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REVIEW

Catalytic asymmetric synthesis of 3-hydroxyoxindole: a potentially bioactive molecule

Akshay Kumar and Swapandeep Singh Chimni*

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The recent emergence of biological activities of chiral 3-substituted-3-hydroxy-2-oxindoles has inspired synthetic chemists to develop new methodologies for their synthesis. Both chiral organocatalysts and organometallic catalysts have provided an important platform for their synthesis and in recent years, great achievements have been made in their catalytic asymmetric synthesis. This review summarizes the catalytic strategies for enantioselective synthesis of targeted frameworks.

1. Introduction

3-Substituted-3-hydroxy-2-oxindole is one of the key structural units found in a large variety of natural products, such as convolutamydines, donaxaridines, maremycins, dioxibrassinines, celogentin K, 3′-hydroxyglucoisatisin, TMC-95A, *etc.* showing a wide spectrum of biological activities (Fig. 1).[1] This structural moiety, especially 3-aryl/alkenyl-3-hydroxy-2-oxindole, constitutes the core of many drug candidates which have been used in a number of recent pharmaceutical studies.[2] For example, SM-130686 (**A**) is a potent growth hormone secretagogue,[2a] compound (−)-**B** has been identified as an effective activator of maxi-K channels[2b] and compound **C** possesses improved anti-HIV properties compared to the FDA-approved NNRTI drug efavirenz[2c] (Fig. 2). Structure–activity relationship studies have shown that the biological activities of these compounds are greatly affected both by the configuration of the C3 carbinol carbon and its substituent pattern.[2] In recent times, chiral 3-substituted-3-hydroxy-2-oxindole molecules have been favourably placed in new drug discovery programs.

Consequently, the chiral 3-substituted-3-hydroxy-2-oxindole moiety has attracted the attention of synthetic chemists for developing synthetic methods for the synthesis of these molecules possessing advanced pharmaceutical values.

Owing to the importance of natural and synthetic chiral 3-substituted-3-hydroxy-2-oxindoles in medicinal chemistry, a significant effort has continuously been devoted to develop new methods for their preparation. The asymmetric hydroxylation of

Department of Chemistry, U.G.C. Centre of Advance Studies in Chemistry, Guru Nanak Dev University, Amritsar, 143005, India.
E-mail: sschimni@yahoo.com; sschimni.chem@gndu.ac.in;
Fax: (+)91-183-2258820

Akshay Kumar

Akshay Kumar was born in 1983 at Maslana Kalan, a small village in Hamirpur District of Himachal Pradesh in India. He obtained his B.Sc. From Himachal Pradesh University in 2004. After completing his M.Sc. from Guru Nanak Dev University, Amritsar, in 2007, he moved to the R&D centre of Ind. Swift. Company Mohali. In February 2008, he joined the group of Prof. Swapandeep Singh Chimni at the Department of Chemistry, Guru Nanak Dev University, Amritsar and started his Ph.D. His current research is the development of chiral organocatalysts for carbon–carbon bond-forming reactions.

Swapandeep Singh Chimni

Swapandeep Singh Chimni was born in 1962 at Amritsar, India. He received his M.Sc. (Hons. Sch.) in Chemistry in 1985 and Ph.D. in 1991 from Guru Nanak Dev University, Amritsar. After two years as a lecturer at Regional Engineering College (now NIT) Jalandhar, he joined the Department of Chemistry, Guru Nanak Dev University as Lecturer in 1992. He is presently working as a Professor in the same department. He has 22 years of research experience and published over 80 publications. He works in synthetic organic chemistry with emphasis on asymmetric organocatalysis, biocatalysis and phase-transfer catalysis as well as green chemistry.

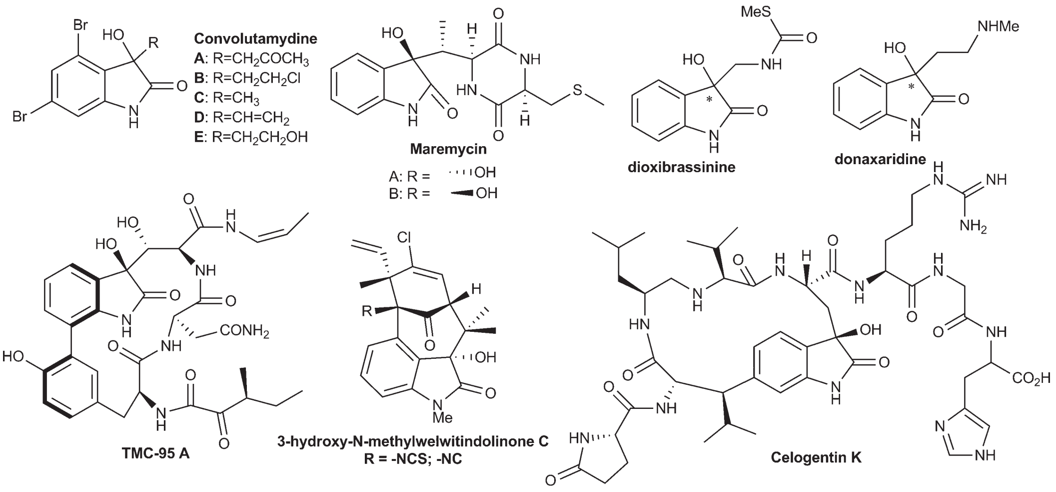


Fig. 1 Some example of bioactive molecule containing the tetrasubstituted 3-hydroxyoxindole structural motif.

enolates employing chiral oxaziridine developed by Davis *et al.* and use of chiral auxiliaries are some of the old and uncommon strategies utilized for the synthesis of chiral 3-substitited 3-hydroxy-2-oxindoles.[3] With the advancement in the field of asymmetric catalysis, a large number of strategies for the synthesis of a diverse range of chiral 3-substituted-3-hydroxy-2-oxindoles have been developed. Organometallic catalysis[4] and organocatalysis[5] have played an important role in their synthesis. Metal catalysts, in particular transition metal complexes, have been shown to catalyze many reactions such as the nucleophilic addition to the C3 carbonyl of isatins, hydroxylation reaction of 3-substituted 2-oxindoles and anilide cyclization to procure chiral 3-substituted-3-hydroxy-2-oxindole derivatives.

Many organocatalytic reactions such as the aldol reaction, Michael reaction, Morita–Baylis–Hillman reaction, Henry reaction and Friedel–Crafts reaction have been used effectively for the synthesis of chiral 3-substituted-3-hydroxy-2-oxindole derivatives.

In recent times, due to the biological activities associated with oxindole derivatives they have been the subject of many reviews.[6] The majority of these reviews discuss the synthetic strategies for the synthesis of spirooxindoles and 3,3′-disubstituted oxindoles, but none of these have focused on the catalytic asymmetric synthesis of chiral 3-substituted-3-hydroxy-2-oxindoles. In this review we present the strategies developed for the asymmetric synthesis of 3-substituted-3-hydroxy-2-oxindoles using chiral catalysts (Fig. 3).

For simplicity in presentation and understanding, the review has been divided into two classes, based on the catalytic approach used in the synthesis of chiral 3-substituted-3-hydroxy-2-oxindoles: 1) organocatalysis and 2) organometallic catalysis. Each of these have been further discussed based on the substrate employed in the reaction.

2. Organocatalysis

2.1 Isatin as an electrophile

2.1.1 Aldol reaction. The aldol reaction is one of the most well known reactions, efficiently exploited for more than a century for the synthesis of β-hydroxy carbonyl compounds. The synthesis of tetrasubstituted-3-hydroxyoxindole *via* aldol reaction of isatin with acetone was reported in 1933,[7] and 72 years later, in 2005, Tomasini *et al.*[8] developed the first enantioselective organocatalyzed process for the synthesis of chiral 3-alkyl-3-hydroxy-2-oxindoles (**3**) using dipeptide catalyst **1**. The catalyst **1** derived from proline and β-homophenylglycine catalyzed the aldol addition of acetone to isatins (**2**) providing aldol adduct **3** in high yield (90 to >99%) and with a good level of enantioselectivity (73–77% ee) (Scheme 1). This methodology was extended to develop the first enantioselective synthesis of (*R*)-convolutamydine A (**3a**).[9] The aldol reaction of 4,6-dibromoisatin (**2a**) and acetone catalyzed by dipeptide **1** provided **3a** in quantitative yield with 68% enantiomeric excess, which could be enantioenriched to 97% ee after a single crystallization (Scheme 1).

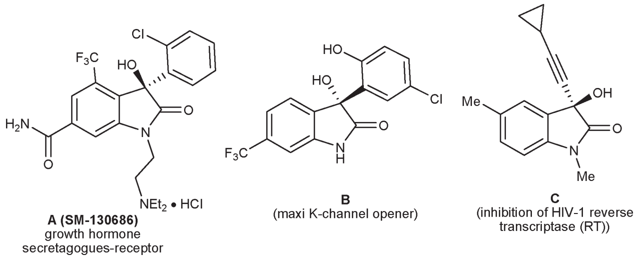


Fig. 2 Representative example of some drug candidates.

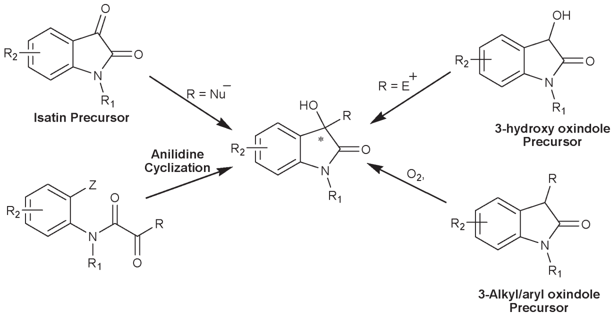
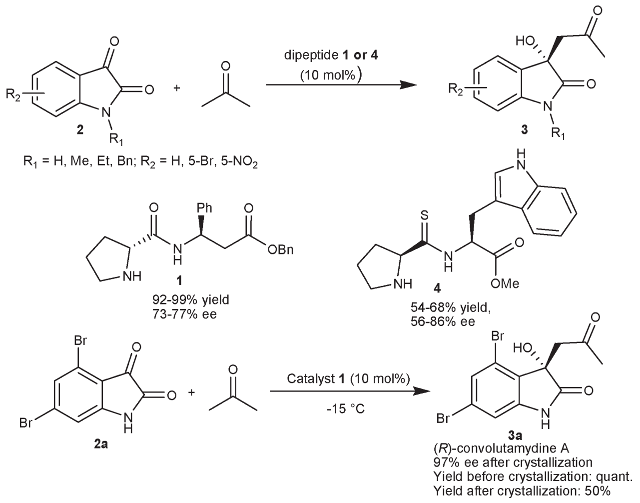


Fig. 3 Strategies for catalytic asymmetric synthesis of 3-substituted-3-hydroxy-2-oxindoles.

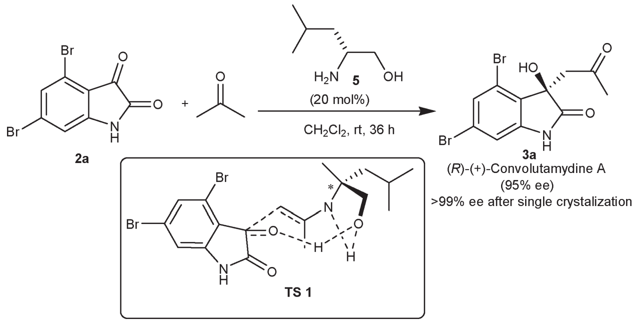


Scheme 1 Dipeptide-catalyzed aldol reaction of acetone with isatins.

Recently, Juaristi *et al.*[10] developed a solvent-free high speed ball-milling (HSBM) procedure for direct asymmetric aldol reaction of acetone to isatins (**2**) using thio-dipeptides as organocatalysts. The thio-peptide **4** catalyzed the formation of 3-acetonyl-3-hydroxy-2-oxindoles (**3**) in moderate yield (54–68%) and moderate to good enantioselectivity (56–86% ee) (Scheme 1). The thio-dipeptides proved to be better organocatalysts relative to their analogous amides for this reaction using a HSBM procedure.

In 2007, Malkov and co-workers[11] reported highly enantioselective synthesis of **3a** catalyzed by primary amino alcohols derived from natural α-amino acids. L-Leucinol (**5**) catalyzes the aldol reaction between acetone and 4,6-dibromoisatin (**2a**) affording **3a** in excellent yield (98%) with an enantiomeric excess of 95% (Scheme 2). It was established with the help of designed experiments that the hydrogen bonding between the hydroxyl group of the catalyst and the keto group of the isatin is a prerequisite for highly enantioselective aldol reaction, since the reaction performed in methanol provided a racemic adduct. Further, the catalysis by *O*-methylleucinol and *O*--trimethylsilylleucinol organocatalysts gave product with low enantioselectivity (50% ee) (TS 1, Scheme 2).

The aldol reaction of ketones with variety of isatins (**2**) catalyzed by carbohydrate-derived amino alcohol **7** provides the corresponding aldol adducts **3** in good to excellent yield (80–99%) and moderate to good enantioselectivity (55–75% ee).[12]

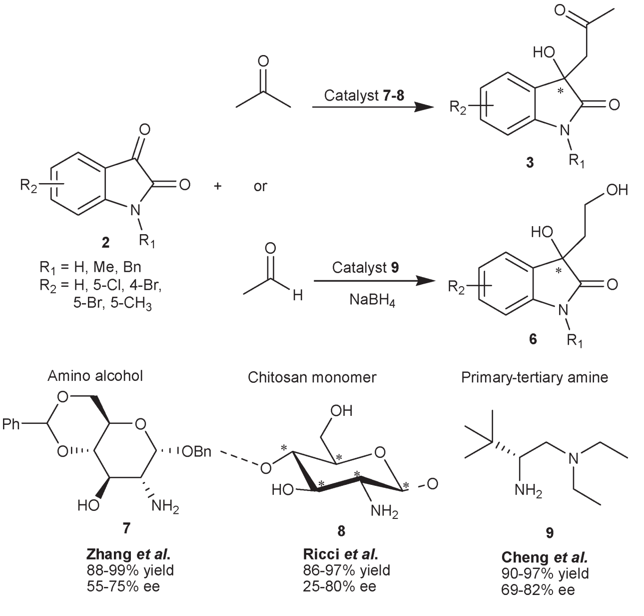


Scheme 2 Synthesis of (*R*)-convolutamydine A.

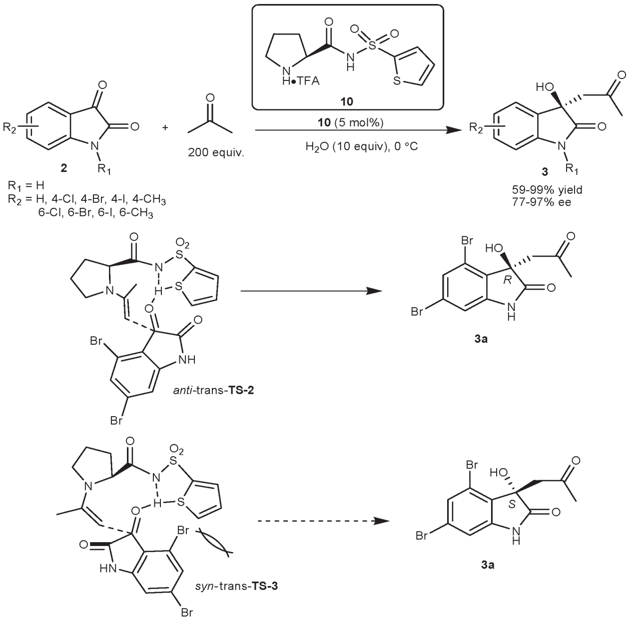
The heterogeneous organocatalyst chitosan **8**, a renewable feedstock material, has been successfully used to catalyze the aldol reaction of ketones with isatins (**2**), providing aldol adducts (**3**) in high yield, albeit with low enantioselectivity.[13] The recyclability was an important asset for this catalytic protocol (Scheme 3).

The primary amino acid derived primary–tertiary diamine organocatalyst was developed for catalyzing the direct aldol reaction of isatins with acetaldehyde.[14] The L-*tert*-leucine **9** in conjugation with $(H_4SiW_{12}O_{40})_{0.25}$ was identified as the optimal catalytic system which gave aldol products **6** in excellent yield (90–97%) and good enantioselectivity (69–82% ee) (Scheme 3). Nakamura and co-workers have developed the two-point coordinate heteroarylsulfonylprolinamide organocatalyst for aldol reaction of isatins with aldehyde/ketone as a donor.[15,16] The direct aldol reaction between acetone and isatins (**2**) catalyzed by **10** under neat conditions with a small amount of water (10 eq.) afforded aldol adduct **3** in moderate to excellent yield (59–99%) and good to excellent enantioselectivity (77–97% ee) (Scheme 4).[15] The enantioselectivity of all derivatives was enriched to >99% after single crystallization. Hydrogen bonding between the amidic proton and sulfur atom of thiophene in the organocatalyst plays an important role in orienting the reactants for high enantioselectivity. The preferential formation of the *R* enantiomer has been attributed to *anti–trans*-**TS-2**, since *syn–trans*-**TS-3** leads to the formation of the *S* enantiomer, which is destabilized by a steric repulsion between 4-bromo and 2-thienyl groups (Scheme 4).

The organocatalyst **10** have also been used to catalyze the aldol reaction of linear aldehydes (**11**) with isatins (**2**) in THF to provide aldol adducts (**6**) with good to excellent yield (73–99%) and excellent enantioselectivity (89–98% ee).[16] This process was used for the first time for the enantioselective synthesis of (*R*)-convolutamydine E (**6a**) and (*R*)-convolutamydine B (**12**) (Scheme 5). The (*S*)-pyrrolidine tetrazole organocatalyst **13**



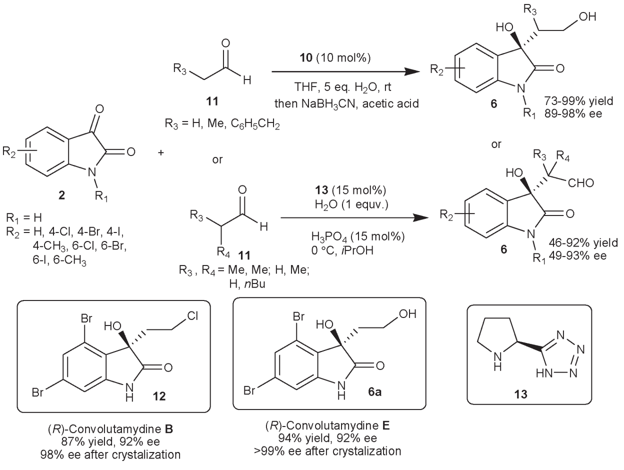
Scheme 3 Primary amine based organocatalyst **7–9** catalyzed aldol reaction of ketones with isatins.



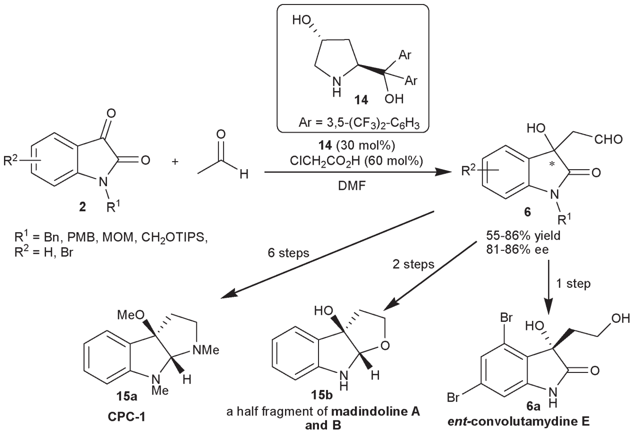
Scheme 4 Heteroarylsulfonylprolinamide **10** catalyzed aldol reaction of acetone with isatins.

catalyzes the aldol reaction of α-branched aldehyde (**11**) with isatins (**2**) providing aldol product **6** with two contiguous stereocentres in moderate to good yield (46–92%) and moderate to good enantioselectivity (49–93% ee) (Scheme 5).[17] Under the reaction conditions studied by the authors, the catalyst **13** was highly efficient for both α-branched and linear aldehydes, whereas catalyst **10** only works efficiently with linear aldehydes.

Hayashi and co-workers[18] have studied the aldol reaction of acetaldehyde (**11a**) with isatins (**2**) catalyzed by 4-hydroxydiarylprolinol **14** (30 mol%) as an organocatalyst in the presence of 60 mol% of chloroacetic acid as an additive. The aldol adducts **6** were isolated in moderate to good yield (55–86%) and good enantioselectivity (81–86% ee). The resulting aldol products **6** have been synthetically transformed to valuable products such as *ent*-convolutamydine E (**6a**), CPC-1 (**15a**) and a half fragment of madindoline A and B (**15b**) (Scheme 6).



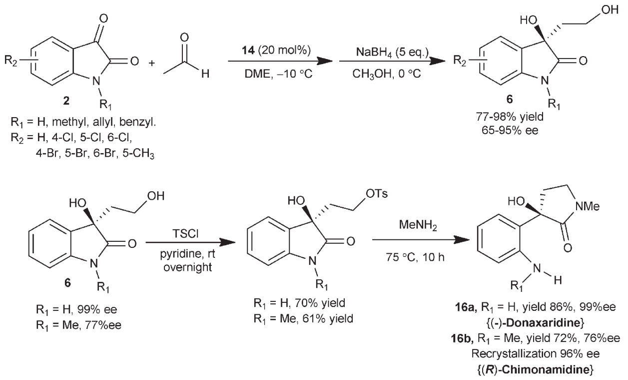
Scheme 5 Aldol reaction of aldehydes to isatins catalyzed by organocatalysts **10** and **13**.



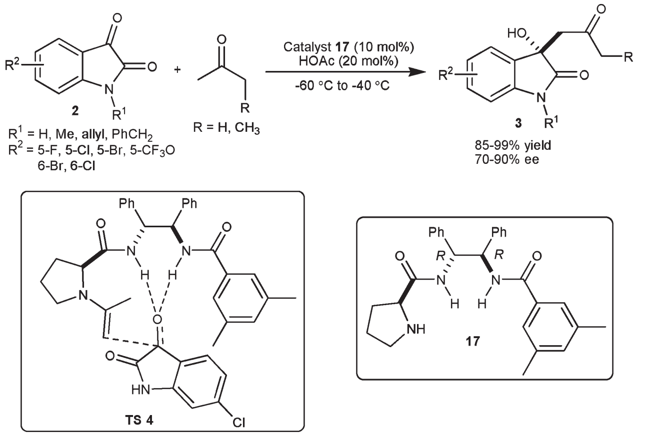
Scheme 6 Prolinol **14** catalyzed aldol reaction of acetaldehyde with isatins.

Yuan *et al.* have also studied the similar transformation with wide substrate scope using the catalyst **14** without acid additive.[19] The aldol adducts **6** was isolated after reduction with sodium borohydride in 65–95% yield and 77–98% enantiomeric excess (Scheme 7). This approach was utilized for the first enantioselective synthesis of optically active (−)-donaxaridine (**16a**) and (*R*)-chimonamidine (**16b**) besides its application in the concise stereoselective synthesis of enantiopure **6a** and **12**. The aldol addition of acetaldehyde to isatins has also been shown to be catalyzed by 9-amino-(9-deoxy)-*epi*-qunine (9-NH_2-*epi*QN) to provide aldol adducts in high yield (up to 96%) and good enantioselectivity (up to 93% ee).[20]

Xiao *et al.* have developed a proline-derived bifunctional organocatalyst for direct aldol reaction of isatin derivatives with acetone and 2-butanone.[21] The 10 mol% of catalyst **17** in combination with acetic acid (20 mol%) catalyzes the direct aldol reaction between ketones (acetone and 2-butanone) and isatins (**2**) to provided aldol products **3** in high yield (85–99%) with good enantioselectivity (70–90% ee) and with regioselectivity of 12 : 1 favouring the linear isomer (Scheme 8). The methodology has been used in the simple synthesis of (*S*)-convolutamydine A in 45% yield and 87% enantiomeric excess. The enantiofacial discrimination in the transition state was governed by the catalyst which controls the enamine geometry and double hydrogen bonds with isatin which fixes its orientation in the transition state (**TS 4**, Scheme 8).



Scheme 7 Aldol reaction of acetaldehyde with isatins catalyzed by **14**.



Scheme 8 Proline-derived catalyst **17** catalyzed aldol reaction of ketone with isatins.

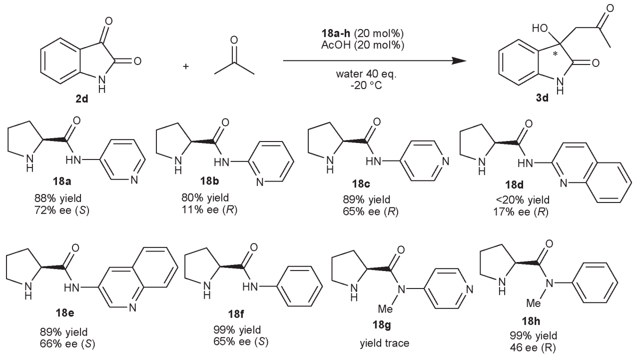
A systematic study on the aldol reaction of isatin and acetone catalyzed by simple *N*-aryl and *N*-heteroaryl pyrrolidine amide organocatalysts (**18a–h**) has been reported.[22] After screening of various *N*-pyridylprolinamide and *N*-quinolinylprolinamide organocatalysts, the prolinamide **18a** in combination with AcOH at −20 °C provided the *S*-isomer of the product **3d** with 72% enantiomeric excess. In the case of aminopyridine (**18a–c**) and aminoquinoline (**18d–e**) based catalysts, the relative position of the amino group and the pyridine nitrogen atom have a major impact on the enantioselectivity of the reaction. In order to analyze the effect of the pyridine nitrogen, the reaction was performed with the simple prolinamide catalyst **18f**, which provided the product with 65% ee; however the reaction was slow. Further, to assess the role of the amidic proton, the same reaction was performed with organocatalyst **18g**, which gave trace amounts of product. These experiments highlighted the importance of the amidic proton for high enantioselectivity and yield of the product (Scheme 9).

L-Proline has also been shown to catalyze the direct aldol reaction of acetone with isatin derivatives (**2**) to provide 3-acetonyl-3-hydroxy-2-oxindoles (**3**) in high yield (76–96%) with moderate to good enantioselectivity (39–79% ee).[23]

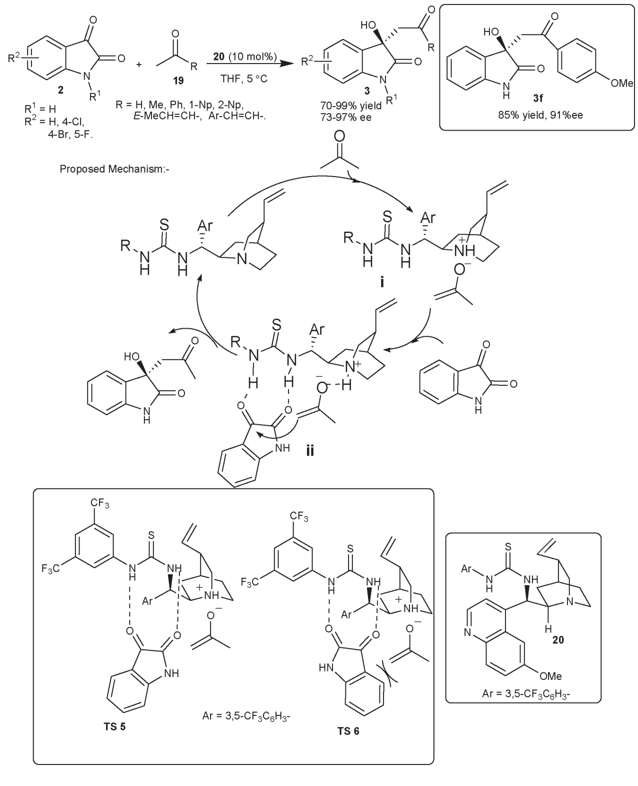
Zhao *et al.* has revised the old protocol of the aldol reaction, involving an enolate mechanism, in the light of enamine-mediated modern aldol reactions.[24] The quinidine thiourea **20** efficiently catalyzes the aldol reaction of unactivated ketones **19** and isatins **2** *via* a noncovalent catalytic mechanism involving an enolate intermediate, providing biologically important 3-alkyl-3-hydroxyindolin-2-ones (**3**) in good yield and enantioselectivity (Scheme 10). This approach was utilized for the first enantioselective synthesis of 3-hydroxyindolin-2-one **3f**, which is the lead compound for treating Ewing's sarcoma discovered most recently by Toretsky and co-workers.[25] The mechanism of reaction was proposed to be initiated by initial deprotonation of acetone by the tertiary amine of the quinidine thiourea catalyst backbone. After deprotonation, the enolate associates closely with quinuclidine nitrogen of the catalyst through ionic interactions (**i**), while thiourea moiety of the quinidine thiourea catalyst forms two hydrogen bonds with isatin carbonyl groups (**ii**), which activate the ketone group for the enolate attack and also direct the approach of isatin in the transition state. Among the two possible transition states, **TS-5** is favoured over **TS-6**, since the unfavourable interaction between the aromatic ring of isatin and the enolate is avoided (Scheme 10). The key importance of this methodology has been realized in those cases of aldol reactions where the formation of enamine was difficult.

Recently, Wang and co-workers[26] extended the above methodology to various α,β-unsaturated ketones as an aldol donor. The quinidine thiourea **20** and its epimer catalyzes the aldol reaction of **19** with **2** to provide both enantiomers of the aldol adduct **3** in low to excellent yield (18–98%) and moderate to excellent enantioselectivity (30–97% ee).

Singh *et al.* developed the first enantioselective aldol reaction of cyclohexanone with isatins for procuring chiral 3-cycloalkane-3-hydroxyoxindoles, which are potentially bioactive molecules.[27] The organocatalyst **24** in the presence of TFA as an additive



Scheme 9 L-Prolinamide organocatalysts catalyzed aldol reaction of **2d** with acetone.



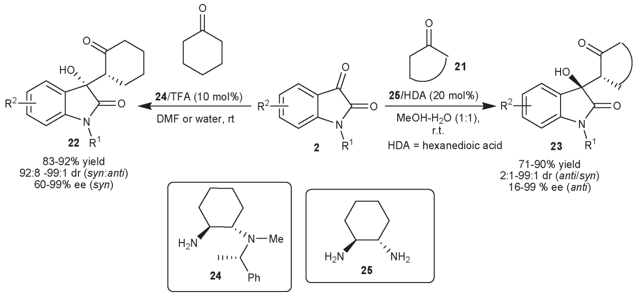
Scheme 10 Thiourea **20** catalyzed aldol reaction of ketone with isatins.

efficiently catalyzes the aldol reaction affording adducts **22** in quantitative yield, dr of 99 : 1 (*syn*/*anti*) with 99% enantiomeric excess of the *syn* isomer (Scheme 11). The prolinamide catalyst failed to catalyze this reaction, in contrast to their successful use in the aldol reaction of cyclohexanone with aldehydes,[28] thus highlighting the utility of primary amine organocatalysts in the catalysis of sterically demanding molecules.

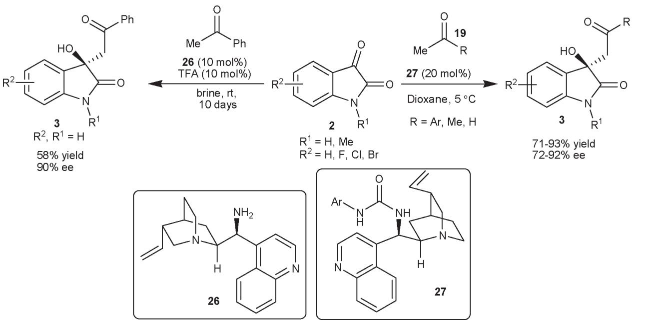
1,2-Diaminocyclohexane–hexanedioic acid (**25**–HDA) efficiently catalyzes the *anti*-selective direct aldol reaction of cycloketones (**21**) and various isatin derivatives (**2**) in MeOH–H_2O providing the corresponding products **23** in good yield (71–90%) with high diastereoselectivity (up to 99 : 1 *anti*/*syn*) and enantioselectivity of up to 99% ee for the *anti* isomer (Scheme 11).[29]

Later, the authors used *Cinchona* alkaloid-derived organocatalysts to extend the scope of the above reaction to various acyclic aldol donors.[30] The 10 mol% of the catalytic mixture of **26**–TFA (1 : 1) catalyzes the aldol reaction of acetophenone with isatin to provide the aldol product in ten days with good enantiomeric excess of 90%, and yield of 58% (Scheme 12). Further, they explored *Cinchona* alkaloid-derived urea organocatalysts (**27**) for a variety of acetophenone derivatives (**19**) employing a noncovalent catalysis mechanism. The 3-substituted-3-hydroxy-2-oxindoles **3** were obtained in good yield (71–93%) and good enantioselectivity (72–92% ee) (Scheme 12). The application of the catalyst **27** has been successfully extended to different aldol donors such as acetone and acetaldehyde. The methodology finds its application in the synthesis of **3a** in 92% enantiomeric excess.

2.1.2 Mukaiyama-aldol reaction. Zhou *et al.* have developed the first highly enantioselective Mukaiyama-aldol reaction for synthesis of 3-difluoroalkyl-3-hydroxyoxindole compounds, catalyzed by a bifunctional organocatalyst.[31] The *Cinchona* alkaloid-derived bifunctional urea catalyst **30** was found to be the best organocatalyst for the reaction of silyl enol ethers (**28**) and isatins **2**, using THF as the solvent at 0 °C. The product **29** was obtained in good yield (70–91%) and high enantioselectivity (88–96% ee) (Scheme 13). The enantioenriched products **29** were used as precursors for the synthesis of variety of new fluorinated compounds such as difluoro analogues of natural products convolutamydines A–E. The synergistic activation of difluoroenoxysilane by the tertiary amine of the quinuclidine moiety and activation of isatins with the urea part of the catalyst through double hydrogen bonding has been proposed for the observed enantiofacial control in the reaction.



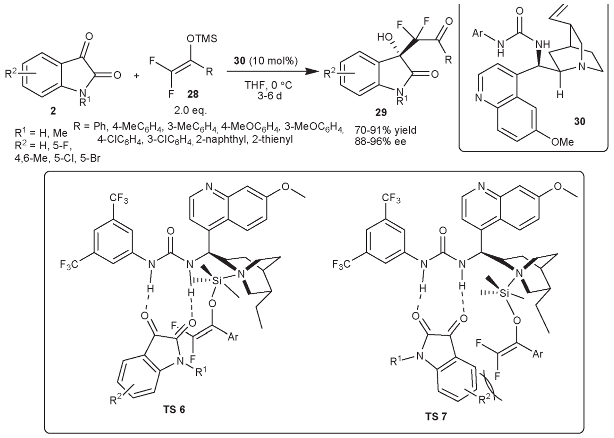
Scheme 11 Cyclohexyl diamine-based organocatalysts (**24** and **25**) catalyzed aldol reaction of ketones with isatins.



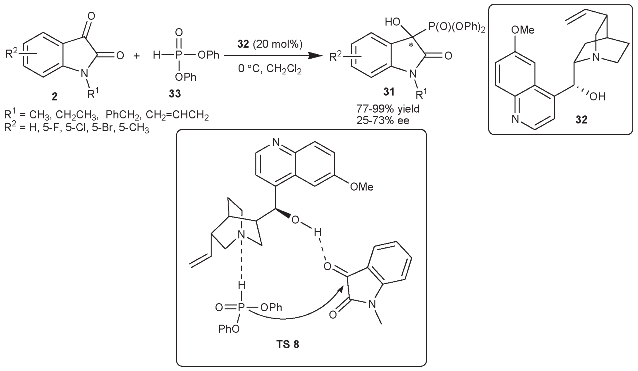
Scheme 12 *Cinchona* alkaloid-derived catalyst **26** and **27** catalyzed aldol reaction of ketone and aldehyde with isatins.

2.1.3 Phospho-aldol reaction. Wang and co-workers[32] developed the first enantioselective phospho-aldol reaction of isatins catalyzed by a *Cinchona* alkaloid to access bioactive 3-hydroxy-3-phospho-substituted oxindoles. Diphenylphosphite (**33**) reacts with various *N*-alkylated isatin derivatives (**2**) in the presence of quinine (**32**) at 0 °C affording phospho-aldol adducts **31** in good to excellent yield (77–99%) with low to moderate enantioselectivity (25–73% ee) (Scheme 14). The transition state was proposed to involve a ternary complex involving the catalyst, *N*-methylisatin and diphenylphosphite in which the OH group of the catalyst activates the *N*-methylisatin through hydrogen bonding and the tertiary amine moiety activates the diphenylphosphite to afford the product with desired enantiocontrol (**TS 8**, Scheme 14).

2.1.4 MBH reaction. The Morita–Baylis–Hillman (MBH) reaction is one of the most useful and interesting carbon–carbon bond forming reactions for synthesizing β-hydroxycarbonyl compounds with an α-alkylidene group. The catalytic enantioselective Morita–Baylis–Hillman (MBH) reaction of isatins was developed independently by four groups to obtain optically active 3-hydroxyoxindole derivatives. Zhou and co-workers[33] reported the first catalytic enantioselective Morita–Baylis–Hillman (MBH) reaction of isatins (**2**) with acrolein (**33**)



Scheme 13 Aldol reaction of silyl enol ethers to isatins.

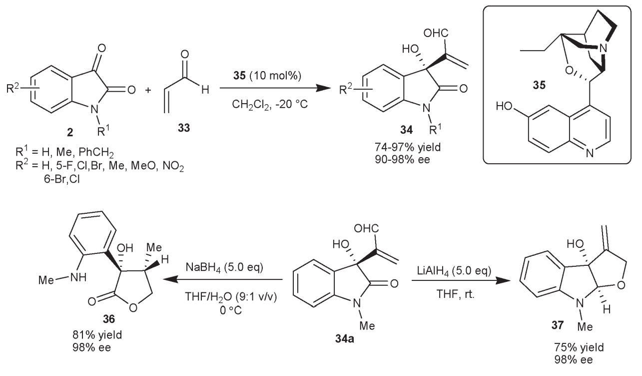


Scheme 14 Phospho-aldol reaction of isatins.

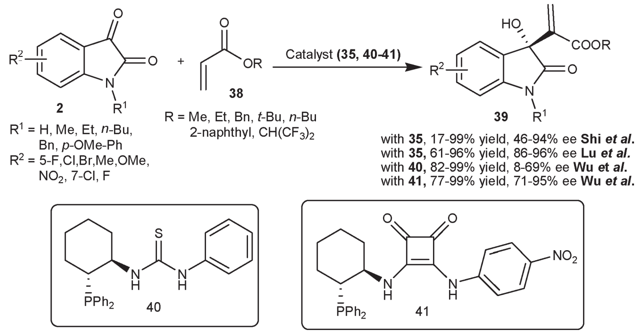
catalyzed by β-isocupreidine (**35**) at −20 °C in dichloromethane to provide enantiomerically enriched 3-substituted-3-hydroxyoxindoles **34** in good to excellent yield (65–97%) and high enantioselectivity (90–98% ee) (Scheme 15). This was also the first report on the use of ketone as an electrophile in the catalytic asymmetric MBH reaction. The product **34a** served as a precursor for the synthesis of chiral lactone **36** and 3a-hydroxyfuroindoline (**37**).

Shi and co-workers[34] have also reported the application of β-isocupreidine as a catalyst for asymmetric MBH reaction of acrylate **38** with isatin derivatives (**2**) to generate a quaternary hydroxylated stereocenter on the oxindole (**39**) with moderate to excellent yield (17–99%) and good enantioselectivity (46–94% ee) in dichloromethane at room temperature. Lu *et al.*[35] also reported the similar transformation in good yield (61–96%) and high enantioselectivity (86–96% ee) catalyzed by 10 mol% of β-isocupreidine in chloroform with 4 Å molecular sieves (MS) as additives at room temperature.

Wu *et al.*[36] have also studied the MBH reaction of acrylates **38** with isatins (**2**) employing bifunctional phosphinothiourea organocatalyst based on a chiral cyclohexane scaffold. The reaction proceeded smoothly in the presence of 10 mol% of catalyst **40** to provide 3-hydroxy-2-oxindoles **39** in good to excellent yield (82–99%) and low to moderate enantioselectivity (8–69% ee) (Scheme 16). In order to increase the enantioselectivity of the reaction, the authors have recently developed a new bifunctional phosphine organocatalyst bearing squaramide as H-bond donor.[37] The phosphine–squaramide **41** catalyzed the MBH reaction of **38** with **2** in high yield (77–99%) and good enantioselectivity (71–95% ee) (Scheme 16). The squaramide catalyst (**41**) proved to be superior to the thiourea catalyst (**40**) for this transformation.



Scheme 15 β-Isocupreidine catalyzed MBH reaction of acrolein to isatins.

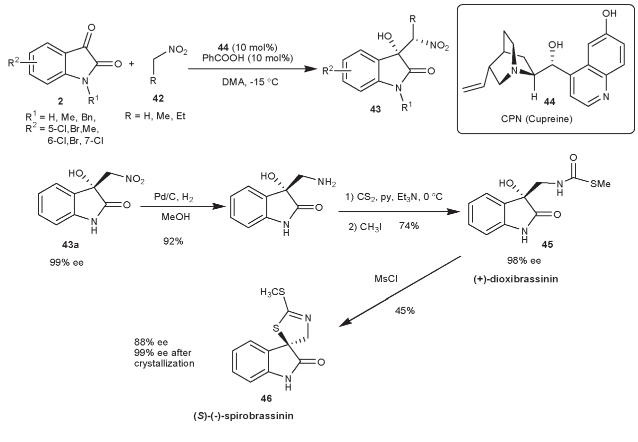


Scheme 16 MBH reactions of acrylate to isatins.

2.1.5 Henry reaction. The asymmetric Henry reaction has emerged as a powerful transformation to produce chiral β-nitro alcohol. Recently, Wang and co-workers[38] at the University of New Mexico developed the first asymmetric Henry reaction of isatin derivatives catalyzed by a *Cinchona* alkaloid. The cupreine (**44**) catalyzes the nitro-aldol reaction of nitroalkanes such as nitromethane, nitroethane and nitropropane (**42**) with various isatin derivatives (**2**) to provide an easy access to chiral 3-substituted-3-hydroxyoxindole derivatives (**43**) in quantitative yield and good to high enantioselectivity (74–95% ee) (Scheme 17). The chiral adduct **43a** was used as a precursor for the synthesis of oxindole alkaloids such as (+)-dioxibrassinin (**45**) and (*S*)-(−)-spirobrassinin (**46**).

Two independent reports have been published on a similar transformation catalyzed by 9-*O*-protected cupreine. The 9-*O*-benzyl cupreine[39] (**47**) and 9-*O*-3,5-trifluoromethylbenzoyl cupreine[40] (**48**) have been shown to catalyze the Henry reaction of nitromethane with isatin derivatives to provide the nitro aldol adduct in high yield (up to 98%) and moderate to good enantioselectivity (up to 95% ee) (Fig. 4).

Very recently, Rao and co-workers[41] have developed the biscinchona alkaloid **49** catalyzed Henry reactions of isatins with nitromethane. The resulting Henry adducts bearing a C3



Scheme 17 Cupreine (**44**) catalyzed Henry reaction of isatins.

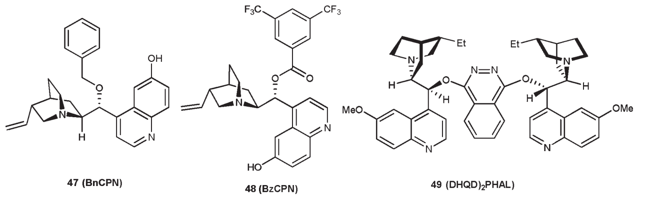
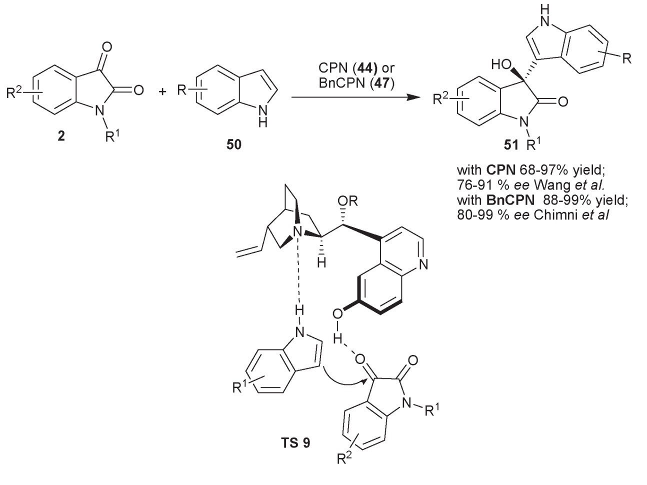


Fig. 4 Organocatalysts (**47–49**) used to catalyze the Henry reaction of isatins.

quaternary stereocentre were obtained in high yield (79–94%) and with a good level of enantioselectivity (64–97% ee) (Fig. 4).

2.1.6. Friedel–Crafts reaction. The asymmetric Friedel–Crafts reaction has emerged as a powerful carbon–carbon bond formation reaction for the synthesis of chiral arene derivatives. Wang and co-workers[42] have reported a highly efficient cupreine-catalyzed Friedel–Crafts reaction of indole (**50**) and isatin derivatives (**2**) to provide 3-indolyl-3-hydroxyoxindoles (**51**) in high yield (68–97%) and good enantioselectivity (76–91% ee). (Scheme 18). Concurrently, Chauhan and Chimni[43] have developed a highly enantioselective Friedel–Crafts reaction of indole and isatin derivatives catalyzed by 9-*O*-benzylcupreine (Scheme 18). The 3-indolyl-3-hydroxyoxindole derivatives (**51**) were obtained in high yield (88–99%) and good to excellent enantioselectivity (80–99% ee) under mild reaction conditions. The methodology was free from competing double addition of indole to isatin. On the basis of several experiments the bifunctional mode of activation of the catalyst was demonstrated. The protection of either 6′-OH or quinuclidine-*N* results in the failure of the reaction. This was further proved by the lack of product formation when *N*-methylindole was used. The proposed transition state (**TS 9**) involves a ternary complex between the catalyst, isatin and indole, in which the tertiary amine activates and orients the indole by forming a hydrogen bond with the NH of the indole, and the aromatic OH group activates the isatin with hydrogen bonding.

2.1.7. Decarboxylative addition to isatins. Recently, Shibata and co-workers[44] developed a highly enantioselective decarboxylative addition of malonic acid half thioesters (**52**) to isatins using a squaramide catalyst (**54**) to afford the products (**53**) in high yield (91–99%) and moderate to good enantioselectivity (46–92% ee). The synthetic utility of this methodology has been demonstrated in the first enantioselective synthesis of (−)-flustraminol B (**55**) (Scheme 19).



Scheme 18 Friedel–Crafts reaction of indoles with isatins.

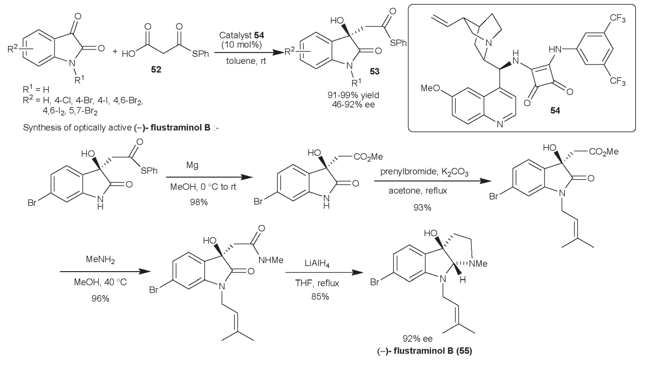
2.2 Oxindole as a nucleophile

2.2.1 Hydroxylation reaction. The organocatalytic hydroxylation reaction of oxindoles was studied by Itoh and co-workers[45] using molecular oxygen as an oxidant. The phase-transfer catalyst (PTC) **58** catalyzes the hydroxylation reaction of oxindoles **56** with molecular oxygen in high yield (91–99%) and good enantioselectivity (82–93% ee), but in the case of 3-propyl-2-oxindole derivative **56d**, a lower enantioselectivity of 67% was obtained (Scheme 20). The tetrasubstituted-3-hydroxyoxindole product (**57**) was synthetically transformed into optically active 3-allyl-3-hydroxy-2-oxindole, a synthetic precursor of alkaloid CPC-1.

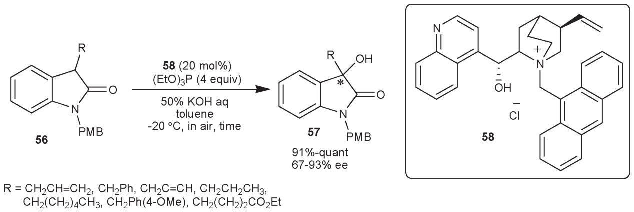
2.2.2 Michael reaction. Very recently, Melchiorre *et al.*[46] developed an organocatalyzed Michael addition of dioxindoles **59** to β-substituted nitroalkenes **60**, providing a new approach to the synthesis of optically active 3-substituted-3-hydroxy-2-oxindole derivatives (**61**). The bifunctional primary amine thiourea **62** turned out to be a promising catalyst affording 3-substituted-3-hydroxy-2-oxindoles (**61**) in good yield (50-98%) and good stereoselectivity (up to 3.6 : 1 dr, 94% ee), while minimizing the formation of isatide. The potential synthetic usefulness of this methodology has been shown in the straightforward preparation of compound **63** which bears the hexahydropyrrolo[2,3-*b*]indole unit found in many natural molecules (Scheme 21).

2.3 Miscellaneous

Barbas and co-workers[47] have described a novel aminooxygenation of oxindoles **56** with nitrosobenzene catalyzed by a newly designed quinidine dimer **65** that affords the desired product **64** in good yield (65–86%) and good to high enantioselectivity (73–96% ee). Interestingly, in most of the cases aminooxygenation is *O*-selective. The reaction mechanism proceeds initially through enolate (**i**), which add to nitrosobenzene in an *O*-selective fashion



Scheme 19 Squaramide **54** catalyzed decarboxylative aldol reaction of malonic acid half thioesters (**52**) with isatins.



Scheme 20 Hydroxylation reaction of isatins catalyzed by PTC **58**.

in a chiral environment provided by the *Cinchona* catalyst. Finally, the proton transfer from the protonated amine catalyst to species (**ii**) provides the desired product (Scheme 22).

Melchiorre *et al.*[48] developed a new catalytic strategy for synthesis of 3-substituted-3-hydroxy-2-oxindoles. The prolinol **68** promotes the nucleophilic addition of dioxindole **59** to unsaturated aldehyde **66** by imminium ion activation. The spiro oxindole γ-butyrolactones (**67** and **67′**) were obtained after direct oxidation of crude reaction mixture in good yield and optical purity. 3-Substituted-3-hydroxy-2-oxindole was easily obtained after simple chemical manipulation of the product **67** (Scheme 23). The utility of this methodology was highlighted by the total synthesis of maremycine A.

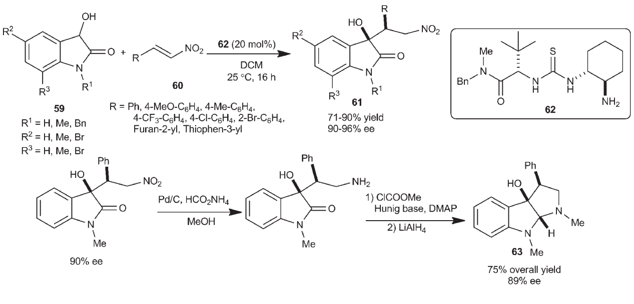
Scheidt *et al.*[49] developed an enantioselective NHC(**69**)–Lewis acid catalyzed homoenolate annulation of enals **66** with isatins **2** to provide spiro oxindole γ-butyrolactone **67** in moderate to high yield (36–93%), good diastereomeric ratio (up to 20 : 1) and low to high enantioselectivity (13–98% ee) (Scheme 24). This approach was utilized in the concise total synthesis of maremycin B, which posseses anticancer activity.

3. Organometallic catalysts

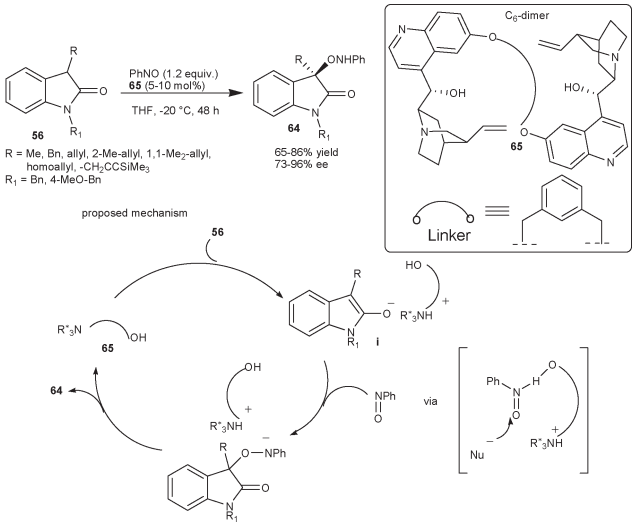
3.1 Isatins as electrophiles

3.1.1 Addition of diethyl zinc to isatins. The first catalytic enantioselective synthesis of 3-alkyl-3-hydroxy-2-oxindole was reported by Shibasaki *et al.*[50] The addition of diethyl zinc $\{(CH_3)_2Zn\}$ to *N*-methylisatin catalyzed by **70** provided 3-methyl-3-hydroxy-1-methyl-2-oxindole in 82% yield with 76% ee (Scheme 25).

3.1.2 Addition of organoboronic acids to isatins. Hayashi *et al.*[51] have developed the first rhodium-catalyzed asymmetric addition of arylboronic acids **71** to isatins **2** to obtain biologically relevant 3-aryl-3-hydroxy-2-oxindoles. After careful screening of various ligands, (*R*)-MeO-mop (**73**), an axially chiral monophosphine ligand, turned out to be the best ligand for achieving high enantioselectivity. The catalyst Rh–(*R*)-MeO-mop in a molar ratio of 1 : 2 catalyzes the reaction to furnish 3-aryl-3-hydroxy-2-oxindoles (**72**) in good yield (79–98%) and enantioselectivity (72–93% ee) (Scheme 26). The Rh–(*R*)-MeO-mop complex also catalyzes the addition of alkenylboronic acids to give tertiary allylic alcohol derivatives (**72**) in good yield (91–93%) and enantioselectivity (88–93% ee) (Scheme 26).



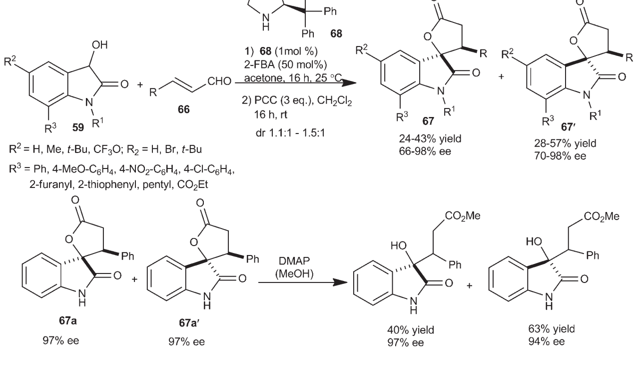
Scheme 21 Michael addition of dioxindole to nitroalkenes.



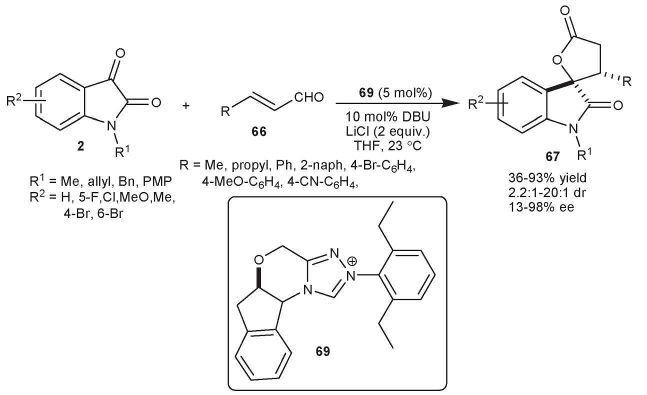
Scheme 22 Aminooxygenation of oxindoles.

Almost concurrently, another report on rhodium-catalyzed asymmetric addition of phenylboronic acid to isatin employing phosphoramidite ligand appeared in the literature. The catalyst generated from 3 mol% of $[(C_2H_4)_2Rh(acac)]$ and 9 mol% of **74** provided 3-phenyl-3-hydroxy-2-oxindole in virtually quantitative yield and 55% ee, which can be enantioenriched up to 94% ee with 59% yield after a single crystallization in 2-propanol.[52] Recently, a new report on Rh-catalyzed asymmetric arylation of *N*-PMB-5-chloroisatin with phenylboronic acid, employing simple sulfur–alkene hybrid ligand **75**, provided the desired product in good yield (87%) and moderate enantioselectivity (76% ee) (Scheme 26).[53]

This methodology is normally limited to *N*-protected isatins,[51–53] while *N*–H isatins afford products with low enantioselectivity and low yield. Very recently, a rhodium-catalyzed



Scheme 23 Prolinol **68** catalyzed Michael addition of dioxindole to unsaturated aldehydes.



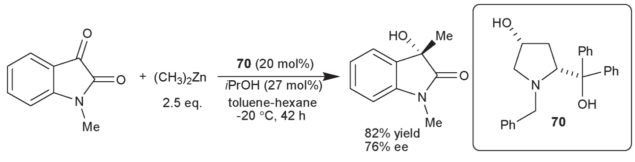
Scheme 24 NHC **69** catalyzed homoenolate annulation of enals with isatins.

asymmetric variant of this reaction employing chiral sulfoxide phosphine as ligand (**76**) has been reported for the addition of arylboronic acid (**71**) to *N*–H isatins as well as *N*-protected isatins to provided chiral 3-aryl-3-hydroxy-2-oxindoles (**72**) in excellent yield (93–99%) and good enantioselectivity (85–92% ee) (Scheme 26).[54]

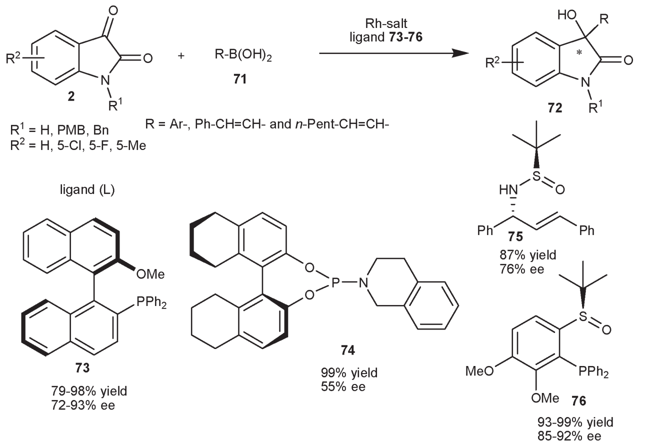
In 2009, Qin *et al.*[55] prepared an enantiopure tetra-*ortho*-substituted phosphinoimine ligand with a biphenyl backbone, which finds application in the asymmetric arylation of *N*-benzylisatin at the C3 position. 3-Aryl-3-hydroxy-2-oxindoles (**72**) were obtained in moderate to good yield (36–78%) and moderate to good enantioselectivity (38–73% ee) *via* nucleophilic addition of arylboronic acid (**71**) to *N*-benzylisatin catalyzed by a catalytic mixture of $Pd(OAc)_2$ and ligand **77** in molar ratio of 1 : 2 (Scheme 27). In 2011, Shi and co-workers[56] developed the enantioselective arylation of isatins with arylboronic acids by using chiral C_2-symmetric cationic NHC-Pd^{2+} diaqua complex (**78**) as the catalyst under mild conditions. The 3-aryl-3-hydroxy-2-oxindoles (**72**) were obtained in good yield (79–92%) and moderate to good enantioselectivity (60–80% ee) (Scheme 27).

3.1.3. Addition of organotrimethoxysilanes to isatins.

Shibasaki and co-workers[57] have studied the intermolecular CuF-catalyzed enantioselective alkenylation and arylation of isatins using silicon-based nucleophiles (**79**), which are generally more facile than those using boron-based nucleophiles, under CuF catalysis. The isatin derivatives (**2**) react with alkenyl-/aryl-trimethoxysilanes (**79**) in the presence of $CuF{\cdot}3PAr_3{\cdot}2EtOH$, chiral phosphine ligand **81**, and additive ZnF_2 in toluene to afford tetrasubstituted-3-hydroxyoxindoles (**80**) in high yield (90–99%) and good enantioselectivity (81–97% ee) (Scheme 28). The catalytic amount of additive ZnF_2 was found to be essential for acceleration of the reaction. The methodology was applied for the synthesis of SM-130686, a highly potent and orally active non-peptidic growth hormone secretagogue, which was isolated in low yield (26%) and low enantioselectivity (44% ee) using *i*Pr-DuPHOS as the chiral ligand.



Scheme 25 Addition of diethyl zinc to *N*-methylisatin.

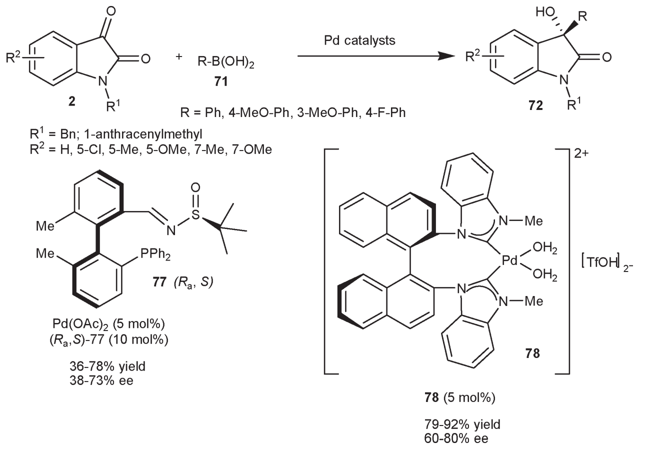


Scheme 26 Organoboronic acids (**71**) addition to isatins (**2**) catalyzed by a Rh complex.

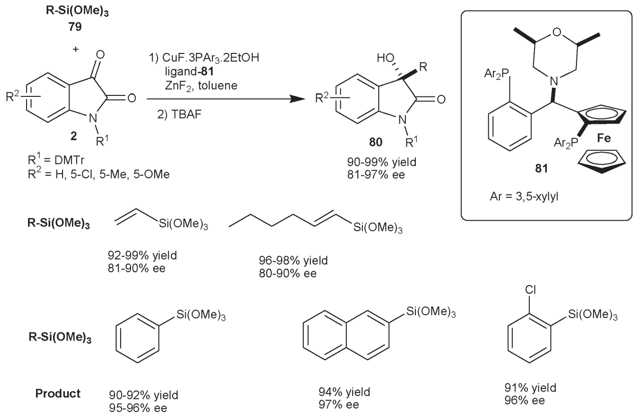
3.1.4. Friedel–Crafts reaction.

Franz *et al.*[58] have reported the first asymmetric Friedel–Crafts reaction for the preparation of chiral 3-aryl-3-hydroxyoxindoles in the newly designed direct reaction of isatin derivatives with arene/heteroarene employing a Lewis acid catalyst in combination with chiral ligand **83**. On comparing the reactivity and selectivity profile of diverse Lewis acid catalysts, the chiral scandium(III) and indium(III) complexes were found to give comparable results, affording only one product (**82**) *via* direct monoaddition of indole to isatin derivatives (**2**) in good to excellent yield (73–99%) and high enantioselectivity (88–99% ee). The formation of the bis product (double addition of indole to isatin) was not observed. Further, investigating the scope of this methodology, the chiral scandium(III)-pybox complex efficiently catalyzes the enantioselective addition of electron-rich π-nucleophiles to isatins in high yield (73–99%) and enantioselectivity (80–99% ee) (Scheme 29).

Later in 2011, they extended the scope of this methodology for the nucleophilic addition of pyrrole derivatives to isatins



Scheme 27 Arylboronic acid addition to isatins catalyzed by a Pd complex.

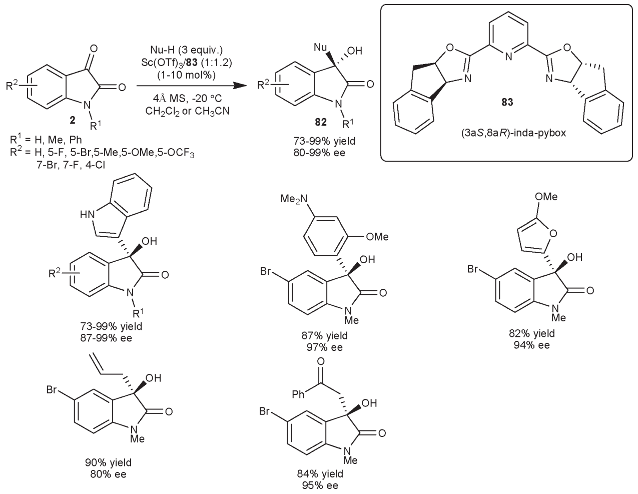


Scheme 28 Reaction of organotrimethoxysilanes with isatins.

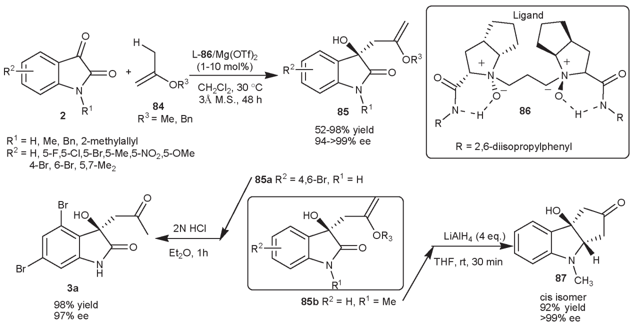
catalyzed by indium(III)-inda-pybox complex (10 mol%) to provide products in moderate to good yield (45–98%) with excellent level of enantioselectivity (94 to >99% ee).[59]

3.1.5 Hetero-ene reaction. Feng and co-workers[60] discovered the hetero-ene reaction of isatins with alkyl enol ether (**84**) using a rare earth metal complex catalyst to obtain new enantioenriched 3-substituted-3-hydroxyoxindole derivatives, which may serve as important building blocks for the synthesis of natural products and pharmaceuticals. The formation of the *R* isomer of the products **85**, catalyzed by a complex generated *in situ* by $Mg(OTf)_3$ with ligand **86**, in good yield (52–98%) and excellent enantioselectivity (94 to >99%) (Scheme 30). The allylated product **85a** could be hydrolyzed into **3a** in high yield (98%) with excellent enantioselectivity (97% ee). Diastereoselective reduction of **85b** with $LiAlH_4$ gave **87**, which is a common motif found in pyrrolidinoindoline-type natural products (Scheme 30).

Chiral dicationic Pd-complex catalyzed enantioselective hetero-ene and Mukaiyama-aldol reactions of isatins result in the formation of optically active tertiary alcohols (Scheme 30).[61] In the hetero-ene reaction, the isopropenyloxy(triisopropyl)silane **84c** reacted with isatin derivatives (**2**) in the presence of 10 mol% of Pd complex **90** to provide the corresponding products (**85**) in good yield (72–98%) and good to excellent enantioselectivity (80–>99% ee). The methodology was applied in the synthesis of **3a** in good yield (87%) and excellent enantioselectivity (99% ee). Additionally, the ene product could be transformed into other valuable products. After the success of hetero-ene reaction, the author extended the application of the Pd complex catalyst **90** to the aldol reaction of isatin derivatives (**2**) with trimethylsilyl ketene thioacetal (**88**). The aldol adducts **89** were isolated in good yield and enantioselectivity and could be used as synthons for the synthesis of a variety of natural products (Scheme 31).



Scheme 29 Friedel–Crafts reaction of arene/heteroarenes with isatins.

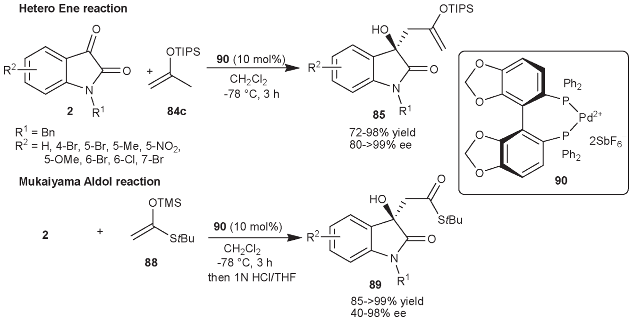


Scheme 30 Hetero-ene reaction of isatins.

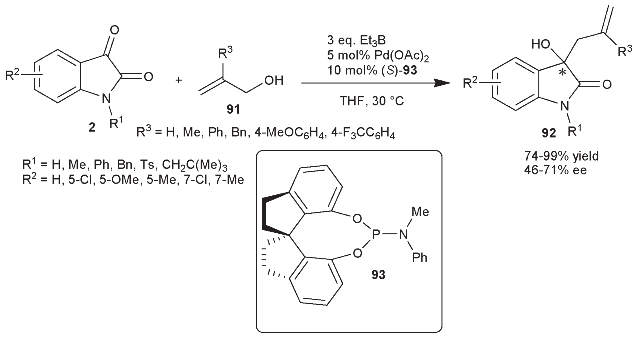
3.1.6 Allylation, crotylation and prenylation of isatins. Takayama *et al.*[62] reported the allylation of isatin with tetraallylstannane using a catalytic mixture of (*R*)-(+)-BINOL and $Ti(OiPr)_4$ to afford allylated compounds (**92a**) in 89% yield with 42% ee. Two successive recrystallizations of the product from ethyl acetate provided the enantiomerically pure *S* isomer of the product.

Zhou and co-workers[63] have developed the palladium-catalyzed asymmetric allylation of isatins (**2**) with allylic alcohols (**91**) as an allyl donor using chiral spiro phosphoramidite ligand (**93**). The chiral tertiary homoallylic alcohols (**92**) were obtained in excellent yields (up to 99%) and with moderate enantioselectivity (48–71%) (Scheme 32).

Krische and co-workers[64] reported the highly enantioselective allylations, crotylations, and prenylations of isatin catalyzed by an Ir complex in the absence of stoichiometric amounts of allylmetal reagents, unlike conventional allylation methodologies which employ stoichiometric quantities of allyl–metal reagents. The allylations, crotylations, and prenylations of *N*-benzylisatin derivatives have been performed using cyclometalated *C*,*O*-benzoate complex **96** generated *in situ* from $[\{Ir(cod)Cl\}_2]$,



Scheme 31 Hetero-ene and Mukaiyama-aldol reaction of isatins.



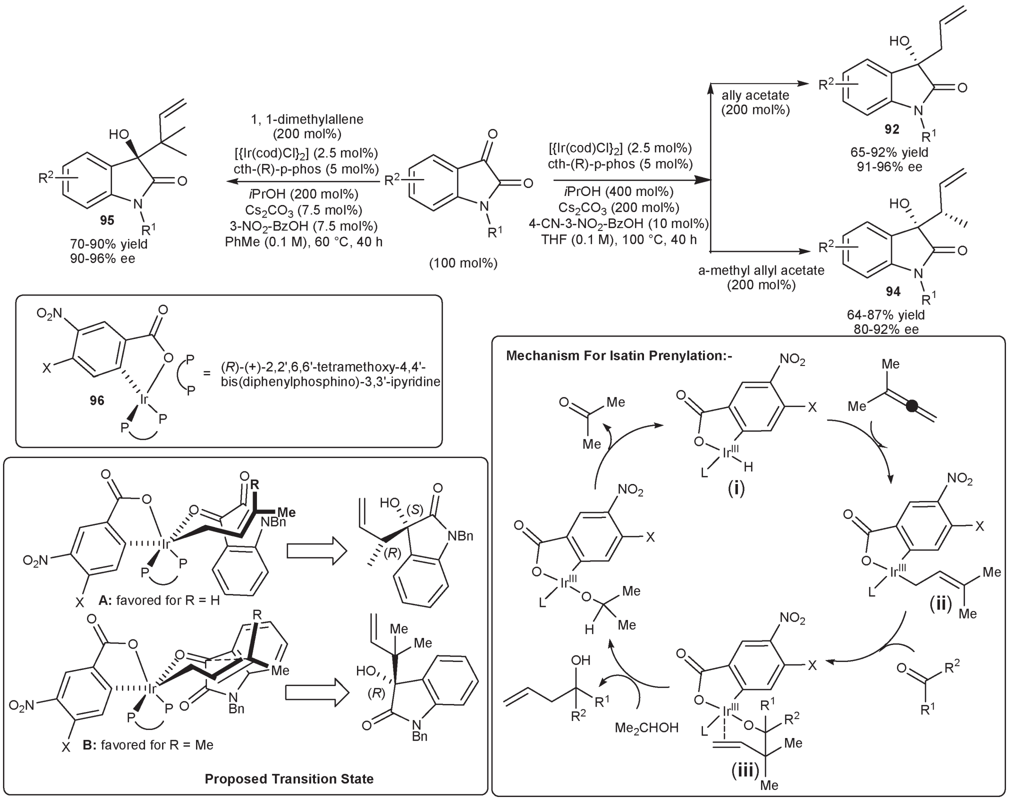
Scheme 32 Allylation of isatins with allylic alcohols.

cth-(*R*)-p-phos (ligand) and 3-nitrobenzoic acid or 4-cyano-3-nitrobenzoic acid (Scheme 32). Allylation of isatin using allyl acetate produce tertiary homoallyllic alcohols **92** in good yields (65–92%) with uniformly high levels of optical enrichment (91–96% ee). The crotylation of isatins employing α-methyl allyl acetate as the crotyl donor afford **94** in good yield (64–87%) and good enantioselectivity (80–92% ee). The reverse prenylation of isatins has been performed using 1,1-dimethylallene to provide **95** with two contiguous quaternary carbon centers in good yield (70–90%) and high levels of optical enrichment (90–96% ee) under mild reaction conditions. The mechanism for reverse prenylation is depicted in Scheme 33. The deprotonation of complex (**i**) in the presence of Cs_2CO_3 to furnish the anionic iridium *C*,*O*-benzoate, which undergo oxidative addition to 1,2-dimethylallene leads to the formation of (*E*)-σ-crotonyl iridium intermediate (**ii**). Isatin addition to the intermediate (**ii**) occurs through a chair-like transition structure, which delivers the homoallylic iridium alkoxide (**iii**). The enantiofacial selectivity of carbonyl addition is opposite to crotylation which occurs by way of the transition structure **A**, whereas isatin prenylation occurs by way of the transition structure **B**. The basis of this partitioning may arise from nonbonding interactions of the axial methyl group of the σ-prenyl iridium intermediate with the amide π-bond of isatin, which is presumably more destabilizing than nonbonding interactions of the axial methyl group with the electron-deficient rim of the arene (Scheme 33).

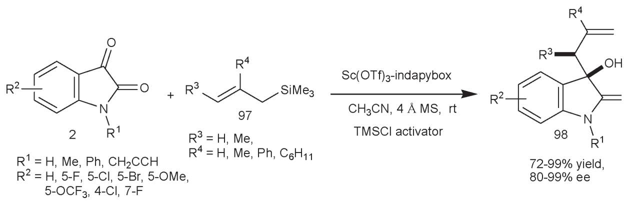
Very recently, Franz *et al.*[65] developed the enantioselective Hosomi–Sakurai allylation of isatins (**2**) with substituted allylic silanes (**97**) catalyzed by $Sc(OTf)_3$-indapybox catalyst with a TMSCl activator and additive such as $NaSbF_6$. The 3-substituted-3-hydroxy-2-oxindoles (**98**) were obtained in good to excellent yield (72–99%) and enantioselectivity (80–99% ee) (Scheme 34). The important features of the methodology are low catalyst loading of 0.05 mol%, wide substrate scope of isatins, and use of various substituted allylic silanes and application to gram scale preparation.

3.2 Oxindole as a nucleophile

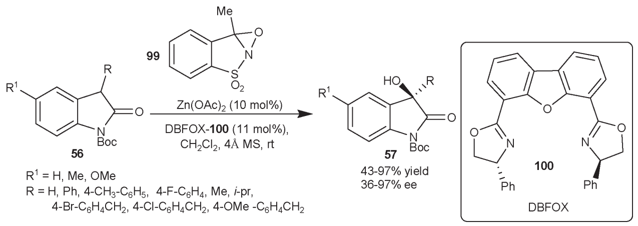
3.2.1 Hydroxylation reaction. Shibata and co-workers[66] have described the first catalytic enantioselective hydroxylation reaction of 3-aryl-2-oxindoles (**56**) using the DBFOX-Zn(II) (**100**-Zn(II)) catalyst with oxaziridine **99** as oxidant, leading to pharmaceutically important chiral 3-aryl-3-hydroxy-2-oxindoles **57** in high yield (76–95%) and high enantioselectivity (90–97% ee) (Scheme 35). The 3-alkyl-2-oxindoles (**56**) provide chiral



Scheme 33 Allylations, crotylations and prenylations of isatins.



Scheme 34 Hosomi–Sakurai allylation of isatins.



Scheme 35 Hydroxylation reaction of isatins using oxaziridine **99**.

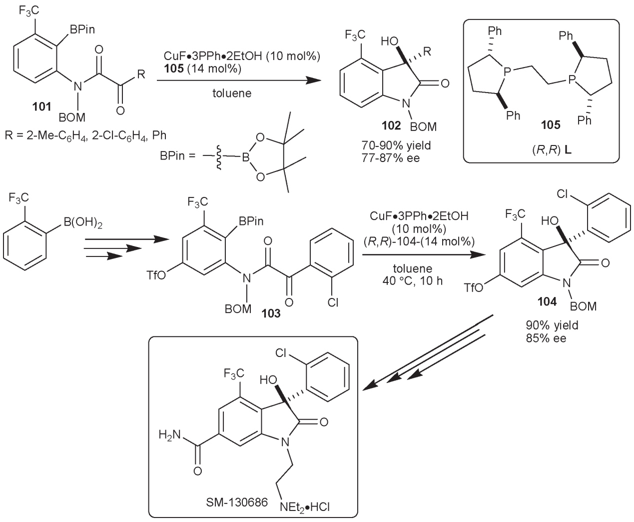
3-alkyl-3-hydroxy-2-oxindoles (**57**) in good yield (68–90%) and good enantioselectivity (83–86% ee), while 3-perfluorophenyl-2-oxindole provide hydroxylated product **57h** with lower yield (36%) and enantioselectivity (60% ee).

Feng and co-workers[67] have developed the enantioselective hydroxylation of 3-methyl-2-oxindole using TMPO as the oxygen source. The 3-methyl-3-hydroxy-2-oxindole was obtained in moderate yield (63%) and enantioselectivity (43% ee) by using $Sc(OTf)_3$/L-**86** complex as a catalyst.

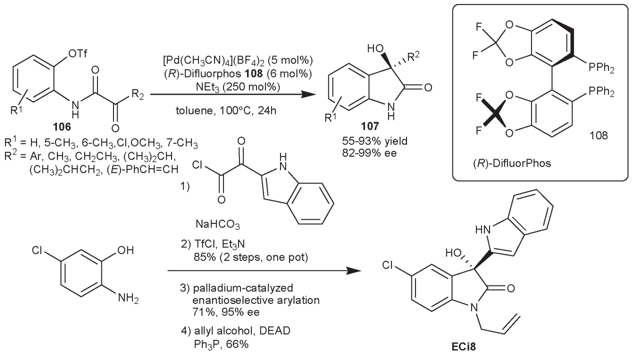
3.3 Anilide cyclization

Shibasaki *et al.*[57] have successfully developed the highly enantioselective intermolecular arylation of isatins leading to 3-hydroxy-3-aryl-2-oxindoles. The methodology found its limitation in the case of isatin derivatives with a bulky CF_3 group at the C4 position, which dramatically decreases the reactivity and enantioselectivity of the reaction. To overcome this limitation, they developed a catalytic enantioselective intramolecular arylation of α-keto amides **101** as an alternative strategy.[57] After screening of different ligands, the Ph-BPE **105** was found to be an optimum ligand for the intramolecular cyclization reaction providing product **102** with high yield and enantioselectivity. This strategy was applied in the total synthesis of SM-130686, involving the enantioselective intramolecular arylation of **103** in the presence of 10 mol% CuF-(*R*,*R*)-**105** catalyst, to obtain **104** in 90% yield with 85% ee, which could be synthetically transformed to SM-130686 (Scheme 36).

Recently Shibasaki *et al.*[68] described the palladium–difluorphos complex catalyzed intramolecular arylation of α-keto amides, leading to the formation of enantiomerically enriched 3-substituted-3-hydroxy-2-oxindoles. The chiral catalyst derived from (*R*)-DifluorPhos (**108**) and $[Pd(CH_3CN)_4](BF_4)_2$ could efficiently promote the intramolecular cyclization of triflate **106** to furnish tetrasubstituted-3-hydroxyoxindoles **107** in good yield (53–92%) and enantioselectivity (83–99% ee). This methodology was applied to the total synthesis of ECi8, which is a potent antimicrobial lead drug[69] (Scheme 37).



Scheme 36 Total synthesis of SM-130686 by anilide cyclization.

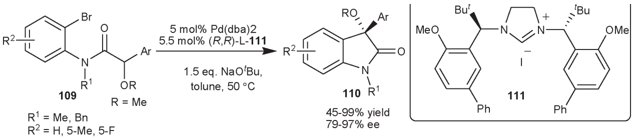


Scheme 37 Palladium–difluorphos complex catalyzed intramolecular arylation of α-keto amides.

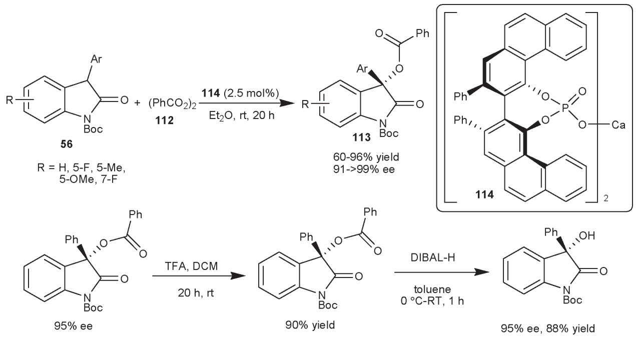
3.4 Miscellaneous

Kündig *et al.*[70] have developed an asymmetric Pd-catalyzed intramolecular arylation of α-alkoxy amide (**109**) using chiral *N*-heterocyclic carbene ligand **111**. The 3-alkoxy-3-aryl-2-oxindoles (**110**) were obtained in moderate to excellent yield (45–99%) and good enantioselectivity (79–97% ee) (Scheme 38).

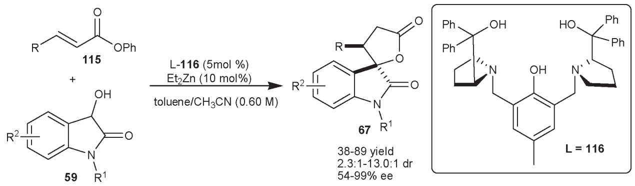
Antilla *et al.*[71] have reported the asymmetric benzoyloxylation of 3-aryl-2-oxindoles (**56**) using readily available benzoyl peroxide (**112**) as a benzoyloxylation reagent catalyzed by a chiral VAPOL calcium phosphate salt **114**. A series of 3-aryl-3-benzoyl-2-oxindoles (**113**) were obtained in good yield (60–96%) and excellent enantioselectivity (91 to >99% ee). The potential synthetic utility of this methodology has been demonstrated in



Scheme 38 Intramolecular arylation of α-alkoxy amide (**109**).



Scheme 39 Benzoyloxylation of oxindoles.



Scheme 40 Zinc-ProProlinol catalyzed tandem Michael addition–transestrification.

the two step synthesis of 3-aryl-3-hydroxy-2-oxindole in good yield (88%) and enantioselectivity (95% ee) (Scheme 39).

Trost and Hirano[72] developed a highly enantioselective tandem Michael addition–transesterification process for synthesis of spirooxindole using ligand **116**. The zinc-ProPhenol complex catalyzes the Michael addition of dioxindole (**59**) to α,β-unsaturated esters (**115**) and subsequent transesterification gave spirooxindole γ-butyrolactone (**67**) in moderate to good yield (38–89%) with good diastereoselectivity (up to 86%) and moderate to excellent enantioselectivity (54–99% ee) (Scheme 40). Spirocyclic oxindole products (**67**) serve as an important synthetic building blocks for synthesis of various 3-alkyl-3-hydroxy-2-oxindoles.

Conclusions

Inspired by the biological activities associated with the chiral 3-hydroxy-2-oxindole framework, considerable achievements have been made in their synthesis, especially in last few years. Both chiral organocatalysts and metal complex catalysts play an important role in the asymmetric synthesis of 3-substituted-3-hydroxyoxindoles. Since the first report on the organocatalytic enantioselective aldol reaction of isatins with acetone, a number of new enantioselective reactions catalyzed by a variety of organocatalysts have been reported. Metal catalysts have also proved to be useful in catalyzing many reactions. So, with the advancement in catalytic approaches, an impressive progress has been made in the synthesis of natural products and drug candidates containing this structural moiety. Biocatalysts still wait their turn in their synthesis which may add an important tool in the portfolio of catalysts.

Isatins are an ideal substrate employed in the majority of the reactions in comparison with 3-substituted 2-oxindoles. Dioxindole has very recently emerged as an important precursor in the synthesis of targeted frameworks. There is still enough room for the nucleophilic addition of dioxindole to variety of electrophiles, which may lead to new 3-substituted-3-hydroxy-2-oxindole derivatives with improved bioactivities.

This area has recently blossomed and become more mature as new catalysts, new substrates and reaction conditions are being explored and shall be explored in the future. We envision that new chiral 3-substituted-3-hydroxy-2-oxindoles having enhanced medicinal properties will be synthesized in the future.

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