AN OVERVIEW ON ASYMMETRIC SYNTHESIS OF 3-SUBSTITUTED ISOINDOLINONES

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In memoriam of Prof. Carlos F. Barbas III

Abstract. *We describe the most common methods for the asymmetric construction of the isoindolinone ring system. The discussion begins with early methodologies based on the resolution of racemic mixtures and the use of chiral auxiliaries and then moves to the most recent catalytic approaches. The new technologies include a wide range of synthetic strategies developed by the use of chiral metal catalysts, organocatalysts and chiral phase transfer catalysts. Nevertheless, given the importance of this heterocyclic nucleus, present in a number of natural products and synthetic biologically active compounds, it is easy to predict a further increase of the interest of these compounds in the coming years with the subsequent development of new effective catalytic asymmetric methodologies.*

Contents

1. Introduction

Isoindolinone ring is characterized by a bicyclic nucleus **1** (Figure 1) derived from the fusion of a γ-lactam (ring A) with a benzene ring (ring B). These compounds, also called phthalimidines, are internal amides of the corresponding γ- amino carboxylic acids (Figure 1).

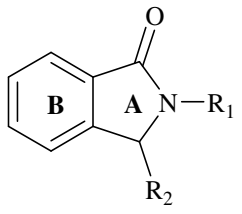

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Figure 1. Isoindolinone nucleus.

The isoindolinone structure has been attracting the interest of scientists since many years. It can be found in a great number of naturally occurring substances variously substituted and functionalized (Figure 2), showing a wide range of biological properties.[1-8]

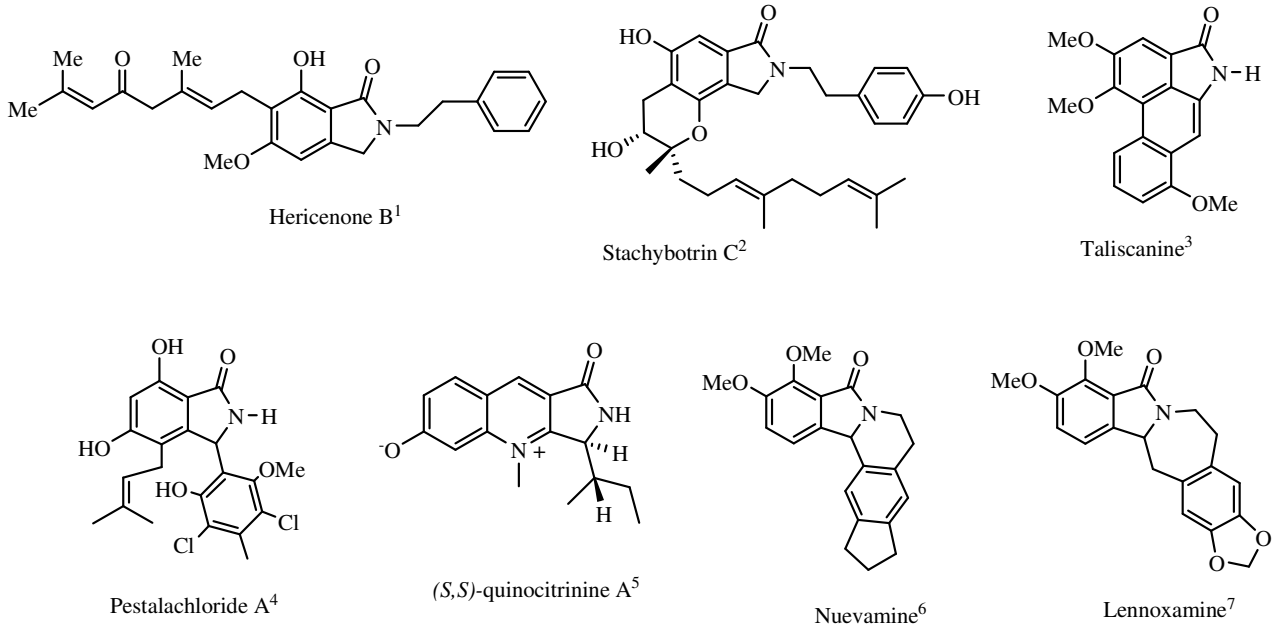


Figure 2. Natural compounds containing isoindolinone nucleus.

Inspired by the Nature often investigators direct their efforts toward the search of new pharmaceuticals represented by small molecules having the structural motif of natural products. In the case of isoindolinone nucleus these efforts led to an impressive number of compounds with biological activity and pharmaceutical applications (Figure 3).[9-23] Among them, many structures present a tertiary or quaternary stereocenter at the lactam ring, hence the importance of asymmetric synthesis in the testing the biological properties of enantio-enriched compounds. The great success in the therapeutic applications and the molecular diversification of these heterocycles is probably related to the variety of effective synthetic strategies developed in the course of the years. Several asymmetric syntheses have been developed, ranging from early methods about the resolution of racemic mixtures and the use of chiral auxiliaries, until more recent times, with the development of relatively few catalytic asymmetric methodologies, giving to this subject still a particular interest for the current organic chemistry.

Based on these introductory considerations, the following review aims to give an overview on the methods of asymmetric synthesis of isoindolinones. This choice derives not only from the interest of our research group, but we believe that this topic can be useful for the scientific community and inspire new researches.

Nevertheless, in the course of the discussion some typical non-asymmetric synthesis will be disclosed, considering that in the early asymmetric methods the resolution of racemates is usually performed in the last stage of the synthetic pathway. For other recent non-asymmetric synthesis of isoindolinones see ref. 24. Previous reviews on isoindolinones have been reported.[25,26] They partially describe synthetic strategies for the construction of this heterocyclic core, even if they do not focus on asymmetric methodologies. The retro-

synthetic analysis for the asymmetric construction of this heterocyclic nucleus involves three main approaches leading to readily available starting materials (Scheme 1).

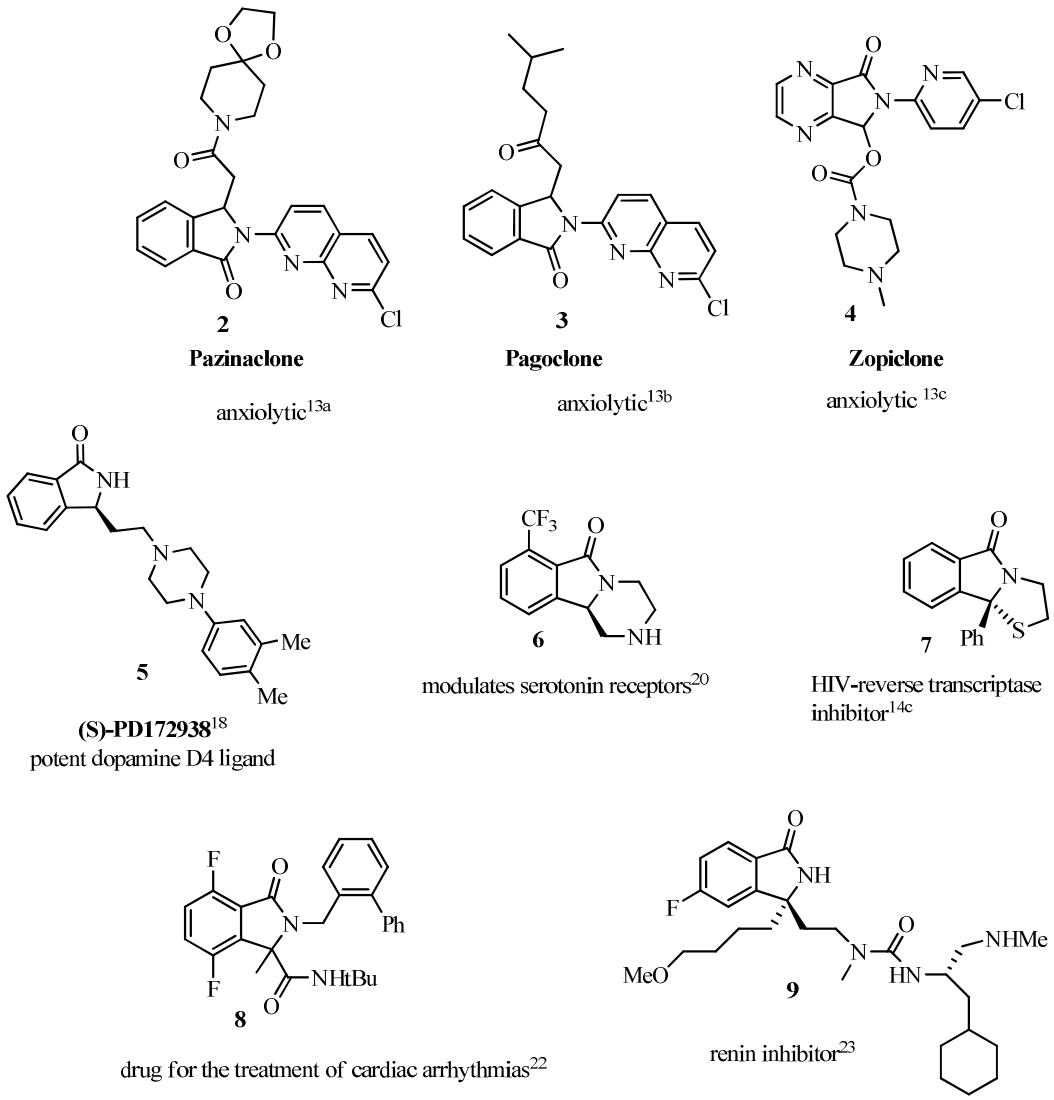
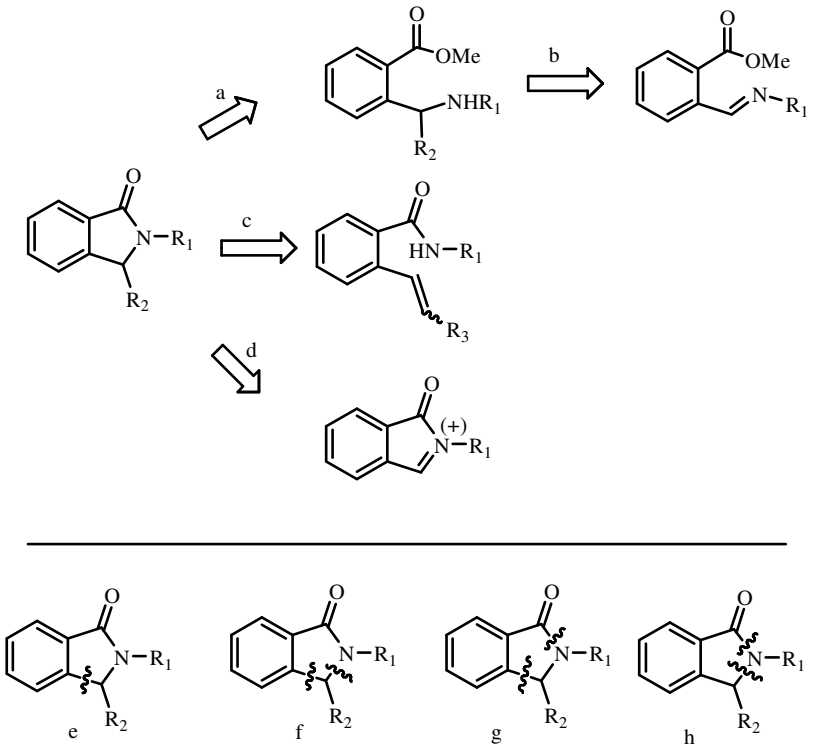


Figure 3. Biologically active compounds containing isoindolinone nucleus.

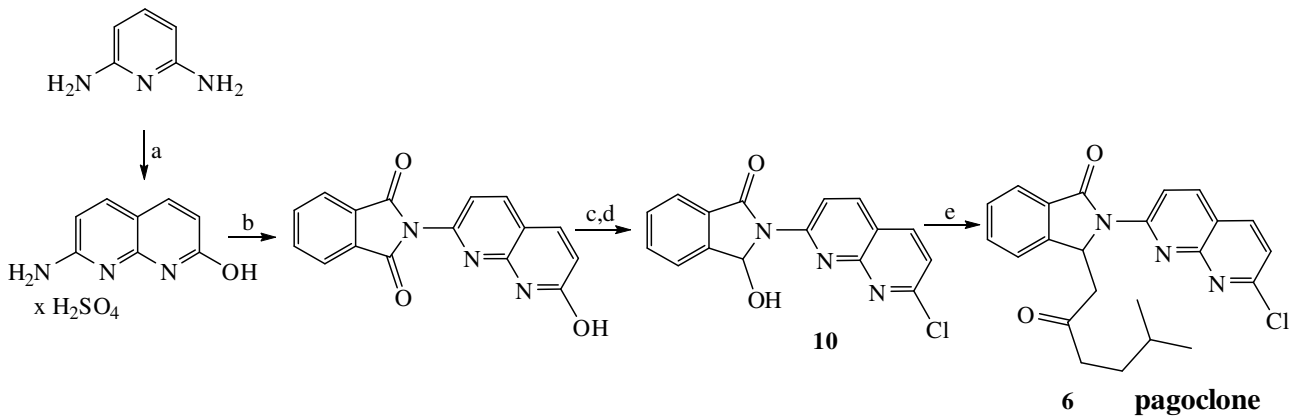
The pathway **a** is common for several tandem methodologies. The lactamization usually follows the formation of a chiral amine, obtained for example after the asymmetric addition at the *o*-imine group (pathway **b**). This can be performed either with a chiral auxiliary installed on the imine or, more effectively, in the presence of a chiral metal catalyst. Also pathway **c** is common: direct attacks of the nitrogen of the amide group at an *ortho*-alkylidene carbon lead to the cyclization and to the formation of the new stereocenter. Asymmetric additions to *in situ* generated iminium ions intermediates have also been reported in several methodologies for the functionalization of preformed isoindolinone rings (pathway **d**). A variety of other synthetic pathways, corresponding to the disconnections **e-h**, can be found in literature in asymmetric as well as in non asymmetric[24] synthesis. They have been performed either as sequences of reactions in multi-steps synthesis or in one-pot cascade reactions. Often, mono- functionalized starting materials are used and their *ortho*-metalation constitutes a viable route in the asymmetric construction of the isoindolinone ring.



Scheme 1. Retrosynthetic strategies and bond disconnections.

2. Asymmetric synthesis of isoindolinones: from early methodologies to catalytic asymmetric synthesis

In view of the biological importance of these heterocyclic compounds and the stringent requirements that the legislation poses with regard to the optical purity of the pharmaceutical substances, it has a long time that synthetic chemists are committed to obtaining substituted chiral isoindolinones in enantiomeric pure form.



Reagents, conditions and yields: a) D,L malic acid, H_2SO_4 conc., 85%; b) Phtalic anhydride, Et_3N, AcOH, 95%; c) $POCl_3$, CH_3CN; d) KBH_4, H_2O, 85%; e) Na_2CO_3, $PPh_3CHCOCH_2CH_2CH(CH_3)_3$, xylene, 82%.

Scheme 2. Efficient and cost-effective synthesis of Pagoclone.

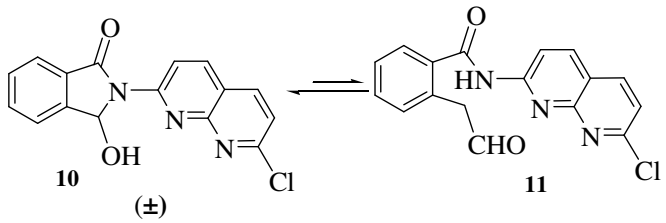
The first successful approaches, based on the resolution by crystallization of racemic mixtures with chiral acids or bases or by chiral stationary phase HPLC, are applied to specific substrates at the end of a synthetic sequence. However, these methodologies lack of efficiency in terms of yields of isolated products.

Thus, in the course of the years, the search of more efficient processes led to use chiral auxiliaries and, more recently, to asymmetric catalysis.

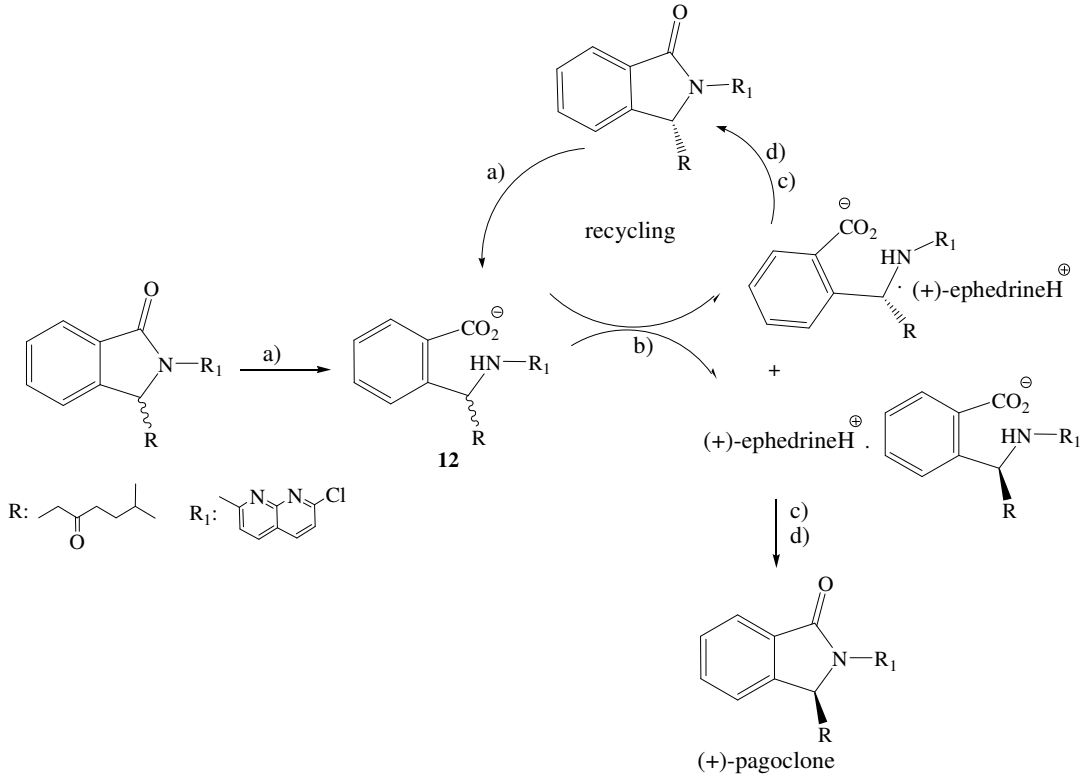
2.1. Resolution of racemic mixtures

In 2003 Stuk et *al.* proposed a practical, scalable and cost-effective commercial synthesis of the anxiolytic pagoclone **6** (Figure 2), starting from inexpensive starting materials (Scheme 2).[13b]

A Wittig reaction with the 3-hydroxyisoindolinone **10** was used to produce racemic pagoclone **6**, based on the assumption that, under certain conditions, the hydroxyisoindolinone **10** is in equilibrium with the aldehyde tautomer **11** (Scheme 3). In this case, a Wittig olefination of that aldehyde followed by a Michael-type ring closure afforded the desired racemic product.



Scheme 3. Equilibrium between the hydroxy-isoindolinone and the aldehyde tautomer.

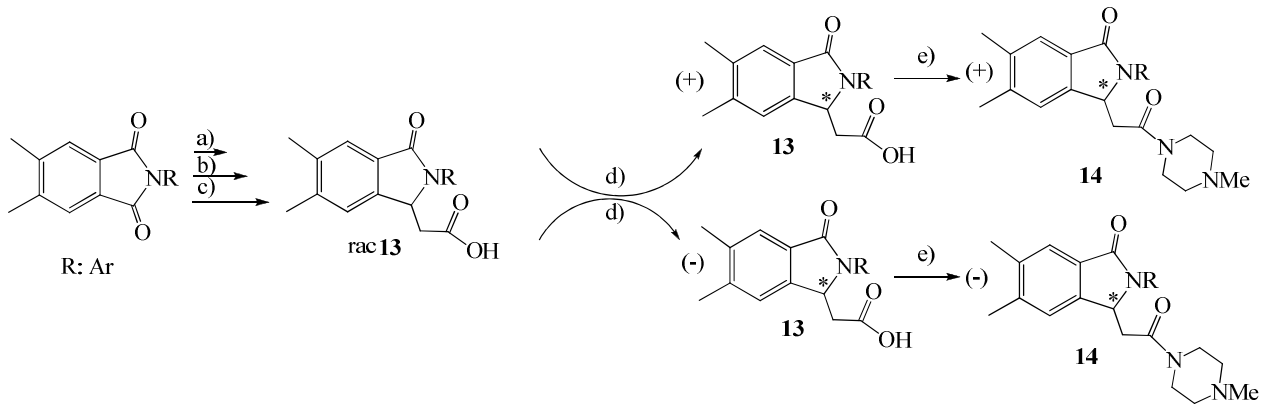


Scheme 4. a) HCl; b) (+)-ephedrine; c) HCl; d) carbonyldiimidazole (CDI) or acetic anhydride/imidazole.

Based on this approach, Stuk also reported an asymmetric version to give enantiomerically pure drug (+)-pagoclone, starting from its racemic form, by resolution of the intermediate carboxylic acid **12**, *via* diastereomeric salt formation using ephedrine (Scheme 4).[13b] Although the method allows the recycling of the unwanted enantiomer by means of its racemization and re-use, the total yield of (+)-pagoclone resulted

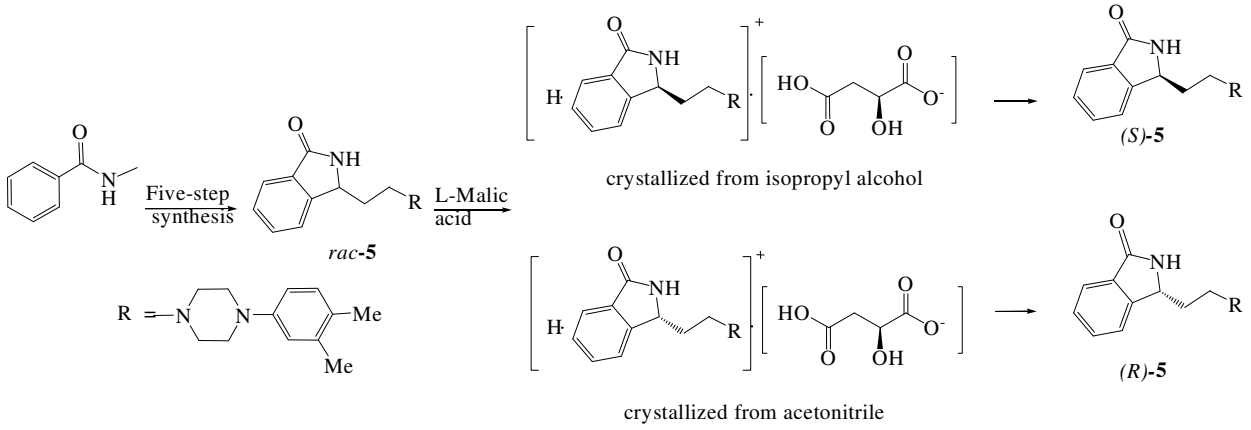
lower than 30%. In alternative, a chiral multicolumn chromatography has been developed for the resolution of the racemate with an overall cost of the final drug substance downed by >60%.

Analogously, exploiting the diastereoisomeric salts formation of the racemic acid intermediate **13** with (*R*)- or (*S*)-1-phenylethylamine and repeated re-crystallization, Kanamitsu *et al.* in 2007 achieved the asymmetric synthesis of several isoindolin-1-one derivatives **14** with proved sedative-hypnotic effects (Scheme 5).[27] Also in this case the yields in enantiopure isoindolinones are very low (about 5%) because of a scarcely efficient crystallization process.



Scheme 5. a) $NaBH_4$; b) $Ph_3P{=}CHCO_2Et$; c) K_2CO3;d) (*S*)-$PhCH(CH_3)NH_2$ or (*R*)-$PhCH(CH_3)NH_2$; e) HN⌒NMe

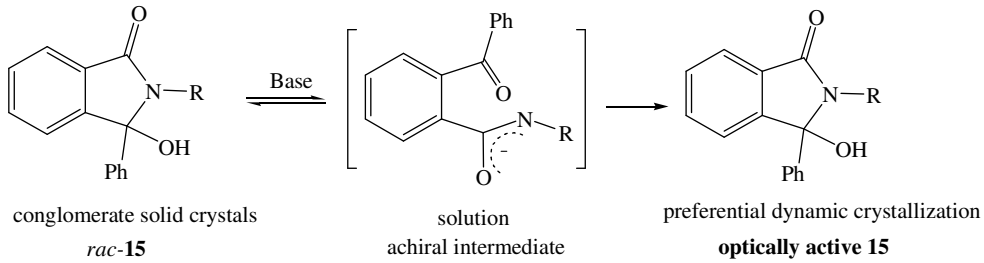
On the other hand, *via* a reverse process, L-malic acid could be used for the resolution of the racemic isoindolinone **5**, the potent dopamine D_4 ligand (Figure 3), whose diastereoisomeric salts have been fractionally crystallized (two times) from either isopropyl alcohol or acetonitrile as reported by Belliotti (Scheme 6).[19] The separated (*S*)- and (*R*)-C enantiomers were then converted to their free bases and tested for affinity at various dopamine receptors with different results.



Scheme 6. Resolution of isoindolinone **5**, *via* diastereoisomeric salt formation with L-malic acid.

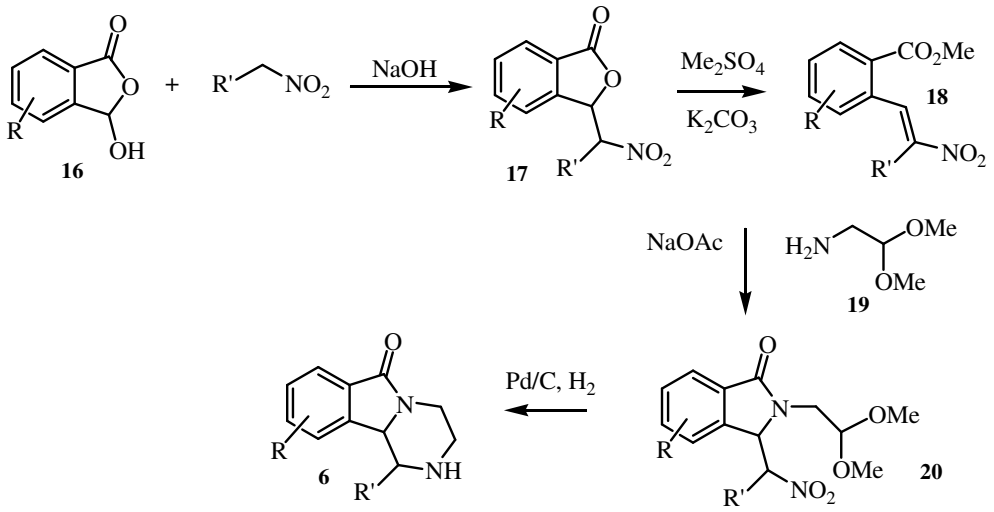
As shown, although feasible, the above described resolutions suffer from several disadvantages which severely limit their practical use mainly from an industrial point of view. The low yields are frequently observed because of multistep syntheses and the operational difficulties related to time-consuming

development of efficient and reproducible crystallizations. While the asymmetric synthesis logically arises as the most convenient way to address these problems, some particular cases of spontaneous resolution of isoindolinones **15** without an external chiral source have been recently reported by Sakamoto[28] and Vlieg.[29] In this case, starting from a racemic conglomerate and exploiting an equilibrium reaction with DBU *via* an achiral intermediate, the dynamic preferential crystallization leads to a resolution of the racemate with good to high e.e. Though this method is applicable to a very narrow range of isoindolinone derivatives that fulfill stringent prerequisites, favorably offers the advantage of overcoming, in terms of yield, the theoretical limit (i.e. 50%) of a traditional resolution (Scheme 7).



Scheme 7. Deracemization of isoindolinones **15** *via* an achiral intermediate.

Separation by HPLC on preparative chiral columns has also been exploited in racemate resolution of several bioactive isoindolinones, as **6** and **8** (Figure 3).[20-22] In the case of the derivatives **6**, which modulate serotonine receptor,[20] the described synthesis is interesting and worthy to be described. The phthalides **17**, obtained after condensation of **16** with nitro compounds, were subjected to ring opening to give the unsaturated benzyl esters **18**. These intermediates were treated with the amine **19** to give the cyclic isoindolinone **20** *via* a tandem conjugated addition/lactamization. Reduction of the existing functional groups allowed the further cyclization to give the fused piperazine ring in **6** (Scheme 8).

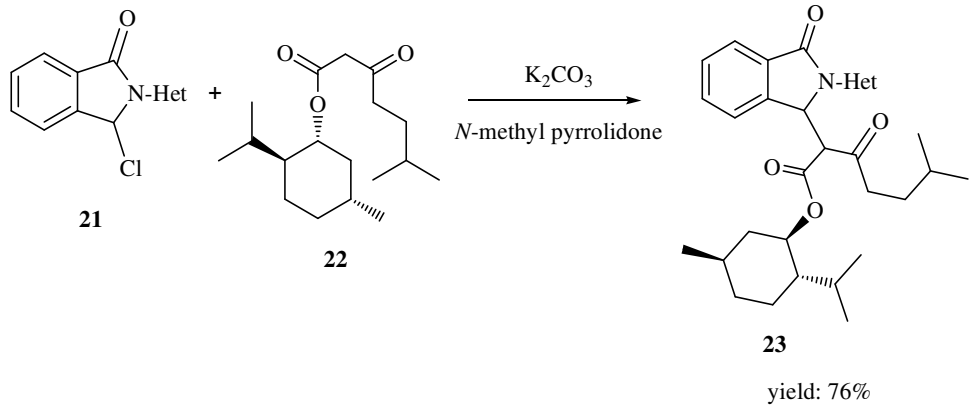


Scheme 8. An approach to fused tricyclic isoindolinones derivatives which modulate serotonine receptor.

2.2. Use of chiral auxiliaries and chiral pool

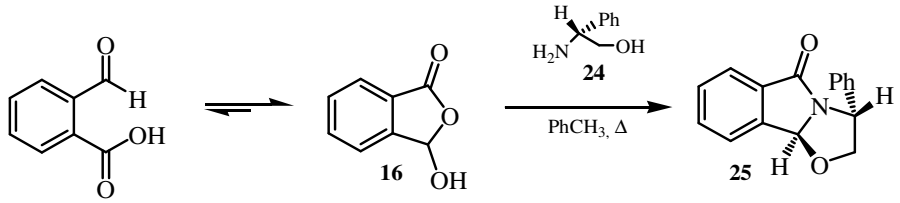
In 1993, Bousson *et al.* described in a patent a method for the isolation of dextrorotatory isoindolinone isomer **23** by preparing an optically active (-)-menthyl ester **22** (Scheme 9).[30] The synthesis is based on a

typical approach to obtain isoindolinones, found in many syntheses,[26] consisting of a substitution reaction at the preformed 3-chloro isoindolinone ring **21**. Dextrorotatory isomer was separated by preparative HPLC, using Kromasil column.



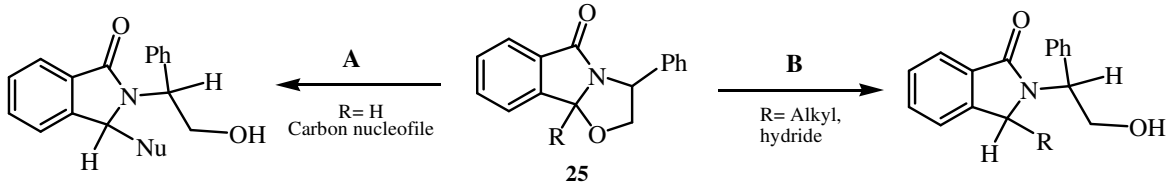
Scheme 9. Optically active menthyl ester isoindolinone derivative.

In 2000, Allin *et al.* have developed one of the first asymmetric synthesis of chiral isoindolinones using chiral auxiliaries. The tricyclic γ-lactam **25** was produced in good yield and as single diastereoisomer by condensation of (*R*)-phenylglycinol **24** with 2-formylbenzoic acid **16** (Scheme 10).[31]



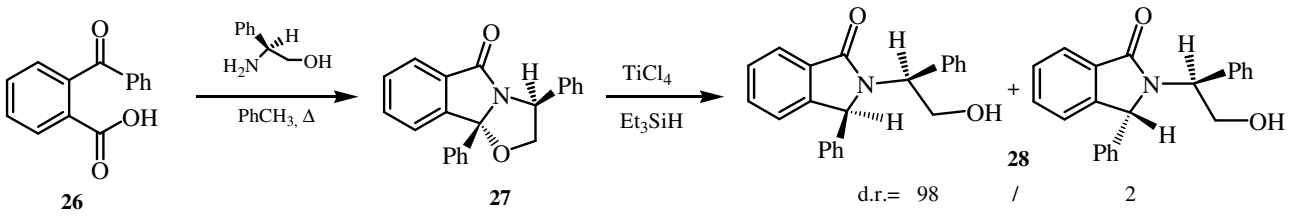
Scheme 10. (*R*)-phenylglycinol in the synthesis of tricyclic derivatives.

Then, **25** was subjected to an aminal ring-opening reaction using a carbon nucleophile in order to introduce the substituent in 3-position (Scheme 11, Pathway A). The substituent can also be introduced during lactam preparation, and subsequently the aminal was opened stereoselectively using a source of hydride (Scheme 11, Pathway B).



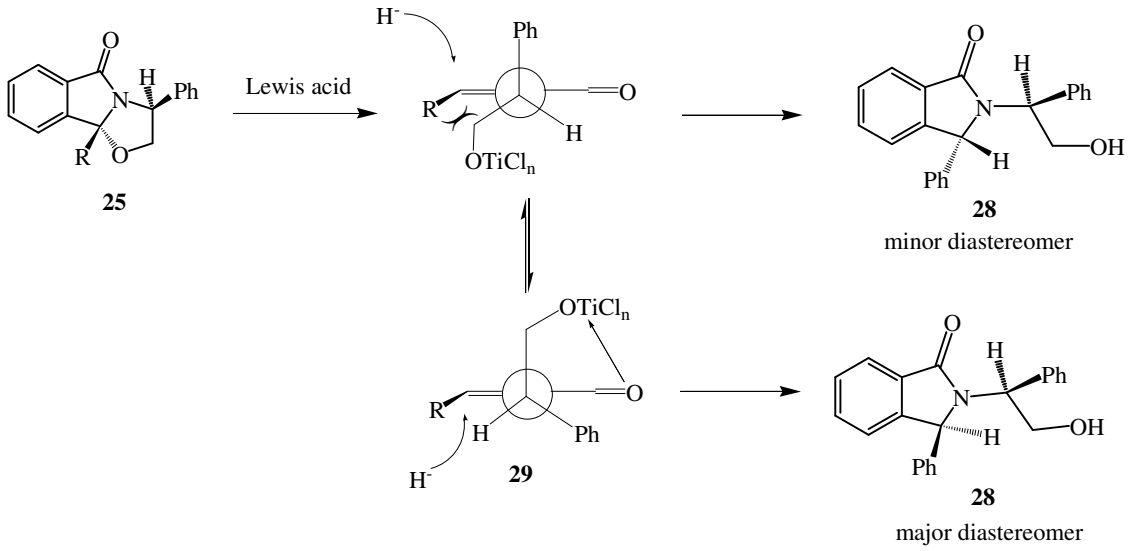
Scheme 11. (*R*)-phenylglycinol as chiral auxiliary.

For example substrate **27**, prepared as a single diastereoisomer by condensation of (*S*)-phenylglycinol with the corresponding ketoacid **26**, was treated with $TiCl_4$ and then with triethylsilane giving **28** with high levels of diastereoselectivity (Scheme 12).



Scheme 12. (*R*)-phenylglycinol as chiral auxiliary.

Higher levels of diastereoselectivity can be achieved depending on the Lewis acid activator. The remarkable increase in diastereoselectivity for the aminal ring-opening reaction can be rationalized by the transition state models. The "size" of the angular substituent R appears to be a significant factor contributing to the observed level of diastereoselectivity. When R = H, the *N*-acyliminium species suffers from free rotation about the extra-annular N–C bond with little preference for the competing transition state conformations during nucleophilic attack. When R = Ph, the steric effect provided by this substituent is sufficient to favor one transition state intermediate, leading to retention of configuration at the new asymmetric centre (Scheme 13). Thus, the relative size of the alkyl substituent is a major factor in determining the diastereoselectivity, which can depend on the ability of the Lewis acid activator to form the chelated intermediate **29**.

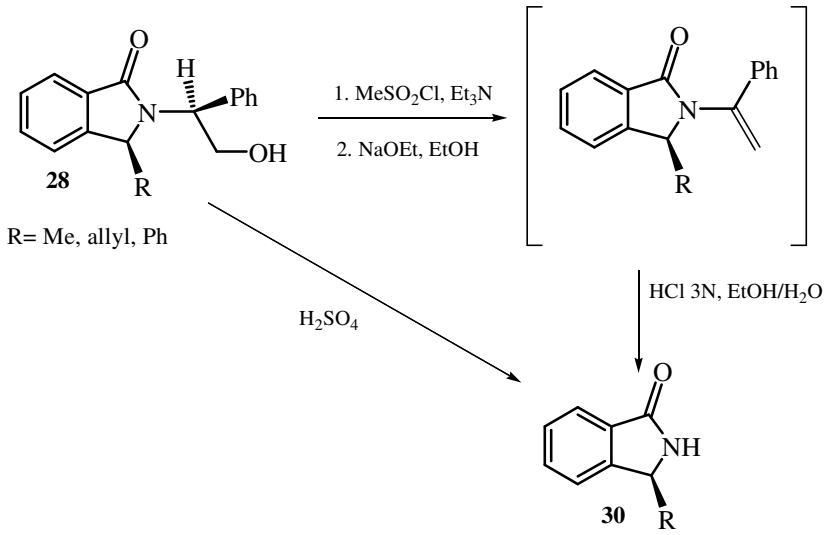


Scheme 13. Proposed TS for reaction of tricyclic lactam substrate with nucleophile.

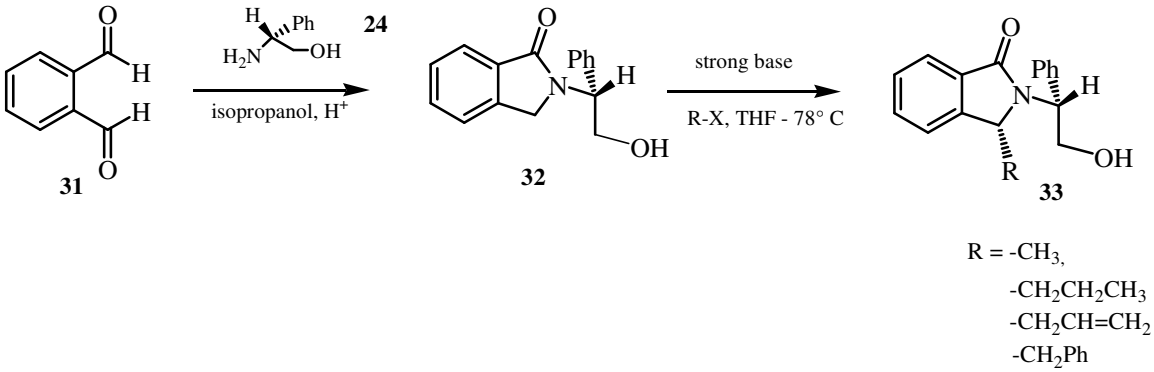
Cleavage of the chiral auxiliary to give isoindolinones **30** in high enantiomeric excesses can be achieved without racemization at the newly created asymmetric centre either *via* a two-step procedure or directly using concentrated sulfuric acid (Scheme 14).

In 2002, Viret and coworkers reported an asymmetric synthesis of 3-alkyl substituted isoindolinones **33** *via* the alkylation of the intermediate **32** obtained by condensation of (*R*)-phenylglicinol **24** with phtalic dialdehyde **31** (Scheme 15).[32] Direct functionalization at the isoindolinone ring **32** was achieved by deprotonation in the presence of strong bases, followed by alkylation. High diastereoselectivities were observed with LDA or LiHDMS while the isolated yields were modest. In contrast, the use of NaHDMS

gave good isolated yield (up to 85%) but lowered diasteroselectivities. The different diastereoselectivities observed through the use of different bases suggested the formation of a chelated intermediate. The chelation would be better with lithium than with sodium or potassium. Cleavage of the chiral auxiliary in **33** occurred without loss of stereoselectivity, exploiting the procedure reported by Allin, according to Scheme 14.[31]



Scheme 14. Deprotections from (*R*)-phenylglycinol.



Scheme 15. Diastereoselective alkylation of chiral isoindolinones.

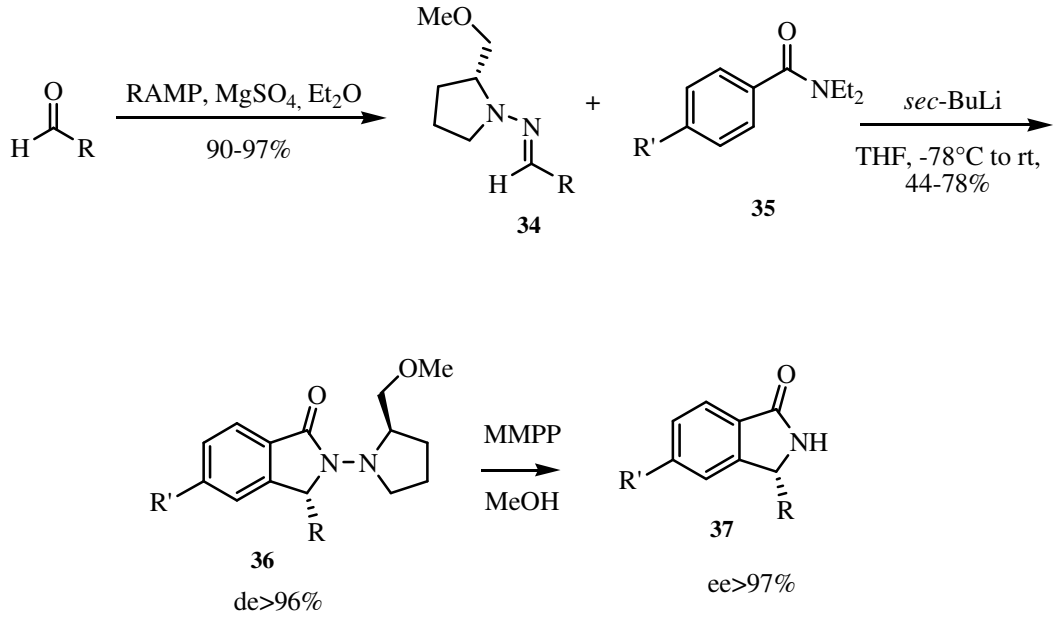
Furthermore, studies on the diastereoselective alkylation of (*R*)-phenylglycinol derived phthalimide by Grignard reagents have also been reported.[33] However, usually only moderate diastereoselectivity was observed.[33]

In 2001 Enders *et al.* described an interesting asymmetric construction of isoindolinones by the use of the chiral auxiliaries RAMP and SAMP, under very strongly basic conditions (Scheme 16).[34]

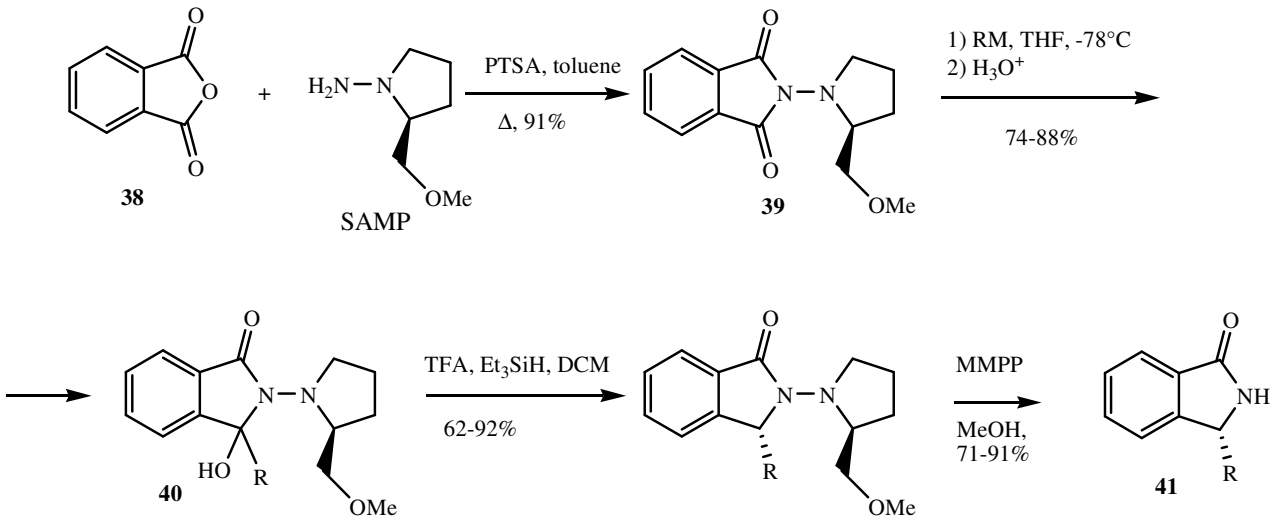
The key steps of the synthesis consist of the *ortho*-lithiation of the amide **35**, the subsequent highly stereoselective addition to the chiral hydrazones **34** and the lactamization, an approach corresponding to strategy **f** of the retrosyntetic analysis of Scheme 1. Then, the deprotection of **36** leads to the title heterocycles **37** with high enantiomeric excesses.

In another work the chiral phthalhydrazide **39**, which was easily prepared by condensation between phthalic anhydride **38** and (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP), was allowed to react with an array of organometallic reagents (Scheme 17).[35] This procedure delivered a series of hemiaminals **40** with

fairly good yields and as mixtures of diastereomers. The resulting 3-hydroxy isoindolinone derivatives **40** were subsequently treated with trifluoroacetic acid and triethylsilane which triggered the formation of the 3-alkyl and 3-aryl isoindolinones **41** with a high level of diastereoselection.



Scheme 16. Use of SAMP and RAMP chiral auxiliaries.

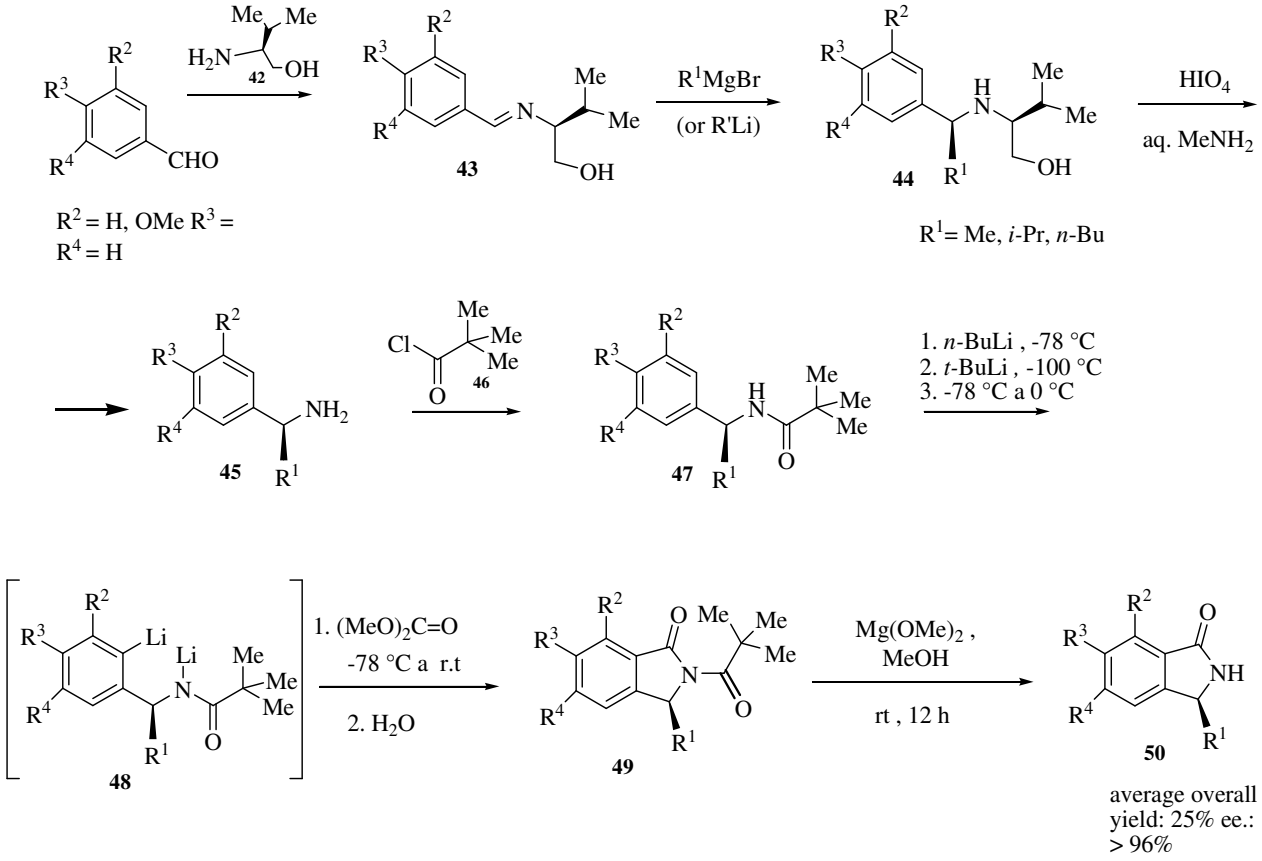


Scheme 17. Another application of SAMP and RAMP in the stereoselective addition of Grignard reagents.

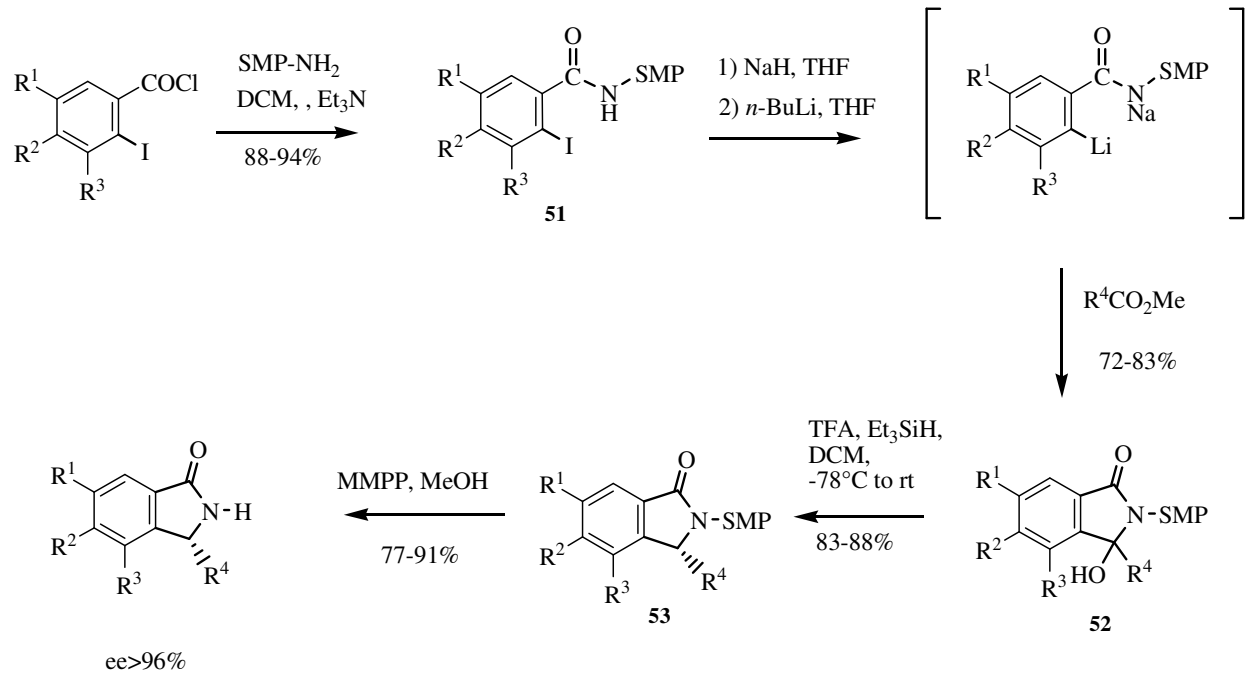
Another example of use of chiral auxiliaries is given by the following multi-step construction of the heterocyclic scaffold.[36] The synthesis, described by Couture, Grandclaudon *et al.* in 2008, is based upon the highly diastereoselective addition of organometallic reagents on chiral aldimines **43** derived from (*S*)-valinol **42** (Scheme 18).[36]

Removal of the chiral auxiliary in **44** followed by installation of a pivaloyl group **46**, delivered the amides **47**. Then, the capture of the di-lithiated species **48** with dimethyl carbonate afforded the annulated compounds **49**. The removal of the pivaloyl functionality spared the stereochemistry at C-3 and delivered in

high yield the virtually enantiopure NH free isoindolinones **50**. This technique allowed the access to poly- and diversely substituted compounds but several synthetic steps were required for the construction of the heterocyclic core with sometimes rather low overall yields.



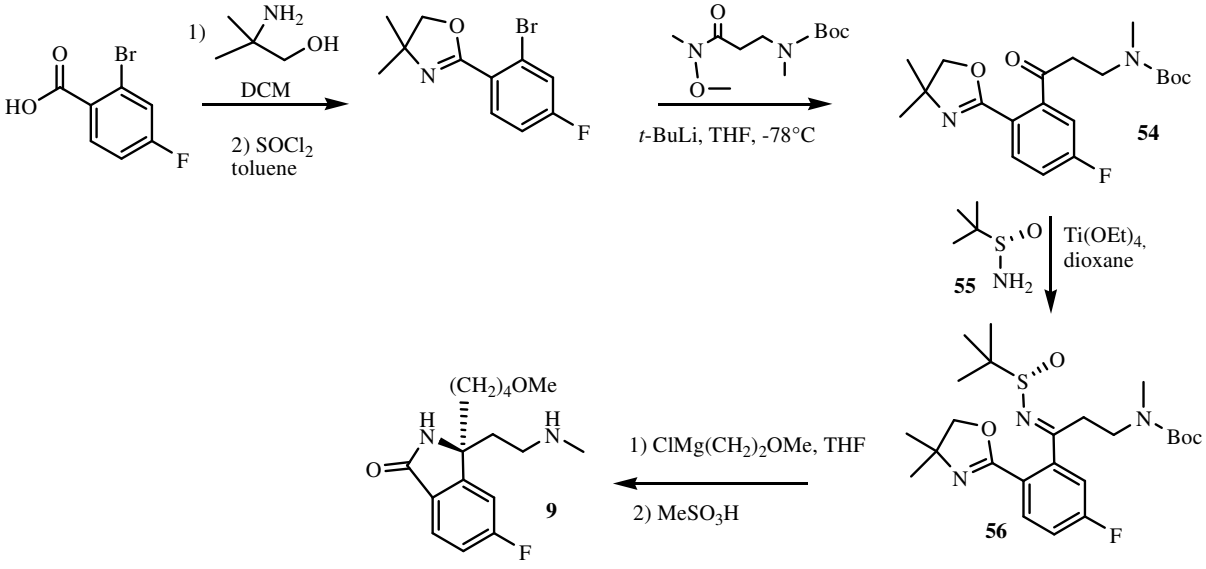
Scheme 18. Use of valinol as chiral auxiliary in the asymmetric synthesis of 3-substituted isoindolinones.



Scheme 19. Another application of SAMP diastereoselective reduction of hydroxy-isoindolinones.

Another approach reported by the same group is based on the use of (*S*)-2-methoxymethyl-pyrrolidine (SAMP) as chiral auxiliary, installed, this time, on the amide **51** (Scheme 19).[37] Then, bis-metalation and cyclization with esters lead to the 3-hydroxy isoindolinones **52**. These compounds with the hemiaminal functionality were subsequently treated with trifluoroacetic acid and triethylsilane. This operation triggered the formation of the 3-alkyl and 3-aryl isoindolinones **53** released from the hydroxy appendage with a high level of diastereoselection. Removal of the chiral auxiliary without racemization was readily achieved by oxidative cleavage of the nitrogen–nitrogen bond promoted by magnesium mono-peroxyphthalate hexahydrate (MMPP).

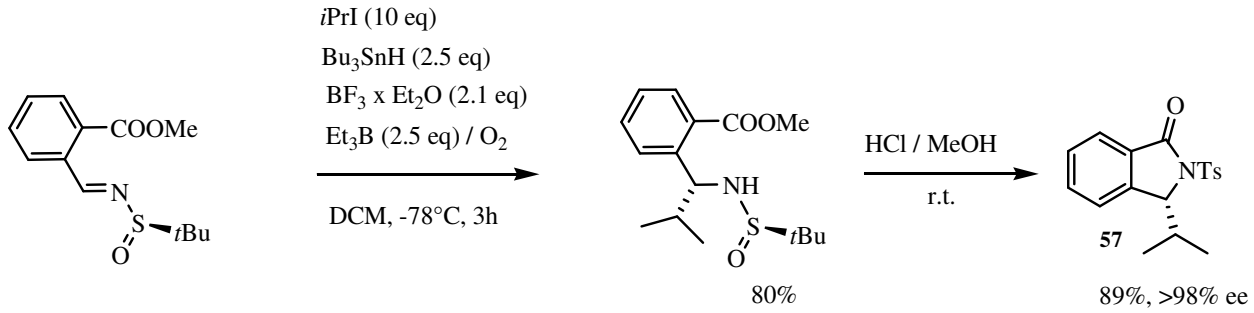
In 2008, Baldwin *et al.* reported in a patent a multistep synthesis of chiral 3-disubstituted isoindolinone **9**, showing renin inhibitor activity (Scheme 20, Figure 3).[23] The synthesis follows the general strategy of formation of a chiral imine derivative, but in this case using the (*S*)-sulfinamide **55** as chiral auxiliary. Thus, the stereoselective addition of a Grignard reagent to **56** and the subsequent lactamization of the obtained chiral amine lead to the chiral isoindolinone **9**. The synthesis of the structurally complex ketone **54** gives the opportunity to introduce in the isoindolinone scaffold a quaternary stereocenter with high stereoselectivity. The same type of chiral auxiliary was used very recently by Maestro *et al.* in the synthesis of one isoindolinone under conditions to perform alkyl radical addition reaction (Scheme 21).[38] Then, the usual lactamization after deprotection led to the chiral compound **57**.



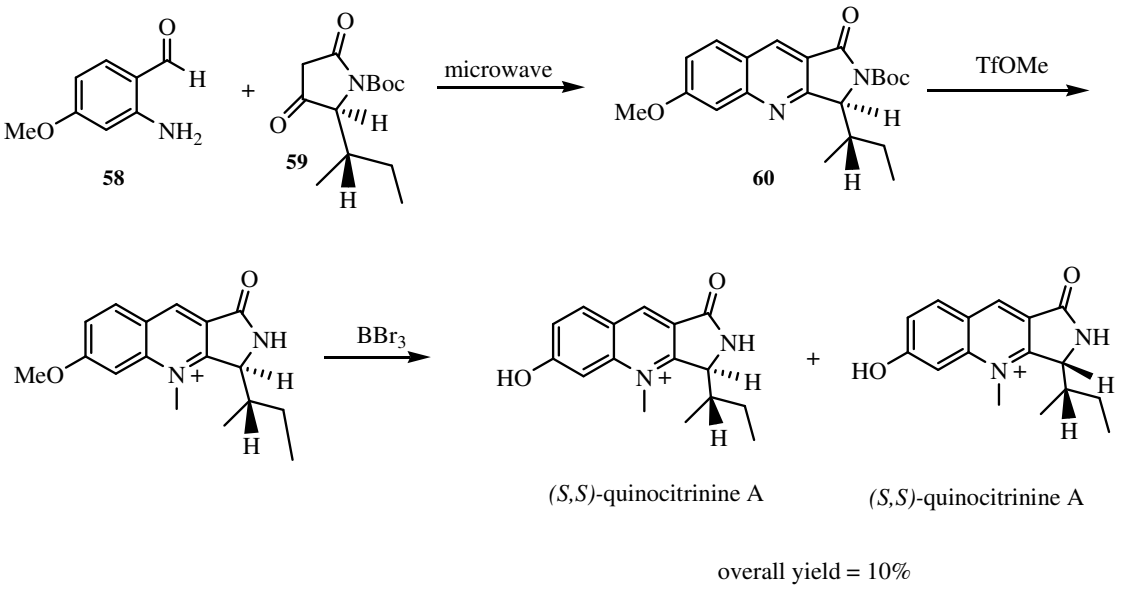
Scheme 20. The use of (*S*)-sulfinamide as efficient chiral auxiliary in Grignard addition.

In 2011 Byk *et al.* reported an enantioselective synthesis of the isoindolinone analogues, the quinocitrinines, isolated from *Penicillium citrinum*,[5a] which exhibit a broad range of biological activities (Figure 2).[5b] The synthesis is based on a chiral pool approach, employing the optically active substituted (*S,S*)-tetramic acids **59**, obtained from the corresponding natural amino acids (Scheme 22).[5d] The polycyclic scaffold **60** was constructed in a microwave assisted Friedlander condensation between substituted 2-amino-benzaldehydes **58**. Then, methylation with methyl triflate and deprotection with BBr_3 afforded the final products.

However, the products were obtained in a rather low overall yield and epimerization at the isoindolinone stereocenter was also observed. Exhaustive NMR analysis of the obtained synthetic quinocitrinines revealed a substantial lack of correlation between the chemical shifts of the synthetic and the natural products with the conclusion that the structures proposed for the natural quinocitrinines A and B in previous reports should be reconsidered.



Scheme 21. Chiral sulfinamide in diastereoselective alkyl radical addition reaction.



Scheme 22. Attempt at asymmetric synthesis of quinocitrinines.

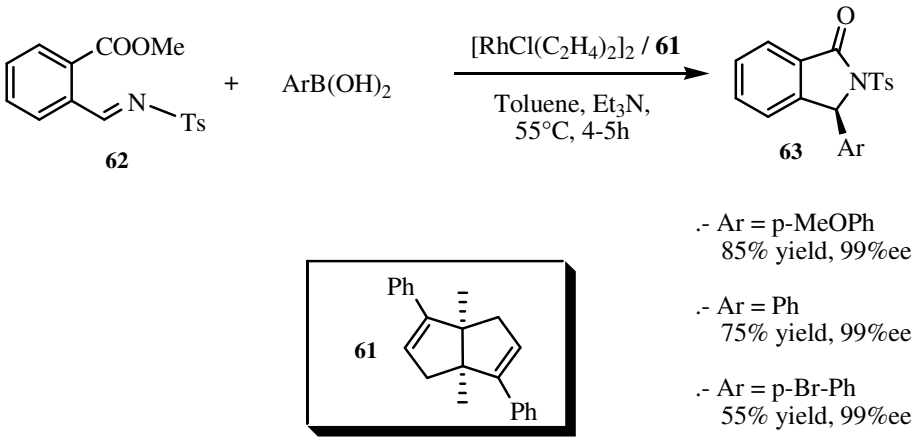
3. Catalytic asymmetric syntheses

Besides the resolution of racemic mixtures and the use of chiral auxiliaries, which have been almost the unique successful approaches in the past, in recent years several asymmetric catalytic systems have been developed. The use of chiral catalysts is preferable in order to avoid the low yields of resolutions as well as the numbers of additional unavoidable steps that accompany the use of stoichiometric amounts of chiral auxiliaries. Thus, the recent literature highlighted the development of a series of methodologies employing chiral transition metal catalysts, organocatalysts and chiral phase transfer catalysts. If on one hand some of the new methods can be considered an evolution of the strategies previously developed for the chiral auxiliaries, based, for example, on enantioselective addition of aryl-nucleophiles to imine derivatives. On the

other, a variety of approaches have been developed, including multi-component, asymmetric oxidation of double bond or tandem reactions, highlighting the diversification of the obtained products and at the same time the variety of conditions and the efficiency belonging to modern organic chemistry.

3.1. Chiral transition metal catalysts

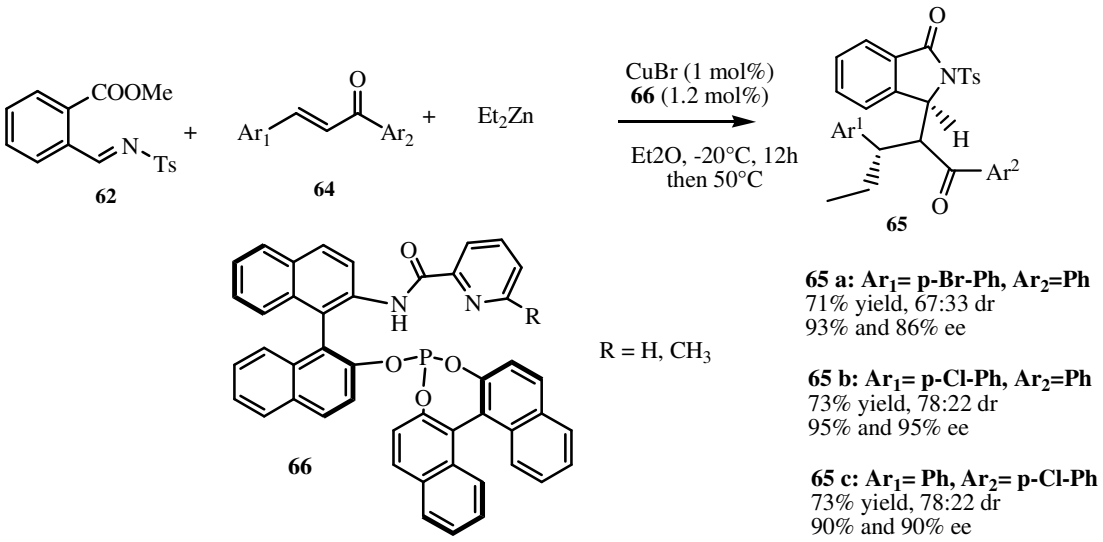
In 2007, Xu, Lin *et al.* reported the first catalytic enantioselective synthesis of 3-substituted isoindolinones using chiral Rh-catalysts (Scheme 23).[39] This goal was achieved as a consequence of investigations of the arylation of *N*-tosylarylimines with arylboronic acids to generate chiral diarylmethylamines. The success of the reported methodology can be ascribed to the development of new *C2*-symmetric chiral diene ligand **61** bearing a simple bicyclic [3.3.0] backbone. The ligand **61** was readily prepared in a three-step sequence from enantiomerically enriched octahydropentalene-1,4-diol in good yields, as alternatives of chiral phosphine ligands. This method proved to be remarkably enantioselective when applied to the arylation of methyl 2-formylbenzoate *N*-tosylimines **62** (Scheme 23). The tandem asymmetric arylation of the imine followed by lactamization was the key strategy to obtain the final isoindolinone **63** employing only 3 mol % of Rh(I) chiral catalyst. However, only three examples were described with different aryl groups, but further substitutions, for example, on the aromatic ring of the isoindolinone, have not been considered.



Scheme 23. Chiral Rh-catalysts in the asymmetric arylation of *N*-tosylarylimines.

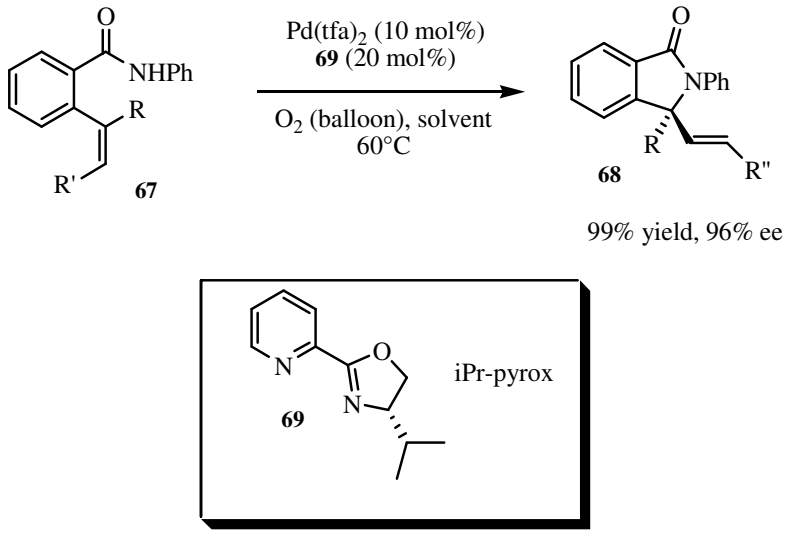
The same starting material **62** was particularly useful in another approach to the synthesis of chiral isoindolinones **65**, as reported in 2010 by Huang *et al.*[40] In this work the authors exploited a highly diastereo- and enantioselective multicomponent tandem Michael addition / Mannich reaction in the presence of Cu(I) catalyst with the chiral ligand **66** at only 1 mol% loading (Scheme 24). The entire process is particularly interesting from a mechanistic point of view, consisting firstly of the conjugated Michael addition of Et_2Zn to chalcones **64**, followed by a Mannich addition of the imine **62** at the nucleophilic α-position of the Michael adduct and finally lactamization of the resulting amine. This complex sequence of reactions led to the formation of isoindolinones with three contiguous tertiary stereocenters in good yield and with very good diastereo- and enantioselectivity, considering that only two of the four diastereomers were detected. Also in this case, as part of a wider substrate screening, only three examples were reported with no

substitution onto the aromatic ring of the isoindolinone. The configuration of enantiopure **65a** (Ar^1= *p*-Br-Ph, Ar^2=Ph) was determined to be *1S,2R,3S* after X-ray analysis of single-crystal.



Scheme 24. Chiral copper catalysts in multicomponent tandem reactions.

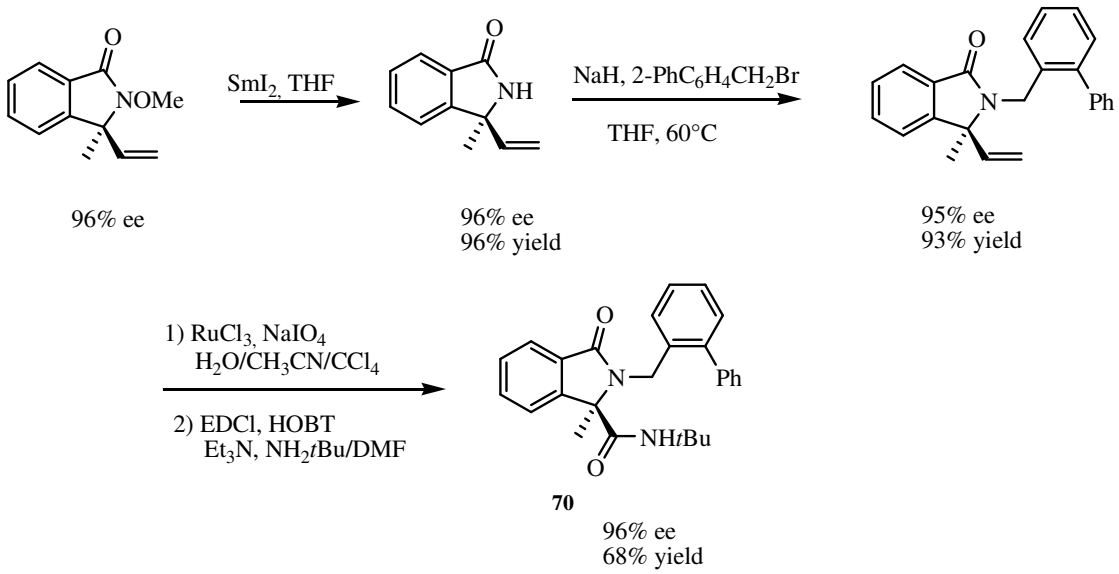
In 2012, Zhang *et al.* described the asymmetric synthesis of isoindolinones **68** with quaternary stereocenters, an important goal considering the number of biologically active compounds having this feature (Figure 3). The procedure exploited an asymmetric Pd(II) catalyzed aerobic aza-Wacker-type cyclization performed on the banzamide **67** bearing alkene groups in *ortho* position, and in the presence of the chiral ligand **69** (Scheme 25).[41] Several alkenes were reacted giving good results in terms of yields and enantioselectivities, even if in some cases products with isomeric double bond were obtained.



Scheme 25. Asymmetric Pd(II) catalyzed aerobic aza-Wacker-type cyclization.

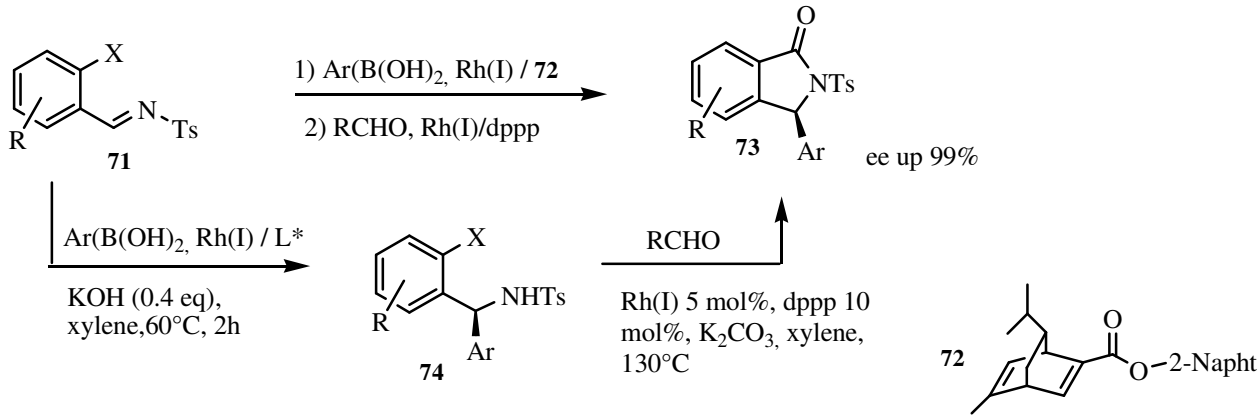
The described methodology has allowed the access to a useful intermediate for the asymmetric synthesis of **70** (Scheme 26), which is an analogue of a drug for the treatment of cardiac arrhythmias **8**

(Figure 3). The product **70** was obtained in further 4 steps, with a good total yield and most importantly with unchanged enantiomeric purity.[41]



Scheme 26. An approach to analogue of a drug for the treatment of cardiac arrhythmias **11** (Figure 3).

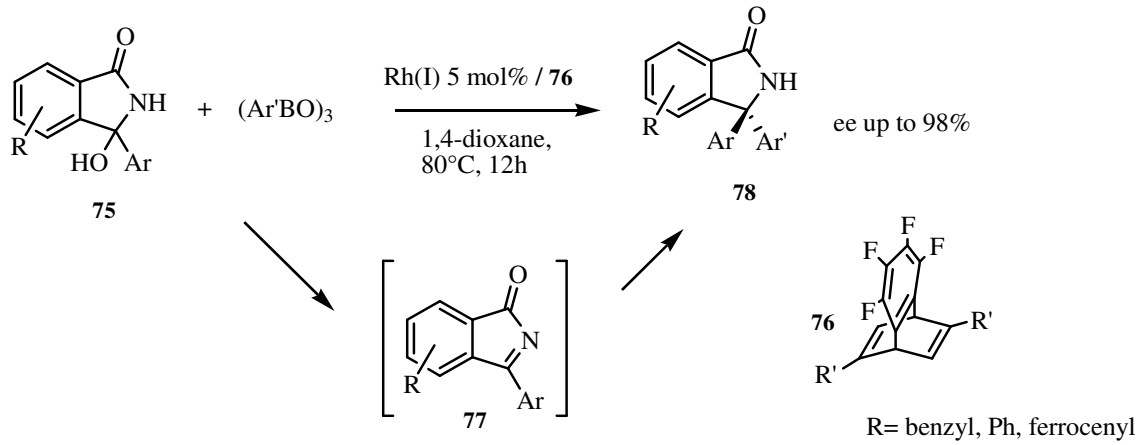
In 2013, Morimoto *et al.* reported that 1 mol% of the rhodium(I) catalyst with chiral diene ligand **72** was particularly useful in the asymmetric construction of isoindolinone ring starting from 2-halo-aryltosylimines **71** (Scheme 27).[42] The two-step synthesis consists of the asymmetric arylation of 2-halo-benzaldimines **71** with boronic acids and subsequent Rh(I)-catalyzed intramolecular aminocarbonylation of **74** in the presence of an aldehyde as the carbonyl source for the construction of the isoindolinone ring. The method tolerates a variety of functional groups, yielding isoindolinone derivatives **73** in moderate to high yields with high ee-values. In addition, the two Rh(I)-catalyzed transformations could be efficiently accomplished in an one-pot sequence to give chiral isoindolinones by the simple addition of the dppp ligand and an aldehyde after the Rh(I)-catalyzed asymmetric arylation.



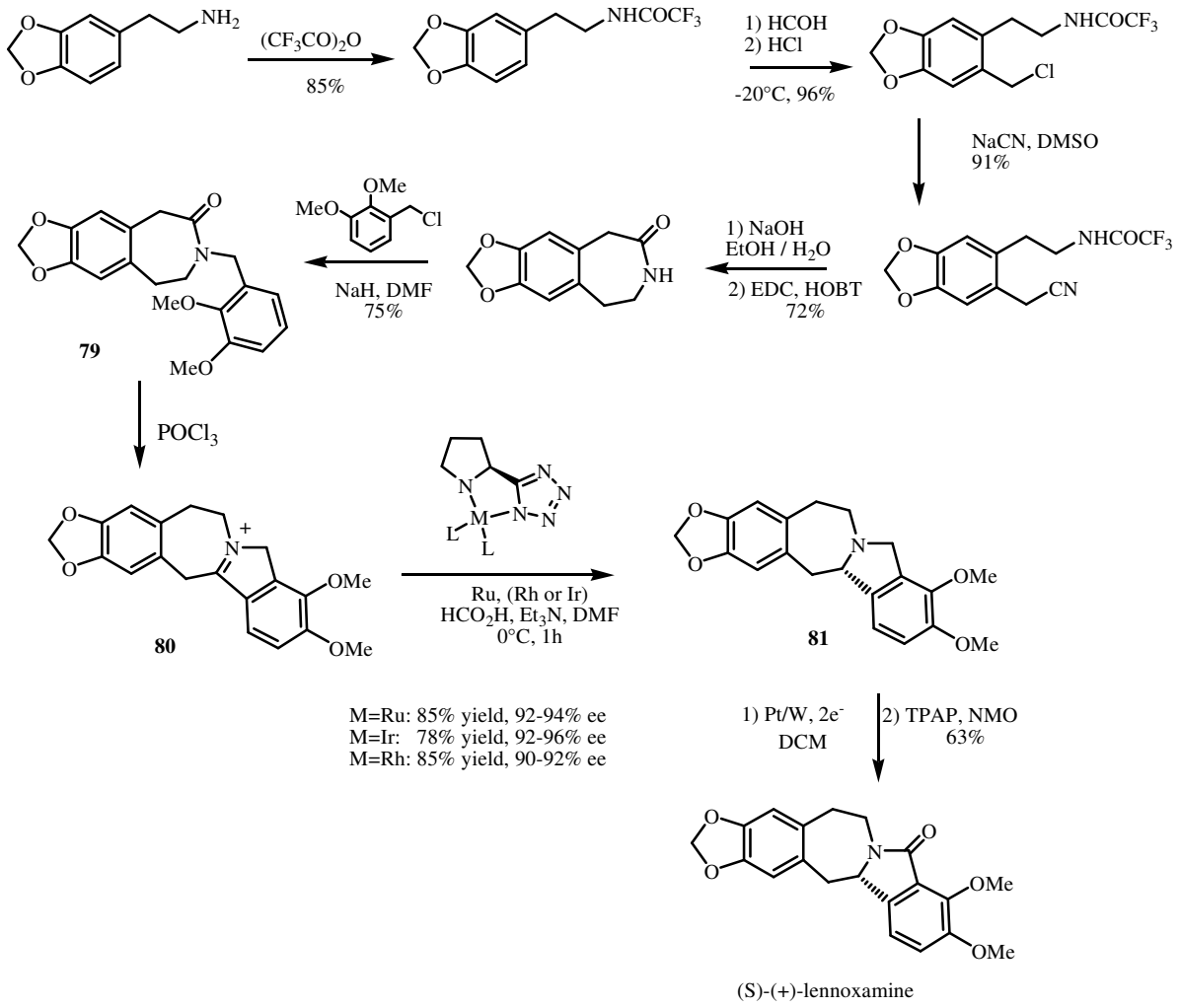
Scheme 27. Chiral rhodium(I) catalyst in sequential tandem arylation/carbonylation.

In 2013 Nishimura, Hayashi *et al.* found that a hydroxorhodium complex with the chiral diene **76** was effective in catalyzing the asymmetric arylation at the preformed isoindolinone scaffold **75** with

arylboroxines (Scheme 28).[43] The 3-aryl-3-hydroxyisoindolin-1-ones **75** revealed stable precursors for the generation of cyclic N-carbonyl ketimines **77** to produce chiral isoindolin-1-ones **78** with quaternary stereocenters in high yields and ees. (*R*)-binap was also tested, but revealed less effective than **76** in terms of yield and enantioselectivity.



Scheme 28. A chiral hydroxorhodium complex in asymmetric arylation of 3-hydroxy isoindolinones.



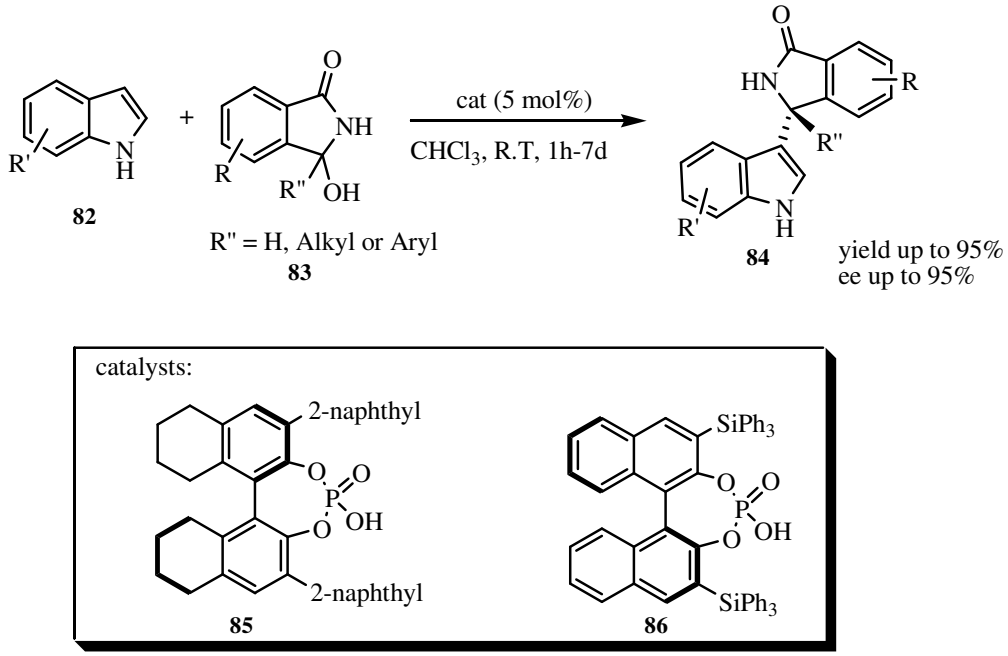
Scheme 29. An asymmetric synthesis of (*S*)-lennoxamine *via* asymmetric hydrogenation.

Metal catalyzed enantioselective procedures were also useful in the asymmetric synthesis of the natural product (*S*)-(+)-lennoxamine (Figure 2), as recently reported by Santos *et al.* in 2012.[7f] This goal was achieved *via* asymmetric hydrogenation of **80** catalyzed by *L*-proline-tetrazole ruthenium catalyst in a multi-step synthesis, starting from readily available materials (Scheme 29). The natural product was obtained in 7 steps and with a 34% overall yield. The potentiality of this route involved the Bischler–Napieralsky cyclization with $POCl_3$ of **79** that leads to tetracyclic indolinium skeleton. The generation of chiral center was then achieved *via* asymmetric hydrogen-transfer reaction on **80** employing *L*-proline-tetrazole as chiral ligand. A screening of catalysts highlighted Ru more effective that Ir and Rh in terms of yields and ee.

Anodic oxidation of **81** was also necessary to get the final product. This can be considered another key step of the synthesis.

3.2. Organocatalysis and chiral phase transfer catalysis

In the last years, few interesting organocatalytic methodologies have been reported. In 2011 Zhou, Wang *et al.*, described an asymmetric Friedel–Crafts alkylation of a series of indoles **82** with the preformed 3-hydroxy isoindolin-1-ones **83**, catalyzed by chiral phosphoric acids **85** (Scheme 30).[44] Investigation on the backbone effect of the binaphthyl skeleton indicated that H8-binol-derived phosphoric acid **85** generally showed higher enantioselectivities, even though very long reaction times were usually observed. The same authors described in the same year an improved version of the asymmetric F-C reaction for the construction isoindolinones **84** with a quaternary stereocenter (Scheme 30).[45]

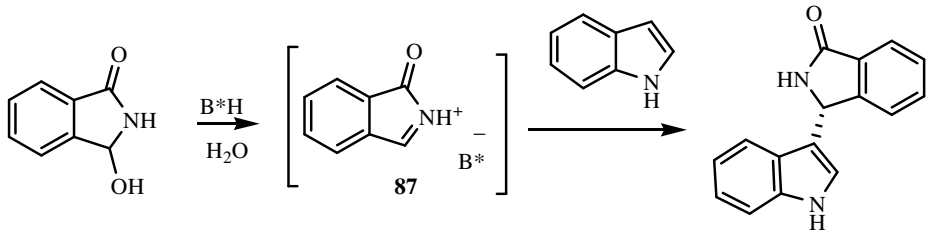


82 **83** **84** **85** **86**

Scheme 30. An organocatalytic Friedel–Crafts alkylation of indoles.

A great number of substrates were reacted giving good yields and enantioselectivities from moderate to excellent. The best results were obtained with the catalyst **86** bearing -$SiPh_3$ groups in 3 and 3' position of chiral binaphthyl rings. In these articles the reaction mechanism was also discussed (Scheme 31). In general, in the presence of Brønsted acids, alcohols can readily dehydrate to give *in situ* a carbonium ion, which is not very stable and prone to undergo side reactions (rearrangement, olefin formation and etherification). The

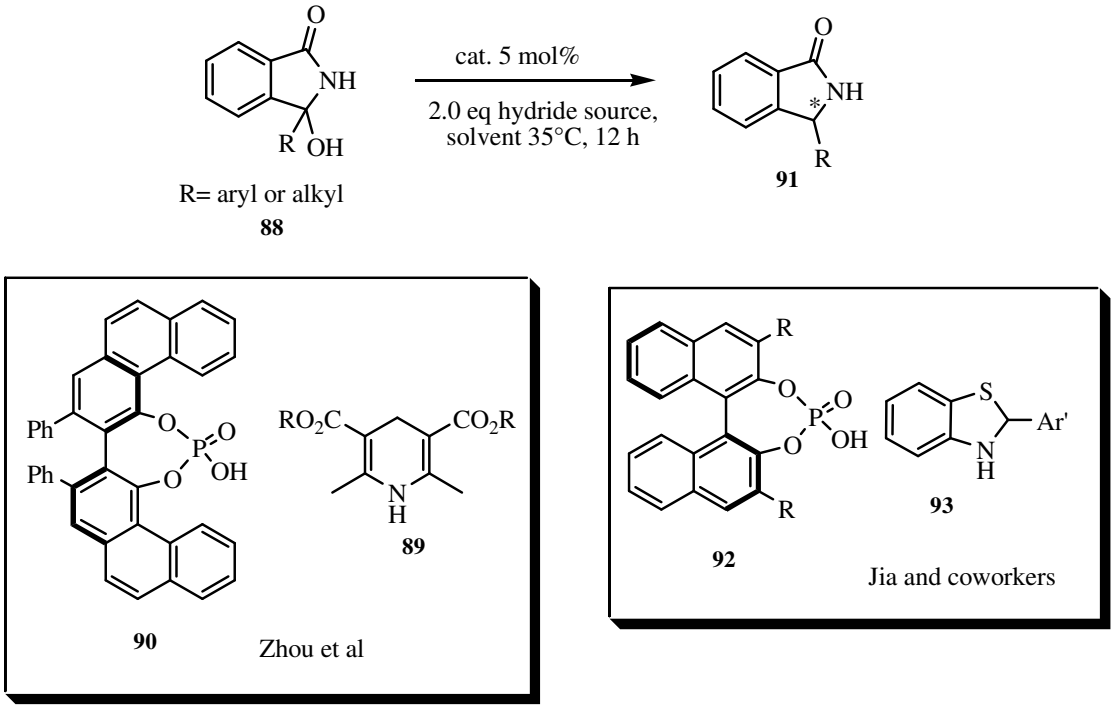
introduction of a heteroatom at the center of carbonium ion can generate a stable form with positive charge on the heteroatom. Thus, the N atom stabilizes the carbonium ion into an acyliminium ion **87**, while the presence of the chiral phosphoric acid yields the suitable chiral environment responsible for the observed enantioselectivity (Scheme 31).



Scheme 31. Mechanism of Friedel–Crafts alkylation.

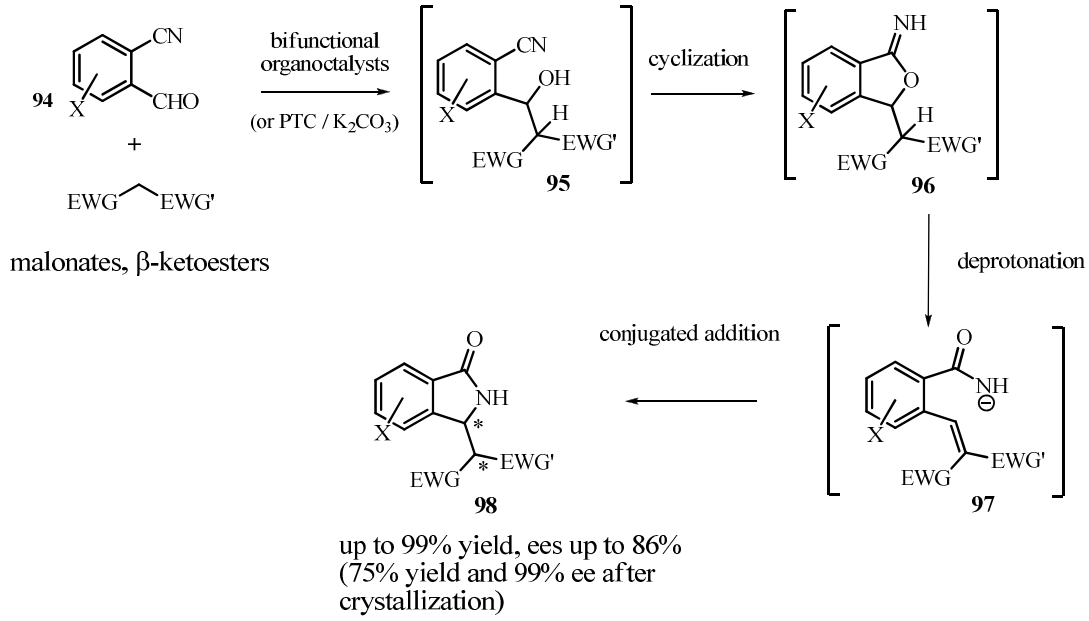
In 2012, chiral phosphoric acids were also used by Zhou *et al.* as catalysts in asymmetric hydrogenolysis of racemic 3-substituted 3-hydroxy isoindolin-1-ones **88** in the presence of a Hantzsch ester **89** as the hydrogen source (Scheme 32).[46] Several substrates were reacted with moderate to high enantioselectivity in the presence of VAPOL-derived phosphoric acid **90**. However, yields of **91** were usually moderate or low and in the case of substrates bearing alkyl groups like *n*-butyl, dehydration byproducts were observed. The reaction mechanism was discussed and also in this case the reaction was supposed to occur *via* acyliminium ion intermediate.

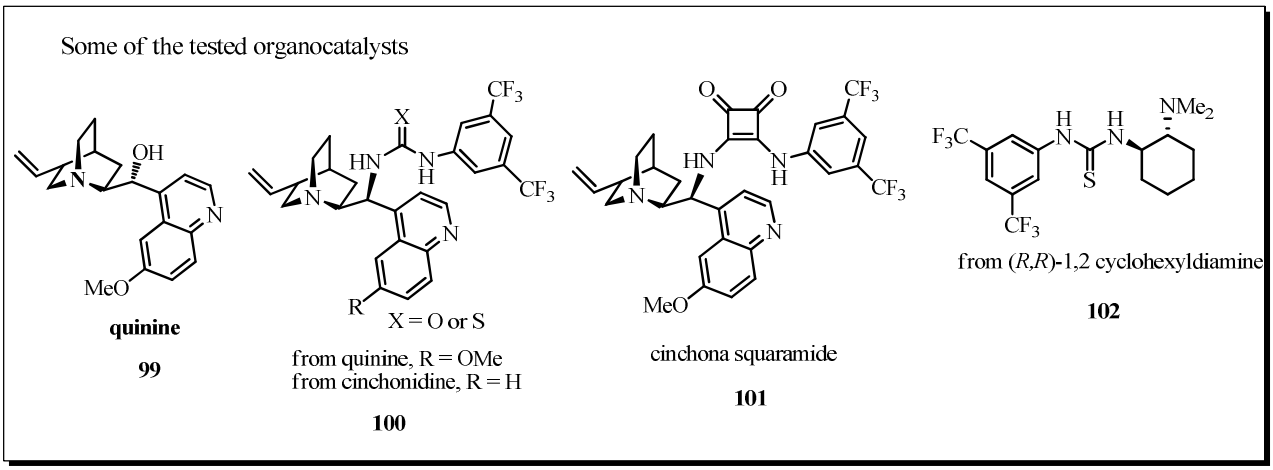
Similar studies were reported in 2013 by Jia and coworkers in which the asymmetric hydrogenolysis of racemic 3-aryl-3-hydroxy isoindolin-1-ones is catalyzed by the chiral phosphoric acid **92**. Good yields and enantioselectivity up to 89% ee were obtained for the aryl-3-substituted isoindolinones **91** using benzothiazoline **93** as the hydride source (Scheme 32). [47]

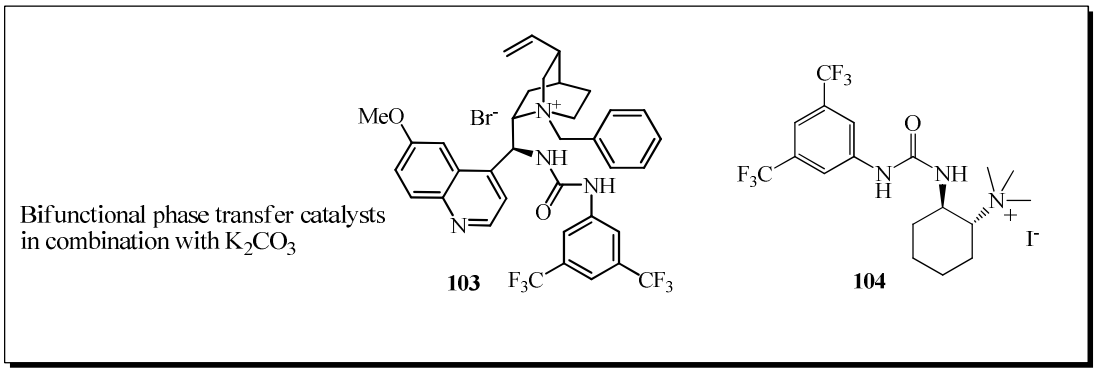


Scheme 32. Chiral phosphoric in asymmetric hydrogenolysis of racemic 3-substituted 3-hydroxy isoindolin-1-ones.

In 2011, on the basis of previous studies on the aldol reactions of malonate and β-ketoesters,[48] our group developed a convenient tandem approach for the construction of the isoindolinone ring using 2-cyano benzaldehydes **94** as readily available starting materials.[49,50] In general, the reaction of active methylene compounds with aromatic aldehydes, the well-known Knoevenagel condensation, leads to the dehydration products, while the aldol intermediates can be isolated only under specific conditions.[48]





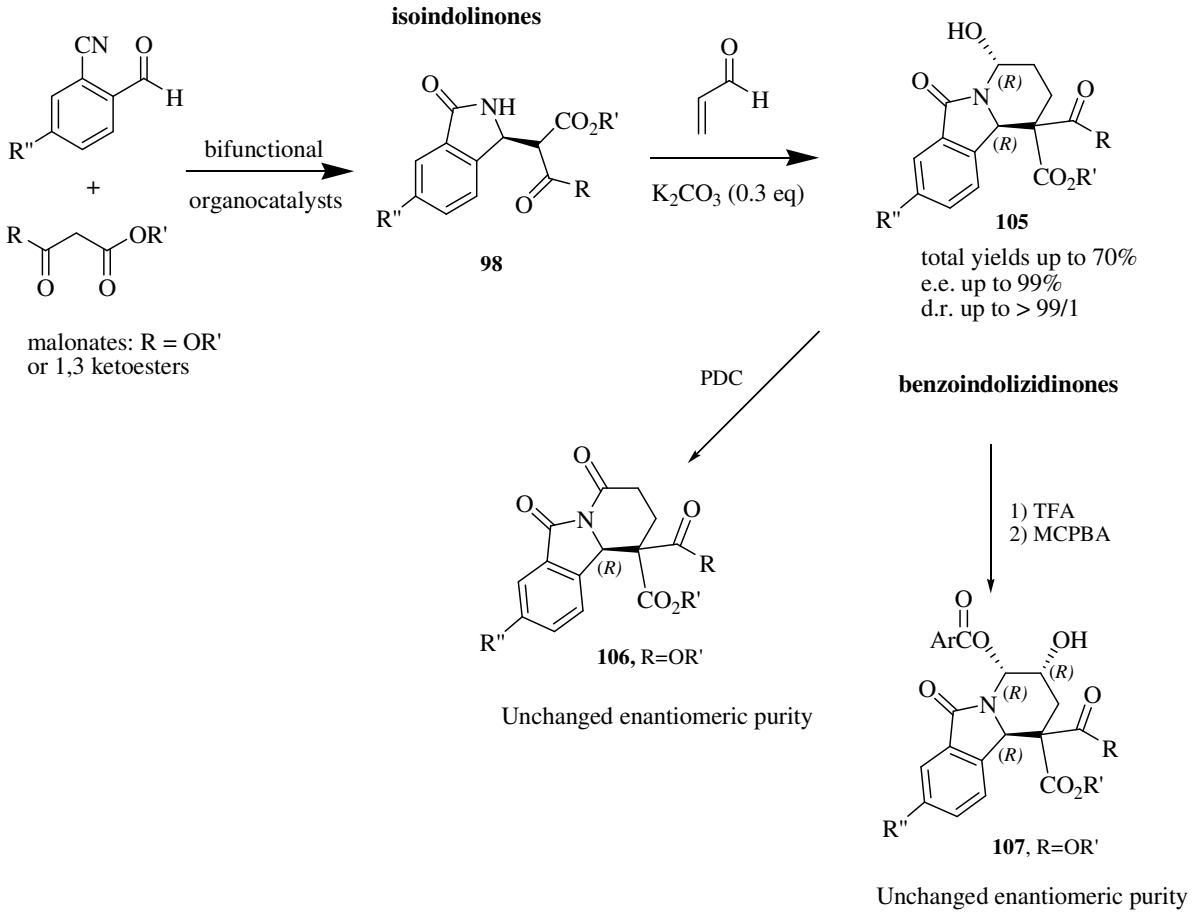


Scheme 33. Organocatalysts and phase transfer catalysts in tandem synthesis of isoindolinones.

On the other hand, the reaction of 2-cyano benzaldehydes in the presence of bases such as Et_3N or K_2CO_3 follows a different pathway (Scheme 33).[49,50] After the aldol addition, the intramolecular entrapping

of the -OH at the 2-cyano group in **95** gives the imidate intermediate **96**.[51] Then, the deprotonation of the imidate and the subsequent intramolecular aza-Michael reaction in **97** lead to the isoindolinone formation (Scheme 33).

This tandem approach has proved particularly useful for the development of the first asymmetric organocatalytic construction of 3-substituted isoindolinones **98**, reported by us in 2012.[52] Considering that the stereochemical determining step is supposed to occur during the intramolecular aza-Michael reaction in **97**, investigation focused on a series of readily available bifunctional organocatalysts (prepared from quinine, cinchonidine, quinidine, cinchonine, (*R,R*)-1,2-cyclohexyldiamine, (1*R*,2*S*) -*N*-methylephedrine).[53] While quinine **99** gave almost racemic compounds, the urea- and thiourea-quinine **100**, the squaramide **101** and Takemoto's catalyst **102** proved to be effective in the range 5 and 15 mol%, leading to the isoindolinones **98** in high yields and with enantiomeric excesses from moderate to good.[52] Malonates were more effective (86% ee)[52] than β-ketoesters (72% ee).[54] Several aldehydes, were reacted giving a wide range of chiral isoindolinones **98**: better results, in terms of yields and enantioselectivity, were obtained with those bearing electron-withdrawing groups onto the aromatic ring.[52]



Scheme 34. Asymmetric synthesis of fused benzoindolizidinones.

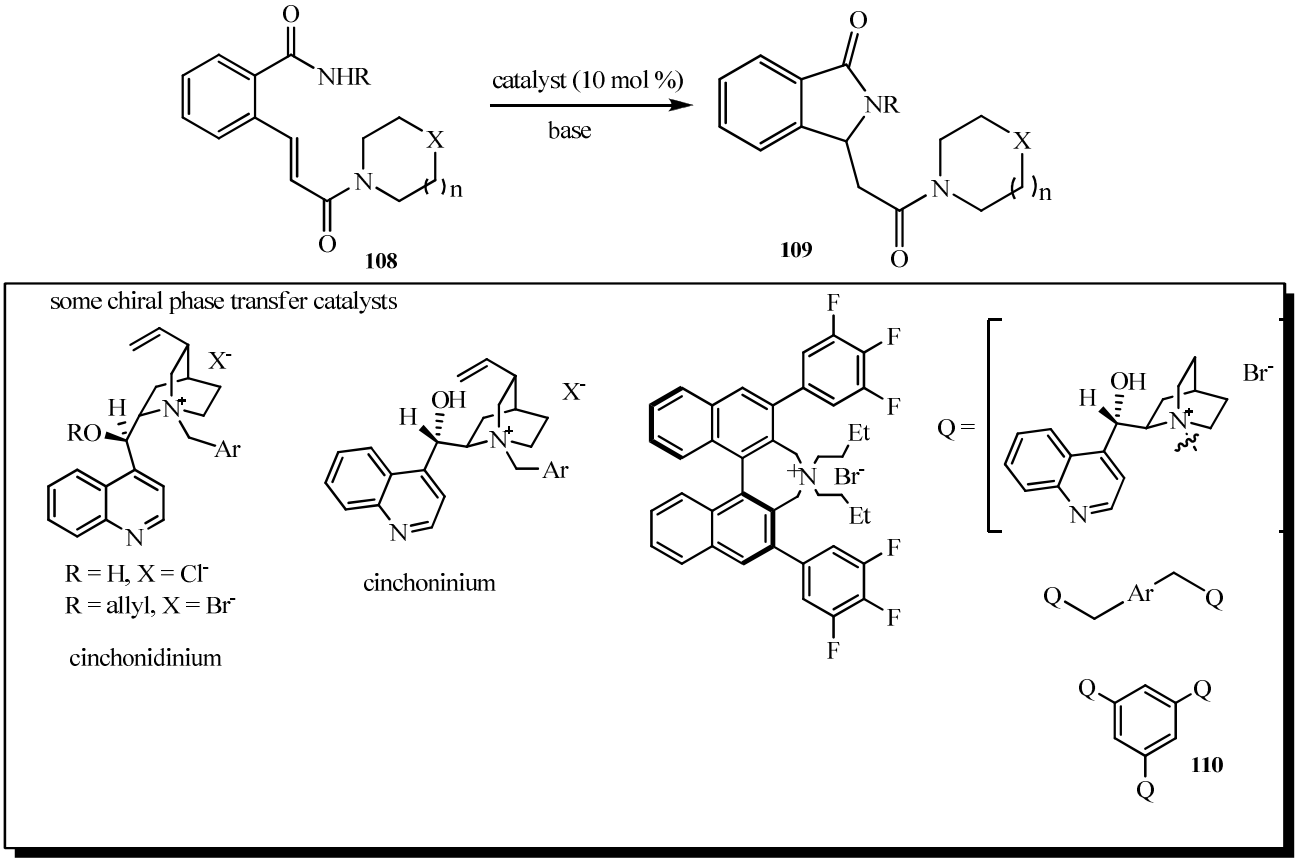
The tandem process of Scheme 32 was also useful in the development of an asymmetric version under phase transfer conditions with combinations of chiral ammonium salts and inexpensive inorganic bases like K_2CO_3.[55] High yields and ees up to 46%, were observed in the presence of the bifunctional chiral phase

transfer catalyst **103** obtained from quinine[56] or with **104** derived from cyclohexyldiamine.[52,55] On the other hand, commercially available PTCs like the cinchona alkaloids ammonium salts and a Maruoka's catalyst[57] were less effective.

An efficient process of heterochiral crystallization (isoindolinones crystallize as racemic solids, while the highly enantioenriched compounds are recovered from the solution) led to a further enrichment up to >99% ee for several substrates still in good yields (up to 75%), making the entire process particularly useful from a preparative point of view. The crystallization was efficient also for substrates showing moderate enantiomeric excesses and for β-ketoesters derivatives crystallized from the diastereomeric mixture.

The absolute configuration of the enantioenriched isoindolinone **98a**, synthesized from dimethyl malonate, was attributed as (*S*) by VCD (vibrational circular dicroism) spectroscopy employing a new semi-empirical method based on the extended coupled oscillator (ECO) formalism. This finding was also confirmed by classical quantum mechanical calculations.[58] The obtained enantioenriched isoindolinones **98** were particularly useful for other transformations like the cascade 1,4-conjugated addition with the acrolein, followed by the cyclization at the amide group (Scheme 34).[54,59]

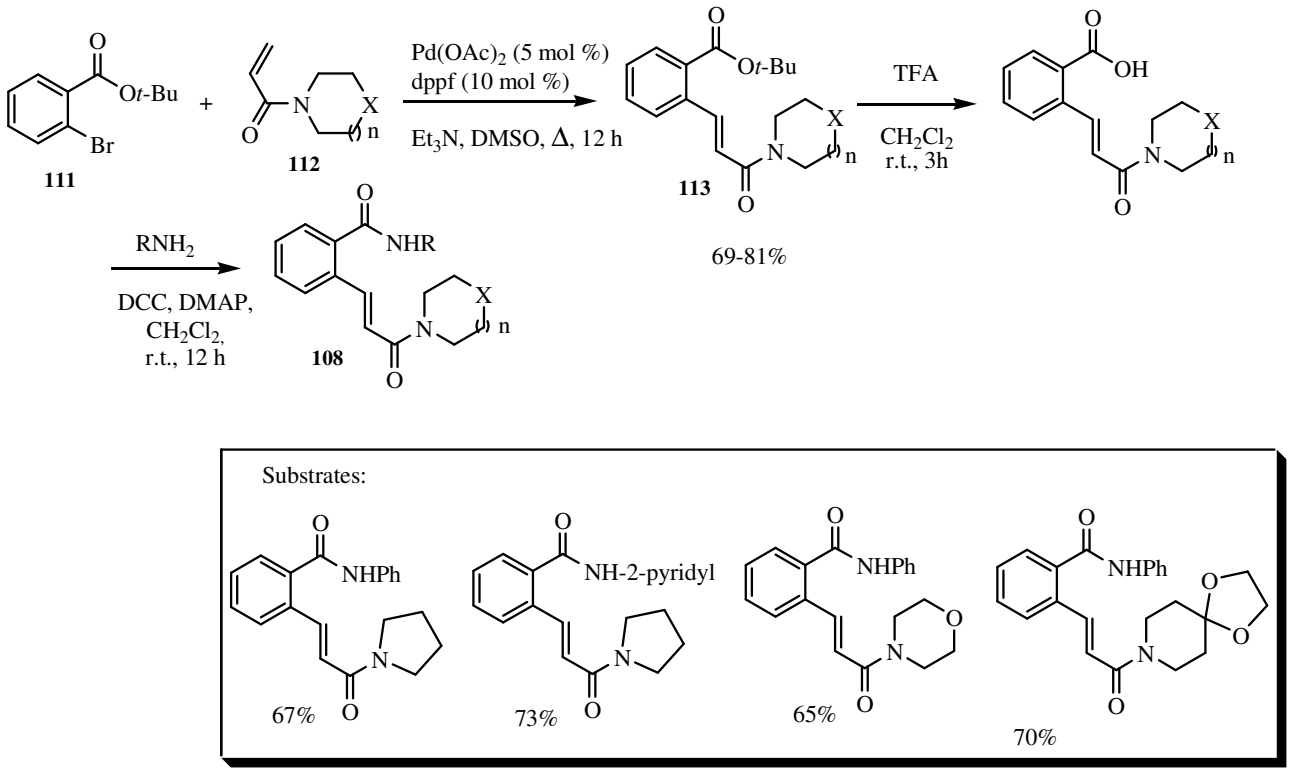
This process gave the access to other interesting heterocyclic compounds known as fused benzoindolizidinones **105** in high yields, high diastereoselectivity and unchanged enantiomeric purity. X-ray structure of **105a** (derived from **98a)** was also available, confirming the described structure with the hydroxyl group in axial position. Moreover, exploiting the reactivity of the hemiaminal functionality of these tricyclic adducts, further stereoselective transformations were performed, giving the derivatives **106** and **107** with up to 3 stereocenters in good yields and with high selectivity. [54,59]



Scheme 35. Chiral phase transfer catalysts in intra-molecular aza-Michael cyclization.

In 2013, Deniau, Michon *et al.* described an asymmetric approach to 3-functionalized isoindolinones **109** in the presence of chiral phase transfer catalysts (Scheme 35).[60] Unsaturated benzamides **108** were employed as starting materials in an asymmetric intramolecular aza-Michael reaction leading to the construction of the lactam ring system and the concomitant formation of the stereogenic center at C3 (Scheme 35). The substrates were designed to yield compounds, analogues of Pazinaclone **2** and of other benzodiazepine-receptor agonists (Figure 3). However, good yield and enantioselectivity of 76% ee was obtained only in the presence of the ammonium salt **110** and with one substrate (R=Ph, n=0, x=CH_2), while the other tested substrates gave rather low ees probably because of background non-asymmetric cyclization.

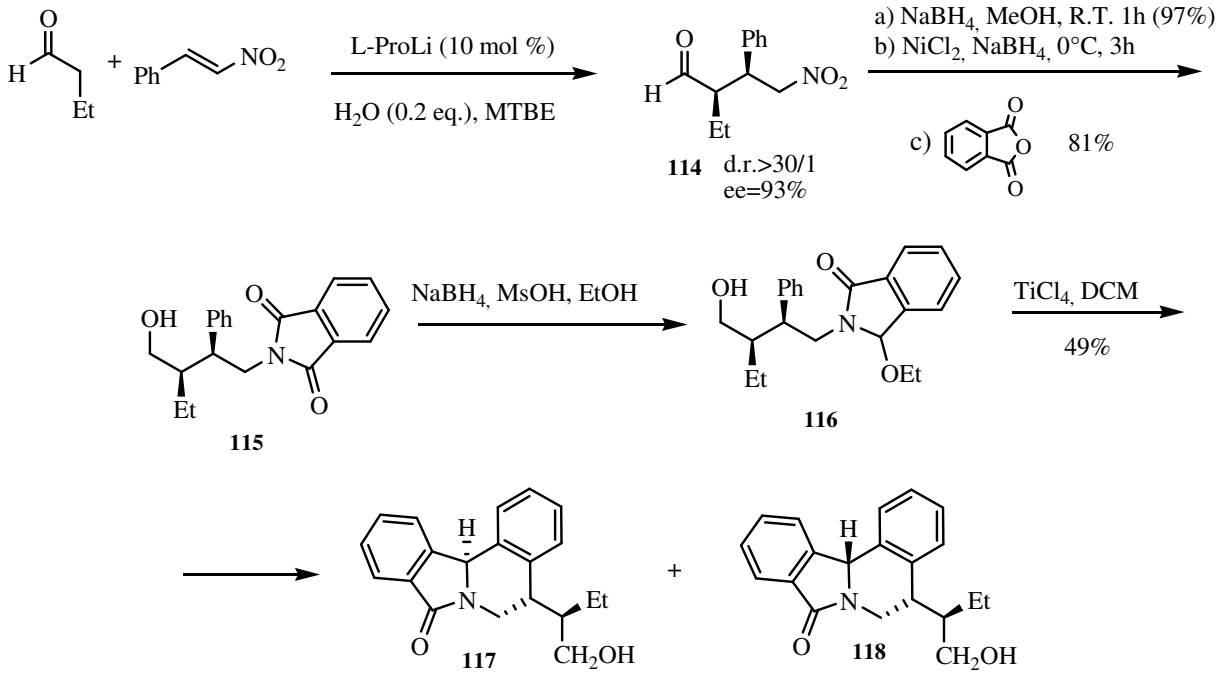
The starting materials **108** were prepared according to the Scheme 36, *via* a two-step sequence consisting of a cross-coupling Heck type reaction between the 2-bromoester **111** and acrylamides **112** followed by deprotection of the *t*-butyl esters **113** and finally the formation of the amide **108**.



Scheme 36. Synthesis of the unsaturated substrates used in the asymmetric intra-molecular conjugated addition.

Recent studies about highly diastereo- and enantioselective Michael reactions of propanal to β-nitrostyrene catalyzed by proline lithium salt afforded a key intermediate **114** employed in the multi-step synthesis of isoindoloisoquinolinones **117** and **118** at gram scale (Scheme 37).[61]

The lithium ion plays a crucial role in improving the chemical yield and stereoselectivity of the product, giving the adduct in predominantly *syn* manner and with high ee. Then, the reduction of the formyl and nitro groups in separate steps, afforded an aminoalcohol which was classically reacted with phthalic anhydride to give the phthalimide derivative **115**. Then, the reduction of **115** with $NaBH_4/CH_3SO_3H$ in anhydrous EtOH, followed by cyclization of **116** *via* an *N*-acyliminium ion intermediate, led to the formation of isoindoloisoquinolinone derivatives **117** and **118** in a 1:1 ratio.



Scheme 37. Proline organocatalyst in the synthesis of polycyclic derivatives.

4. Conclusions

The last years have highlighted an increasing interest in the asymmetric synthesis of chiral 3-substituted isoindolinones due to the numbers of applications as bioactive compounds. Considering the necessity of testing enantio-enriched compounds and comparing the activity with the respective racemates, since the early days of isoindolinones story, the employed techniques reflect the advancing of the state of the art in the asymmetric synthesis. In other words, this story can be considered an emblematic example of the evolution of asymmetric synthesis: starting from resolution of racemates by crystallization or by chiral HPLC, passing from the use of chiral auxiliaries it comes to the current catalytic asymmetric approaches in the presence of chiral metal complexes or organocatalysts.

Acknowledgments

MIUR and University of Salerno for financial support.

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