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Graphical Abstract

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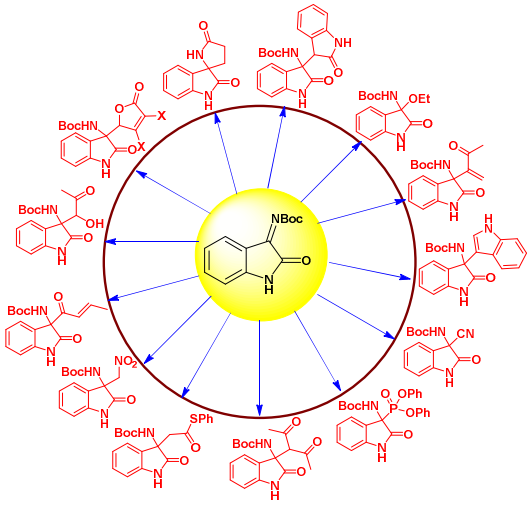

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ARTICLE TYPE

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

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3-Substituted-3-aminooxindoles have attracted the attention of organic and medicinal chemists because these motifs constitute the core structure of 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[1] such as gastrin/CCK-B receptor antagonist AG-041R,[2] the vasopressin VIb receptor antagonist SSR-1494153[3] and antimalarial drug candidate NITD609 (**Figure 1**).[4]

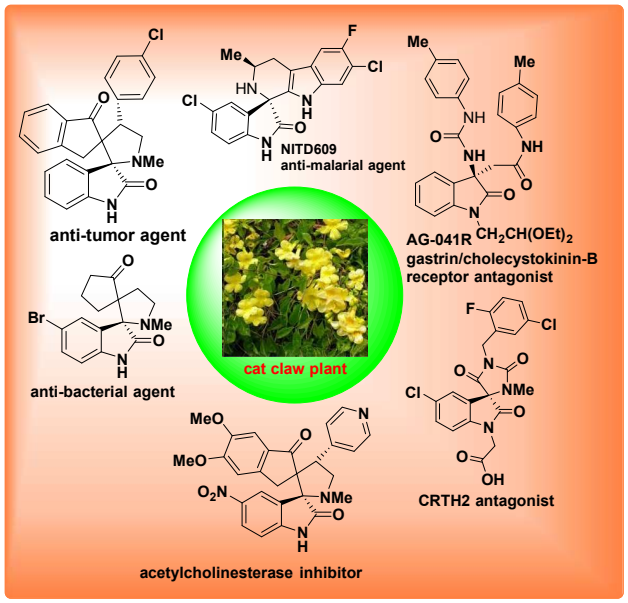

Figure 1: Examples of bioactive quaternary aminooxindoles and related natural compounds.

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.[5] 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.[6]

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, Strecker 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 involves isatin derived ketimine as a substrate are shown in **Figure 2.**

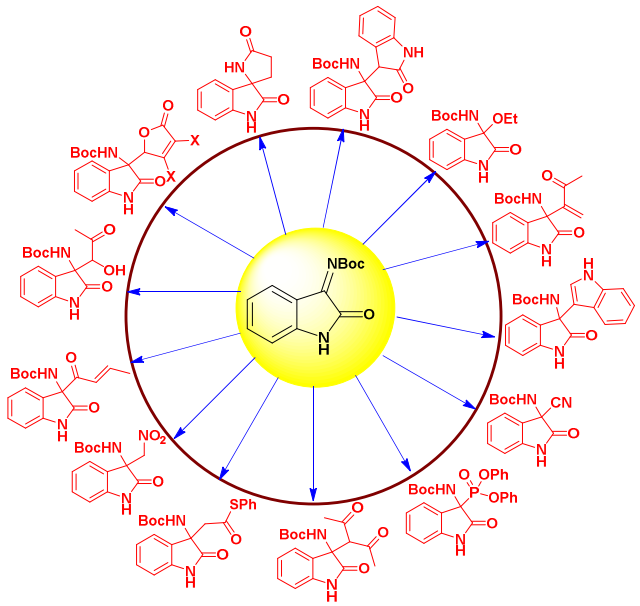

Figure 2: Representative examples from isatin imine framework.

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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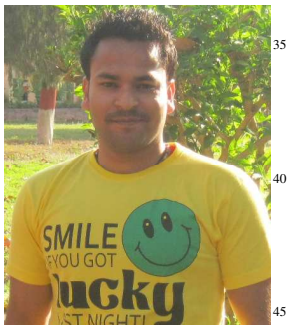
Swapandeep Singh Chimni was born in 1962 at Amritsar, India. He received his M.Sc. (Hons. Sch.) in Chemistry in 1985 and Ph.D. in 1991 from Guru Nanak Dev University, Amritsar. After two years as a lecturer at Regional Engineering College (now NIT) Jalandhar, he joined the Department of Chemistry, Guru Nanak Dev University as Lecturer in 1992. He is presently working as a Professor in the same department. He has a research experience of 25 years and published over 107 publications. He works in the area of synthetic organic chemistry with emphasis on asymmetric organocatalysis, biocatalysis and phase transfer catalysis as well as green chemistry.



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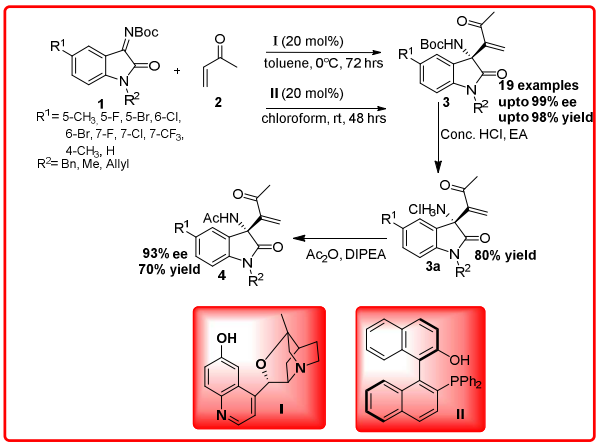
(1) Enantioselective *aza*-Morita-Baylis-Hillman reaction

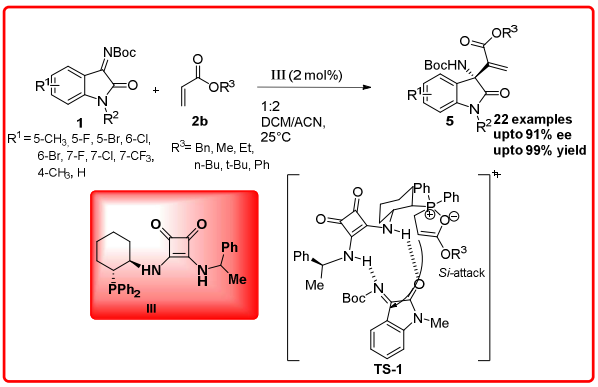
The Morita-Baylis-Hillman/*aza*- Morita-Baylis-Hillman reaction has received increasing interest since it combines two important requirements, atom economy and generation of functional groups.[7] The last decade has seen exponential growth of Morita-Baylis-Hillman (MBH) reaction and its applications. 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 *aza*-Morita-Baylis-Hillman reaction of isatin imines (**1**) with methyl vinyl ketones (MVK) **2** catalyzed by *β*-isocupreidine **I** and chiral phosphines **II** (Scheme 1).[8] 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.



Scheme 1. Enantioselective *aza*-Morita-Baylis-Hillman reaction of isatin imines with MVK.

The synthetic use of this methodology was illustrated by the synthesis of *N*-acyl-3-aminooxindole **4** after treating with acetic anhydride, in 70% yield.

Subsequent to this report, Feng Sha *et al* reported the phosphine squaramide catalyzed enantioselective *aza*-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*).

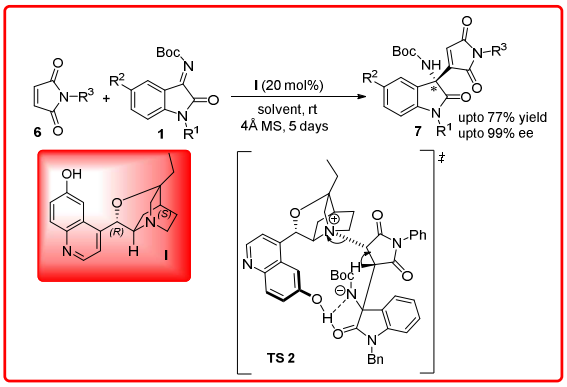


Scheme 2: Asymmetric *aza*-MBH reaction of isatin imines with acrylates catalyzed by phosphine-squaramide organocatalyst.

In the proposed transition state **TS 1**, the catalyst activates the

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).[9]

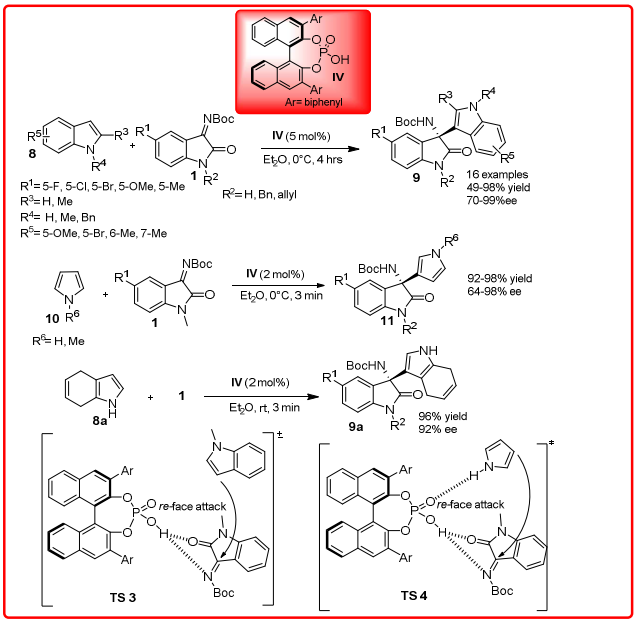
Recently, our group reported an organocatalyzed *aza*-Morita-Baylis-Hillman reaction of maleimides **6** with isatin imines **1** using *β*-isocupreidine **I** as an organocatalyst (Scheme 3).[10] Maleimide as a MBH donor is more challenging task because maleimides are traditionally Michael acceptors. 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.

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.[11] 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).[12a] 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.

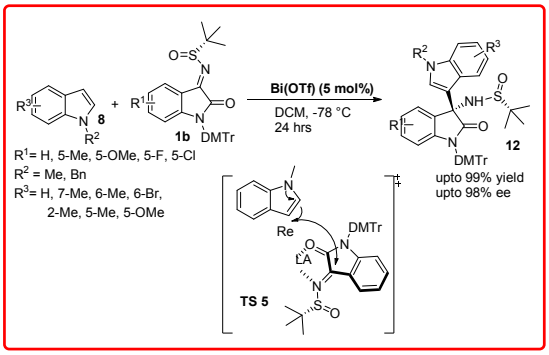


Scheme 4: Chiral phosphoric acids catalyzed enantioselective addition of indole and pyrrole derivatives to isatin imine.

Recently, Xu *et al* reported the same reaction using only 5 mol% of $Bi(OTf)_3$ (Scheme 5).[12b] 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.[13]

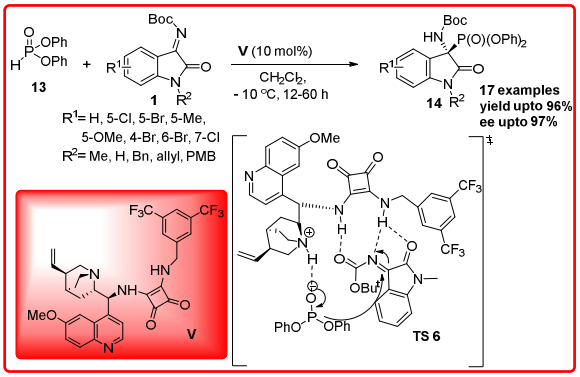


Scheme 5: Diastereoselective Friedel-Crafts reaction of *N*-sulfinyl isatin imines with indoles.

In particular, *α*-aminophosphonic acid derivatives[14] are known to exhibit a broad spectrum of biological activities such as peptide mimetics, antibacterial,[15] antiviral agents[16] and enzyme

inhibitor.[17] Inspite of this, there are only a few reports on asymmetric addition of phosphite to simple ketimines.[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 *et al* reported the first asymmetric organocatalytic hydrophosphonylation reaction of isatin imines (**Scheme 6**).[19] Quinine squaramide **V** was identified as the best catalyst for the reaction of isatin imines **1** with diphenyl phosphite **13** to provide 3-amino-oxindoles **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 **TS 6** for this enantioselective hydrophosphonylation reaction involves a hydrogen bonding activation of ketimine **1** through the NH of the squaramide and simultaneous generation of phosphonate anion from diphenylphosphite **13** by the tertiary amine of the catalyst. In addition to this synergic activation, the catalyst **V** also provides a favourable orientation to both substrates to provide the desired adduct in high enantioselectivity.

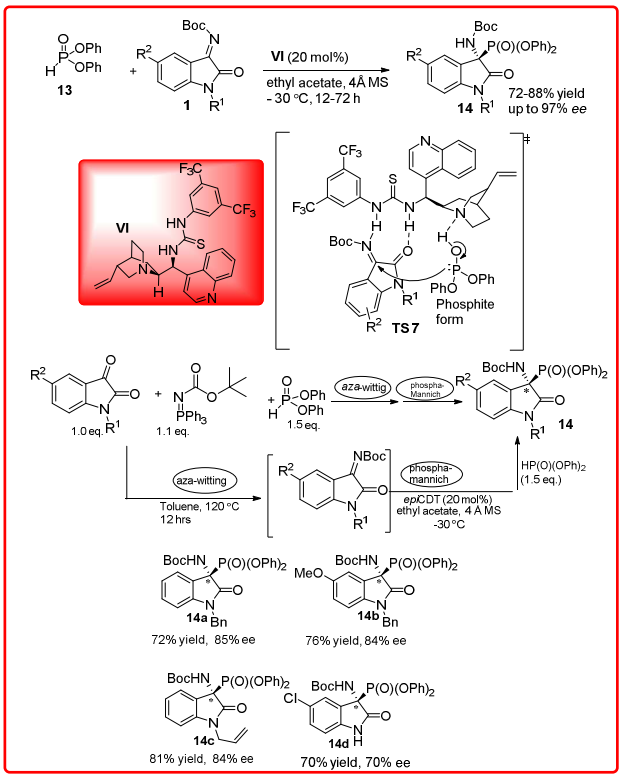


Scheme 6: Quinine-squaramide catalyzed enantioselective addition of diphenyl phosphite to isatin imines.

Soon after this, our group published the same reaction catalyzed by Cinchonidine derived thiourea **VI** for the synthesis of 3-amino -2-oxindoles **14** in good to excellent yields (72-88%) and excellent enantioselectivity up to 97% (**Scheme 7**).[20] To improve the synthetic efficiency, the combination of *aza*-Wittig and phospha-Mannich one pot sequential protocol was developed resulting in *α*-amino phosphonates in good yield and good enantioselectivity. The proposed transition state **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 *Re* face orientation is favoured which avoids the steric interaction between the isatin imine benzene ring and aryl group of phosphate.

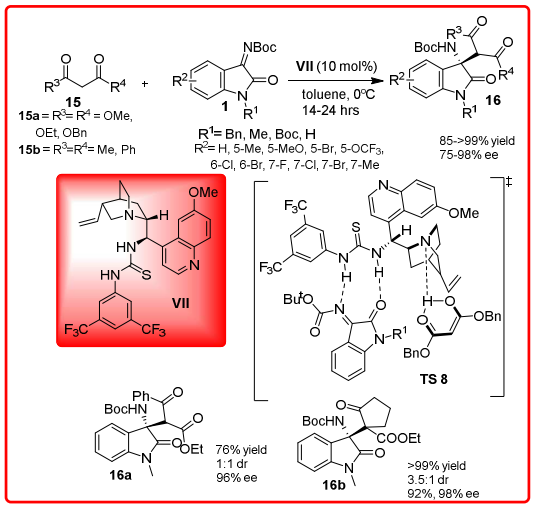
(4) Enantioselective Mannich reaction

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



Scheme 7: Cinchonidine derived thiourea catalyzed hydrophosphonylation reaction of diphenylphosphite and 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 *et al* synthesized *N*-alkoxycarbonyl isatin imines *via aza*-Wittig reaction and used them for the synthesis of chiral 3-aminooxindoles by the enantioselective addition of 1,3-dicarbonyl compounds (**Scheme 8**).[22]

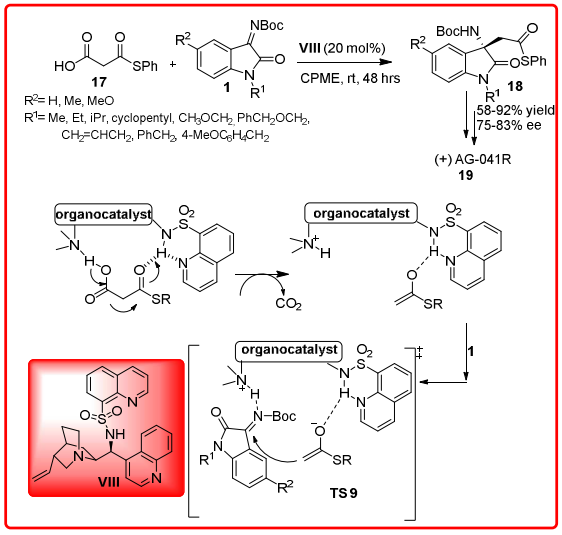


Scheme 8: *Cinchona*-derived thiourea catalyzed enantioselective addition of 1,3-dicarbonyl compounds to *N*-Boc isatin imines.

Quinidine derived thiourea **VII** catalyzes the Mannich reaction of malonates **15a** and diketones **15b** with isatin imines **1** providing 3-amino-2-oxindoles **16** in high yield (>99%) and excellent enantioselectivities (up to 98%). In the proposed transition state **TS 8**, the bifunctional organocatalyst **VII** deprotonates the

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 enantioface to afford the desired product with *S* stereochemistry.

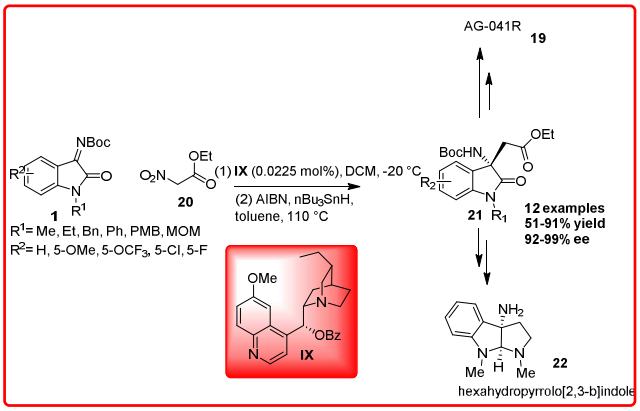
Shibata *et al* reported an organocatalytic enantioselective decarboxylative Mannich reaction of malonic acid half thioesters **17** with isatin imines **1** (**Scheme 9**).[23] Out of various catalysts examined, the best results were obtained with *N*-heteroarenesulfonyl *Cinchona* alkaloid **VIII** 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.



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

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 catalyst in which the thioester enolate approaches the *Re* face of ketimine to provide the observed *S* enantiomer of the product **18.**

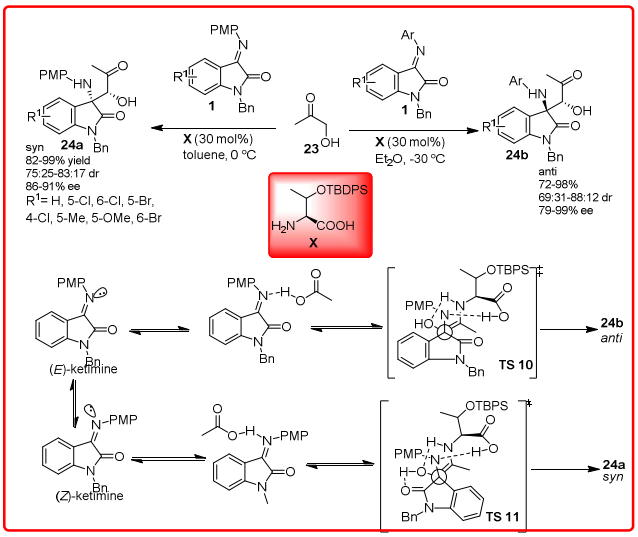
Recently, Enders group reported the enantioselective organocatalytic addition reaction of ethyl nitroacetate **20** to isatin imine **1** (**Scheme 10**).[24] A wide variety of desired adduct **21** was formed in good to excellent yields (51-91%) and excellent enantioselectivities (92-99%). The desired product **21** could be efficiently transformed into AG-041R **19** and hexahydrofurano[2,3-b]indole **22** which is the skeleton of the natural product physoveninel.



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 hydroxyacetone **23** was reported by Peng and co-workers (**Scheme 11**).[25] 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 carried out 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**.

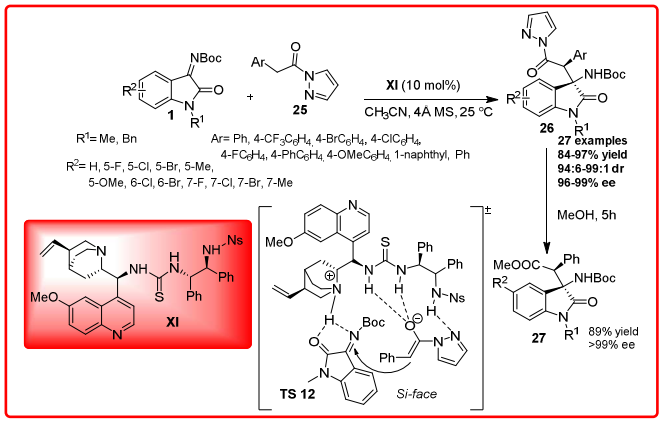
Recently Wu *et al* reported the *Cinchona* alkaloid derived thiourea **XI** catalyzed enantioselective Mannich reaction of pyrazoleamides **25** with isatin imines **1** (**Scheme 12**).[26]



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

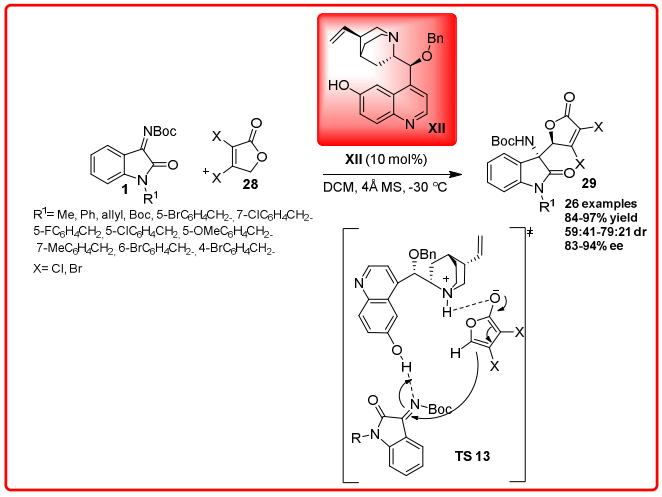
Using 10 mol% of the catalyst **XI** and molecular sieves as

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 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 (3*R*, 1'*S*) configuration.



Scheme 12: Organocatalytic enantioselective Mannich reaction of pyrazoleamide with isatin imines.

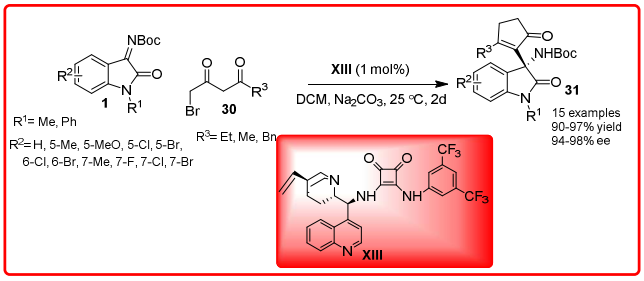
Soon after this Wang *et al* reported an organocatalyzed asymmetric vinylogous Mannich reaction of *γ*-butenolides **28** with isatin imines **1** (Scheme 13).[27]



Scheme 13: Organocatalytic direct asymmetric vinylogous Mannich reaction of γ-butenolides with isatin imines.

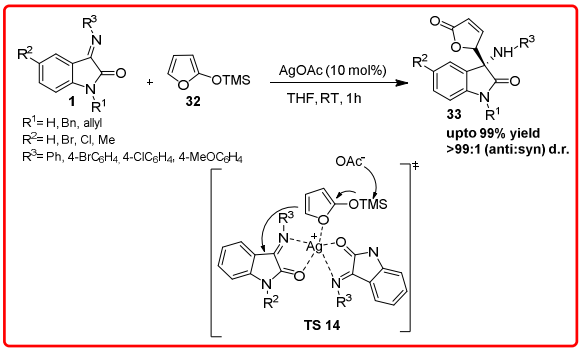
Using Quinidine derived organocatalyst **XII**, the 3-amino-2-oxindoles **29** bearing adjacent quaternary and tertiary stereocentres were synthesized in good to excellent yield (56-97%) and with moderate to good enantioselectivity (83-96%) with moderate *dr* of 79:21. On the basis of the experimental 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.



Scheme 14: Organocatalytic enantioselective squaramide catalyzed domino-Mannich-cyclization reaction of isatin imines.

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 trimethylsilyloxyfuran (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.

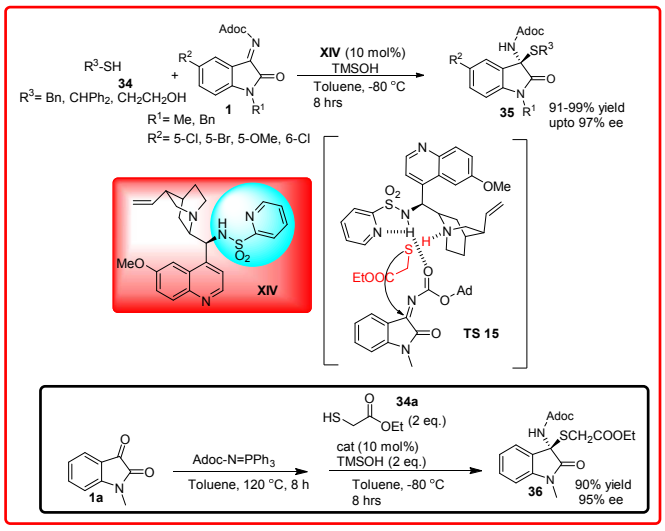


Scheme 15: AgOAc catalyzed vinylogous Mannich reaction of isatin imine and trimethylsiloxyfuran (TMSOF).

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

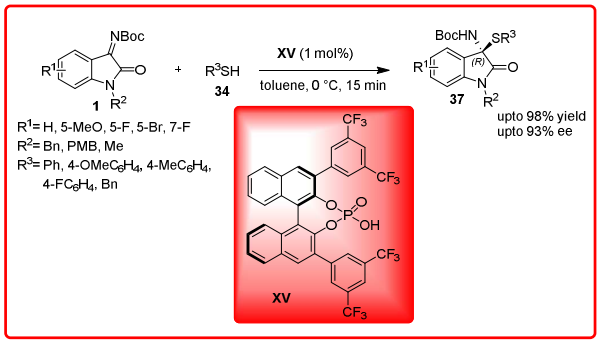
16).[30] Interestingly, the authors demonstrated that a three component version of this reaction could be achieved. The one pot Mannich sequence allowed products to be obtained with comparable enantiomeric excess and yields. In the proposed transition state **TS 15**, the tertiary amine of the catalyst 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.



Scheme 16: Enantioselective synthesis of *N*,*S*-acetals through the addition of thiols to imines and its one-pot asymmetric version.

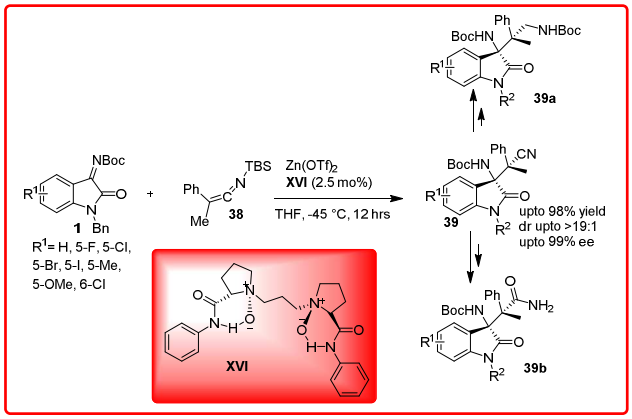
Ender's group published simultaneously the same reaction. The reaction leads to the formation of chiral isatin derived *N*, *S*-acetals **37** in excellent yield up to 98% with excellent enantioselectivities up to 93% (**Scheme 17**).[31] The reaction with non-protected isatin imine resulted in low yields. Both ketimines bearing electron withdrawing and electron donating substituents were well tolerated.

An organocatalytic reaction of silyl ketene imines **38** with isatin imines **1** has been recently reported by Feng and co-workers (**Scheme 18**).[32] A variety of *β*-amino nitriles containing vicinal tetrasubstituted stereocentres **39** were synthesized *via* *N*,*N*'-dioxide/Zn^{II} **XVI** catalyzed mannich reaction in excellent yield upto 98% with *dr* up to >19:1 and with excellent enantioselectivity ranging from 91-99% *ee*.



Scheme 17: Bronsted Acid-catalyzed enantioselective synthesis of isatin-derived *N*,*S*-acetals.

The desired product **39** could be efficiently transformed into 1,3-diamine **39a** and *β*-amino amide **39b** which is analogous structure of AG-041R.

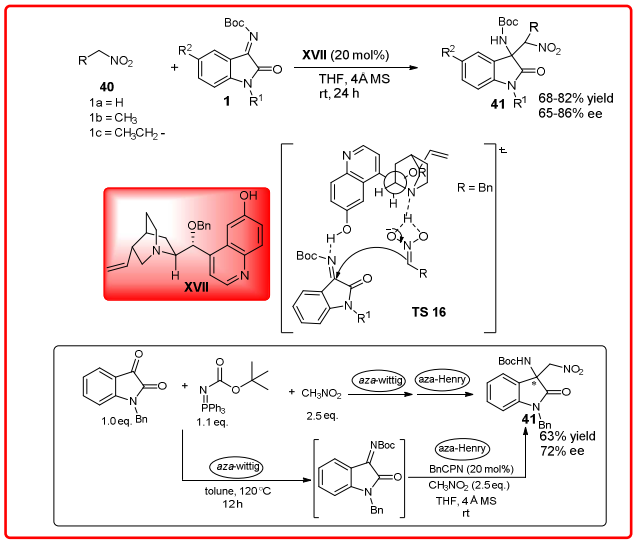


Scheme 18: Enantioselective Mannich reaction of silyl ketene imines with isatin imine.

(5) Enantioselective Henry reaction

The asymmetric Henry reaction has emerged as a powerful transformation to procure chiral *β*-nitro alcohols.[33] Both chiral organocatalysts and chiral metallic complexes have been developed for this reaction. Isatin and various aldehydes have been used as substrates for asymmetric Henry reaction. The use of isatin imines has been less explored as Henry acceptors for the enantioselective construction of chiral centres.

Our group reported the BnCPN **XVII** catalyzed asymmetric Henry reaction of *N*-Boc ketimines **1** and nitromethane **40** to provide the aminooxindoles **41** (**Scheme 19**).[34] This method works efficiently with several ketimines to produce the corresponding 3-substituted 3-amino-oxindoles **41** in good yield (68-82%) and moderate to good enantiomeric excess (65- 86%).



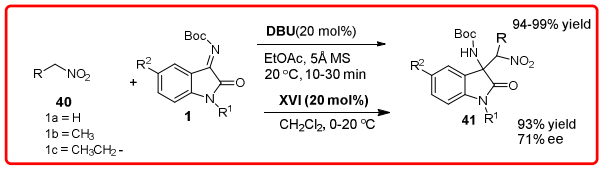
Scheme 19: BnCPN catalyzed asymmetric Henry reaction of *N*-Boc isatin imines with different nitroalkanes.

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

the importance of *6'*-OH-group of **BnCPN** for introducing high enantioselectivity.

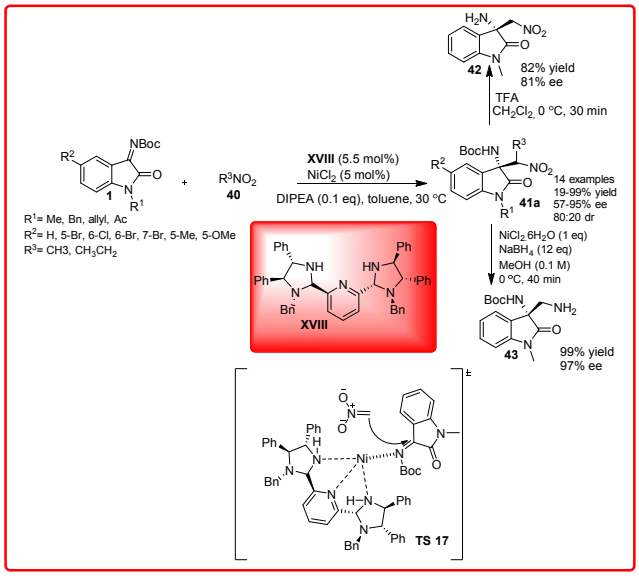
The catalyst having no free amine moiety failed to catalyze the model reaction, suggesting the role of free amine moiety in deprotonation of nitroalkanes. These results show that the tertiary amine present in the catalyst is a prerequisite for this reaction to occur along with the C*6'*-OH group, which 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**).[35] 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 **XVII** 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.

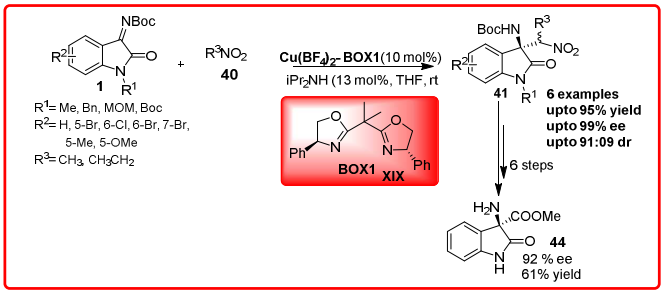
Then, Arai and co-workers have developed the reaction of nitromethane **40** with isatin imine **1** catalyzed by bis(imidazoline)pyridine-$NiCl_2$ **XVIII** (**Scheme 21**).[36]



Scheme 21: PyBidine-$NiCl_2$ catalyzed asymmetric reaction of nitroalkanes with *N*-Boc isatin imine.

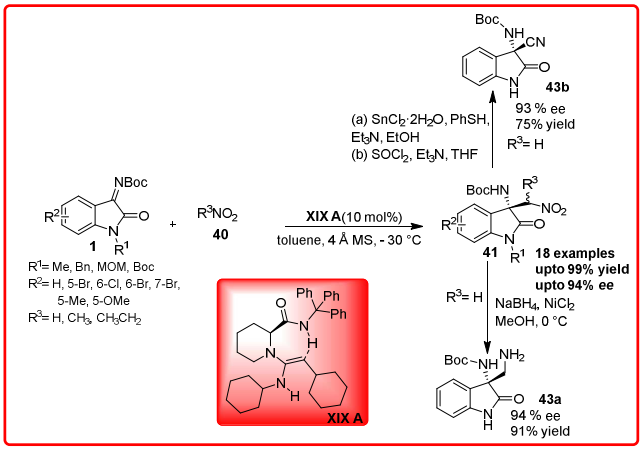
The 3-amino-2-oxindole **41a** was formed with excellent yield (up to 99%) with excellent enantioselectivity (up to 95%) under mild conditions. To illustrate the synthetic utility of the product, the reduction of nitro group leading to **43** and deprotection of Boc group leading to **42** was achieved without loss of enantioselectivity. In the proposed transition state **TS 17**, the pyridine-$NiCl_2$ 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**).[37a] 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 *aza*-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**).[37b]

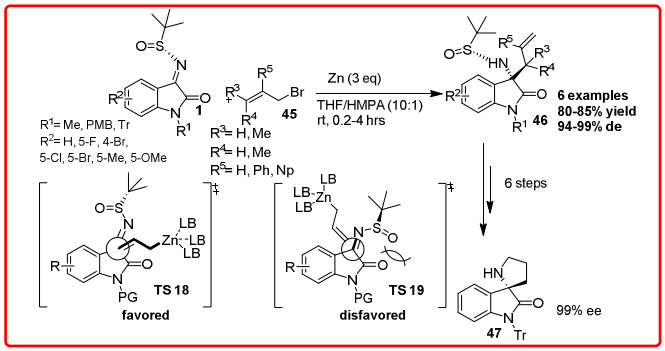


Scheme 23: Enantioselective *aza*-Henry reaction of isatin imine with nitroalkanes catalyzed by chiral bifunctional guanidine catalyst.

(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**).[38]

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.

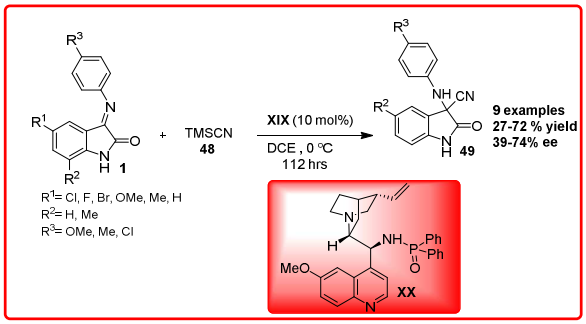


Scheme 24: Zn-mediated diastereoselective allylation of *N*-sulfinyl isatin imine.

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 favoured 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 *syn*periplanar 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

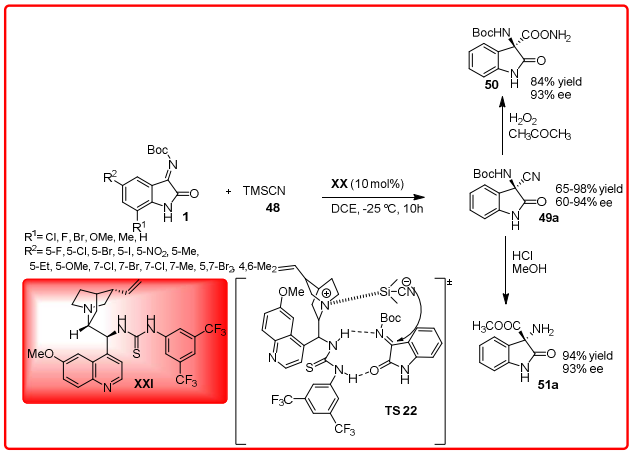
The asymmetric addition of cyanide ions to imines to give *α*-amino nitriles is a useful methodology in organic chemistry.[39] The optically active *α*-amino nitriles are versatile intermediates for the preparation of both natural and unnatural amino acids that have importance in the synthesis of drugs 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-aminooxindoles. 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 phosphoramide 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**). [40]



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

An improved 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]

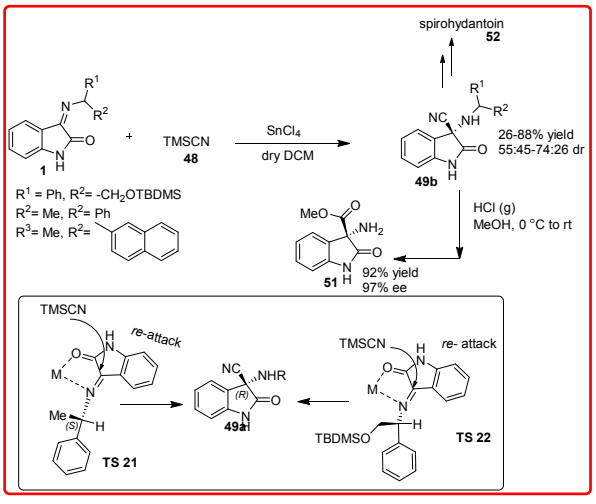
The synthetic utility of this protocol was demonstrated by the conversion of cyano group into amide (**50**) and ester (**51a**) without loss of enantioselectivity.



Scheme 26: Quinine thiourea catalyzed asymmetric Strecker reaction.

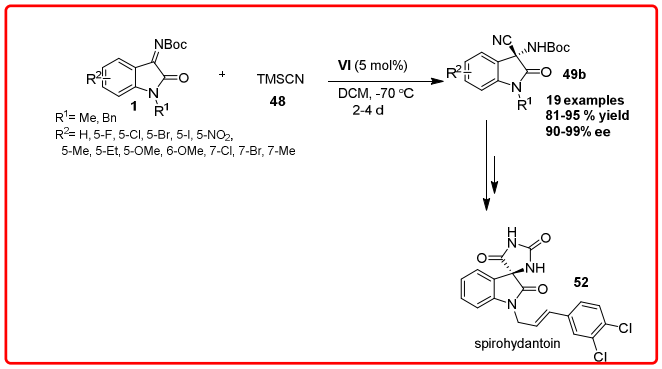
The proposed transition state **TS 20** for the enantioselective cyanation reaction involves H-bonding activation of the ketimine through thiourea moiety and simultaneous generation of nucleophilic cyanide from TMSCN by tertiary amine of the *Cinchona* alkaloid (**Scheme 26**).

The diastereoselective synthesis of 3-amino-3-cyano-oxindoles **49b** was reported by Sacchetti and coworkers using auxillary-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.**



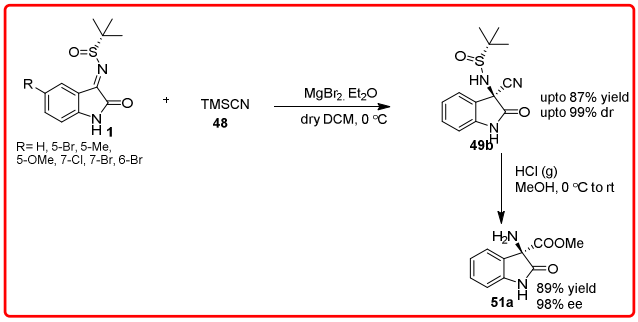
Scheme 27: Addition of TMSCN to chiral isatin imines.

Shortly after this, Zhou *et al*. reported the asymmetric Strecker reaction of isatin imines catalyzed by Cinchonidine derived thiourea **VI** for the asymmetric synthesis of 3-amino-3-cyanooxindoles **49** in high yield (81-95%) and with excellent enantioselectivity (90-99% *ee*) (**Scheme 28**).[43]



Scheme 28: *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 auxillary based approach for highly diastereoselective Strecker reaction of isatin sulfinyl ketimines (Scheme 29).[44] The addition of TMSCN **48** to isatin sulfinyl imines **1** 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.

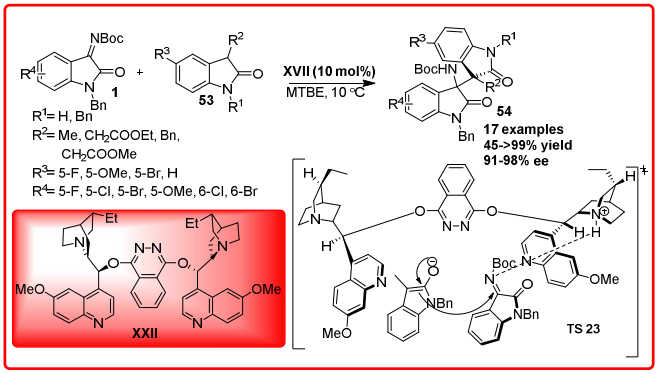


Scheme 29: Lewis acid catalyzed diastereoselective addition of TMSCN to *N*-sulfinyl isatin imines.

(8) Michael reaction

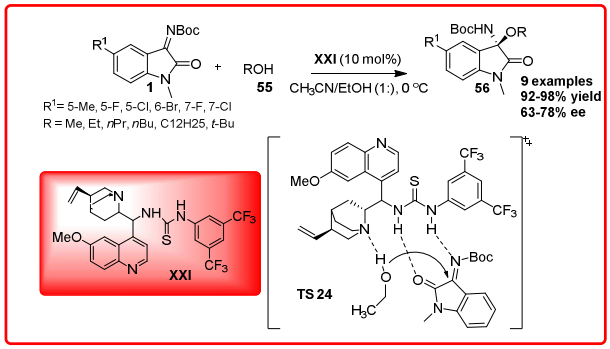
The Michael addition reaction plays an important role among the numerous carbon–carbon bond forming reactions[45] which involves the addition of various active methylene compounds to the electron deficient alkenes. In the past few years, numerous classes of nucleophiles have been extensively used in 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%), excellent enantioselectivity (91-98%) and >99:1 *dr* under mild conditions (Scheme 30).[46] In addition to this *N*-benzyl isatin was also found to be reactive providing the desired adduct in good yield (81-88%) but with low enantioselectivity.



Scheme 30: Organocatalytic asymmetric addition of 3-substituted oxindoles to isatin imines.

Based on the experimental results, the transition state **TS 23** was proposed where the isatin imine is activated by quinuclidine nitrogen *via* H-bonding followed by the deprotonation of oxindole enolate which then preferably attacks from *Re* face of the ketimine to give the desired product in high enantiomeric excess. Sha *et al* reported the first asymmetric organocatalytic addition of alcohols **55** to isatin imines **1** using quinine based bifunctional catalyst **XXI** (Scheme 31).[47] 3-Substituted-3-amino-2-oxindoles **56** were obtained in good to excellent yield (92-98%) and 63-78% 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 **1** 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.



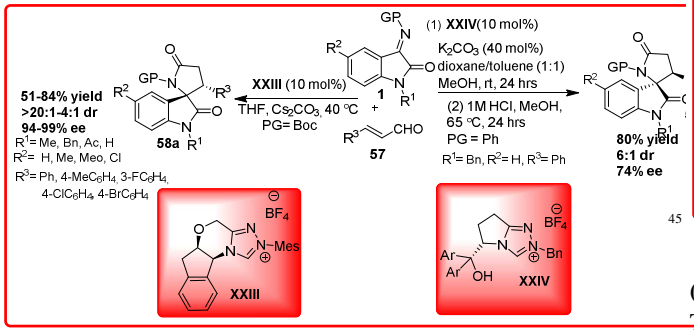
Scheme 31: Quinine catalyzed asymmetric addition of alcohols to isatin imines.

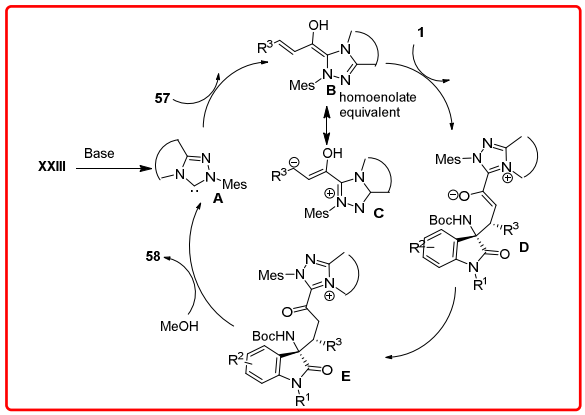
(9) *N*-Heterocyclic carbenes catalyzed reaction

In the past few years, there has been a significant growth in the field of *N*-Heterocyclic carbenes due to their ability to introduce umplong of reaction in aldehydes.[48] 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.[49] However, the reaction of enals by *N*-Heterocyclic carbenes has received great attention. In 2012, Jiao and coworkers reported the asymmetric synthesis of spirocyclic-*γ*-lactam oxindoles **58** using *N*-heterocyclic carbenes **XXIV** for the addition of enals **57** to *N*-aryl isatin imines **1** (Scheme 32).[50] Using 10 mol% of NHC **XXIV** homoenolate 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 1:1-1:6 *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, 6:1 *dr* and 74% enantioselectivity.

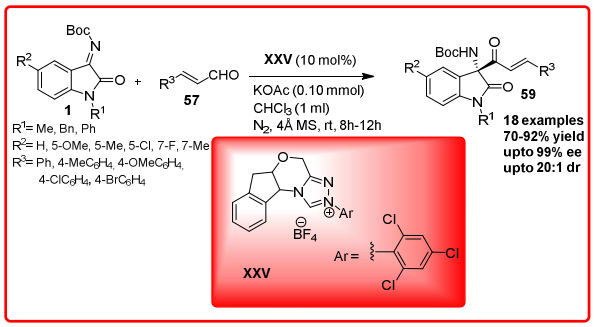
Recently, Chi and coworkers have demonstrated the application of *N*-heterocyclic carbenes **XXIII** for the reaction of enals **57** to isatin imines **1** for the synthesis of spirocyclic-*γ*-lactams **58a** in moderate to good yield (51-84%), good to high diastereoselectivity (4:1 to >20:1 *dr*) and excellent enantioselectivity (94-99% *ee*) (Scheme 32).[51] 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.





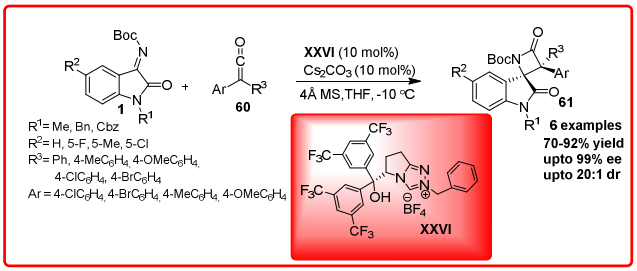
Scheme 32: NHCs catalyzed enantioselective addition of enals to isatin imines.

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).[52] But the reaction to provide the chiral quaternary aminooxindoles **59** in poor to good yield (10-76%) and *er* up to 98:2. Ye and co-workers 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).[53]



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

The product **61** having chiral tetrasubstituted stereocentres was obtained in moderate to good yield (70-92%) with excellent enantioselectity 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.

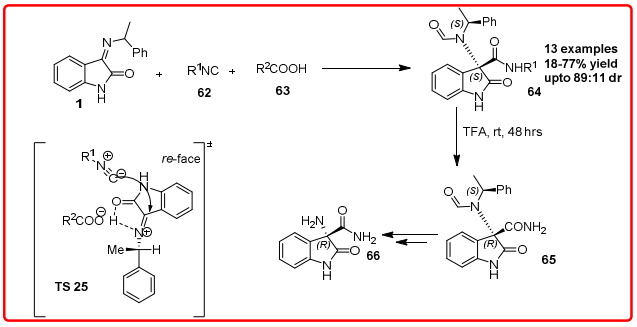


Scheme 34: Enantioselective Staudinger reaction of ketenes with imines.

(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.[54] 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).[55]

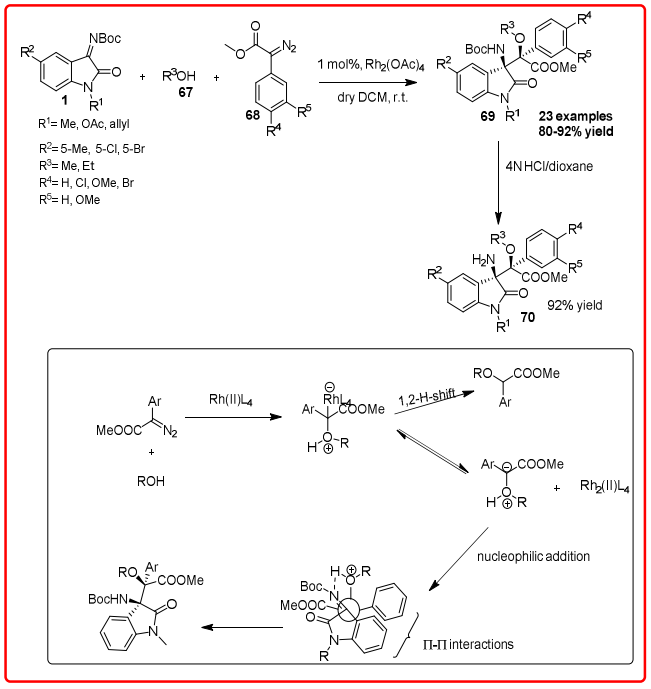


Scheme 35: Asymmetric Ugi-three-component reaction with isatin imines.

(11) Miscellaneous Reaction

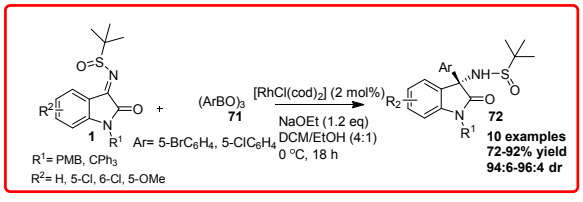
Rhodium-catalyzed reactions are the most versatile for carbon-carbon bond formation among the transition-metal mediated reactions owing to their ability to tolerate a variety of functional

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 $Rh_2(OAc)_4$ to obtain *β*-amino-*α*-hydroxyesters **69** in 80-92% yield, which on deprotection gave **70** in 92% yield (**Scheme 36**).[56] The proposed transition state involves the formation of oxonium ylide from a rhodium carbenoid and alcohol which then attacked the isatin imine **1** 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.

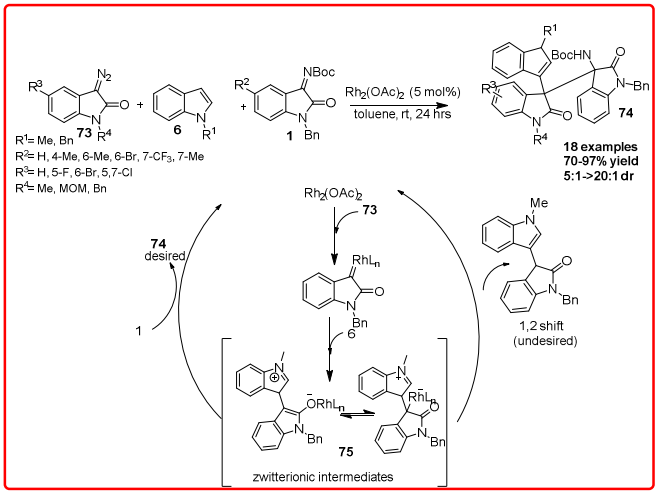
Ellman *et al* realized the diastereoselective synthesis of 3-amino-2-oxindoles **72** bearing a tetrasubstituted stereogenic centre in moderate to good yield (72-92%) with good *dr* (94:6-96:4) *via* $RhCl(cod)_2$ catalyzed reaction of arylboroxines **69** to isatin imine **1** (**Scheme 37**).[57]



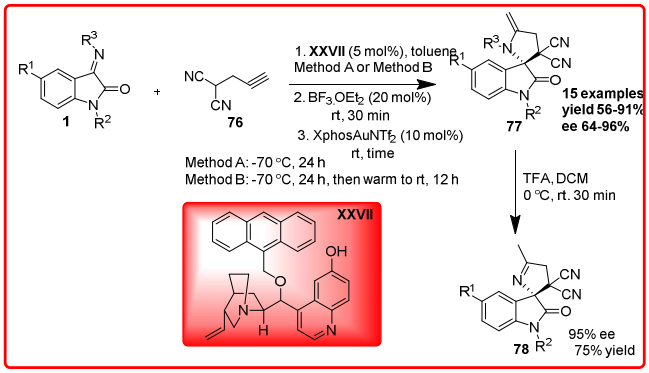
Scheme 37: $RhCl(cod)_2$ catalyzed reaction of arylboroxines to isatin imines.

In 2014, Min Shi and coworkers reported the three component reaction of 3-diazooxindoles **73** with indoles **6** and isatin imines **1**. Using $Rh_2(OAc)_4$ 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**).[58]

Liu *et al* reported an organo-metal catalyzed one-pot sequential Mannich/Hydroamination reaction of isatin imine and propargylated malononitrile (**Scheme 39**).[59] 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.

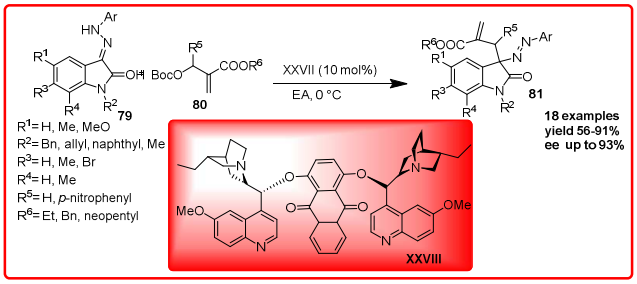


Scheme 38: Rhodium catalyzed 3-component reaction of 3-diazooxindoles with indoles and isatin imines.



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

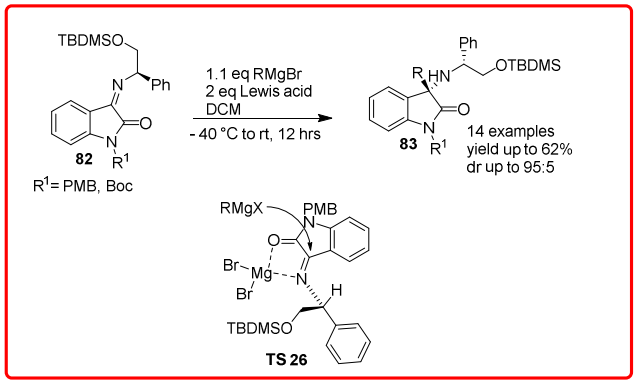
$(DHQ)_2AQN$ catalyzed asymmetric substitution of isatin derived hydrazones was reported by Shi group. Azo compounds incorporating an oxindole scaffold were obtained in up to 91% yield and 93% *ee* (Scheme 40).[60]



Scheme 40: $(DHQ)_2AQN$ catalyzed asymmetric reaction of isatin derived hydrazones with O-Boc-protected *aza*-Morita-Baylis-Hillman adducts.

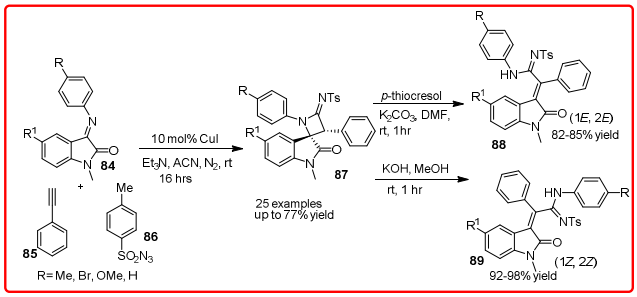
Sacchetti and co-workers reported the addition of Grignard reagent to isatin imine **82** to obtain 3-substituted-3-

aminooxindoles **83** in yield up to 77% and dr up to 95:5. In the proposed transition state **TS 26**, the $MgBr_2$ coordinates 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).[61]



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).[62]



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, Strecker 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

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