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Review

Dinuclear Zn-Catalytic System as Brønsted Base and Lewis Acid for Enantioselectivity in Same Chiral Environment

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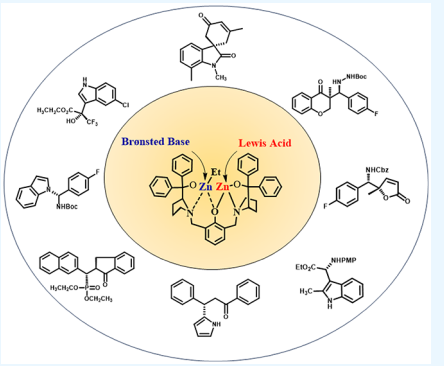
ABSTRACT: Zinc (Zn) is a crucial element with remarkable significance in organic transformations. The profusion of harmless zinc salts in the Earth's outer layer qualifies zinc as a noteworthy contender for inexpensive and eco-friendly reagents and catalysts. Recently, widely recognized uses of organo-Zn compounds in the field of organic synthesis have undergone extensive expansion toward asymmetric transformations. The ProPhenol ligand, a member of the chiral nitrogenous-crown family, exhibits the spontaneous formation of a dual-metal complex when reacted with alkyl metal (R−M) reagents, e.g., $ZnEt_2$. The afforded Zn complex possesses two active sites, one Lewis acid and the other Brønsted base, thereby facilitating the activation of nucleophiles and electrophiles simultaneously within the same chiral pocket. In this comprehensive analysis, we provide a thorough account of the advancement and synthetic potential of these diverse catalysts in organic synthesis, while emphasizing the reactivity and selectivities, i.e., dr and ee due to the design/structure of the ligands employed.



INTRODUCTION

Zinc ($_{30}$Zn) occupies the 24th spot in terms of abundance among the elements found in the Earth's crust. It has five stable isotopes, out of which ^{64}Zn is found most abundantly with 48.6% natural abundance.[1] Due to the inherent elemental properties, Zn(II) salts find extensive application as Lewis acids in various nucleophilic addition reactions. These include the Aldol reaction, the Mannich reaction, the Henry reaction, and the Michael addition reaction. Many efforts have been dedicated to applying these approaches for the construction of new carbon−carbon bonds or carbon quaternary stereocenters. The majority of these processes are believed to follow a mononuclear Zn(II) mediated pathway. Specifically, various compounds such as $ZnCl_2$, $ZnBr_2$, ZnI_2, $Zn(OTf)_2$, Et_2Zn, and organozinc species generated in situ are suggested to involve mononuclear zinc complexes as vital intermediates in promoting nucleophilic additions.

The idea of dinuclear zinc pathways often gets overlooked because researchers are more familiar with the mononuclear pathway while considering the mechanistic study of organic transformations involving zinc. Surprisingly, dinuclear pathways are crucial, especially in enzyme chemistry.[2] The zinc functions as a cocatalyst in the active site of various enzymes as an intrinsic cofactor, i.e., a carbonic anhydrase, which facilitates the transport of carbon dioxide and was the first metalloenzyme known.[3] Currently, zinc-based enzymes belong to all the fundamental enzyme families, including oxidoreductase (dehydrogenase or reductase), transferase (transfer functional groups), hydrolase (involved in hydrolysis), lyase (cleavage of bonds without involving water), isomerase (rearrangement of molecular structures), and ligase or synthetase (involved in the formation of chemical bonds). This has led chemists to develop chiral catalytic systems involving zinc atoms that follow the dinuclear pathway.

Lately, there has been a growing demand for chiral compounds, particularly in industries such as agrochemicals and pharmaceuticals, due to the significant impact that enantiopurity has on the physical and biochemical properties of organic molecules. Consequently, research groups worldwide have placed considerable emphasis on the development of asymmetric catalytic transformations. These catalytic transformations aim to achieve not only exceptional diastereo-, enantio-, and regioselectivities but also high reaction rates within a practical period.[4,5] Although at present many organic reactions are being conducted under catalytically controlled asymmetric environments, the majority of these transformations require the use of valuable and toxic transition metals such as palladium (Pd), iridium (Ir), rhodium (Rh), and ruthenium (Ru) as the catalytic system.[6,7] Compared to

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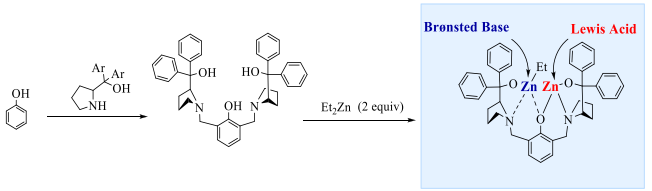
these transition metals commonly employed in catalysis, zinc (Zn), copper (Cu), and iron (Fe) complexes afford the advantages of being inexpensive, easily available, and less toxic.[8]

In 2000, Trost and co-workers developed ProPhenol, an aza-crown ligand derived from proline. The ligand upon reacting with an alkyl metal reagent like Et_2Zn, autonomously affords a bimetallic Zn complex by deprotonating the three hydroxyl groups. The bimetallic complex contains two active sites: the Brønsted base site and the Lewis acid site (Scheme 1).

Scheme 1. Synthesis and Structure of the Bimetallic Zn-ProPhenol Complex



The basic site functions via activating a pronucleophile by simple deprotonation. However, the acidic site functions by activating the electrophilic reactant by coordination with the metal. This activation of both reactants in the same chiral environment accounts for the highly effective bond formation in a stereoselective manner.[9] The present report successfully outlines the advancements in the application of zinc binuclear catalysts in various asymmetric enantioselective transformations, including: Aldol reaction, Friedel–Crafts reaction, Mannich reaction, Michael addition reaction, N-alkylation of indol, 1–6-conjugated addition reaction, Aza-Henry reaction, and one-pot methodologies, i.e., domino and tandem reactions.

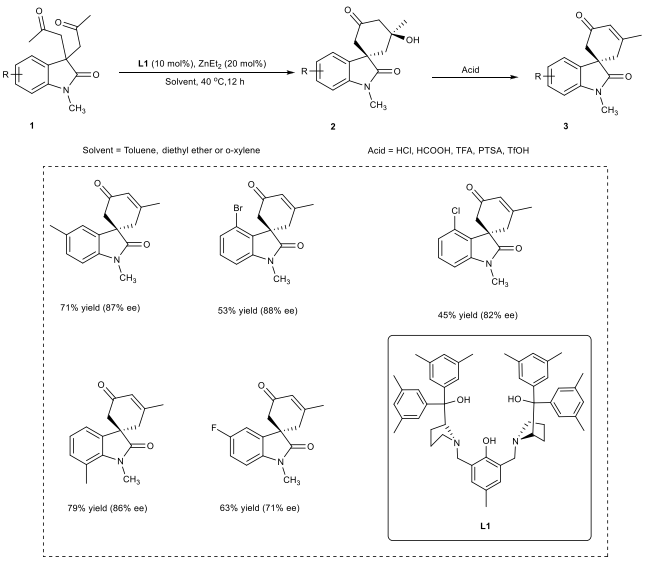
Asymmetric Aldol Reaction. Among the classic reactions for carbon–carbon (C–C) bond formation is an aldol reaction, which delivers a variety of *β*-hydroxy carbonyl compounds or *α,β*-unsaturated carbonyl compounds. The aldol reactions can be catalyzed by employing acidic conditions, basic conditions, metal–catalytic complexes, or enzymes.[10]

In 2016, Zhang et al. employed oxindole-derived diketone derivatives (**1**) as a starting substrate for an asymmetric desymmetrizing intramolecular aldol addition reaction/aldol condensation reaction affording spiro[cyclohexanone-oxindole] derivatives (**2**, **3**) (Scheme 2).

The Trost's bis-ProPhenol binuclear zinc complex of ligand (*S,S*)-**L1** has been employed as a catalytic partner affording moderate to good enantioselectivities of the desired products. At room temperature, (*S,S*)-**L1**, a bis-ProPhenol ligand, is the most effective choice alongside 30 mg of the 4 Å molecular sieves (MS) in the catalytic solution, yielding 80% of the required products with 1:10 diastereoselectivity and 97% enantioselectivity.

The Brønsted acids were added for the dehydration of the aldol products. The reaction goes very well, giving 85–90% yield of the desired products in toluene, diethyl ether, or *o*-xylene with 94–97% ee values and 1:91:10 diastereoselectivity (dr) ratios. However, upon elevating the temperature of the reaction to 40 °C, yield drops to 68%, though the products are obtained with excellent stereoselectivities, i.e., 1:20 dr and >99% ee. The substrates having electron-rich substituents (methyl, methoxy) on the oxindole give aldol product in 50–

Scheme 2. Synthesis of the Spiro[cyclohexanone-oxindole] Related Compounds Employing a Dinuclear Zinc Catalytic System

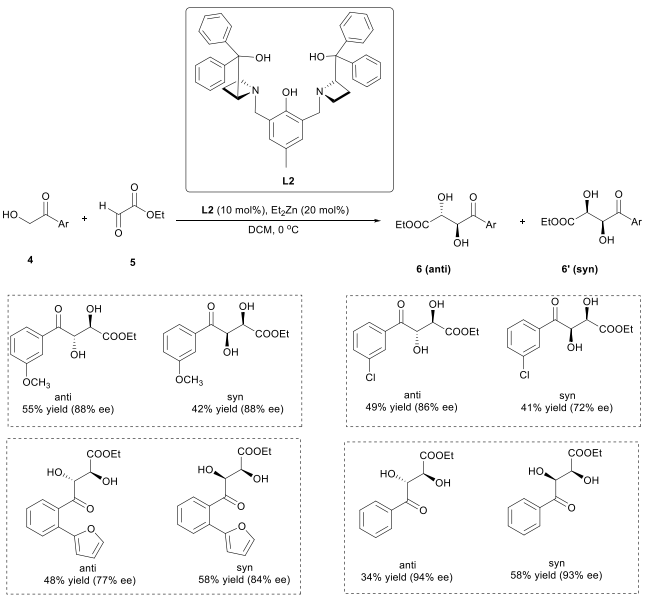


81% yields, with varying enantioselectivities (82–93%) and diastereoselectivities (1:31:20). On the contrary, halogen (X = F, Cl, Br) on the oxindole backbones negatively affects the reaction, giving the desired products with 63–88% ees in 45–70% yield.[11]

The *α,β*-dihydroxy ester-related compounds are significant pharmacophores and asymmetric building blocks that serve as the basis of bioactive polyketide natural and synthetic drugs.[12] In 2019, Zhang et al. synthesized anti- as well syn-*α,β*-dihydroxy *γ*-keto ester derivatives (**6**, **6′**) by the asymmetric aldol addition process involving 2-hydroxy-acetophenone (**4**) and ethyl glyoxylate (**5**) catalyzed by binuclear zinc (Zn)-AzePhenol catalyst (Scheme 3).

The solvent screening verified that dichloromethane (CH_2Cl_2) was the best choice to achieve excellent

Scheme 3. Synthesis of the *α,β*-Dihydroxy *γ*-Keto Ester Derivatives by the Asymmetric Aldol Addition Reaction



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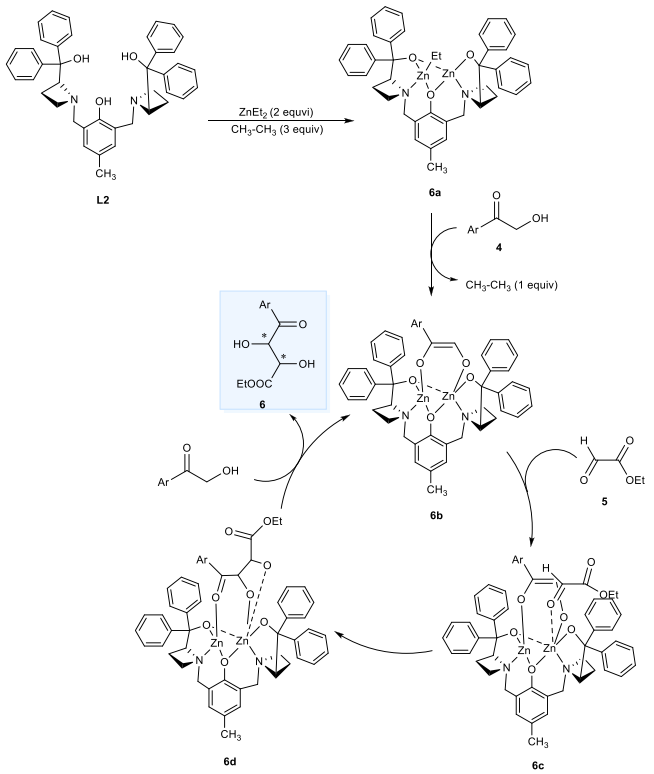
enantioselectivity. Also, the enantioselectivity of desired products has been improved up to 91% by lowering the temperature to 0 °C. The 2-hydroxy-acetophenone substituted with the *p*-methyl group has resulted in the high enantioselectivity (96% ee) of the corresponding syn-product in moderate yield (33%), while the anti-product has been obtained in higher yield (57%) with lower enantioselectivity (93% ee). The substitution with the *p*-methoxy group displayed excellent enantioselectivity (96% ee) but a lower yield (41%). Furthermore, the 2-hydroxy-acetophenone substituted with *o*-methyl or *o*-methoxy groups have shown outstanding enantioselectivities, while electron-deficient substituents, particularly the nitro ($-NO_2$) group, have diminished the enantioselectivities. The reaction is also very well tolerated in the case of heteroaromatic compounds bearing electron-rich substituents.

The mechanism of the reaction involves the deprotonation of 2-hydroxyacetophenone (**4**) by a dinuclear Zn-catalytic system (**6a**) affording the nuclear Zn-AzePhenol complex (**6b**). In the next step, the ethyl glyoxylate (**5**) combines with Lewis acidic Zn nucleus affording the intermediate complex (**6c**) followed by the aldol addition reaction to give (**6d**). Lastly, proton (H^+) exchange with the coming nucleophile takes place, giving the desired product, and one catalytic cycle is completed. The highly reactive ethyl glyoxylate would not bind strictly to the Zn-atom, leading to a diastereoisomeric mixture in the aldol addition reaction (Scheme 4).[13]

Asymmetric Mannich Reaction. Modern synthetic chemists are confronted with the challenge of achieving fast, selective, and atom-economical reactions to synthesize complex organic compounds from simple and readily accessible starting substrates.[5] The presence of quaternary

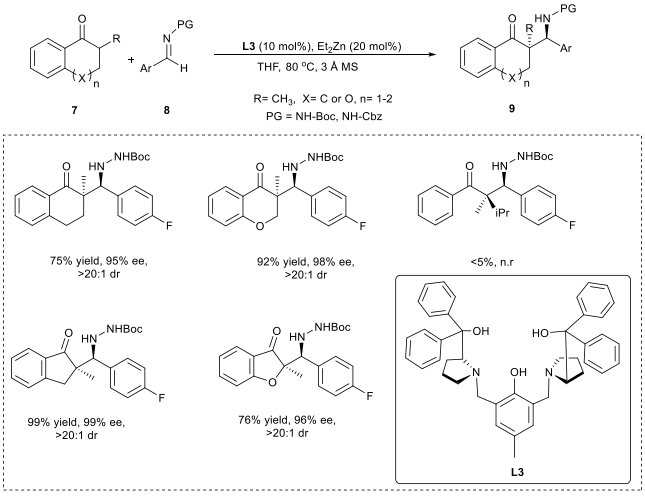
Scheme 4. Asymmetrical Zn-Catalyzed Cycle for the Aldol Addition Reaction



stereocenters is common in natural compounds, but their synthesis, especially through catalytic enantioselective means remains challenging.[14] The Mannich transformation is considered to be among the efficient methods for forming carbon−carbon bonds and a range of asymmetric conversions, including a variety of Mannich transformations, are possible using Zn-ProPhenol ligands.[15]

In 2016 Trost et al. reported a Mannich reaction catalyzed by a Zn-ProPhenol ligand using α-branched ketones as the starting material. The dinuclear catalysts are obtained by reacting the ProPhenol ligand from the aza-hemicrown ligand family with alkyl (R) metal reagents, e.g., diethylzinc (Et_2Zn). The catalytic system Zn-ProPhenol has been highly effective for diastereoselective and enantioselective aldol addition reaction and Mannich reactions. The α-branched ketones (**7**) act as the nucleophile upon reacting with the Boc-protected derivative of aldimine (**8**) affording functionalized β-amino ketones (**9**) with every carbon as quaternary stereocenter utilizing Zn-ProPhenol ligand (***R,R*-L3**) (Scheme 5). The

Scheme 5. Synthesis of the β-Amino Ketones Using Zn-ProPhenol Ligand



reaction at 80 °C results in the end products with high selectivities in good yields. However, upon decreasing the temperature to 60 °C, the selectivities remain unaffected, decreasing the yields due to poor conversion. Both the electron-rich and -deficient groups have been compatible with heteroaromatic imines and aromatic rings during the reaction. The reaction also proceeded smoothly with alkyl imine and vinyl imine, providing the required products in high yields. Moreover, Cbz-protected imine derivatives showed similar efficiency, allowing orthogonal protective group techniques to be utilized.[16]

The butenolides containing nitrogen are found in several natural and medicinal compounds and are valuable synthetic intermediates.[17] The GABA antagonists such as (−)-securinine and its isomers have been explored for their anticancer effects.[18] In 2017, Trost et al. synthesized the tetrasubstituted vinylogous product (**12**) from imine derivatives (**10**) and α-angelica lactone (**11**) using an (*R,R*)-Zn-ProPhenol catalytic system (Scheme 6). The targeted products have been synthesized in good yield having diastereoselectivity up to >30:1 and excellent enantioselectivity, ranging from 97% to greater than 99.5%. According to the mechanistic studies, in

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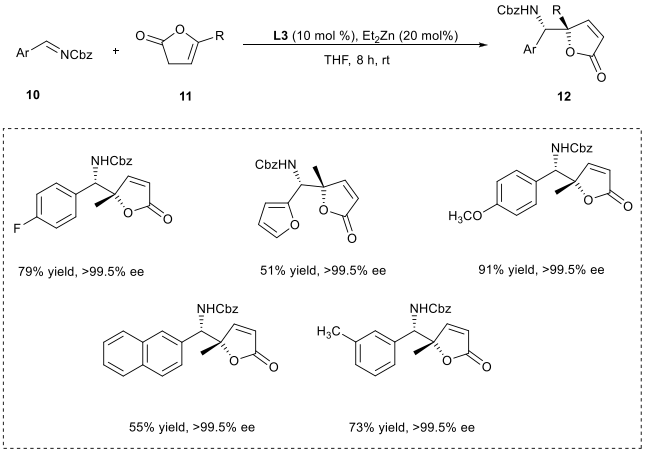
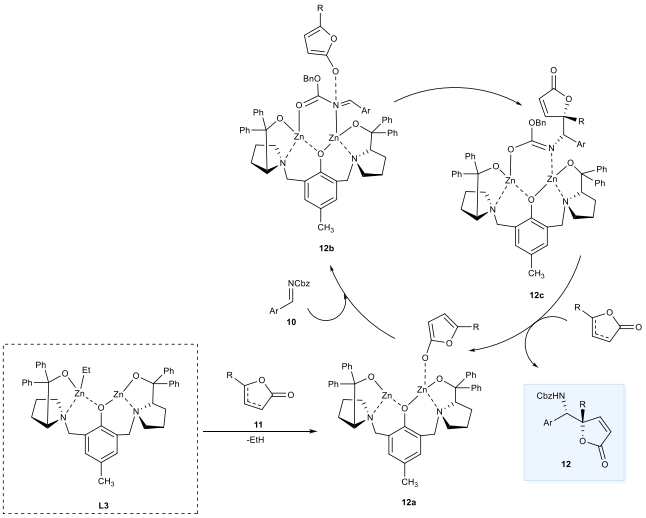
Scheme 6. Mannich Reaction between Butenolides and Imines



the first step, zinc dienolate (**12b**) is formed by deprotonation of butenolide and coordination of dinuclear zinc−ligand complex (**12a**) obtained from ProPhenol-**L3** and $ZnEt_2$. In the next step, complex (**12c**) is produced by two-point attachment of imine, which leads to the binding of the butenolide to the si-face of the derivative of imine. The obtained diastereoselectivity of the product is because the shown conformation is preferred by butenolide minimizing the repulsion among the diphenylprolinol unit and ring structure (Scheme 7). The tetrahydrofuran (THF) has been the best

Scheme 7. Catalytic Cycle of the Mannich Transformation between Butenolides and Imines by Employing Binuclear Complex of (L3)

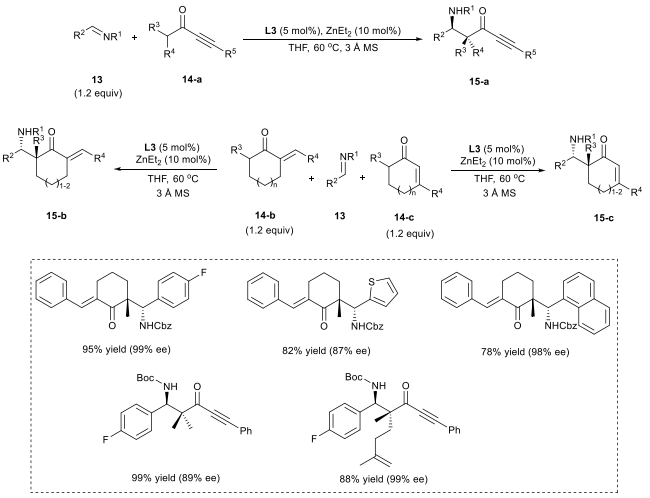


choice of solvent to afford the maximum yield (up to 79%) of the desired products with 99.5% ee. Both the electron-donating and electron-withdrawing imine derivatives react effectively with α-angelica lactone affording the targeted products.[19]

In 2019, Trost et al. carried the Mannich transformation between unsaturated α-branched ketones (**14a−c**) and N-carbamoyl imines (**13**), and synthesized β-aminoketones (**15a−c**) having both cyclic and aliphatic quaternary stereogenic centers (Scheme 8).

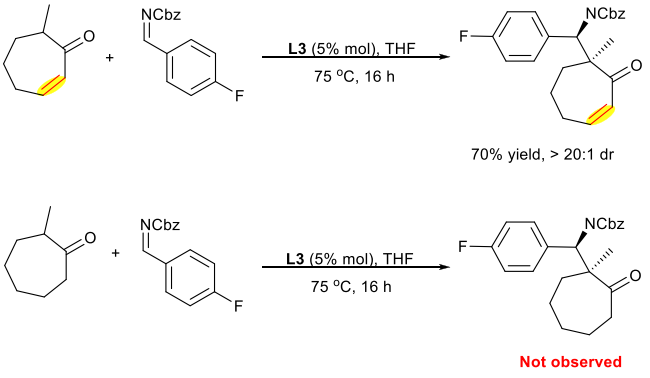
The incorporation of the carbon−carbon (C—C) double-bond adjacent to the carbonyl group (C═O) in α-branched

Scheme 8. Mannich Synthesis between Unsaturated α-Branched Ketone Derivatives and N-Carbamoyl Imines



ketones markedly improves the reactivity of the catalytic system, i.e., (*R*,*R*)-Zn-ProPhenol (Scheme 9). The imines with

Scheme 9. Effect of Unsaturation Added Adjacent to the Carbonyl in α,β-Branched Ketone Derivatives on the Reactivity of Zn-Catalyst



electron-rich, as well as electron-deficient aromatic ring, heteroaromatic, and vinyl imines, were tolerated well under the reaction conditions. The α-branched ketones having small groups at R^3, such as methyl ($-CH_3$), propargyl ($HC{\equiv}C-CH_2-$) afford the products in high yield with remarkable stereoselectivities.[20]

Pyridazinones and cyclic hydroxamates present in natural, as well as pharmaceutically active substances, are imperative intermediates for organic synthesis.[21] Geng et al. in 2021 synthesized α-selective adduct (**18**) via a Mannich addition reaction between β,γ-unsaturated ketone derivatives (**17**) and benzoxazinone cyclic α-imino esters (**16**) (Scheme 10). The α-addition Mannich adducts bearing two consecutive 3° carbon stereocenters, have been obtained with high stereoselectivities, i.e., ee up to 99% and dr ratios of >20:1. The adducts could be employed as intermediates to synthesize multisubstituted tetrahydro pyridazinones and cyclocanalines. The reaction went smoothly upon the incorporation of both electron-donating ($-CH_3$, $-OCH_3$) and electron-withdrawing groups (X = −F, −Cl, −Br) at 4-position on the Ar^2 of the β,γ-unsaturated ketone derivatives.[22]

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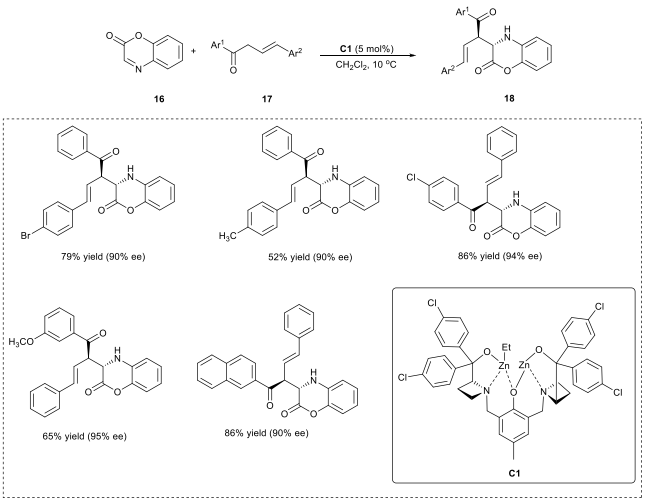
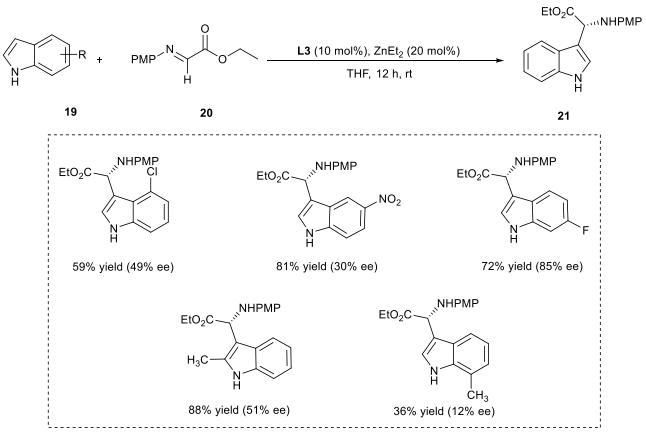
Scheme 10. α-Selective Addition between β,γ-Unsaturated Ketone Derivatives and Benzoxazinone Cyclic α-Imino Esters



Asymmetric Friedel–Crafts Alkylation Reaction. Chemists have been intrigued by the chemical transformation and biological potentials of nonproteinogenic amino acids. In many of the organic synthesis, 3-indolyl glycine compounds are employed as building blocks and essential synthetic intermediates.[23]

Wang et al. synthesized 3-indolyl-amino esters (**21**) via Friedel–Crafts asymmetrical alkylation from indole derivatives (**19**) and ethyl glyoxylate imine (**20**) by employing a dinuclear zinc catalytic system (Scheme 11).

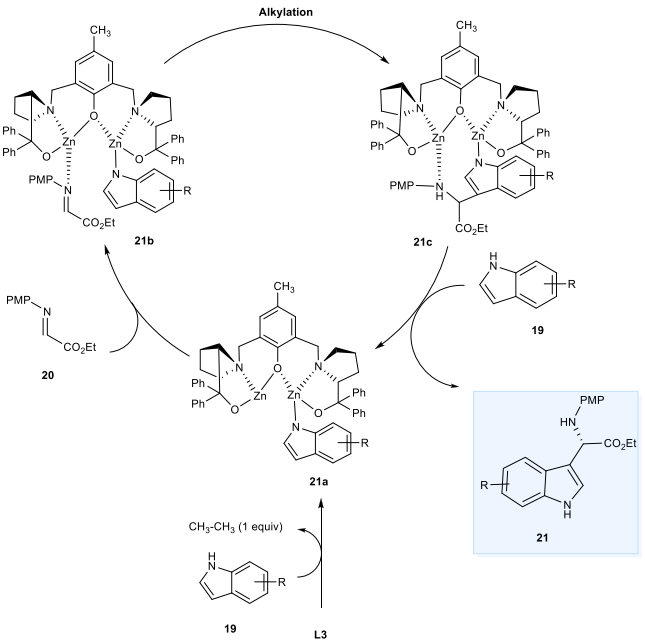
Scheme 11. Synthesis of 3-Indolylglycine Derivatives by Asymmetric Friedel–Crafts Alkylation Using Zn-catalyst



Under mild reaction circumstances, a variety of 3-indolyl glycine compounds have been afforded in medium to excellent yield with exceptional ee (up to >99%) upon only 10 mol % Zn-catalyst loading. The best results of the stereoselective Friedel–Crafts reaction were obtained using THF as a solvent for 12 h at room temperature. The indole derivatives having electron-releasing groups at the 4-position afford the targeted products with remarkable enantioselectivities (ee) of 91–94%. However, the reactivity of indoles has become sluggish upon introducing electron-withdrawing groups, e.g., X = −Cl, −F, affording good enantioselectivities (ee) in the products. The enantioselectivities with 5-substituted and 6-substituted indole derivatives were increased upon decreasing the steric crowding of substituted groups. The imine derivatives have shown high reactivity toward the electron-donating indoles, with excellent yields of the targeted products.

The reaction commences with the deprotonation of indole (**19**) liberating a molecule of ethane, affording the intermediate (**21a**). After coordination of ethyl glyoxylate imine (**20**) with the other zinc atom, the intermediate (**21b**) is obtained. The indole derivatives preferentially attack the imine's C═N bond, from the reface to afford the intermediate (**21c**). In the last step, the desired adduct (**21**) is eliminated after the H^+ transfer takes place between the intermediate (**21c**) and another indole (**19**) molecule, and the catalytic cycle is repeated (Scheme 12).[24]

Scheme 12. Catalytic Mechanism of the Reaction Involving Indole Derivatives and Ethyl Glyoxylate Imine



In 2014, Zhao et al. carried out an enantioselective catalytic Friedel–Crafts alkylation reaction between pyrrole (**22**) and nonchelating derivatives of chalcone (**23**). The (***S*,*S*)-L2** has been employed as the catalyst, and β-pyrrole-substituted dihydrochalcone derivatives (**24**) were obtained with excellent yield and enantioselectivity (Scheme 13). Upon screening the solvents toluene, $CHCl_3$, CH_2Cl_2, and THF have been found to be a suitable choice for the reaction solvent. Moreover, the highest enantioselevities have been observed in the case of THF, and no reaction has been observed in the presence of 1,4-dioxane and CH_3CN as solvent. The desired products have been obtained with excellent ee values regardless of the position or electronic nature of the substituent present on the aryl ring (R^1). However, different effects on the reaction yields have been observed by the position and electronic nature of various substituents on the aryl ring (R^1), and decrease in the yield has been observed in case of *p*-methyl and *o*-chloro. The electron-withdrawing substituents have been found more favorable in the reaction conditions on both (R^1) and (R^2) on the contrary decrease in yield was observed with *m*-methyl on (R^2) without affecting the ee. The reaction has been a failure with alkyl-substituted α,β-unsaturated derivative of

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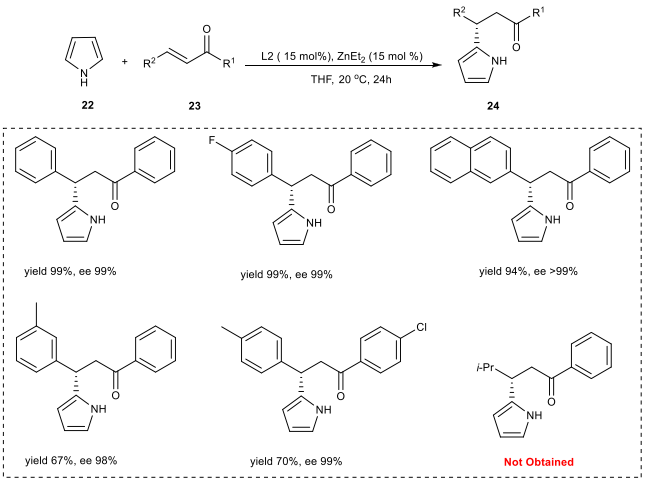
Scheme 13. Synthesis of β-Pyrrole-Substituted Dihydrochalcone Derivatives by Asymmetric Friedel−Crafts Alkylation using Zn-Catalyst.

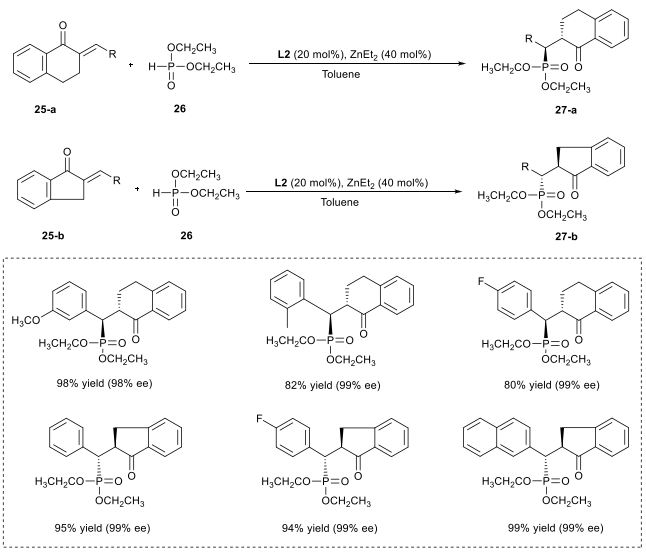


ketones. Upon treating the chalcone with *N*-methylpyrrole, N-benzoylpyrrole, and N-benzylpyrrole, no reaction has occurred, suggesting that the presence of the hydrogen atom on the nitrogen of the pyrrole ring is vital for the activation of reactants by the ligand.[25]

Asymmetric Michael Addition Reaction. Recently, asymmetric organophosphates have become the focus of attention for chemists because of their potent biochemical actions, numerous applications as synthetic intermediates, and usage as a ligand for asymmetric metal-catalyzed reactions.[26]

In 2018, Shao et al. employed a phospha-Michael type addition reaction between α,β-unsaturated benzocyclic ketone derivatives (**25a−b**) and diethyl phosphonate (**26**) to synthesis organophosphate compounds with the skeleton of 1-tetralones (**27a**) or 1-indanones (**27b**) (Scheme 14). The resulting targeted compounds were obtained in high yield with remarkable enantioselectivity, reaching a maximum of 99%. The benzylidene-1-tetralone derivatives having substituents at

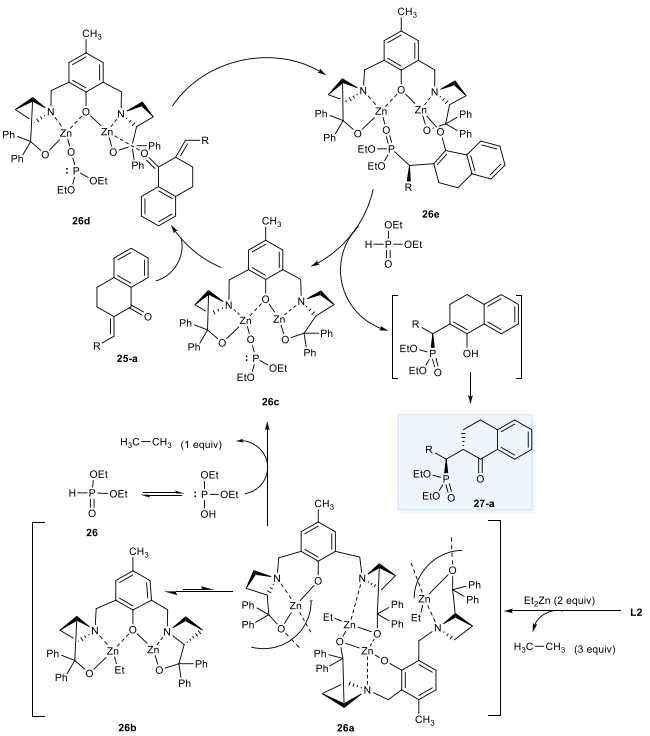
Scheme 14. Synthesis of Organophosphate Compounds with the Skeleton of 1-Tetralones or 1-Indanones Using Zn-Catalyzed Phospha-Michael Reaction



o-, *m*-, or *p*-positions on the β-phenyl ring undergo reaction smoothly, affording the required products in good yields with outstanding enantioselectives. The β-phenyl ring bearing the electron-donating substituents gives better results as compared to substrates with electron-withdrawing substituents. In the case of the substrates having electron-withdrawing groups such as $-CF_3$ and $-NO_2$ at the *p*-position, the enantioselectivity of desired products has been reduced slightly. Impressively, α-benzylidene-1-indanone derivatives have given the required products in remarkable yields with ee as high as 99% regardless of the positions and electronic properties of the substituents present.

In the first step, ligand **L2** reacts with diethyl zinc ($ZnEt_2$), yielding a catalytically inactive dinuclear zinc atom complex (**23a**, **23b**). The inactive complex is then converted to a catalytically active complex (**23c**) upon deprotonating the diethyl phosphonate (**23**) with the release of one ethane molecule. The α-benzylidene-1-tetralone (**22-a**) then combines with the other zinc metal atoms of the catalytic system to form an intermediate (**23d**), followed by the process of phosphoryl transfer to afford (**23e**). In the last step, a proton (H^+) transfer occurs between (**23e**) and the diethyl phosphonate resulting in the final product, and the Zn-catalyzed cycle is repeated (Scheme 15).[27]

Scheme 15. Zn-Catalyzed Cycle for the Synthesis of Organophosphate Compounds with the Skeleton of 1-Tetralones or 1-Indanones



Pyranone and coumarin moieties are well-known structural scaffolds in a variety of bioactive chemicals. Their compounds are known as potential anti-HIV, anticoagulant, and antimalarial drugs.[28] The optically active Michael 1,4-addition between 4-hydroxy pyrones (**28**) and 4-hydroxy coumarins (**29**) has been reported by Liu et al. to obtain β,γ-unsaturated α-keto esters (**30**) by using a CF_3-substituted dinuclear Zn-AzePhenol catalyst (Scheme 16).

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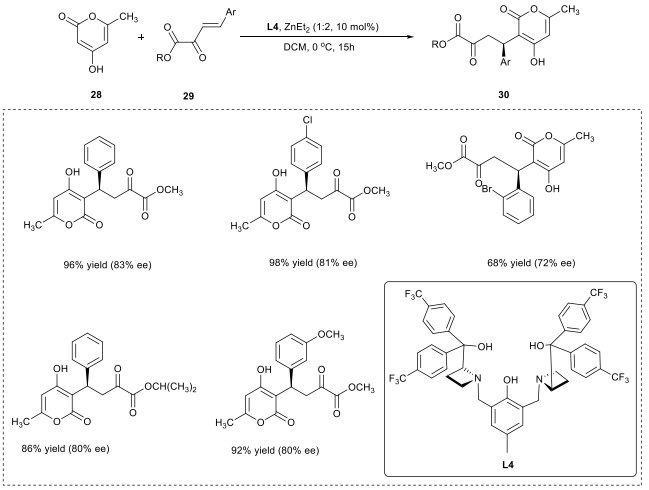
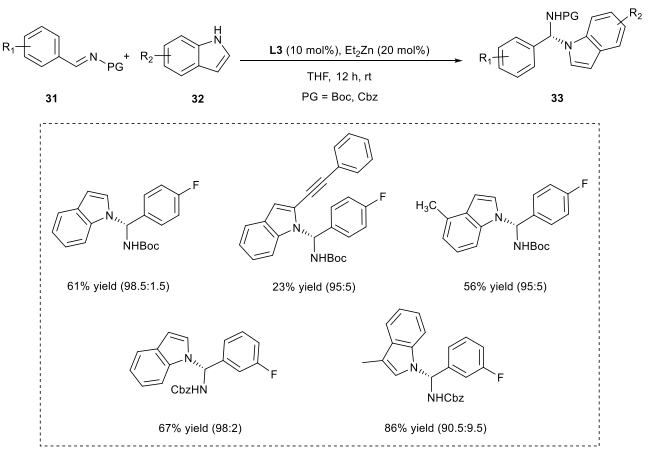
Scheme 16. Synthesis of the β,γ-Unsaturated α-Keto Ester Derivatives via Asymmetric Conjugated Addition



The metallic catalytic strategy is efficient for the production of bioactive warfarin derivatives because of the large substrate scope, excellent enantioselectivity, and moderate reaction conditions. The required products have been obtained in excellent yield with an ee value of 83% under optimal reaction conditions in the presence of DCM at 0 °C. Impressively, the high yield with high enantioselectivity has also been obtained on lowering the Zn-catalyst loading from 20 to 10 mol %. In comparison to electron-withdrawing halogen substituents, the electron-donating substituents (e.g., methyl, methoxy) on the phenyl ring of the α-keto esters had a significant impact on both reactivity and asymmetric induction, because the electron-donating groups would promote the shifting of electronic cloud to carbonyl (C═O) group, making it less challenging to coordinate to stereogenic zinc catalyst.[29]

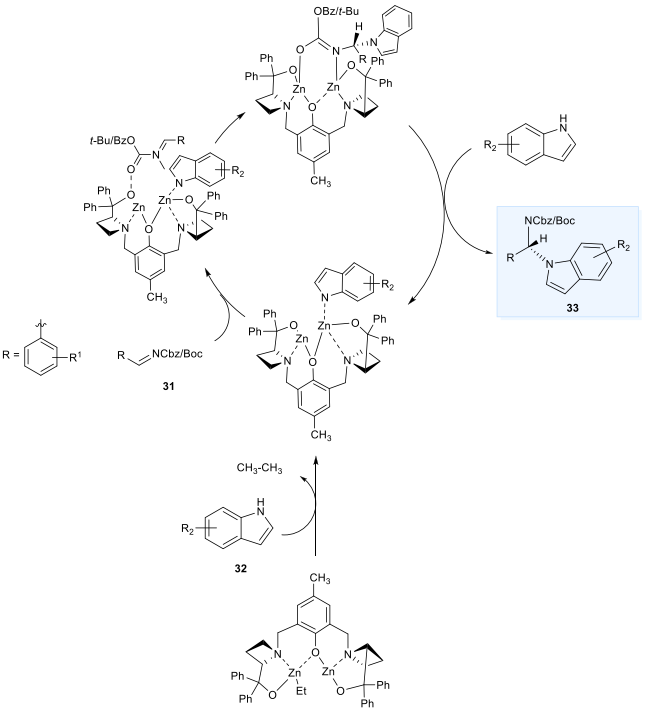
N-Alkylation Reaction. Indole as well as its derivatives have been studied extensively as therapeutic agents.[30] In 2017, Trost et al. employed a zinc-ProPhenol dinuclear complex of ligand (**L3**) to catalyze the enantioselective N-alkylation of derivatives of indoles (**32**) with aldimines (**31**) to obtaine N-alkylated indole derivatives (**33**) (Scheme 17). The reaction affords satisfactory yields of N-alkylated compounds with enantioselectivity up to a 99.5:0.5 enantiomeric ratio (er),

Scheme 17. Synthesis of N-Alkylated Indole Derivatives Using Zn-ProPhenol Dinuclear Complex



consequently opening the doors for their use in organic synthesis. The Zn-ProPhenol is responsible for the asymmetric alkylation at C3 when the Ts-protected imine has been employed as the amino-alkylating agent. However, the carbamate-protected derivatives of imines follow a chemical pathway that prevents C3-alkylation (Scheme 18).[31]

Scheme 18. Binuclear Zn-Catalyzed Mechanism for N-Alkylation



Asymmetric 1,6-Conjugate Addition Reaction. Stereoselective α-hydroxy ketones with two vicinal optically active sites are widely used in asymmetric synthesis as a chiral basic component, and they can be located in several organic products and medicine consequently, asymmetric ways to obtain such structural compounds have gotten much attention in present decades.[32] In 2017, Gao et al. reported the production of chiral β,β-diaryl-α-hydroxy ketone derivatives (**36**) by an asymmetrical 1,6-conjugate addition reaction of α-hydroxy ketone (**35**) to *p*-quinone methides (**34**) (Scheme 19). The ligand (**L5**) outperformed the other employed ligands affording the major anticonformation diastereomers, with the dr value 11:5:1 and ee 98%. The higher diastereoselectivity has been achieved by introducing electron-donating groups (e.g., −OMe, −Me) in comparison to the electron-withdrawing groups at the *p*-position of the aromatic aryl ring. Moreover, the electron-withdrawing groups (e.g., fluoro, chloro, bromo) at the *m*-position of the aromatic aryl ring give the products with comparatively low dr ratios, i.e., 3.5:1−6.5:1. The substitution of electron-donating groups at the *m*-position has given the intended products with dr rations, 10:1−18:1. However, the desired compounds with dr rations, 13:1−99:1 has been obtained using *p*-QMs having different substituents at *o*-position of aromatic aryl ring.[33]

Asymmetric C−F Alkylation Reaction. Fluorinated compounds have received a lot of interest in the past few years because of their unusual properties. The powerful electron-withdrawing effect as well as the absolute config-

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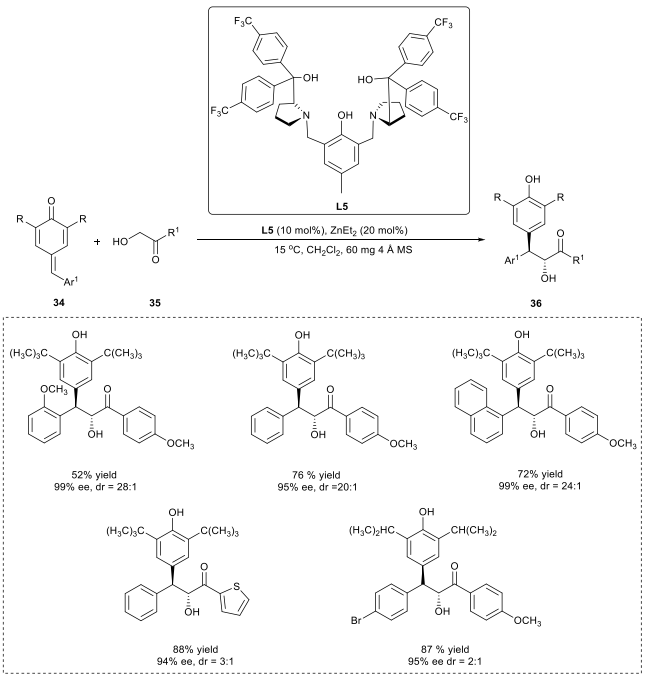
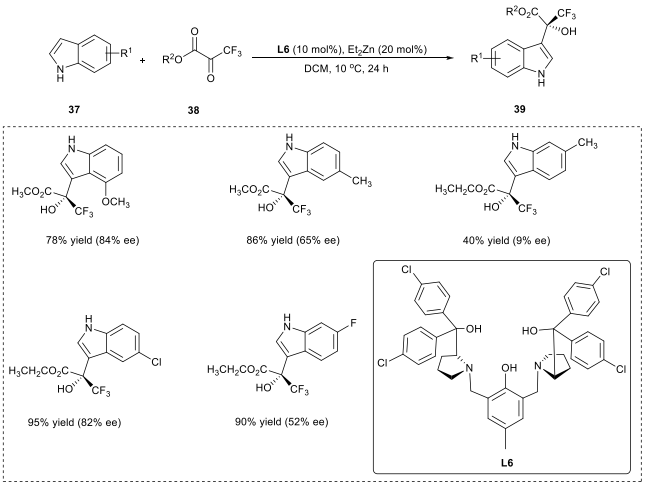
Scheme 19. Synthesis of *β,β*-Diaryl-*α*-hydroxy Ketone Derivatives via 1,6-Conjugated Addition Reaction Using Zn-Catalyst



uration on the $-CF_3$ group result in the unusual biological and physical properties in chiral trifluoromethylated molecules, which are among the most prominent fluorine-containing chemical compounds.[34] The chiral C−F alkylation of indoles (**37**) and trifluoromethylpyruvates (**38**) by dinuclear Zn-catalyst from ligand (***S,S*)-L6** yields useful asymmetric trifluoromethylated indoles (**39**) up to 95% with about 88% enantioselectivity (ee) (Scheme 20). The substrates having a

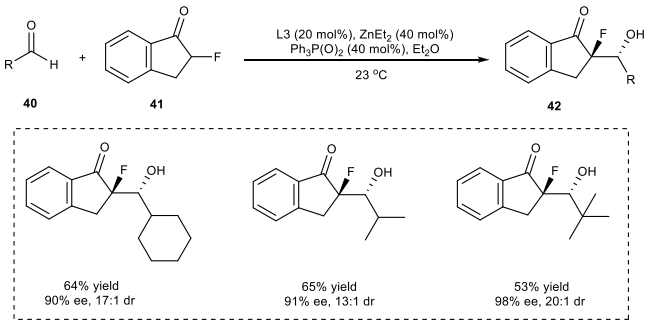
Scheme 20. Catalytic Asymmetric C−F Alkylation Reaction of Indoles and Trifluoromethyl Pyruvate



strong electron-donating group ($-OCH_3$) on the 4-position of the aryl ring performed well, giving 88% enantioselectivity. Conversely, the presence of a slightly weak electron-donating group (−Me) at the 5- or 6- position of the aryl ring has caused a decrease in the enantioselectivity i.e., 9−72% in the desired products. The presence of halogen groups (X= −F, −Cl, −Br) on the indoles has been helpful toward the catalytic Friedel−Crafts reaction, and much of the required products have been obtained with 80% enantioselectivity except for the 6-fluorinated end products. Strong electron-withdrawing groups, i.e., $-CO_2Me$ and $-NO_2$, also affords equivalent compounds but with lower ee values.[35]

In 2016, Trost et al. synthesized tetrasubstituted C−F stereogenic centers by reacting *α*-branched derivatives of aldehyde (**40**) with *α*-fluoroketones (**41**) in the presence of a Zn-ProPhenol catalytic system (Scheme 21). The required

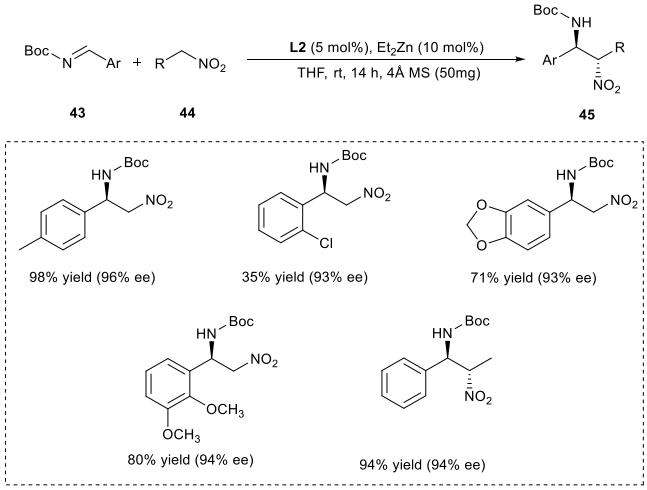
Scheme 21. Synthesis of Tetrasubstituted C−F Stereogenic Centers via Aldol Addition Reaction



products (**42**) have been obtained in high enantio- (98% ee) and diastereoselectivity (>20:1 dr). In this asymmetric reaction triphenylphosphine oxide has been added as a Lewis-basic additive playing the crucial rule in increasing the diastereoselectivity (dr) of the reaction.[36]

Aza-Henry Reaction. Among the most significant transformations for the synthesis of N-containing compounds is the chiral aza-nitroaldol reaction of imines and carbonyl compounds. The resulting asymmetric *β*-nitroamines can be readily transformed into very useful chemical compounds like vicinal diamine and *α*-amino acids.[37] In 2019, Liu et al. synthesized various derivatives of nitroamines (**45**) from N-Boc imines (**43**) and nitroalkanes (**44**) via asymmetric nitro-Mannich transformation catalyzed by dinuclear zinc-AzePhenol system at low temperature (Scheme 22). The reaction

Scheme 22. Synthesis of Nitroamines by an Asymmetric Nitro-Mannich Reaction by Employing Dinuclear Zn-Catalytic System



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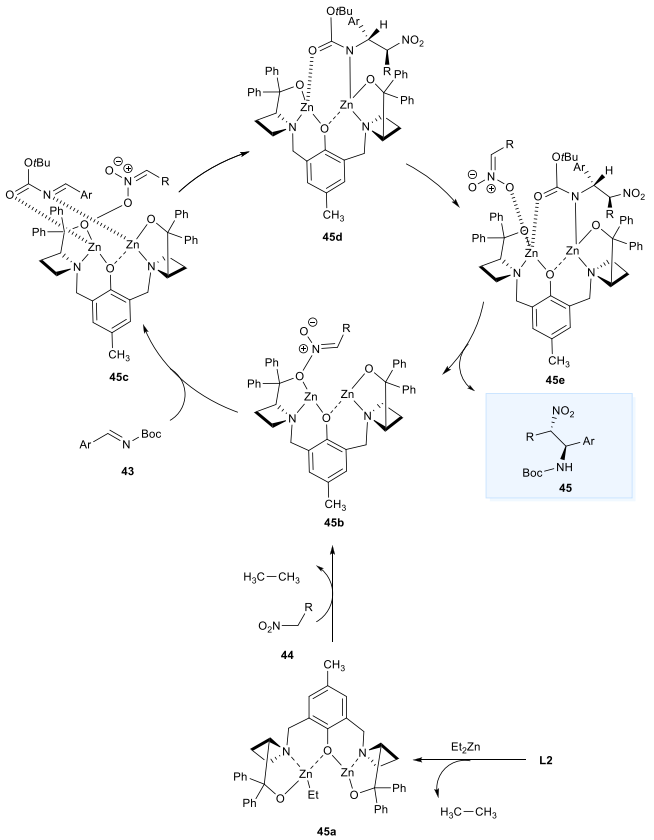
affords high enantioselectivity in the presence of THF in comparison with other solvents. The reactivity was also greatly influenced by molecular sieves. The introduction of 4 Å MS resulted in high yields of the desired products. The imine derivatives having substituents on varied positions of the phenyl ring were well tolerated by the reaction conditions affording good yields with comparable enantioselectivities. The electronic properties of the substituent on the aryl ring had shown a great impact on reactivity. Electron-donating groups such as methoxy ($-OCH_3$) and methyl ($-CH_3$) on the aryl ring affords the products in higher yields in comparison to the electron-withdrawing group such as fluoro ($-F$) and chloro ($-Cl$). The 2,3-dimethoxyl substituted Boc-protected imine improved the enantiomeric excess of the desired product in contrast to imine having the 4-methoxy substituent.

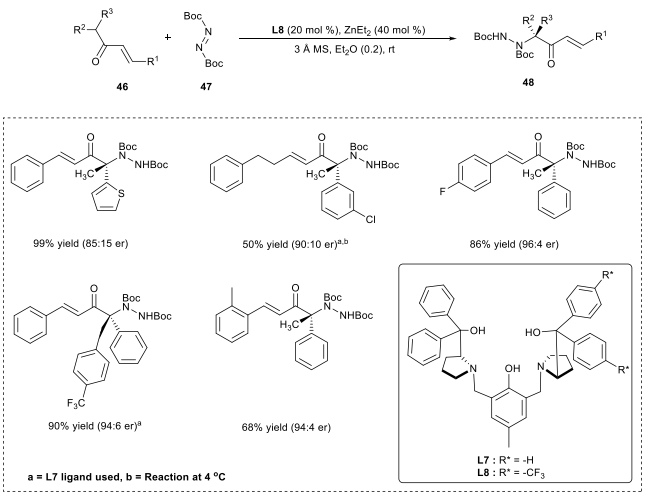
The proposed mechanism for the aza-Henry reaction involves the use of a catalyst (**45a**) for the deprotonation of nitromethane affording the intermediate (**45b**), which is zinc nitronate. The production of complex (**45c**) takes place by the imine coordination of Zn metal atoms to the more sterically susceptible position, which is followed by nitronate attack on the (**45c**) to yield intermediate complex (**45d**) which is responsible for the enantio- and diastereoselectivity of reaction. Then the complex (**45e**) has been produced by the coupling of nitromethane, which after the proton exchange with the nitroalkane regenerates the catalytic cycle, affording the desired product (**45**) (Scheme 23).[38]

Scheme 23. Cyclic Mechanism of Nitro-Mannich Reaction Catalyzed by Dinuclear Zn-AzePhenol System



Asymmetric Amination. Natural products, commercial medications, and biologically active molecules all contain nitrogen-containing molecules. Consequently, in synthetic chemistry, a lot of effort has been put into establishing methods for chemically incorporating nitrogen atoms into organic molecules.[7,39] In 2019, chiral α-tertiary amine related compounds (**48**) were synthesized via electrophilic amination of aliphatic α-branched ketone derivatives (**46**) using di-*tert*-butyl azodicarboxylate (**47**) in the presence of Zn-ProPhenol complex of ligand (**S,S**)-**L8** (Scheme 24). The nitrogen of the

Scheme 24. Synthesis of α-Tertiary Amines via Amination of Vinyl Ketone Derivatives



di-*tert*-butyl azodicarboxylate serves as the electrophilic site where the nucleophilic attack of α-branched ketone derivatives takes place. The ligand (**S,S**)-**L8** having electron-withdrawing groups has shown the highest selectivity rate with excellent enantiomeric ratio (er) of 96:4 and yields of desired products. The reaction is well tolerated upon the introduction of either electron-rich or electron-poor heteroaromatic or aromatic rings at the R^1-position. The electron-withdrawing substituents, i.e., X = $-F$, $-Cl$, at the *p*-position and *o*-position of the R^1 substituent affords the product in high yield (89−92%) with selectivity ranging from 96:4 to 97:3 er. In the case of electron-donating substituent (e.g., -OMe) at the *meta*-position the yields were 75% with an enantiomeric ratio (er) of 93:7. However, the yields were decreased upon the introduction of an electron-donating substituent (e.g., $-Me$) at the *ortho*-position, i.e., 68% yield with comparatively higher er of 96:4.

In asymmetric amination, the formation of the first dinuclear Zn-catalyst is followed by the deprotonation of the vinyl ketone to afford the complex (**48a**). Then, complex (**48b**) is generated after the electrophilic N atoms are coordinated with the two Zn atoms at the binding sites. The dinuclear structure of the Zn-catalyst is responsible for this distinctive chelation by using an electrophilic bidentate ligand, which corresponds to the reactivity and selectivity. Now, among (*E*)-enolate and (*Z*)-enolate, the reaction would take place via (*E*)-enolate reducing 1,3-diaxial repulsion among the sterically crowded Boc groups of complexes (**48b**) and enolate according to the Curtin−Hammett control. The resulting base, i.e., hydrazine complex (**48c**), will deprotonate another molecule of ketones (**46**), affording the desired product (**48**), and the catalyzed cycle is regenerated (Scheme 25).[40]

One-Pot Synthesis. The spirooxindole, which is found in many naturally occurring and man-made compounds, has drawn the attention of researchers because of its vast

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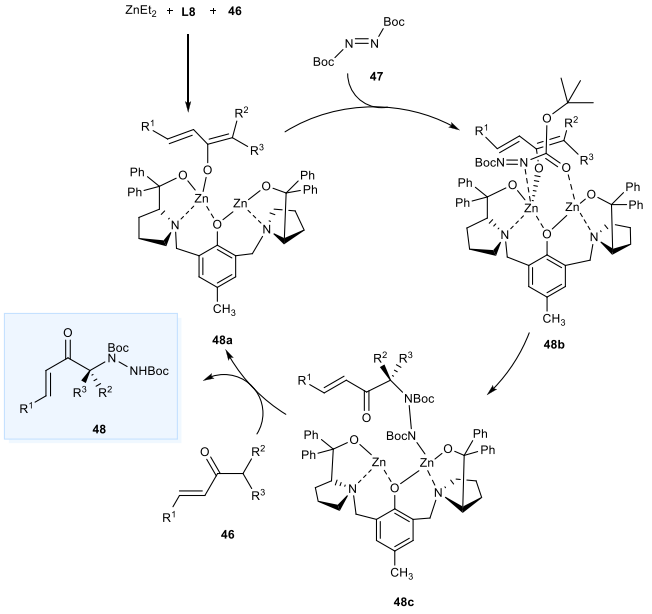
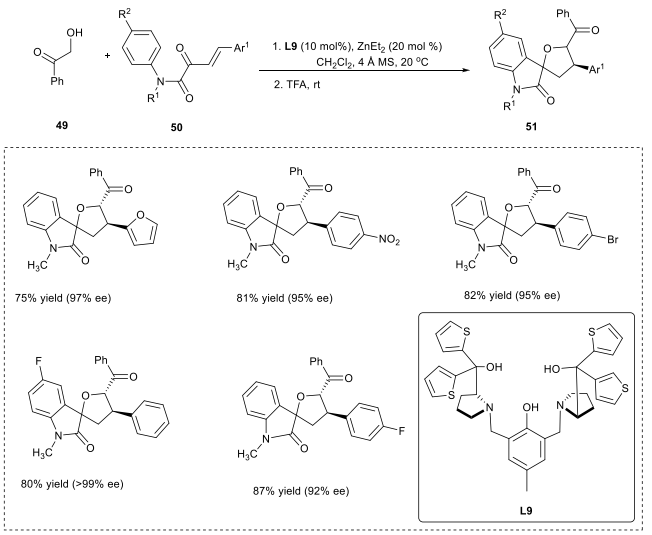
Scheme 25. Synthesis of α-Tertiary Amines via Amination of Vinyl Ketone Derivatives



applicability in both the chemical and pharmaceutical industries.[41,42] Among the spirooxindoles, asymmetric tetrahydrofuran spirooxindole compounds have been found to have exemplary biological properties, such as growth inhibitory and anticancer activities.[43,44] The dinuclear zinc catalyst based on $ZnEt_2$ and an asymmetric multidentate semiazacrown ether ligand (*S*,*S*)-**L9** has led to many enantioselective catalytic reactions. In 2019, Guo et al. carried out the one-pot transformation to obtain tetrahydrofuran spirooxindole-related compounds (**51**) from a variety of α-hydroxy phenyl ketones (**49**) and β,γ-unsaturated α-ketoamide derivatives (**50**). The reaction has been catalyzed by a dinuclear Zn-catalyst and trifluoroacetic acid (CH_3CO_2H) (Scheme 26). The one-pot synthesis involves asymmetric hemiketalization/Michael addition followed by Fridel Crafts reaction. A range of structurally distinct tetrahydrofuran spirooxindole derivatives has been

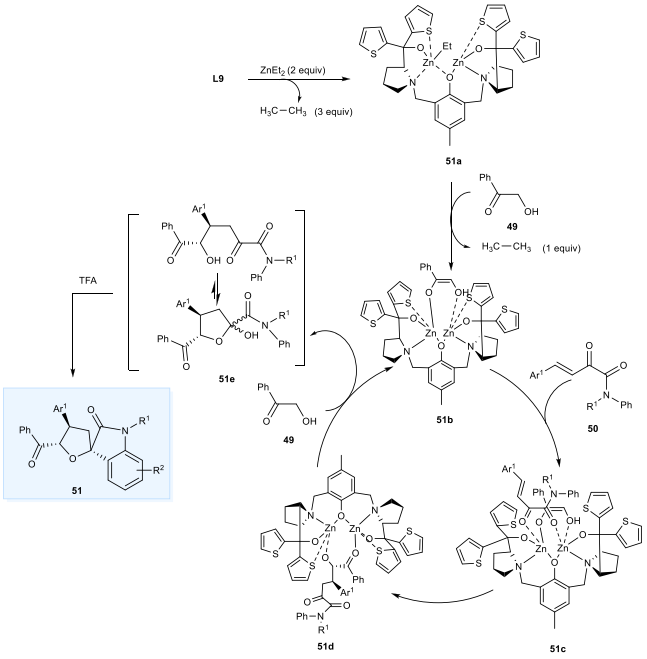
Scheme 26. Synthesis of Tetrahydrofuran Spiro Oxindoles via One-Pot Reaction Using Dinuclear Zn-Catalyst and TFA



obtained in good yields (75% to 87%) with enantioselectivity high as 99% and diastereoselectivity ratio of 3:1−13:1. The *N*-aromatic ring having electron-donating substituents (e.g., −Me, −OMe) or electron-withdrawing substituents (e.g., halogens) at *p*-position undergo reaction more effectively giving 80−85% yields of the desired products with dr ration 8:1−13:1 and ee up to >99%).

The proposed reaction cycle for the synthesis of spiro oxindole derivatives commences with the generation of an in situ dinuclear zinc complex (**51a**) by treating $ZnEt_2$ with a ligand (**L9**). Then, the dinuclear zinc complex (**51a**) works as a catalyst and deprotonates the α-hydroxy acetophenone (**49**), yielding the intermediate (**51b**) with the elimination of one ethane molecule. Subsequently, the β,γ-unsaturated α-ketoamide derivative (**50**) undergoes coordination with the least hindered site of both the Zn metal atoms affording the complexes (**51c**), which further undergoes the Michael 1,4-addition to yield the complex (**51d**) with the examined stereochemical configuration. Then, complex (**51d**) upon the H^+ transfer with another molecule of α-hydroxy acetophenone (**49**) affords the intermediate (**51e**), and the catalytic cycle continues. The intermediate (**51e**) has been the combination of cyclic structure (hemiketalization/Michael adduct) and chain structure, which is the Michael addition product. Finally, the intermediate (**51e**) has been treated with TFA to yield desired product by intramolecular Friedel−Crafts alkylation (Scheme 27).[45]

Scheme 27. Mechanistic Cycle Synthesizing the Tetrahydrofuran Spiro Oxindole Derivatives Using Dinuclear Zn-Complex and TFA



γ-Butyrolactones have been consistently seen as synthetic targets due to their widespread application in biologically active naturally occurring compounds.[46] Many pharmaceutically important drugs have chiral spirocyclic butyrolactones as basic structural components; e.g., a typical drug spironolactone for treating heart failure is a synthetic steroid, and Drospirenone, also called Yasmin, is a powerful contraceptive.[47] In 2019, spiro[1-indanone-5,2′-γ-butyrolactones]

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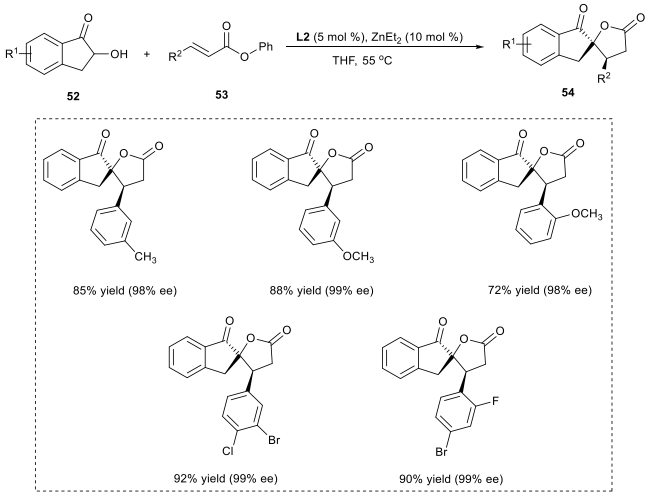
(53) were synthesized from α-hydroxy-1-indanones (52) and α,β-unsaturated ester derivatives (54) via a one-pot reaction catalyzed by dinuclear Zn-catalyst (Scheme 28). The one-pot

Scheme 28. Synthesis of γ-Butyrolactones via Zn-Catalyzed Michael 1,4-Addition Reaction

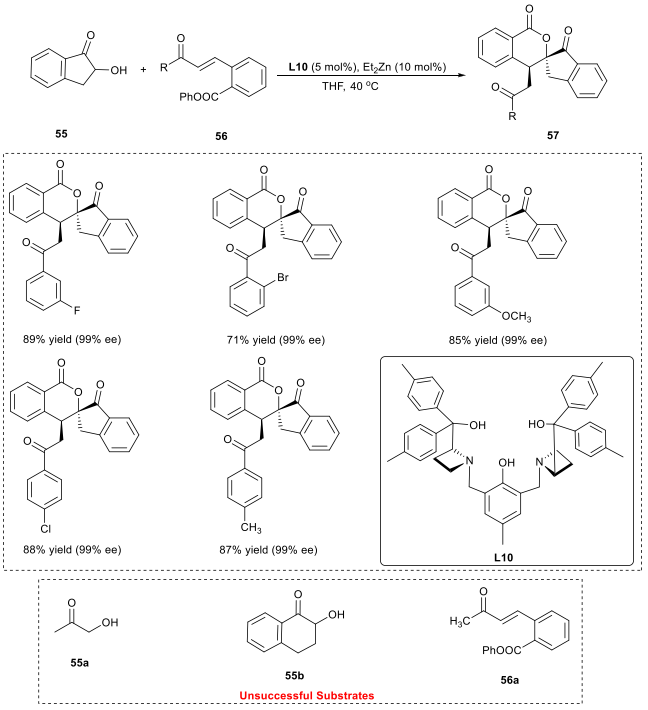


reaction involves Michael 1,4-addition followed by transesterification reaction in CH_2Cl_2, affording the desired product with a dr ratio >20:1 and 92% ee. Both the electron-deficient and electron-rich substitutions at the 5-position of the aromatic ring of the α-hydroxy-1-indanone (**52**) were very well tolerated and had an insignificant impact on the yields, enantioselectivities (ee), or diastereoselectivities (dr) of the desired products.[48]

The isochromanone framework is found in a wide variety of natural products as well as pharmaceutical compounds. The isochromanone analogues, particularly chiral isochromanone molecules, exhibit a diverse range of significant bioactivities.[49] An effective technique for the enantioselective and diastereoselective synthesis of spiro[indanone-2,3′-isochromane-1-one] derivatives (**57**) via transesterification/cascade Michael reaction of *o*-ester chalcones (**56**) with α-hydroxy indanones (**55**) has been reported by Yang et al. (Scheme 29). The ligand (**L10**) has been found most effective, yielding the targeted compounds in 92% yield exhibiting remarkable enantioselectivity and diastereoselective, i.e., >99% ee and >99:1 dr, respectively. The position and electronic nature of the substituents incorporated on the phenyl rings of α-hydroxy indanone derivatives have little impact on the stereoselectivities. Both the disubstituted and trisubstituted aromatic rings were equally tolerated under the reaction conditions. Moreover, the *o*-ester chalcones having a 2-naphthyl or 2-thienyl group have been shown to be appropriate substrates in this tandem approach, giving the intended products in good yield with 99% ee. Notably, nearly a single diastereoisomer has been obtained as the end product in almost all the reactions. The reaction was a failure with α-hydroxy ketone (**55a**) and α-hydroxy indanones (**55b**). Additionally, *o*-ester chalcones (**56a**) did not react, as aliphatic enones have lower reactivities compared to aromatic enones.

The proposed mechanism for isochromanone synthesis takes place with the formation of two dinuclear zinc complexes (**57a**) and (**57b**) by treating $ZnEt_2$ with ligand **L10**. In the next step, deprotonation of α-hydroxy indanone (**55**) gives the

Scheme 29. Synthesis of Spiro[indanone-2,3′-isochromane-1-one] Derivatives via Transesterification/Cascade Michael Reaction



catalytically active complex (**57c**). Now, both Zn atoms have been coupled with ortho-ester chalcones (**56**) from the sterically accessible side to generate the complex (**57d**). The formation of a carbon−carbon single bond by Michael addition generates the complex (**57e**). After that, complex (**57e**) proceeded through intramolecular transesterification, generating product (**57**) and zinc phenoxide species (**57f**). The catalytic cycle has been restarted with another deprotonation of α-hydroxy indanone (Scheme 30).[50]

Endless efforts are being contributed to the developing areas of metal catalysis and organo-catalysis. Catalytic unsymmetrical multicomponent response (CAMCR) is among the foremost capable strategies for quickly increasing the stereochemical complexity. Formation of multiple bonds and numerous stereocenters have been accomplished at the same time by engineering a single-step reaction utilizing a domino response with at least three reacting components using a catalytical number of stereogenic catalysts.[51]

In 2019, Miao et al. utilized three components; isatin (**58**), malononitrile (**59**), and α-hydroxy acetophenone (**60**) in a domino reaction to synthesize chiral 3,3′-dihydrofuran spirooxindole derivatives (**61**) in excellent yield with enantioselectivities (ee) up to 99% (Scheme 31). The domino reaction begins with Knoevenagel condensation/Michael addition, followed by cyclization in CH_2Cl_2. The stereoselectivity of the desired product decreases upon utilizing isatin-bearing N−Me or N−Bn protecting groups. The reaction seems to be well tolerated in the case of several electron-rich as well electron-deficient groups on α-hydroxy acetophenone with excellent ee values. However, in the case of isatins, the presence of an electron-withdrawing group decreases the enantioselectivities.

The Zn-catalyzed cycle for spirooxindole synthesis commences with the formation of ethylzinc complex (**61a**) which

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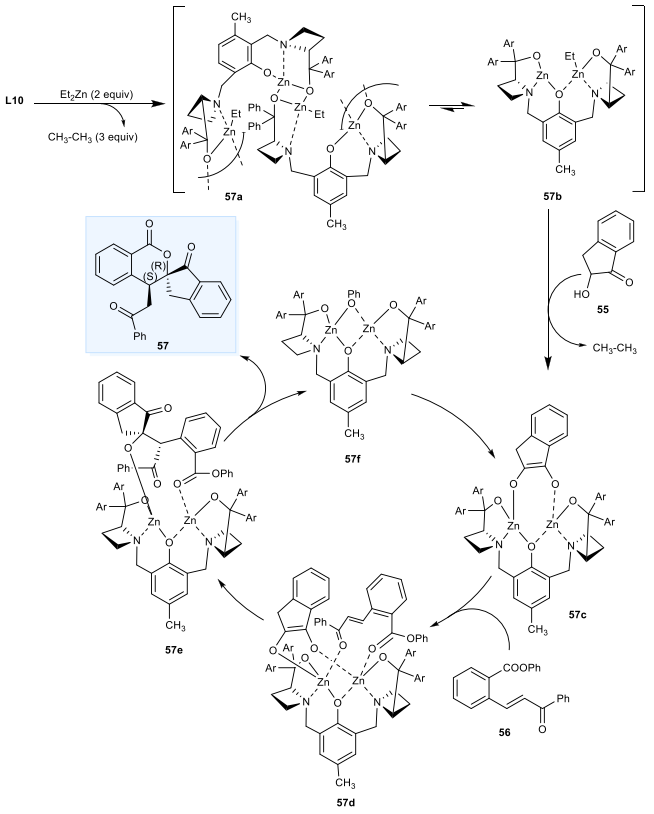
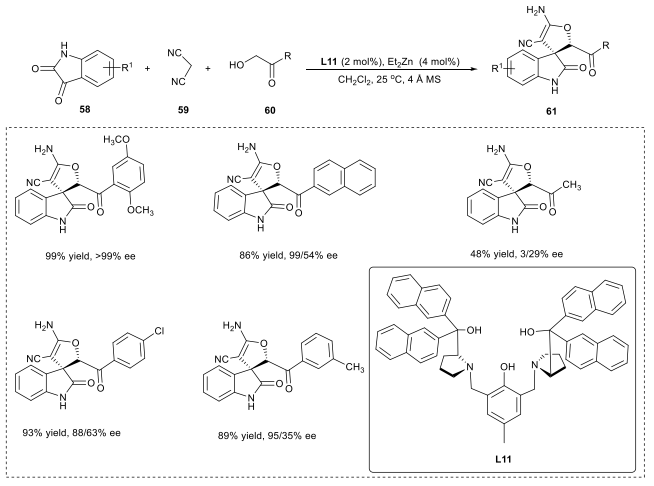
Scheme 30. Catalytic Cycle for the Transesterification/ Cascade Michael Reaction

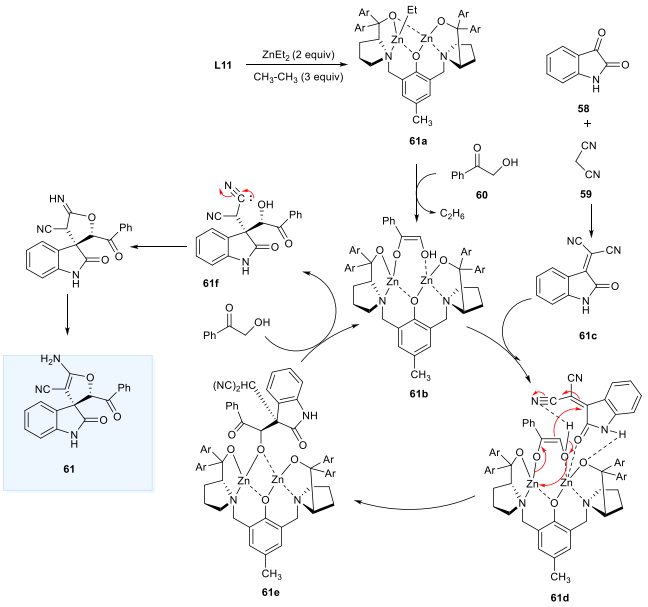


Scheme 31. Synthesis of 3,3′-Dihydrofuran Spirooxindole Derivatives by Domino Reaction



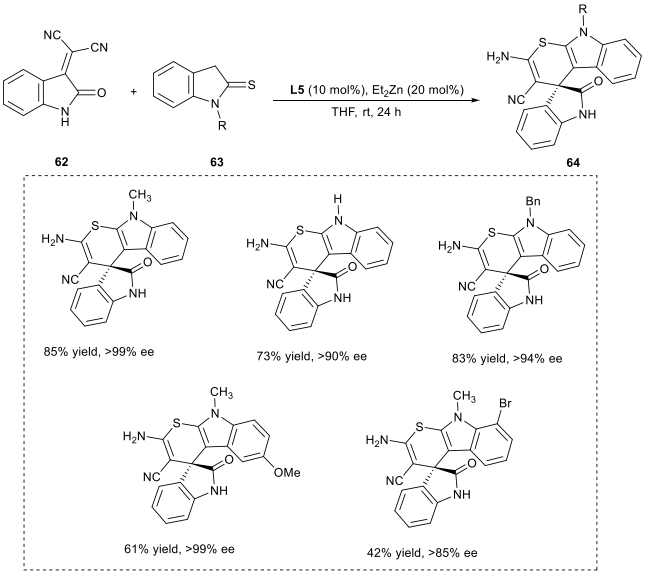
deprotonated the α-hydroxy acetophenone (**60**) to generate bidentate bridging enolate (**61b**). Next, the Knoevenagel condensation product (**61c**) from (**58**) and (**59**) afford the intermediate (**61d**) upon coordinating with the sterically less hindered Zn atom via the indicated orientation. In this well-regulated chiral environment, intermediate (**61e**) has been generated through the parallel generation of new carbon−carbon single bonds and asymmetrical centers, via a Michael 1,4-addition reaction and tautomerization. Lastly, the catalytic cycle undergoes completion upon the H^+ transfer from α-hydroxy acetophenone (**60**) nucleophile affording an unstable product (**61f**). The unstable (**61f**) undergoes Pinner transformation/isomerization to afford the stable desired product (Scheme 32).[52]

Scheme 32. Catalytic Cycle of Three-Component Domino Reaction



In 2022, Liu et al. employed a binuclear Zn-ProPhenol catalytic system to synthesize biologically active chiral spiro[indoline-3,40-thiopyrano[2,3-*b*]indole] compounds (**64**) from isatylidene malononitriles (**62**) and indoline-2-thiones (**63**) via asymmetric cascade [3 + 3] cyclization reaction (Scheme 33). The indoline-2-thiones (**62**) having either electron-rich or electron-deficient groups at the 5-position have been tolerated well, giving the products in moderate to good yields with remarkable ee values (87−99%). Additionally, electron-withdrawing substitutions at the 6-

Scheme 33. Synthesis of Spiro[indoline-3,40-thiopyrano[2,3-*b*]indole] Derivatives by Catalytic Asymmetric Cascade [3 + 3] Cyclization Reaction



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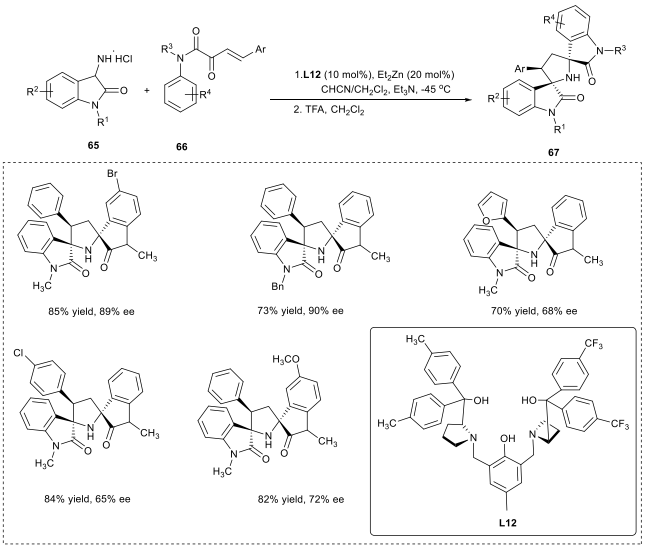
position (−Cl, −Br) and 7-position (−F, −Br) were also tolerated well. Notably, the incorporation of an electron-withdrawing substituent (−Br) at either the 5- or 7-position has shown a negative impact on the product yield as well as the enantioselectivity (ee) of the reaction.[53]

The 2,3-pyrrolidinyl spirooxindole skeletons are prominent structural motifs that are present in a variety of natural as well as synthetic organic molecules.[54−56] These optically pure 2,3-pyrrolidinyl spirooxindoles are found to be responsible for remarkable biological and pharmacological properties.[57,58] The 2,5-pyrrolidinyl dispirooxindole derivatives (**67**) have been synthesized from 3-amino oxindole hydrochlorides (**65**) and β,γ-unsaturated α-keto amide (**66**) upon employing asymmetric semiaza crown ether ligand (***S,S*-L12**) in a tandem reaction (Scheme 34).

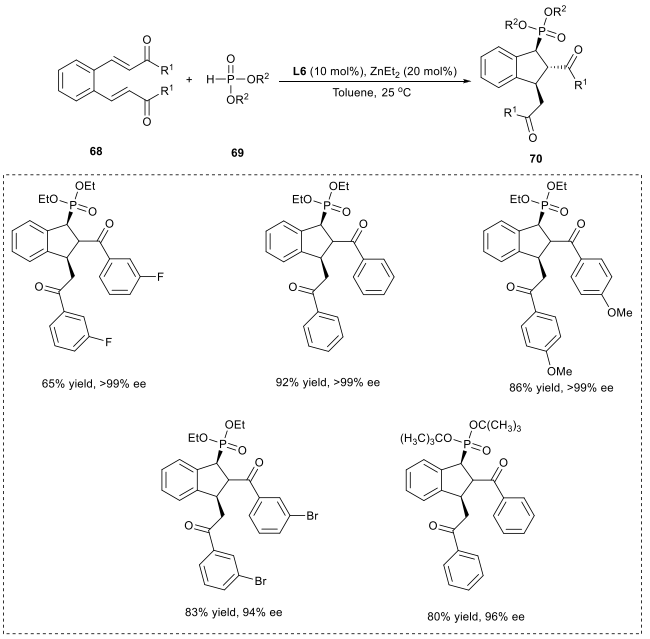
Scheme 34. Synthesis of 2,5-Pyrrolidinyl Di-spirooxindoles Using Semi-aza Crown Ether Ligand via Tandem Reaction



The reaction involves Michael/cyclic keto-imine transformation followed by Friedel−Crafts reaction affording pyrrolidinyl dispirooxindole derivatives having two non-adjacent spiro-quaternary stereogenic centers at C-2 and C-5 of the pyrrolidine aromatic ring. Acetonitrile has been the best-suited solvent for the reaction, giving enantioselectivity up to 76% in good yields of the desired products. The ee values have also been improved upon lowering of temperature up to −45 °C. The starting substrates having electron-rich groups ($-CH_3$, $-OCH_3$) at the *p*-position of the aryl ring (Ar) have given better enantioselectivity than the electron-deficient groups (−F, −Cl, −Br, $-NO_2$). However, both electron-rich and electron-deficient substitutes were tolerated well at R^4 and the *p*-position of the phenyl ring (at the N-atom), furnishing good yields of the products with moderate to good ee.[59]

Indane has been identified in multiple natural and man-made compounds as the core skeleton. Indane derivatives, particularly compounds with chiral Indane, have drawn the interest of chemists across a wide variety of fields because of their unusual biological characteristics.[60] In 2019, Tao et al. synthesized 1,2,3-trisubstituted indane derivatives (**70**) having phosphoryl group from *o*-dienones (**68**) and diethyl phosphate (**69**) via Michael tandem/phospha-Michael addition reaction by employing Zn-catalyst (Scheme 35). The targeted products

Scheme 35. Synthesis of 1,2,3-Tri-substituted Indanes via Michael Tandem/Phospha-Michael Reaction



were afforded with high stereoselectivities, i.e., dr up to >99:1 and ee >99%. The electronic properties of the substituents incorporated upon the phenyl ring (R^1) have shown negligible impact on stereoselectivity. The substrate having either an electron-rich group (−OMe) or electron-withdrawing group (−F) at the 3-position on the aromatic ring exhibits reduced yields, i.e., below 80%. However, the substrates having an electron-withdrawing substituent (−Br) at either the *m*-position or *p*-position yield the products with slightly lower ee values i.e., 94%−95%.

The reaction commences with the formation of dinuclear zinc complex (**70a**) by treating ligand **L6** with $ZnEt_2$ followed by the deprotonation of the diethyl phosphonate (**69**) by (**70a**) generating intermediate (**70b**) upon the removal of one ethane molecule. In the next step, complex (**70c**) is afforded upon the coordination of *o*-dienone (**68**) to the zinc metal from the least hindered site. After that, the phospha-Michael reaction gives the intermediate (**70d**), which promptly generates the intermediate (**70e**) via a Michael addition reaction. Lastly, a proton transfer between (**70e**) and another diethyl phosphonate (**69**) molecule affords the required product (**70**) and intermediate (**70b**), and the catalytic cycle restarts (Scheme 36).[61]

Spirooxindoles are found in a variety of organic bioactive compounds. The chiral spirooxindoles having a tetrahydrofuran backbone have been found to have anticancer potential.[42,43,62,63] A versatile and effective technique facilitated by a dinuclear Zn-AzePhenol for the formation of oxindoles bispiro[3,2′-tetrahydrofuran-5′,2″-indanone] (**73**) via a one-pot reaction from 2-hydroxy-1-indanone (**72**) and β,γ-unsaturated α-ketoamide (**71**) has been reported by Liu et al. (Scheme 37). The one-pot reaction involves Michael/hemiketalization followed by an intramolecular Friedel−Crafts reaction. The results evidenced that enantiomeric selectivity (ee), and yields were significantly influenced by the temperature. A decrease in the temperature to 0 °C led to a higher enantioselectivity value of 95%. However, upon further

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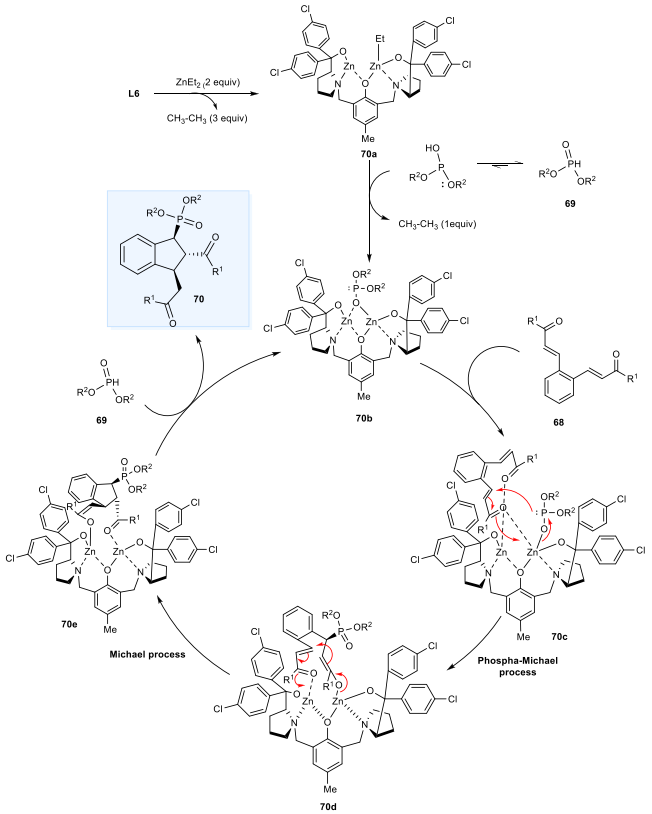
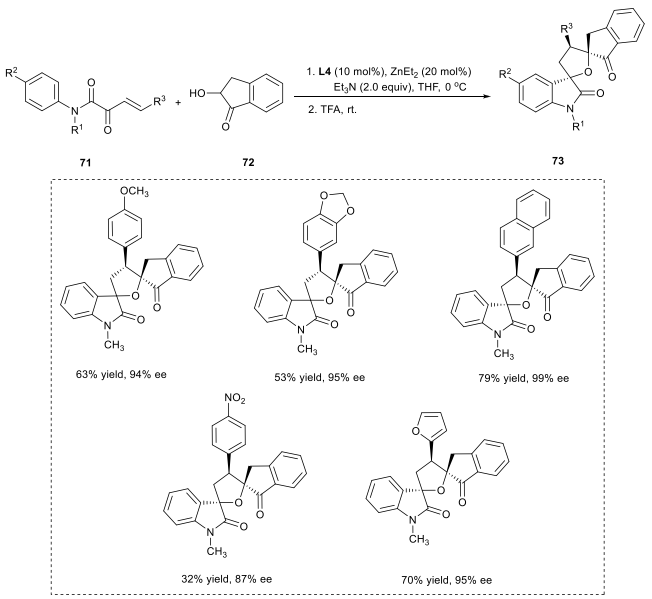
Scheme 36. Mechanism for the Michael Tandem/Phospha-Michael Reaction



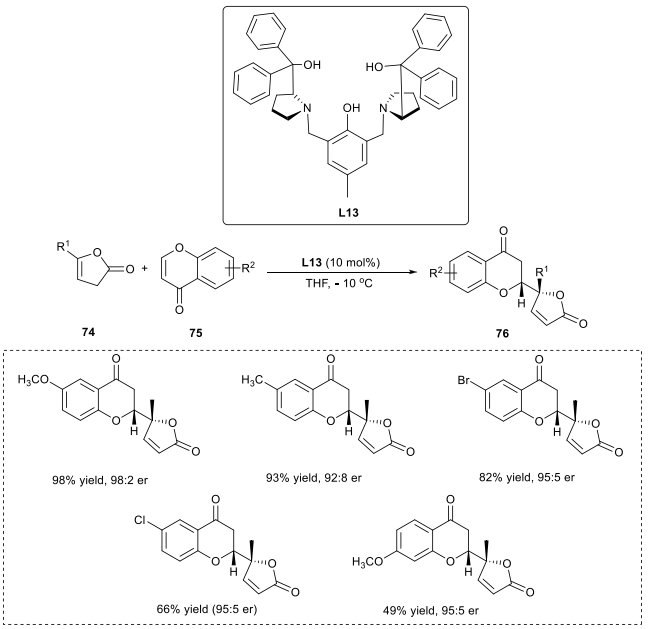
Scheme 37. Synthesis of Oxindoles Bispiro[3,2′-tetrahydrofuran-5′,2″-indanone] via Catalytic One-Pot Reaction



dropping the temperature to either −10 or −20 °C, both the stereoselectivities and yields have been diminished. Furthermore, using triethylamine (NEt_3) as an additive has shown a significant improvement in enantioselectivity (ee) and diastereoselectivity (dr), i.e., 98% ee and dr ratio of 17:1, respectively. The reaction proceeds smoothly upon the incorporation of either electron-donating ($-CH_3$, $-OCH_3$) or electron-withdrawing (−F, -C, -Br) substituents upon the aryl nucleus at the R^3-position. However, upon incorporating a strong electron-deficient group ($-NO_2$), the reactivity has been reduced considerably, diminishing the yield (32%) as well as the enantioselectivity (87%) of the desired products.[62]

The chromanone lactones are naturally occurring compounds composed of 4-chromanones with a five-membered lactone ring at the 2-position.[64] The chromanone lactone family contains various biologically active compounds, for example, Blennolides E and D, exhibiting antialgal and antifungal properties.[65] Although Zn-ProPhenol as a catalyst for 1,2-additions of imines to aldehydes is widely utilized, 1,4-addition reactions catalyzed by Zn-ProPhenol are relatively uncommon. In 2019, Trost et al. utilized the 1,4-asymmetric addition reaction of butenolides (**74**) to chromones (**75**) affording the vinylogous derivatives of the addition product (**76**) (Scheme 38).

Scheme 38. Asymmetric 1,4-Addition of Butanolide Derivatives to the Chromone Nucleus



The chromones having a halogen (−Cl, −Br) at the 6-position have shown excellent ee and dr values. However, chromones having electron-rich substituents at the 6-position have been the best electrophiles for the transformation. The reactivity of the reaction has been reduced upon the incorporation of the electron-donating substituent at the 7-position, although enantioselectivity and diastereoselectivity were not affected.[64]

Xiang et al. reported the synthesis of numerous structurally diverse tetrahydrofuran spirooxindoles (**78a**) and dihydrofurans (**78b**) from β,γ-unsaturated-α-keto derivatives (**79a**−**b**) and 1-tosylindoline-2,3-diols (**77**) via an asymmetrical tandem reaction catalyzed by dinuclear Zn-catalyst. The hemiacetals as α-carbon nucleophiles have been reported to exhibit umpolung activity through chiral dinuclear zinc catalysis (Scheme 39). The 1-tosylindoline-2,3-diol derivatives having either electron-rich or electron-withdrawing substitutions at the 5-positions performed well during the reaction yielding the desired products from 46% to 59% with high stereoselectivities, i.e., d.r. of 20/1 and ee from 83% to 92%. However, upon the

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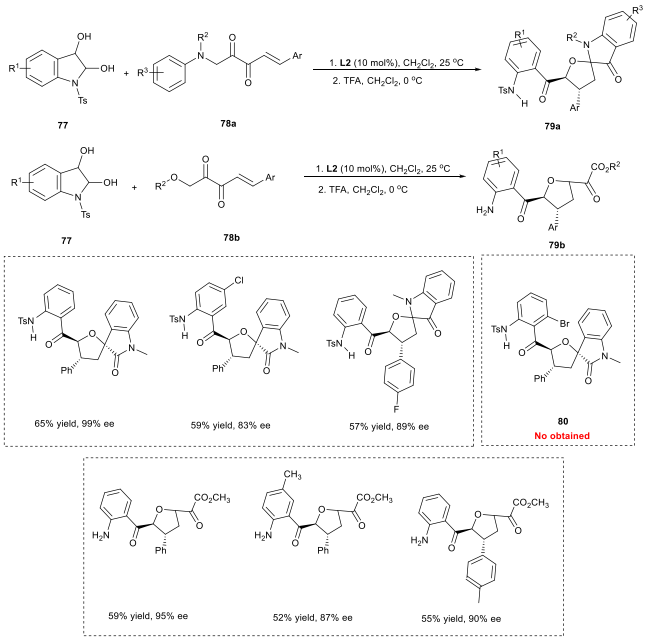
Scheme 39. Synthesis Involving Hemiacetals As α-Carbon Nucleophiles



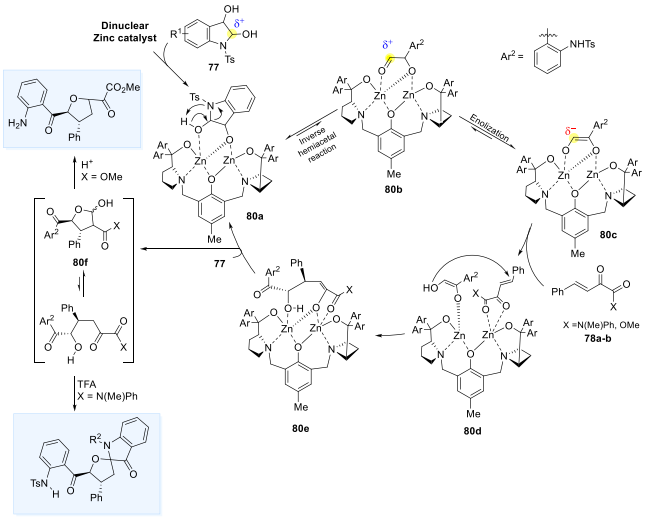
incorporation of −Br at the 4-position of the aromatic ring (**80**), no reaction has been observed due to steric crowding. The presence of both electron-rich (−OMe, −Me) and electron-withdrawing (−F, −Cl, −Br) substitution were also effectively tolerated at *p*-position (R^3) in the N-aromatic ring backbone affording the intended products in fair yields with 90−96% ee. The reaction also proceeded smoothly in the presence of a variety of substituents on β,γ-unsaturated-α-keto (Ar), including heterocyclic substituents.

The reaction commences with the formation of intermediate (**80a**) via deprotonation of (77). Subsequently, the intermediate (**80a**) is converted to intermediate (**80b**) via slow reverse hemiketal reaction, followed by immediate enolization of (**80b**), affording the enediol intermediate (**80c**) which serves as the α-carbon nucleophile, demonstrating the umpolung behavior of hemiacetal. The electrophilic β,γ-unsaturated α-keto derivatives (**78a−b**) has been activated through Zn−O coordination, leading to the formation of the complex (**80d**) from the sterically most accessible side. Subsequently, (**80d**) undergoes a Michael 1,4-addition, forming intermediate (**80e**) with the stereochemical configuration. Lastly, proton transfer with the second molecule of (77) releases the product of the Michael reaction (**80f**), and the cycle is initiated once again. Finally, treatment of (**80f**) with acid affords desired products (**79a−b**) (Scheme 40).[66]

CONCLUSION

In conclusion, the bimetallic ProPhenol Zn complexes exhibit a wide range of capabilities as catalysts, enabling a diverse set of asymmetric transformations for the production of valuable chemical components. The Brønsted basic center of these catalysts facilitates direct enolization/deprotonation of pronucleophilic moieties, allowing the asymmetric addition reactions without the need for prior activation. For instance, various derivatives of ketone can be directly utilized as nucleophiles in Mannich and aldol reactions, eliminating the requirement for the preformation of corresponding silyl enol ethers or enolates.

Scheme 40. Catalytic Cycle Involving Umpolung of Hemiacetal



Furthermore, the Lewis acidic center enhances the stereocontrol upon coordination with the electrophilic moieties. To date, many asymmetric transformations have been devised using metal (M)-ProPhenol catalysts, encompassing direct aldol, Aza-Henry, Mannich reactions, conjugate additions, alkynylations, and the one-pot process. Also, a significant number of documented procedures have been employed in the total synthesis of natural substances and various biologically active compounds. Despite extensive investigations into the chemistry of ProPhenol ligands in the last two decades, there are still areas that offer room for development. For example, the scope of electrophilic substances remains primarily limited to simple aldimines and aldehydes. One approach to overcome the limited reactivity of bulkier electrophilic substances is to modify the chiral environment of the catalyst by adjusting the ligand substitution. Despite the introduction of several new generations of ProPhenol ligands, the highly modular nature of the ligand framework should enable the exploration of more innovative designs involving zinc as well as other metals. Exploring this avenue promises to be a captivating area of research, leading to new asymmetric processes.

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Notes

The authors declare no competing financial interest.

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