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Stereoselective synthesis of 3-amino-2-oxindoles from isatin imines: New Scaffolds for bioactivity evaluation
Stereoselective synthesis of 3-amino-2-oxindoles from isatin imines: New Scaffolds for bioactivity evaluation

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3-Substituted 3-amino-2-oxindoles have attracted the attention of organic and medicinal chemists because these motifs constitute the core structure of a number of natural products and drug candidates. The catalytic potential of chiral organocatalysts and metal catalysts has been successfully exploited for the synthesis of enantioenriched 3-amino-2-oxindoles via the addition of various nucleophiles to isatin imines. This review focuses on the catalytic asymmetric synthesis of chiral 3-amino-3-substituted-2-oxindoles.

Introduction

3-Substituted 3-amino-2-oxindole is a privileged core structure found in a variety of natural products and biologically active compounds such as gastrin/cholecystokinin-B receptor antagonist AG-041R, the vasopressin VIb receptor antagonist SSR-149415 and antimalarial drug candidate NITD609 (Figure 1).

Among these the enantioselective addition of nucleophile to isatin imines is one of the most efficient and straightforward methods. Organocatalytic enantioselective addition reactions such as aza-Friedel-Crafts reaction, Mannich reaction, Henry reaction, Streeker reaction, Morita-Baylis Hillman reaction have been developed to construct 3-substituted-3-amino-2-oxindoles with a chiral quaternary carbon center. The representative examples of these catalytic strategies reported since 2009 involving isatin derived ketimine as a substrate are shown in Figure 2.

Figure 1: Examples of bioactive quaternary amino-oxindoles and related natural compounds.

The bioactivity of these compounds is greatly affected by the nature of the substituent at the C-3 position as well as the absolute configuration of the stereogenic centre. Therefore, the development of efficient and practical methods to synthesize such molecules is of great importance and is the current area of research in asymmetric catalysis. In the past few years, a variety of methods for preparing these compounds have been explored.

Figure 2: Representative examples from isatin imine framework.

For convenience in presentation and easy understanding, this review has been classified according to the type of reaction catalyzed by organocatalysts and metal catalysts.
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Scheme 1. Enantioselective azo-Morita-Baylis-Hillman reaction of isatin imines with MVK. The synthetic use of this methodology was illustrated by the synthesis of N-acyl-3-aminoxindole 4 after treating with acetic anhydride, in 70% yield. Subsequent to this report, Feng Sha et al reported the phosphine squaramide catalyzed enantioselective azo-MBH reaction of isatin imine 1 with acrylates 2b to provide 3-substituted-3-amino-2-oxindole 5 in moderate to excellent yields (43-99%) and good enantioselectivity (70-91% ee).

Scheme 2: Asymmetric azo-MBH reaction of isatin imines with acrylates catalyzed by phosphine-squaramide organocatalyst.

In the proposed transition state TS 1, the catalyst activates the reaction between electron deficient olefins and imines to provide densely functionalized chiral amines. Min Shi et al have developed a highly enantioselective azo-Morita-Baylis-Hillman reaction of isatin imines (I) with methyl vinyl ketones (MVK) 2 catalyzed by β-isocupreidine I and chiral phosphines II (Scheme 1). Similar results were obtained affording 3-amino-2-oxindoles 3 bearing a C-3 tetra-substituted stereogenic centre with excellent enantioselectivity (up to 99% ee) and excellent yield up to 98%. In addition to this, the absolute configuration was also found to be same (R) in both cases.

(1) Enantioselective azo-Morita-Baylis-Hillman reaction

The Morita-Baylis-Hillman/azo- Morita-Baylis-Hillman reaction has received increasing interest since it combines two important requirements, atom economy and generation of functional groups. The last decade has seen exponential growth of Morita-Baylis-Hillman (MBH) reaction and its applications. This is a reaction between electron deficient olefins and imines to provide densely functionalized chiral amines. Min Shi et al have developed a highly enantioselective azo-Morita-Baylis-Hillman reaction of isatin imines (I) with methyl vinyl ketones (MVK) 2 catalyzed by β-isocupreidine I and chiral phosphines II (Scheme 1). Similar results were obtained affording 3-amino-2-oxindoles 3 bearing a C-3 tetra-substituted stereogenic centre with excellent enantioselectivity (up to 99% ee) and excellent yield up to 98%. In addition to this, the absolute configuration was also found to be same (R) in both cases.

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ketimine through H-bonding whereas the cyclohexyl scaffold of the catalyst III provides a favourable orientation to the phosphinoyl associated enolate to attack the activated ketimine from Si-face to form the adduct with S-configuration (Scheme 2).

Recently, our group reported an organocatalyzed aza-Morita-Baylis-Hillman reaction of maleimides 6 with isatin imines 1 using β-isocupreidene I as an organocatalyst (Scheme 3). Maleimide as a MBH donor is more challenging task because maleimides are traditionally Michael acceptors. A wide variety of 3-substituted-3-aminoindolin-2-ones 7 were synthesized in good yield (up to 77%) and excellent enantioselectivities (up to 99%). In the proposed transition state TS 2, the tertiary amine of the catalyst form enolate of the maleimide which simultaneously attacks on the isatin imine to form the favourable R enantiomer.

![Scheme 3: Enantioselective aza-Morita-Baylis-Hillman reaction of isatin imines with maleimide.](image)

### 2. Enantioselective Friedel-Crafts reaction

The Friedel-Crafts reaction is an important reaction for the construction of carbon-carbon and carbon-nitrogen bond which can provide important building blocks for pharmaceutically applicable compounds. To promote these transformations, significant progress has been made by employing both chiral Bronsted acid and Lewis acid catalysts. The first asymmetric aza-Friedel-Crafts reaction of indoles 8 and pyrroles 10 with isatin imines 1 was reported by Wang et al in 2012 (Scheme 4). The phosphoric acid catalyst IV efficiently catalyzed the aza-Friedel-Crafts reaction of N-methylindoles with isatin imines to afford the desired product. In addition to this, the introduction of an indole moiety into an oxindole scaffold produces 3-indolyl-3-amino-2-oxindoles which are promising substrates for the study of their biological activity as well as useful synthetic intermediates for drug candidates and alkaloids. On the basis of the observed stereochemistry, a plausible transition state TS 3 was proposed in which the phosphoric acid proton activates the ketimines and the N-methylindole attacks ketimine from Re-face leading to the S-configured product. The phosphoric acid catalyzed reaction of indole with isatin imine provides the desired product in only 64% ee which suggests that the hydrogen bond between indole and the phosphoryl oxygen could have a negative effect on the enantioselectivity. However, with 2 mol% of catalyst, the pyrrole reacts rapidly with various ketimines to afford the adducts in up to 98% yield and 64-98% enantioselectivity. The reaction of N-methylpyrrole 10 gives only moderate enantioselectivity (70% ee) and lower yield (49%). This shows that the bifunctional nature of the chiral phosphoric acid is responsible for concurrent activation of both the isatin imine and the pyrrole through hydrogen bond interactions.

![Scheme 4: Chiral phosphoric acids catalyzed enantioselective addition of indole and pyrrole derivatives to isatin imine.](image)

Recently, Xu et al reported the same reaction using only 5 mol% of Bi(OTf)3 (Scheme 5). The reaction completes in 24 hours providing the desired adduct in excellent yields (up to 99%) with good to excellent enantioselectivities ranging from 90-98% ee. In the proposed transition state TS 5, the Lewis acidic metal coordinates both with the imine nitrogen and carbonyl oxygen in such a way that the bulky tertiary group blocks the Si-face of ketimine molecule, thus the indole attacks from Re face of ketimine C=N bond to give S-configured product.

### 3 Enantioselective Hydrophosphonylation reaction

Phosphonic esters have received significant attention because of their important role as metabolic intermediates, regulatory switches for proteins and backbones for genetic information.

![Scheme 5: Diastereoselective Friedel-Crafts reaction of N-sulfinyl isatin imines with indoles.](image)

In particular, α-aminophosphonic acid derivatives are known to exhibit a broad spectrum of biological activities such as peptide mimetics, antibacterial, antiviral agents and enzyme...
inshibitor.\textsuperscript{17} Inspite of this, there are only a few reports on asymmetric addition of phosphite to simple ketimines.\textsuperscript{18} The asymmetric addition to functionalized ketimines is more challenging task because of their low reactivity and difficulty in enantiofacial discrimination.

Only two successful enantioselective examples of this reaction has been reported. B.V. Reddy \textit{et al} reported the first asymmetric organocatalytic hydrophosphonylation reaction of isatin imines (Scheme 6).\textsuperscript{19} Quinine squaramide \textit{V} was identified as the best catalyst for the reaction of isatin imines \textit{I} with diphenyl phosphite \textit{13} to provide 3-amino-oxindoles \textit{14} in 80-96\% yield and 52-97\% ee. The reaction was unsuccessful with diethyl/dimethyl-phosphites due to their low reactivity. The proposed transition state \textit{TS 6} for this enantioselective hydrophosphonylation reaction involves a hydrogen bonding activation of ketimine \textit{I} through the NH of the squaramide and simultaneous generation of phosphonate anion from diphenylphosphite \textit{13} by the tertiary amine of the catalyst. In addition to this synergic activation, the catalyst \textit{V} also provides a favourable orientation to both substrates to provide the desired adduct in high enantioselectivity.

Soon after this, our group published the same reaction catalyzed by Cinchonidine derived thiourea \textit{VI} for the synthesis of 3-amino-2-oxindoles \textit{14} in good to excellent yields (72-88\%) and excellent enantioselectivity up to 97\% (Scheme 7).\textsuperscript{20} To improve the synthetic efficiency, the combination of \textit{aza}-Wittig and phospha-Mannich one pot sequential protocol was developed resulting in \textit{α}-amino phosphonates in good yield and good enantioselectivity. The proposed transition state \textit{TS 7} involves the activation and orientation of isatin imine for face selective attack through H-bonding. Out of the two possible orientations of ketimines the \textit{Re} face orientation is favoured which avoids the steric interaction between the isatin imine benzene ring and aryl group of phosphate.

\textbf{(4) Enantioselective Mannich reaction}

Mannich reaction is a classic method for the preparation of optically active \textit{β}-amino carbonyl units, which are useful chiral building blocks for number of biologically active and pharmaceutically important compounds.\textsuperscript{21}

Scheme 6: Quinine-squaramide catalyzed enantioselective addition of diphenyl phosphate to isatin imines.

Scheme 7: Cinchonidine derived thiourea catalyzed hydrophosphonylation reaction of diphenylphosphate and isatin imines.

Scheme 8: \textit{Cinchona}-derived thiourea catalyzed enantioselective addition of 1,3-dicarbonyl compounds to N-Boc isatin imines.

The versatility and potential to create both functional and structural diversity using this reaction have long stimulated the creativity of chemists. Inspired by this, Wang \textit{et al} synthesized \textit{N}-alkoxy carbonyl isatin imines via \textit{aza}-Wittig reaction and used them for the synthesis of chiral 3-amino oxindoles by the enantioselective addition of 1,3-dicarbonyl compounds (Scheme 8).\textsuperscript{22}
dicarbonyl compound with quinuclidine nitrogen, thus stabilizing the enol, while the thiourea moiety binds and activates the ketimines I through double hydrogen bonding with nitrogen and oxygen atoms. The activated enol approaches the ketimine from one preferred enantiface to afford the desired product with S
c stereochemistry.

Shibata et al. reported an organocatalytic enantioselective
decarboxylative Mannich reaction of malonic acid half thioesters 17 with isatin imines 1 (Scheme 9).
Out of various catalysts 19 examined, the best results were obtained with N-heteroarenesulfonyl Cinchona alkaloid VIII as the catalyst which affords the final products 18 in good to high yield (58-92%) and good enantioselectivity (75-83%). This protocol was used efficiently for the synthesis of optically active AG-041R 19, a
gastrin/cholecystokinin-B-receptor.

The proposed transition state TS 9 reveals that the hydrogen on
the sulfonamide forms H-bonds with the nitrogen atoms in
quinoline and quinuclidine. The sulfonamide functionality
activates through H-bonding with the thiocarbonyl oxygen and
the quinuclidine assists the deprotonation and decarboxylation of
17 to give the thioester enolate. The ketimine 1 is activated by
the protonated quinuclidine through H-bonding. The reaction of
thioester enolate with ketimine 1 in the chiral environment of
VIII gives 18 with high enantioselectivity. The proposed transition state TS 9 involves a ternary complex of substrates and
a catalyst in which the thioester enolate approaches the Re face of
ketimine to provide the observed S enantiomer of the product 18.

Recently, Enders group reported the enantioselective organocatalytic addition reaction of ethyl nitroacetate 20 to isatin
imine 1 (Scheme 10). A wide variety of desired adduct 21 was
formed in good to excellent yields (51-91%) and excellent enantioselectivities (92-99%). The desired product 21 could be
efficiently transformed into AG-041R 19 and hexahydrofuran[2,3-b]indole 22 which is the skeleton of the natural product physoveninel.

Scheme 9: Organocatalytic enantioselective decarboxylation Mannich-type reaction of malonic half thioesters with isatin imines.

Scheme 10: Organocatalytic Mannich/denitration reaction for the asymmetric synthesis of ethyl 2-((S)-3-amino-2-oxoindolin-3-yl)acetate derivatives.

Primary amino acid catalyzed Mannich reaction of N-substituted
isatin imines 1 with hydroxycetone 23 was reported by Peng and co-workers (Scheme 11). The chiral amino acid in diethyl ether catalyzed this reaction to afford the anti-Mannich adduct 24b in
good to high yield (72-98%) and low to good diastereoselectivity
(69-31:88:12 dr) and good to excellent enantioselectivity (79-99%). However, the imine derived from 7-chloroisatin affords the
desired adduct in a ratio of 47:53 in favour of syn-diastereomer.

When toluene was used as solvent, it provides syn-Mannich adduct 24a in high yield (82-99%) and moderate diastereoselectivity (75:25-83:17 dr) and good enantioselectivity
(86-91%). On using isatin imines in toluene, only anti-Mannich product 24b was formed. The reason for this behaviour was
explained on the basis of differential E/Z ratio of isatin imine in
different solvents. It was assumed that, when this reaction was
conducted in ether, the amount of E-isomer was greater than the
Z-isomer and the reaction proceeded through transition state TS
10 to provide anti product. But in toluene, the major component
was Z-isomer, which afforded syn adduct via TS 11.

Recently, Wu et al. reported the Cinchona alkaloid derived thiourea XI catalyzed enantioselective Mannich reaction of
pyrazoleamides 25 with isatin imines 1 (Scheme 12). The

Scheme 11: Diastereo-divergent enantioselective Mannich reaction of hydroxycetone with isatin imines.

Using 10 mol% of the catalyst XI and molecular sieves as
additive, the product with tetra-substituted stereogenic carbon centre at the C-3 position of oxindoles 26 was obtained in good to excellent yield (84-97%) with excellent dr 99:1 and perfect enantioselectivity (96-99%). The pyrazole amide could easily be transformed to β-amino ester 27 by one pot alcoholysis with high yield (89%) and with excellent enantioselectivity (>99% ee). Methyl 2-phenylacetate and (2-phenyl-1-pyrrolidin-1-yl)ethanone were unreactive nucleophiles with isatin imine suggesting the importance of pyrazole group in facilitating the Mannich reaction. Based on the observed stereochemistry, a plausible 10 transition state TS 12 was proposed in which bifunctional organocatalyst XI deprotonates the pyrazoleamide 25 with quinuclidine nitrogen, while the thiourea moiety binds and activates the ketimine 1 through double hydrogen bond formation with the nitrogen and oxygen atoms. The activated enolized pyrazoleamide approaches the ketimine from one preferred enantioface i.e. Si face to afford the desired product with (3R, 1'S) configuration.

Soon after this Wang et al reported an organocatalyzed asymmetric vinylogous Mannich reaction of γ-butenolides 28 with isatin imines 1 (Scheme 13). 27 Using Quinidine derived organocatalyst XII, the 3-amino-2-oxindoles 29 bearing adjacent quaternary and tertiary stereocentres were synthesized in good to excellent yield (56-97%) and with moderate to good enantioselectivity (83-96%) with moderate dr of 79:21. On the basis of the experimental results, the transition state TS 13 was proposed in which γ-butenolide is activated by tertiary amine of the catalyst XII and ketimine I is activated by hydroxyl group of catalyst. So, the activated butenolide approaches from one preferred enantioface to afford the desired product 29 with observed stereochemistry. Wu et al successfully disclosed an enantioselective Mannich-cyclization reaction of isatin imine 1 with 4-bromo-3-oxobutanoates 30 (Scheme 14). 28 Cinchona alkaloid derived squaramide XIII catalyzed the reaction of various isatin imines I with 4-bromo-3-oxobutanoates 30 to provide the 3-substituted-3-amino-2-oxindoles 31 in 90-97% yield and 94-98% enantioselectivity. Another study on vinylogous Mannich reaction was reported by Deng and co-workers in which AgOAc was used to promote the reaction of isatin imine 1 and trimethylsiloxyfuran (TMSOF) 32 to provide 3-aminooxindoles 33, which leads to desired products in excellent yields (94-99%) and excellent anti-diastereoselectivity (>99%) under mild conditions, is a frequent core unit in natural products (Scheme 15). 29 The ability of AgOAc to promote this reaction was higher than that of other metal salts, such as Cu, Zn, Ni. On the basis of proposed transition state TS 14, the Ag(I) is coordinated as a Lewis acid to two equivalents of the substrate and also acts as a base after coordinating to TMSOF and releasing -OAc, which is the real base that captures the TMS group and consequently promotes the attack of TMSOF over the isatin imine. Recently, Nakamura et al have reported the Cinchona alkaloid sulphonamide XIV catalyzed enantioselective addition of thiols 34 to isatin imine 1 to provide N,S-acetals 35 with excellent yield (91-99%) and excellent enantioselectivities up to 97% (Scheme

![Scheme 12: Organocatalytic enantioselective Mannich reaction of pyrazoleamide with isatin imines.](image1)

![Scheme 13: Organocatalytic direct asymmetric vinylogous Mannich reaction of γ-butenolides with isatin imines.](image2)

![Scheme 14: Organocatalytic enantioselective squaramide catalyzed domino-Mannich-cyclization reaction of isatin imines.](image3)

![Scheme 15: AgOAc catalyzed vinylogous Mannich reaction of isatin imine and trimethylsiloxyfuran (TMSOF).](image4)
Interestingly, the authors demonstrated that a three component version of this reaction could be achieved. The one pot Mannich sequence allowed products to be obtained with comparable enantiomeric excess and yields. In the proposed transition state TS 15, the tertiary amine of the catalyst activates the thiol via H-bonding and simultaneously the ketimine gets activated by pyridine-sulfonamide through H-bonding providing the desired adduct with high enantioselectivity.

To improve the synthetic utility, the multicomponent version of this reaction was also studied by combination of the aza-Wittig and aza-Henry reaction in a one-pot sequential protocol. The product 41 was isolated in 63% yield with lower enantioselectivity (72% ee). The mechanism of this reaction was illustrated with the help of designed experiments which indicated

Scheme 19: BnCPN catalyzed asymmetric Henry reaction of N-Boc isatin imines with different nitroalkanes.
the importance of 6'-OH-group of BnCPN for introducing high enantioselectivity.

The catalyst having no free amine moiety failed to catalyze the model reaction, suggesting the role of free amine moiety in deprotonation of nitroalkanes. These results show that the tertiary amine present in the catalyst is a prerequisite for this reaction to occur along with the C6'-OH group, which provides favourable orientation for high enantioinduction. As shown in the transition state TS 16 the catalyst behaves as a bifunctional catalyst by providing favourable orientation and synergistic activation of both the substrate via deprotonation of nitroalkane with quinuclidine nitrogen and activation of ketimine by phenolic –OH of the catalyst.

Subsequently, in the same year, Zhou and coworkers had reported the asymmetric Henry reaction of nitromethane 40 to N-Boc isatin imine 1 and α-ketoester derived N-tosyl isatin imine catalyzed by DBU (Scheme 20). Only 5 mol% of catalyst in the presence of molecular sieves efficiently catalyzes the reaction of nitromethane 40 with various isatin imine derivatives 1 to provide an easy access to chiral 3-substituted-3-aminooxindole derivatives 41 in excellent yields (94-99%). They had also reported an enantioselective reaction catalyzed by BnCPN XVIII to afford the desired adduct 41 in moderate enantioselectivity (71% ee) but with excellent yield of 93%.

Scheme 20: Catalytic enantioselective addition of nitroalkanes to isatin imines.

Then, Arai and co-workers have developed the reaction of nitromethane 40 with isatin imine 1 catalyzed by bis(imidazoline)pyridine-NiCl₂ XVIII (Scheme 21).

Scheme 21: PyBidine-NiCl₂ catalyzed asymmetric reaction of nitroalkanes with N-Boc isatin imine. The 3-amino-2-oxindole 41a was formed with excellent yield (up to 99%) with excellent enantioselectivity (up to 95%) under mild conditions. To illustrate the synthetic utility of the product, the reduction of nitro group leading to 43 and deprotection of Boc group leading to 42 was achieved without loss of enantioselectivity. In the proposed transition state TS 17, the pyridine-NiCl₂ complex acts as Lewis acid which activates the ketimines through coordination to the nickel centre through the lone pair of isatin imine which is then attacked by nitronate carbanion to provide the desired adduct.

A similar work was reported by Pedro et al with Cu(II) BOX XIX complex as a catalyst (Scheme 22). The catalyst efficiently catalyzes the reaction to gave the desired Henry adduct 41 in excellent enantioselectivity up to 99.9% with good to excellent yield (84-99%). The nitroamines 41 can be easily transformed to amino nitriles that are useful synthetic intermediates for spirocyclic oxindoles. On treatment with dry HCl in methanol, the amino ester 44 was obtained in 61% yield with 92% enantioselectivity.

Scheme 22: Highly enantioselective αα-Henry reaction of N-Boc isatin imines and nitroalkanes using a Cu(II)-BOX complex as a catalyst.

Recently, the same reaction was reported by Feng and co-workers using chiral guanidine-amide XIX A as a catalyst. The product 41 was formed in excellent yield up to 99% and excellent enantioselectivity up to 94%. The nitro group can be further transformed either to an amine 43a or nitrile 43b in a good yield and enantioselectivity (Scheme 23).

Scheme 23: Enantioselective αα-Henry reaction of isatin imines with nitroalkanes catalyzed by chiral bifunctional guanidine catalyst.

(6) Enantioselective Zn-mediated allylation of isatin derived ketimines

Xu et al reported the zinc-mediated diastereoselective allylation and propargylation of isatin N-tert-butanesulfinyl imines 1 for the synthesis of tetrasubstituted 3-aminooxindoles 46 (Scheme 24).
The product 46 was formed in good yield (up to 85%) and de of up to 99%. 46 could be easily transformed into chiral spirocyclic oxindoles 47 under mild conditions.

Scheme 24: Zn-mediated diastereoselective alkylation of N-sulfinyl isatin imine.

In order to rationalize the observed diastereofacial selectivity, the transition state model TS 18 was proposed where the chelation of allyl zinc to imine nitrogen or carbonyl oxygen was less favored in solution due to the strong metal cation coordination ability of HMPA. The bulky tert-butyl group is positioned at the Si-face of ketimine molecule due to the adoption of synperiplanar configuration by uncoordinated N-sulfinyl group. Thus, the allyl zinc reagent preferentially attacks from the Re-face of ketimine facilitating (S)-amine formation.

(7) The Strecker reaction

The asymmetric addition of cyanide ions to imines to give α-amino nitriles is a useful methodology in organic chemistry.\(^{(19)}\) The optically active α-amino nitriles are versatile intermediates for the preparation of both natural and unnatural amino acids that have importance in the synthesis of drugs and pharmaceuticals. In the past years, there has been a tremendous growth in the field of asymmetric Strecker reaction, of which, the stereoselective synthesis of 3-amino oxindoles bearing quaternary carbon centre has received great attention due to bioactivity associated with 3-amino oxindoles. The first report on the asymmetric addition of TMSCN 48 to isatin imines 1 was given by Zhou et al. using 10 mol% of newly developed phosphoramidate catalyst XX derived from Cinchona alkaloids, 3-Cyano-3-amino-2-oxindole derivatives 49 were obtained in low to good yield (27-72%) and moderate enantioselectivity of 39-74% ee (Scheme 25).\(^{(43)}\)

Scheme 25: Cinchona derived phosphoramidate catalyzed asymmetric Strecker reaction of isatin imines.

A modified version of the asymmetric Strecker reaction of isatin imine was developed by Wang et al. using quinine thiourea XXI as a catalyst. 3-Amino-3-cyano oxindoles 49a was obtained in moderate to excellent yields (65-98%) and with moderate to high enantioselectivity (60-94%) (Scheme 26).\(^{(41)}\) The synthetic utility of this protocol was demonstrated by the conversion of cyano group into amide (50) and ester (51a) without loss of enantioselectivity.

Scheme 26: Quinine thiourea catalyzed asymmetric Strecker reaction.

The proposed transition state TS 20 for the enantioselective cyanation reaction involves H-bonding activation of the ketimine through thiourea moiety and simultaneous generation of nuclophilic cyanide from TMSCN by tertiary amine of the Cinchona alkaloid (Scheme 26).

The diastereoselective synthesis of 3-amino-3-cyano-oxindoles 49b was reported by Sacchetti and coworkers using auxiliary-based approach for the addition of TMSCN 48 to the chiral ketimines 1, the reaction was performed in the presence of Lewis acid (Scheme 27).\(^{(42)}\) The desired products 49b were obtained in moderate to good yields (26-88%) and with moderate diastereomeric ratios (55:45-74:26 dr). The cyanide functionality was transformed to obtain amino esters 51 and spirohydantoin 52.

Scheme 27: Addition of TMSCN to chiral isatin imines.

Shortly after this, Zhou et al. reported the asymmetric Strecker reaction of isatin imines catalyzed by Cinchonidine derived thione \(\text{VI}\) for the asymmetric synthesis of 3-amino-3-cyano-oxindoles 49 in high yield (81-95%) and with excellent enantioselectivity (90-99% ee) (Scheme 28).\(^{(43)}\)
Cinchona-derived thiourea catalyzed asymmetric Strecker reaction of N-Boc isatin imines. A tandem aza-Wittig/Strecker reaction was carried out involving the in situ formation of isatin imine from isatin followed by enantioselective cyanation mediated by catalyst VI to provide the product 49 in 41-86% yield and 76-96% enantioselectivity. The synthetic utility of this methodology was demonstrated by transformation of adducts into spirohydantoin 52. Very recently, Xu and coworkers used chiral auxiliary based approach for highly diastereoselective Strecker reaction of isatin sulfinyl ketimines (Scheme 29). The addition of TMSCN to isatin sulfinyl imines catalyzed by magnesium bromide diethyl ether and potassium fluoride as cocatalyst gave the desired product in high yield (up to 87%) and with high diastereoselectivity (up to 99%). The synthetic utility of the product was shown by its conversion to an ester 51a without loss of enantioselectivity.

(8) Michael reaction
The Michael addition reaction plays an important role among the numerous carbon–carbon bond forming reactions which involves the addition of various active methylene compounds to the electron deficient alkenes. In the past few years, numerous classes of nucleophiles have been extensively used in conjugate addition.

In 2014, Zhu et al reported an organocatalytic addition of 3-substituted oxindoles to isatin imines catalyzed by chiral Lewis base to provide bisoxindole 54 with two chiral vicinal quaternary carbon centres in good to excellent yield (45->99%) and 91-98% enantioselectivity. The substituent at 6-position had positive effect on the reaction but substituent at 7-position resulted in decrease in enantioselectivity of the product 56. In the proposed transition state TS 24, the ketimine is activated by the thiourea moiety through H-bond interaction while the alcohol gets activated by the tertiary-amine which attacks the ketimine from Re-face to generate the product with (R)-configuration.

(9) N-Heterocyclic carbenes catalyzed reaction
In the past few years, there has been a significant growth in the field of N-Heterocyclic carbenes due to their ability to introduce umpolung of reaction in aldehydes. The Classic N-Heterocyclic carbene catalyzed reactions such as benzoin condensation and Stetter reaction proceed via nucleophilic Breslow intermediates which are generated by the addition of N-heterocyclic carbenes to aldehydes. However, the reaction of enals by N-Heterocyclic carbenes has received great attention. In 2012, Jiao and coworkers reported the asymmetric synthesis of spiropyrrolic-γ-lactam oxindoles 58 using N-heterocyclic carbenes XXIV for the addition of enals 57 to N-aryl isatin imines 1 (Scheme 32). Using 10 mol% of NHC XXIV homoenoate equivalents of enals
were added to isatin imines 1 and subsequent acid hydrolysis of the addition product generated various spirocyclic oxindoles in 35-88% yield and 6:1-1:6 dr. The catalytic enantioselective version of this reaction was also developed using chiral NHC catalyzed addition of cinnamaldehyde to N-phenyl isatin imine to provide spirocyclic oxindole 58 in 80% yield, 1:1-1:6 dr.

Recently, Chi and coworkers have demonstrated the application of N-heterocyclic carbenes XXIII for the reaction of enals 57 to isatin imines 1 for the synthesis of spirocyclic-γ-lactams 58a in moderate to good yield (51-84%), good to high diastereoselectivity (4:1 to >20:1 dr) and excellent enantioselectivity (94-99% ee) (Scheme 32). The mechanism of the reaction involves the generation of NHC XXIII by the deprotonation of imidazolium salt in the presence of base which undergoes addition to enal 57 resulting in the formation of Breslow intermediates B and C. The attack of intermediate B on isatin ketimine 1 produces intermediate D which after tautomerization generates intermediate E. Subsequent cyclization of E generates spirocyclic oxindoles γ-lactams 58a with regeneration of NHC to complete the catalytic cycle.

Scheme 32: NHCs catalyzed enantioselective addition of enals to isatin imines.

After this pioneering example, the same group reported the chemoselective cross-aza-Benzoin reaction of isatin imines 1 with enals 57 proceeded via the formation of acyl anion catalyzed by the N-heterocyclic carbene XXV (Scheme 33). But the reaction to provide the chiral quaternary aminoxindoles 59 in poor to good yield (10-76%) and er up to 98:2. Ye and coworkers developed a bifunctional N-heterocyclic carbene XXVI catalyzed enantioselective synthesis of spirocyclic oxindolo-β-lactams 61 by performing the reaction of isatin imines 1 with ketenes 60 (Scheme 34).

Ketene 60 (Scheme 34).

The product 61 having chiral tetrasubstituted stereocentres was obtained in moderate to good yield (70-92%) with excellent enantioselectivity up to 99% and dr up to 20:1. The resulting N-Boc protected β-lactam 61 could be easily deprotected to afford the free β-lactam in high yield without any loss of enantioselectivity.

Scheme 33: NHC catalyzed chemoselective cross-aza-Benzoin reaction of enals with isatin imines.

(10) Ugi reaction:
The Ugi reaction was first reported by Ivar Ugi in 1959. This multicomponent reaction with one of its component as an isocyanide results in the formation of α-N-acylamino amide. This reaction has received much attention due to its ability to construct complex heterocyclic scaffolds via tandem reaction. Recently Silvani et al reported the synthesis of optically active 3,3-disubstituted-3-aminooxindoles 64 by means of a three component Ugi reaction of isatin imines 1 with isonitrile 62 and trifluoroacetic acid 63 (Scheme 35).

Scheme 34: Enantioselective Staudinger reaction of ketenes with imines.

Scheme 35: Asymmetric Ugi-three-component reaction with isatin imines.

(11) Miscellaneous Reaction
Rhodium-catalyzed reactions are the most versatile for carbon-carbon bond formation among the transition-metal mediated reactions owing to their ability to tolerate a variety of functional
groups. The Rhodium catalyzed diastereoselective synthesis of 3-amino-3-substituted-2-oxindoles has been reported by three independent groups. B.V. Reddy et al reported a highly diastereoselective reaction of α-diazoesters 68 with aryl alcohols 67 and isatin imine 1 catalyzed by Rh₂(OAc)₄ to obtain β-amino-α-hydroxyesters 69 in 80-92% yield, which on deprotection gave 70 in 92% yield (Scheme 36). The proposed transition state involves the formation of oxonium ylide from a rhodium carbenoid and alcohol which then attacked the isatin imine through the formation of five-membered transition state. The transition state is stabilized by the intramolecular H-bonding between the H-attached to oxonium ylide and imine N-atom and π-π interaction between the aryl group of diazoester and oxindole resulting in the formation of erythro isomer.

Scheme 36: Highly diastereoselective reaction of α-diazoesters with aryl alcohols and isatin imines.

Ellman et al realized the diastereoselective synthesis of 3-amino-2-oxindoles 72 bearing a tetrasubstituted stereogenic centre in moderate to good yield (72-92%) with good dr (94:6-96:4) via RhCl(cod)₂ catalyzed reaction of aryloboroxines 69 to isatin imine 1 (Scheme 37).

Scheme 37: RhCl(cod)₂ catalyzed reaction of aryloboroxines to isatin imines.

In 2014, Min Shi and coworkers reported the three component reaction of 3-diazooxindoles 73 with indoles 6 and isatin imine 1. Using Rh₂(OAc)₄ as catalyst, the functionalized 3,3',3''-trisindoles 74 were synthesized in moderate to good yield (70-97%) with good dr (5:1->20:1) via in situ generation of an active zwitterionic intermediate 75. (Scheme 38). Liu et al reported an organo-metal catalyzed one-pot sequential Mannich/Hydroamination reaction of isatin imine and propargylated malononitrile (Scheme 39). The product was isolated in good yield (up to 91%) and with excellent enantioselectivity (up to 97% ee). The deprotection of the final cyclic adduct resulted into spiro[pyrrolidin-3,2'-oxindole] derivative in 75% yield and 95% enantioselectivity.

Scheme 38: Rhodium catalyzed 3-component reaction of 3-diazooxindoles with indoles and isatin imines.

Scheme 39: Organocatalyzed and metal catalyzed one-pot sequential Mannich/Hydroamination reaction of isatin imine.

(DHQ)₂AQN catalyzed asymmetric substitution of isatin derived hydrazones was reported by Shi group. Azo compounds incorporating an oxindole scaffold were obtained in up to 91% yield and 93% ee (Scheme 40).

Scheme 40: (DHQ)₂AQN catalyzed asymmetric reaction of isatin derived hydrazones with O-Boc-protected aza-Morita-Baylis-Hillman adducts.

Sacchetti and co-workers reported the addition of Grignard reagent to isatin imine 82 to obtain 3-substituted-3-
aminooxindoles 83 in yield up to 77% and up to 95:5. In the proposed transition state TS 26, the MgBr coordinate both with the imine nitrogen and the carbonyl oxygen in such a way that the attack of nucleophile is oriented from the less hindered Re face of the imine (Scheme 41).  

Scheme 41: Addition of Grignard reagent to isatin imines. Copper(I) catalyzed one pot, three component diastereoselective synthesis of 3-spiroazetidinimine-2-oxindoles was reported by Shanmugam group. The product 87 was obtained in up to 77% yield, which undergoes a facile ring opening reaction of the spiroazetidinimine unit on treatment with p-thiocresol or KOH/MeOH to yield products 88 and 89, respectively (Scheme 42).  

Scheme 42: Copper(I) catalyzed one-pot, three-component diastereoselective synthesis of 3-spiroazetidinimine-2-oxindoles.  

Summary and outlook

Quaternary 3-amino-2-oxindoles are important and ubiquitous motifs in many natural products and pharmaceuticals. In the past few years, a variety of methods like enantioselective addition of nucleophiles to C=N bonds, Mannich reaction, Morita-Baylis-Hillman reaction, Streeker reaction are used to construct 3-substituted-3-amino-2-oxindoles with a chiral quaternary carbon centre. The synthesis of these derivatives has been achieved by using different catalyst providing the product in moderate to good yields and enantioselectivity. This collection provides a broad vision of the current status of research in the synthesis of 3-amino-3-substituted-2-oxindoles using both metal and organocatalysts. Still, there is an extensive room for the addition of various other nucleophiles to isatin imines. We believe that much more can still be done in this area.

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Notes and references


