

# Recent Advancement in H<sub>8</sub>-BINOL Catalyzed Asymmetric Methodologies

Rajpratap Kshatriya\*

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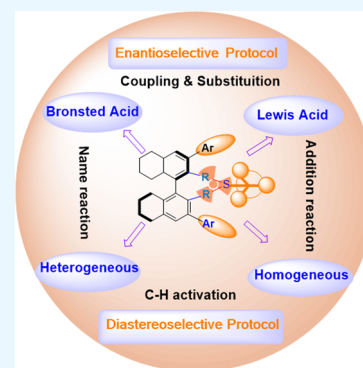
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**ABSTRACT:** H<sub>8</sub>-BINOL, a partially reduced form of BINOL, is widely employed in a broad array of organocatalyzed asymmetric methodologies. Over the last 25 years, asymmetric organocatalysis has witnessed an incredible improvement, and an advancement still continues to get a single enantio-enriched product. The broad-spectrum applications of H<sub>8</sub>-BINOL organocatalyst in C–C bond formation, C-heteroatom bond construction, name reactions, pericyclic reactions, and one pot and multicomponent reaction are attracting the attention of researchers. A diversified unique H<sub>8</sub>-BINOL-based catalyst has been synthesized and screened for catalytic activity. In this Review we frame out the H<sub>8</sub>-BINOL catalyzed novel discoveries from the last two decades.



## 1. INTRODUCTION

H<sub>8</sub>-BINOL constitutes newly designed catalysts to control stereochemistry of products. Owing to the economic and scientific significance of asymmetric methodology, enormous amounts of organocatalyst were screened.<sup>1</sup> Among the pool of organocatalysts, H<sub>8</sub>-BINOL-based organocatalysts are interesting to control the stereochemistry of the product by their unique orientation (Figure 1) in the transition state.<sup>2</sup> The sterically controlled transition state guides the researcher to design new catalysts to use in varied asymmetric chemical transformations.<sup>3</sup>

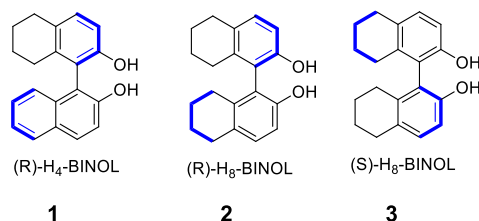


Figure 1. H<sub>4</sub>-BINOL and H<sub>8</sub>-BINOL.

H<sub>8</sub>-BINOL-based catalysts have evidently attracted the attention of the scientific community because of their remarkable chemical properties (Bronsted & Lewis acid, base, and dual activity) and wide range of pharmaceutical privileges. H<sub>8</sub>-BINOL with diversified structural modifications have found applications in several fields such as asymmetric C–H activation, asymmetric C–C & C-heteroatom bond formation, rearrangement reactions, cycloaddition reactions, photoredox

catalysis reactions, asymmetric hydrogenations, addition reactions, elimination reactions, and substitution reactions, as well as in well-known name reactions<sup>4</sup> summarized in Figure 2.

Biomolecules and enzymes in biological systems are frequently enantioselective to their binding ligands. All through designing bioactive scaffolds to interact with these targets,

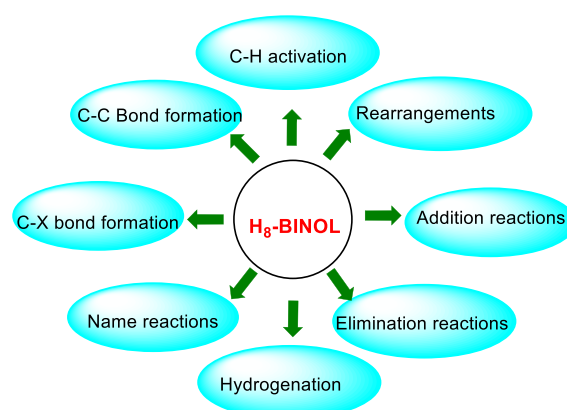


Figure 2. Unique applications of H<sub>8</sub>-BINOL.

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stereoselectivity is an important part. Attention is given while exploring structure since chirality is increasingly important. Binding affinity for a chiral drugs can bind targets with unique selectivity. A market survey depicts that about 80% of drugs (4–9) are chiral<sup>5</sup> (Figure 3).

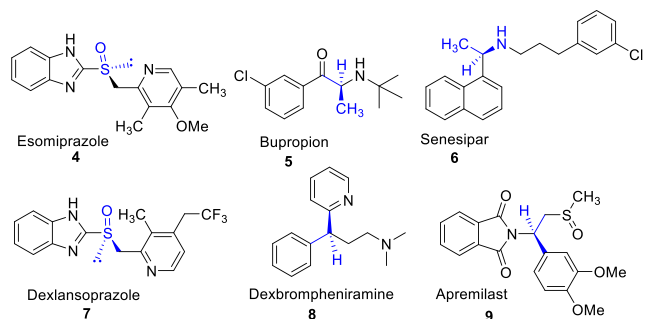


Figure 3. Potent blockbuster chiral drugs.

Axially chiral H<sub>8</sub>-BINOL catalysts are more flexible than BINOL catalysts. Due to the flexibility in structure they can mold themselves in such a way in the transition state to install excellent enantioselectivity. Chiral BINOL catalyst (13) reduced to H<sub>8</sub>-BINOL (2) by platinum/palladium catalyst.<sup>6</sup> Chiral H<sub>8</sub>-BINOL (2-3), H<sub>8</sub>-BINOL phosphoric acid (10), and phosphoramides (11-12) have been widely applied in the past couple of years. Representative catalysts (10–12) with acidic functional groups are shown in (Figure 4).

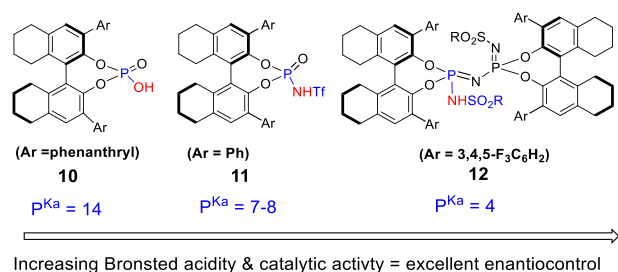


Figure 4. H<sub>8</sub> BINOL catalysts.

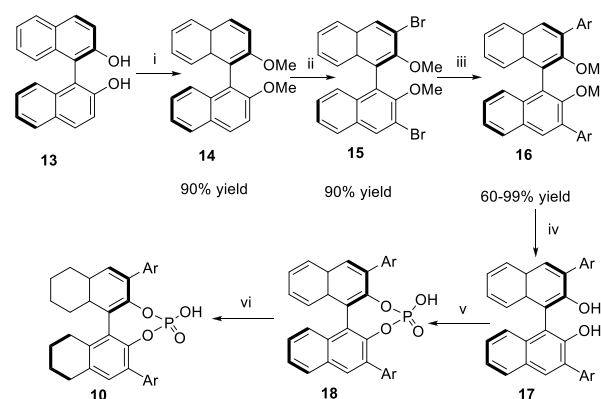
## 2. SYNTHESIS OF H<sub>8</sub>-BINOL MOLECULES

H<sub>8</sub>-BINOL is a reduced form of BINOL organocatalyst possessing the more excellent key topographies of the completely aromatic complements of precursor BINOL. It is distinguished from BINOL by different solubilities, acidities, and racemization outlines as well as different geometries and bite angles. The critical widespread scenerios of this scaffold make it of exact importance to asymmetric organocatalysis. Mostly, the high degree of tunability, conformational rigidity, and C<sub>2</sub> symmetry of H<sub>8</sub>-BINOL 2, make it a comparatively more versatile catalyst. In accumulation of phosphate groups, other types of functionalities can be affixed to the H<sub>8</sub>-BINOL scaffold to tune its Bronsted acidity like its counterpart precursor fully aromatic BINOL. H<sub>8</sub>-BINOL-based *N*-triflyl phosphoramides and disulfonimides have settled as more powerful alternatives to BINOL-CPAs (Figure 4).

Chiral H<sub>8</sub>-BINOL with metals like titanium, calcium, and aluminum and other metals forms complexes to employ as a chiral Lewis acid which are uniquely used for enantioselective

synthesis (Figure 4). H<sub>8</sub>-BINOL catalysts are synthesized from BINOL 13 by reduction. Preparation is accomplished by multistep synthesis of BINOL and its reduction. The first step comprises alkylation of the hydroxy group of BINOL followed by selective bromination or iodination using *n*-BuLi. The second step is the Suzuki coupling reaction of dihalogenated BINOL with various substituted aromatic boronic acids. Finally, 2,2' substituted BINOL is subjected to deprotection converting OMe to hydroxy group by using tribromoboron to get a compound with free hydroxy groups. These hydroxy groups at 2,2' are used for installation of phosphoric acid. After installation of acidic functionalities the BINOL molecule is subjected to partial hydrogenation using platinum oxide at room temperature<sup>7</sup> (Scheme 1).

**Scheme 1. Reagents and Conditions:** (i) MeOH, acetone, reflux, 6 h; (ii) I<sub>2</sub>, THF, −78 °C, 3 min; (iii) Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %), TMEDA, ArB(OH)<sub>2</sub> (3 equiv), THF, K<sub>2</sub>CO<sub>3</sub> (1 M), reflux, 3 h; (iv) BBr<sub>3</sub>, DCM, 0 °C; (v) POCl<sub>3</sub>, Pyridine, 80 °C, H<sub>2</sub>O, HCl, 6 M, 100 °C; (vi) H<sub>2</sub>, Pd/C (7 mol %), EtOH, 70 °C, 1 h



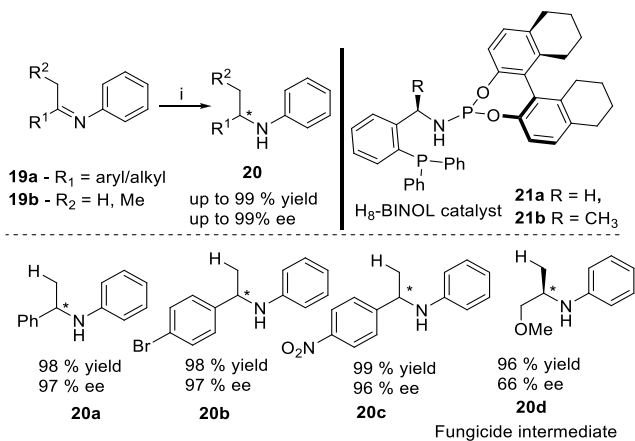
## 3. APPLICATIONS OF H<sub>8</sub>-BINOL MOLECULE

The development in synthesis of a varied scaffold with innumerable functionalities of enantiopure and thermally stable (*R*)- and (*S*)-H<sub>8</sub>-BINOL catalysts 2–3 and 10–12 initiates a key milestone in the field of asymmetric organocatalysis. Principally, a great assortment of chiral binaphthyl-based chiral phosphorus acid compounds 10–12, H<sub>8</sub>-BINOL installed metal complexes having Lewis acid nature, have been given significant weight owing to their adaptability as ligands in enantioselective metal catalyzed reactions, addition reactions, and substitution reactions. The application of these organocatalysts for the preparation of optically active products with the anticipated enantiopurity has been widely explored. This Review highlights that in addition to phosphate, other sorts of functionalities can be affixed to the BINOL scaffold to augment the Bronsted acidity of the catalyst. For example, BINOL-based *N*-triflyl phosphoramides and disulfonimides, dual functionalities as Lewis acid & base, and metal complexes with Lewis acidity have recently been developed as more powerful alternatives to CPAs (Figure 4). The utmost applicable concepts and books concerning wide-ranging synthetic reactions for binaphthyl-based organocatalysts having acidic and basic functionalities have been published and added in this review. Numerous natural building blocks have been extensively used for the development of chiral ligand libraries, though intrinsic

margins were frequently executed by the natural presence of a single enantiomer in the last few decades. Still, the nascent synthetic availability of H<sub>8</sub>-BINOL in both (R) and (S) enantiomerically pure forms has guided the scientific community towards a massive development in synthesis of new materials and chiral ligands as organocatalyst (Figure 3). Currently, BINOL and more preferably the partially hydrogenated H<sub>8</sub>-BINOL (Figure 4) are considered typical and unique ligands, systematically used in a range of asymmetric catalytic reactions. The most selective ones are carbon–carbon and carbon–heteroatom bond formation reactions, asymmetric  $\alpha$ -allylation and alkylation, hydrogenation, and name reactions including Mannich and Strecker, cycloaddition like Diels–Alder, Aldol, Friedel–Crafts, Robinsons annulation, Michael addition and olefin methathesis, asymmetric C–H activation reactions as well as in heteroatom-transfer reactions, such as epoxidation and Baeyer–Villiger, among rearrangement reactions. The imperious need to develop active and selective systems with the prospect of catalyst recycling and, by the fact that there are no reviews covering this subject, exhaustive examples of the preparation of functionalized ligands is engrossing.<sup>8</sup>

Hu and his group (Scheme 2) invented a reaction catalyzed with iridium metal and H<sub>8</sub>-BINOL ligand (21a–21b) for

**Scheme 2. Reagents and Conditions:** (i) Ir[CODCl<sub>2</sub>]<sub>2</sub> (0.5 mol %), catalyst 21a–b (1.1 mol %), KI (5 mol %), H<sub>2</sub> (20 bar), CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h



enantioselective hydrogenation of sterically hindered *N*-arylimines 19a and 19b. Phosphoramidite ligands (21a–21b) have been developed for utilization in enantioselective hydrogenation. The electron donating and withdrawing groups of the phenyl ring of the substituent exhibited a partial impact on the enantioselectivity. Methyl 2-(2,6-dimethylphenylamino)propanoate 20d can be used as an intermediate for the preparation of the chiral herbicide (1*S*)-Metolachlor. Their process optimization depicts that KI is a key additive in the presence of dichloromethane as the solvent. The catalytic system employed by Hu and his group gave high enantioselectivities up to 99%. The reduced products are 20a–20c from the hydrogenation of a variety of sterically hindered *N*-arylimines.<sup>9</sup>

Antilla and his group (Scheme 3; Figure 5) brilliantly developed a protocol utilizing an organocatalyst, a 4-*tert*-butyl phenyl substituted (R)-H<sub>8</sub>-BINOL calcium phosphate 25, for enantioselective amination of 3-aryl-2-benzofuranone with dibenzylazo dicarboxylate 23. The appeal of the green protocol

**Scheme 3. Reagents and Conditions:** (i) Catalyst 25 (1 mol %), trifluoromethylbenzene, 4 Å molecular sieves, 30 min, rt

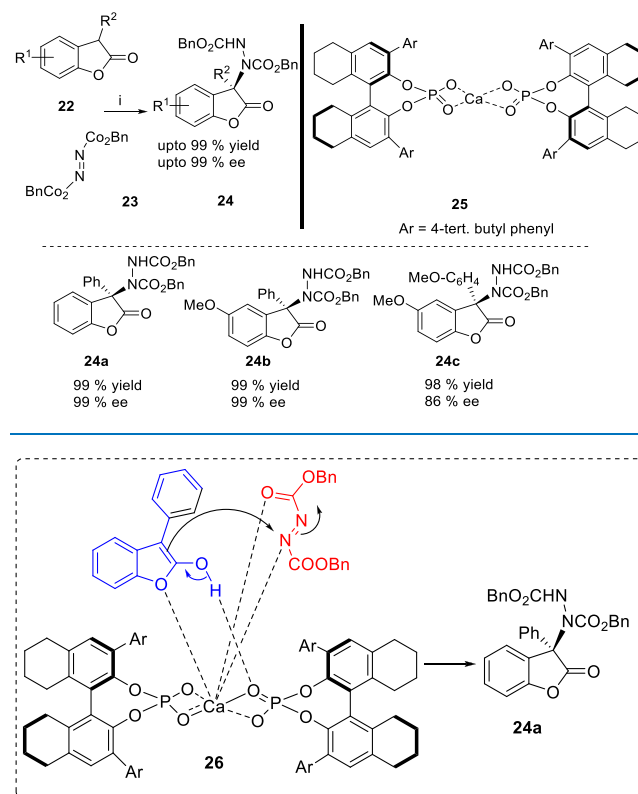
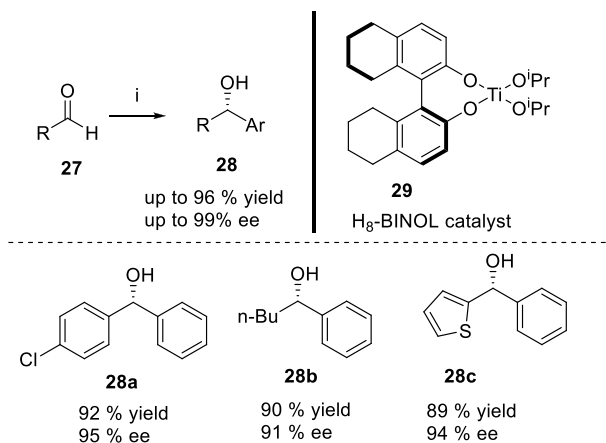


Figure 5. Mechanism of the reaction: Scheme 3.

is the formation of a C–N bond  $\alpha$  to the carbonyl group. The product of this reaction, chiral 3-amino-2-benzofuranone, is an intermediate for medicinally important products like (–) fumigycin (antibacterial), sorbicillactone A (antileukemic), and hopeahainol A (acetylcholinesterase inhibitor). The process optimization study reported trifluoromethylbenzene as a best solvent along with molecular sieves of 4 Å. The reaction has broad substrate scope, requires short reaction times (30 min), and requires a relatively low catalyst loading (1–10 mol %). This conversion is superficial via intermediate 26 having a high degree of atom economy, which gave products 24a–24c with good yields and high enantioselectivities (up to 99%). This reaction has excellent ee and a broad substrate scope with mild reaction conditions.<sup>10</sup>

Asymmetric aryl addition reactions for the synthesis of chiral alcohol 28 were reported by Gau and his group (Scheme 4). Addition of triaryl aluminum in THF solvent to aldehydes 27 catalyzed by the Ti(IV) catalyst of (R)-H<sub>8</sub>-BINOL 29 produced 28 with varied substituents. In this protocol, substituted arylaluminum reagents were used to afford chiral alcohols 28a–28c in excellent enantioselectivities (up to 97%). The catalytic system was applied to the most diversified aldehydes with electron donating and withdrawing groups. Moreover, diarylmethanols 28 in both R- and S-configurations can be obtained. This protocol is superior to the organozinc compound which is used for the synthesis of diaryl alcohol, propargyl alcohol, and allyl alcohols. These alcohols are very useful intermediates for natural products (macrolide antibiotics). Notably, the catalytic system is extremely efficient

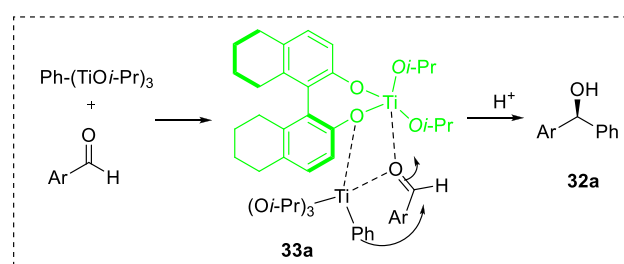
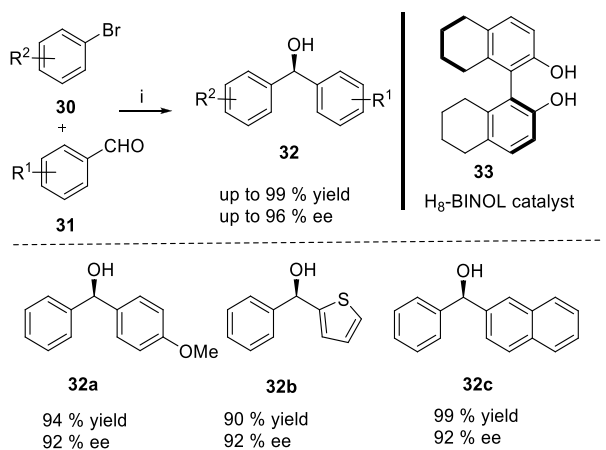
**Scheme 4. Reagents and Conditions:** (i)  $\text{Al}(\text{Ar})_3$ , THF (1.2 equiv),  $\text{H}_8$ -BINOL catalyst **29** (10 mol %),  $\text{Ti}(\text{O-}i\text{-Pr})_4$  (1.25 equiv), THF/hexane, 0 °C, 10 min



with respect to times when the suppression of the background reaction is not required.<sup>11</sup>

Da et al. successfully developed (Scheme 5; Figure 6) a highly enantioselective catalytic arylation of substituted aldehyde **31**

**Scheme 5. Reagents and Conditions:** (i)  $n\text{-BuLi}/-78\text{ }^\circ\text{C}$ ,  $\text{AlCl}_3/0\text{ }^\circ\text{C-rt}$ , TMEDA,  $\text{Ti}(\text{O}i\text{Pr})_4$ , catalyst (S)- $\text{H}_8$ -BINOL **33**



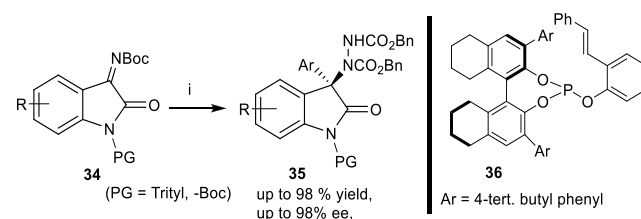
**Figure 6.** Mechanism of the reaction: Scheme 5.

consuming aryl bromide **30** as the starting aryl source. The catalyst (S)- $\text{H}_8$ -BINOL- $\text{Ti}(\text{O}i\text{-Pr})_2$  **33** complex was used under mild reaction conditions in one pot.<sup>12</sup> TMEDA works as a supportive additive to stop racemization. The transmetalation strategy is used to transfer aryllithiums to less reactive arylmetals like titanium is less costly compared to use of aryl Grignard and

zinc reagents. The solvent and additive screening gives the best result with THF/hexane as a solvent and TMEDA as an additive. The mechanistic pathway of the reaction demonstrates that an intermediate **33a** is formed which gives products **32a–32c** with 99% yield and 96% ee.

An efficient rhodium-catalyzed enantioselective arylation by reacting arylboroxines  $(\text{ArBO})_3$  with isatin-derived *N*-Boc/trityl ketimine **34** has been developed by Xu and his group (Scheme 6). Essential enantioselectivity is accomplished by engaging the

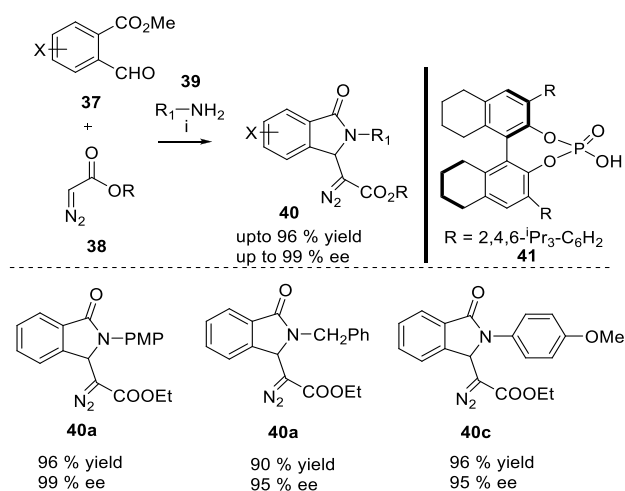
**Scheme 6. Reagents and Conditions:** (i)  $[\text{Rh}(\text{COE})_2\text{Cl}]_2$ ,  $\text{H}_8$ -BINOL catalyst **36**,  $(\text{ArBO})_3$



$\text{H}_8$ -BINOL-derivative phosphite-olefin **36** as a chiral organocatalyst. The screening of various BINOL and  $\text{H}_8$ -BINOL catalysts reveals that  $\text{H}_8$ -BINOL is the most versatile catalyst. Base and solvent study examined with TEA, DBU, DABCO, and DIPEA showed the use of 3 equiv of DIPEA and dioxane giving the adduct in 82% yield and 96% ee. This method allowed access to a broad variety of valuable tetrasubstituted 3-amino-2-oxindole derivatives **35** in excellent yield (up to 98%) with excellent enantioselectivities.<sup>13</sup>

$\alpha$ -Diazoesters are basic nucleophiles for enantioselective C–C bond formation in strategies with the retention of diazo functionality. Singh and his group described (Scheme 7; Figure

**Scheme 7. Reagents and Conditions:** (i) catalyst **41** (5 mol %), DCE, 4 Å molecular sieves,  $-20\text{ }^\circ\text{C}$



7) enantioselective syntheses of phthalides **40** by using a  $\text{H}_8$ -BINOL **40a**-based chiral Bronsted acid as an organocatalyst. The reaction has been accomplished via tandem Mannich lactamization and aldol-lactonization reactions, respectively, via intermediate **41a**. The optimization study showed that  $\text{H}_8$ -BINOL is a better catalyst than BINOL, with dichloethane as solvent at 0 °C. Total synthesis of (S)-PD 172938 (dopamine  $\text{D}_4$  ligand) has been established by using this protocol.<sup>14a</sup> A variety

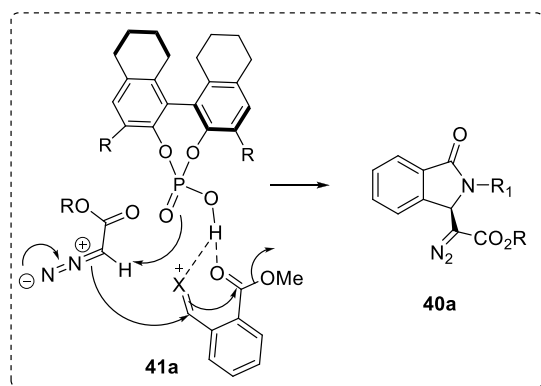
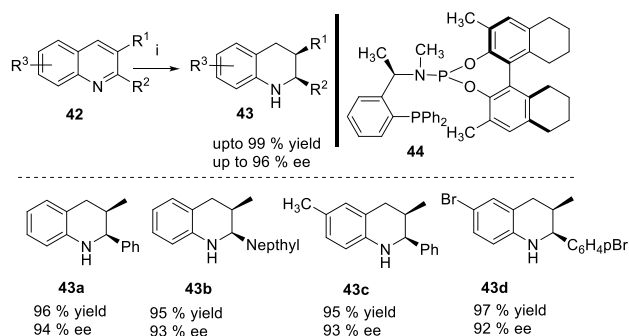


Figure 7. Mechanism of the reaction: Scheme 7.

of enantioenriched phthalides **40a–40c** (up to 85% ee) containing  $\alpha$ -diazoesters were afforded in excellent yields.<sup>14b</sup>

Hu and his group grasped (Scheme 8) Ir-catalyzed hydrogenation of 3-alkyl-2-arylquinolines **42** by using chiral

**Scheme 8. Reagents and Conditions:** (i)  $[\text{Ir}(\text{COD})]\text{Cl}_2$  (0.5 mol %), **L** = **44** (1.1 mol %),  $\text{H}_2$  (10 bar), 1,4 dioxane, 80 °C, 24 h



phosphine–phosphoramidite ligand **44** with a (Sa)-3,3'-dimethyl  $\text{H}_8$ -naphthyl moiety. The hydrogenation by organo-catalyst **44** proceeded in cis-diastereoselectivity and gave the hydrogenation products in >20:1 dr. The substitution pattern on phenyl rings  $\text{R}^1$  and  $\text{R}^2$  slightly affected the enantioselectivity and yield. The hydrogenation protocol exhibited broad functional group tolerance, furnishing a wide range of optically active 2,3-disubstituted tetrahydroquinolines **43a–43d** in up to 96% ee and with continuous cis-diastereoselectivity.<sup>15</sup>

Xu and his co-worker invented (Scheme 9; Figure 8) an Rh-catalyzed asymmetric arylation of 1,2,5-thiadiazolidine 1,1-dioxide **46** type cyclic ketimines utilizing chiral phosphite-based hybrid olefin ligand **48** and aromatic boronic acid. The eclectic diversity of boronic acids with different electronic and steric demands was effectively reacted with a sequence of cyclic ketimines. Sterically hindered arylboronic acids with ortho substituents on the phenyl rings as well as more inspiring heteroarylboronic acids were well abided. The optimization study showed that the reaction performed with 1.0 equiv of  $\text{K}_3\text{PO}_4$  (2.5 M) in toluene gives better results. The reactions generate quaternary carbon containing gem-diaryl-substituted sulfahydantoin **46a–46d** and 4-ethoxy-2,3-dihydro-1,2,5-thiadiazole 1,1-dioxides **47** with excellent enantioselectivities.<sup>16</sup> The mechanism of reaction favors the formation of less hindered Re-face intermediate **50**.

**Scheme 9. Reagents and Conditions:** (i)  $[\text{Rh}(\text{COE})_2\text{Cl}]_2$ ,  $\text{Ar}_2\text{B}(\text{OH})_2$ ; (ii) LAH, catalyst **48**

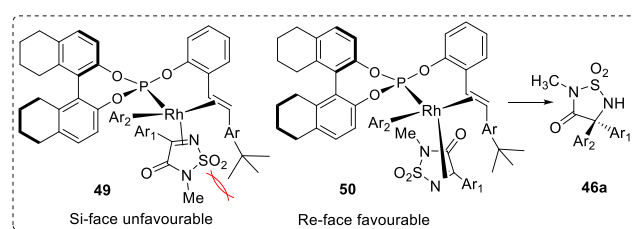
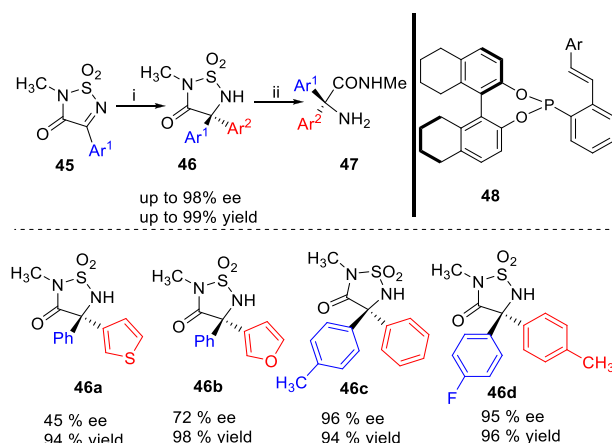
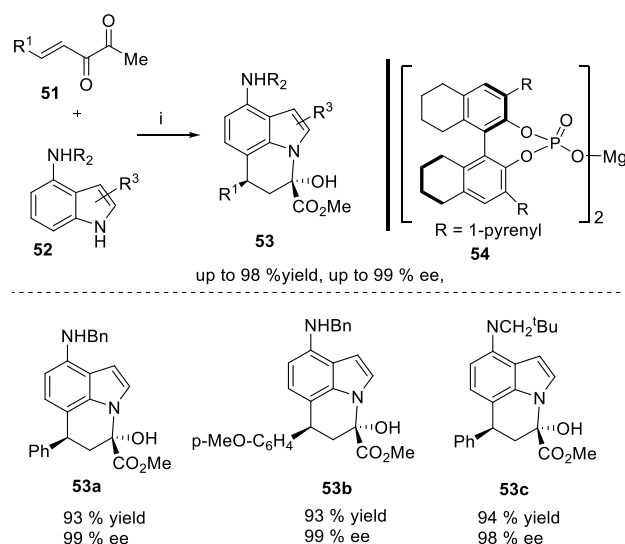


Figure 8. Mechanism of the reaction: Scheme 9.

Cascade reaction of 4-aminoindoles **52** with  $\beta,\gamma$ -unsaturated  $\alpha$ -keto esters **51** via C-7 Friedel–Crafts alkylation/*N*-hemiacetalization catalyzed by  $\text{H}_8$ -BINOL catalyst **54** has been developed by Antilla and his group (Scheme 10; Figure 9).

**Scheme 10. Reagents and Conditions:** (i) catalyst **54** (10 mol %), 4 Å molecular sieves,  $\text{Et}_2\text{O}$ , rt



Using a chiral magnesium  $\text{H}_8$ -BINOL-derived bis(phosphate) complex as organocatalyst, the functionalized 1,7-annulated indole scaffolds **53a–53c** are obtained in high yields (up to 98%) and excellent enantioselectivities (up to 99%) and diastereoselectivities (up to >20:1) under mild reaction conditions.<sup>17</sup> The solvent screening and metal salt with  $\text{H}_8$ -

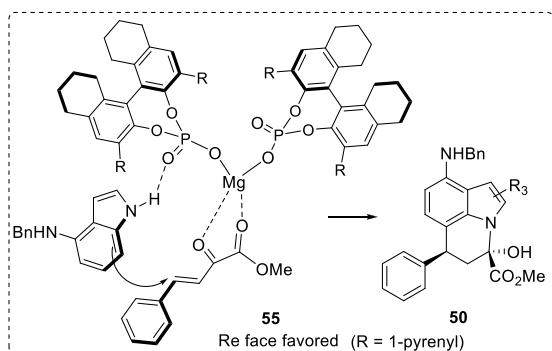


Figure 9. Mechanism of the reaction: Scheme 10.

BINOL complex showed that diethyl ether and Mg complexes are the best solvent and complex, respectively, which results in high enantioselectivity and yield. The *N*-methylated indole substrate was also verified, but it could not provide the C-7-functionalized product, thus indicating that 1-H on the indole substrates is the key to the process. The proposed mechanism of the reaction shows that intermediate **55** was formed and gets converted into product **50** with required enantioselectivity.

Jiang and his group investigated (Scheme 11; Figure 10) the hetero-Diels–Alder reaction between substituted aldehyde **58**

**Scheme 11. Reagents and Conditions: (i) catalyst **59** (20 mol %), TFA, toluene, 0 °C**

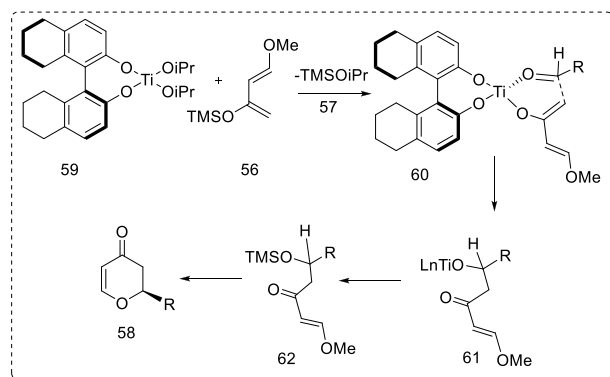
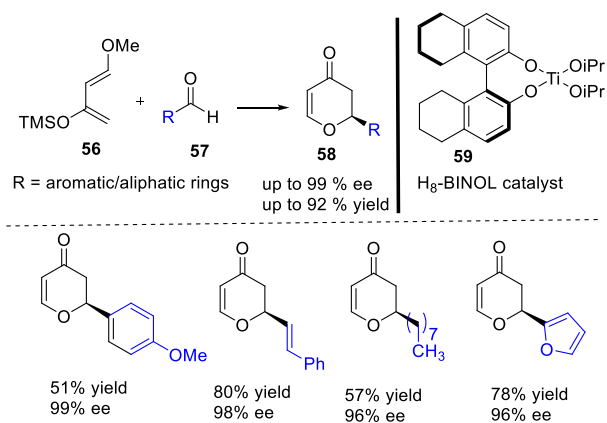


Figure 10. Mechanism of the reaction: Scheme 11.

and Danishefsky's diene **56** using readily accessible Ti(IV)-H<sub>8</sub>-BINOL (TiHBOL) complex **60** leading to products 2,3-dihydro-2-phenyl-4-pyranone **58** with very high enantioselectivity

(up to 99% ee) and yield (92%).<sup>18</sup> Screening of alkaloids such as Ti(OiPr)<sub>4</sub>, Al(OiPr)<sub>3</sub>, Zr(OEt)<sub>4</sub>, Sm(OiPr)<sub>3</sub>, Yb(OiPr)<sub>3</sub>, and Ce(OiPr)<sub>3</sub> reported Ti(OiPr)<sub>4</sub> improved yield of reaction. Ratio of Ti(OiPr)<sub>4</sub> to ligand is 1:1.5 gave high enantioselectivity. All reactions were carried out in toluene using 20 mol % of Ti–H<sub>8</sub>–BINOL catalyst at 0 °C temperature.

Zhou and his group prepared (Scheme 12; Figure 11) a palladium catalyst supported by a new, (R)-H<sub>8</sub>-BINOL-derived

**Scheme 12. Reagents and Conditions: (i) 2% PdMe<sub>2</sub>(TMEDA), 2.4% catalyst **66**, LiOAc; (ii) TFA**

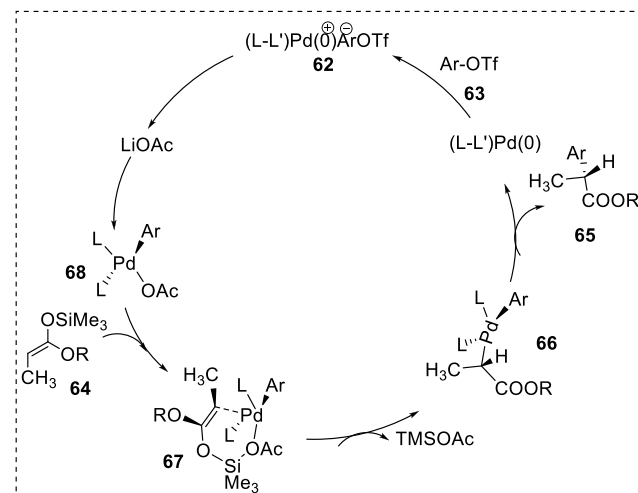
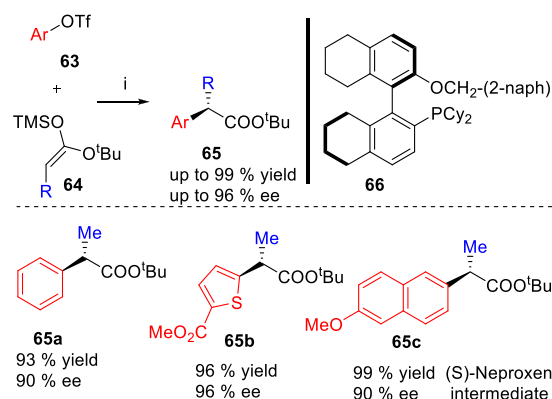
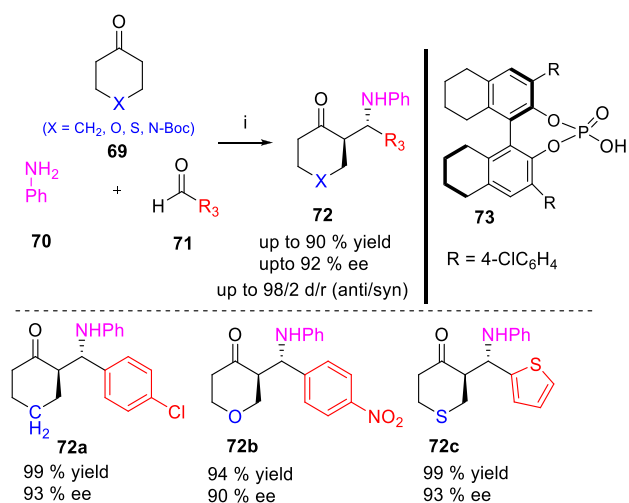


Figure 11. Mechanism of the reaction: Scheme 12.

monophosphine **66**. Arylation of 1-naphthyl triflate **63** by efficient coupling of an *O*-trimethylsilyl ketene acetal **64** produces tertiary centers with high ee. The usefulness of the reaction was demonstrated in a gram-scale synthesis of (S)-Neproxen in 92% enantiomeric excess.<sup>19</sup> The mechanism of reaction follows the formation of **62** which reacts with LiOAc to give **68**. Intermediate **68** reacts with precursor **64** and forms complex **67** which finally gets converted into product **65**.

Gong and his group described (Scheme 13) a protocol employing chiral H<sub>8</sub>-BINOL catalyst **73** as a Bronsted acid. Direct asymmetric Mannich reaction of cyclic ketones **69** with aldimines yielded a product formed by condensation of **70** and **71**. The Mannich reaction gave chiral β-amino carbonyls **72a–72c** in high yields with excellent enantioselectivities up to 98% and high diastereomeric ratios up to 98/2 diastereomeric ratio.<sup>20</sup> The stereochemical results influenced by electronic properties of the substituent on benzaldehyde precursor **71**. Electron

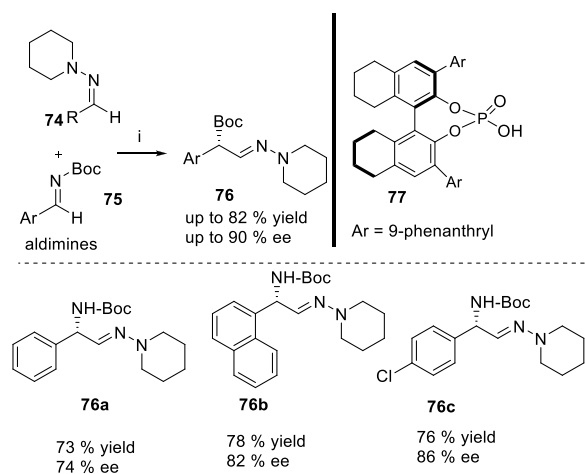
**Scheme 13. Reagents and Conditions:** (i) catalyst **73** (0.5–5 mol %), PhCH<sub>3</sub>, 0 °C



donating groups decreases the enantioselectivity. An aliphatic aldehyde follows Mannich reaction with 84/16 dr and 75% ee. Tetrahydropyranone (X = CH<sub>2</sub>) and *N*-Boc-protected piperidin-4-ones (X = N-Boc) **69** are both highly reactive toward the imine generated in situ from *para*-nitrobenzaldehyde **70** and phenylamine **71**, leading to the formation of anti-Mannich products with 90% yield and 91% ee, respectively.

Rueping et al. and his group (Scheme 14) reported synthesis of aminohydrazone **76** via enantioselective Bronsted acid **77**

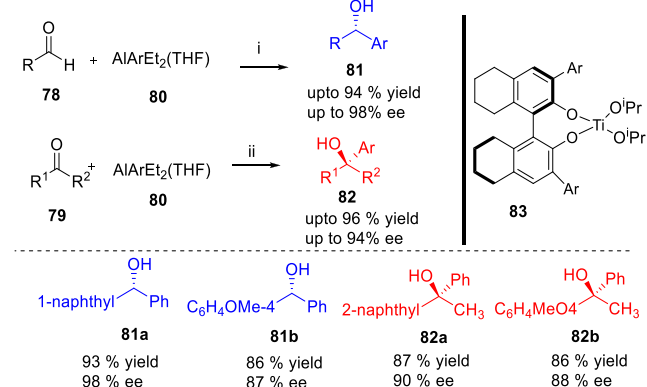
**Scheme 14. Reagents and Conditions:** (i) catalyst **77**, CHCl<sub>3</sub>, 0 °C



catalyzed addition of methyleneaminopyrrolidine **74** to *N*-Boc imines **75**. The matching aminohydrazone **76a–76c** have been synthesized in good yields up to 90% ee.<sup>21</sup> *N*-Boc-protected aldimine and the pyrrolidine-derived hydrazine give better yield than *N*-benzyloxycarbonyl- or *N*-benzoyl-protected aldimines. The process optimization study reported chloroform to be a better solvent at 0 °C using 10 mol % catalyst. The process optimization study screened *N*-protection of imine with CO<sub>2</sub><sup>t</sup>Bu, CO<sub>2</sub><sup>t</sup>CH<sub>2</sub>Ph, COPh, CH<sub>2</sub>Ph, 4F-PhCH<sub>2</sub>, and 4Br-PhCH<sub>2</sub> showed that CO<sub>2</sub><sup>t</sup>Bu protected imine gives better selectivity. Solvent screening reported that trifluorobenzene is supportive for the reaction.

Gau and his group (Scheme 15) synthesized diaryl methanols **81a–81b** and triarylmethanols **82a–82b** in excellent yield with

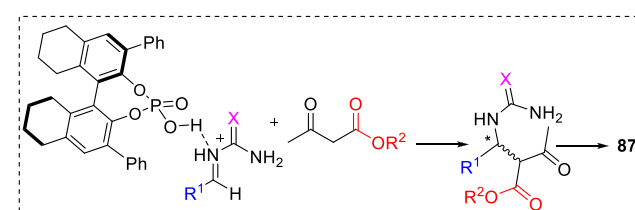
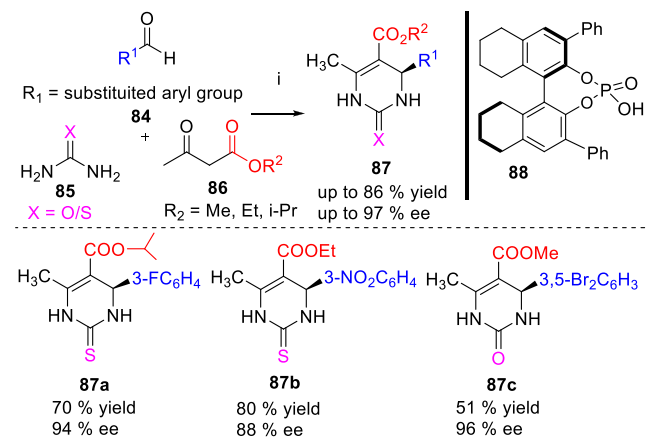
**Scheme 15. Reagents and Conditions:** (i) catalyst **83** (10 mol %), 1.5 equiv Ti(OiPr)<sub>4</sub>, toluene, 0 °C; (ii) cat. **83** (10 mol %), Ti(OiPr)<sub>4</sub> (3.5 equiv), toluene, 0 °C



high enantioselectivity. These products formed by reacting AlArEt<sub>2</sub>(THF) **80** to aldehydes **78** or ketone **79**. The titanium complex of (*R*)-H<sub>8</sub>-BINOL catalyst **83** is used for this transformation.<sup>22</sup> A screening study of the reaction depicted that the steric hindrance of the substrates had an effect on the reactivity of phenyl transfer to ketones. The phenyl addition to hindered ketones required more times to give products in advanced yields.

Gong and his group (Scheme 16; Figure 12) discovered that the first organocatalytic asymmetric Biginelli reaction using

**Scheme 16. Reagents and Conditions:** (i) catalyst **88** (10 mol %), CH<sub>2</sub>Cl<sub>2</sub>, 250 °C

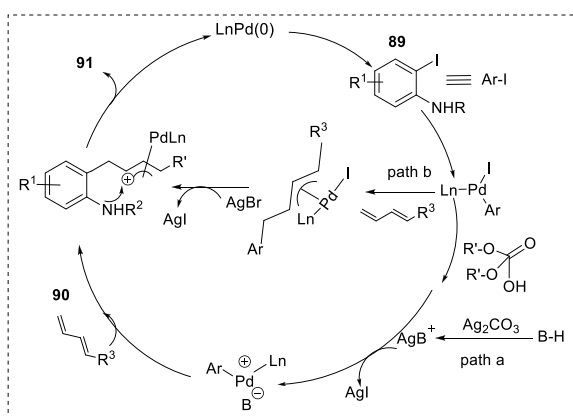
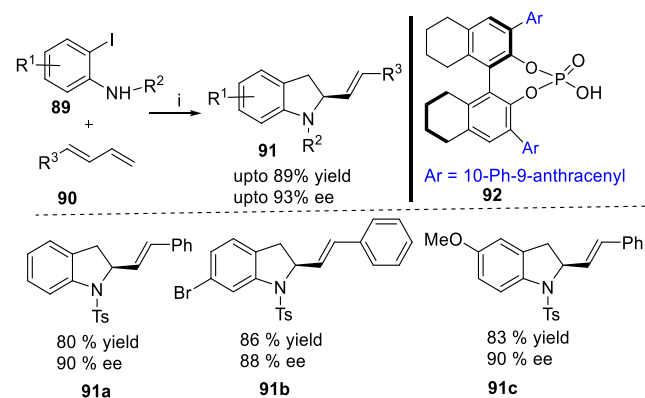


**Figure 12.** Mechanism of the reaction: Scheme 16.

chiral phosphoric acid, derived from  $H_8$ -BINOL **88**, afforded the reaction in high yields of chiral 3,4-dihydropyrimidin-2-(1*H*)-ones **87a–87c** up to 97% ee. Varied substrates, including aldehydes **84**,  $\beta$ -keto esters **86**, and urea derivatives **85** could be used in this protocol.<sup>23</sup> Validation of the reaction protocol improved yield and enantioselectivity slightly by increasing temperature and reaction time in the presence of optimized dichloromethane as a solvent.  $H_8$ -BINOL catalyst with various substituents at the 3,3' positions showed that substituents other than naphthyl worked well.

Han and his group (Scheme 17; Figure 13) developed a chiral ligand **92**-based protocol for enantioselective synthesis of chiral

**Scheme 17. Reagents and Conditions: (i) Pd(PPh<sub>3</sub>)<sub>4</sub>, catalyst **92**, Ag<sub>2</sub>CO<sub>3</sub>**



**Figure 13.** Mechanism of the reaction: Scheme 17.

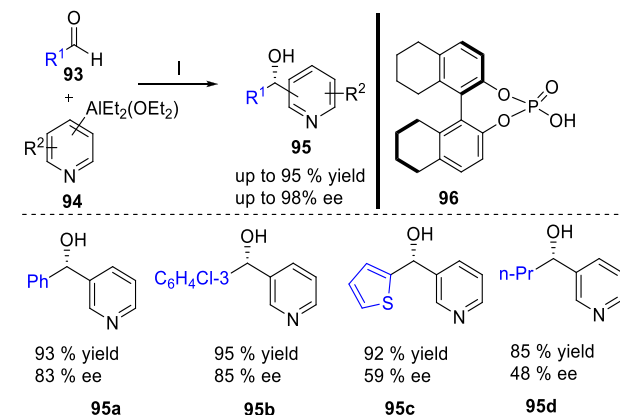
indolines **91a–91c**. The present invention describes a chiral anion-mediated asymmetric Heck/Tsuji–Trost reaction of aryl iodides **89** and 1,3-dienes **99** to afford higher yields and enantioselectivities.<sup>24</sup> Chiral anion-mediated chemistry employing chiral phosphate anions as the sole chiral source to generate enantioselective C–C bond via Heck-type reaction was established in this protocol. The precursor for this reaction modified by replacing the aryl diazonium salt with aryl halide enhanced the synthetic utility of the present protocol.

The steric hindrance of substituents at the 3,3'-positions of the binaphthyl backbone in R-BINOL and SPINOL improves yield. The protocol improved further by using  $H_8$ -BINOL-based phosphoric acids. Switching silver carbonate to other metal carbonates, such as K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, and PbCO<sub>3</sub>, did not improve enantioselectivity. An optimization study reported that

addition of a small amount of DMSO to the system significantly improve the outcome of the reaction up to 81%.

Zhou and his group (Scheme 18) have successfully developed a methodology for synthesis of pyridyl containing diaryl

**Scheme 18. Reagents and Conditions: (i) 10 mol % catalyst **96**, Ti(iOP)<sub>4</sub>, toluene, 0 °C, 12 h**



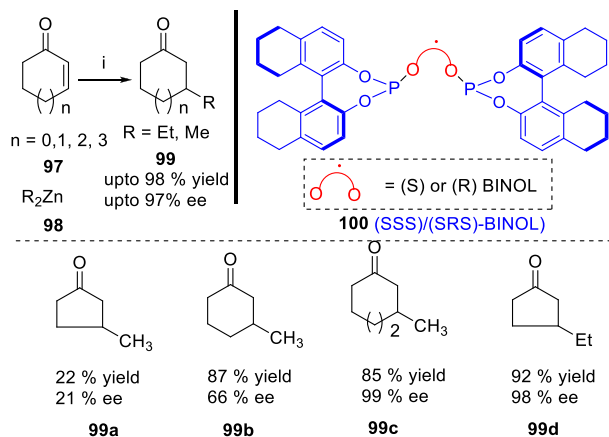
methanol **95** using a titanium(IV) catalytic system of (R)- $H_8$ -BINOLate **96** up to 98% ee from easily available precursors pyridyl aluminum reagents **94** and aldehydes **93**.<sup>25</sup> Various arylating agents like arylboronic acids, arylzinc, arylaluminum, aryltitanium, aryl lithium, and aryl Grignard reagents were employed for asymmetric protocols. However they gave excellent reports with Ti(O<sup>i</sup>Pr)<sub>4</sub>. Diverse chiral ligands were tested for asymmetric carbon addition reactions across the carbon oxygen double bond. Comparative study presented that the modified (S)-BINOL derivatives afforded the addition reactions with lower enantioselectivity than (R)- $H_8$ -BINOL. In the present scheme (R)- $H_8$ -BINOL is the most efficient to afford in 91% yield with excellent enantioselectivity of 90%. The dihedral angle in the transition state of the reaction of  $H_8$ -BINOL catalyst compared with BINOL is lower. This is the reason that asymmetric addition at aldehydes by a nucleophile gives excellent results. Lowering the temperature up to –10 °C did not recover the enantioselectivity of the product. Aromatic aldehydes with electron withdrawing or electron donating substituents at the para- or meta- position afforded the corresponding alcohols in high yields.

Chan and his group described (Scheme 19) the 1,4-addition of dialkylzinc **98** to 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone **97** to yield 3-methyl and ethyl substituted cyclopentenone **99a–99d** with 99% ee by using chiral aryl diphosphite ligand **100** derived from  $H_8$ -binaphthol.<sup>26</sup> Deploying (CuOTf)<sub>2</sub>·C<sub>6</sub>H<sub>6</sub> as the metal source, **100** as the ligand, and diethyl ether as the solvent delivered the desired product up to 98% yield and 97% ee. An optimized protocol provides a key step en route to anticarcinogenic clavularin B. The ring size also affects the yield of the reaction. Smaller rings gives lower yield and enantioselectivity.

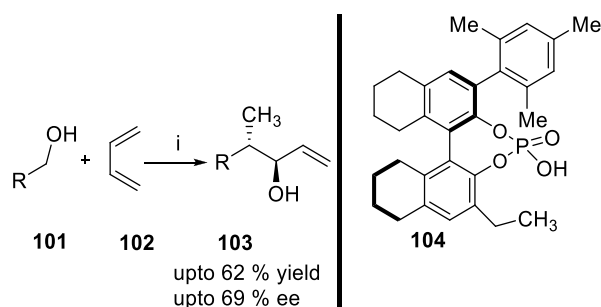
Krische and his group developed a protocol (Scheme 20) for the chiral-anion-dependent inversion of diastereo- and enantioselectivity in butadiene **102** hydrohydroxy alkylation with alcohol **101** to form products of carbonyl syn-crotylation **103**. The observed diastereo- and enantioselectivity is opposite (anti-crotylation) to that observed using  $H_8$ -BINOL-derived phosphate counterions **104** in combination with DPPF or even (S)-SEGPHOS.<sup>27</sup> The importance of this protocol is that for the



**Scheme 19. Reagents and Conditions:** (i)  $(\text{CuOtf})_2 \cdot \text{C}_6\text{H}_6$  (1 mol %), catalyst **100** (2 mol %),  $\text{R}_2\text{Zn}$ ,  $\text{Et}_2\text{O}$ ,  $-30^\circ\text{C}$



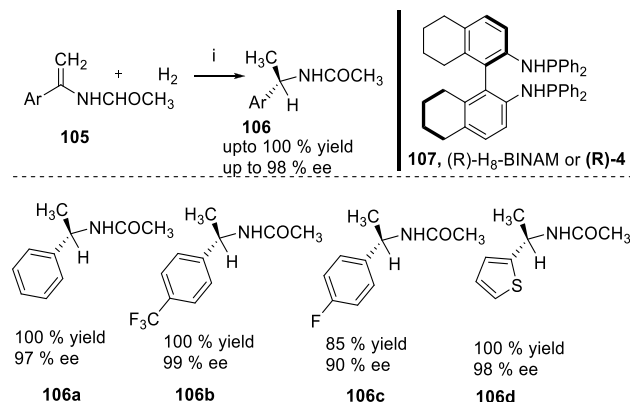
**Scheme 20. Reagents and Conditions:** (i)  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  (5 mol %), (S) SEGPHOS (5 mol %), catalyst **104** (10 mol %)



first time the X-ray crystal structure of a ruthenium complex modified by a chiral phosphate counterion is interpreted.

Chan and his group have developed a protocol (Scheme 21) for asymmetric hydrogenation of enamides **105** leading to  $\alpha$ -

**Scheme 21. Reagents and Conditions:** (i)  $[\text{Rh}(\text{R})-4(\text{COD})]\text{BF}_4$ , catalyst **107**

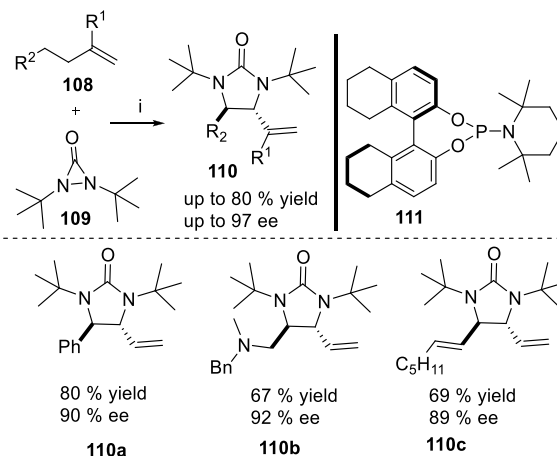


arylethylamine derivatives **106a–106d** with excellent enantioselectivities 99.0% ee using chiral bisaminophosphine ligand **107** and Rh.<sup>28</sup> It was noted that the enantioselectivity of the catalyst (R)-**4**, **107** was sensitive to the solvent used. Higher ee values of **106** were achieved in protic and/or polar solvents. The hydrogen pressure had very little effect on the enantioselectivity. For example, in the hydrogenation of **105** using Rh-(R)-**4**

catalyst in THF, the following results were obtained:  $P_{\text{H}_2} = 14.5$  psi, ee = 92.1%;  $P_{\text{H}_2} = 100$  psi, ee = 90.7%;  $P_{\text{H}_2} = 1000$  psi, ee = 89.5%. Substitution at the meta- or para-position of the phenyl ring of the parent enamide **105** did not give much influence on the enantioselectivity for the products.

Shi and his group developed (Scheme 22) a catalytic asymmetric allylic and homoallylic C–H diamination of

**Scheme 22. Reagents and Conditions:** (i) 5–10 mol %,  $\text{Pd}_2(\text{dba})_3$ , catalyst **111** (1:4.4),  $65^\circ\text{C}$ , 6 h

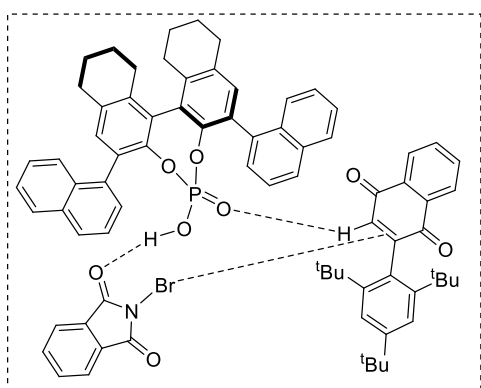
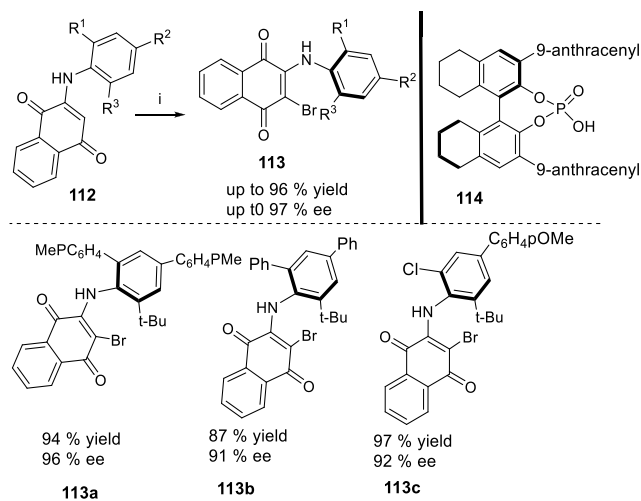


terminal olefins **108** using di-*tert*-butyldiaziridinone **109** and  $\text{H}_8$ -BINOL-derived phosphorus amidite ligand **111**, giving diamination products **110a–110c** in good yields with high regio-, diastereo-, and enantioselectivities.<sup>29</sup> The ee was determined by chiral GC (Chiraldex B-DM column) unless otherwise stated. The ee was determined by chiral HPLC (Chiralpak AD column) after the removal of *t*-butyl groups of **110**. The (R,R) configuration was determined by comparing the optical rotation with the reported one. The ee was determined by chiral GC (Chiraldex B-DM column) after the removal of *t*-butyl groups. The ratio was determined by achiral GC (VA-SMS column). The (2R,3S,4R) configuration was determined by the X-ray structure of diamination product after the removal of the TMS group.

Gustafson and his group discovered (Scheme 23; Figure 14) new atropisomer selective synthesis of a diarylamine **114** via phosphoric acid catalyzed **114** halogenation of *N*-aryl quinoids **112** yielding products **113a–113c** in upwards of 95:5 er and 90% yield.<sup>30</sup> Atropisomerism, or axial chirality, is ubiquitous throughout modern FDA-approved drugs like binimetinib, bosutinib, and a VEGFR inhibitor from Wyeth on behalf of a potentially atropisomeric *N*-aryl quinoid. Evaluation study of reaction parameters such as temperature  $24^\circ\text{C}$ , time (6–12 h), solvent (toluene + hexane, 1:1), catalyst (5 mol %) loading, and bromination reagent (0.06 mol). The reaction scope proved to be tolerant of diverse aryl substitutions of the 2,4-positions of the aniline. Electron-rich aryl substitutions yield ers above 95:5 and electron-poor aryl substitutions yield ers around 90:10. The present halogenation protocol was acquiescent to chlorination in the presence of a Lewis basic catalyst and NCS (91% yield with 87:13 er) and iodination using NIS (93% yield 80:20 er), although with somewhat attenuated selectivities.

Zhang and his co-worker established a protocol (Scheme 24) of enantioselective addition reaction of pyrrole **117**/indoles **116** to 3-vinylindoles **115** by applying chiral imidodiphosphoric acid

**Scheme 23. Reagents and Conditions:** (i) catalyst **114**, halogen source, NXS, NXP (X = Br)

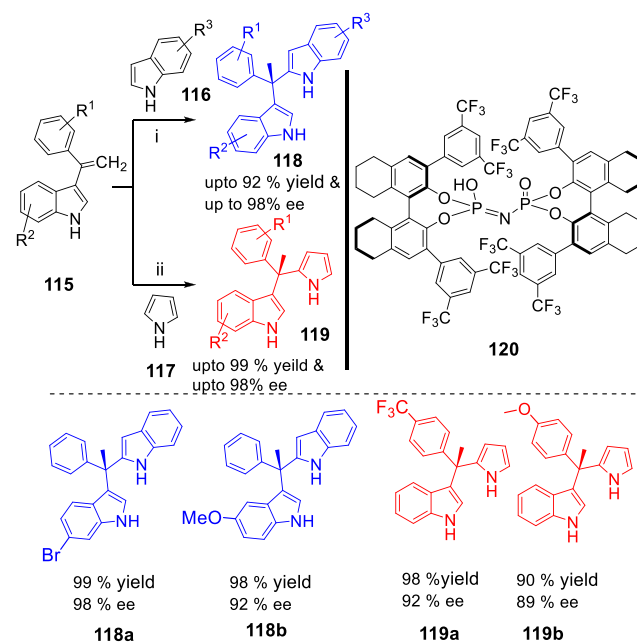


**Figure 14.** Mechanism of the reaction: **Scheme 23**.

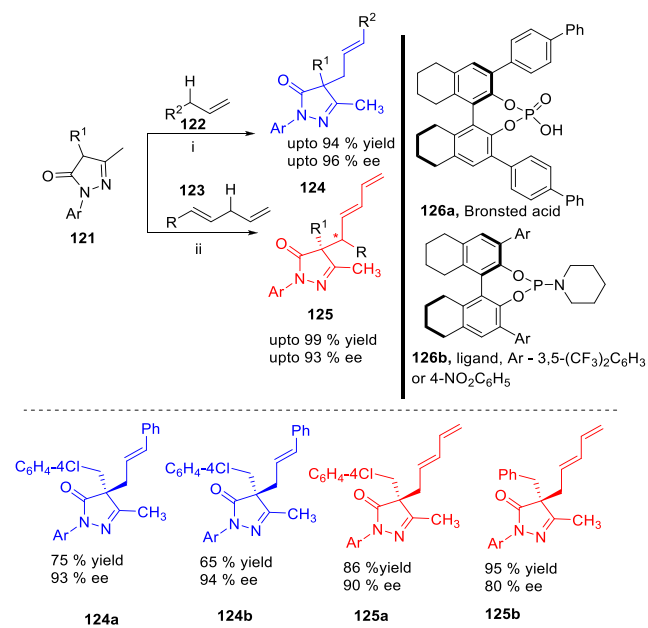
**120** to afford triarylmethane **118** and **119** with a quaternary chiral center. A series of optically active 1,1,1-triarylethanes bearing quaternary stereocenters **118a–118b** and **119a–119b** were synthesized in excellent yields up to 99% and enantioselectivities up to 98%.<sup>31</sup> The optimization study found that the substrates with electron donating groups have an inverse pattern in comparison to the substrates with halogen or electron withdrawing groups when they contribute in the reaction.

Gong and his group performed (**Scheme 25**; **Figure 15**) enantioselective allylic C–H alkylation reaction of allylarenes **122** with pyrazol-5-ones **121** by the cooperative catalyst of a complex of a palladium and chiral H<sub>8</sub>-BINOL **126a/b** to afford chiral *N*-heterocycles **124** and **125** in high yields and enantioselectivity (up to 96% ee).<sup>32</sup> The palladium-catalyzed C–H activation for C–C bond formation needed an oxidant, and the ligands are expected to survive in the oxidized conditions during the catalytic cycle. Most of the phosphine ligands can be very easily oxidized to five-valence phosphorus species, which are unable to accelerate palladium catalysis. This process has limitations for using chiral ligands. Few of the BINOL-derived phosphoramidite ligands are appropriate with quinone-type oxidants (2,5 DMBQ) in the palladium-catalyzed asymmetric allylic C–H oxidation. Introduction of even more electronically poor 3,5-bis(trifluoromethyl)phenyl groups or 4-nitrophenyl substituents at 3,3'-positions of the binaphthyl backbone

**Scheme 24. Reagents and Conditions:** (i) catalyst **120**, CHCl<sub>3</sub>, –20 °C, (ii) Cl–CH<sub>2</sub>CH<sub>2</sub>Cl, 0–20 °C, 5 Å molecular sieves



**Scheme 25. Reagents and Conditions:** (i) and (ii) catalyst **126a** and **b** (15 mol %), Pd(dba)<sub>2</sub> (7.5 mol %), 2,5-dimethyl benzoquinone (1.2 equiv)



increases stereoselectivity. Modification of the amine moiety in the phosphoramidite ligands found that the assimilation of a cyclic piperidine moiety significantly enhanced the catalytic efficiency and enantioselectivity. The chiral H<sub>8</sub>-BINOL phosphoric acid cocatalyst with H<sub>8</sub>-BINOL phosphoramidite showed a considerable effect on the reaction. The scope of the protocol was tolerant to a broad spectrum of allylbenzene derivatives **122** and **123**, installed with either an electronically rich or deficient substituent in different substitution patterns, capable of offering excellent enantioselectivity ranging from 87%

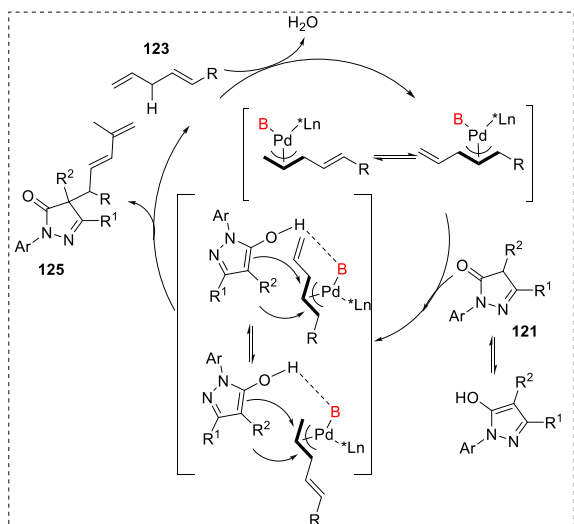
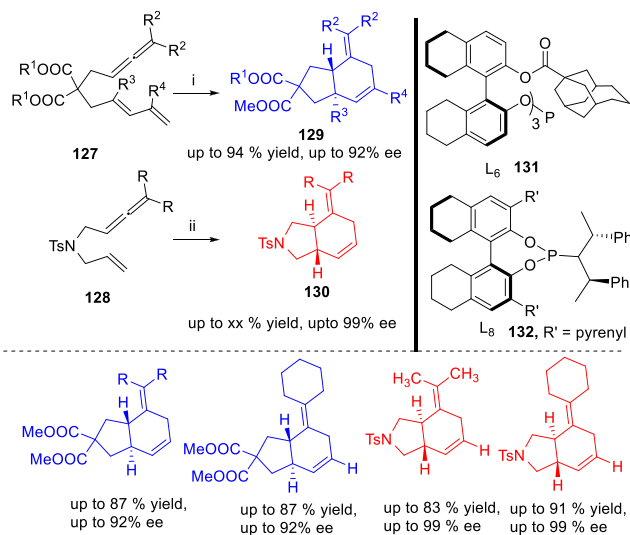


Figure 15. Mechanism of the reaction: Scheme 25.

to 96% ee. Pyrazol-5-one **121** is tolerable to the presence of an electron donating and withdrawing group on the benzyl ring at the C-4 position. The desired products attained excellent yield and enantioselectivity up to 93%.

An enantioselective gold(I)-complex- $H_8$ -BINOL **131** catalyzed intramolecular [4 + 2]-cycloaddition of allenes **127** and dienes **128** is reported by Toste and his group (Scheme 26). The

**Scheme 26. Reagents and Conditions: (i)  $L_6AuCl$  cat. **131** (0.5 mol %),  $AgBF_4$  (5 mol %); (ii)  $L_6AuCl$  catalyst **131** (0.5 mol %),  $AgSbF_6$  (5 mol %)**



reactions allow for the asymmetric synthesis of trans hexahydroindenes **129** and pyrrolidine **130** products using  $C_3$ -symmetric phosphite gold(I) and ortho aryl phosphoramidite gold(I) complexes as catalysts, respectively.<sup>33</sup> Chiral catalyst optimization study of bidentate phosphines toward an enantioselective [4 + 2]-cycloaddition failed to produce any of the desired cycloadduct. This study demonstrated that, despite the linear geometry of gold(I) complexes, chiral monodentate phosphorus-based ligands can be employed in asymmetric gold(I) catalysis.

Allylic alcohol and amine are synthesized by alkenyl boronates and alkenyl metals which is an important protocol for  $SP^3$  and  $SP^2$  carbon-carbon single bond formation. Guo and his group described a novel protocol (Scheme 27; Figure 16) for the

**Scheme 27. Reagents and Conditions: (i) catalyst **136** (10 mol %), DCE, 3 Å molecular sieves, 30 °C**

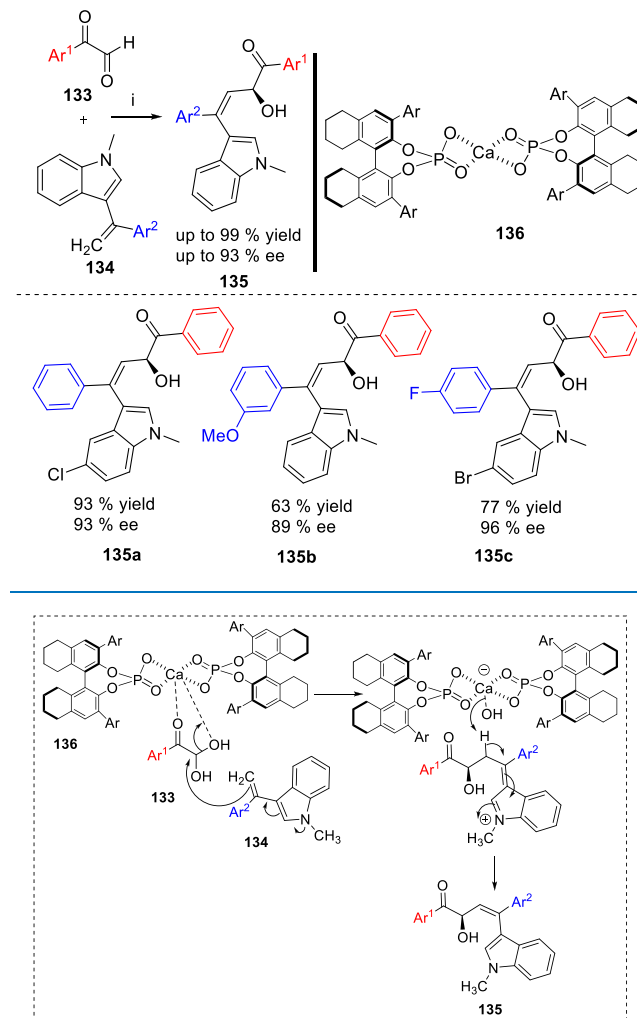


Figure 16. Mechanism of the reaction: Scheme 27.

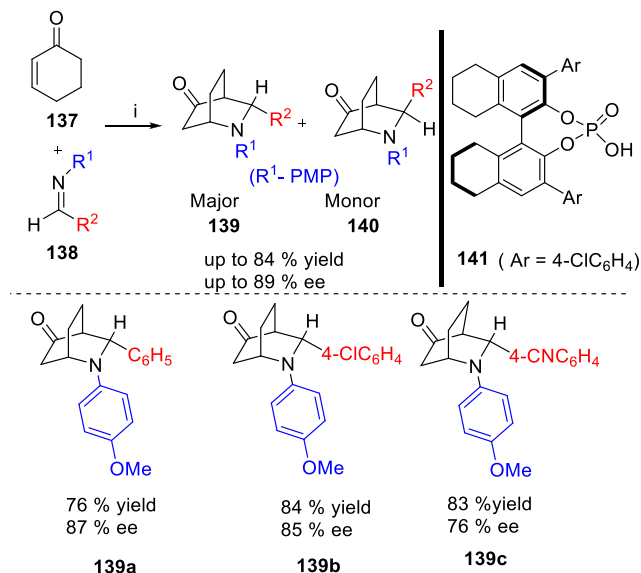
synthesis of structurally diverse allylic indole alcohols **135** employing arylglyoxals **133** with 3-vinylindoles **134** in the presence of chiral calcium phosphate **136**. The catalyst **136** was prepared by reaction of  $Ca(OH)_2$  with  $H_8$ -BINOL in dichloromethane solvent.<sup>34</sup> Phenylglyoxals **133** with a para-substituted phenyl ring with an electron withdrawing or electron donating group did not affect the reaction protocol. The steric effect of ortho-substituents of phenyl could affect the stereoselectivity of the products.

Catalyst optimization study reported that the absence of phosphoric acid increased the difficulty to control the stereoselectivity. By referencing Hosomi's work, the author found that  $CaCl_2$  was a suitable catalyst for the aldol reaction of silyl enolates and arylglyoxals. They envisioned that the chiral alkali or alkaline earth phosphates would be good catalysts for reaction. Chiral phosphoric acid catalyst and its metal complexes with Li, Na, Mg, K, Ca, and Ba were screened, but calcium

complex was found to be more efficient in terms of enantioselectivity and yield.

Gong and his group described (Scheme 28) chiral Bronsted acid **141** catalyzed asymmetric aza-hetero-Diels–Alder reaction

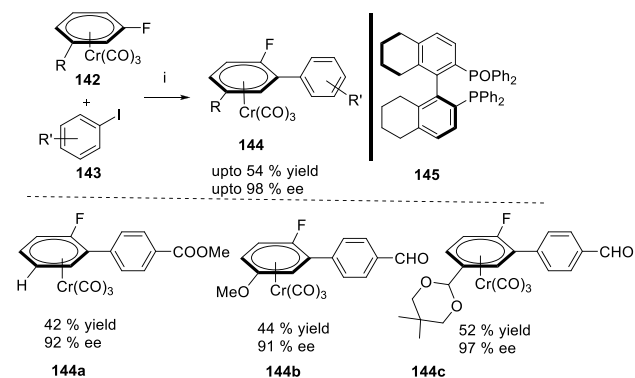
**Scheme 28. Reagents and Conditions:** (i) catalyst **141** (5 mol %), PhCH<sub>3</sub>, 20 °C



between aromatic aldimines **138** and  $\alpha$ - $\beta$  unsaturated cyclohexanone **137**. Series of chiral phosphoric acid catalysts were prepared from (R)-BINOL and H<sub>8</sub>-BINOL as a starting material. Both types of catalyst execute asymmetric addition of cyclohexanone **137** with *N*-PMP-benzaldimine **138** to afford corresponding bridged compounds **139a–139c** with expected enantioselectivity.<sup>35</sup> The solvent optimization study reported that nonpolar aprotic solvents toluene and *m*-xylene led to higher yields than their polar counterparts like halogenated solvents. The phosphoric acid **141**-catalyzed direct aza Diels–Alder reaction was extended to a series of benzaldimines (**138**), with an electron donating or electron withdrawing substituent afforded endoisomer **139** in 70–82% yield and with up to 87% enantioselectivities.

Larrosa and his group (Scheme 29) synthesized planar-chiral compounds **144a–144c** by a catalytic asymmetric direct C–H

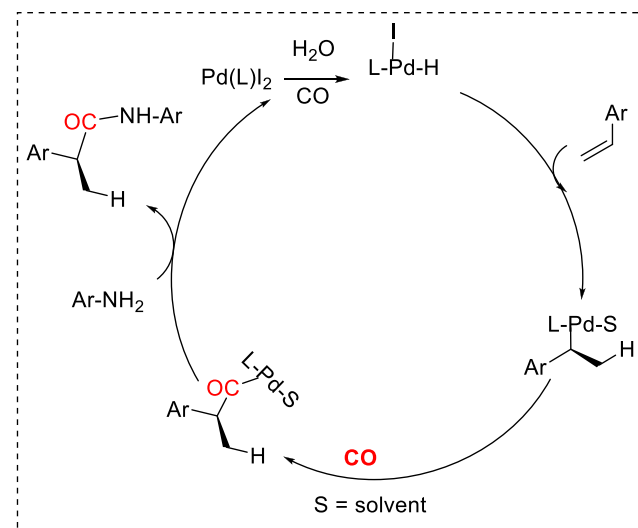
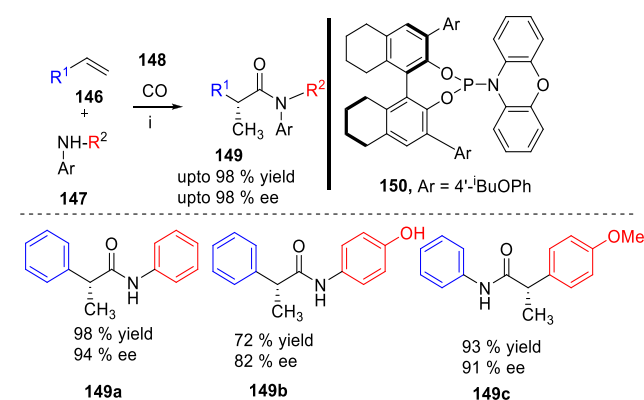
**Scheme 29. Reagents and Conditions:** Pd(dba)<sub>2</sub> (5 mol %), organocatalyst **145** (5.5 mol %), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv), Ag<sub>2</sub>CO<sub>3</sub> (0.65 equiv), Cy<sub>2</sub>CHCOOH (0.5 equiv)



arylation of (6-arene)-chromium complexes **142** and aromatic iodides **143**. The required enantioselectivity developed by using hemilabile ligand **145** H<sub>8</sub>-BINAP.<sup>36</sup> H<sub>8</sub>-BINAP with various substituents at the 2,2' position screened like alcohol, ester, and amide reports low enantioselectivity. H<sub>8</sub>-BINAP with oxidized phosphine at the 2,2' position produces excellent yield. The methodology was screened with respect to the fluoroarene chromium complex bearing electron donating and withdrawing groups reported excellent results without any group. Mechanistic studies suggested that the reaction proceeds through a Pd/Ag bimetallic double catalytic cycle where the C–H activation is carried out by Ag.

Guan and his lab have stated a protocol (Scheme 30; Figure 17) for the synthesis of 2-substituted propanamides **149a–**

**Scheme 30. Reagents and conditions:** (i) PdI<sub>2</sub>, catalyst **150**, THF, rt



**Figure 17. Mechanism of the reaction: Scheme 30.**

**149c.** The reaction was subjected to pressure to 50 atmospheric of CO in an autoclave. The glass vessel filled with the first palladium iodide (10 mol %), chiral H<sub>8</sub>-BINOL phosphoramidate **150** (11 mol %), followed by addition of styrene and various *N*-substituted anilines was subjected to CO pressure in an autoclave. The reaction followed the asymmetric Markovnikov rule for hydroaminocarbonylation of alkenes **146** with anilines **147** and carbon monoxide **148** for construction of a

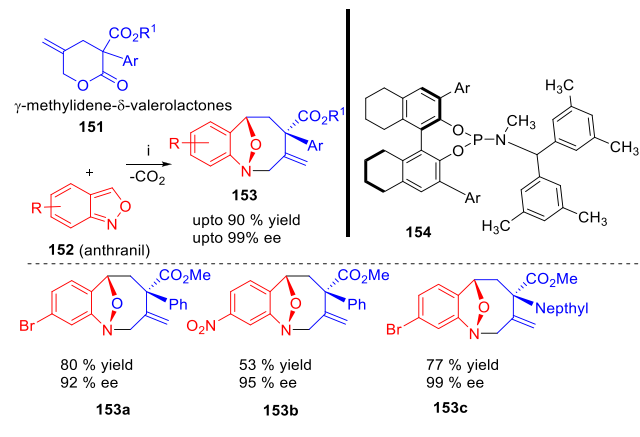
diverse array of 2-substituted propanamides **149a–149c** with high yields (99%) and enantioselectivities (84%).<sup>37</sup>

Varied catalysts optimized for enantioselectivity showed that a monodentate chiral phosphine ligand showed the best result in terms of reactivity, regioselectivity, and enantioselectivity. Catalysts were further screened with basic phosphoramidite ligand–ligand scaffolds with a range of electronic variation at the 3,3'-positions of the H<sub>8</sub>-BINOL framework were prepared and screened. Encouragingly, the yield and ee of ligand **150** achieved good results. 4-<sup>t</sup>BuOPh and phenoxazinyl (POA) substituents at phosphorus atoms afforded excellent results. The optimal reaction conditions for anilines **147** with electron donating substituents, such as alkyl and methoxy, afforded the desired products in high yield (62–98%) and high ee (91–98%).

The sterically hindered anilines like bulky 2,6-dimethylaniline and 2,6-diisopropylaniline were compatible with the optimized reaction conditions. Halogen substituted anilines and strong electron withdrawing groups were tolerated in the reaction to deliver the desired products in high yields and ee's. The synthetic utility of this Pd-catalyzed asymmetric Markovnikov hydroaminocarbonylation screened for synthesis of intermediates of ibuprofen, naproxen, flurbiprofen, and ketoprofen and were worked out effectively.

Li and his group reported (Scheme 31; Figure 18) a palladium-catalyzed asymmetric [4 + 4] cycloaddition of  $\gamma$ -

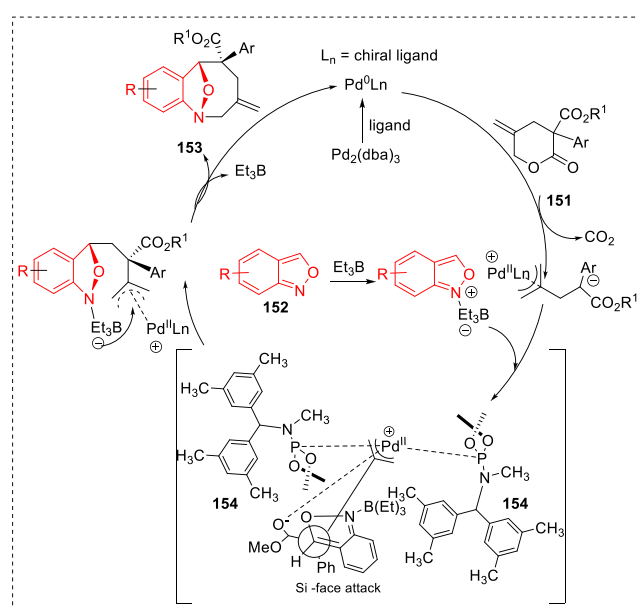
**Scheme 31. Reagents and conditions: (i) Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2.5 mol %), catalyst **154** (11%), Et<sub>3</sub>B (20 mol %), xylene/PhCl (1:1), 10 °C, 4 Å molecular sieves**



methylidene- $\delta$ -valerolactones **151** with substituted anthranils **152** using H<sub>8</sub>-BINOL organocatalyst **154** producing functionalized tetrahydrobenzo[*b*]-azocine derivatives **153a–153c** with yield up to 92%. The product obtained with 20:1 diastereoselectivity and 99% enantioselectivity.<sup>38</sup> The electron donating group on anthranils increases yield, and withdrawing groups reduce the yield of the reaction. The catalyst screened for varied substituents on the nitrogen atom of the P–N bond of catalyst **154** showed that diaryl methane group with methyl substituent on aromatic ring afforded high enantioselectivity.

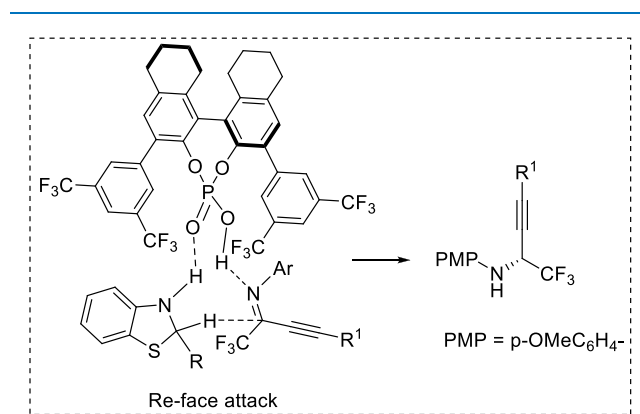
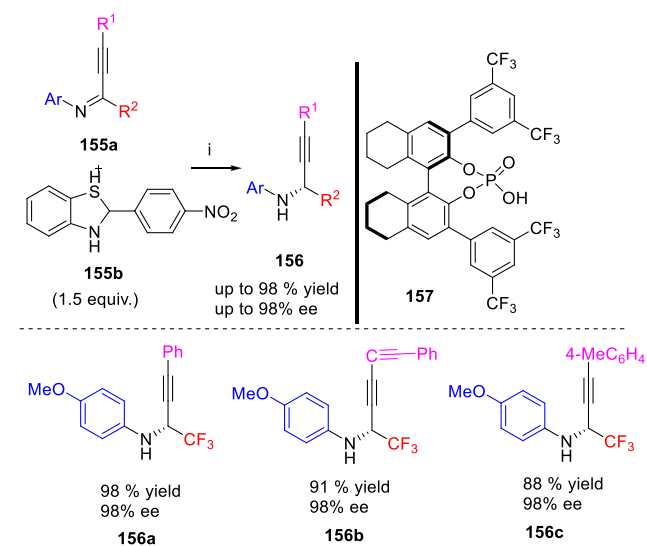
Anthranils with various functional groups, such as halides (F, Cl, Br), methyl ester, trifluoromethyl group, nitrile, silyl ether, and benzoate, were compatible, affording the [4 + 4] cycloaddition products *n* in good to excellent yields, diastereoselectivities, and enantioselectivities (up to 92% yield, 12:1 dr, 99% ee).

Peng and his group (Scheme 32; Figure 19) developed chemoselective catalytic transfer hydrogenation of fluorinated



**Figure 18. Mechanism of the reaction: Scheme 31.**

**Scheme 32. Reagents and Conditions: (i) H<sub>8</sub>-BINOL catalyst **157** (10 mol %), CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 48 h**



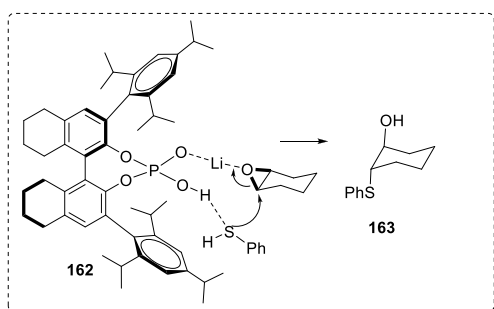
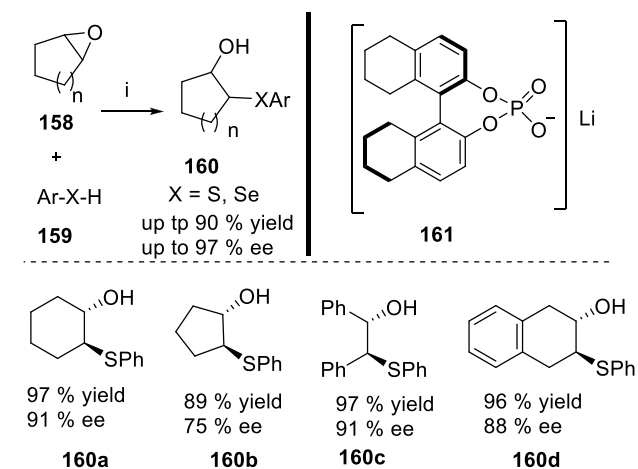
**Figure 19. Mechanism of the reaction: Scheme 32.**

alkynyl ketimines **155a** achieved by employing chiral phosphoric acid **157** as catalyst with benzothiazoline **155b** as hydride source, providing the corresponding chiral fluorinated propargylamine **156a–156c** products.<sup>39</sup>

Under optimal conditions the scope of various substituted fluorinated alkynyl ketimines (**156a**), *N*-arylsubstituted substrates with electron donating or electron withdrawing substituent on the aromatic ring, slickly converted to the corresponding products in high yields and excellent enantioselectivities.

Antilla and his group reported (Scheme 33; Figure 20) an enantioselective method for desymmetrization of meso-

**Scheme 33. Reagents and Conditions: (i) Li, catalyst 161 (10–20 mol %), *p*-xylene, 4 Å molecular sieves, 48 h, rt**



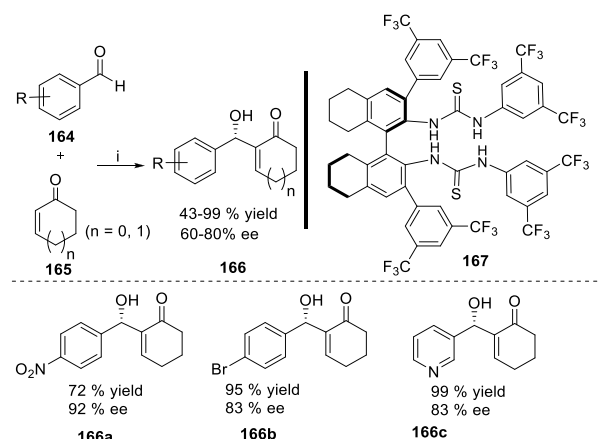
**Figure 20. Mechanism of the reaction: Scheme 33.**

epoxides **158** using aromatic thiols and aromatic selenium hydrides **160** using metal  $H_8$ -BINOL phosphates **161** resulting in  $\beta$ -hydroxyl sulfides and selenides **160a–160d** obtained in excellent yield with enantioselectivity.<sup>40</sup> Historically, a wide range of azide, amine, oxygen, and carbon-centered nucleophiles have been employed for the desymmetrization of meso-epoxides, but the use of thiols remains relatively limited. A recent report of Shibasaki and Sun for the epoxide ring opening using thiol is restricted to particular substrates. Antilla and his group used Li- $H_8$ -BINOL phosphate could activate epoxides toward nucleophilic addition, generating chiral 1,2-functionalized thiols. Aromatic thiols with electron withdrawing, donating groups, bulky thiols, heteroatom-containing functional groups produces  $\beta$ -hydroxy sulfides in excellent yield and asymmetric induction. Epoxides were screened by using fused six-membered rings, cycloheptene oxide, and cyclopentene oxide *cis*- and *trans*-1,4-cyclohexadiene dioxide as a substrate for

this reaction, thus obtaining the  $\beta$ -hydroxyl sulfide in excellent yield but only moderate ee. For acyclic epoxide, Li- $H_8$ -BINOL phosphate did not yield the desymmetrization product.

Liu and his group settled an asymmetric version of the Morita-Baylis-Hillman reaction using  $H_8$ -BINAM organocatalyst. Catalyst  $H_8$ -BINAM thiourea catalyst **167** was synthesized using  $H_8$ -BINAM and isothiocyanate (Scheme 34). Asym-

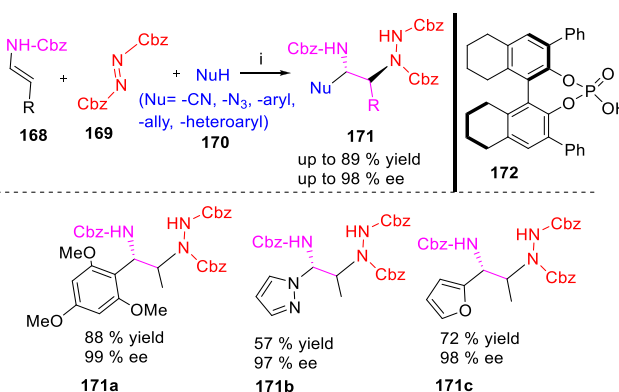
**Scheme 34. Reagents and Conditions: (i) catalyst 167 (20 mol %), DABCO (20 mol %), toluene, rt, 43–99%**



metric Morita-Baylis-Hillman reaction adduct was synthesized using 2-cyclohexen-1-one or 2-cyclopenten-1-one **165** with substituted aromatic aldehydes **164**. The organocatalyst  $H_8$ -BINAM was used in combination with 1,4-diazabicyclo[2.2.2]octane (DABCO). The adduct of Morita-Baylis-Hillman reactions **166a–166c** obtained up to 79% yield and up to 88% enantiomeric excess.<sup>41</sup>

Masson and his group described (Scheme 35) a chiral phosphoric acid **72** catalyzed electrophilic amination of

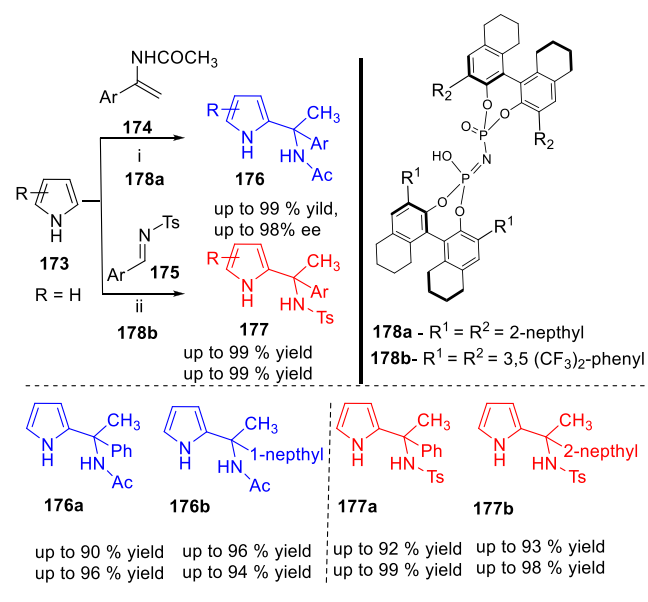
**Scheme 35. Reagents and Conditions: (i) catalyst 172 (10 mol %), NuH promoter; (ii) Raney Ni,  $R_2O$**



enecarbamates **168** with dibenzylazodicarboxylate **169** and oxygenated, aromatic ring, heterocycle, or thiol containing nucleophiles **170** affording a wide range of 1,2-disubstituted 1,2-diamines **171a–171c** with excellent enantioselectivity.<sup>42</sup>

Zhang and his group (Scheme 36) developed an aza-Friedel-Crafts reaction between pyrrole **173** and enamides **174** (*N*-acetyl)/**175** (*N*-tosyl). The  $H_8$ -BINOL phosphoramidate catalyst **178a** was used for reaction of pyrrole **173** with enamide **174** employing catalyst **178a** to give product **176**. Similarly,

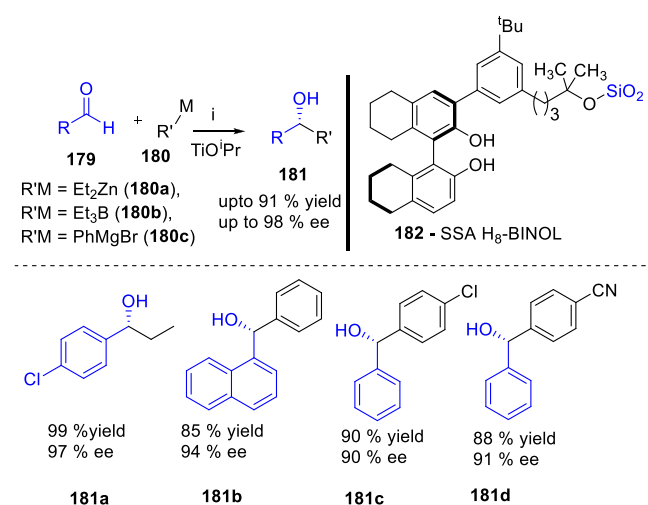
**Scheme 36. Reagents and Conditions:** (i) 0.2 mol % catalyst 178a; (ii) 0.3 mol % cat. 178b



catalyst **178b** was used for the reaction between pyrrole **173** with *N*-tosyl enamide **175** to afford product **177**. The products aryl-(2-pyrrolyl)methanamine **176a**–**176b** and **177a**–**177b** mentioned in the reaction were obtained in excellent yield.<sup>43</sup> Optimization of various solvents showed that 96% ee was observed when the solvent was 1,4-dioxane with less chemoselectivity. The yield was improved intensely by adding 5 Å molecular sieves.  $\alpha$ -Phenyl-substituted enamides **174** with electron withdrawing or donating groups at the ortho, meta, and para positions of the phenyl rings gave rise to the quaternary carbon centered products **177a**–**b** in high yields with excellent enantioselectivities.

Harada and his group developed a protocol (Scheme 37) using 3-aryl H<sub>8</sub>-BINOL **182** grafted on the surface of silica gel using a hydrosilane derivative as a precursor, and the ensuing silica-supported ligand was employed in the enantioselective alkylation and arylation of aromatic aldehydes **179** in the

**Scheme 37. Reagents and Conditions:** (i) catalyst **182** (6 mol %) reused 14 times

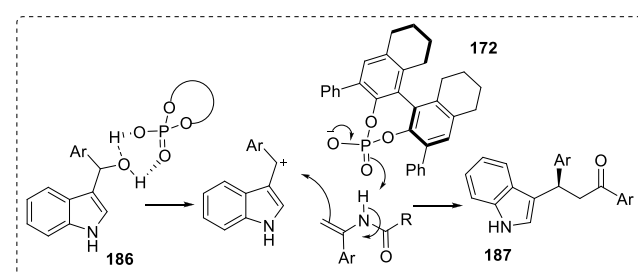
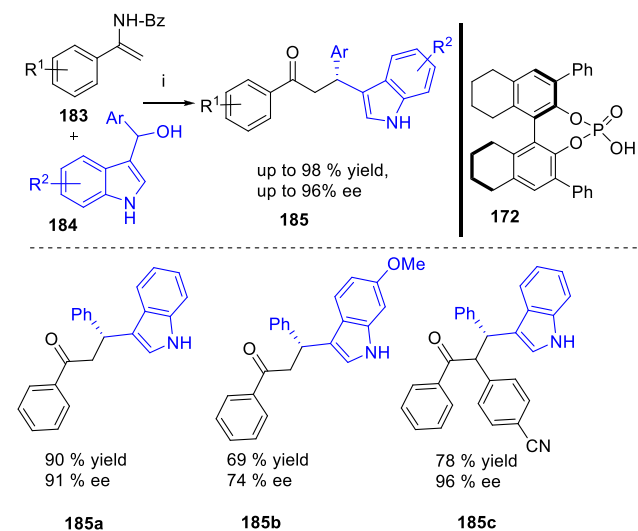


presence of Ti(OiPr)<sub>4</sub>. The reactions via Et<sub>2</sub>Zn, Et<sub>3</sub>B, and ArMgX **180** reagents corresponding chiral alcohols **181a**–**181d** with excellent ee.<sup>44</sup>

The heterogeneous titanium catalyst derived from the silica-supported H<sub>8</sub>-BINOL ligand exhibited high activity and enantioselectivity at 6 mol % loading not only in the reaction using Et<sub>2</sub>Zn but also using Et<sub>3</sub>B and aryl Grignard reagents with the fact that it could be reused up to 14 times without appreciable deterioration of the activity.

Chiral counterion directed organocatalysis reaction was established by Gong and his group. The protocol described reaction (Scheme 38; Figure 21) of enamides **183** with indolyl

**Scheme 38. Reagents and Conditions:** (i) cat. (10 mol %) **172**, CH<sub>2</sub>Cl<sub>2</sub>, –30 °C

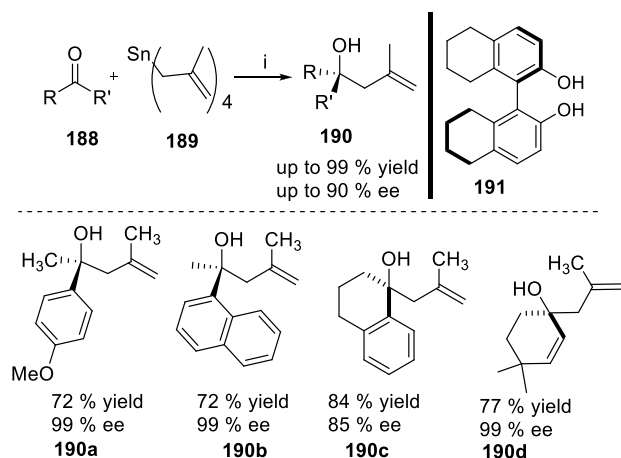


**Figure 21. Mechanism of the reaction: Scheme 38.**

alcohols **184** using H<sub>8</sub>-BINOL phosphoric acid **172**. H<sub>8</sub>-BINOL reacted with indolyl alcohol **186** to give a carbocation as an electrophilic center. Nucleophile enamide **183** attacks **186** selectively from one side to afford  $\beta$ -aryl 3-(3-indolyl)propanones **185a**–**185c** in high yields (up to 96%) and enantioselectivity (up to 96% ee).<sup>45</sup> A survey of solvents revealed that dichloromethane initiates reaction with excellent yield. The *N*-protecting group of enamide has a great influence on the enantioselectivity, hence replacement of Ac (acetyl) with benzoyl as the protecting group improves the yield. The scope of the reaction explored for the aryl substituent of (1*H*-indol-3-yl)(aryl)methanols (**184**) depicted that electron-rich and electron-deficient aryl groups were tolerable.

Walsh and co-worker reported (Scheme 39) catalytic asymmetric addition of allyl group to ketones and generated  $\alpha$ -allylic alcohols. Methylation of ketones **188** achieved by

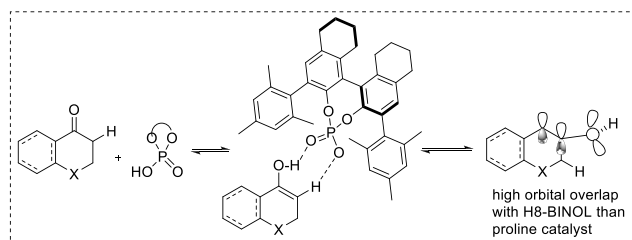
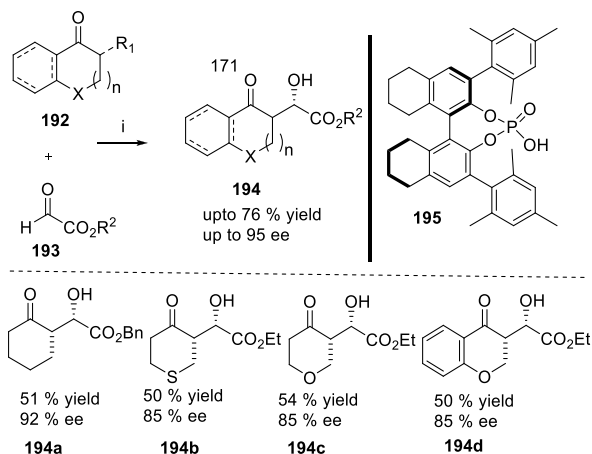
**Scheme 39. Reagents and Conditions:** (i) catalyst **191** (30 mol %),  $\text{Ti}(\text{O-}i\text{Pr})_4$  (30 mol %), isopropanol (20 equiv),  $\text{CH}_2\text{Cl}_2$ , rt



employing catalytic system of titanium tetraisopropoxide and  $\text{H}_8$ -BINOL. Various ketones **188** and tetramethylallylstannane **189** reacted enantioselectively to afford tertiary homoallylic alcohols **190a–190d** in excellent yields (up to 99% and enantioselectivity up to 90%). Ozonolysis of the resulting products provides access to chiral  $\alpha$ -hydroxy ketones, which are not readily prepared from direct asymmetric aldol reaction of acetone with ketones.<sup>46</sup> The catalyst screening study for various substituent at 3,3' and 6,6' positions of (R)-BINOL phosphoric acid produced low enantioselectivity. Further comparative study with these BINOL phosphoric acids with  $\text{H}_8$ -BINOL chiral phosphoric showed that  $\text{H}_8$ -BINOL produced better results. To maximize enantioselectivity, a variety of solvents were examined in the protocol with  $\text{H}_8$ -BINOL, and it was reported that acetonitrile and propionitrile produce highest yield.

Blanchet and co-worker developed (Scheme 40; Figure 22) an enantioselective aldol reaction between ethyl 2-oxoacetate **193** and alicyclic ketones **192** to afford chiral  $\beta$ -hydroxyketones **194a–194d**. The protocol was developed by using Bronsted acid catalyst- $\text{H}_8$ -BINOL-derived phosphoric acid **195**. Various catalysts like pTSA, BINOL, and  $\text{H}_8$ -BINOL were screened, and it was found that  $\text{H}_8$ -BINOL gives better stereoselectivity.

**Scheme 40. Reagents and Conditions:** (i) catalyst **195** (5 mol %), toluene, rt–0 °C



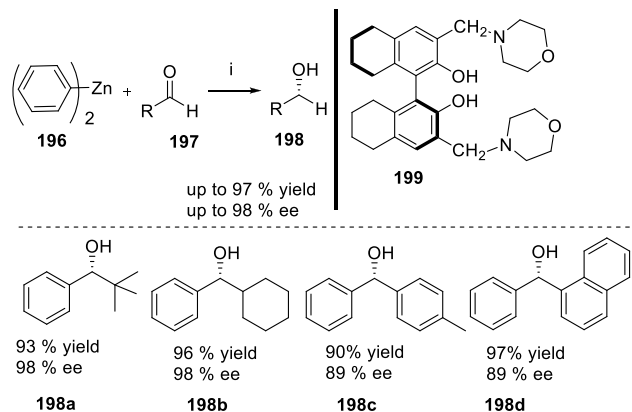
**Figure 22.** Mechanism of the reaction: Scheme 40.

The protocol tolerates diverse nucleophilic ketones **192** present in alicyclic rings, aliphatic groups, fused alicyclic-aromatic rings, and  $\alpha,\beta$ -unsaturated ketones. The electrophilic precursor aldehydes **193** like benzyl glyoxalate, *i*-propyl glyoxalate, and ethyl glyoxalate were screened and their tolerability reported. This method affords an efficient synthesis of various  $\beta$ -hydroxy ketones, most of which could not be synthesized using enamine organocatalysis as possible by present protocol.<sup>47</sup>

To optimize the yield and selectivity of the aldol product of various nonprotic solvents tested (toluene, xylene, THF,  $\text{Et}_2\text{O}$ ,  $\text{Bu}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{CN}$ ), toluene was identified to afford the highest diastereo- and enantioselectivity at room temperature. Interestingly, reactions could be performed at 50 °C with little erosion of enantioselectivity. Decreasing the reaction temperature had a beneficial impact on the overall selectivity. An optimal amount of 5 mol % catalyst was determined, while 1.5 mol % led to slightly decreased selectivity and 10 mol % to no improvement. Carrying out the reaction in nearly solventless conditions, using only toluene provided by the commercial solution of the glyoxylate, led to a significant improvement of both reaction rates and selectivities (dr syn/anti 70:30 and 93:7 er for the syn isomer). Investigated nucleophile partners (**192**) such as pentan-2-one, tetrahydrothiopyran-4-one, tetrahydropyran-4-one, and cyclopentanone gave slightly lower selectivities than cyclohexanone under optimized reaction conditions.

Lin Pu and co-workers reported (Scheme 41; Figure 23) the addition of diphenylzinc **196** to aromatic aliphatic aldehydes

**Scheme 41. Reagents and Conditions:** (i) 10 mol % catalyst **199**, THF, rt



**197** catalyzed by organocatalyst **199** to yield chiral alcohols **198a–198d** up to 89% ee.<sup>48</sup> Chiral catalyst (S)-4 **199** used to catalyze the reaction of diphenylzinc with various aliphatic and aromatic aldehydes by applying the optimum conditions exhibited high enantioselectivity for all the substrates. The



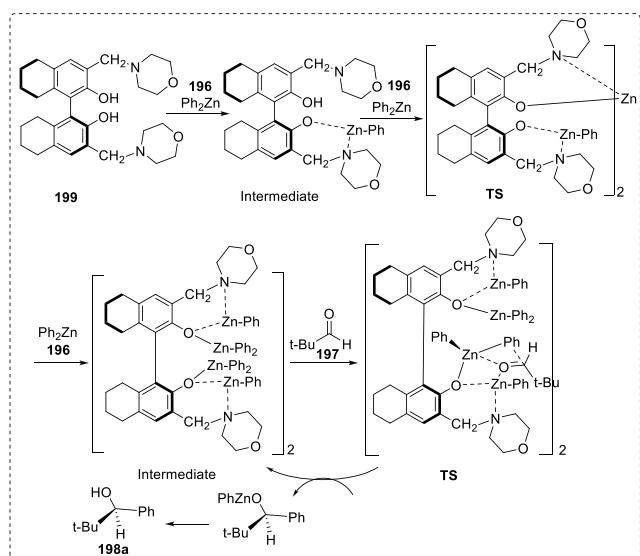
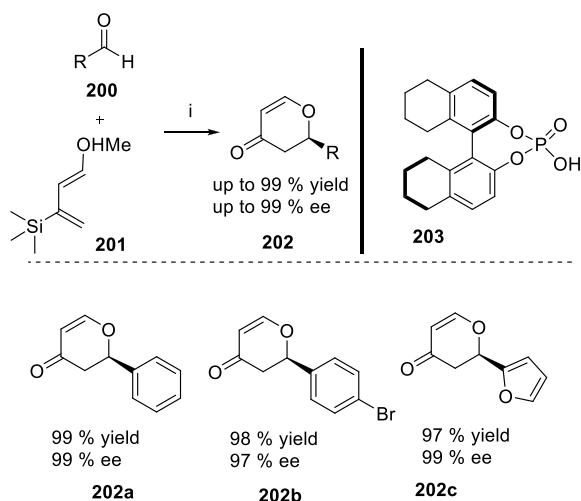


Figure 23. Mechanism of the reaction: Scheme 41.

solvent screened showed that THF is the best solvent in the presence of 10 mol % catalyst.

Ding and his group (Scheme 42) successfully applied a combinatorial coordination chemistry strategy combined with

Scheme 42. Reagents and Conditions: (i) 0.1–0.005 mol %  $\text{Ti}(\text{O}^i\text{Pr})_4$ ; catalyst 203 (1:1), solvent free, rt; (ii)  $\text{CF}_3\text{COOH}$

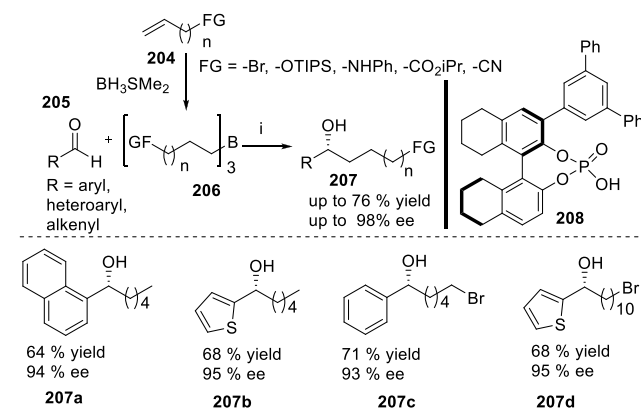


high-throughput screening techniques to engineer practical enantioselective catalysts for asymmetric hetero-Diels–Alder reaction. Reaction of varied substituted aldehydes **200** with Danishefsky's diene **201** in the presence of  $\text{H}_8$ -BINOL catalytic system **203** produced heterodienone **202** with excellent yield and enantioselectivity.<sup>49</sup> The diol ligands employed for catalyst preparation include commercially available or easily prepared tartaric acid derivatives, BINOL, 6,6'- $\text{Br}_2$ -BINOL,  $\text{H}_4$ -BINOL,  $\text{H}_8$ -BINOL, 3,3'- $\text{Br}_2$ -BINOL, 3,3'- $\text{H}_8$ -BINOL, 3,3'- $\text{Ph}_2$ -BINOL, 3,3'- $\text{Ph}_2$ - $\text{H}_8$ -BINOL, and 3,3'-(SPh)<sub>2</sub>- $\text{H}_8$ -BINOL were examined, and it was concluded that **203** is an excellent catalyst. The solvent effect was examined on the reaction in both catalyst preparation and the reaction process, and it was found that the catalyst prepared in toluene is superior to that obtained in diethyl ether. The most important

report was that solvent-free conditions gave quantitative yield and much higher enantioselectivity (up to 99%). Screening of diversified substituted aromatic and heterocyclic aldehyde **200** showed up to 98% ee and >99% yield.

Harada and his group developed (Scheme 43) a methodology for the synthesis of chiral secondary alcohols **207** employing

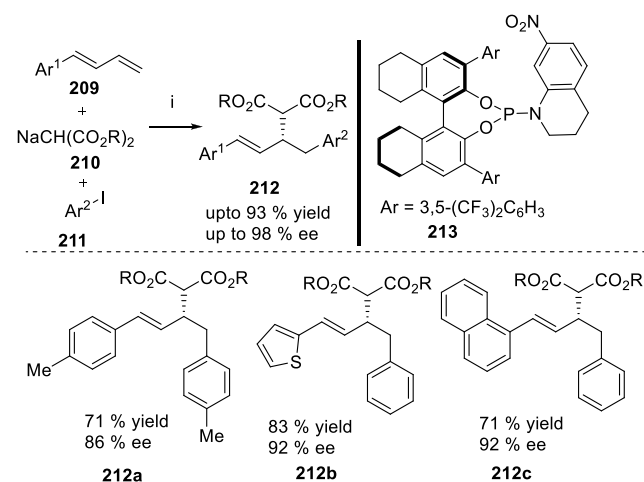
Scheme 43. Reagents and Conditions: (i) catalyst **208** (5 mol %),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (3 equiv), THF, reflux



organocatalyst. The protocol mentioned is enantioselective alkylation of aldehydes **205** using functionalized alkylboron reagents **206**. This reagent is prepared from terminal olefin precursors **204** by hydroboration reaction. Akly bornane **206** undergo enantioselective addition to aldehydes in the presence of a catalytic amount (5 mol %) of 3-(3,5-diphenylphenyl)- $\text{H}_8$ -BINOL **208**. Reaction produced corresponding functionalized alcohols **207a**–**207d** in 99% ee in the presence of excess titanium tetraisopropoxide.<sup>50</sup>

Gong and his group performed a novel asymmetric multi-component reaction (Scheme 44). The protocol settled under inert atmosphere by adding initially  $\text{Pd}(\text{OAc})_2$  phosphoramidate ligand **213** and dialkylmalonate **210** in a Schlenk tube. Under vacuum 1,3-butadiene **209** and aryl iodides **211** in MTBE were added. This reaction proceeded via a palladium-catalyzed cascade arylation and asymmetric allylic alkylation reaction, providing an efficient strategy for the enantioselective 1,2

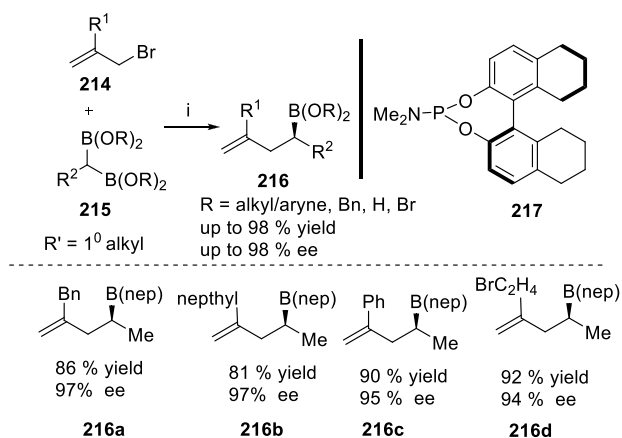
Scheme 44. Reagents and Conditions: (i)  $\text{Pd}(\text{OAc})_2$  (5 mol %), catalyst **213** (10 mol %), MTBE, 80 °C, 72 h



difunctionalized **212a–212c** product.<sup>51</sup> Reaction optimization study using solvents like MTBE, THF, DCM, MeCN, and DMF showed that the highest enantioselectivity of 87% ee was observed in MTBE. A variety of arylbutadienes **209** and aryl iodides **211**, possessing same aryl groups, were first examined in the presence of 5 mol % of Pd(OAc)<sub>2</sub> and 10 mol % of catalyst in MTBE at 80 °C. It is necessary to mention that the structures of two different regiomers are generated. The presence of either electron-releasing or -deficient substituent at the para-position was nicely tolerated and highly regioselectively generated the target products in high yields and enantioselectivity. The substitution pattern had considerable effect on both regio- and stereoselectivities.

Baik and his group invented an asymmetric protocol using (Scheme 45) copper bromide and H<sub>8</sub>-BINOL catalytic system

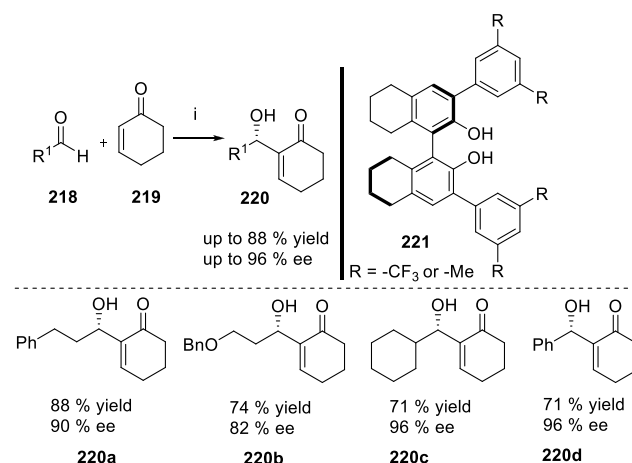
**Scheme 45. Reagents and Conditions: (i) 0.1 equiv catalyst 217, 5 mol % CuBr, 2 equiv LiO<sup>t</sup>Bu, THF, rt, 30 h**



for enantiotopic selective allylation of gem-diborylalkanes **215** with allyl bromides **214**. The combination of copper(I) bromide and H<sub>8</sub>-BINOL derived phosphoramidite ligand **217** worked out to be the most effective catalytic system to provide various enantio-enriched homoallylic boronate esters **216a–216d**. The product **216** contained a boron-substituted stereogenic center that is solely derived from gem-diborylalkanes **215**, in good yields with high enantiomeric ratios under mild conditions.<sup>52</sup> The effect of an amino group of (R)-BINOL-derived phosphoramidite ligands found them to have negative effects; on the other hand, (R)-H<sub>8</sub>-BINOL-based phosphoramidite as a ligand afforded **216** in good yield with 95:5 er. Spirobiindandiol and TADDOL-derived phosphoramidite ligand displayed lower efficiencies. Allyl bromides **214** bearing methyl, hexyl, cyclohexyl, and phenyl ring bearing electronically neutral, donating, or withdrawing substituents, naphthyl- and heteroaryl-containing as a substituent at the C<sub>2</sub>-position were produced in good yields and er.

Schaus and co-worker performed (Scheme 46) the Morita-Baylis-Hillman reaction using organocatalyst. The reaction started with the precursor by the addition of cyclohexanone **219** to aldehydes **218** in the presence of catalyst **221** and produced chiral alcohols **220** with maximum yield and enantioselectivity.<sup>53</sup> The catalyst optimization and recruitment study revealed that partially reduced H<sub>8</sub>-BINOL with substituent at 3,3' influences the yield of the reaction. Screening of trialkylphosphines such as PMe<sub>3</sub> or P(*n*-Bu)<sub>3</sub> in the reaction afforded a yield similar to that of PEt<sub>3</sub> but lower enantioselectivities (50% and

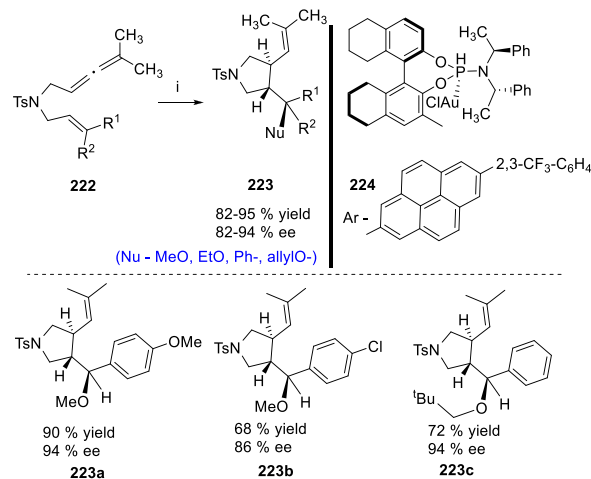
**Scheme 46. Reagents and Conditions: (i) 2–20 mol % catalyst 221, P(OEt)<sub>3</sub>**



64% ee, respectively). The variety of aromatic and aliphatic aldehydes screened with a diverse substituent pattern leads to optimum yield and enantioselectivity.

Toste and his group (Scheme 47) utilized phosphoramidite ligand **224** with AuI catalyst in the development of intra-

**Scheme 47. Reagents and Conditions: (i) catalyst 224 AuCl (5 mol %), 5% AgBF<sub>4</sub>, MeOH**

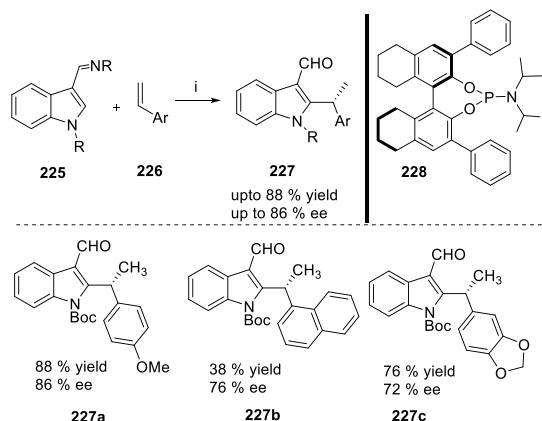


molecular cycloadditions of allenenes **223** to give 3,4-disubstituted pyrrolidines **223** as major products.<sup>54</sup> Comparative study of BINOL with diverse 3,3' substituent, VANOL backbone, VAPOL backbone derived catalyst, and H<sub>8</sub>-BINOL 3,3' substituted catalyst showed that H<sub>8</sub>-BINOL-based catalyst favors reaction. Allenes **222** with various electron donating and withdrawing groups cyclizes in the presence of MeOH, H<sub>2</sub>O, aromatic rings, and allyl alcohol EtOH to produce corresponding products. Stereochemical observation noted in this protocol that both cis and trans pathways are competitive, but in the presence of a nucleophile (MeOH), the trans pathway is preferred. On the other hand, in the absence of a viable nucleophile, the cis pathway is operative. These findings also suggest that a more polar solvent, such as MeNO<sub>2</sub>, could further increase the preference for the trans pathway. In addition, we speculate that the interaction between the carbocation and gold

may serve to direct the attack of the nucleophile from the opposite side trans attack.

Yoshikai and his group (Scheme 48) developed a protocol for enantioselective installation of an alkyl group at the C<sub>2</sub> position

**Scheme 48. Reagents and Conditions: (i) catalyst Co(acac)<sub>3</sub>, L-228, Me<sub>3</sub>SiCH<sub>2</sub>MgCl, THF, rt, 12 h, 88%**

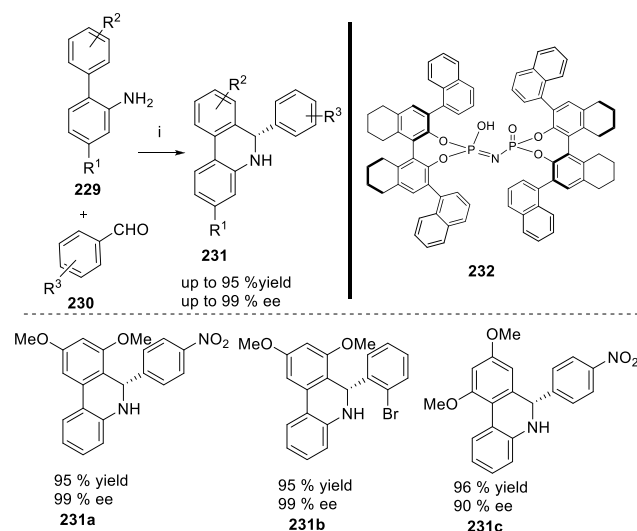


of indole **225** whose nitrogen is protected by the Boc protecting group. Styrene **226** was used as the alkyl source. Cobalt–chiral phosphoramidite catalyst generated from Co(acac)<sub>4</sub> and **228** was used to induce the required enantioselectivity. The reaction affords 1,1-diarylethane **227** products in moderate to good yields with good enantioselectivities under mild conditions.<sup>55</sup> The chiral catalyst screening during optimization of chiral ligands like BINOL-phosphoramidite, (S)-Monophos (MOP), (–) TADDOL-phosphoramidite, (S)-BINAP, and H<sub>8</sub>-BINOL-phosphoramidite depicted that H<sub>8</sub>-BINOL-phosphoramidite results high yield and enantioselectivity. Diversified *N*-protected indoles **225** with protection at nitrogen such as benzyl, phenyl, Cbz, Tosyl (Ts), Boc, and –CONEt<sub>2</sub> were screened, and results were excellent with -Boc protection. The reactions of indole with a substituent on the 5- or 6-position and 4-methoxystyrene were achieved with enantioselectivities higher than 83% ee. The 7-ethylindole substituent resulted in reduced reactivity and enantioselectivity. Use of CoBr<sub>2</sub> instead of Co(acac)<sub>3</sub> was essential to achieve a reasonable conversion; otherwise, the reaction was rather sluggish.

Styrenes **226** bearing a para- or meta-substituent on the aromatic ring afforded the corresponding hydroarylation products in yields of 48–88% ee. High ee values (85–86%) were achieved in the reactions of 4-methoxystyrene and 4-trimethylsilylstyrene.

Zhang and his group developed (Scheme 49) organocatalytic H<sub>8</sub>-BINOL **232** catalyzed Pictet-Spengler reaction of biphenyl-2-amines **229** and aromatic aldehydes **230** to yield 6-aryl-5,6-dihydrophenanthridines **231** with high yields (up to 98%) and enantioselectivities (up to 99% ee).<sup>56</sup> Solvents screened with the best catalyst **232** enantioselectivity could be improved to 79–89% ee by using *o/m*-xylene as solvent, but the yield decreased slightly. The reaction was performed in chloroform resulting in 97% yield and 93% ee obtained in only 18 h. The catalyst loading from 2% to 10% 5 Å molecular sieves in chloroform at 0 °C. Aromatic aldehydes with different substituents like electron withdrawing 4-NO<sub>2</sub>, 4-CN, and 4-CF<sub>3</sub> groups afforded products with excellent yields and enantioselectivities (95–98% yields, 94–99% ee). The scope of biphenyl-2-amines was subsequently

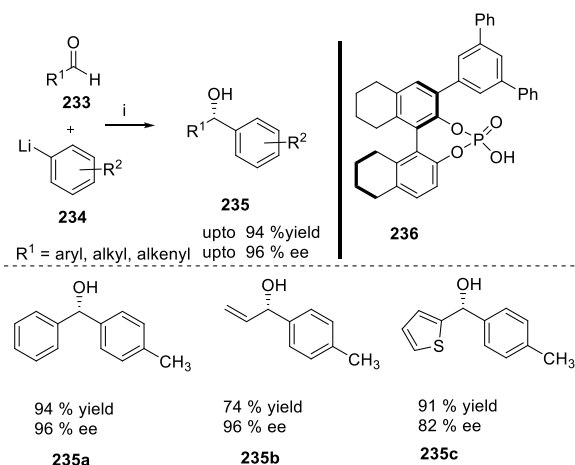
**Scheme 49. Reagents and Conditions: (i) 5 mol % catalyst 232, CHCl<sub>3</sub>, 5 Å molecular sieves**



investigated with electron withdrawing substituents on the 4-position of the aniline moiety providing the corresponding 5,6-dihydrophenanthridines **232** in 79–88% yields and 82–99% ee.

Harada and his group (Scheme 50) described a method for preparing enantio-enriched secondary alcohols **235** by starting

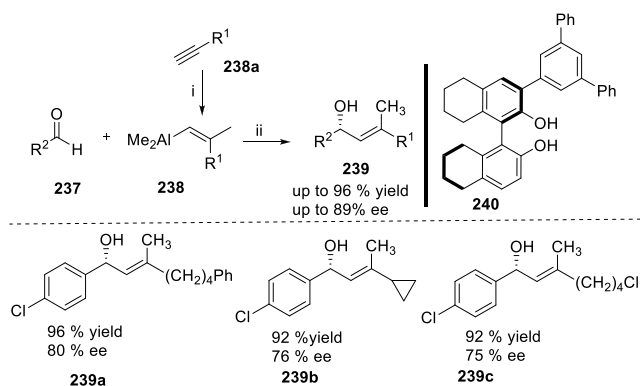
**Scheme 50. Reagents and Conditions: (i) catalyst 236 (2 mol %), Ti(O<sup>i</sup>Pr)<sub>4</sub>, MgBr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>**



from aryl bromides **231** and aldehydes. Aryl bromides were first treated with BuLi, and the resulting aryllithium reagents **234** were mixed with titanium tetraisopropoxide and magnesium bromide in the presence of 3-(3,5-diphenylphenyl)-H<sub>8</sub>-BINOL **236** and titanium tetraisopropoxide, producing the corresponding chiral alcohols **235a**–**235c** in high enantioselectivities and in high yields.<sup>57</sup>

An enantioselective protocol for the synthesis of β,β-disubstituted allylic alcohols **239** has been developed by Harada and his group (Scheme 51). The reaction was started with readily available terminal alkynes **238a** and aldehydes **237**. Trisubstituted (*E*)-vinylaluminum reagent **238** was generated regio- and stereoselectively by the Zr-catalyzed carboalumination of the alkynes **238** with Me<sub>3</sub>Al. Intermediate **238** was used in consequent enantioselective addition reactions with alde-

**Scheme 51. Reagents and Conditions:** (i)  $\text{Me}_3\text{Al}$ ,  $\text{Cp}_2\text{ZrCl}_2$ ; (ii) 5 mol % catalyst **240**,  $\text{Ti}(\text{iOPr})_4$ , THF, 0 °C

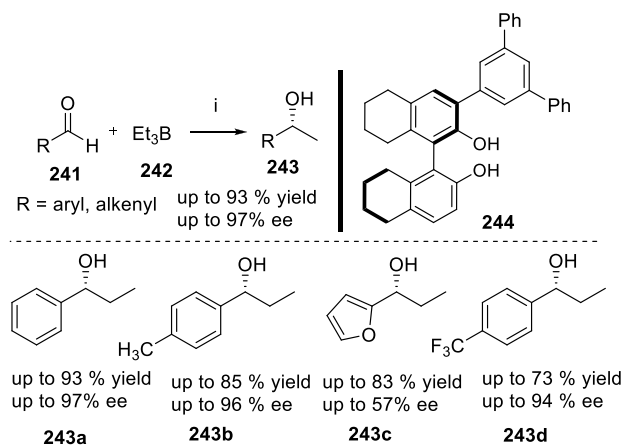


aldehydes **237** using a DPP- $\text{H}_8$ -BINOL-derived titanium catalyst **240** at a catalytic amount.<sup>58</sup>

To replace the undesirable racemic pathway, reaction parameters, such as the amount of  $\text{Me}_3\text{Al}$  (2.4 equiv) for the carbometalation step, temperature (25 °C), solvent (THF), and concentrations of catalyst, were optimized.

Harada and his group developed a protocol (Scheme 52) for the asymmetric alkylation of aldehydes **241** by triethyl borane

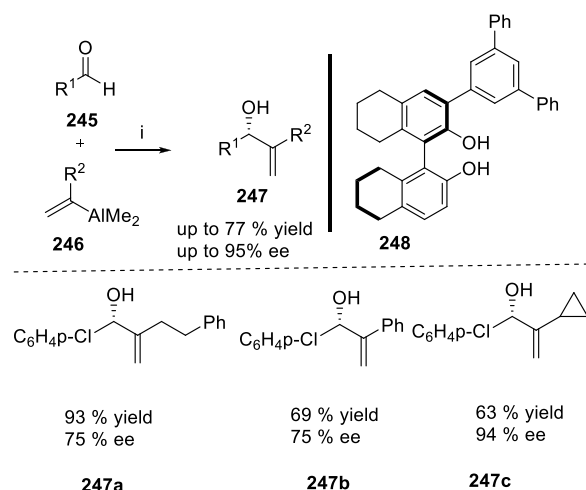
**Scheme 52. Reagents and Conditions:** (i) 2 mol % catalyst **244**,  $\text{Ti}(\text{OiPr})_4$  (3 equiv), THF, 66 °C



**242** and chiral catalyst 3-(3,5-diphenylphenyl)- $\text{H}_8$ -BINOL-derived titanium(IV) **244** in the presence of an excess amount of titanium tetraisopropoxide. The reaction proceeds with a low catalyst, exhibiting high enantioselectivity in the chiral secondary alcohol **243** product.<sup>59</sup>

Harada et al. developed a general one pot method (Scheme 53) for the highly enantioselective synthesis of  $\alpha$ -substituted allylic alcohols **247a**–**247c** starting from readily available terminal alkynes **246** and aldehydes **245** and proceeding via vinylaluminum reagents.  $\text{Ni}(\text{dppp})\text{Cl}_2$  (3 mol %) was treated with terminal alkyne (3 equiv) and  $\text{Me}_2\text{AlH}$  (3 equiv) and stirred, and subsequently  $\text{H}_8$ -BINOL substituted aldehydes and titanium isopropoxide were added at 0 °C to produce  $\alpha$ -substituted allylic alcohols. High enantioselectivities were achieved at a low catalyst loading (5 mol %) in the subsequent addition reaction. The study showed the applicability of the DPP- $\text{H}_8$ -BINOL derived titanium catalyst **248** for the

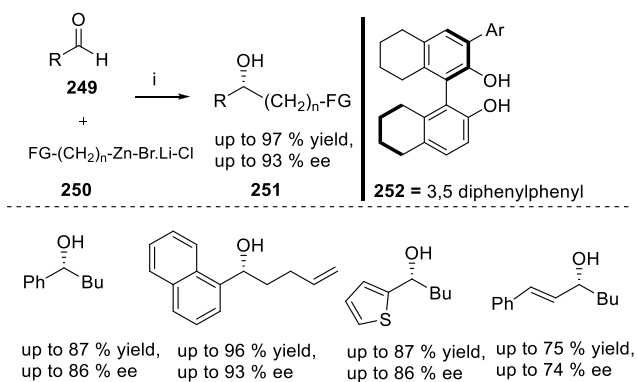
**Scheme 53. Reagents and Conditions:** (i) 5 mol % catalyst **248**,  $\text{Ti}(\text{O}^i\text{Pr})_4$  (3 equiv), THF, 0 °C



enantioselective carbonyladdition of organoaluminum reagents **246** and demonstrates the versatility of this catalytic system.<sup>60</sup>

Functionalized alkylzinc halides **250** can be employed in the enantioselective addition to aldehydes **249** by using a titanium(IV) catalyst derived from a  $\text{H}_8$ -BINOL **252** in the presence of  $[\text{Ti}(\text{OiPr})_4]$  and  $\text{MgBr}_2$  (Scheme 54). A range of functionalities,

**Scheme 54. Reagents and Conditions:** (i)  $[\text{Ti}(\text{OiPr})_4]$  (7.2 equiv) and catalyst **252**,  $\text{MgBr}_2$  (1.2 equiv),  $\text{CH}_2\text{Cl}_2$ , 0 °C, 3 h

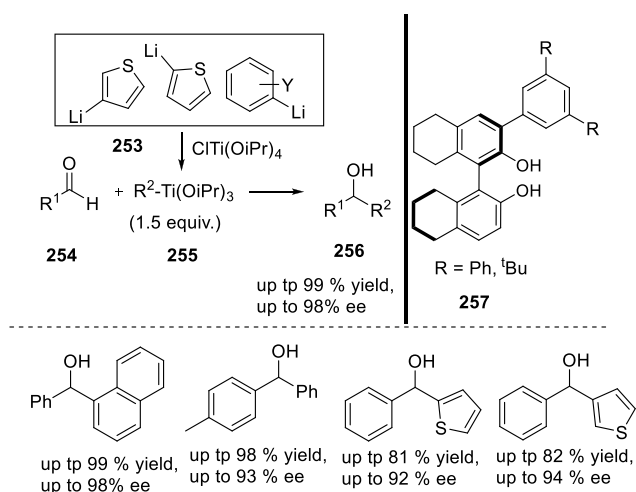


including olefin, chlorine atoms, protected alcohols, amides, and cyano groups, are tolerated in the present reaction, providing the corresponding functionalized alcohols **251** in high yields and enantioselectivities.<sup>61</sup>

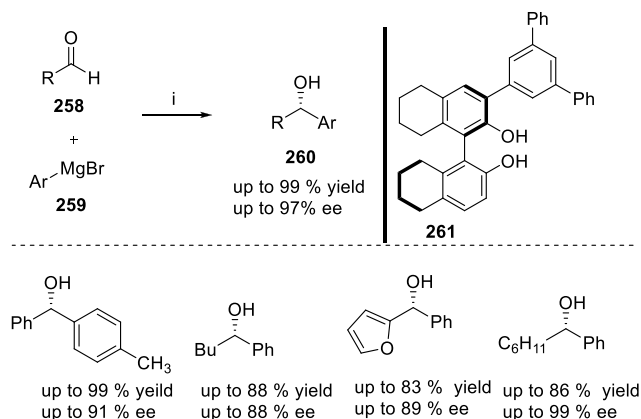
Harada and his co-worker performed arylation of the carbonyl group of diversified aldehydes **254** enantioselectively with organotitanium **255** and  $\text{H}_8$ -BINOL catalyst. Heteroaryl-lithium reagents **253** were treated with  $\text{Ti}(\text{OiPr})_3$  to produce organotitanium precursor **255**. Titanium complexes formed with  $\text{H}_8$ -BINOL **257** (Scheme 55) exhibit excellent catalytic activity for nucleophilic addition of heteroaryl group across the carbon oxygen bond of aldehyde **254**. The protocol produced diaryl-, aryl-, heteroaryl-, and diheteroarylmethanol derivatives **256** in high enantioselectivity at low catalyst loading (0.2–2 mol %).<sup>62</sup>

Harada and his group (Scheme 56) investigated that Grignard reagent **259** can be used in asymmetric arylation of aldehydes **258** for the synthesis of chiral alcohols **260** in the presence of the

**Scheme 55. Reagents and Conditions:** (i) 0.2–2.0 mol % catalyst **257**, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C



**Scheme 56. Reagents and Conditions:** (i) 2 mol % catalyst **261**, Ti(O<sup>i</sup>Pr)<sub>4</sub> (1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 3 h

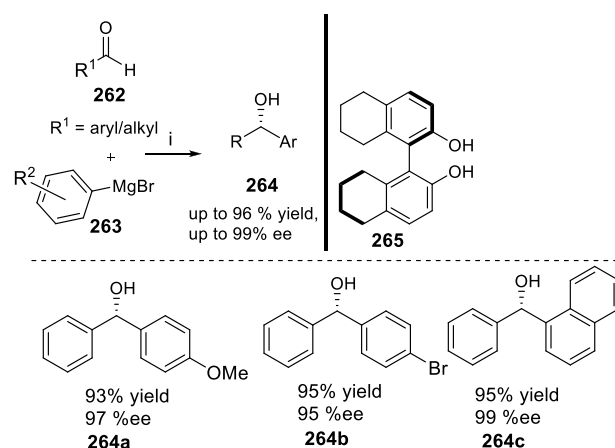


chiral titanium catalyst derived from H<sub>8</sub>-BINOL **261** and titanium tetraisopropoxide.<sup>63</sup> The scope of the protocol was expanded to electron withdrawing and donating group phenyl rings of the Grignard reagent and aldehydes with aryl and alkyl groups.

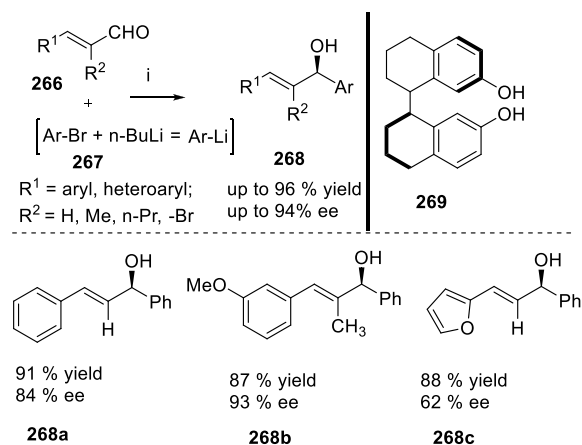
Da and his group (Scheme 57) have successfully employed H<sub>8</sub>-BINOL organocatalyst **265** for catalytic asymmetric arylation of aldehydes **262** by using a variety of aryl and heteroaryl Grignard reagent **263** with enantioselectivities as high as 99% of chiral alcohols **264** products.<sup>64</sup> Different ArMgBr reagents, with electron donating or electron withdrawing para-substituents, gave excellent enantioselectivities and yields, up to 99%. The aromatic and heteroaromatic aldehydes with electron donating and electron withdrawing substituents were found to undergo arylation with PhMgBr with excellent enantioselectivities at 94% yield and up to 99% ee.

Da and his group (Scheme 58) developed a protocol which involved a catalytic asymmetric addition of aryllithium nucleophiles **267** (generated from aryl bromide and *n*-BuLi) to  $\alpha$ -bromoaldehydes or  $\alpha$ -methylenealdehydes **266** to afford product  $\alpha$ -methyl or bromo-substituted allylic alcohols **268**. (S)-H<sub>8</sub>-BINOL catalyst **269** was used along with titanium isopropoxide under inert reaction condition.<sup>65</sup> A series of solvents, ether, toluene, acetonitrile, hexane, and THF, were investigated so as

**Scheme 57. Reagents and Conditions:** (i) 15% catalyst (S) H<sub>8</sub>-BINOL **265**, Ti(OiPr)<sub>4</sub>, THF, rt, 90% yield



**Scheme 58. Reagents and Conditions:** (i) cat. **269**, AlCl<sub>3</sub>, TMEDA, Ti(OiPr)<sub>4</sub>, THF/hexane, 40 °C, 3 h



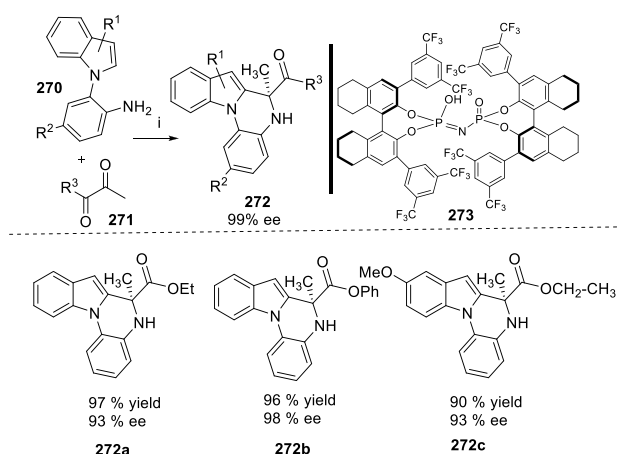
to improve enantiomeric excess. THF/hexane resulted in a slightly higher ee than THF; both of these achieved higher enantioselectivity than the other four solvents. Hence, THF/hexane was the ideal solvent. PhLi was produced in situ from PhBr and *n*-BuLi; the ratio of PhBr to *n*-BuLi could influence on the enantioselectivity.

Enantioselectivity was highest at 1:1.2 of PhBr/*n*-BuLi. The protocol was also applicable to electron donating and withdrawing substituent on precursor cinnamaldehyde **267** with excellent enantioselectivity.

Zhang and his group reported an asymmetric version of the Pictet-Spengler reaction for synthesis of chiral 5,6-dihydroindolo[1,2-*a*]quinoxalines **272** (Scheme 59). His group synthesized H<sub>8</sub>-BINOL-imidodiphosphoric acid catalyst **273** and applied for the Pictet-Spengler-type reaction involving indolyl anilines **270** and ketones **271**. They afforded products **272a–272c** with excellent selectivity.<sup>66</sup>

The enantioselectivity was increased when the reaction condition was optimized in terms of temperature (–20 °C), solvent (anisole), and organocatalyst (2 mol %) using molecular sieves. The synthetic scheme showed tolerance to a variety of substituent patterns on precursor molecules. Substrate **270** with a methyl group on a 3-position of the indole moiety gave rise to **273** in high yield with excellent enantioselectivity (up to 92% yield and up to 95% ee). Replacing the substituent ethyl group

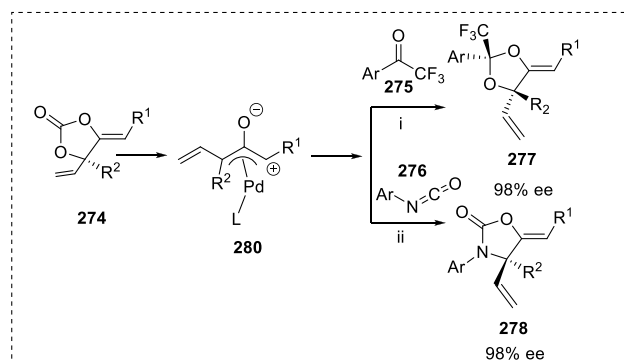
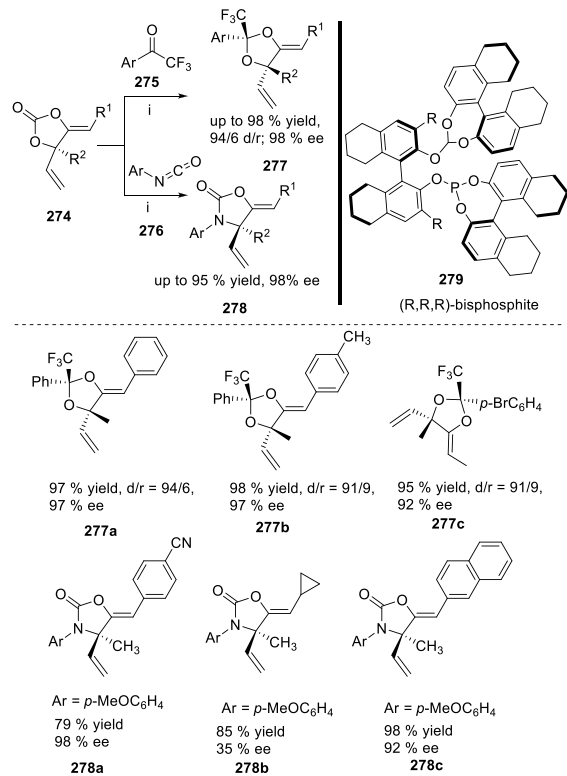
**Scheme 59. Reagents and Conditions: (i) 2 mol % catalyst 273, 5 Å molecular sieves anisole or 1,4 dioxane**



on pyruvate **271** to phenyl group afforded DHIQ **273** with 96% yield and 94% ee. Substrate **270** bearing electron donating, electron withdrawing, or aryl groups on the 5-position of the indole part reacted with either ethyl pyruvate/phenyl pyruvate **271** vigorously produced the chiral DHIQs **272** with high yields and enantioselectivities.

Cao and his team (Scheme 60; Figure 24) invented a protocol by using vinyl-substituted oxallyl carbonates **274** as a new C,O-dipole catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>-H<sub>8</sub>-BINOL **279** for enantioselective (3 + 2) cycloaddition. The corresponding oxallyl-Pd species **280** was weakly nucleophilic to react with activated carbonyl compounds **275** and **276**, affording multisubstituted

**Scheme 60. Reagents and Conditions: (i) Pd<sub>2</sub>(dba)<sub>3</sub>, ligand catalyst 279, THF**

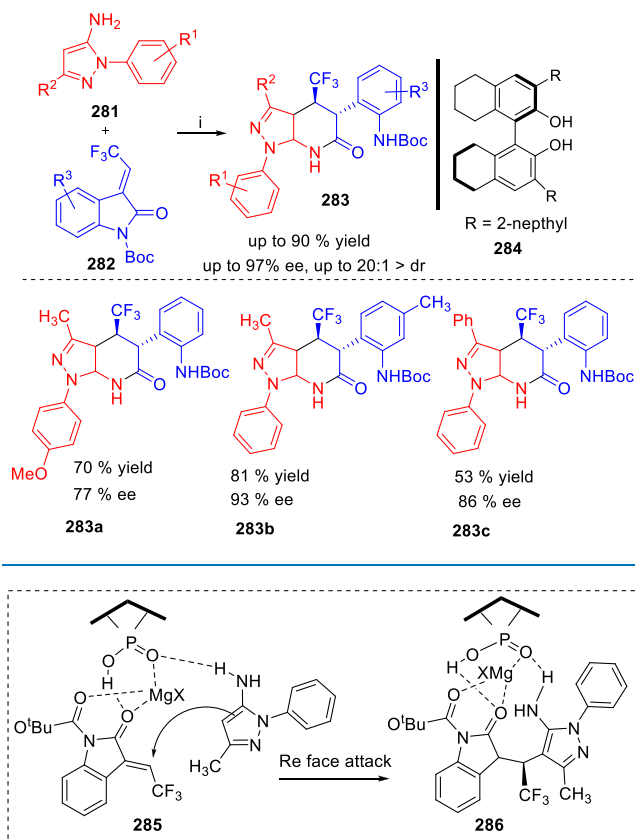


**Figure 24.** Mechanism of the reaction: Scheme 60.

and entio-enriched oxazolidinones **277** and 1,3-dioxolanes **278** with a high degree of chemo- and stereoselectivity. The synthetic transformations of the oxazolidinone product were carried out to build entio-enriched  $\alpha$ -chiral aminoketone and epoxy derivatives.<sup>67</sup>

Lin and his group (Scheme 61; Figure 25) applied a [3 + 2] addition protocol via a novel asymmetric Friedel–Crafts

**Scheme 61. Reagents and Conditions: (i) CPA catalyst 284, MgSO<sub>4</sub>, 1,4-dioxane; CCl<sub>4</sub> (1:1), 40 °C**



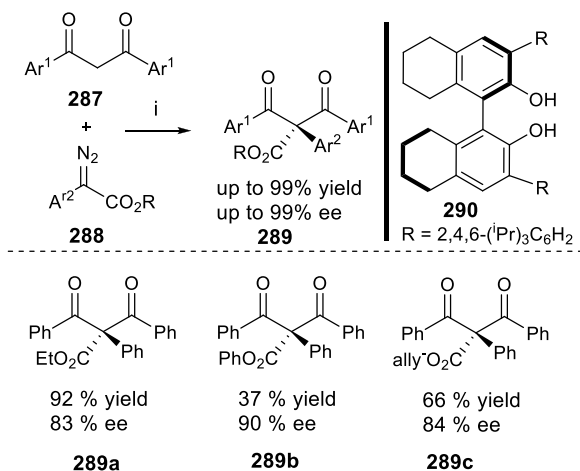
**Figure 25.** Mechanism of the reaction: Scheme 61.

alkylation/trans- amidation tandem reaction using *N*-arylpyrazoline **281** and 2-oxindole **282** for the enantio- and diastereoselective synthesis of pyrazolo[3,4-*b*]pyridin-6-ones **283** employing synergistic chiral phosphoric acid **284** and MgSO<sub>4</sub> catalysis.<sup>68</sup> Investigation of various additives such as MgSO<sub>4</sub>, Na<sub>2</sub>SO<sub>4</sub>, and molecular sieves (5 Å, 4 Å, and 3 Å molecular

sieves), but only  $\text{MgSO}_4$  is suitable for this conversion. Solvent screening also reports a mixed result about dichloroethane, 1,4-dioxane, and carbon tetrachloride.<sup>69</sup>

Hui and his group developed (Scheme 62) a photochemical carbene **288** insertion reaction in 1,4-dicarbonyl compound **287**

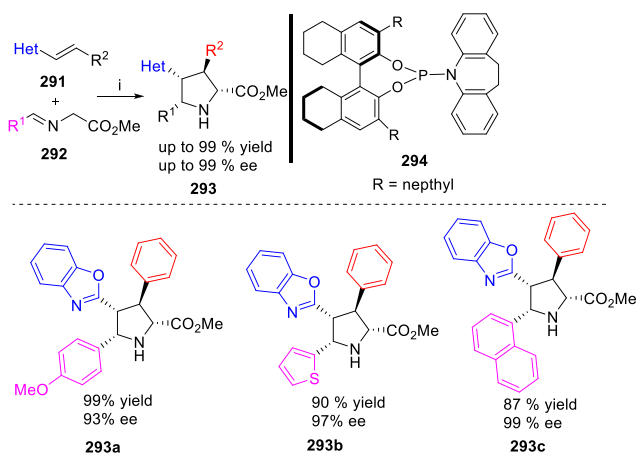
**Scheme 62. Reagents and Conditions: (i) 5 mol % catalyst 290,  $\text{MgSO}_4$ , DCM,  $\text{N}_2$ ,  $-25^\circ\text{C}$ , 24 h**



for the construction of enantio-enriched under visible light and  $\text{H}_8\text{-BINOL}$  catalyst **290**-based Bronsted catalyst.<sup>70</sup> The carbene species with transition metal can participate in a variety of chemical transformations. However, transition metal catalysts are difficult to recover and expensive and replaced by visible light (blue LED) in this protocol. During process optimization study, additives such as  $\text{Na}_2\text{SO}_4$ ,  $\text{MgSO}_4$ , and 4 Å molecular sieves were screened.  $\text{MgSO}_4$  was a beneficial additive and dichloromethane is a supportive solvent.

The  $\text{Cu}(\text{CH}_3\text{CN})\text{BF}_4$  reacted with chiral ligand **294** to produce a metal complex which catalyzes asymmetric 1,3-dipolar cycloaddition (Scheme 63) of azomethine ylides **292** and electron deficient alkenes **291**. The reaction produced various enantio-enriched pyrrolidine derivatives **293a–293c**. The protocol has been established by Wang and his co-workers.<sup>71</sup> Triethyl amine as a base and toluene as a solvent were identified as the best choices in terms of reactivity and

**Scheme 63. Reagents and Conditions: (i)  $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$  and L-294 (5 mol %),  $\text{Et}_3\text{N}$  (20 mol %), PhMe,  $10^\circ\text{C}$**



enantioselectivity. Enantio-enriched pyrrolidine derivatives are very useful synthetic building blocks for natural alkaloids and pharmaceuticals.

#### 4. SUMMARY

The present review covers the most competent asymmetric enantioselective protocols catalyzed by  $\text{H}_8\text{-BINOL}$ , an axially chiral catalyst used as a Bronsted acid as well as Lewis acid in C–C and C-heteroatom bond formation. These catalysts have also made entry into asymmetric C–H activation reactions since the early 2000s. Recently, the trend to develop enantioselective and diastereoselective protocols underwent scale up in industries for chiral drugs, agrochemicals, natural products, and other chiral medicinally important molecules using organocatalyst with unique features. The present review highlighted the challenges, problems, limitations, and future prospects of organocatalyst with the hope that by referring to this review new work with innovative protocols will be done in the next decade by scientists.

#### AUTHOR INFORMATION

##### Corresponding Author

Rajpratap Kshatriya – School of Chemical Sciences, UM-DAE Centre for Excellence in Basic Sciences, University of Mumbai, Mumbai, Maharashtra 400098, India; [orcid.org/0000-0003-1482-6009](https://orcid.org/0000-0003-1482-6009); Email: [drkshatriya123@gmail.com](mailto:drkshatriya123@gmail.com)

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acsomega.2c05535>

##### Notes

The author declares no competing financial interest.

##### Biography



Dr. Rajpratap Kshatriya completed his Master of Science in Chemical Sciences from S. P. Pune University, India with first rank in Organic Chemistry Specialization. He worked in Pharmaceutical Process Development R & D of IPCA Laboratory, Mumbai, RPG Life Sciences Mumbai & other pharmaceutical Research and development organizations. He completed his PhD course from S. P. Pune University in the area of Synthetic Natural Products. After submission of PhD thesis he started to work with Prof. Arvind Lali (Institute of Chemical Technology, Matunga Mumbai, previously known as UDCT) as a Post Doc RA on a project “HPLC Method development and validation for natural products using analytical techniques”. In 2016 he moved to University of Kwazulu Natal South Africa for postdoctoral research at Department of Pharmacy, School of Pharmaceutical Sciences. He worked with Prof. Tricia Naicker & Thavender Govender at Catalysis and Peptide Research Unit (CPRU) in Department of Pharmacy in the

area of medicinal chemistry and organocatalysis. In 2017 he moved to Institute of Chemical Technology (previously known as UDCT), Mumbai, India at department of Fine Chemical Technology (previously Dyestuff Technology), in the group of Dr. Satyajit Saha. He worked on CSIR fellowship as CSIR-Post Doc in the area of asymmetric organocatalysis using R-BINOL catalyst. In 2019 he moved to Uka Tarsadia University as Research Professor. In 2022 he joined with Prof. Vimal K. Jain as Post Doc RA at School of Chemical Sciences, UM-DAE Centre for Excellence in Basic Sciences, University of Mumbai, Kalina, Santacruz (E), Mumbai, India. He worked there in the area of Organometallic Chemistry. He worked on methodology development of selenium, sulphur and phosphorus-based organic chemistry and asymmetric organometallic chemistry. Presently he is working in Anant Pharmaceutical Pvt. Ltd. as a Senior Research Scientist (Group Leader). He is working with Dr. Ajit Godbole in the area of impurity development, novel chiral methodology development & Contract research work.

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