

REVIEW



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Synthesis and stereoselective catalytic transformations of 3-hydroxyisoindolinones

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This review focuses on the synthesis of 3-hydroxyisoindolinones, and their application as substrates in stereoselective catalytic transformations reported from 2010 to date. These compounds have attracted much attention among synthetic chemists, as they are integral structural parts of a number of natural products and biologically active compounds. The first part of this review covers methods based on electrochemical, photochemical, and thermal reactions for the synthesis of 3-hydroxyisoindolinones. The second part focuses on their employment as substrates in transition metal-catalyzed and organocatalyzed stereoselective transformations for the preparation of chiral 3-substituted isoindolinone derivatives.

Introduction

The ever-increasing demand for bioactive compounds and materials exhibiting beneficial properties has led to the discovery of new synthetic designs for the incorporation of chemical building blocks that can be easily and strategically modified in a minimal number of operational steps. As such, 3-hydroxyisoindolinones and 3-substituted isoindolinones have attracted much attention among synthetic chemists, as they are integral structural parts of a number of natural products and biologi-

cally active compounds (Scheme 1).^{1–15} Consequently, the synthesis of these structural motifs and the natural products that contain them has been the subject of much elegant and effective research. From a synthetic point of view, the attractiveness of 3-hydroxyisoindolinones lies in the ease of their preparation from relatively cheap and easily accessible chemicals. In addition, the ability to form highly reactive species under mild conditions renders them as an attractive substrates in various transformations for the preparation of 3-substituted isoindolinones, with the emphasis on stereoselective transition metal-catalyzed and organocatalyzed reactions.

Because of the increasing number of publications in the past decade regarding the synthesis of 3-hydroxyisoindolinones and their transformations into chiral 3-substituted isoindolinones, we believe there is a need for a summary

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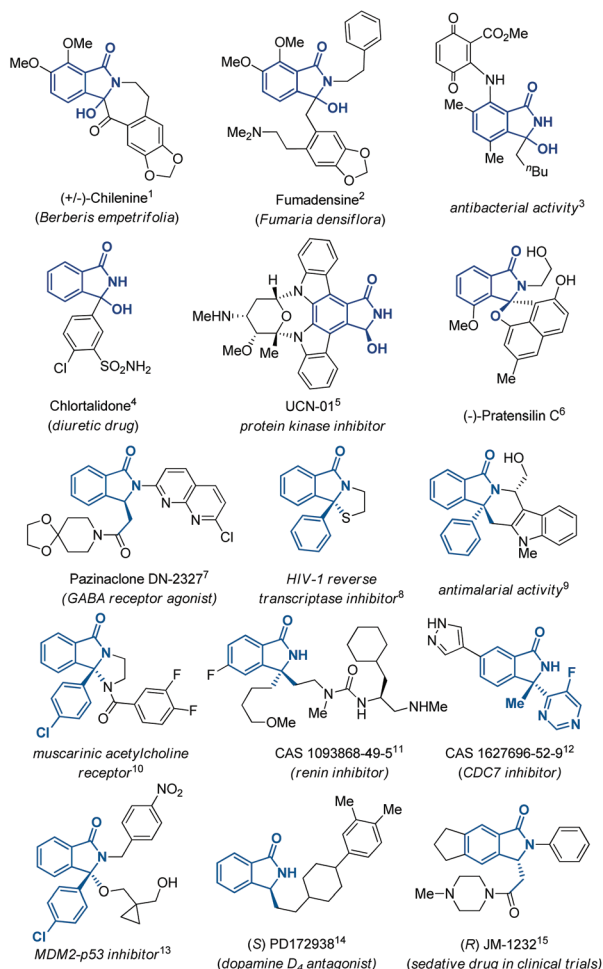
research is focused on a stereoselective organocatalytic transformations.

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Scheme 1

of achievements involving these quite versatile compounds. Some excellent reviews addressing the synthesis of chiral 3-substituted isoindolinones have been published in recent years. In 2018, a section of Cheng's and Shao's review on organocatalytic transformations based on five-membered cyclic imines is devoted to stereoselective transformations of 3-hydroxyisoindolinones.¹⁶ Most recently, Peng's summary on general catalytic stereoselective synthesis of isoindolinones included examples of nucleophilic additions to ketimines derived from 3-hydroxyisoindolinones.¹⁷

By summarizing the literature from 2010 to date, the goal of this comprehensive review is to give an overview of the synthetic methods developed for the preparation of 3-hydroxyisoindolinones, and their employment as substrates in the stereoselective catalytic transformations yielding chiral 3-substituted isoindolinones. All of the depicted examples were selected in a way that emphasizes the important advantages of individual methodologies, as well as their limitations. The numbering of structures in schemes follows the numbering of the corresponding compounds in the associated text and – despite structural similarities – each type of reagents and products were assigned with their own number.

Synthesis of 3-hydroxyisoindolinones

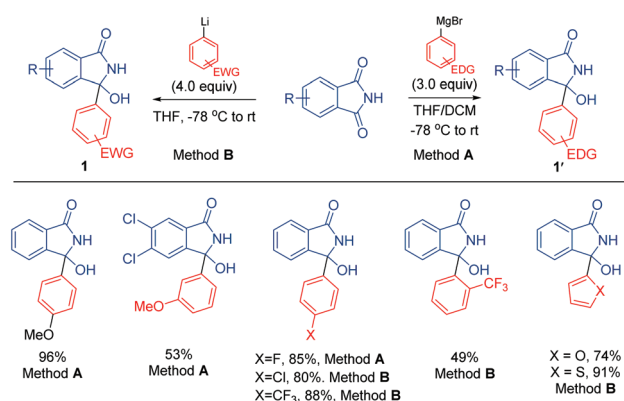
To this end, methods based on electrochemical, photochemical, and thermal reactions for the synthesis of 3-hydroxyisoindolinones, including C–H activation, annulation, and reactions of organometallic reagents have been developed. Among these, addition of organomagnesium or organolithium compounds to phthalimides represents the most straightforward approach to 3-substituted 3-hydroxyisoindolin-1-ones thus avoiding sometimes tedious pre-functionalization of starting materials.

Metal-mediated/catalyzed synthesis

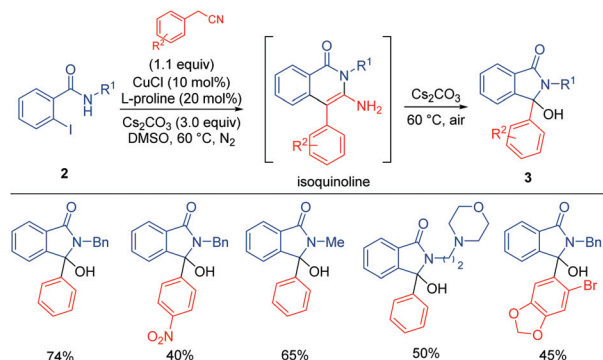
In 2017, Gredičak *et al.* performed a detailed study of the synthesis of 3-aryl 3-hydroxyisoindolinones **1** and **1'** comprising various functional groups and unsubstituted phthalimide nitrogen (Scheme 2).¹⁸ Until then, methods for their preparation either did not tolerate wide range of functional groups, or yielded 3-hydroxyisoindolinones as *N*-substituted products, which made them inapplicable as substrates for the stereoselective transformations. Phenyl substituents with electron donating groups were easily introduced by employing the Grignard reaction, while electron-poor arenes require a lithium exchange or direct lithiation strategy. The protocols tolerated various functional groups on the nucleophile, and a wide range of 3-hydroxyisoindolinones were afforded in good to excellent yields.

As an extension of their developed strategy for the synthesis of benzopyridoindolone derivatives,^{19,20} Yao *et al.* described a one-pot two-step copper-catalyzed reaction towards 3-hydroxyisoindolinones **3** employing benzyl cyanide as benzoyl synthon (Scheme 3).²¹ Intermolecular annulation of 2-iodobenzamides **2** and variously substituted benzyl cyanides in the presence of CuCl and Cs₂CO₃ gave a range of target compounds possessing sterically and electronically divergent substituents. Effectiveness of the reaction was drastically improved by using L-proline as a complexation ligand. A two-step process consists of formation of 3-aminoisoquinolinone intermediate followed by ring contraction accessing the isoindolinone structure.

It is important to note that when ethylcyanoacetate and malononitrile were employed, only isoquinoline products were formed, even after prolonged reaction time.



Scheme 2



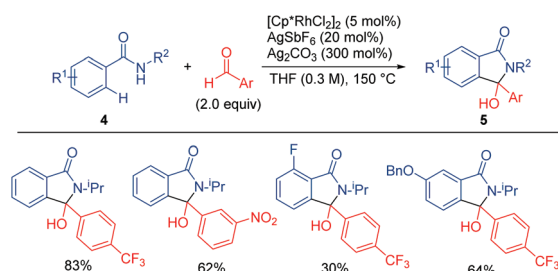
Scheme 3

On the ground of previously established method for C–H functionalization of benzamides,²² Kim *et al.* developed a route to 3-hydroxyisoindolinones **5** based on *ortho*-directed C(sp²)–H bond activation/acylation/intramolecular amino cyclization relay.²³ A cationic Rh(III)-complex derived from [Cp*RhCl₂]₂ and AgSbF₆, in the presence of Ag₂CO₃ as an oxidant, enabled relatively efficient coupling between *N*-substituted benzamides **4** and aromatic aldehydes (Scheme 4).

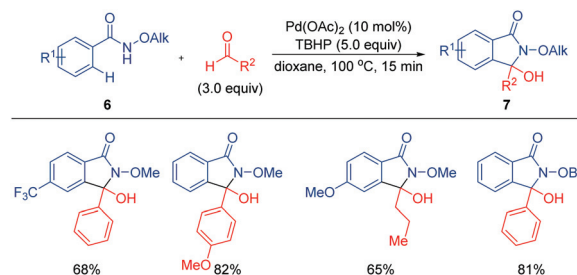
N-Isopropyl benzamide gave products in significantly higher yield compared to other substitution patterns (Me, ⁱBu, ^tBu, MeO, Ph, Ts, Bn). Reaction conditions tolerated a wide range of substitution functionalities on both reaction partners, though increased electron density on the aldehyde ring drastically diminished its reactivity, presumably because of the problem associated with metal insertion into aldehyde C–H bond.

In 2013, Huang, Zhao *et al.* performed similar transformation between *N*-alkoxy benzamides **6** and aldehydes in a reaction catalyzed by Pd(OAc)₂, and with *tert*-butyl hydrogen peroxide (TBHP) as an oxidant (Scheme 5).²⁴ A fast tandem C–H activation/annulation process yielded *N*-protected 3-hydroxyisoindolinones **7** at elevated temperatures in mere minutes.

A successful example with *N*-methyl benzamide as reactant was also presented, though *p*-toluenesulfonic acid (20 mol%) was required as an additive. Unfortunately, the reaction did not occur when heteroamides were employed, such as *N*-methoxypicolinamide and *N*-methoxynicotinamide. The authors investigated the reaction mechanism, and proved that



Scheme 4



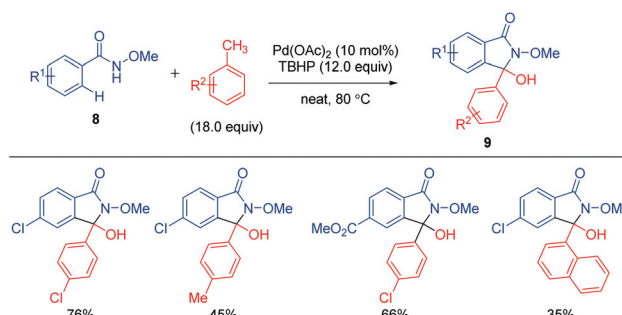
Scheme 5

the transformation is a radical process initiated by nitrogen, and that reductive elimination of Pd occurs after the cyclization.

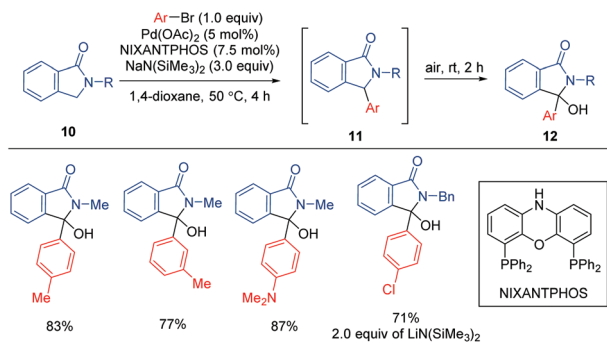
Li *et al.*²⁵ developed Pd(OAc)₂-catalyzed reaction between *N*-methoxy benzamides **6** and phenylglyoxylic acids in almost identical fashion as Huang and Zhao. The main difference is the employment of ammonium persulfate (NH₄)₂S₂O₈ as an oxidant instead of TBHP. The reaction was performed at room temperature, and the majority of obtained 3-hydroxyisoindolinones were isolated in >60% yield.

In contrast to previous examples where aldehydes were employed in metal-catalyzed annulation of benzamides, Zhang and co-workers developed Pd-catalyzed *ortho*-directed acylation/annulation sequence with toluene derivatives and *N*-methoxy benzamides **8**.²⁶ Interestingly, the presence of any solvent had detrimental effect on the reaction outcome. Hence, the reaction had to be performed in neat toluene-derived reagents with large excess of the oxidant. In general, electron-deficient toluenes afforded higher yields of product **9**, compared to electron-rich ones, while *o*-methylpyridine was unreactive (Scheme 6).

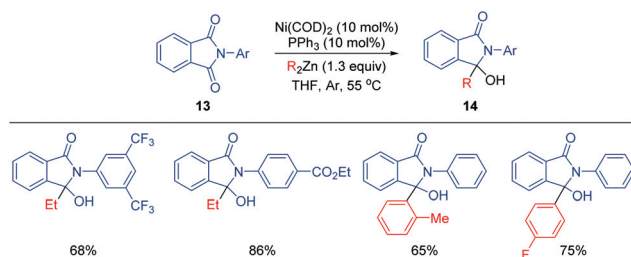
While previously described transition metal-catalyzed methods for accessing 3-aryl-3-hydroxyisoindolinones were based on C(sp²)–H activation of benzamides, Walsh reported Pd(OAc)₂/NIXANTPHOS tandem C(sp³)–H activation/arylation/oxidation functionalization of *N*-substituted isoindolinones **10**.²⁷ Under strongly basic conditions, one-pot Pd-catalyzed arylation gave the corresponding 3-aryl isoindolinone intermediate **11**, which underwent another deprotonation followed by the reaction with dioxygen to give the final products **12** in good to high yields (Scheme 7).



Scheme 6



Scheme 7



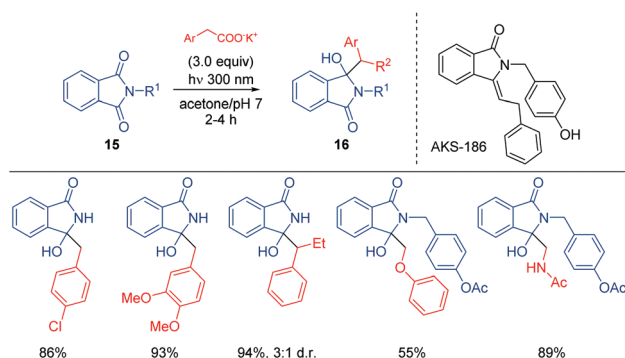
Scheme 8

In 2013, Johnson *et al.* developed a nickel-catalyzed addition of diorganozinc reagents generated from aryl bromides to *N*-protected phthalimides **13** (Scheme 8).²⁸ The methodology enabled the synthesis of variously *N*- and 3-substituted 3-hydroxyisoindolinones **14** in moderate to high yields. The authors noted a limitation in terms of the addition of alkyl ester organozinc reagent, where the product immediately underwent dehydration, thus generating a mixture of alkenes.

It is worth noting that this methodology was suitable for obtaining 3-hydroxyisoindolinones with *ortho*-substituted phenyl rings placed at C3 position of isoindolinone. Johnson *et al.* extended this methodology to the uncatalyzed addition of organozinc nucleophiles to cyclic imides.²⁹ The reaction was limited to phthalimides having heterocyclic *N*-substitutions, implicating that the presence of Lewis basic directing group is required for the reactivity, presumably *via* the coordination of diorganozinc reagent.

Photochemical transformations

In 2010, Oelgemöller *et al.* developed inter- and intramolecular acetone-sensitized photodecarboxylations involving phthalimides **15** to generate 3-substituted 3-hydroxyisoindolinones **16**.^{30,31} In a reaction between phthalimide and potassium phenylacetates irradiated at $\lambda = 300$ nm in a mixture of acetone and pH 7 buffer for up to 5 hours, addition products were generally isolated in excellent yields (Scheme 9). Out of 18 reported examples, 2 of them were products of addition of branched phenylacetates that generated products in moderate diastereoselectivity. The authors extended their photodecarboxylation methodology to *N*-(*p*-acetoxy)benzyl substituted



Scheme 9

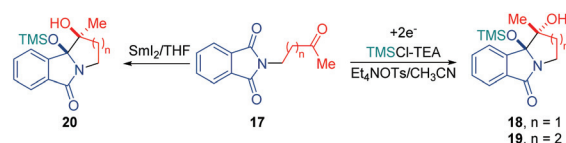
phthalimides by performing irradiation at $\lambda = 300$ nm in aqueous acetone.³²

Obtained products can easily be dehydrated in a sulfuric acid-catalyzed reaction to produce alkylidenes in excellent yields and high *E*-selectivities. Since under these conditions acetoxy-substituted derivatives underwent partial hydrolysis of the ester group, dehydration of these compounds was achieved in the mixture of acetone, water, and concentrated HCl. This enabled synthesis of AKS-186³³ – a compound reported to inhibit thromboxane A2 induced vasoconstriction – and its analogues.

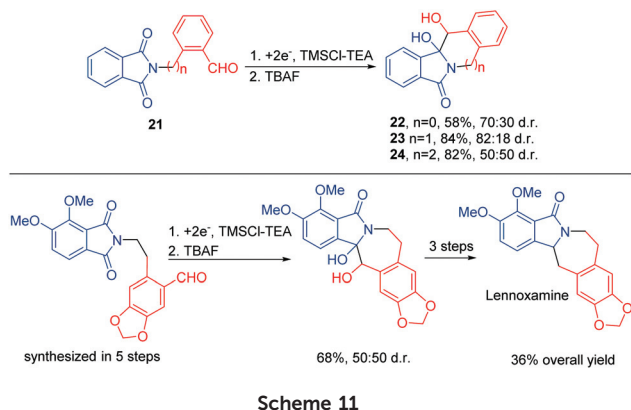
Electrochemical reactions

In 2010, Kise and Sakurai developed intramolecular electroreductive coupling of methyl ketone-containing phthalimides **17** to generate five- (**18**) and six-membered (**19**) *trans*-cyclized 3-hydroxyisoindolinones (Scheme 10).³⁴ Reaction conditions included trimethylsilyl chloride (TMSCl) and triethylamine (TEA) as the essential additives for the success of the transformation, tetraalkylammonium salt in acetonitrile as the catholyte, and lead cathode of the divided cell. On the other hand, by using previously reported SmI₂ in THF for the reductive cyclization,³⁵ products **20** were obtained in *cis* form. Both reactions can be extended to aldehydes, though with somewhat lower yields and stereoselectivities. Obtained products were quantitatively transformed into *trans* 1,2-diols by employing TBAF in THF. Unfortunately, systematic investigation of the substrate scope was not conducted beyond model examples.

The Kise group extended this methodology to the intramolecular reaction with aromatic aldehydes **21** to generate five-, six-, and seven-membered fused cyclic products **22–24** in moderate to very good yields, and moderate diastereoselectivity (Scheme 11).³⁶ Although the substrate scope was not pre-



Scheme 10



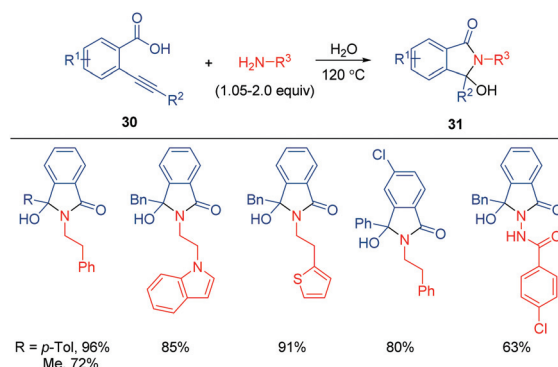
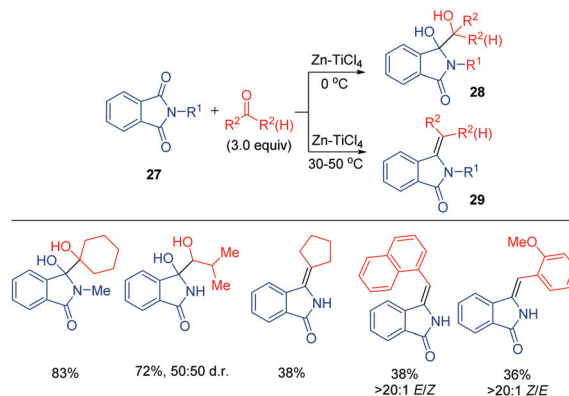
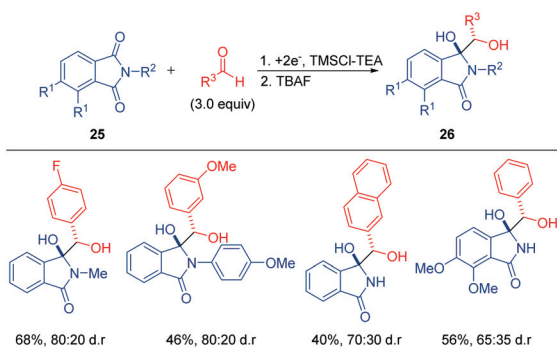
sented, the transformation was successfully employed as the key step in the synthesis of naturally occurring isoindolobenzazepine alkaloid lennoxamine³⁷ in 36% overall yield.

In 2012, the same group employed this methodology in an intermolecular reaction between phthalimides **25** and aldehydes.³⁸ Electroreductive coupling followed by deprotection afforded 3-hydroxy-3-(1-hydroxyalkyl)isindolinones **26** in moderate yields and diastereoselectivities (Scheme 12). The reaction was tolerant of aromatic and aliphatic aldehydes, as well as *N*-protected and *N*-unsubstituted phthalimides.

The authors also reported reaction of phthalimides **27** with symmetric ketones in reductive coupling with low-valent titanium generated from Zn-TiCl₄.³⁹ Depending on the reaction conditions (temperature and equivalents of Zn and TiCl₄), the reaction can yield either two- or four-electron reduced products (Scheme 13). When the reaction was performed at 0 °C, pinacol derivative **28** was isolated as the sole product, while elevating the reaction temperature to 50 °C afforded exclusively alkylidenes **29**. The reaction was also tolerant on aldehydes, however, both types of products were mostly obtained as mixtures of stereoisomers.

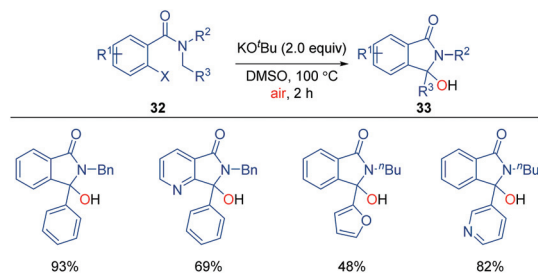
Miscellaneous

J. Zhao, F. Zhao and co-workers developed an eco-friendly method for the construction of 3-hydroxyisindolinones **31** involving 2-alkynylbenzoic acids **30** and nitrogen-containing



nucleophiles (Scheme 14).⁴⁰ This catalyst-free and additive-free cascade reaction performed in water represents a high atom and step-economy process, featuring readily available starting materials and broad substrate scope.

Another transition metal-free and environmentally friendly approach towards 3-hydroxyisindolinones utilized earth-abundant alkali metal salts, and air as oxygen atom donor.⁴¹ The KO^tBu mediated C-C coupling and subsequent C(sp³) hydroxylation for the regioselective synthesis of substituted 3-hydroxyisindolinones **32** was achieved with various *ortho*-halobenzamides **33** providing hydroxylated products, and some of them exhibit antitumor and anti-inflammatory properties (Scheme 15). The fluoro-, chloro-, bromo-, and iodo-substituted substrates afforded products in descending yields, respectively. These observations indicate a nucleophilic substitution as one of the mechanistic steps where the leaving group ability of the halide shows a clear trend (F > Cl > Br > I). Control experiments performed without base provided only 3-substituted isoindolinones, while replacing air with isotopically labeled ¹⁸O afforded product with ¹⁸O hydroxyl group. This observation strongly supports the indication of air as oxygen donor. In addition, reaction in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) proceeded uneventfully, thus ruling out the formation of radical species.

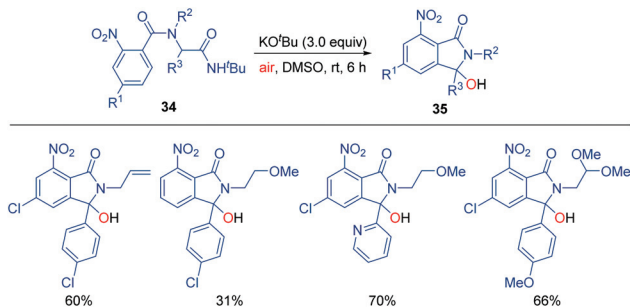


Scheme 15

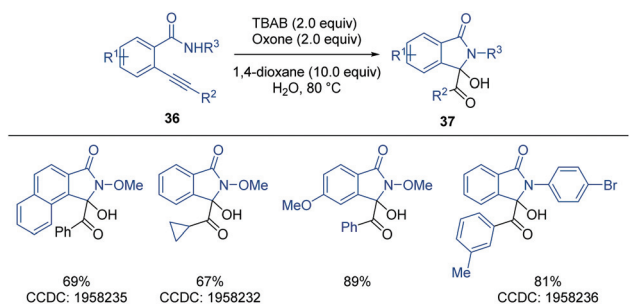
In a similar fashion, products obtained from Ugi reaction of *o*-nitrobenzoic acid derivatives can be converted to the corresponding 3-substituted-3-hydroxyisoindolinones **35** under basic conditions.⁴² Cyclization of Ugi adducts **34** triggered by KO^tBu involves S_NAr/deamidification/oxidation process under aerobic and mild conditions (Scheme 16).

An access to 3-substituted 3-hydroxyisoindolinones **37** was disclosed *via* 1,4-dioxane-mediated hydroxylhydrative aza-cyclization of 2-alkynylbenzamides **36**.⁴³ In this *N*-centered radical pathway, regioselective 5-*exo-trig* cyclization afforded an array of 3-hydroxyisoindolinones bearing different classes of substituents (Scheme 17). As this transformation proceeds in tap water, it represents a “greener” route compared to other methodologies.

Bromine sources other than *n*-tetrabutyl ammonium bromide (TBAB) such as KBr, ZnBr₂, and NBS gave inferior results. Isotope labeled experiments with H₂O¹⁸ revealed that



Scheme 16



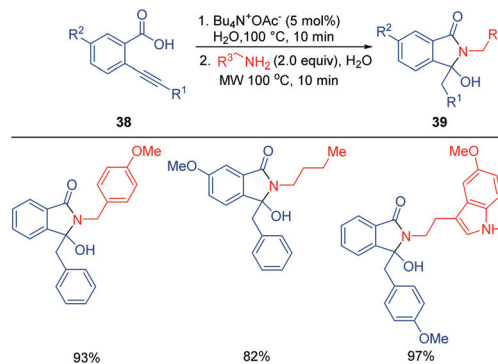
Scheme 17

the hydroxyl and carbonyl oxygen atoms in products came from water.

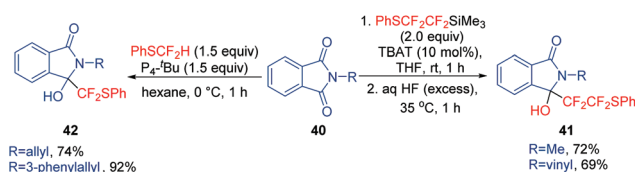
A mild and effective phase-transfer-catalyzed synthesis of 3-hydroxyisoindolinones **39** from 2-alkynyl benzoic acids **38** and primary alkyl amines was achieved under microwave irradiation by Liu *et al.* (Scheme 18).⁴⁴ The reaction can be performed without microwave irradiation, as well as with other tetrabutylammonium salts, and is tolerant of a wide range of substrates without any significant limitations. Reaction mechanism includes formation of lactone under phase-transfer conditions, followed by aminolysis with a primary amine, and intramolecular nucleophilic addition.

Beier *et al.* investigated fluoride-catalyzed nucleophilic addition of trimethyl(1,1,2,2-tetrafluoro-2-phenylsulfanylethyl) silane (PhSCF₂CF₂SiMe₃) – a tandem anion and radical tetrafluoroethylene synthon – to *N*-substituted cyclic amides **40** (Scheme 19, right).⁴⁵ Within the general study of this methodology, two examples included formation of 3-hydroxyisoindolinones **41**. In the reaction catalyzed by tetrabutylammonium triphenyldifluorosilicate (TBAT) as the initiator, tetrafluoroethyl-containing products were isolated as TMS ethers, which were converted to target products with an excess of aqueous hydrofluoric acid.

Soorukram *et al.* reported difluoromethylation of non-enolizable carbonyl compounds by employing difluoro-(phenylsulfanyl)methane (PhSCF₂H) (Scheme 19, left).⁴⁶ Within the performed systematic study, two products **42** were the result of additions to *N*-protected phthalimides. The key to success of this transformation was the use of phosphazene (P₄-^tBu) as a base to generate PhSCF₂[−], and to avoid α-elimination of a fluoride anion from thus formed difluoroalkylating species.



Scheme 18



Scheme 19

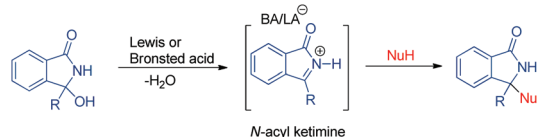
Stereoselective transformations of 3-hydroxyisoindolinones

The most straightforward way to functionalize 3-hydroxyisoindolinones includes Lewis- or Brønsted-acid activation of hydroxy group, followed by its elimination *via* rearrangement of electron pair on adjacent nitrogen atom, which leads to the formation of highly reactive *N*-acyl ketimine species. Electrophilic nature of formed ketiminium ions allows addition of various carbon- and heteroatom-based nucleophiles and hydrides, thus expanding the repertoire of compounds otherwise inaccessible by other methods (Scheme 20).

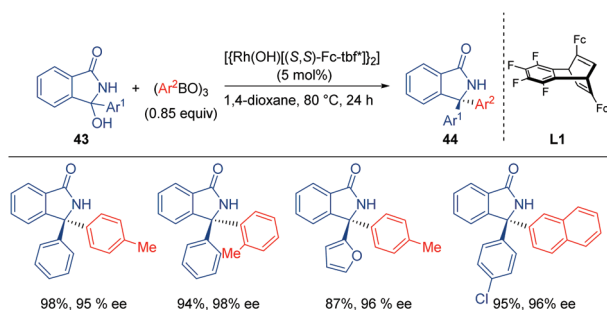
It follows that the employment of the chiral catalyst would result in the stereochemical induction in the formed products. Needless to say, this strategy was exploited in various transition metal-catalyzed and organocatalyzed stereoselective transformations of 3-hydroxyisoindolinones.

Transition metal-catalyzed reactions

In 2013, Nishimura and Hayashi developed a rhodium-catalyzed stereoselective arylation of cyclic *N*-carbonyl ketimines generated *in situ* by dehydration of 3-aryl 3-hydroxyisoindolinones **43** with arylboroxines, thus providing an access to diaryl-substituted isoindolinones **44** bearing quaternary center of chirality (Scheme 21).⁴⁷ Arylboroxines have dual role: they are both dehydrating reagents for the generation of ketimines, and arylating reagents in the subsequent rhodium-catalyzed arylation. The highest catalytic activity was observed with the hydroxrhodium complex coordinated with chiral ferrocenyl substituted tetrafluorobenzobarrelene (tb⁺) ligand **L1**. A variety of 3-aryl groups with electron-donating and electron-withdrawing substituents at the *ortho*, *meta*, and *para* positions



Scheme 20

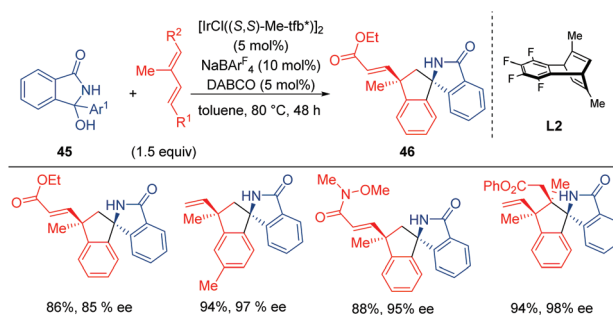


Scheme 21

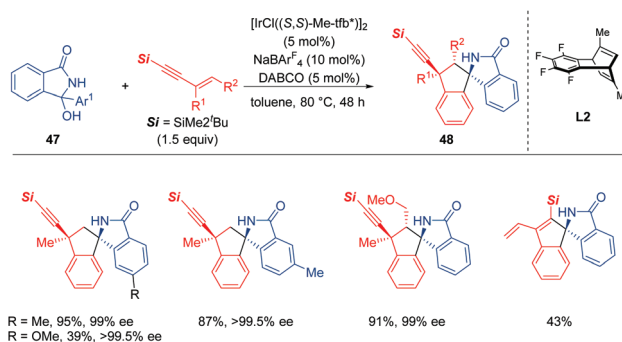
reacted successfully with a range of arylboroxines to give the addition products in high yield and enantioselectivity.

Nishimura *et al.* extended this methodology to stereoselective [3 + 2] annulation between *N*-acyl ketimines and 1,3-dienes catalyzed by cationic Ir/chiral diene complex.⁴⁸ The use of chiral diene ligand **L2** enabled stereoselective annulation providing chiral spiroisoindolinones **46** in high yields, and regio- and enantioselectivities. Catalytic system consisting of [IrCl((*S,S*)-Me-tfb*)]₂, DABCO and NaBAr^F₄ effectively annulated various 3-aryl 3-hydroxyisoindolinones **45** and different 1,3-dienes (Scheme 22).

Developed methodology was further extended to enantioselective [3 + 2] annulation of cyclic aromatic ketimines with 1,3-enynes to give 3-alkynyl-1-aminoindane derivatives.⁴⁹ Under the identical reaction conditions as for the annulation with 1,3-dienes, the reaction between hemiaminals **47** and conjugated enynes bearing *tert*-butyldimethylsilyl group at the alkyne terminus afforded annulation products **48** in >99% ee in almost all investigated cases (Scheme 23). Enantioselectivity of the reaction with hemiaminals bearing *para*-substituted aryl group remained high, however, the yield and reaction time depended on the electronic nature of the substituent. Only a trace amount of the annulation product was obtained with the *para*-methoxy group (yield increased to 39% using 15 mol% of DABCO), while longer reaction time was needed for the reaction with *para*-chloro substituent. Most probable explanation for this observation is because the electron-withdrawing chloro group slows down dehydration of the parent 3-hydroxyisoindo-



Scheme 22



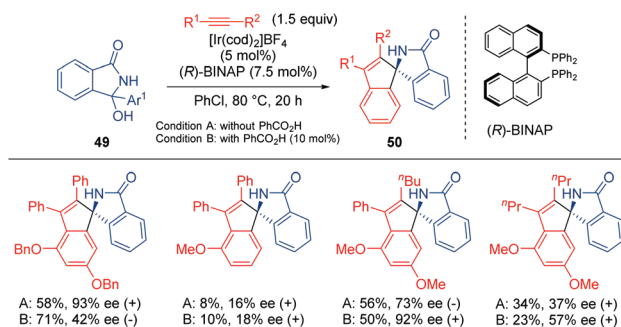
Scheme 23

linone to the reactive ketimine. The formation of a single regioisomer was observed in the reaction with *meta*-substituted hemiaminals, where the reaction occurred at the less hindered *ortho*-position. Sterically hindered 1,3-enyne bearing trisubstituted alkene moiety afforded the annulation product in high enantioselectivity and yield. Interestingly, reaction with unsubstituted enyne resulted in the formation of the conjugated diene where the alkyne moiety participated in the C–C bond formation.

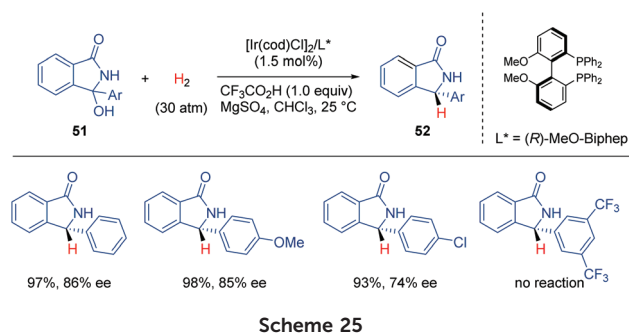
By taking advantage of knowledge obtained in their previous methodologies, Nishimura and co-workers developed a stereoselective annulation of cyclic *N*-acyl ketimines with internal alkynes *via* C–H activation catalyzed by chiral Ir(*R*)-BINAP catalyst system to give spiroaminoindene derivatives **50** (Scheme 24).⁵⁰ The reaction proceeded smoothly with symmetrical and unsymmetrical internal alkynes and 3-hydroxyisindolinones **49** giving products with high regioselectivity. The most interesting observation was the inversion of the stereochemistry in the products induced by a carboxylic acid; in most cases, addition of 10 mol% of benzoic acid switched the enantioselectivity yielding the opposite enantiomer, however, the authors do not give probable explanation for this observation. The same inversion effect was observed in the presence of acetic and pivalic acid.

In 2017, Jia *et al.* developed Ir(*i*)/(*R*)-MeOBiphep complex-catalyzed stereoselective hydrogenolysis of 3-aryl 3-hydroxyisindolinones **51** under 30 atm H₂.⁵¹ The corresponding isindolinone derivatives **52** were afforded in good to excellent yields, whereas enantioselectivities depended on the electron properties of the 3-aryl group. Electron-donating substituents had positive effect on the enantioselectivity, while electron-withdrawing ones lowered the ee values (Scheme 25). Interestingly, the reaction with 3-(3,5-ditrifluoromethylphenyl)-substituent did not yield the product.

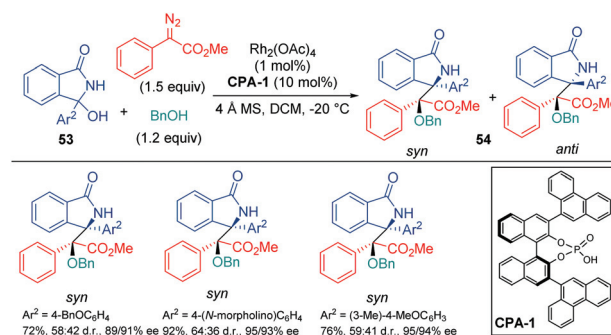
Hu *et al.* described a stereoselective three-component formal S_N1 reaction of oxonium ylides with 3-aryl 3-hydroxyisindolinones **53**.⁵² In a reaction catalyzed by Rh₂(OAc)₄/chiral phosphoric acid **CPA-1** system, isindolinone derivatives **54** with two contiguous quaternary centers of chirality were isolated in high enantioselectivities and moderate diastereoselectivities (Scheme 26).



Scheme 24



Scheme 25



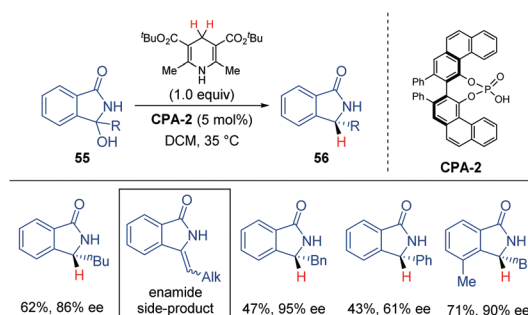
Scheme 26

Control experiments performed without **CPA-1** or with *N*-methylated 3-aryl 3-hydroxyisindolinone did not yield the desired product, thus indicating that the free N–H functionality and chiral phosphoric acid both have a crucial role in the formation of the reactive ketiminium intermediate.

Organocatalyzed reactions

Reduction

In 2012, Zhou *et al.* developed a strategy for the construction of chiral 3-substituted isindolinones **56** through stereoselective transfer hydrogenolysis using di-*tert*-butyl Hantzsch ester as a hydrogen source, and catalyzed by VAPOL-derived chiral phosphoric acid **CPA-2** (Scheme 27).⁵³ Most examples included 3-alkyl 3-hydroxyisindolinones **55**, and the products



Scheme 27

were obtained in moderate yield, and moderate to high enantioselectivities. The competitive process was isomerization of the reactive acyliminium intermediate to the corresponding enamide. Formed enamide did not react in the hydrogenolysis process under standard conditions, suggesting that the tautomerization between the imine and enamide is irreversible, and thus explaining lower yields of the products. Control experiments showed that the reaction does not proceed with *N*-substituted 3-alkyl 3-hydroxyisindolinones, implicating that free N-H group is required for the formation of the ketimine intermediate.

The same transformation utilizing chiral phosphoric acid **CPA-1** was also achieved with 2-phenylbenzothiazoline as the hydride source (Scheme 28).⁵⁴ In this case, the conversion of starting isindolinones **57** and the enantioselectivity in products **58** were greatly affected by the position and electronic nature of the substituents. For instance, almost racemic mixture was obtained with 3-(2-methylphenyl)- and 3-(3,5-dimethyl) phenyl-substituted isindolinones, while the best result (with respect to both yield and ee value) was obtained with electron-donating 3-(4-methoxyphenyl)-substituted substrate.

Shi's approach using SPINOL-derived chiral phosphoric acid **CPA-3** and sterically demanding Hantzsch ester as hydride source was more effective in providing chiral 3-aryl/heteroaryl substituted isindolinones **60** with higher levels of enantioselectivity (Scheme 29).⁵⁵ Various substituted substrates **59** gave satisfactory yields, while enantioselectivity strongly depended on the steric hindrance around the center

of reactivity. For example, hydrogenolysis of *ortho*-cresol substituted isindolinone resulted in a racemic mixture, while *para*-substituted one afforded product in high yield and enantiomeric ratio. 3-Thiophenyl and 3-furanyl containing isindolinones were also reduced effectively, albeit with quite low enantioselective response.

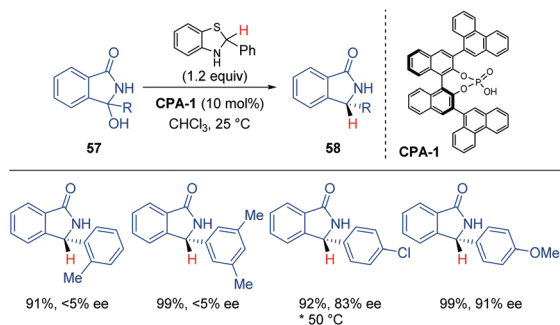
In 2013, You *et al.* developed chiral phosphoric acid **CPA-4** catalyzed hydrogenation of tryptamine-derived hydroxylactams **61** by employing Hantzsch ester as hydride donor, which proceeded uneventfully providing reduced products **62** in satisfactory yields and enantioselectivities (Scheme 30).⁵⁶

Interestingly, when hydroxylactams were submitted to hydrogenation with substoichiometric amount of Hantzsch ester under the standard reaction conditions, an enantio-enriched starting hydroxylactams was isolated as well. This result indicates a moderate kinetic resolution during the stereoselective transfer hydrogenation.

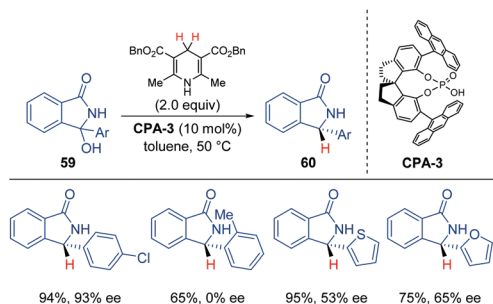
Aza-Friedel-Crafts reaction

The synthesis of enantioenriched 3-indolyl-substituted isindolinones **64** was achieved through stereoselective chiral phosphoric acid **CPA-5**-catalyzed aza-Friedel-Crafts reaction between indoles and 3-hydroxyisindolinones **63** (Scheme 31).⁵⁷

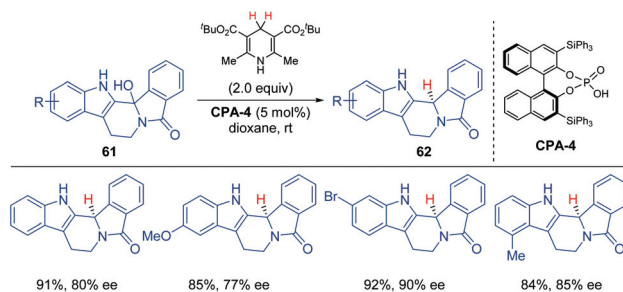
Substitution on indole had little or no effect on the reaction yield, however, the best enantioselectivity was obtained with unsubstituted indole. It is worth noting that the enantiomeric



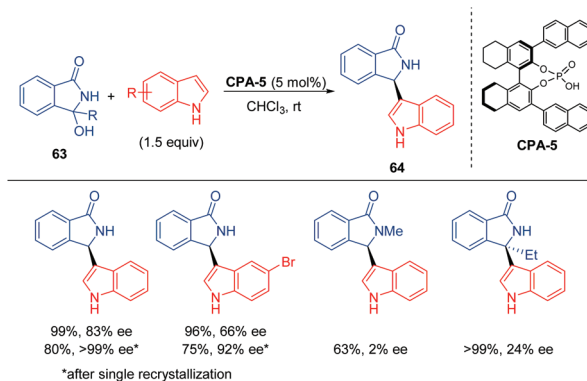
Scheme 28



Scheme 29



Scheme 30



Scheme 31

ratios were significantly improved upon recrystallization. *N*-Methyl substituted isoindolinone gave the product in high yield, but unfortunately without stereochemical induction.

Since the methodology was not particularly effective in the synthesis of products with quaternary centers of chirality, the authors developed a different protocol for this purpose (Scheme 32).⁵⁸ In the arylation of 3-hydroxyisoindolinone **65** catalyzed by chiral phosphoric acid **CPA-4**, 3-alkyl and 3-aryl-3-indolyl isoindolinone derivatives **66** were obtained in high yields and moderate enantioselectivities. Again, a single recrystallization provided products in enantiomerically pure form.

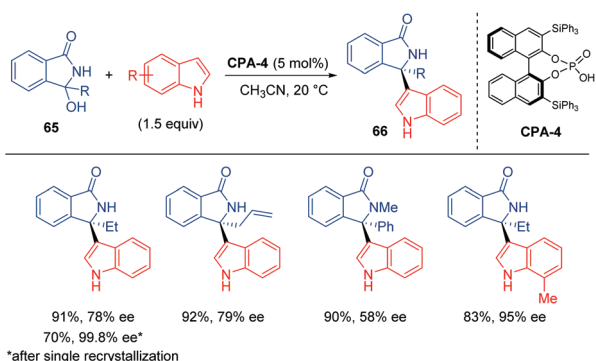
In 2017, Gredičak and You developed a method for the construction of (3-indolyl)-(diaryl)methanamines **68** via a stereoselective addition of indoles to *in situ* generated *N*-acyl imines catalyzed by SPINOL derived chiral Brønsted acid **CPA-6**.⁵⁹ Compared to Wang and Zhou's work which reported a stereoselective aza-Friedel-Crafts reaction of indoles with 3-alkyl 3-hydroxyisoindolinones, here the authors described stereoselective heteroarylation of 3-aryl 3-hydroxyisoindolinones **67** (Scheme 33).

Stereochemical outcome highly depended on the structure of the ketimine, where 3-(3,5-disubstituted)aryl 3-hydroxyisoindolinones provided the best results. Control experiments included reactions with (i) *N*-methylated isoindolinone derivative and (ii) *N*-benzylated indole. In both cases, products were

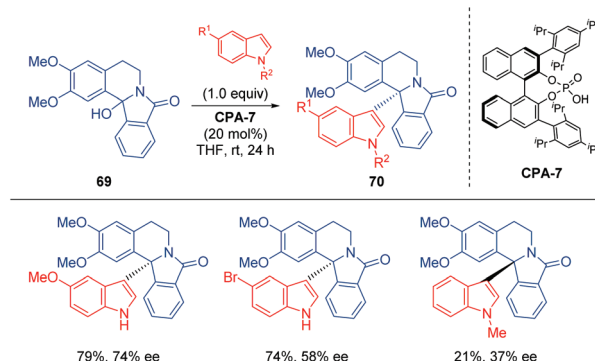
isolated as racemic mixtures, indicating *N*-H of both reaction partners as essential for the favourable interaction with the catalyst.

α -Amidoalkylation of indoles with *N*-acyliminium ions generated from 3-hydroxyisoindolinones **69** using chiral BINOL-derived phosphoric acid **CPA-7** leading to quaternary carbon-containing isoindoloisoquinolines **70** was developed by Lete *et al.* (Scheme 34).⁶⁰ In a limited substrate scope comprising only four examples, indoles with electron-donating groups in C5 position yielded products in moderate yields and enantioselectivity. On the other hand, electron-withdrawing substituent in the same position completely suppressed nucleophilicity of indole. In the reaction with *N*-methylated indole a significant decrease in yield and enantiomeric ratio was observed, along with the inversion of absolute configuration in the product, indicating that hydrogen bonding between *N*-H of indole and chiral catalyst is crucial for the chiral induction.

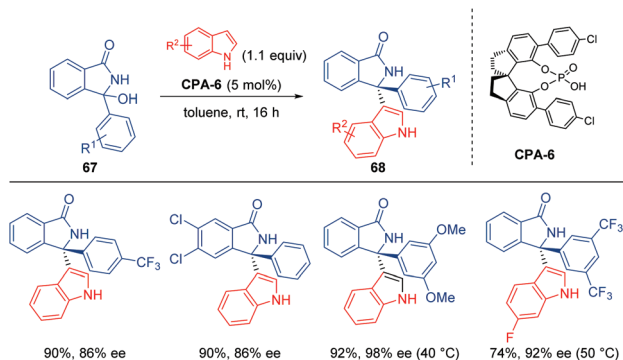
In 2015, Shi *et al.* reported a similar stereoselective aza-Friedel-Crafts reaction between indoles and 3-hydroxyisoindolinones **71** by utilizing a different BINOL-based chiral phosphoric acid **CPA-8** (Scheme 35).⁶¹ Target products **72** were mostly obtained in high yields and enantioselectivities, though substitution patterns on indoles had significant effect on the reaction outcome. The reaction with *N*-methyl indole proceeded smoothly in high yield, albeit with low chiral



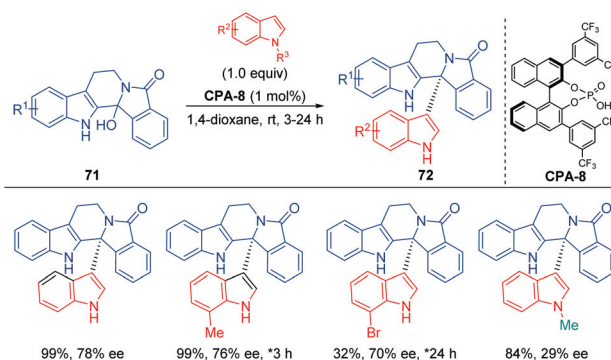
Scheme 32



Scheme 34



Scheme 33



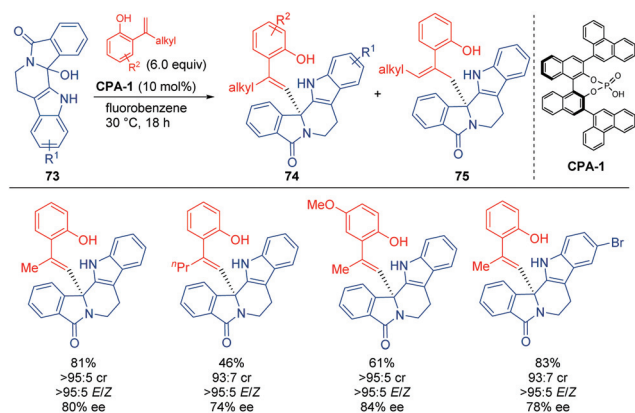
Scheme 35

response, thus confirming previously established conclusions about the importance of *N*-*H* in the stereochemical induction.

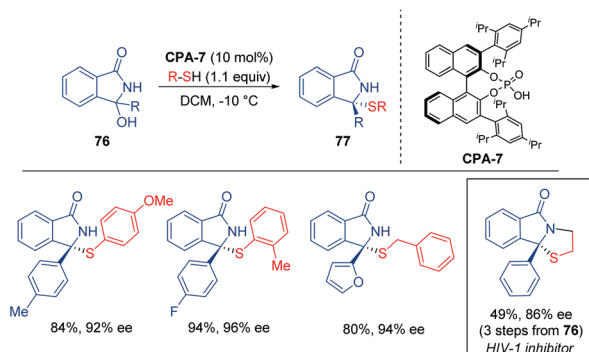
Shi's work on the chiral phosphoric acid **CPA-1** catalyzed stereoselective formal alkenylation of hydroxylactams **73** with *o*-hydroxystyrenes represents an elegant approach to chiral isoindolo- β -carbolines **74** and **75** (Scheme 36).⁶² This method provides a sustainable alternative to alkenylation using metal-based catalysts, and to protocols employing alkenyl metal reagents. Developed strategy was applicable to various indole-derived hydroxylactams having electron distinct substituents positioned on the indole ring yielding products in good to high chemo- and enantioselectivities. It is worth mentioning that in all cases only (*E*)-isomer was formed. Control experiment with *o*-methoxy styrene under the standard reaction conditions did not yield the desired product, indicating that *O*-*H* is essential for the activation of the double bond.

Addition of heteroatom nucleophiles

In 2016, Gredičak *et al.* reported addition of thiols to 3-aryl 3-hydroxyisoindolinones **76** catalyzed by chiral phosphoric acid (*R*)-TRIP **CPA-7** (Scheme 37).⁶³ The transformation afforded a wide spectrum of corresponding thioacetals **77** in excellent yields and enantioselectivities, though *ortho* substitution on 3-phenyl substituent had decremental effect on both



Scheme 36



Scheme 37

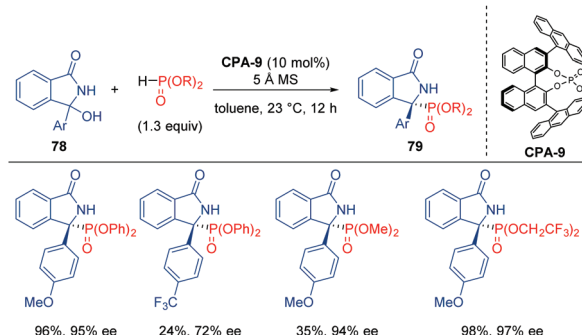
yield and the enantiomeric excess. The utility of the developed protocol was demonstrated in the synthesis of a known HIV-1 reverse transcriptase inhibitor¹³ from **76** in three synthetic steps.

Independently, the Singh group reported the same methodology by employing the same catalyst, though with different reaction conditions (5 mol% catalyst loading, in toluene at 40 °C).⁶⁴ The authors also transformed one of the obtained products into aforementioned HIV-1 inhibitor.

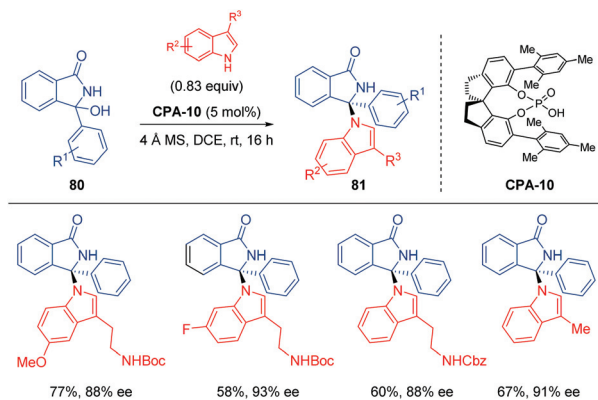
In 2017, Singh *et al.* developed a strategy towards chiral isoindolinone-based α -amino phosphonates **79** having C3 quaternary center of chirality by employing (*S*)-BINOL-derived phosphoric acid **CPA-9**-catalyzed hydrophosphonylation of 3-hydroxyisoindolinones **78** in high yields and enantioselectivities (Scheme 38).⁶⁵ In contrast to aliphatic phosphites, aromatic phosphites had negative effect on the yield, while the enantioselectivity remained high. On the other hand, reaction with bis(2,2,2-trifluoroethyl)-phosphite gave the corresponding phosphonate in high yield and excellent ee values. Authors speculated that the low reactivity of dialkyl phosphites could be contributed to the higher p*K*_a values of the P-*H* bond leading to the inefficient phosphonate-phosphite tautomerism.⁶⁶

Control experiments showed that *N*-methyl isoindolinone did not react with phosphite even at elevated temperatures, thus implicating that the reactive acyliminium intermediate does not form under these conditions. Also, a trace amount of the phosphonate product was formed with trimethyl phosphite as nucleophile suggesting that the OH group is also crucial for the successful transformation.

In 2018, Zhong and Zeng reported a chiral phosphoric acid **CPA-10** catalyzed strategy for the stereoselective intermolecular *N*-alkylation of C3-substituted indoles with ketimines derived from 3-aryl 3-hydroxyisoindolinones **80** providing products **81** (Scheme 39).⁶⁷ The competitive C2-alkylation was completely suppressed under the used reaction conditions, as well as the dearomative cascade (electrophilic attack at C3 of tryptamine derivative, followed by intramolecular trapping of the resulting iminium ion). Control experiments have shown that *N*-protected indole yields C2-alkylation product, and that – as in the majority of previous reports – the reaction with *N*-methylated isoindolinone was unproductive.



Scheme 38



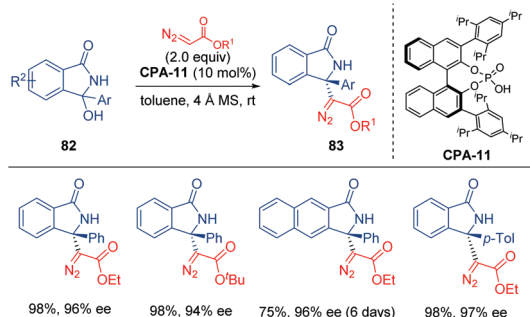
Scheme 39

Addition of carbon-centered nucleophiles

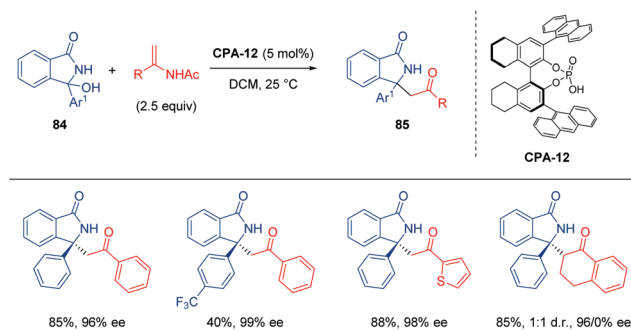
Stereoselective intermolecular addition of diazo esters to functionalized 3-aryl 3-hydroxyisoindolinones **82** afforded chiral isoindolinone-based α -amino diazo esters **83** (Scheme 40).⁶⁸ (*S*)-BINOL-derived chiral phosphoric acid **CPA-11** efficiently catalyzed addition of various α -diazo esters in the Mannich-type reaction providing products bearing quaternary center of chirality.

Substitution on both reaction partners did not significantly affect the stereochemical outcome, however, in some cases the reaction time was prolonged up to six days. In addition, the use of 4 Å molecular sieves was essential to promote the reaction. Unfortunately, under the standard reaction conditions, the transformation was not tolerant on 3-alkyl-substituted 3-hydroxyisoindolinones.

Ma and co-workers developed a stereoselective reaction between 3-hydroxyisoindolinones **84** and acyclic enamides catalyzed by chiral H_8 -BINOL-derived chiral phosphoric acid **CPA-12**.⁶⁹ The reaction takes place tolerating wide substrate scope with respect to both *in situ* generated ketimines and enamides, providing products **85** (Scheme 41). The presence of the electron-withdrawing trifluoromethyl group at the C3-aryl group diminished yield, although enantioselectivity remained high, while reaction proceeded uneventfully with aromatic and heteroaromatic ring-containing enamides. Cyclic enamide was



Scheme 40

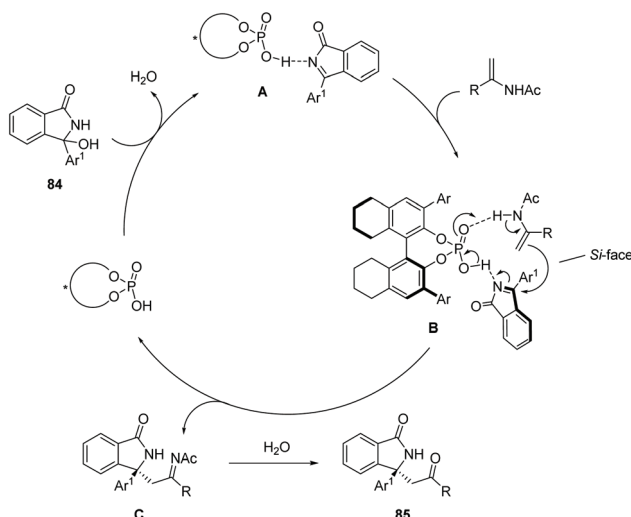


Scheme 41

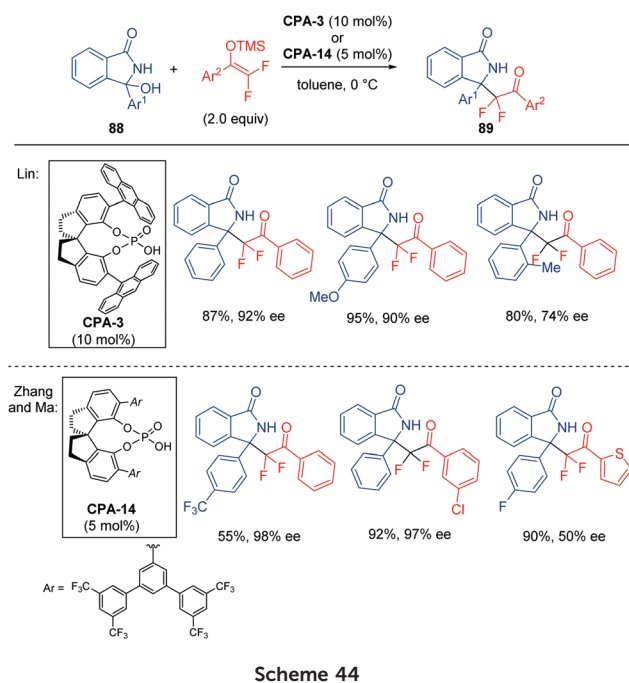
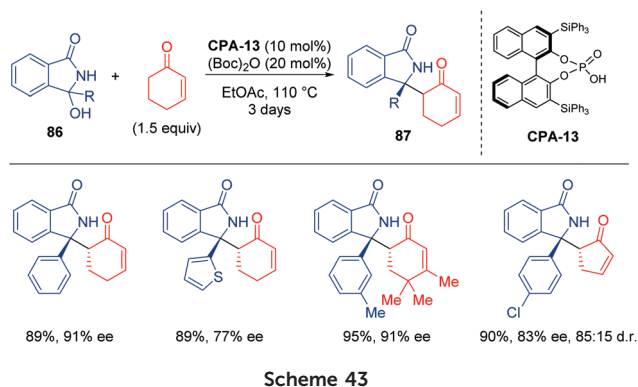
tolerated as well, providing product with two adjacent centers of chirality.

Based on the previous reports and their experimental data, the authors proposed a possible reaction mechanism for the formation of 3,3-disubstituted isoindolinones **85** (Scheme 42). The first step is the activation of hydroxyl group of **84** by chiral phosphoric acid, followed by dehydration to form the reactive ketimine intermediate **A**. Addition of enamide proceeds presumably *via* an aza-ene-type pathway through the intermediate **B** giving rise to the adduct **C**, and regenerating the catalyst. Hydrolysis of imine **C** affords the final ketone **85**.

Stereoselective Mannich reaction between cyclohexenones and 3-hydroxyisoindolinones **86** catalyzed by chiral phosphoric acid **CPA-13** represents a one-step protocol for the synthesis of chiral 3-alkyl isoindolinones **87** bearing adjacent quaternary and tertiary centers of chirality (Scheme 43).⁷⁰ Developed methodology was successfully applied to substrates bearing C3-aryl and heteroaryl groups. On the other hand, the reaction with 3-hydroxyisoindolinones bearing C3-aliphatic substituent resulted in the formation of the corresponding enamide. In contrast to the addition of cyclohexenones where products



Scheme 42



were obtained with good to high yield and stereoselectivity, the reaction with cyclopentenone resulted in diminished ee value. In addition, aliphatic enone, methyl vinyl ketone did not give the desired product.

In 2020, Lin⁷¹ and Zhang and Ma⁷² independently reported chiral phosphoric acid-catalyzed (CPA-3 and CPA-14, respectively) Mukaiyama–Mannich reaction of difluoroenoxyisilanes and *N*-acyl ketimines (Scheme 44). Developed protocols proved to be applicable to a wide range of functionalized hydroxyisoindolinones **88**, and difluoroalkylated products **89** were obtained in high yields and enantioselectivities. While Lin was not able to obtain the product with 2-thienyl-derived difluoroenoxyisilane, Ma's reaction conditions effectively gave the desired product, albeit with low enantioselectivity. On the other hand, alkyl substituted difluoroenoxyisilane was unreactive in both methodologies.

Conclusion

In this review, we summarized recent advances in the synthesis of 3-hydroxyisoindolinones, as well as their applications in the stereoselective catalytic reactions for the preparation of enantioenriched 3-substituted isoindolinones. Methods described for the synthesis of 3-hydroxyisoindolinones are based on electrochemical, photochemical, and thermal reactions, including C–H activation, annulation, and addition of organometallic reagents. Methodologies for their stereoselective transformations are mostly based on chiral phosphoric acid catalysis, though several transition metal-catalyzed processes were successfully developed as well. The emerging number of publications suggests great interest among researchers for these compounds, consequently resulting in a lot of progress made in this field. However, there are still methodologies that remain underexplored in both synthesis and stereoselective transformations of 3-hydroxyisoindolinones, such as (i) free radical reactions, (ii) photoredox catalysis, (iii) more efficient catalytic systems, including dual or relay transition metal-organocatalyzed systems, (iv) cascade protocols for the synthesis of multiple ring systems, (v) construction of two or more centers/axes of chirality in the isoindolinone system, and (vi) QSAR studies of chiral isoindolinones for their employment as lead compounds in drug discovery research. We believe that the following years will see breakthroughs in various strategies for the preparation of these valuable compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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