** with excellent selectivity for the *anti* diastereomer, though with only moderate selectivity for the branched product over the linear.<sup>181</sup> The enantioselectivity for catalyst **112** was also high. Trinitroanilide catalyst **116** also favors the *anti* adduct, but the reaction conditions are less appealing, as HMPA is used as solvent.<sup>185</sup> Thiourea catalyst **152** also provide the *anti* adduct in good selectivity.<sup>214</sup> Luo and Cheng's cyclohexanediamine catalyst **125** gave the *syn* adduct in excellent selectivity and yield.<sup>195</sup> With these developments, each aldol adduct isomer can be synthesized with good selectivity.

Luo and Cheng's diamine catalyst **125** displays very interesting selectivity (Table 21). When unsymmetrical ketones are employed, such as 2-butanone **167**, the adduct (**38a** for example) resulting from reaction through the more substituted enamine is observed, producing the *syn* branched isomer **38**. When 3-hexanone is used, the adduct resulting from the least sterically-hindered enamine (**38b**) was formed almost exclusively. When 2-pentanone was used, a competition between reaction through the more reactive highly-substituted enamine and the less sterically-hindered enamine. The major product resulted from reaction through the less hindered enamine, yielding adduct **38c** in 5:1 selectivity. When the ketone was made even more hindered, the selectivity increased dramatically, giving adduct **38d**. Benzyl-protected hydroxyacetone also gave excellent selectivity for the *syn* branched product **38e**. Luo and Cheng's catalyst **125** provides a very useful selectivity unavailable from proline.

When hydroxyacetone is used as a donor under proline-catalysis, good diastereoselectivity is observed with  $\alpha$ -branched aldehydes, favoring the *anti* branched isomer, but some aryl (particularly *ortho*-chlorobenzaldehyde) and  $\alpha$ -unbranched aldehydes result in poor diastereoselectivity. Silyl protected hydroxyacetone, as well as methylated derivatives,<sup>227</sup> also gave the *anti* branched isomer selectively. A variety of catalysts have been tested with hydroxyacetone and protected derivatives (Table 22). When hydroxyacetone was used as substrate, diester catalyst **95** gave excellent selectivity for the linear isomer, with excellent enantioselectivity.<sup>228</sup> Other catalysts were not very selective with unprotected hydroxyacetone.<sup>111, 168, 224, 229</sup> Wu and Zhao's primary amine catalyst **175** gave the *syn* isomer in 4:1 selectivity with 80% ee.<sup>230</sup> Luo and Cheng's catalyst **176** gave even higher selectivity for the *syn* isomer.<sup>231</sup> Silyl protected hydroxyacetone was also used as a substrate with threonine derivatives **173**<sup>219</sup> and **174**,<sup>232</sup> both of which favored the *syn* branched isomer in excellent enantioselectivity. Methyl and benzyl protected hydroxyacetone were also used, and depending on the chosen catalyst, could be obtained in either the *anti* or *syn* configuration. Binaphthyl catalysts **108**,<sup>227, 233</sup> **172**,<sup>175</sup> and **111**,<sup>180</sup> as well as thioamide **119**<sup>189</sup> all gave the *anti* isomer selectively. The *syn* isomer was obtained when threonine

derivative **174** or primary-tertiary amine catalyst **176** was used. All three isomers are now available through judicious choice of protecting group and catalyst.

Dihydroxyacetone and its protected derivatives have also been used with many different catalysts. Proline gives the *anti* derivative with excellent selectivity with a variety of aldehydes. When untethered dihydroxyacetone derivatives are used only binaphthyl catalyst **108** gave the *anti* isomer with moderate selectivity (Table 23).<sup>227</sup> The *syn* isomer, on the other hand, is favored by a variety of primary amine catalysts including threonine derivative **174**,<sup>232</sup> cyclohexyl catalyst **125**,<sup>195, 234</sup> primary-tertiary amine catalyst **176**,<sup>231</sup> and amino alcohols **179**,<sup>235</sup> **180**,<sup>60</sup> and **130**.<sup>200</sup> When tethered dihydroxyacetone derivative 2,2-dimethyl-1,3-dioxan-5-one (**177**, R = -CMe<sub>2</sub>-) was used, only the *anti* isomer was observed with all of the catalysts.<sup>236</sup> When the *anti* isomer is desired, proline should be the catalyst of choice, as it gives good selectivity as is inexpensive. When the *syn* isomer is desired, a number of primary amine catalysts can be used. Diamine catalyst **125** is particularly useful, as it can be used in the lowest catalyst loading (10 mol%).

Thioether and halogenated ketone derivatives have also been examined (Table 24). When  $\alpha$ -chloroacetone was used as a substrate, the *anti* branched product was obtained in excellent selectivity with a variety of catalysts,<sup>180, 237</sup> though only good yield was obtained with the binaphthyl catalyst **108**<sup>180, 238</sup> and the trinitroanilide catalyst **116**.<sup>185</sup>  $\alpha$ -Fluoroacetone was used as a substrate with Gong's diester catalyst **94**,<sup>228, 239</sup> and was capable of yielding either the branched product in 2:1 dr or the linear product, depending on the reaction conditions. When water was added, the linear adduct **183** was favored, while running the reaction in dry THF gave the branched adduct **182**. A thioether-substituted ketone was also used as a substrate, both with the diester catalyst **116** and with binaphthyl catalyst **108**. Both catalysts favor the linear product **183**, with diester catalyst **116** giving slightly better selectivity.

A number of interesting substrates other than aryl and alkyl aldehydes have been employed for the direct catalytic aldol reaction (Scheme 15). The use of enals **185** and **186** was reported by Maruoka using binaphthyl amino acid **123** in the aldol reaction with acetone.<sup>192</sup> The adducts were obtained in 73% yield with 90% ee and 81% yield with 96% ee, respectively. Saito and Yamamoto demonstrated the use of chloral **187** and trifluoroacetaldehyde ethyl hemiacetal **188** as acceptors using tetrazole catalyst **91** in 2004. The authors used a variety of ketones with these acceptors, including  $\alpha$ -ketoester **189** and methyl aryl ketones **190** with yields between 55–93% and with 82–97% ee.<sup>157</sup> Zhang and Wang have used methyl aryl ketones **190** as well, employing triflamide catalyst **191**.<sup>240</sup> Trifluoroacetaldehyde ethyl hemiacetal **188** was also used by Gong as an acceptor using cyclohexanone as the donor. The authors found that prolinamide catalyst **82** gave the best results.<sup>241</sup> Acetal derivatives **192** were employed by Luo and Cheng using cyclohexanediamine catalyst **125**, giving the desired adducts in 30–98% yield and with 49–99% ee.<sup>242</sup> Ynone donor **193** was used by Gouverneur and coworkers with aromatic aldehydes as acceptors employing sulfonamide catalyst **99**. The adducts were obtained in 26–90% yield, 3:1–19:1 dr, and 77–95% ee.<sup>243</sup> The reaction appears to be limited to electron-poor aryl aldehydes. This collection of interesting substrates should prove useful for the synthesis of more functionalized products.

There have been a few reports of ketone electrophiles in the direct catalytic asymmetric aldol reaction (Table 25). Tomasini used catalyst **195** with isatin, a highly reactive and non-enolizable ketone to give the aldol adduct **194** in 92% yield and 72% ee.<sup>244</sup> Luo and Gong developed pyridine catalyst **196** for the aldol reaction of acetone with  $\alpha$ -keto acids.<sup>245, 246</sup> The aldol adducts were obtained in excellent yield and enantioselectivity, even when an enolizable substrate was used. Feng reported the use of stilbene catalyst **100** with  $\alpha$ -keto esters.<sup>247</sup> When R<sub>1</sub> = Ph and R<sub>2</sub> = CO<sub>2</sub>Me, the aldol adduct was obtained in 92% yield and

in 93% ee. Binaphthyl catalyst **127** also was used with  $\alpha$ -keto esters, for example, when  $R_1 = p\text{MeO-Ph}$  and  $R_2 = \text{CO}_2\text{Me}$ , the aldol adduct was obtained in 98% yield and 96% ee.<sup>197</sup> Bispidine catalyst **128** was used with benzoyl phosphonates.<sup>198</sup> When  $R_1 = p\text{-NO}_2\text{-Ph}$  and  $R_2 = \text{P(O)(OEt)}_2$ , the  $\alpha$ -hydroxyphosphonate was obtained in 90% yield and in 98% ee. Thiophene catalyst **195** was used for substituted isatins, such as 4,6-dibromoisatin, which yielded the desired adduct **194** in 99% yield and 95% ee.<sup>248</sup> Isatin itself gave the aldol adduct in 99% yield, however, the product was only obtained in only 3% ee. Nakamura and Toru used this methodology for the synthesis of (*R*)-convolutamydine A. Non-enolizable and highly reactive ketone derivatives have been used successfully with proline as well, which should be the first choice of catalyst for most substrates (Table 3).

Aldehyde cross-aldol reactions have been achieved with a number of different catalysts (Table 26). MacMillan first described the cross-aldol reaction with proline,<sup>130</sup> and later reported the use of catalyst **200** for the reaction.<sup>249</sup> The reaction proceeds with good yield and enantioselectivity for a wide array of substrates, favoring the *anti* isomer. Proline, however, is also a good catalyst for this reaction, and is a simpler catalyst (Table 4). Barbas reported the use of diamine **89**, together with an equal amount of trifluoroacetic acid, for the creation of quaternary stereocenters adjacent to an aldehyde (**201**).<sup>250</sup> The reaction works well with electron poor aryl aldehydes, but the yields are lower for benzaldehyde and other more electron rich aryl aldehydes. The diastereoselectivity is only moderate with this catalyst, and future developments should improve this highly useful reaction. Hayashi reported the use of prolinamide **82** for the self-aldol reaction of propanal in an aqueous environment, which was followed by reduction of the resulting aldehyde with sodium borohydride to give the diol.<sup>251</sup> Unfortunately low diastereoselectivity and yield was obtained under these conditions. Maruoka's binaphthyl catalyst **202** gave very impressive results when applied to the cross-aldol reaction.<sup>252</sup> Unlike proline, catalyst **202** produces the *syn* diastereomer in good diastereoselectivity, yield and enantioselectivity. This provides a complement to the proline catalyst, making the selective production of either diastereomer possible. Prolinol **203**, reported by Hayashi in 2008, has been reported for the use of acetaldehyde in self-aldol and cross-aldol reactions.<sup>253, 254</sup> Hayashi demonstrated that proline itself was an inefficient catalyst for this reaction (which was followed by sodium borohydride reduction of the resulting aldehyde) giving very little of the desired adducts. The use of catalyst **203** allows the substrate scope of enamine-catalyzed cross-aldol reactions to be extended to the use of acetaldehyde. Wang and Pan have also used their phosphine oxide catalyst **151** for the cross-aldol reaction, but this catalyst appears to have no advantage over use of the far simpler catalyst proline.<sup>213</sup> The aldehyde self- and cross-aldol reaction may now be used for a variety of aldehydes, including  $\alpha$ -branched and  $\alpha$ -unbranched aldehydes, and even acetaldehyde. The *syn* diastereomeric products are also now available, providing access to an ever-growing family of products.

Enamine-catalysis is a burgeoning field, and its impact on the direct aldol reaction is far-reaching. The scope of this reaction has been extended from the original report of acetone as a donor to include more substituted ketones, cyclic ketones, unsymmetrical ketones,  $\beta$ -keto esters, aryl ketones, ynones, and even aldehydes. The acceptor component can be a variety of different aldehydes and highly reactive ketone derivatives. Importantly, the selectivity of the reaction has been extended to include production of isomers not observed when proline is used, through the development of alternate catalysts. Selective formation of linear and branched products is possible, as well as control over the diastereoselectivity. One of the remaining challenges is the development of more reactive catalysts, as the need for excess donor component, high catalyst loadings, and long reaction times remains a problem for most of the described methods.

### 3. Non-Enamine Organocatalysts for the Aldol Reaction

Several reports of tertiary amines and quaternary ammonium salts for use aldol reactions have been reported. Some of the catalytic systems reported for the aldol reaction reported in this section use stoichiometric or even larger amounts of base, and are therefore not direct aldol reactions. This includes phase-transfer catalysts that use hydroxide-based aqueous phases. The tertiary amine catalysts can act through either of two mechanisms, formation of a chiral enolate (Scheme 16, equation 1), or formation of a tight ion pair (equation 2), followed by aldehyde addition. The quaternary ammonium salt catalyzed processes proceed through an ion pair mechanism (equation 3). Formation of the enolate requires the counterion to act as a base, limiting the substrate scope to highly acidic substrates, or requiring the use of stoichiometric base. The substrate scope for these types of processes is typically much smaller than that available to enamine-catalyzed processes due to mechanistic requirements.

Romo and coworkers reported an intramolecular aldol-lactonization protocol in 2001 for the generation of bicyclic  $\beta$ -lactones (Scheme 17).<sup>255–257</sup> The mechanism of this process is proposed to go through an iminium enolate as shown in equation 1 (Scheme 16). This reaction uses super-stoichiometric amounts of Hünig's base, as well as Mukaiyama's reagent (2-chloro-1-methyl-pyridinium iodide)<sup>258</sup> in order to activate the carboxylic acid and therefore is not a direct aldol process. The authors note that Hünig's base was sufficiently hindered so as not to cause a significant background reaction. The adducts **211** are obtained in 70–82% yield with 91–98% ee using syringe-pump addition of the substrate **209**. Related intermolecular reactions have been reported by Wynberg<sup>259, 260</sup> and Romo.<sup>261, 262</sup>

One of the most popular substrate classes for phase-transfer catalysis are the glycine Schiff bases, such as *tert*-butyl ester **212**. In 1991 Gasparski and Miller reported the first aldol reaction of a glycine Schiff base using cinchona alkaloids as catalysts (Scheme 18).<sup>263</sup> The process favored the *syn* adduct **214** with about 2:1 selectivity, but with almost no enantioinduction. Since that time several new catalysts have been reported for this reaction, but the enantioselectivity of these processes remains low (Scheme 19).<sup>264, 265</sup> It is noteworthy that either diastereomer of adduct **214** can be favored (though in a modest excess) by choosing the appropriate catalyst.

A significant improvement to the enantioselectivity of the aldol reactions employing glycine Schiff bases was reported by Maruoka in 2002 (Scheme 20).<sup>266, 267</sup> The chiral C<sub>2</sub>-symmetric quaternary salts designed by Maruoka are not based on the cinchona alkaloid family. Using only 2 mol% of catalyst **217** delivers the desired aldol adducts **214** with 40–78% yield. The *anti* adduct is favored and the enantioselectivity is better than the previous reports employing cinchona-derived catalysts.

Maruoka reported several further modifications of the catalyst, one of which, catalyst **218**, favors the *syn* adduct, providing a complement to the original catalyst (Scheme 21).<sup>268, 269</sup> These catalysts take numerous steps to synthesize and have a rather large molecular weight. Fortunately, they can be used in only 1 mol% catalyst loading. These catalysts provide significantly better results than the more easily prepared cinchona-derived catalysts.

In 2009 Mlynarski and coworkers reported the use of quinidine for the direct catalytic aldol reaction of hydroxyacetone **220** (only 2 equivalents of the donor were needed) with a variety of aldehydes **25** (Scheme 22).<sup>270</sup> The aldol adducts **222** were isolated in 11–96% yield (with aliphatic aldehydes giving the lowest yields) with the *syn* diastereomer favored in up to 9:1 selectivity. A *syn* selective direct aldol employing hydroxyacetone as the donor is not



currently available using enamine catalysis, and would be valuable. Unfortunately, the enantioselectivity of the quinidine-catalyzed (**221**) process was rather low.

Arai and Nishida reported the use of cinchona alkaloid-derivatives for the aldol reaction of diazo ester **223** in 2004 (Scheme 23).<sup>271, 272</sup> The reaction requires long reaction times and the enantioselectivity is highly dependent on the aldehyde used. *para*-Methoxybenzaldehyde, for example, gave racemic product, while 1-naphthaldehyde gave the product in 79% ee. This reaction also employs rubidium hydroxide as the basic aqueous phase, which is fairly expensive. The authors demonstrated that these diazo products **225** could be reduced to give amino acids.

The use of highly activated ketone electrophiles has also been demonstrated. Calter and coworkers reported an aldol-cyclization reaction in 2005 catalyzed by cinchona dimer **228** (Scheme 24).<sup>273</sup> The authors propose a mechanism in which the  $\alpha$ -keto ester **226** is activated by hydrogen-bonding to protonated catalyst **228**, followed by rate-determining attack of the enol form of diketone **227**. This reaction could also proceed *via* an ion-pair mechanism (equation 3, Scheme 16). Proton sponge was used to neutralize the equivalent of hydrogen bromide that is generated in this reaction. Tetrabutylammonium bromide was found to enhance, rather than deteriorate the enantioselectivity, suggesting that an ion-pair mechanism is not likely, as achiral ammonium salts would be expected to give a background reaction. The reaction produced bicyclic compounds **229** in excellent yields and enantioselectivities, favoring the *cis* diastereomer.

In 2007 Shibata and Toru reported the use of oxindoles **231** as donors with ethyl trifluoropyruvate **230** as the acceptor (Scheme 25).<sup>274</sup> This reaction is a direct catalytic aldol reaction, as there is no need for stoichiometric reagents. A variety of cinchona alkaloids were screened for the reaction, and (DHQD)<sub>2</sub>PHAL **232** was found to give high yield, diastereo- and enantioselectivity. (DHQ)<sub>2</sub>PHAL was used to provide access to the enantiomer of adduct **233** with similar levels of selectivity. The authors note the importance of the trifluoromethyl group, both for reactivity and enantioselectivity. An ion-pairing mechanism is proposed for this transformation (equation 3, Scheme 16).

Tertiary amines and quaternary ammonium salts have been used successfully for a number of aldol reactions, although most of these processes require stoichiometric or superstoichiometric amounts of base. The *syn* selective hydroxyacetone direct aldol reaction described by Mlynarski is among those reactions that does not require stoichiometric base. This reaction could prove useful if the enantioselectivity were improved as a complement to the reactivity observed with proline-catalysis. The oxindole chemistry is also noteworthy, as these motifs are frequently found in biologically-active compounds.

#### 4. Metal-Catalyzed Aldol Reactions

A variety of metal-catalyzed processes have been reported for the direct catalytic asymmetric aldol reaction. These can be compared mechanistically to the type II aldolases, which employ a zinc ion to acidify the  $\alpha$ -proton of the donor component to form an enolate. Many of the catalysts described in this section function by dual activation of the donor and the acceptor, and are therefore classified as bifunctional catalysts. Numerous reviews of this type of activation mode have appeared, particularly focusing on BINOL-based systems.<sup>275–278</sup> These catalysts are frequently milder than enamine-based catalysts as they do not employ nucleophilic amines that may undergo side reactions, allowing for the use of sensitive substrates such as methyl vinyl ketone and ynones.

#### 4.1 Precious Metals as Catalysts for the Aldol Reaction

One of the first direct catalytic aldol reactions was reported by Ito, Sawamura and Hayashi (Scheme 26).<sup>279–281</sup> This gold-catalyzed reaction of  $\alpha$ -isocyanocarboxylate **234** with aldehydes **25** produces *trans* oxazolines **236** in good yield, diastereo- and enantioselectivity. The gold catalyst is believed to bind both the enolate and the aldehyde, with the ligand acting as a base to generate the enolate (**A**). This reaction has been developed extensively, expanding the scope of the donor to include more substituted derivatives as well as substrates in which the ester group is replaced with sulphonic and phosphonic esters.<sup>8, 282–303</sup>

Silver has also been used with ferrocenyl ligand **235** to catalyze the direct aldol reaction (Scheme 27).<sup>304, 305</sup> Slow addition of the donor is required to maintain high enantioselectivity when  $\alpha$ -isocyanocarboxylates **234** were used. Unlike the corresponding gold catalyst, the silver complex resting state is tetracoordinate when a high concentration of the  $\alpha$ -isocyanocarboxylate **234** is present, and this complex leads to the production of adduct **236** in decreased selectivity. Palladium catalysts have also been used for this transformation (Scheme 28).<sup>306–314</sup> The reported enantioselectivities are much lower than those obtained with gold. These complexes also favor the *trans* isomer.

Rhodium has also been used to catalyze direct aldol reactions. Substituted  $\alpha$ -cyanocarboxylates have been employed with 1 mol% of a ferrocenyl rhodium complex to deliver adducts **242** bearing a quaternary carbon center in up to 91% ee (Scheme 29).<sup>315</sup> The reaction was not very general, for example, no reaction was observed with benzaldehyde. The bulky ester was necessary to achieve these levels of enantioselectivity. Kuwano and Ito propose coordination of the acceptor through the cyanide nitrogen, followed by attack on the aldehyde through an open transition state.

In 2007 Nishiyama reported the use of a rhodium-Phebox complex for the direct catalytic asymmetric aldol reaction of cyclohexanone, cyclopentanone, and acetone with aromatic aldehydes **243** (Scheme 30).<sup>316</sup> Recently, the same catalyst has been reported for the use of cyclohexenones and cyclopentenones as donors, though with generally low yields.<sup>317</sup> When acetone was used with *para*-nitrobenzaldehyde the adduct **245** was obtained in 63% yield with 74% ee. Cyclohexanone gave 57% yield in a 11:89 *syn:anti* ratio with 86% ee for the *anti* product **245** when *para*-trifluoromethylbenzaldehyde was used. With cyclopentanone, the adduct **245** was obtained in 75% yield in a 20:80 *syn:anti* ratio with 91% ee for the *anti* isomer. The authors propose structure **A** as the transition state to account for the observed selectivity. Though these results are fairly good, particularly the ability to use  $\alpha,\beta$ -unsaturated donors, use of an expensive metal catalyst is unlikely to supplant the use of an inexpensive catalyst such as proline. The reaction was not applied to electron-rich aromatic substrates for which proline is a poor catalyst, but given that the reactions with cyclohexanone and cyclopentanone took 72 hours with electron-poor substrates at 60 °C, this system likely is not reactive enough for such substrates.

#### 4.2 BINOL-Based Catalysts

Numerous catalysts have been developed that are based on the structure of BINOL, most notably, those designed and developed by Shibasaki. Shibasaki's first report on catalysis for the direct aldol reaction, however, employed a TADDOL-based complex (Scheme 31). In 1992 Shibasaki reported the use of a catalyst generated from yttrium trichloride, a lithiated TADDOL ligand (**246**), and sodium *tert*-butoxide, for the Hajos-Parrish-Eder-Sauer-Wiechert reaction of triketone **12**, the first report of a direct catalytic asymmetric intramolecular aldol other than proline.<sup>318</sup> The adduct **247** was obtained in 60% yield with 52% ee after 6 days at –52 °C. The authors note that the ee of the isolated product **247** was

degraded when exposed to the catalyst at  $-30\text{ }^{\circ}\text{C}$ , suggesting a retro-aldol reaction.<sup>319</sup> This provided a proof of concept that rare-earth alkoxides could be used catalytically for the direct aldol reaction.

Shibasaki later reported the first intermolecular direct catalytic aldol of simple ketones using lanthanum-lithium-BINOL complex **248** (Table 26).<sup>320</sup> With 20 mol% catalyst **248** a variety of ketones, including aryl ketones, acetone and 2-butanone (**205**) were coupled with alkyl aldehydes (**25**). Neopentyl aldehydes gave the best enantioselectivities, in moderate yield.  $\alpha$ -Branched aldehydes gave decreased enantioselectivity, while  $\alpha$ -Unbranched aldehydes gave both poor enantioselectivity and yield. Interestingly, 2-butanone gave the linear product selectively, with only a trace amount of the branched product. The reactivity of this catalyst was rather low, necessitating the use of 7.4–50 equivalents of the donor (**205**) relative to the aldehyde (**25**). The reaction times were very long as a result of this low activity. Adduct **206e**, for example, was obtained in 59% yield in 54% ee after 11.5 days.

Shibasaki reported an improved catalyst for the direct aldol reaction in 1999 (Table 27).<sup>321</sup> The addition of an equimolar amount of KHMDS to complex **248** gave a more reactive catalyst, allowing the loading to be dropped to 8 mol% and the number of equivalents of the ketone to be decreased to 3–15 equivalents. The reaction time was also shorter, although still could take up to 4 days. The enantioselectivity was slightly lower than when catalyst **248** was employed without added KHMDS. Cyclopentanone was used as a donor, giving adduct **38b** in good yield and *syn* selectivity with 76% ee. This provides a nice complement to the enamine-catalyzed reaction, which favors the *anti* adduct. Shibasaki demonstrated the utility of aryl ketones as ester surrogates through a Baeyer-Villiger oxidation, which was used to synthesize a key intermediate for the synthesis of bryostatin **7** and for the total syntheses of epothilones A (both arising from adduct **38a**). This strategy was later used to complete the syntheses of epothilones A and B.<sup>322</sup>

Shibasaki also reported a barium BINOL-derived catalyst for the direct aldol reaction of acetophenone (**249**) with alkyl aldehydes (**25**) (Scheme 32).<sup>323</sup> The catalyst could be used in 5 mol% loading with only 2 equivalents of the donor (**249**). The reaction took between 18–48 hours to complete. Unfortunately, although the catalytic activity was improved, the enantioselectivity was not as high as the original lanthanum-lithium-BINOL catalyst **248**. A similar catalyst (**253**) was recently used with  $\beta,\eta$ -unsaturated esters to generate Baylis-Hillman adducts **254** in a dynamic kinetic asymmetric transformation through isomerization of the initial aldol adduct (DYKAT).<sup>324</sup>

In 2001 Shibasaki extended the use of his BINOL-based catalysts to 2-hydroxy-1-phenylethanone **255** (Scheme 33).<sup>325, 326</sup> With 10 mol% of catalyst **248**, modified with KHMDS, the *anti* adduct **256** was obtained in 2:1–5:1 selectivity in 78–92% yield, and in 90–95% ee for the major diastereomer. The *syn* diastereomer *epi*-**256** could be obtained by using 2 equivalents of diethylzinc together with BINOL-derived ligand **257** in 10 mol% loading, as well as with 20 mol% triphenylphosphine oxide. Although this catalyst was originally thought to be dinuclear in zinc, mechanistic studies later indicated the active catalyst likely contains 7 zinc atoms.<sup>327</sup> Shibasaki demonstrated the applicability of both sets of conditions to  $\alpha$ -unbranched aldehydes, a substrate class that gives poor results with enamine catalysis.

Shibasaki reported the development of the lanthanum-lithium-BINOL-derived catalyst **259** for the asymmetric direct aldol in 2001 (Scheme 34).<sup>328</sup> A variety of unsymmetrical ketones were examined with catalyst **259**, including an enone substrate. These reaction conditions produced the desired adduct **260** in 62–71% yield with 40–67% ee. The results were generally poorer with this catalyst than the original BINOL-derived catalyst **248**. 3-

Pentanone was also examined as a substrate, but gave poor reactivity and enantioselectivity under a variety of conditions.

Mahrwald and Ziemer reported a titanium-based BINOL and (*R*)-mandelic acid catalyst **263** in 2002 for the direct aldol reaction of 3-pentanone **261** (Scheme 35).<sup>329</sup> The *syn* isomer **262** was favored for a variety of aldehydes, including aryl, neopentyl, alkynyl,  $\alpha$ -branched and  $\alpha$ -unbranched aldehydes. Interestingly, the aldehyde (**25**) was used in excess under these conditions. These conditions provide a complement to the proline-catalyzed reaction, which favors the *anti* adduct.

Shibasaki reported the use of the previously developed BINOL-linked ligand **257** for reaction with  $\alpha$ -hydroxy donors **264** using either 2 or 4 equivalents of diethylzinc (Scheme 36).<sup>327, 330</sup> These donors provide *syn* adducts **265** in good yield and high diastereoselectivity (lower for  $R_2 = \text{Me}$ ). Changing the linker atom from an oxygen to a sulfur atom changes the diastereoselectivity to favor the *anti* adduct, though in generally poor ratios. Ligand **257** ( $X = \text{O}$ ) could be used in as little as 1 mol% loading with substrate **264** ( $R_2 = \text{H}$ ). The *ortho*-methoxy group provides an additional binding site, likely responsible for the increased activity of this substrate. This aryl group was used as an auxiliary, and was removed with a Baeyer-Villiger oxidation.

The lanthanum-lithium-BINOL catalyst **248** was applied to glycine Schiff base substrate **266** in 2002 for the synthesis of serine derivatives **267** (Scheme 37).<sup>331</sup> The *anti* adduct **267** was favored for  $\alpha$ -branched and aryl aldehydes in modest selectivity. 1-Hexanal, however, favored the *syn* diastereomer in only 1% ee. 2-Furfural also gave poor enantioselectivity for both the *syn* and *anti* diastereomers.  $\alpha$ -Branched aldehydes were the best substrates, delivering the desired products in 71–93% ee, in a 59:41–86:14 *anti:syn* ratio with 69–76% ee. The imine was hydrolyzed in a second step to give the free amino acids **267**. The results obtained with catalyst **248** were inferior to that obtained with Maruoka's quaternary ammonium salt **217**, but given the synthetic ease for the preparation of the BINOL-based catalyst **248**, this procedure may be preferred when high enantioselectivity is not required or when the product can be recrystallized to higher enantiomeric purity.

In 2003 Yao and Wang reported a zirconium-BINOL catalyst for the direct aldol reaction of diazo ester **268** (Scheme 38).<sup>332</sup> The reaction was applied to aryl, heteroaryl, styrenyl, and alkyl aldehydes. The adducts **270** were obtained in 47–82% yield and in 53–87% ee. These adducts could be acylated and then oxidized to transform the diazo esters **270** into  $\alpha$ -keto esters **271**. Use of diazo esters **268** allows for the extension of the substrate scope of BINOL-based catalysis to donors at the carboxylic acid oxidation state.

Shibasaki reported the use of ynones (**273**) as donors for the direct catalytic aldol reaction catalyzed by lanthanum-lithium-BINOL-derived complex **248** in 2005 (Scheme 39).<sup>333</sup> This reaction demonstrates the mildness of these conditions. When unsubstituted ynones were used with enamine catalyst **99**, very little of the desired adduct was observed.<sup>243, 334</sup> Products resulting from aldol condensation and 1,4-addition were also obtained under these conditions. Shibasaki used this methodology for the synthesis of fostriecin **277** and a fostriecin epimer.

### 4.3 ProPhenol-Based Catalysts

In 2000 Trost reported dinuclear zinc catalyst **279**, using the ligand known as ProPhenol, for the aldol reaction of aryl methyl ketones (**278**) with a wide variety of aldehydes (**25**) (Scheme 40).<sup>335</sup>  $\alpha$ -Unbranched aldehydes gave lower yields and enantioselectivities than  $\alpha$ -branched aldehydes, which were excellent substrates, giving the adducts **280** in 93–99% ee.

The reaction employed 5–10 equivalents of the donor **278** and 5 mol% of catalyst **279** over the course of 2–4 days.

Modified catalyst **281** was reported in 2001 for the direct aldol reaction of acetone (Scheme 41).<sup>336</sup> The best enantioselectivities were observed for  $\alpha$ -branched aldehydes, as before, while  $\alpha$ -unbranched and aryl aldehydes gave slightly lower enantioselectivities. The reactions proceeded with 5–10 mol% catalyst with 10–15 equivalents of acetone over 2 days. The success of the dinuclear zinc ProPhenol catalyst **281** with  $\alpha$ -unbranched aldehydes is particularly noteworthy, as these are poor substrates for proline catalysis.

Dinuclear zinc ProPhenol-catalysis has also been applied to the synthesis of 1,2-diols **283** (Scheme 42).<sup>337</sup> The adducts **283** were obtained with *syn* selectivity (4:1–100:0) in 86–98% ee in 65–97% yield. The reaction only required 2.5–5 mol% catalyst and 1.5 equivalents of the donor. The reaction took less time than the ProPhenol-catalyzed methyl ketone aldol reaction as well, indicating the increased reactivity of  $\alpha$ -hydroxy donors **282**. The  $\alpha$ -hydroxy ketone **282** was proposed to chelate one of the zinc atoms to give the  $\alpha$ -stereocenter in excellent selectivity (**A**). Attack from the more open face gave the major *syn* isomer, while attack from the opposite face gave the *anti* isomer (with the opposite configuration at the  $\beta$ -stereocenter). The low catalyst loading, small excess of the donor, and commercial availability of the ProPhenol ligand together with the high selectivity and yields make this reaction a practical choice for the synthesis of *syn* diols, especially when sensitive functional groups are present. Indeed, this reaction has found use for the synthesis of spiroketals.<sup>338</sup>

Dinuclear zinc ProPhenol catalysis has also been applied to sensitive ynone substrates **285** together with  $\alpha$ -ketal aldehydes **284** (Scheme 43).<sup>339</sup> The aldol adducts **286** were obtained in 61–84% yield with up to 98% ee using 5–10 mol% of catalyst **279** after 4–17.5 hours using only a slight excess of the ynone donor. The authors noted a large nonlinear effect and accounted for this observation by suggesting that the product **286** modifies the catalyst after the first catalyst turnover. Indeed, addition of several different chelating additives had a pronounced effect on the enantioselectivity of the reaction. The dinuclear zinc ProPhenol-catalyzed ynone aldol has found use for the synthesis of dephosphofostriecin (**287**).<sup>340</sup>

In 2005 Trost reported the use of dinuclear zinc ProPhenol catalysis for the direct aldol reaction of methyl vinyl ketone (**288**) (Scheme 44).<sup>341</sup> Given the propensity of methyl vinyl ketone (**288**) to undergo polymerization, the ability to use this donor under the ProPhenol catalysis conditions is a testament to the mildness of these conditions. With 10 mol% catalyst **279** the adducts **289** were obtained in moderate yield with generally high enantioselectivity. This reaction should prove quite useful as the aldol adducts (**289**) possess many functional groups for further modifications. Indeed, these adducts (**289**) were used as substrates for cycloadditions with nitrile oxides.

In 2008 Da and coworkers reported the use of a catalyst resembling both the BINOL-catalysts of Shibasaki and the ProPhenol catalyst of Trost (Scheme 45).<sup>342</sup> This catalyst was used for the aldol reaction of methyl aryl ketones **278** with aryl aldehydes **243**. The adducts **291** were obtained in moderate yields and enantioselectivities using 20 mol% catalyst with 80 mol% triethylamine over 5 days.

In 2009 Trost and coworkers reported the direct aldol of diazo esters **268** using dinuclear magnesium catalyst **292** (Scheme 46).<sup>343</sup> With 5 mol% catalyst **292** and 5 mol% diol **293** the aldol adducts **270** were obtained in 50–92% yield with 87–98% ee. The reactants could be used in equimolar amounts, allowing for the minimization of waste. These adducts **270** can be modified in a number of ways to transform the diazo group into other functional groups. This allows for the use of substrates at the carboxylic acid oxidation state with the

ProPhenol ligand. The results obtained with the ProPhenol ligand for diazo ester **268** are superior to those obtained with quaternary ammonium salt **217** and zirconium-BINOL catalyst generated from BINOL-derivative **269** (Scheme 23 and 38).

#### 4.4 Miscellaneous Catalysts

Shibasaki reported the use of a calcium catalyst for the direct catalytic aldol reaction in 2001 (Scheme 47).<sup>344</sup>  $\alpha$ -Branched aldehydes gave adducts with 66–91% ee and in 70–88% yield, while  $\alpha$ -unbranched aldehydes gave poor yield and enantioselectivity, favoring the opposite enantiomer of adduct **251**. Only 3 mol% of the catalyst was needed with a reaction time of 10–24 hours. The donor was used in 10–100-fold excess under these conditions.

Calter and Orr reported the use of 20 mol% diamine **295** with 10 mol% zinc nitrate for the aldol reaction of acetone **26** with *para*-nitrobenzaldehyde **74** in 2003 (Scheme 48).<sup>345</sup> Unfortunately, the adduct **27a** was obtained in only 37% yield and 22% ee.

Darbre reported the use of a zinc proline catalyst for the asymmetric aldol of acetone with aromatic aldehydes in 2003 (Scheme 49).<sup>346, 347</sup> The authors noted that under the reaction conditions proline itself gave only 6% yield of adduct **296** in 21% ee, favoring the opposite enantiomer as the one produced when proline and zinc were used together as the catalyst. These results indicate that the two reactions are mechanistically distinct and that zinc plays an important role in the reaction. A number of different mechanisms were suggested by the authors. One possibility is a pathway mirroring that of the type II aldolases, with the zinc activating the donor to generate a zinc enolate, or an enamine mechanism in which the zinc activates the aldehyde (**243**) and stabilizes the enamine. Unfortunately, the enantioselectivity of this process was rather low.

Gathergood and Jørgensen reported the use of copper-BOX catalyst **298** for the direct aldol of  $\alpha$ -keto ester **297** with ethyl trifluoromethylpyruvate **230** (Scheme 50).<sup>348</sup> Unfortunately the adduct **299** was obtained in low yield with poor diastereoselectivity, although the enantioselectivity was generally quite high.

Zhou and Shan reported the use of spiroboronate ester **300** for the direct acetone aldol reaction in 2006 (Scheme 51).<sup>349</sup> The authors do not propose a mechanism for this unusual catalytic system. The adducts **296** were obtained in low to moderate yield with generally high enantioselectivity for most aryl aldehydes. The authors report the use of an  $\alpha$ -unbranched aldehyde as well, which gives the aldol adduct **296** in 34% yield and in 96% ee.

Stilbene ligand **100** together with an equimolar amount of zinc triflate was used for the direct catalytic aldol reaction by Mlynarski and coworkers in 2007 (Scheme 52).<sup>350</sup> The reaction was applied to a variety of ketone donors, including acetone, cyclohexanone and cyclopentanone as well as unsymmetrical ketones. Unsymmetrical ketones gave the linear product with 21–54% yield and in 84–88% ee. Cyclohexanone gave the *anti* products in excellent diastereoselectivity and enantioselectivity. Use of cyclopentanone, however, produced the desired aldol with only 44:66 diastereoselectivity favoring the *syn* adduct. Electron-poor aryl aldehydes gave better yields than electron-rich aryl aldehydes, as observed with proline itself. The authors suggest an enamine mechanism, in which the zinc stabilizes the enolate as well as activates the aldehyde, as suggested by Dabre for the zinc proline catalyst.

Recently Shibasaki has reported a dinuclear nickel catalyst **302** for the direct catalytic aldol reaction of  $\beta$ -keto esters **301** with aqueous formaldehyde (also known as formalin) (Scheme 53).<sup>351</sup> The reaction proceeds with only 0.1–1 mol% catalyst **302** to give the desired adducts in 22–94% yield and in 66–94% ee. The use of formaldehyde as the acceptor component in

direct catalytic asymmetric aldol reactions is rare and should prove valuable. There have also been a few reports of the use of formaldehyde with enamine,<sup>157, 352, 353</sup> rhodium,<sup>315, 354</sup> and palladium catalysts.<sup>355</sup>

In 2009, Feng and coworkers reported the use of cinchonine (**304**), together with BINOL and titanium for the direct catalytic aldol of diazo esters with a variety of aldehydes, including aryl, heteroaryl, and one example of an alkyl aldehyde (which gave the lowest enantioselectivity) (Scheme 54).<sup>356</sup> The diazo ester is used in a significant excess under these conditions, and the reaction times are extremely long, even with 20 mol% catalyst loading, indicating that this catalytic system suffers from rather low activity.

Wang and coworkers reported the use of ligand **305** together with copper as a catalyst for the direct aldol reaction of aryl aldehydes in 2009 (Scheme 55).<sup>357</sup> The authors propose an enamine mechanism, combined with activation of the aldehyde by the copper (II) bound to the ligand (**A**). Most of the reported aldehyde acceptors are electron poor species, and the donors include acetone, cyclopentanone, cyclohexanone and 2-butanone. The regioselectivity in the case of 2-butanone is rather poor, though the diastereoselectivity and enantioselectivity in such cases is high.

## 5. Conclusions

A great deal of research has been dedicated to the development of the direct catalytic aldol reaction in recent years. The most practical of the described catalysts is proline, a simple and inexpensive amino acid that can be used for a wide array of substrates. The reactivity of proline, however, is rather low, and has spurred the development of a plethora of new catalysts. Despite the growing number of reported catalysts, however, very few increase the reactivity of the parent system dramatically, although the yield and enantioselectivity have been increased through use of alternate catalysts.

One of the most notable achievements in this area is the development of catalysts that provide access to isomers not favored by proline catalysis. The use of non-enamine catalysts is also noteworthy. Because these catalysts proceed through a different mechanism, they offer different drawbacks and benefits. One of these benefits is the exceptional mildness of some of the reported reaction conditions. The ability to use methyl vinyl ketone, for example, is extraordinary. The mildness of many of the metal-catalyzed conditions has allowed for a significant increase in the scope of the donor, and in some cases, the acceptor as well. The main area that remains to be improved is the low reactivity of the reported catalysts. Most of the reported conditions use a large excess of the donor, together with a high catalyst loading and long reaction time. This limits the utility of the aldol reaction to highly reactive substrates. A more reactive catalyst would allow the scope of the reaction to be extended to less reactive donors and acceptors. A number of catalysts have shown improved reactivity and this will undoubtedly continue to be an area of intense research in the future.

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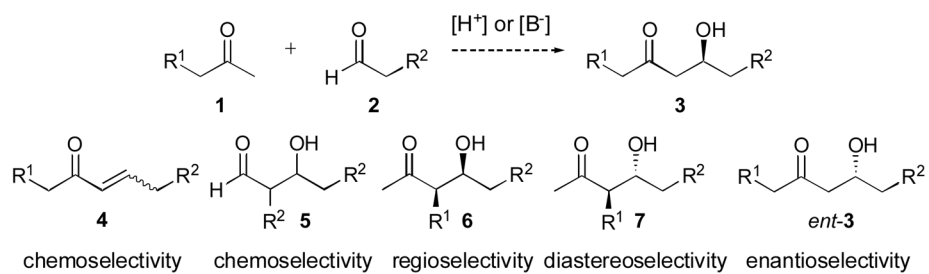
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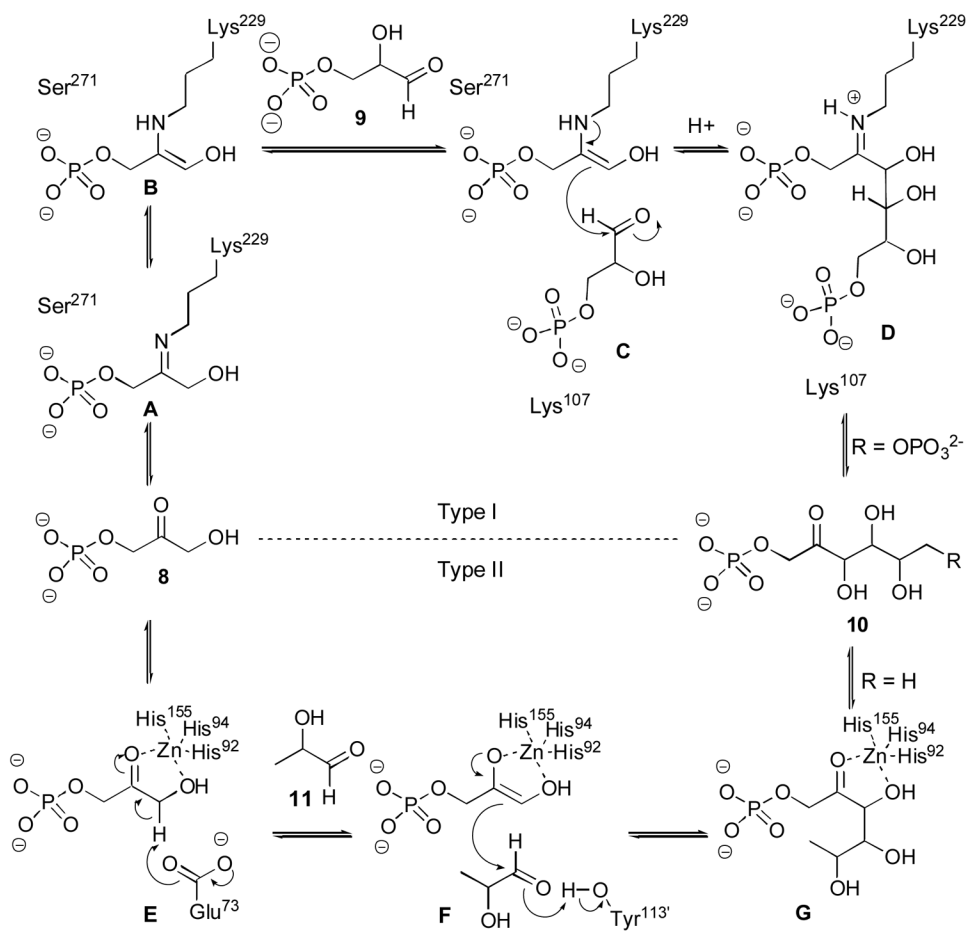
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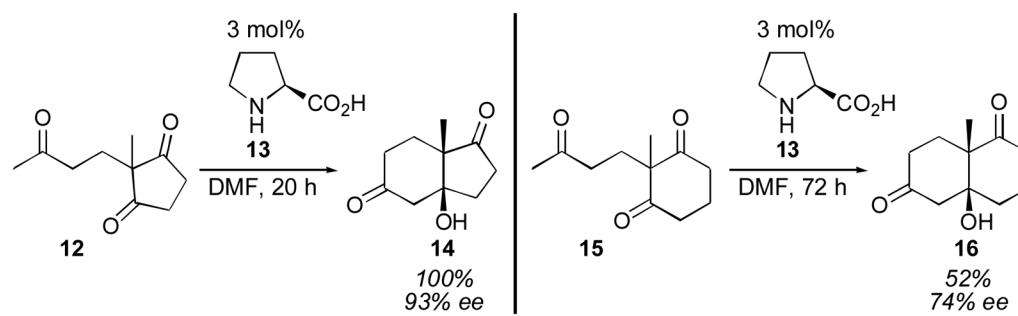


**Scheme 1.**

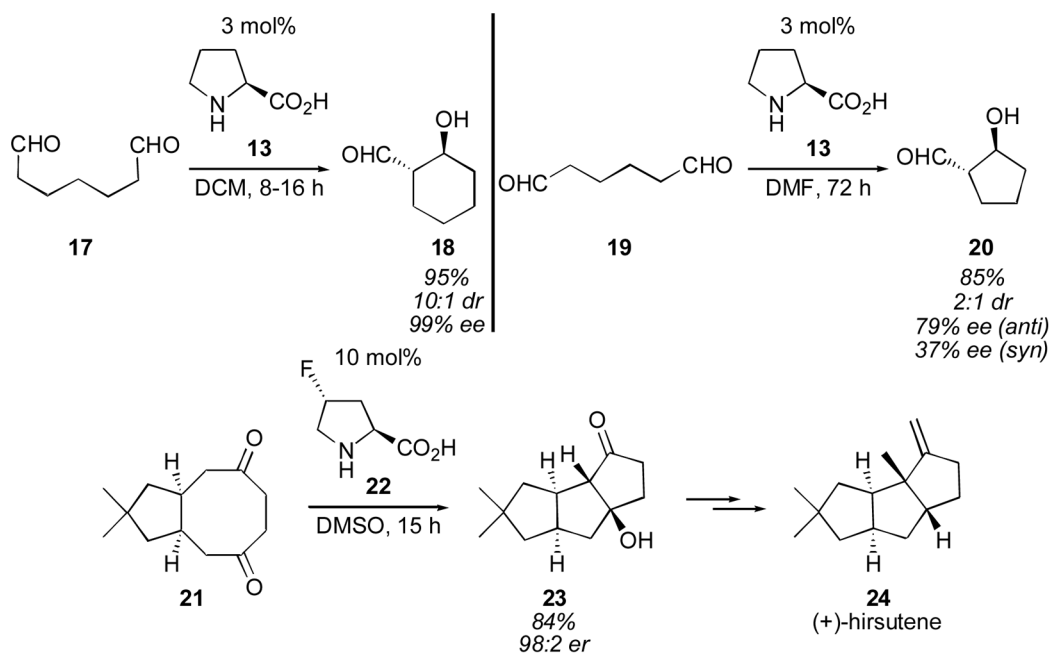
The direct catalytic asymmetric aldol and issues of selectivity.



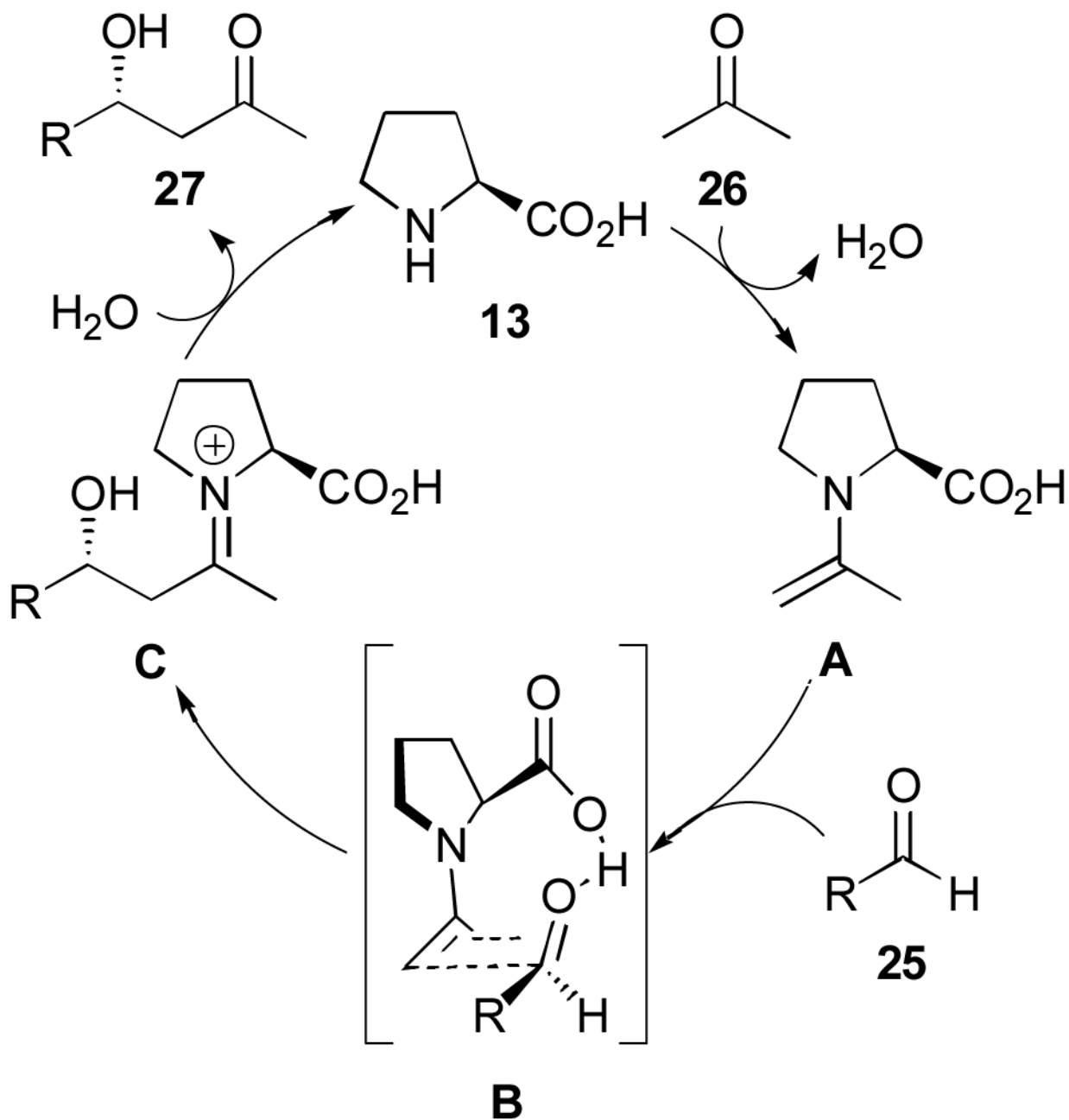
**Scheme 2.**  
Mechanism of type I (RAMA FDP) and type II (fucose-1-phosphate) aldolases.<sup>9</sup>



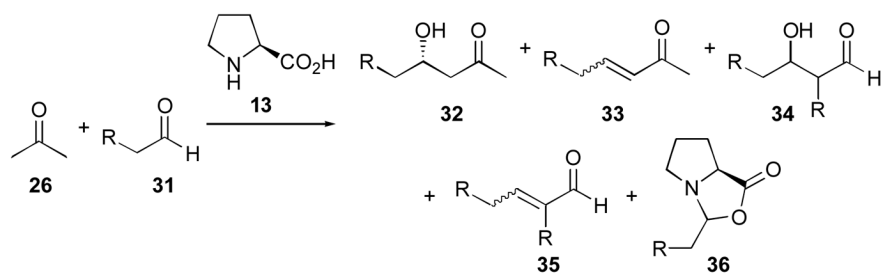
**Scheme 3.**  
Hajos-Parrish-Eder-Sauer-Wiechert aldol reaction.<sup>61, 62</sup>



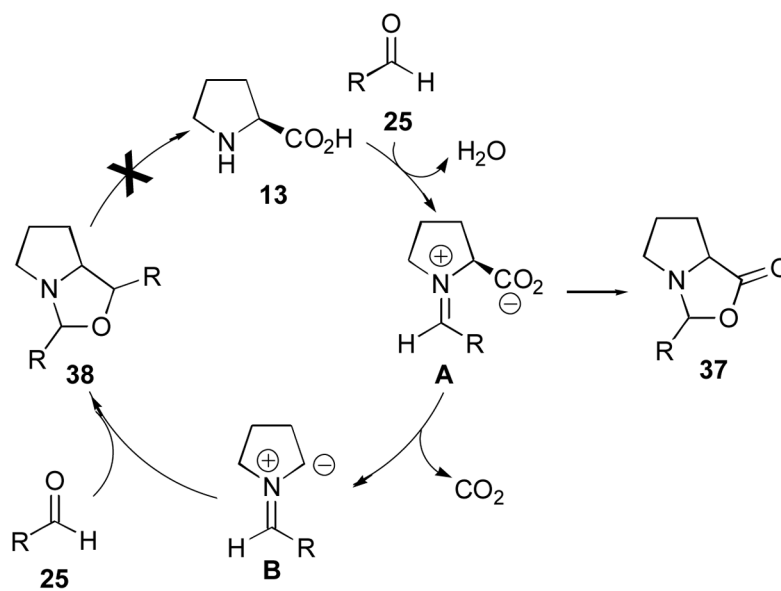
**Scheme 4.**  
Proline-catalyzed enol-exo and transannular cyclizations.<sup>63, 64</sup>



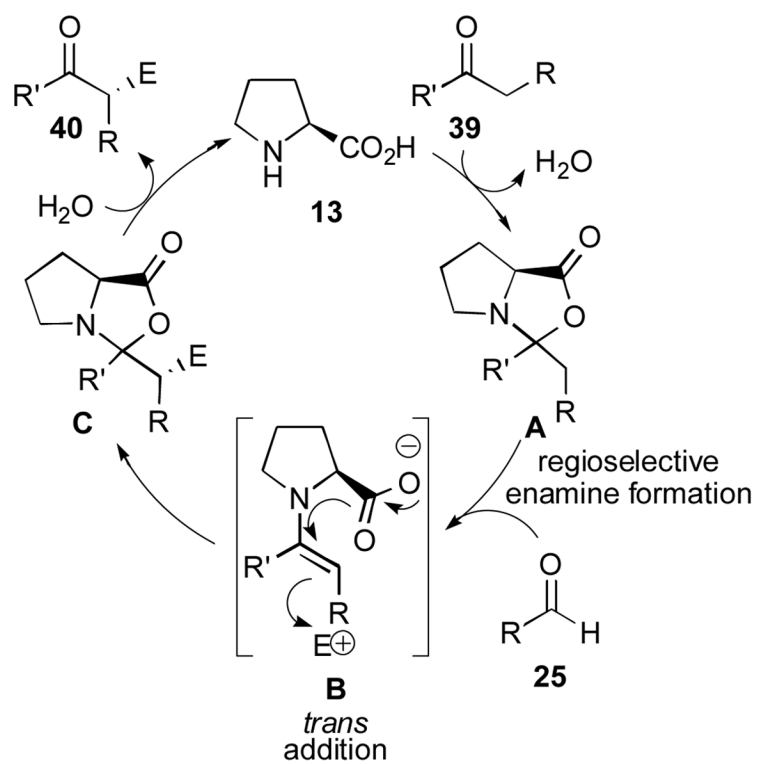
**Scheme 5.**  
Mechanism of the intermolecular proline-catalyzed aldol.<sup>76</sup>



**Scheme 6.**  
Side products obtained in the proline-catalyzed aldol reaction.

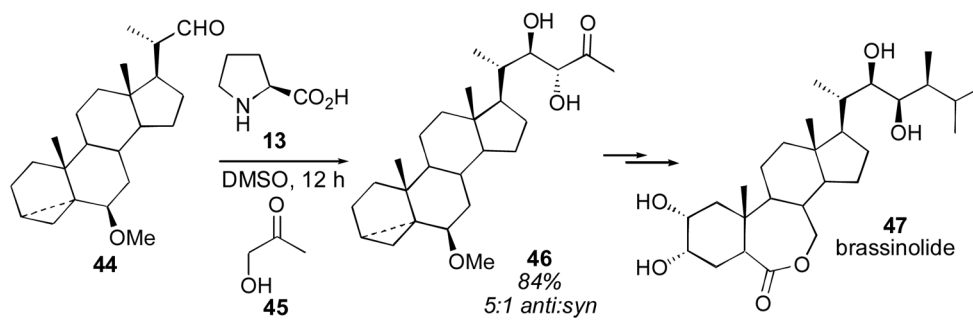


**Scheme 7.**  
Off-cycle processes that are ameliorated by the addition of water.<sup>106</sup>

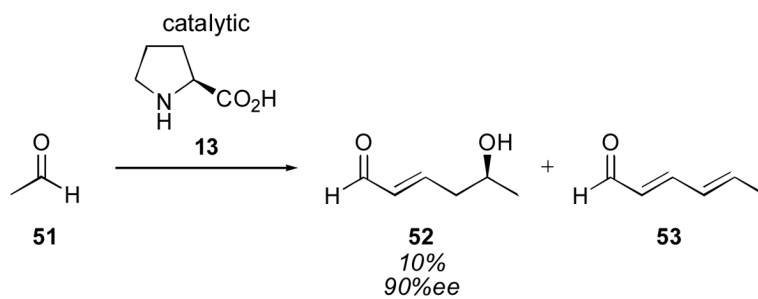


**Scheme 8.**  
Alternative oxazolidinone mechanism proposed by Seebach and Eschenmoser.<sup>110</sup>

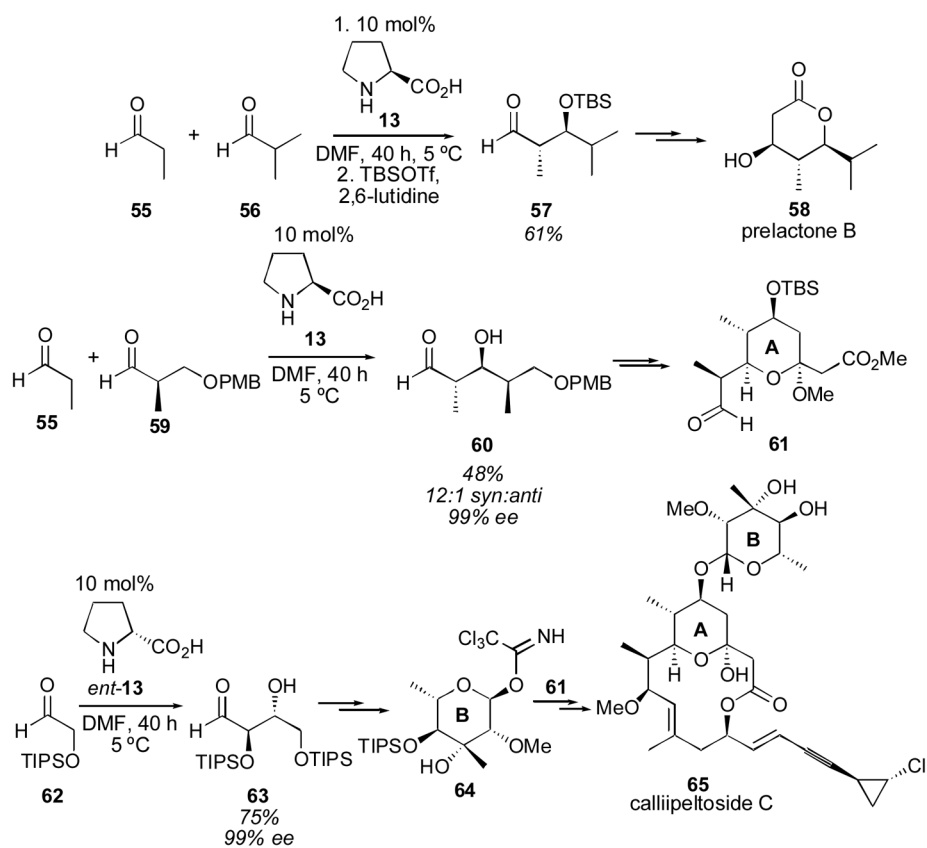


**Scheme 9.**

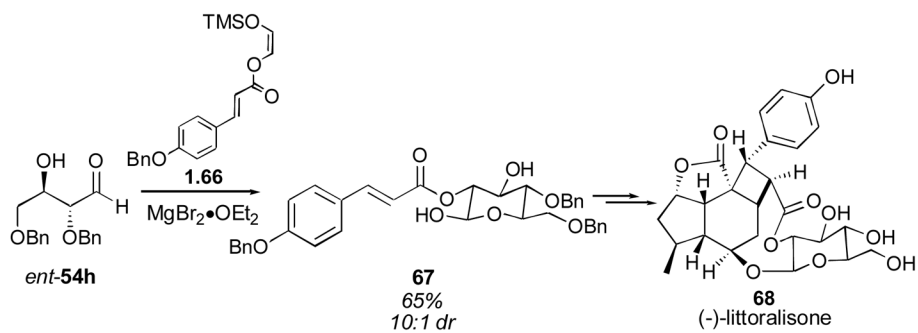
Use of the proline-catalyzed hydroxyacetone aldol reaction for the synthesis of brassinolide.<sup>116</sup>



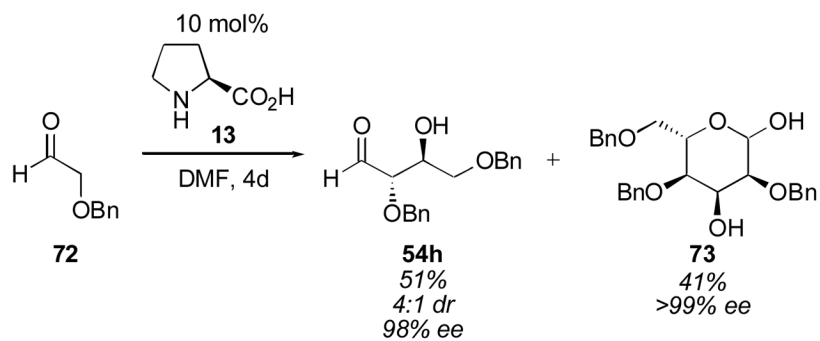
**Scheme 10.**  
Trimerization of acetaldehyde.<sup>128</sup>

**Scheme 11.**

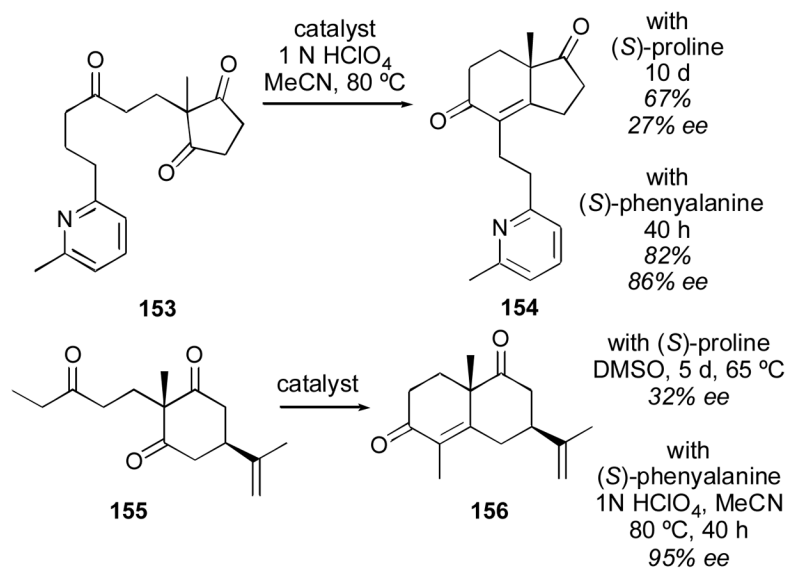
Application of the aldehyde aldol reaction to the syntheses of prelaetone B and calliipeltoside C.<sup>131, 132</sup>



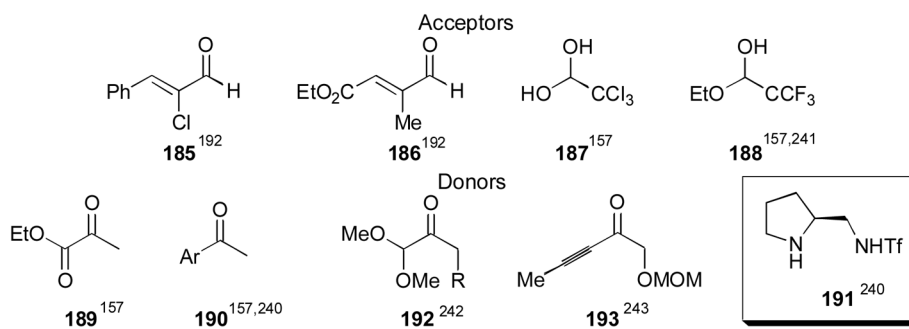
**Scheme 12.** MacMillan's direct aldol/Mukaiyama aldol sequence: application to the synthesis of (-)-littoralisone.<sup>135</sup>



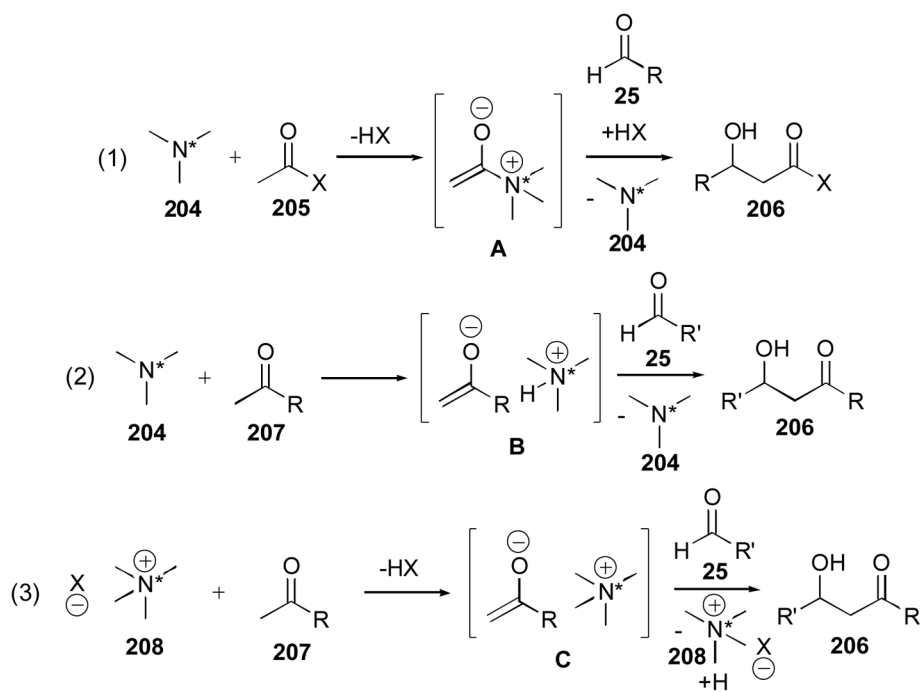
**Scheme 13.**  
Proline-catalyzed sugar synthesis.<sup>140</sup>



**Scheme 14.** Improved reactivity and enantioselectivity with primary amine catalysts for sterically-hindered substrates.<sup>214, 215</sup>

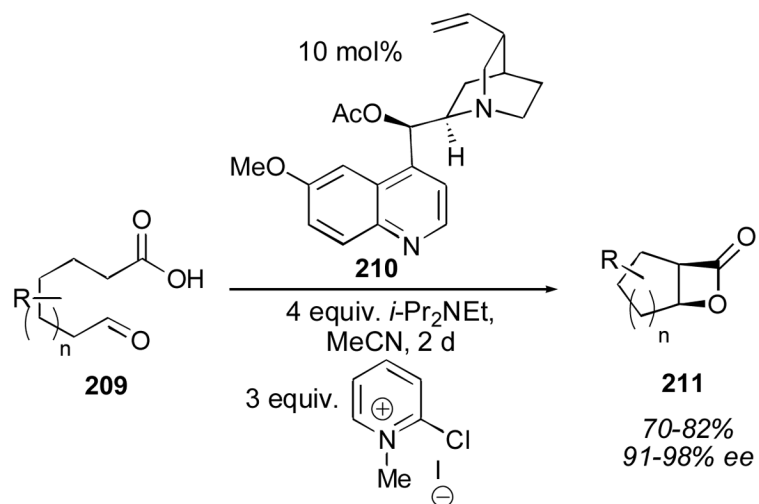


**Scheme 15.**  
Additional acceptors and donors.

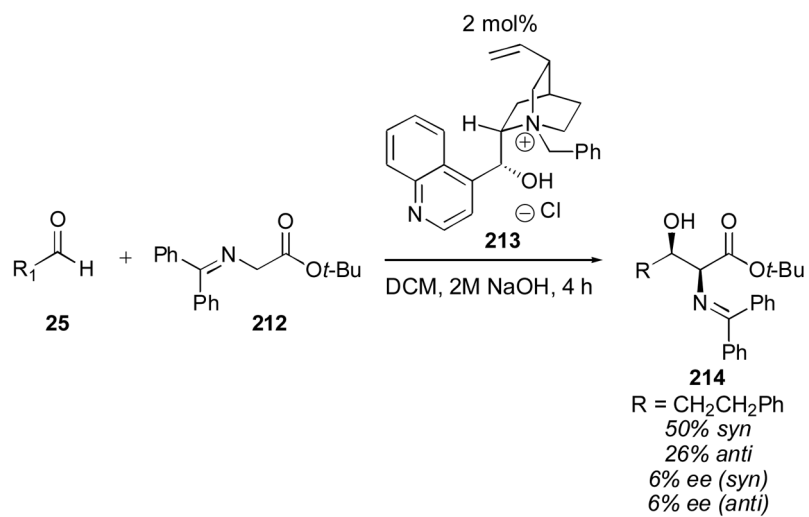


**Scheme 16.**  
Potential mechanisms for the direct aldol catalyzed by tertiary amines and quaternary ammonium salts.

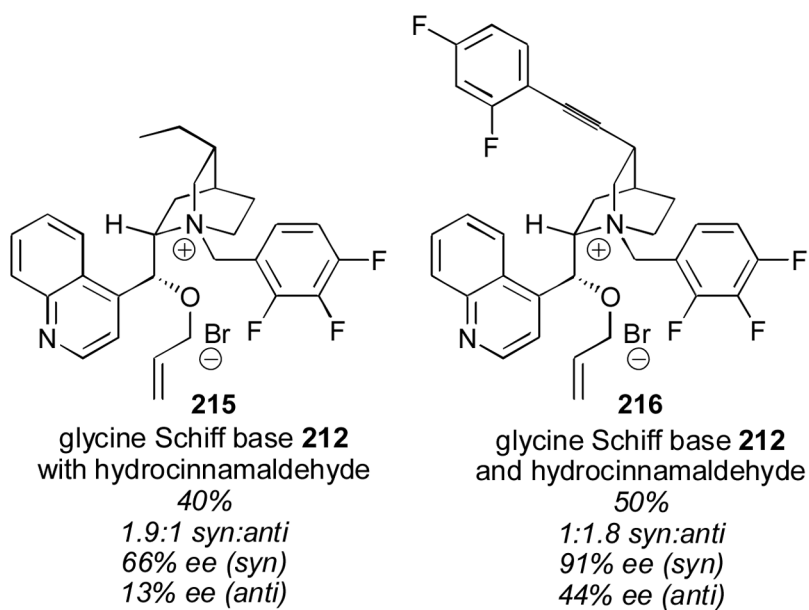




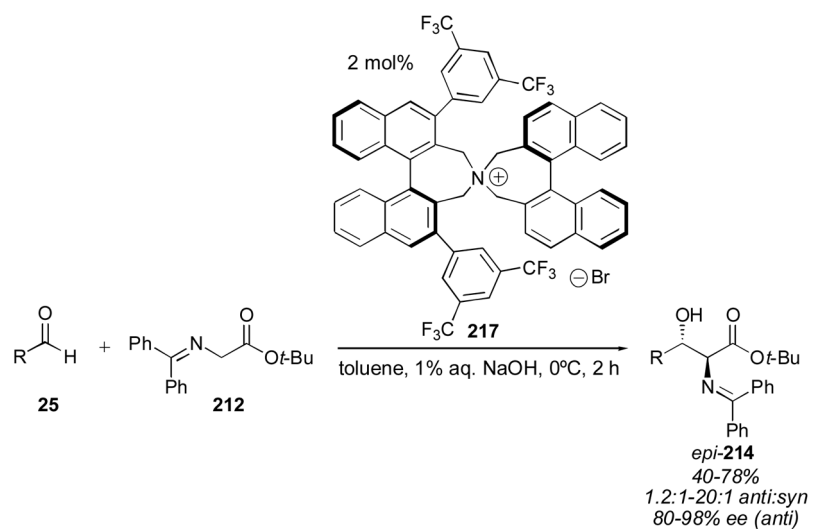
**Scheme 17.**  
Intermolecular aldol-lactonization.<sup>255-257</sup>



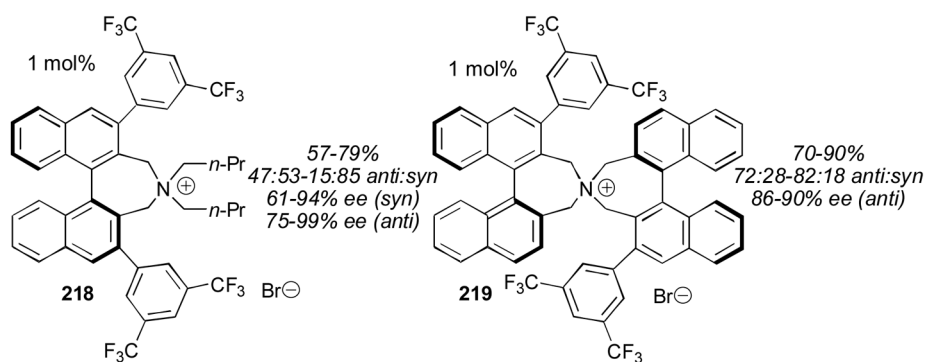
**Scheme 18.** Cinchona alkaloid-catalyzed aldol reactions of glycine Schiff bases.<sup>263</sup>



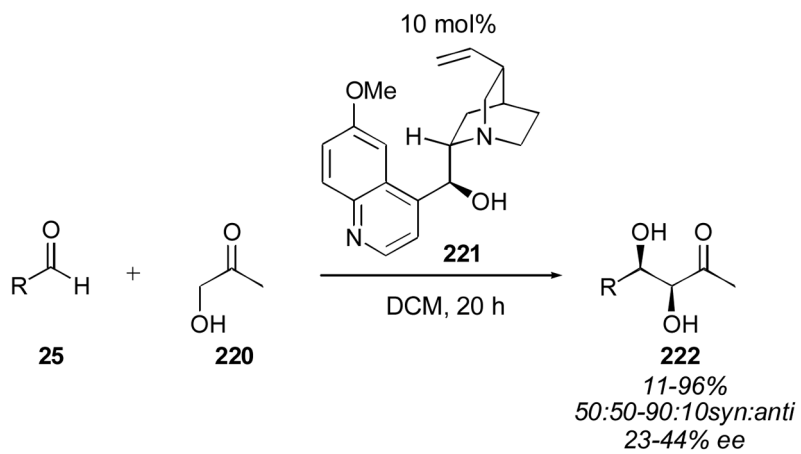
**Scheme 19.**  
Alternate cinchona derivatives.<sup>264,265</sup>



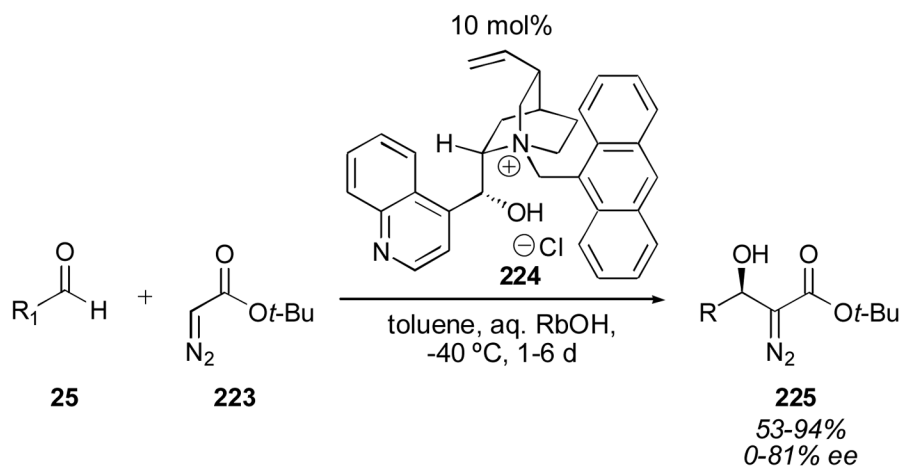
**Scheme 20.**  
Maruoka's C<sub>2</sub>-symmetric quaternary ammonium salt **216**.<sup>266,267</sup>



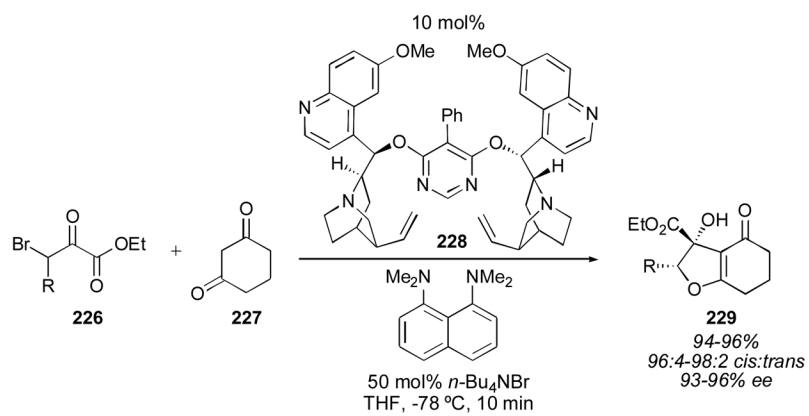
**Scheme 21.**  
Additional non-cinchona derived quaternary ammonium salts.<sup>268,269</sup>



**Scheme 22.**  
Quinidine-catalyzed direct aldol of hydroxyacetone.<sup>270</sup>

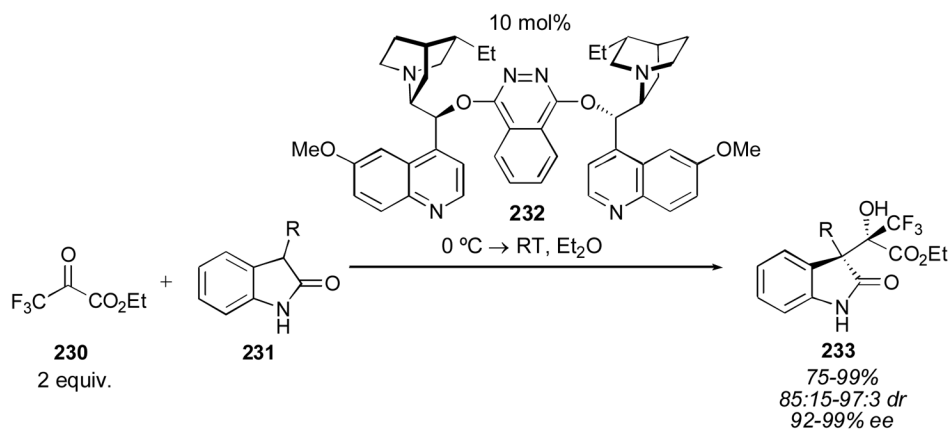
**Scheme 23.**

Diazo ester aldol catalyzed by cinchona alkaloid derivative **224**.<sup>271,272</sup>

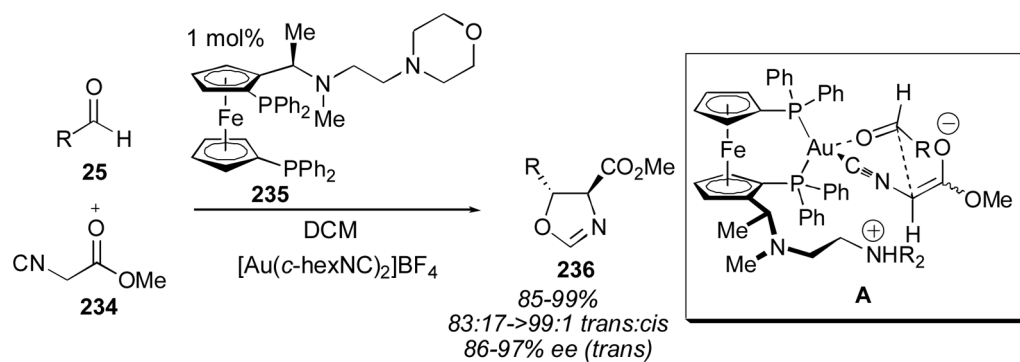


**Scheme 24.**  
Cinchona alkaloid-catalyzed aldol-cyclization.<sup>273</sup>

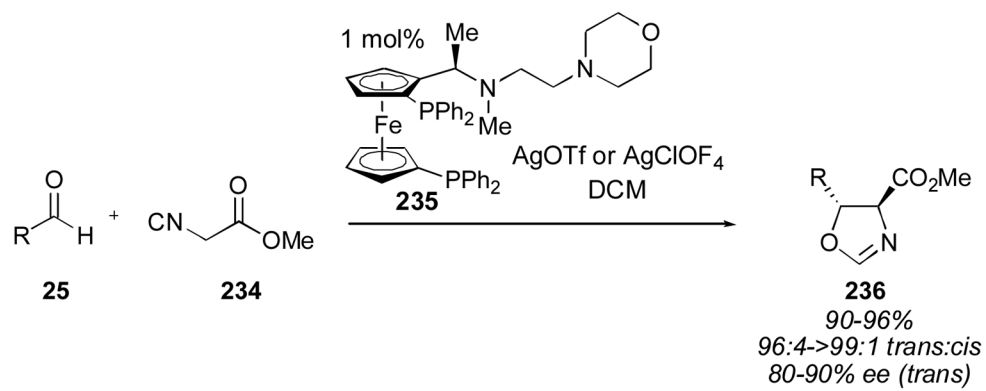




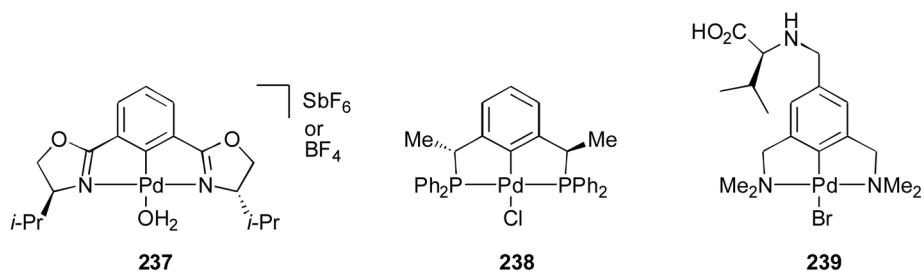
**Scheme 25.**  
Oxindole aldol reaction with ethyl trifluoropyruvate.<sup>274</sup>



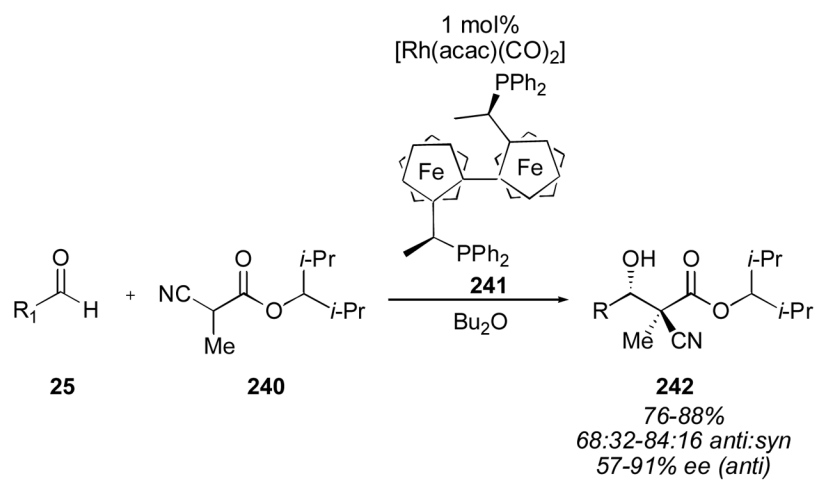
**Scheme 26.**  
 Gold-catalyzed direct catalytic aldol reaction.<sup>279-281</sup>



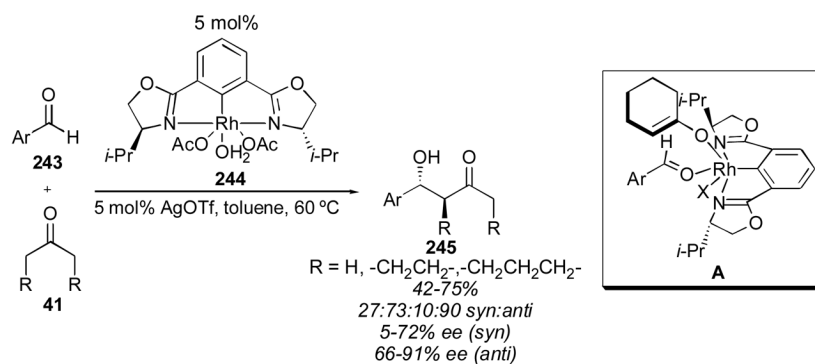
**Scheme 27.**  
Silver-catalyzed direct aldol reaction.<sup>304,305</sup>



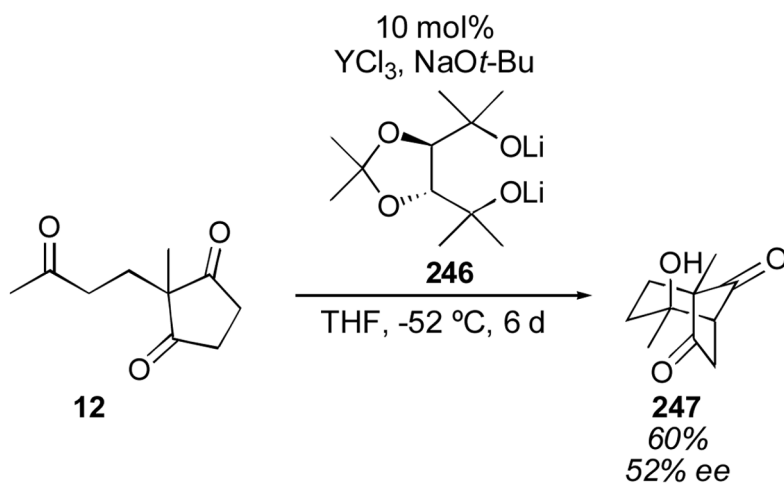
**Scheme 28.** Palladium catalysts for the direct aldol of  $\alpha$ -isocyanocarboxylates and aldehydes.<sup>306–314</sup>



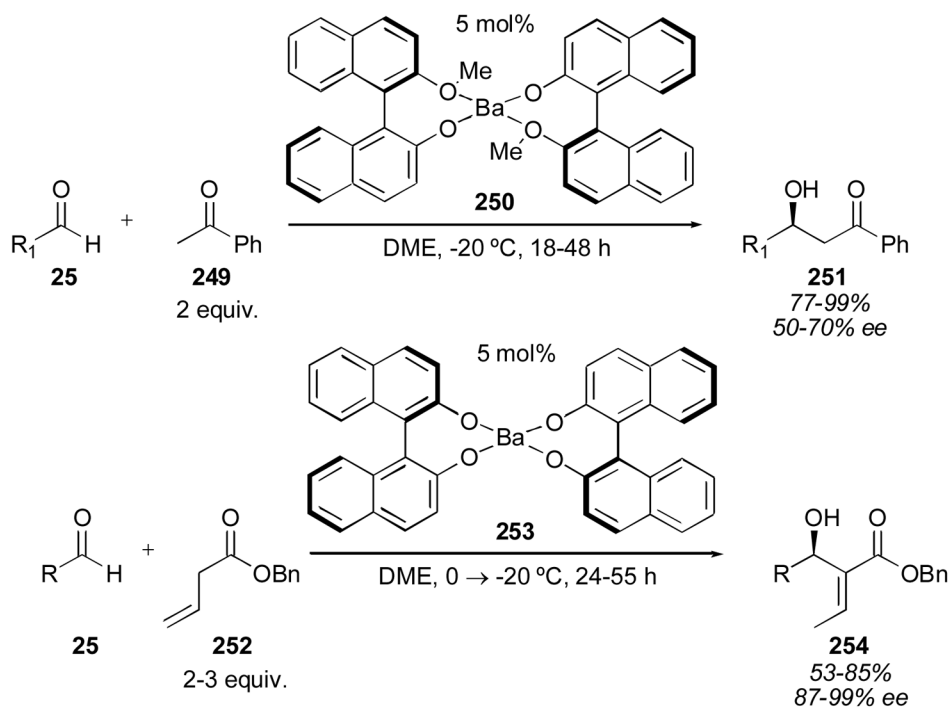
**Scheme 29.**  
Rhodium-catalyzed direct aldol reaction of  $\alpha$ -cyanocarboxylates.<sup>315</sup>



**Scheme 30.**  
 Rhodium-catalyzed aldol reaction of cyclohexanone and cyclopentanone.<sup>316</sup>

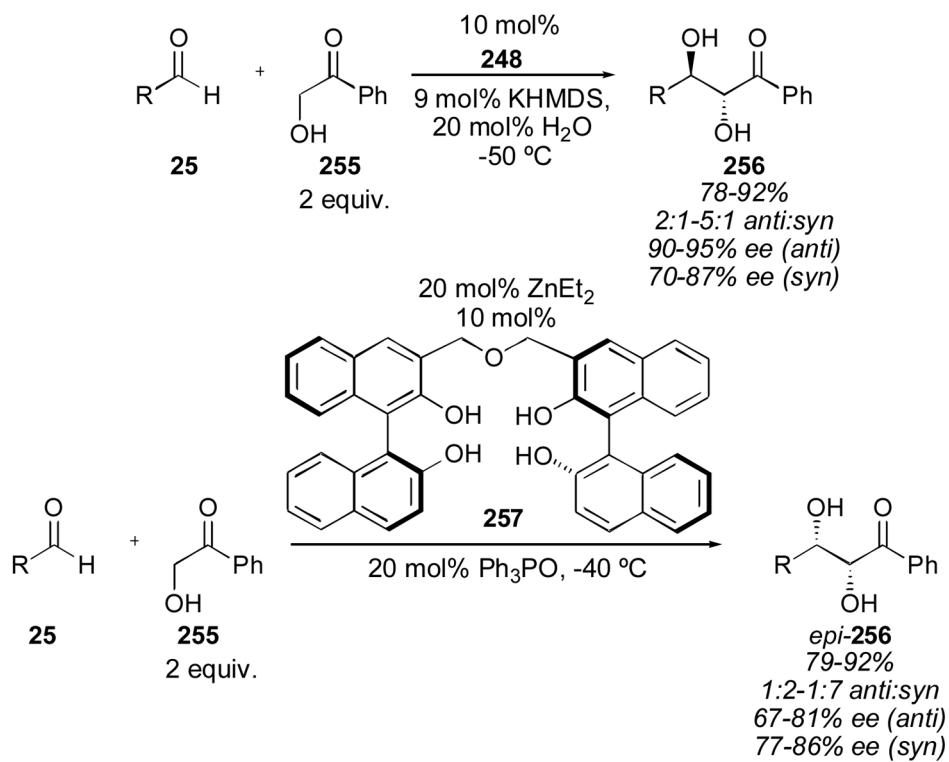


**Scheme 31.**  
Rare-earth alkoxide catalyzed aldol reaction.<sup>318</sup>

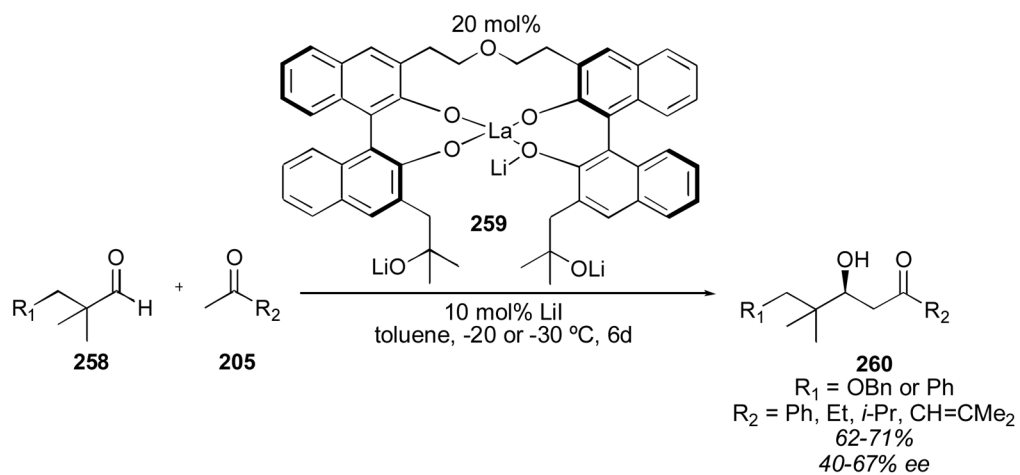


**Scheme 32.**  
Barium BINOL-derived catalyst for the direct aldol.<sup>323,324</sup>

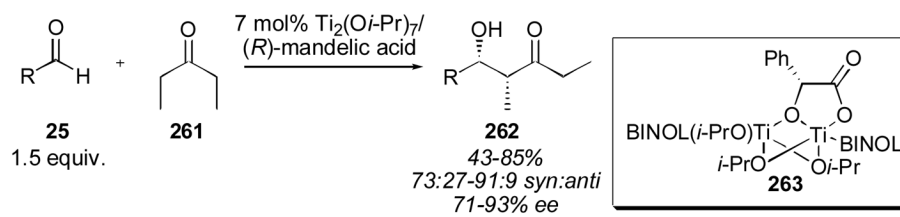


**Scheme 33.**

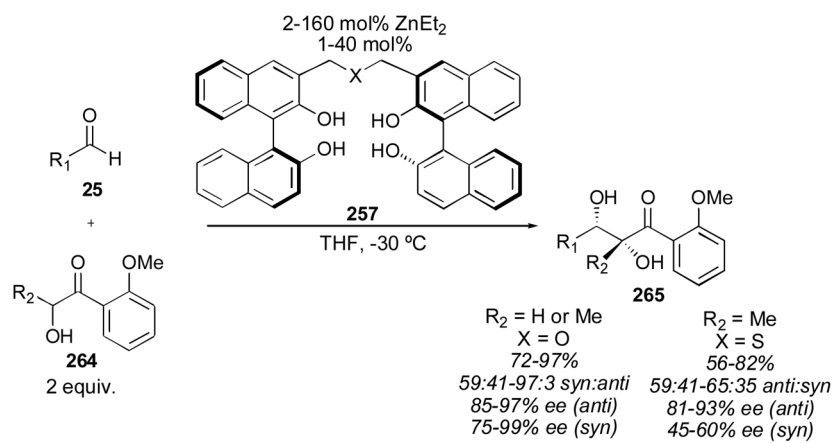
BINOL-based catalysts for the aldol reaction of 2-hydroxy-1-phenylethanone.<sup>325,326</sup>



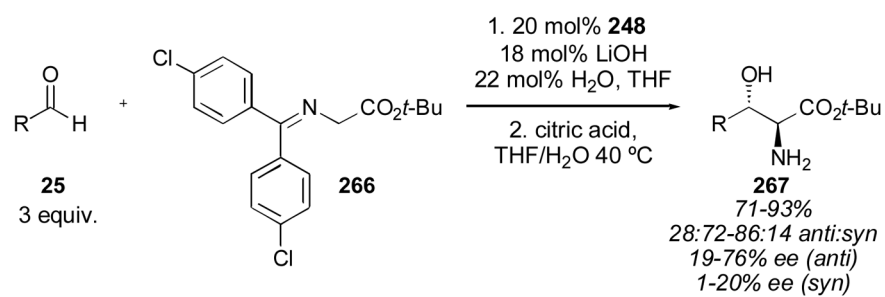
**Scheme 34.**  
 Linked BINOL catalyst for the direct aldol reaction.<sup>328</sup>



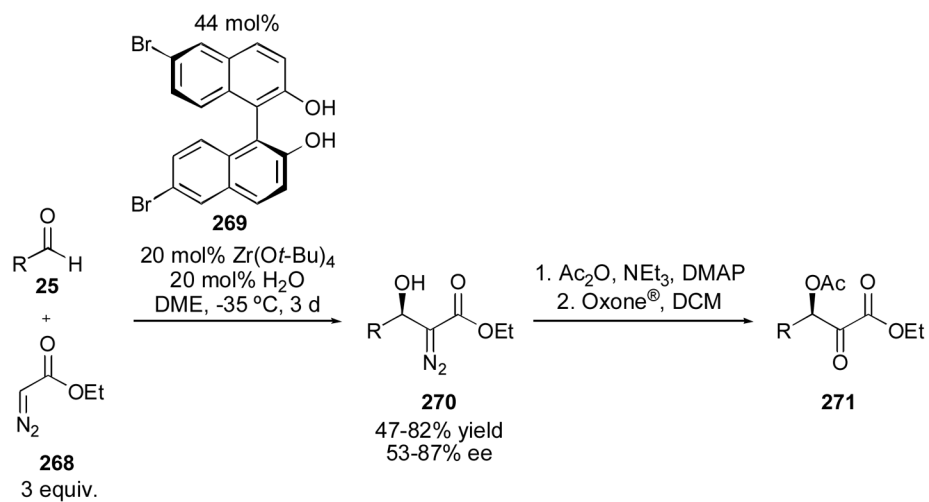
**Scheme 35.**  
Titanium BINOL catalyst for the direct aldol reaction.<sup>329</sup>

**Scheme 36.**

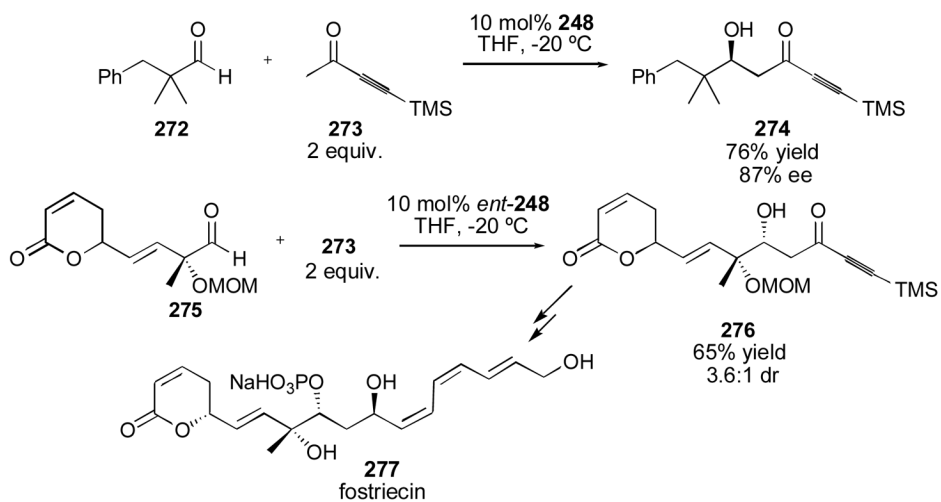
Linked-BINOL zinc-catalysts for the Synthesis of 1,2-diols.<sup>327, 330</sup>



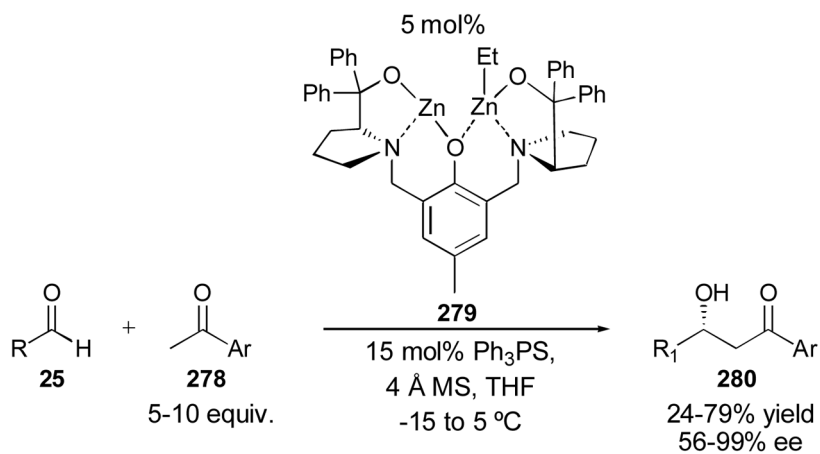
**Scheme 37.**  
Application of catalyst **248** to glycine Schiff bases.<sup>322</sup>



**Scheme 38.**  
Zirconium-BINOL catalyzed diazo ester aldol.<sup>328</sup>

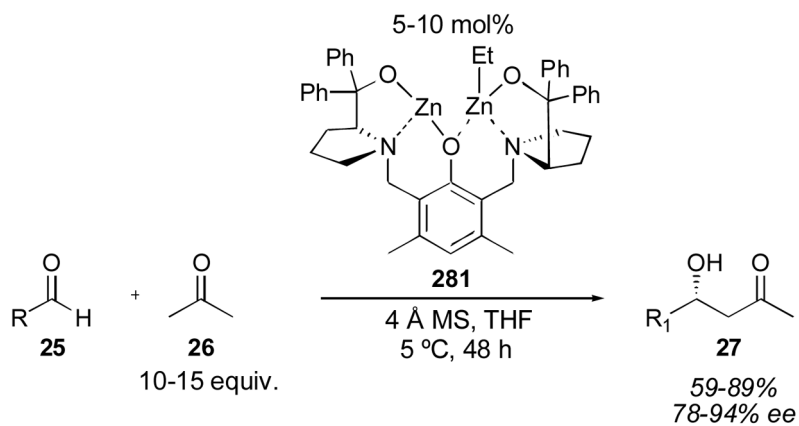


**Scheme 39.** Lanthanum-lithium-BINOL-catalyzed ynone aldol and its application to the synthesis of fostriecin.<sup>333</sup>

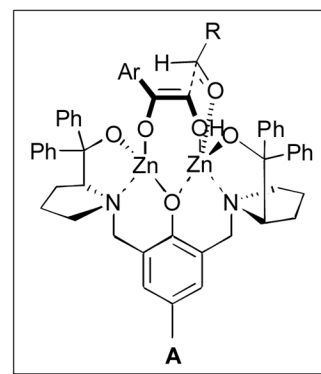
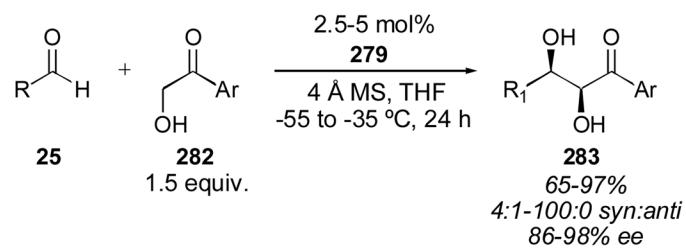


**Scheme 40.**  
ProPhenol-catalyzed aldol reaction of aryl ketones.<sup>335</sup>

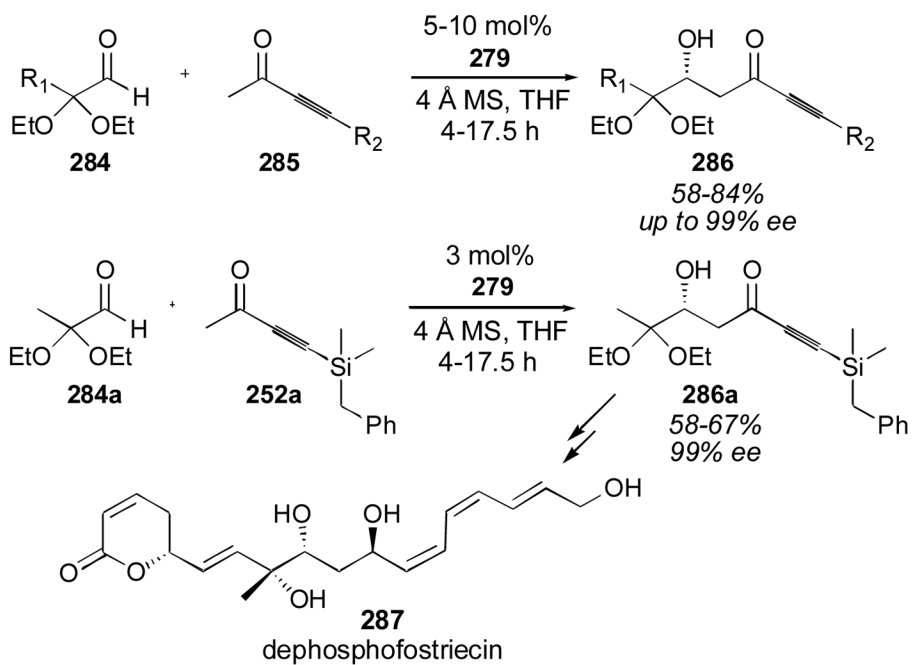




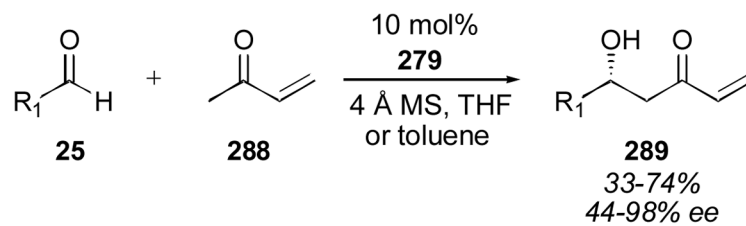
**Scheme 41.**  
ProPhenol-catalyzed acetone aldol.<sup>336</sup>



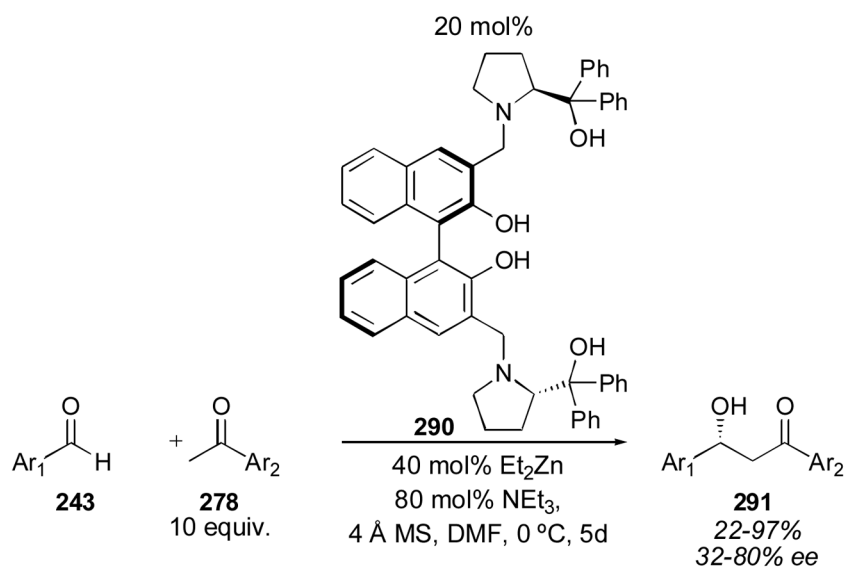
**Scheme 42.**  
Dinuclear zinc ProPhenol-catalyzed aldol for the synthesis of *syn* diols.<sup>337</sup>

**Scheme 43.**

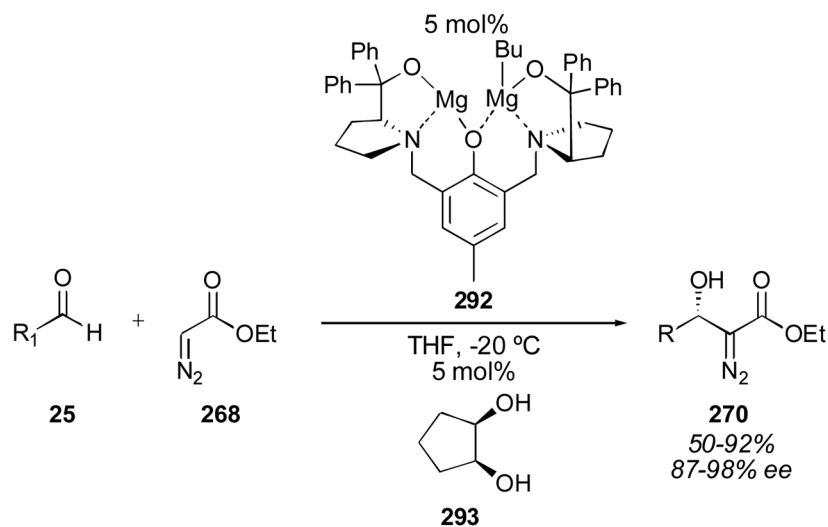
ProPhenol-catalyzed ynone aldol and its application to the synthesis of dephosphofostriecin.<sup>339, 340</sup>



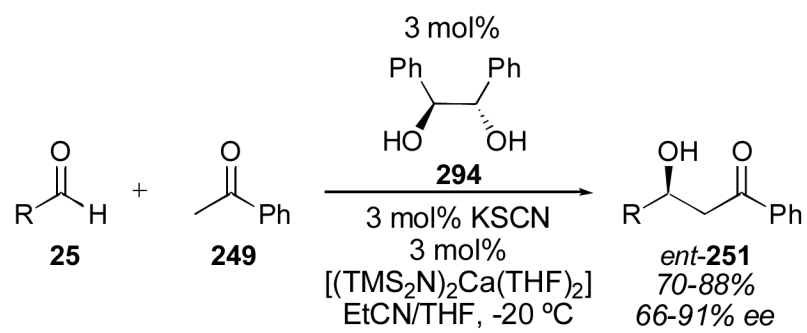
**Scheme 44.** Dinuclear zinc ProPhenol-catalyzed aldol reaction of methyl vinyl ketone.<sup>341</sup>



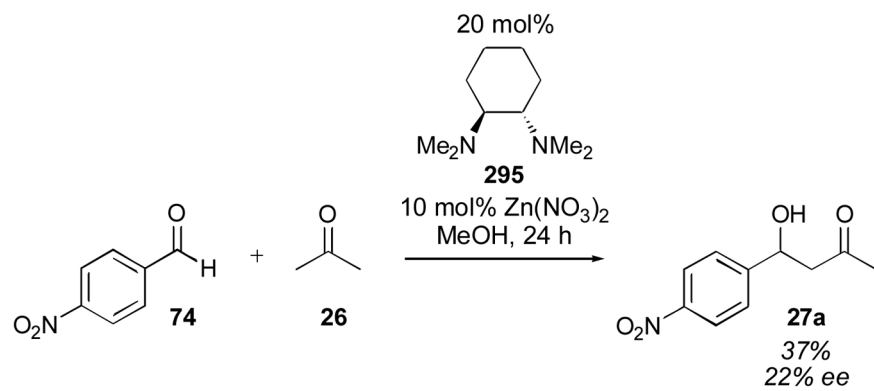
**Scheme 45.**  
BINOL-derived zincate catalyst for the aldol reaction of aryl ketones and aryl aldehydes.<sup>342</sup>



**Scheme 46.**  
Magnesium-ProPhenol catalyzed diazo ester aldol.<sup>343</sup>

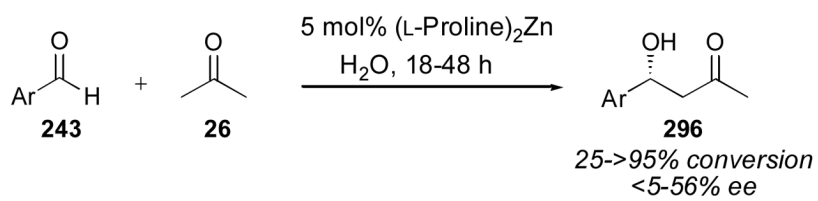


**Scheme 47.**  
Calcium-catalyzed aldol of acetophenone.<sup>344</sup>

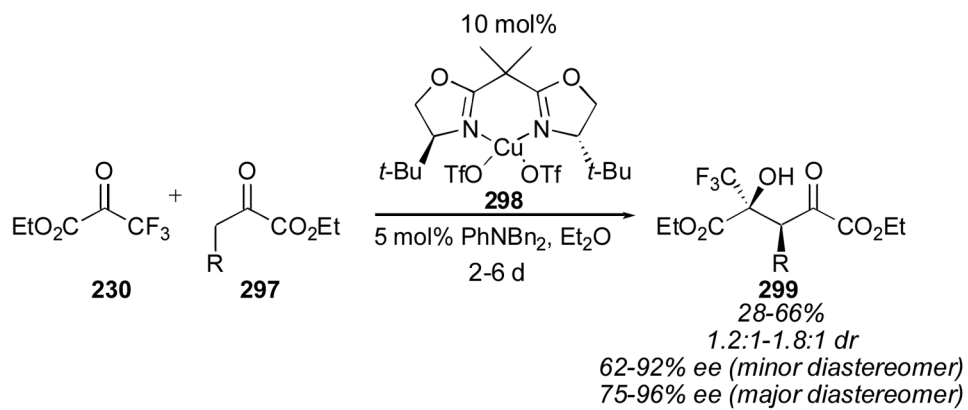


**Scheme 48.**  
Zinc-diamine catalyzed acetone aldol.<sup>345</sup>

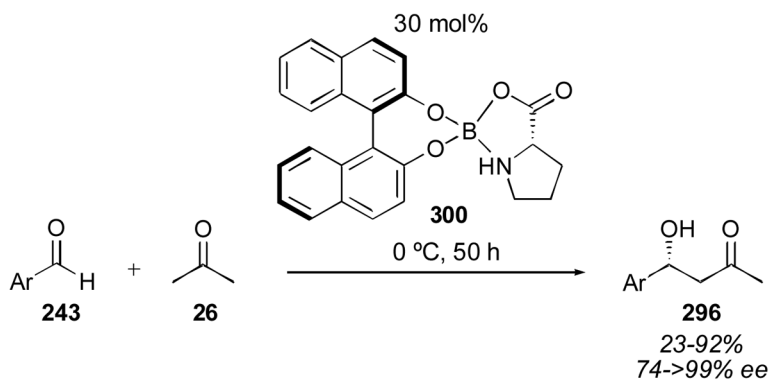




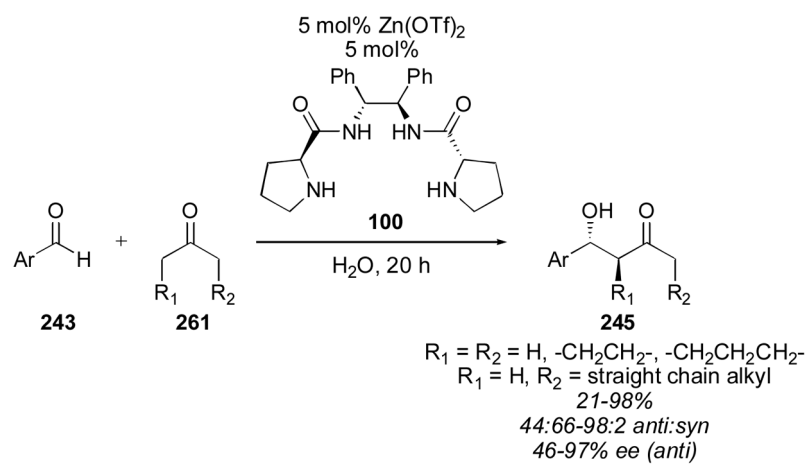
**Scheme 49.**  
Zinc-proline catalyzed acetone aldol.<sup>346, 347</sup>



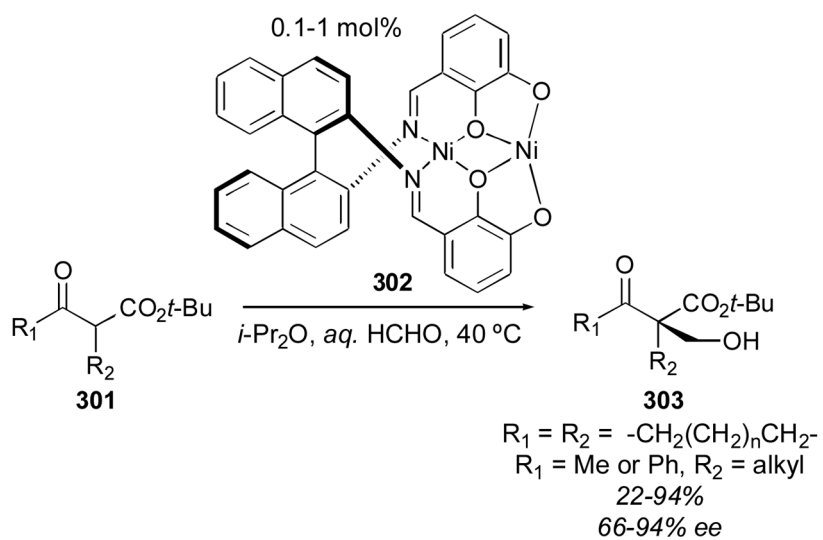
**Scheme 50.**  
Copper-catalyzed aldol of trifluoropyruvate.<sup>348</sup>



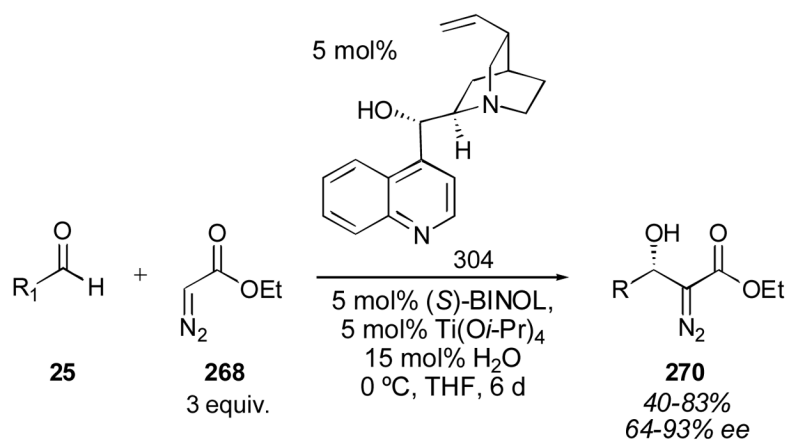
**Scheme 51.**  
Spiroborate ester-catalyzed acetone aldol.<sup>349</sup>



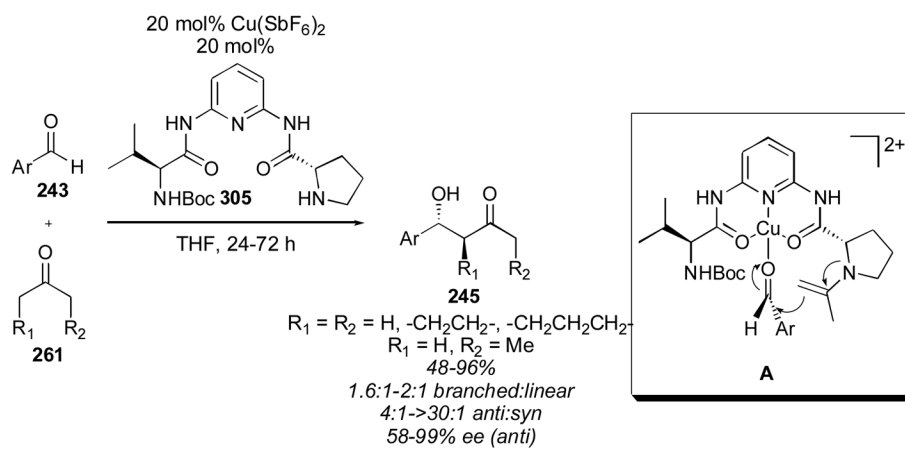
**Scheme 52.**  
Zinc-proline catalyzed aldol.<sup>350</sup>



**Scheme 53.**  
Dinuclear nickel Schiff base catalyzed aldol.<sup>351</sup>



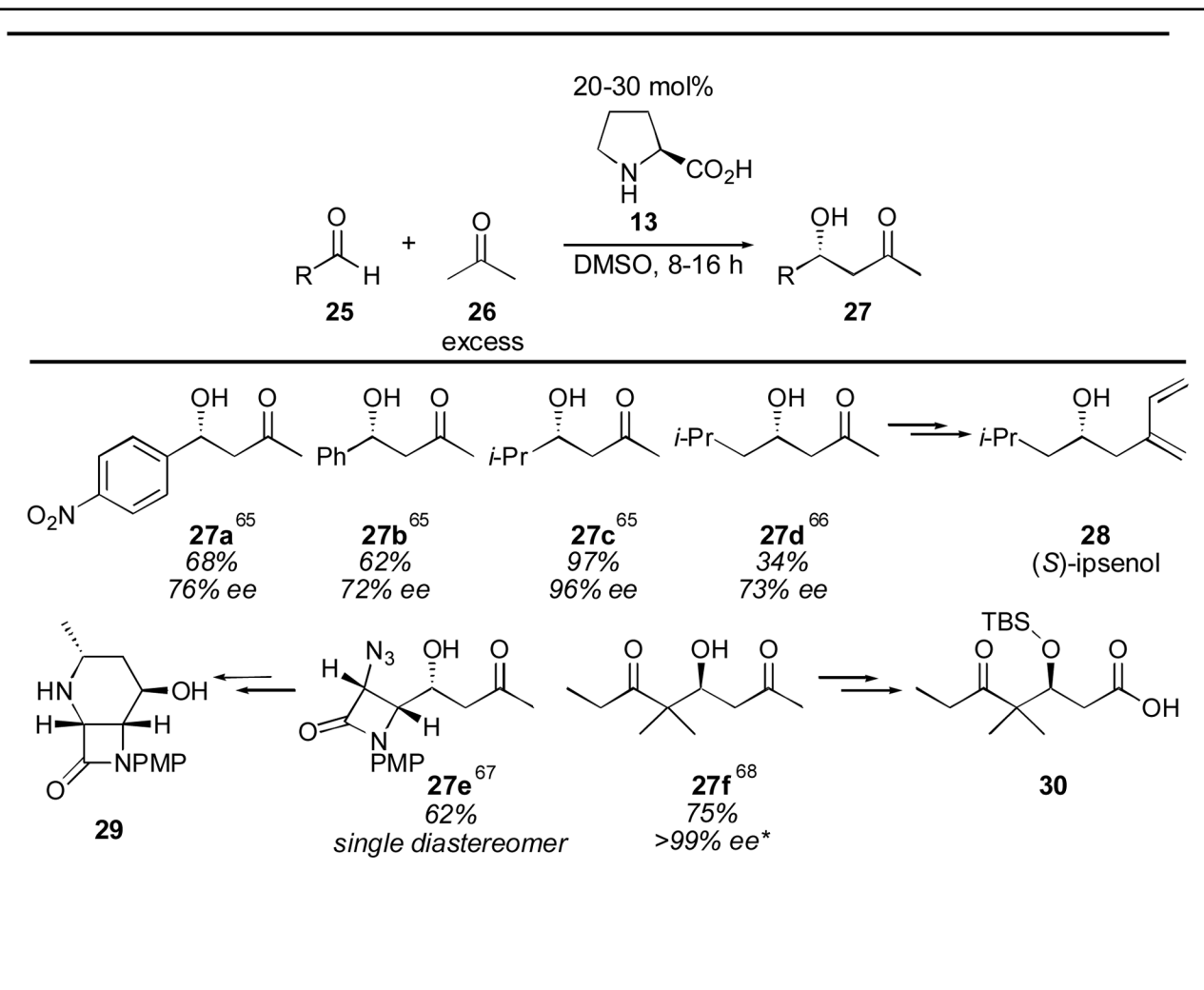
**Scheme 54.**  
Cinchonine-BINOL-titanium catalyzed diazo acetate aldol.<sup>356</sup>



**Scheme 55.**  
Copper-catalyzed aldol reaction of aryl aldehydes.<sup>357</sup>

Table 1

Proline-catalyzed acetone aldol.



\* D-Proline was used. References are given for each product as a superscript.



Table 2

Substituted ketone donors in the proline-catalyzed aldol reaction.

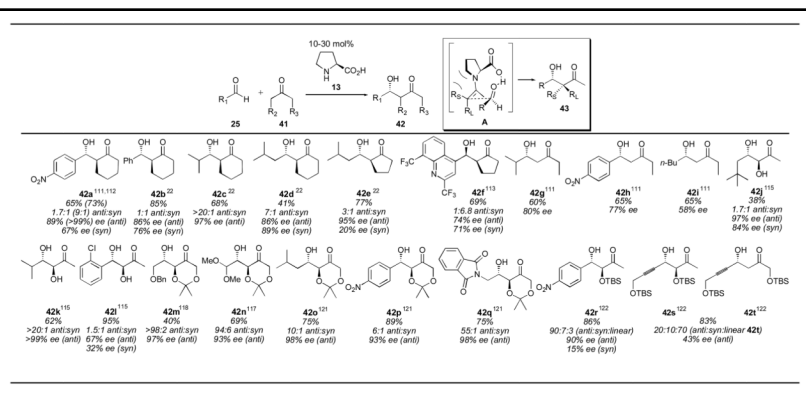
<sup>a</sup>References are given for each product as a superscript.

Table 3

Ketone electrophiles in the proline-catalyzed aldol reaction.

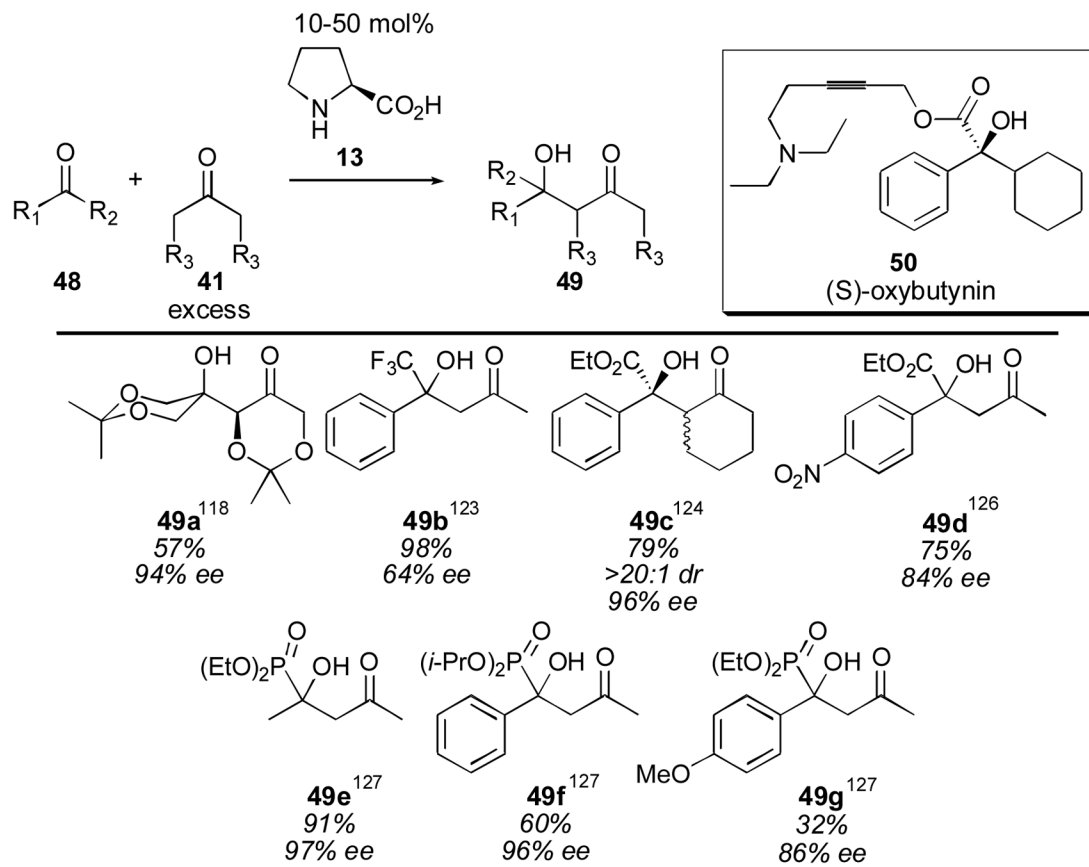
<sup>a</sup>References are given for each product as a superscript.

Table 4

Aldehyde donors in the proline-catalyzed aldol reaction.

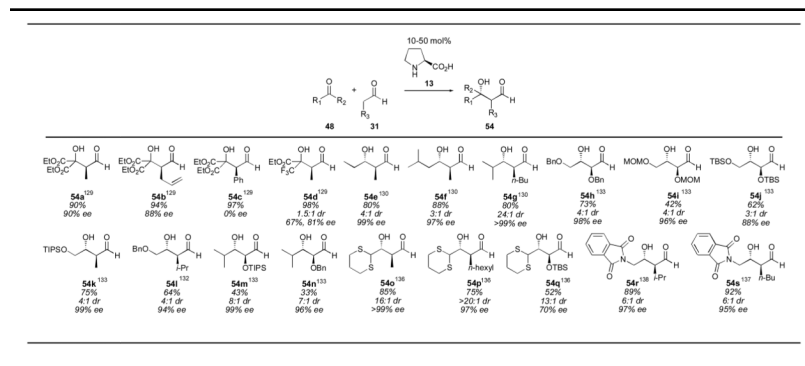
<sup>a</sup>References are given for each product as a superscript.

Table 5

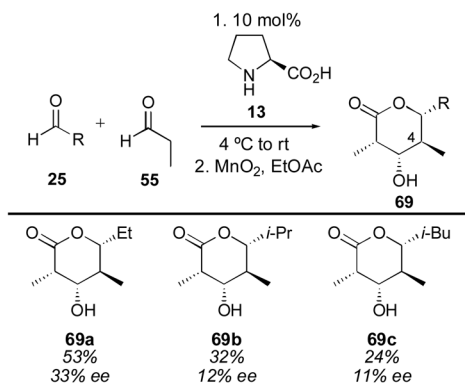
Pyranose formation with proline-catalysis.<sup>135</sup><sup>a</sup>Relative stereochemistry between C3, C4 and C4, C5 corrected.<sup>136</sup>

Table 6

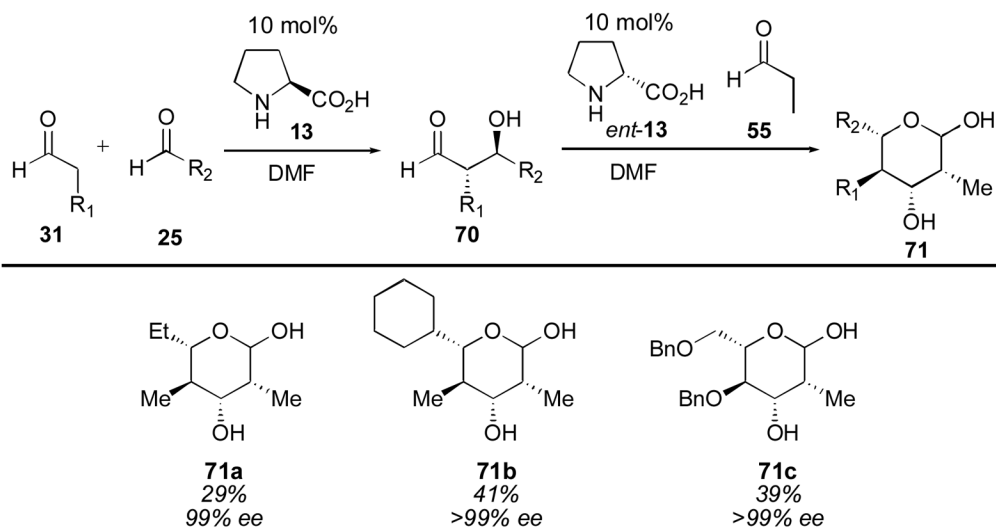
Two-step polyketide synthesis.<sup>139</sup>

Table 7

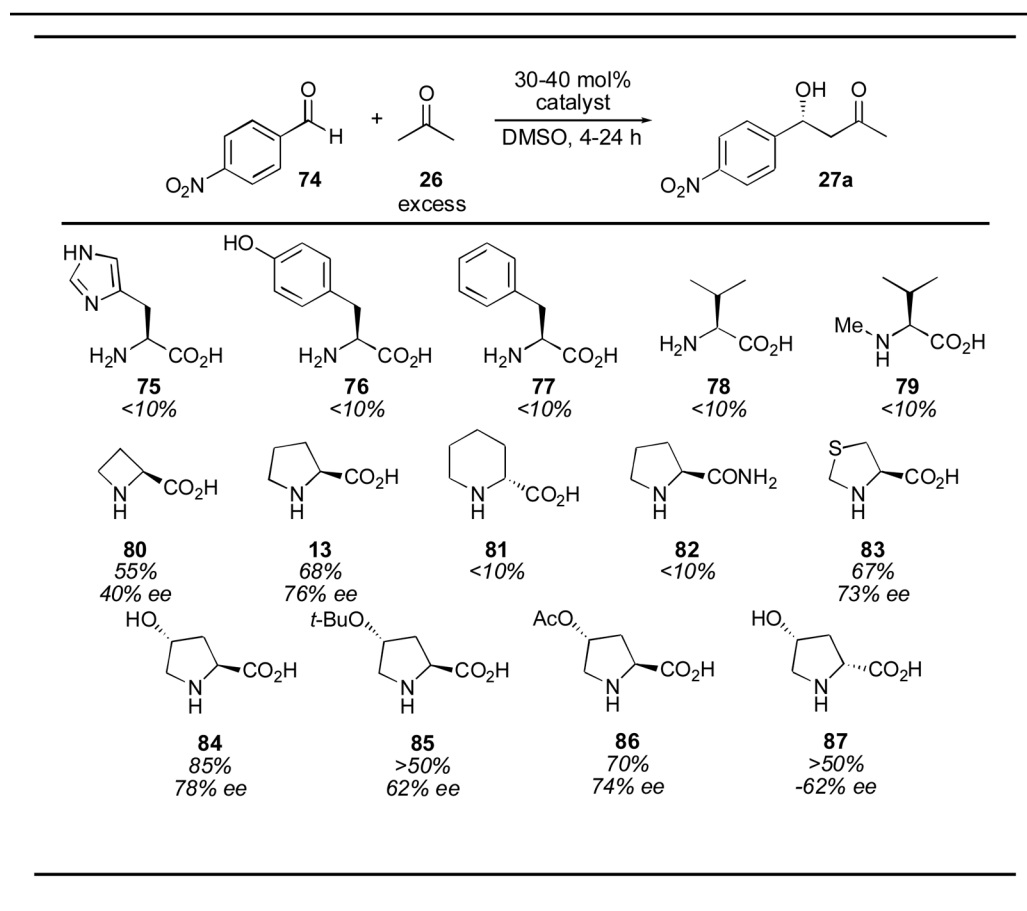
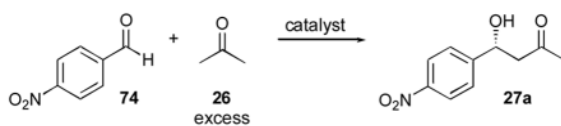
Initial catalyst screen for the acetone aldol reaction.<sup>65, 66</sup>

Table 8

Screen of amino acids and small peptides for the acetone aldol reaction.

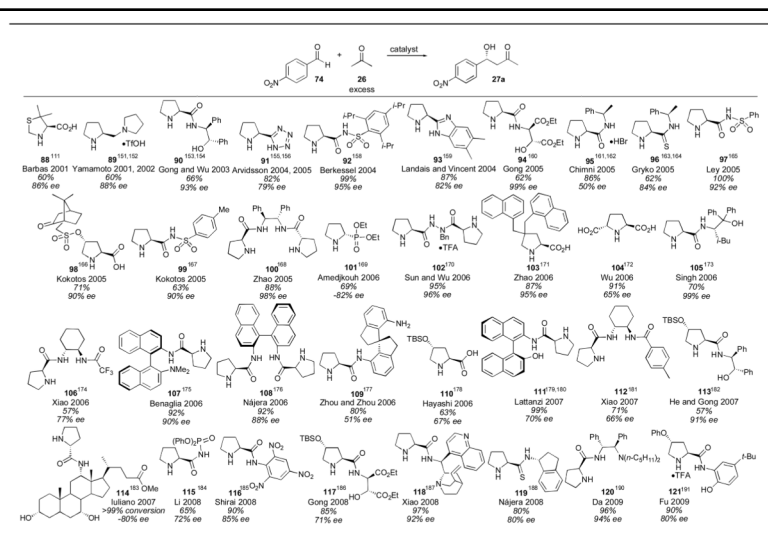


Catalyst	catalyst loading (mol%)	Yield (%)	ee (%)
L-Pro <sup>65</sup>	20	68	76
L-Asp <sup>142</sup>	20	35	40
L-Glu <sup>142</sup>	20	36	18
L-Thr <sup>142</sup>	20	37	42
L-Pro-L-Ala-NPh, HOAc <sup>146</sup>	20	88	38
4-NHBoc-L-Pro-L-Pro <sup>144</sup>	15	83	73
L-Pro-L-Ser <sup>143</sup>	30	87	77
L-Pro-L-ThrOTBS <sup>147</sup>	20	91	82
L-Leu-L-His <sup>145</sup>	30	87	71
4-NHBoc-L-Pro-L-Pro-L-Pro-L-Pro <sup>144</sup>	5	62	75
L-Pro-D-Ala-D-Asp-NH <sub>2</sub> <sup>148</sup>	10	73	70
L-Pro-L-Pro-L-Asp-NH <sub>2</sub> <sup>148</sup>	1	99	-80

<sup>a</sup>References are given for each product as a superscript.

Table 9

## Proline-based catalysts for the acetone aldol reaction



<sup>a</sup>References are given for each product as a superscript.



Table 10

Non-proline based catalysts for the acetone aldol reaction

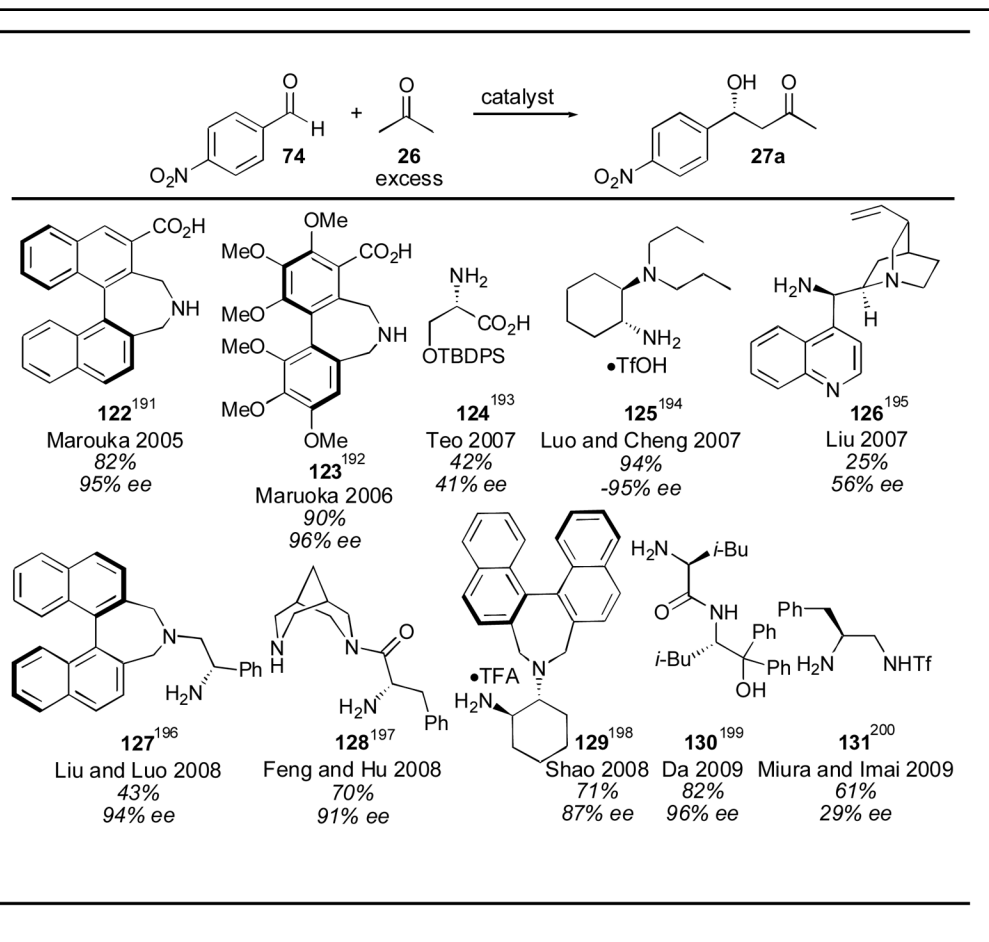
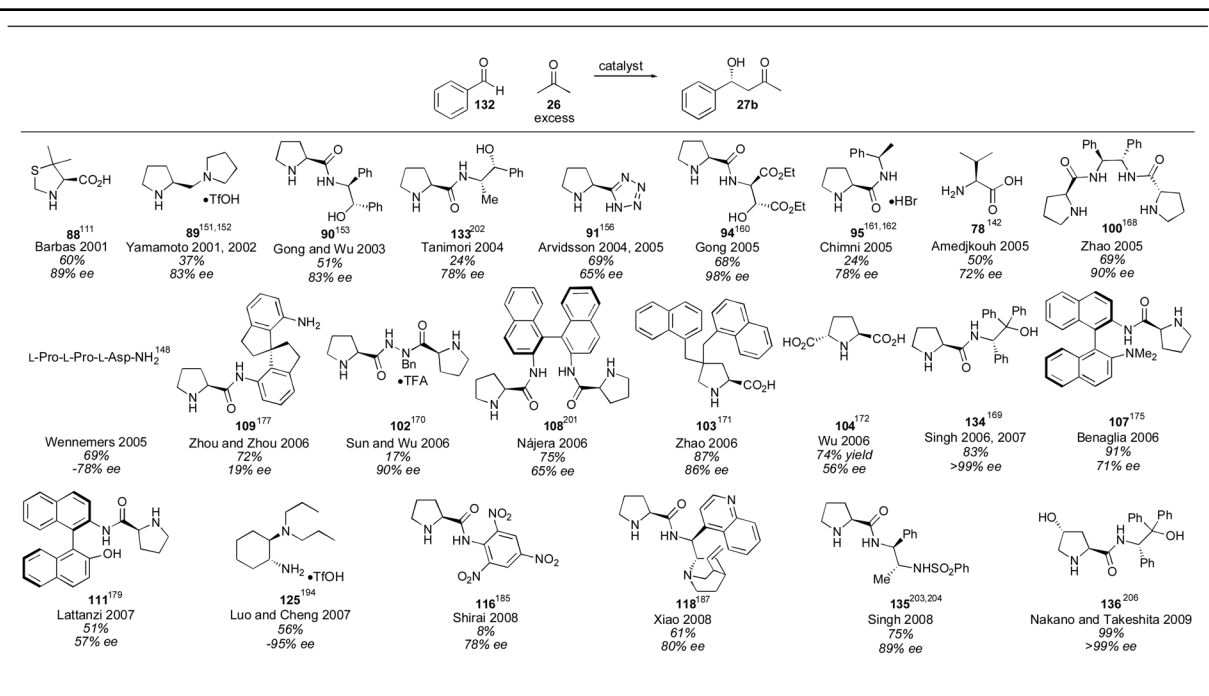
<sup>a</sup>References are given for each product as a superscript.

Table 11

Use of benzaldehyde for the acetone aldol reaction.



<sup>a</sup>References are given for each product as a superscript.

Table 12

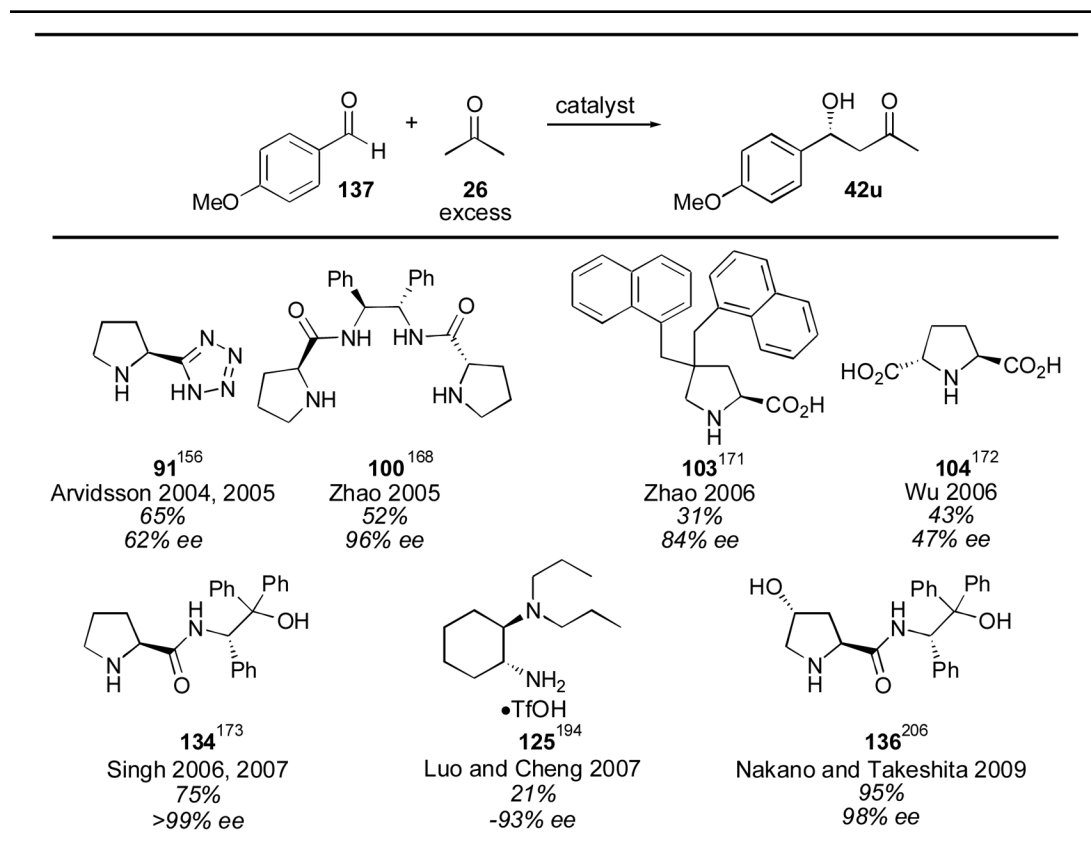
Use of *para*-methoxybenzaldehyde for the acetone aldol.<sup>a</sup>References are given for each product as a superscript.

Table 13

Catalysts examined for the acetone aldol with isobutyraldehyde.

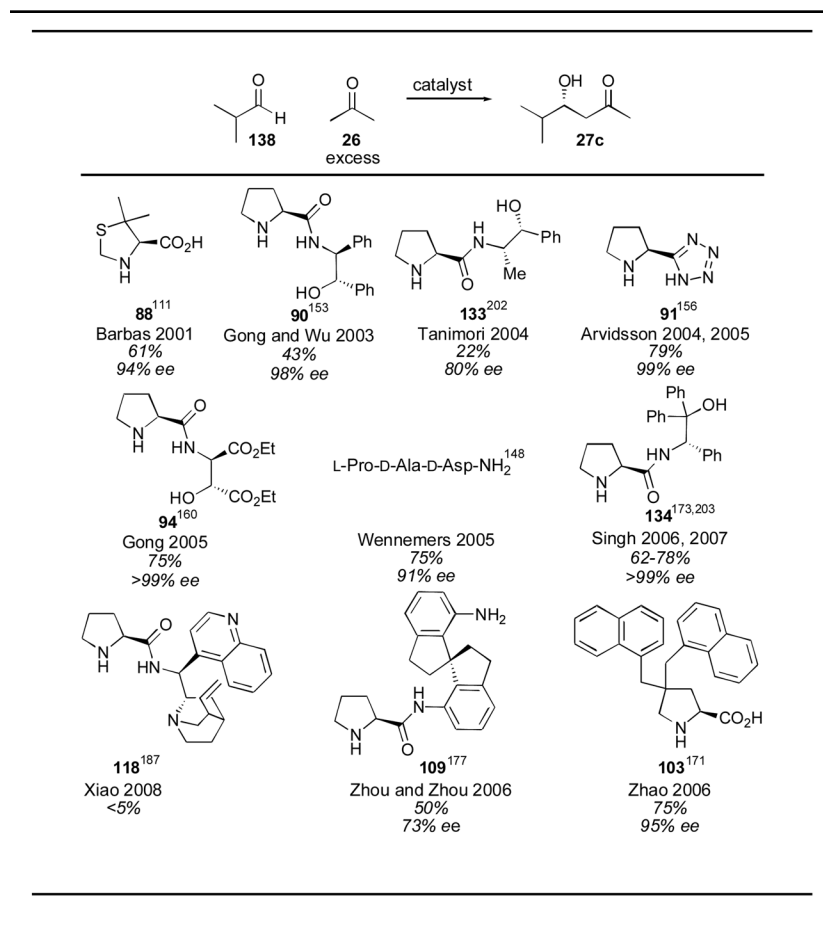
<sup>a</sup>References are given for each product as a superscript.

Table 14

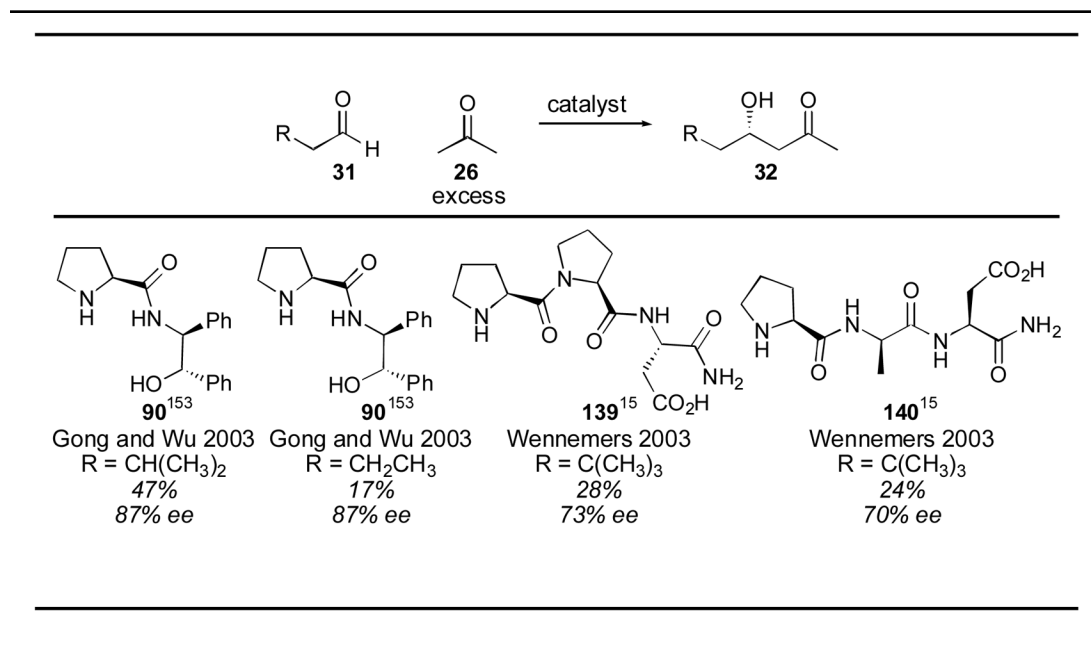
Aldol reactions with  $\alpha$ -unbranched aldehydes.<sup>a</sup>References are given for each product as a superscript.

Table 15

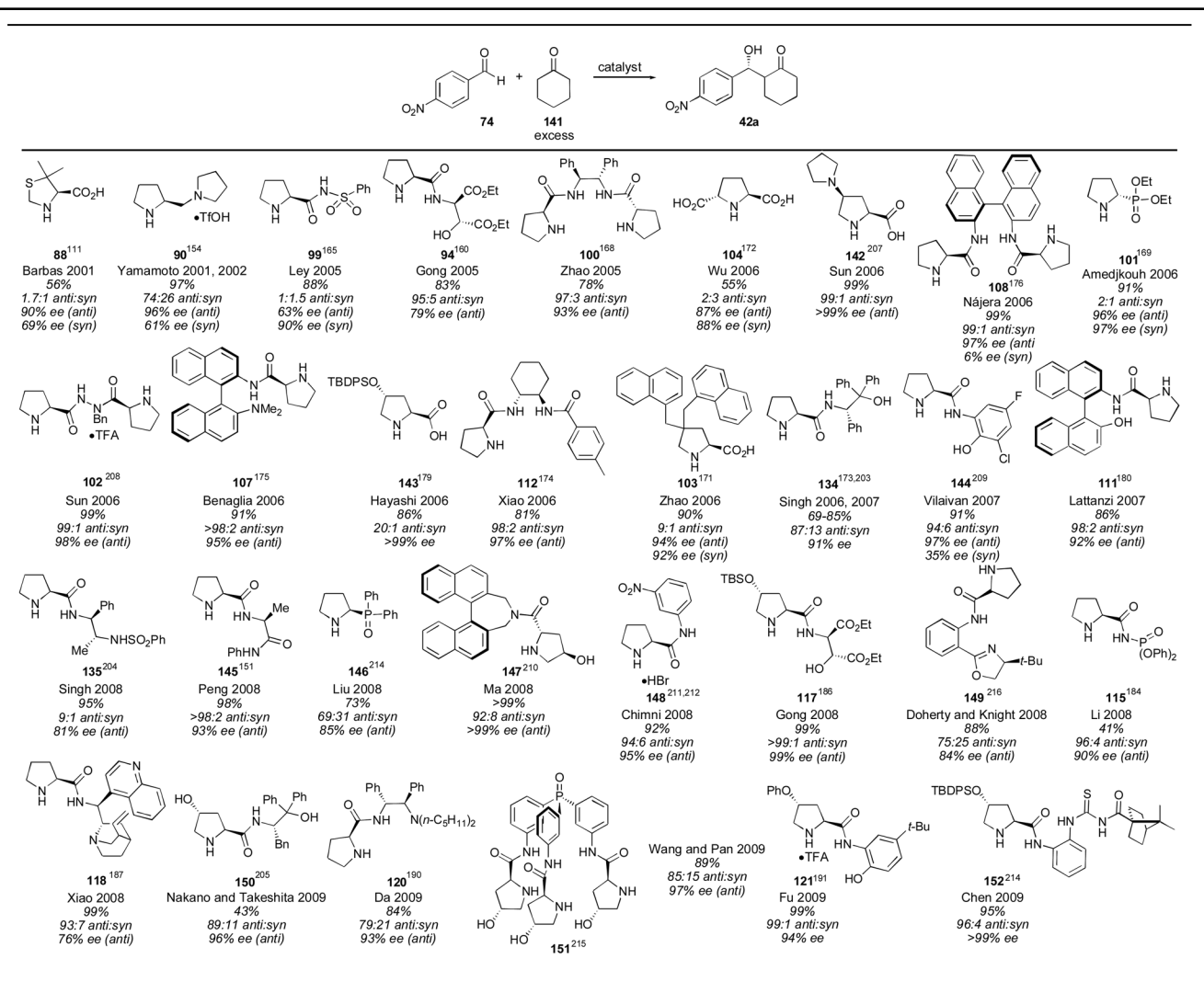
Catalysts for the aldol reaction of cyclohexanone with *para*-nitrobenzaldehyde.<sup>a</sup>References are given for each product as a superscript.

Table 16

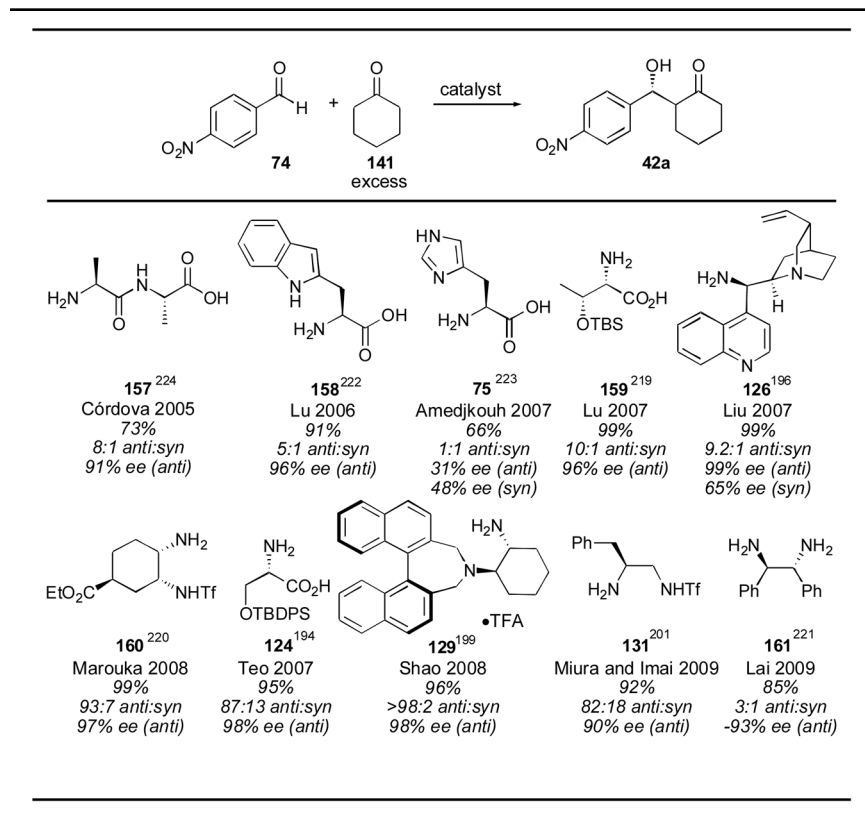
Non-proline derived catalysts for the aldol reaction of cyclohexanone with *para*-nitrobenzaldehyde.<sup>a</sup>References are given for each product as a superscript.

Table 17

Catalysts for less reactive aldehydes with cyclohexanone.

<p><b>143</b><sup>178</sup> Hayashi 2006 R = H 78% R = OMe 21% 13:1 anti:syn &gt;99% ee (anti)</p>	<p><b>107</b><sup>175</sup> Benaglia 2006, 2007 R = H 80% R = OMe 57% 99:1 anti:syn 93% ee (anti)</p>	<p><b>102</b><sup>207</sup> Sun 2006 R = H 84% R = OMe 39% 94:6 anti:syn 92% ee (anti)</p>	<p><b>142</b><sup>208</sup> Sun 2006 R = H 81% R = OMe 28% 97:3 anti:syn 99% ee (anti)</p>	<p><b>108</b><sup>176</sup> Nájera 2006 R = H 99% R = OMe 47% 4.3:1 anti:syn 90% ee (anti) 72% ee (syn)</p>	<p><b>158</b><sup>222</sup> Lu 2006 R = H 47% R = OMe 89% ee (anti)</p>	<p><b>105</b><sup>173</sup> Singh 2006, 2007 R = H 69-85% R = OMe 69-85% 94:6 anti:syn &gt;99% ee (anti)</p>
<p><b>162</b><sup>41</sup> Armstrong 2007 R = H 84% 9:1 anti:syn 94% ee (anti)</p>	<p><b>112</b><sup>174</sup> Xiao 2007 R = H 72% 85:15 anti:syn 83% ee (anti)</p>	<p><b>126</b><sup>195</sup> Liu 2007 R = H 31% R = OMe 19% 1:1 anti:syn 86% ee (anti) 3.7:1 anti:syn 89% ee (anti) 54% ee (syn) 14% ee (syn)</p>	<p><b>144</b><sup>208</sup> Vilaivan 2007 R = H 68% 88:12 anti:syn 90% ee (anti) 29% ee (syn)</p>	<p><b>159</b><sup>219</sup> Lu 2007 R = OMe 54% 5:1 anti:syn 93% ee (anti)</p>	<p><b>123</b><sup>191</sup> Teo 2007 R = H 63% R = OMe 41% 86:14 anti:syn 92% ee (anti)</p>	<p><b>148</b><sup>208</sup> Chimni 2008 R = H 62% 87:13 anti:syn 82% ee</p>
<p><b>135</b><sup>204</sup> Singh 2008 R = H 82% R = OMe 60% 98:2 anti:syn 96% ee (anti)</p>	<p><b>145</b><sup>146</sup> Peng 2008 R = H 98% 81:19 anti:syn 87% ee (anti)</p>	<p><b>117</b><sup>186</sup> Gong 2008 R = H 75% &gt;99:1 anti:syn 92% ee (anti)</p>	<p><b>149</b><sup>216</sup> Doherty and Knight 2008 R = H 59% 83:17 anti:syn 7% ee (anti)</p>	<p><b>160</b><sup>220</sup> Marouka 2008 R = H 53% 96:4 anti:syn 98% ee (anti)</p>	<p><b>129</b><sup>198</sup> Shao 2008 R = H 61% R = OMe 23% 94:6 anti:syn 94% ee (anti)</p>	<p><b>120</b><sup>190</sup> Da 2009 R = OMe 10% 92:8 anti:syn 79% ee (anti)</p>
<p><b>150</b><sup>205</sup> Nakano and Takeshita 2009 R = H 70% 96:4 anti:syn 96% ee (anti)</p>	<p><b>151</b><sup>215</sup> Wang and Pan 2009 R = H 68% R = OMe 43% 78:2 anti:syn 87% ee (anti) 83:17 anti:syn 95% ee (anti)</p>	<p><b>131</b><sup>200</sup> Miura and Imai 2009 R = H 23% R = OMe 12% 84:16 anti:syn 89% ee (anti)</p>	<p><b>161</b><sup>221</sup> Lai 2009 R = H 15% 87:13 anti:syn 92% ee (anti)</p>	<p><b>121</b><sup>191</sup> Fu 2009 R = H 72% R = OMe 26% 92:8 anti:syn 84% ee (anti)</p>	<p><b>152</b><sup>214</sup> Chen 2009 R = H 55% R = OMe 26% 97:3 anti:syn 94% ee (anti) 85:15 anti:syn 80% ee (anti)</p>	

<sup>a</sup>References are given for each product as a superscript.



Table 18

Aldol reactions with alkyl aldehydes.

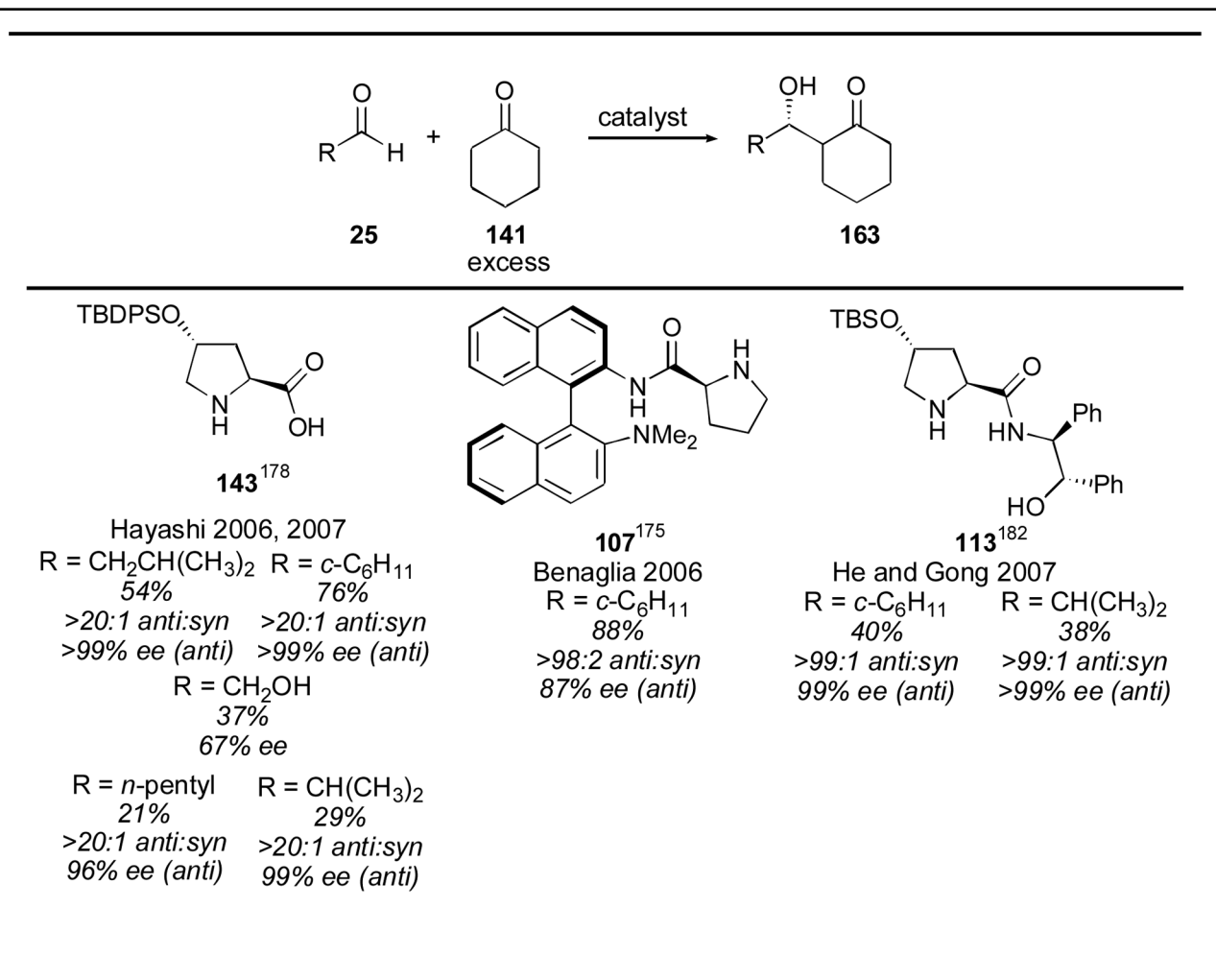
<sup>a</sup>References are given for each product as a superscript.

Table 19

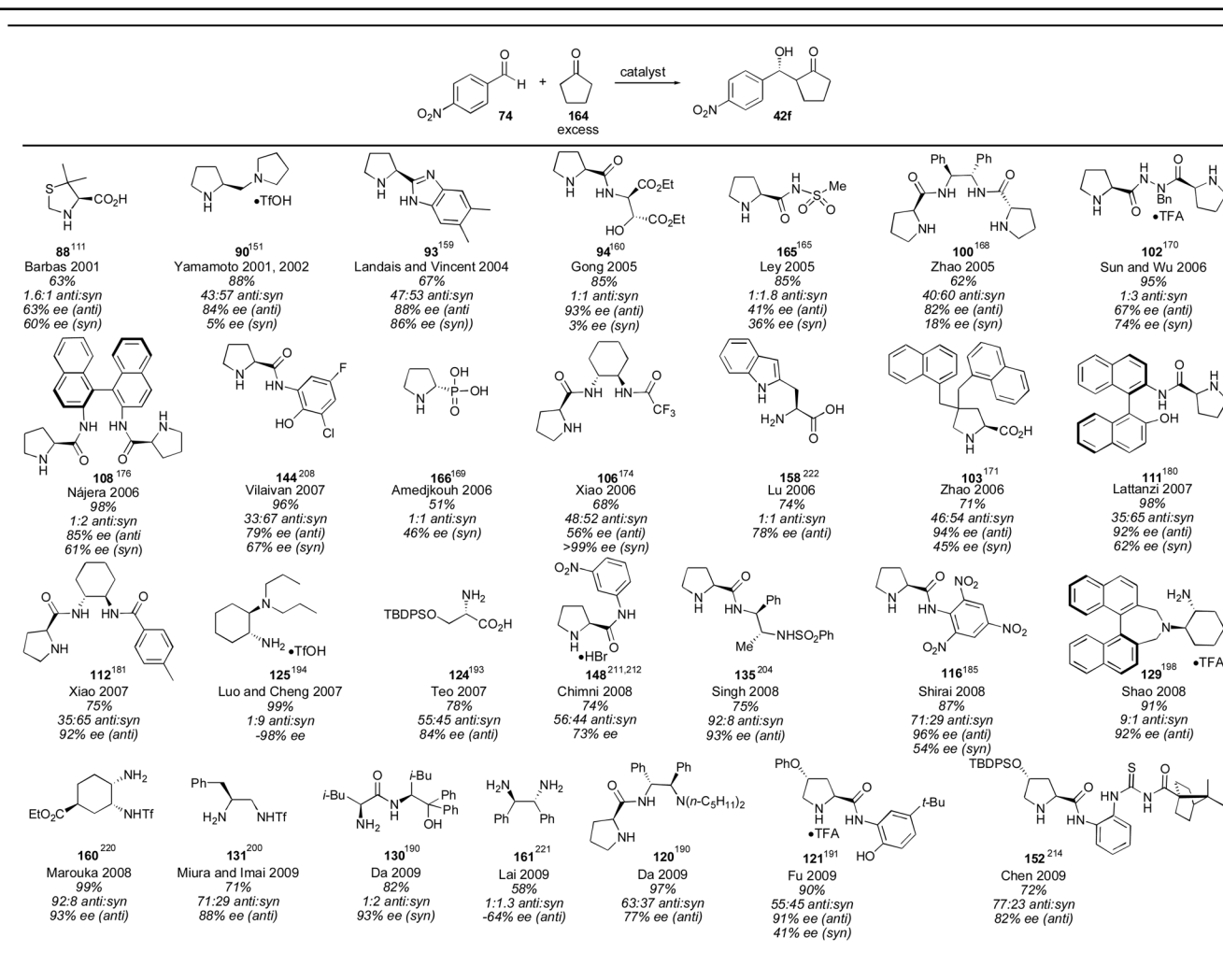
Catalysts used in the aldol reaction between cyclopentanone and *para*-nitrobenzaldehyde.<sup>a</sup>References are given for each product as a superscript.

Table 20

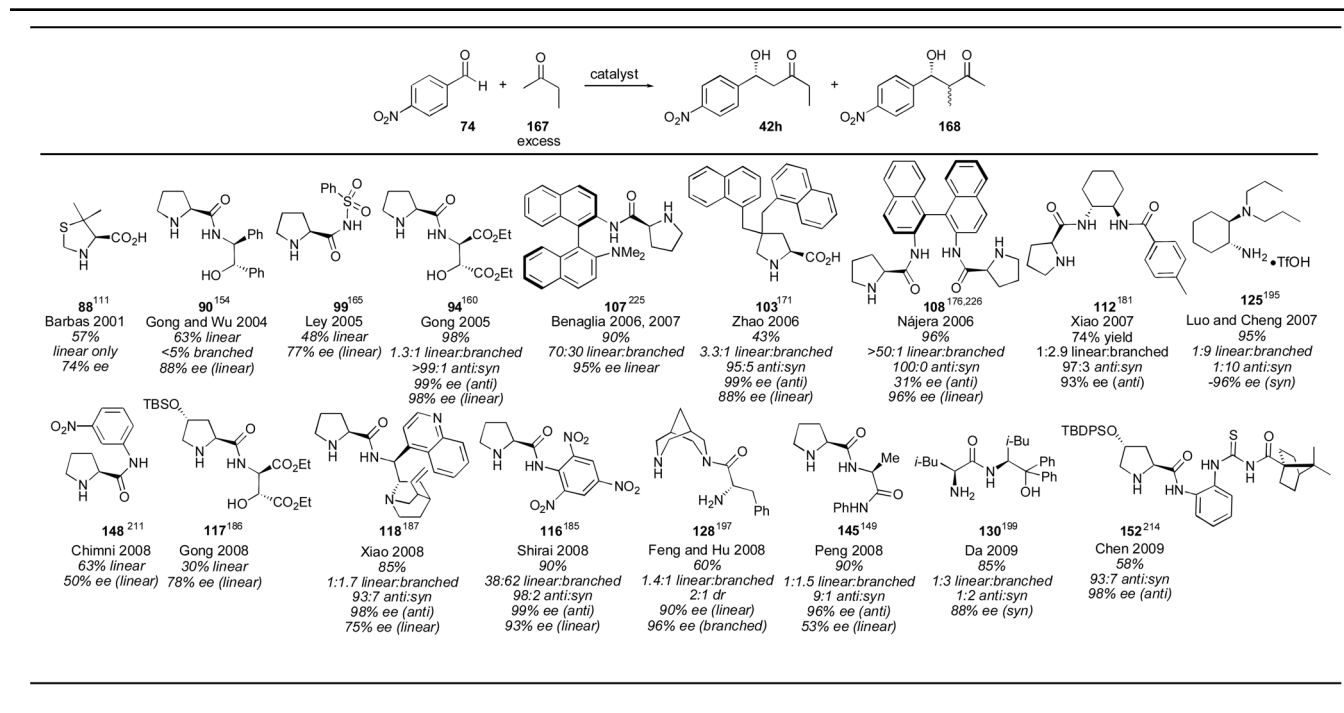
Catalysts used in the aldol reaction between 2-butanone and *para*-nitrobenzaldehyde.<sup>a</sup>References are given for each product as a superscript.

Table 21

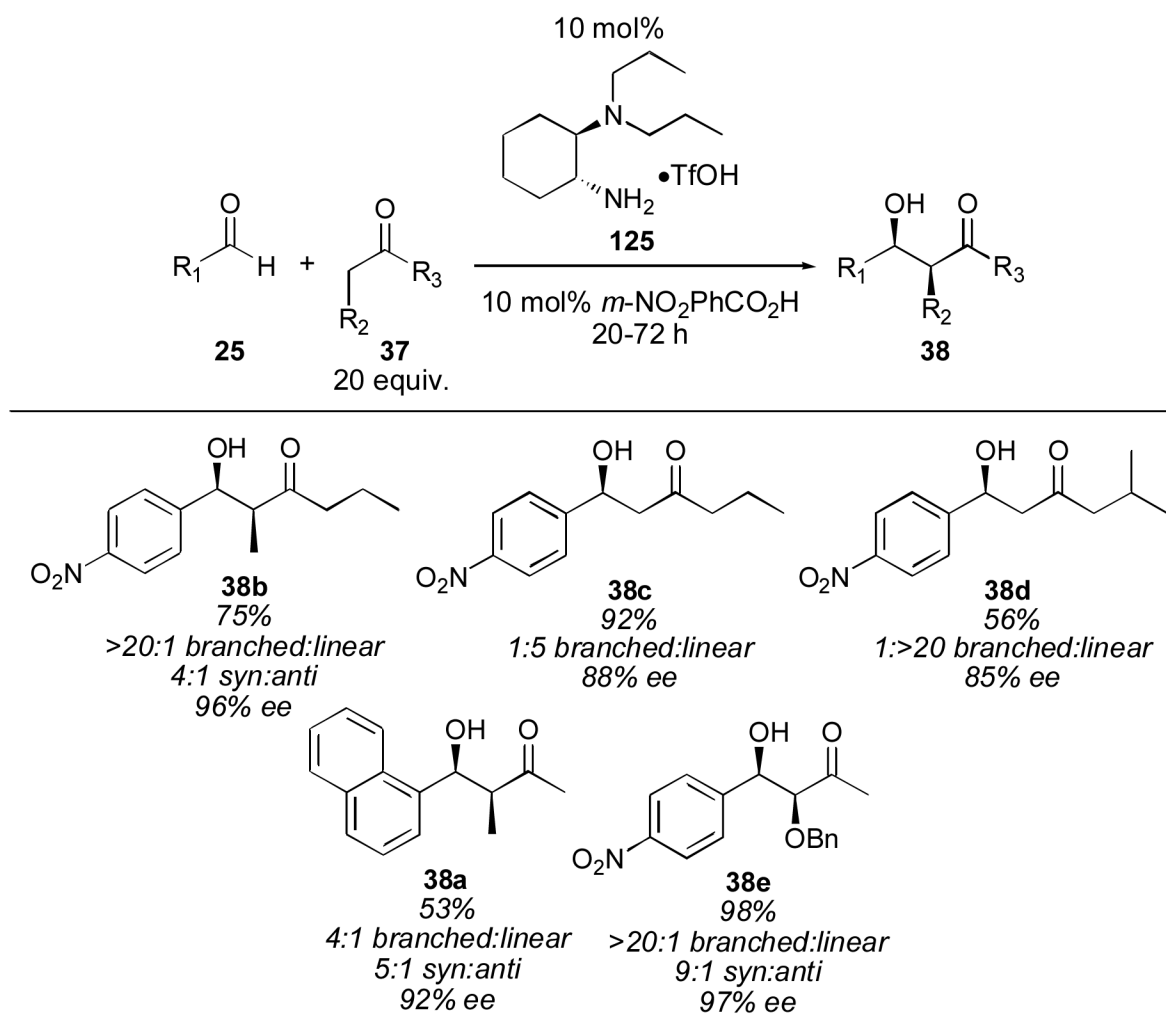
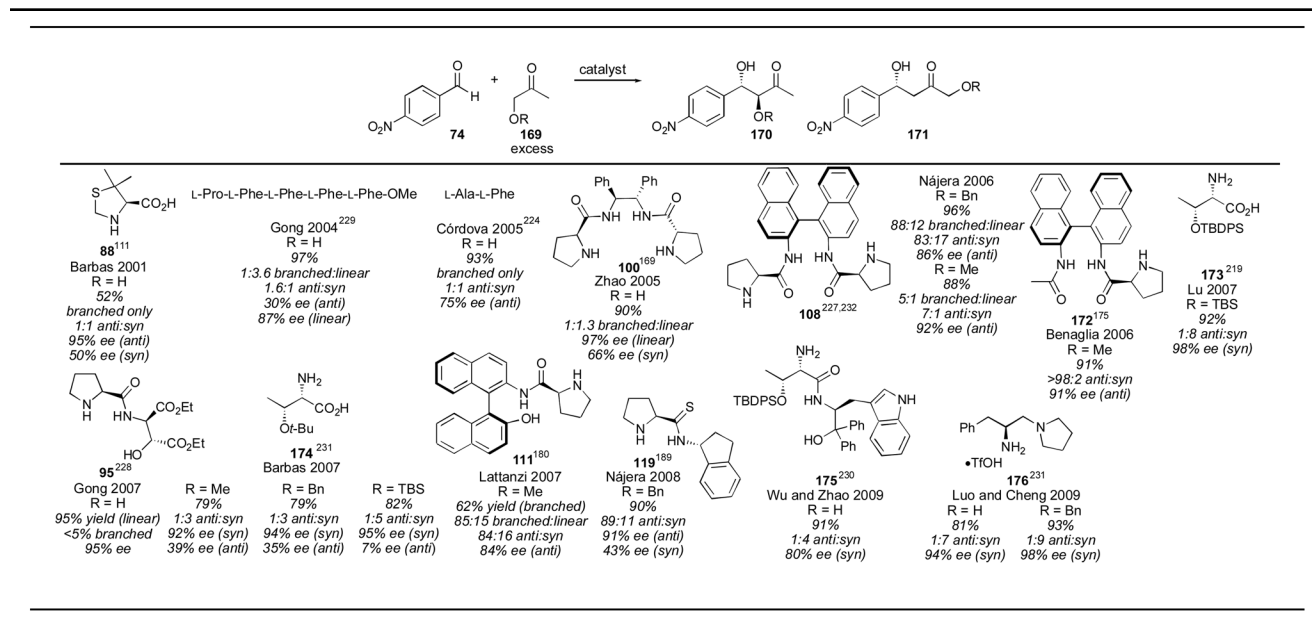
Lou and Cheng's *syn* selective aldol.<sup>195</sup>

Table 22

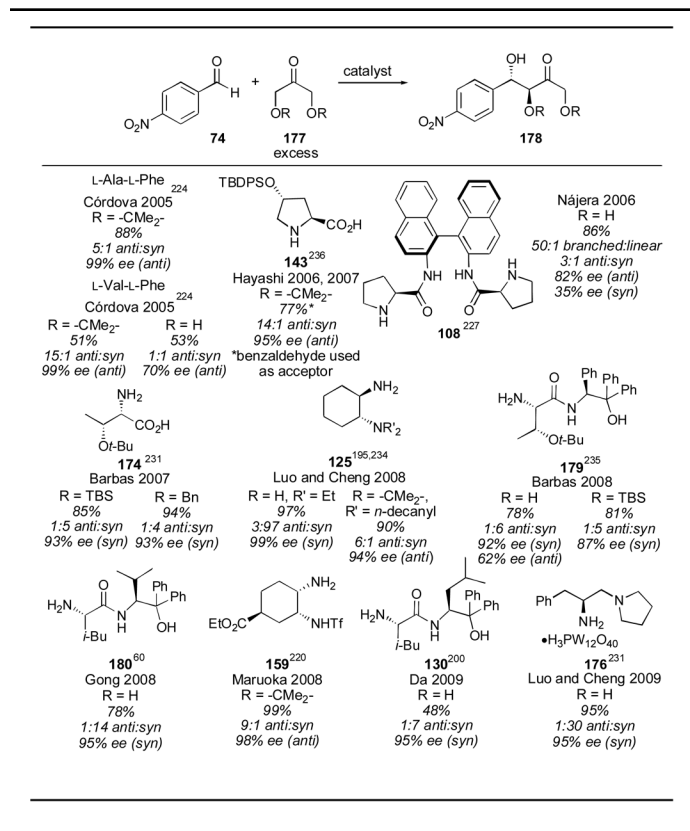
Hydroxyacetone aldol reactions and protected derivatives.



<sup>a</sup>References are given for each product as a superscript.

Table 23

## Dihydroxyacetone aldol reactions.



<sup>a</sup>References are given for each product as a superscript.

Table 24

Halogenated and sulfur-containing substrates.

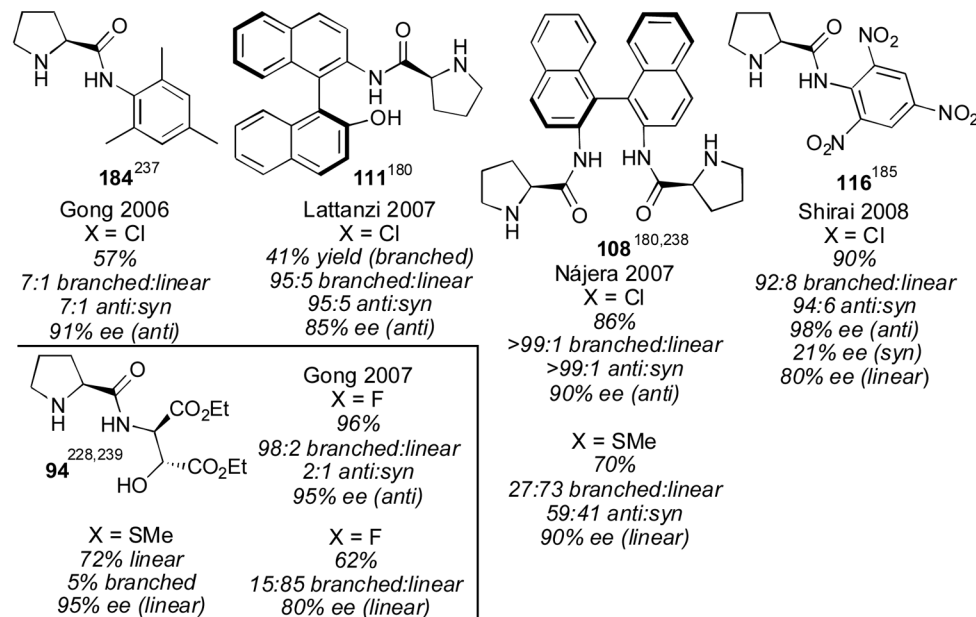
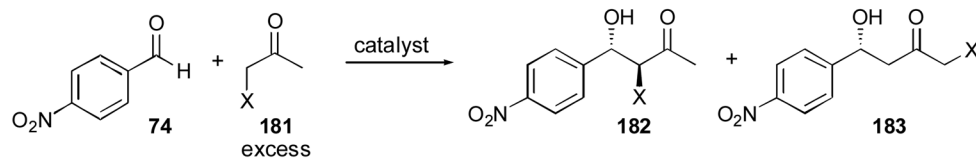
<sup>a</sup>References are given for each product as a superscript.

Table 25

Ketone electrophiles in the acetone aldol reaction.

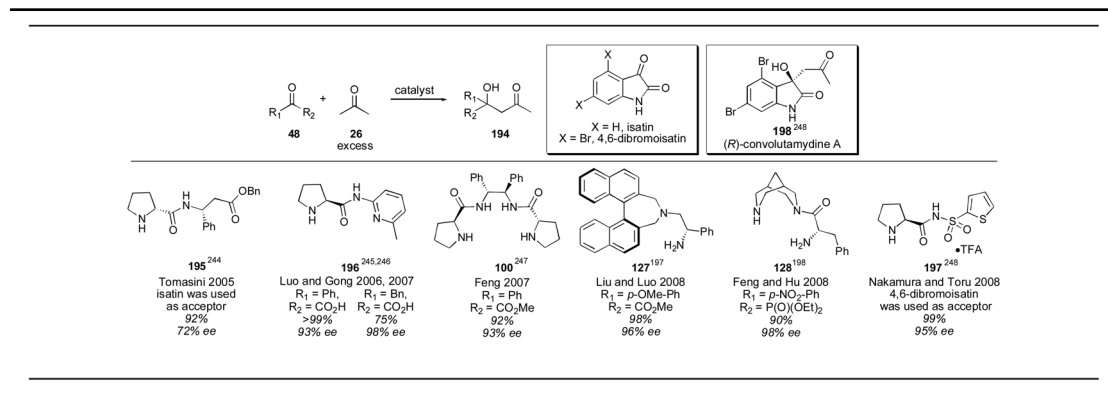
<sup>a</sup>References are given for each product as a superscript.



Table 26

Aldehyde donors in self-aldol and cross-aldol reactions.

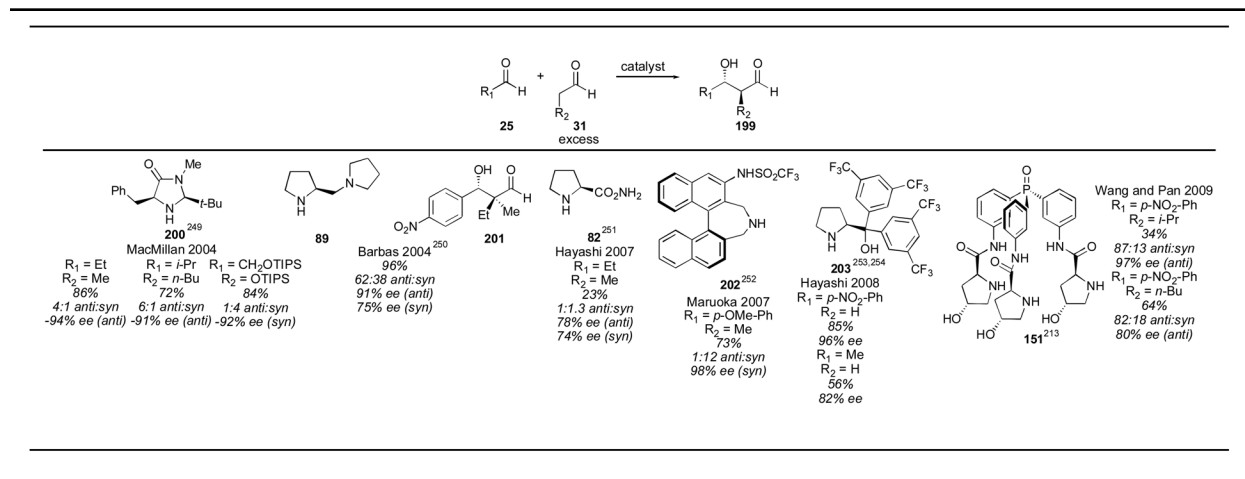
<sup>a</sup>References are given for each product as a superscript.

Table 26

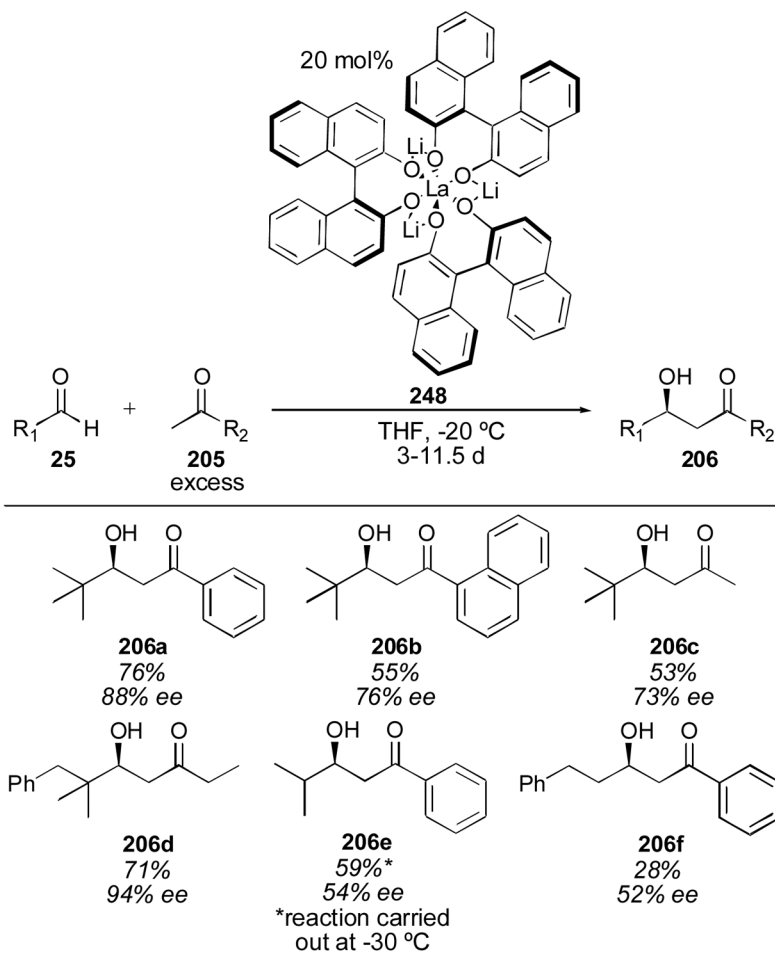
Lanthanum-lithium-BINOL catalyzed direct aldol reactions.<sup>320</sup><sup>a</sup>References are given for each product as a superscript.

Table 27

Improved activity of potassium modified catalyst.<sup>321</sup>