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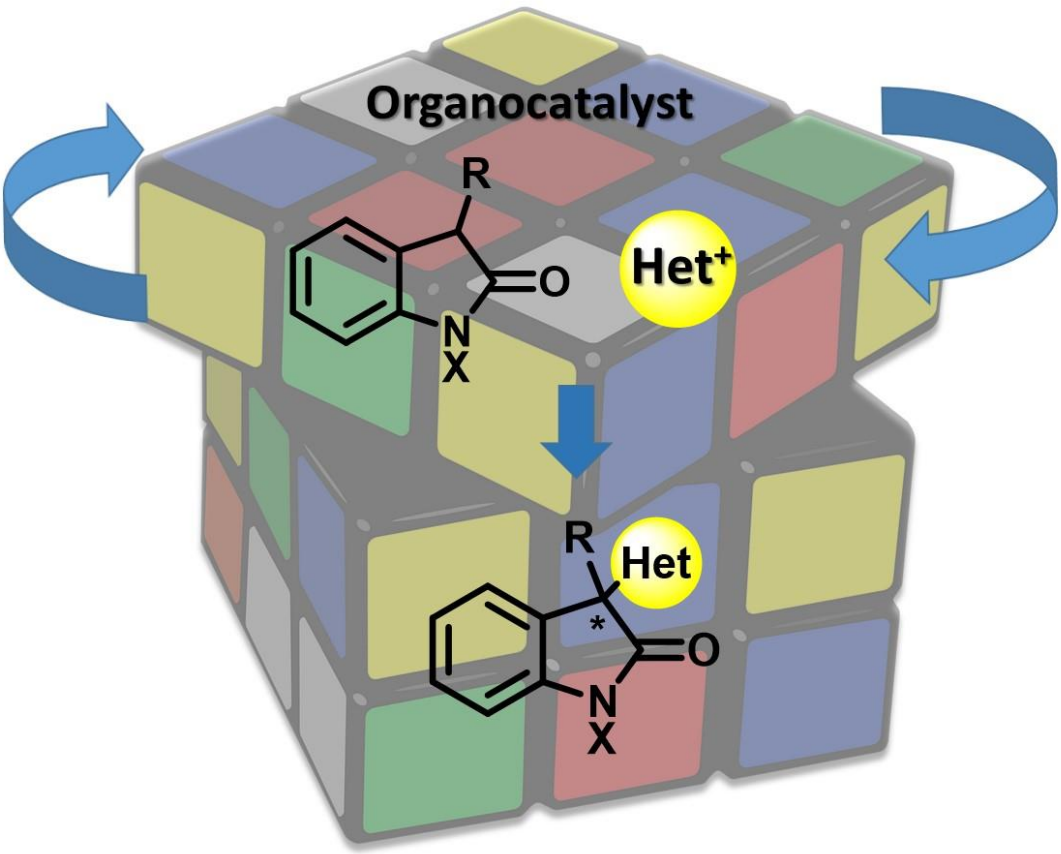
REVIEW

Asymmetric Organocatalytic Electrophilic Heterofunctionalization of Oxindoles

Megan Freckleton,[a] Alejandro Baeza,*[a] Llorenç Benavent,[a] Rafael Chinchilla*[a]

Dedication ((optional))



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REVIEW

Abstract: The asymmetric synthesis of 3-substituted oxindoles is a topic of importance due to the presence of this moiety in many natural products and drugs. In the last decade, great advances have been made in the asymmetric synthesis of 3-heteroatom-substituted oxindoles mainly due to major improvements in asymmetric organocatalysis. This review will focus on the different types of asymmetric electrophilic organocatalised reactions which oxindoles can undergo to form enantioenriched 3-heterosubstituted oxindoles, such as amination, halogenation, hydroxylation and sulfenylation processes.

1. Introduction

Oxindoles are aromatic heterocyclic organic compounds with a bicyclic structure that are found in the tissues and body fluids of mammals, and in the natural products of some plants.[1] They are credited to have a wide range of applications and are reported to exhibit an extensive range of biological effects which include antiviral, antifungal, antibacterial, antiproliferative, anticancer, anti-inflammatory, antihypertensive and anticonvulsant activities.[2] Particularly, substituted oxindoles containing a chiral centre with a heteroatom at the C3 position are attractive targets in organic synthesis as drug cadidates and also for their use as intermediates in alkaloid synthesis.[3] Among the different strategies developed for the asymmetric construction of these oxindoles, the asymmetric organocatalysed electrophilic heterofunctionalization has emerged as a powerful tool.[4] There are many advantages in the use of organocatalysts: usually they are simple to prepare, easy to handle and there is no risk of metal contamination in the final product.[5] This review will focus on the many types of electrophilic heterofunctionalization reactions that oxindoles can undergo using organocatalysis, such as amination, halogenation, hydroxylation and sulfenylation, in order to create chiral C3 centres. For the sake of clarity, the corresponding heterofunctionalization reaction has been divided according to the type of organocatalyst employed.

2. Amination

The development of efficient methods to prepare 3-aminooxindoles is of current interest[6] owing to the wide presence of these frameworks in bioactive natural products[7] and pharmaceutically active compounds.[8] In the last years, many studies have shown that the organocatalytic asymmetric 3-amination of oxindoles is a simple and straightforward reaction, which can drive to high enantioselectivities with a broad substrate scope.[9]

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Alejandro Baeza was born in Alicante in 1979. After studying chemistry at the University of Alicante, he received the M.Sc. (2003) and Ph. D. degrees (2006) from the same University. In 2007 he joined Prof. Pfaltz group in Basel University as postdoctoral researcher for 3 years. In 2010 he moved back to Alicante as associate researcher and in 2015 he was appointed Assistant Professor. His interests are focused in the development of new methodologies, especially in asymmetric catalysis area.

Llorenç Benavent was born in Valencia in 1993. After studying chemistry at the University of Valencia (2015), he received the M.Sc. (2016) at the University of Alicante under the supervision of Dr. A. Baeza. Currently, he is pursuing his Ph.D. studies within the same research group in the field of asymmetric organocatalysis.

Rafael Chinchilla was born in Alicante and studied chemistry at the University of Alicante from which he was graduated (1985) and doctorated (1990). After a postdoctoral stay at the University of Uppsala (1991-1992) with Prof. J.-E. Bäckvall, he moved back to the University of Alicante where he was appointed Associate Professor in 1997 and Full Professor in 2012. His research interests are mainly focused on enantioselective syntheses by using organocatalysis.

2.1. Brønsted Base Catalysis

In 2009 three independent research groups reported, almost simultaneously, the organocatalytic enantioselective electrophilic amination reaction of 3-substituted oxindoles, using azodicarboxylates as nitrogen source and a cinchona alkaloid as an organocatalyst. Chronologically, the group of Liu and Chen

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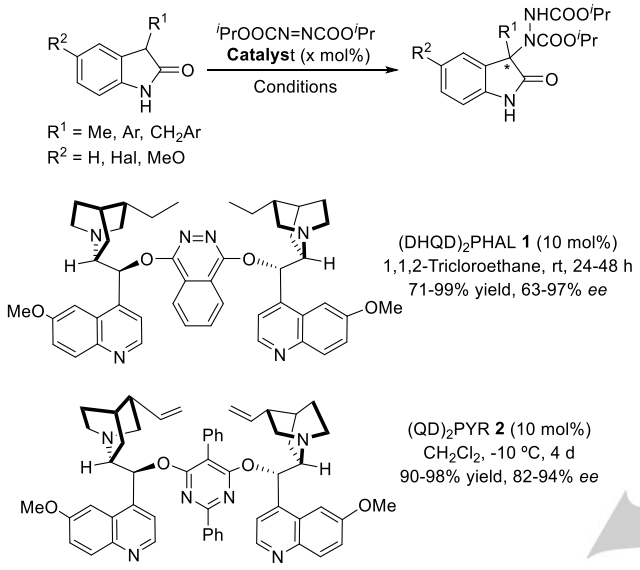
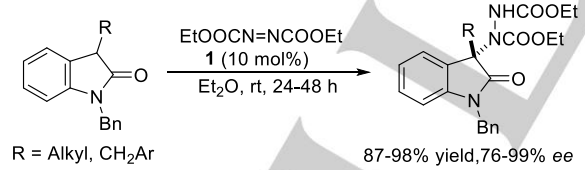
reported high yields and enantioselectivities ranging from good to high when the amination of unprotected oxindoles was performed using dimeric dihydroquinidine-derived $(DHQD)_2PHAL$ (**1**) as an organocatalyst and diisopropyl azodicarboxylate (DIAD) as amination reagent.[10] Similar results were obtained by Zhou and co-workers when the conditions were slightly varied. Thus, in this case dimeric quinidine-derived $(QD)_2PYR$ (**2**) and CH_2Cl_2 were the preferred organocatalyst and solvent, respectively (Scheme 1).[11]



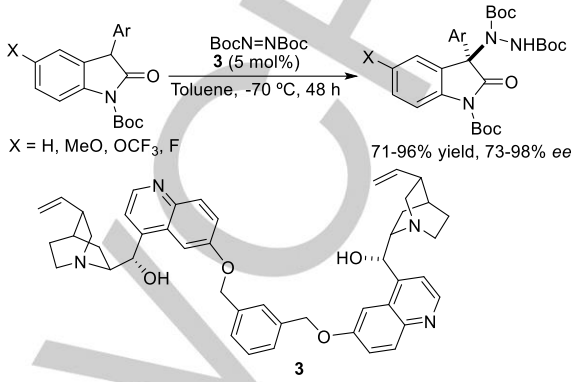
Scheme 1. Amination of unprotected oxindoles with DIAD.

Shortly after, Barbas and co-workers reported the asymmetric C3-amination of *N*-benzyl protected oxindoles, using dimeric cinchona-derived organocatalyst **1** and diethyl azodicarboxylate (DEAD) as electrophilic aminating reagent (Scheme 2). The protection of the nitrogen allowed broadening the scope of oxindoles used, obtaining slightly better results than when the unprotected analogues were employed.[12]



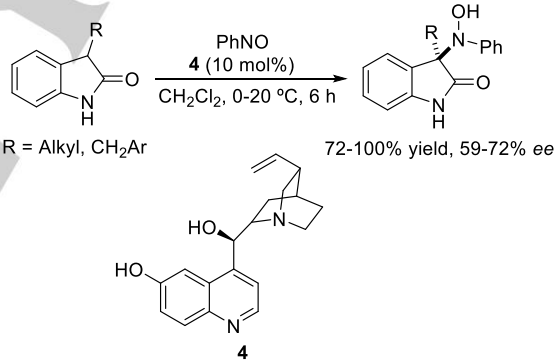
Scheme 2. Organocatalytic amination of *N*-benzyl protected oxindoles.

In another study, the same group reported the amination of *N-tert*-butoxycarbonyl (Boc)-protected 3-aryloxindoles, which was carried out using dimeric quinidine **3** as an organocatalyst (Scheme 3).[13] The desired C3-aminated oxindoles were obtained with good yield and excellent enantioselectivities. The researchers also looked further into the role of the dimeric quinidine structure of the catalyst in its stereoselective behavior by studying its analogues. They discovered that the catalyst is multifunctional, as it contains Brønsted acid, Lewis basic and π-stacking sites to ensure the high enantioselection achieved. In addition, it has been found that the asymmetric aminooxygenation of *N*-arylmethyl-protected oxindoles with nitrosobenzene can be accomplished using the same catalyst **3**.[14] However, instead of forming a C-N bond at the C3 position, a C-O bond is created, providing a new method of synthesizing 3-hydroxyoxindoles.



Scheme 3: Organocatalytic amination of *N*-Boc-protected oxindoles.

However, using nitrosobenzene and unprotected oxindoles, Liu and Chen could obtain the corresponding hydroxyamination products with high yields and good enantioselectivities by employing cinchona organocatalyst **4** (Scheme 4).[15]



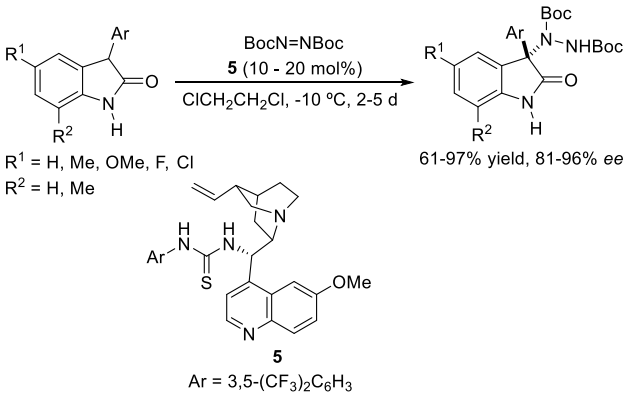
Scheme 4: Hydroxyamination of oxindoles with nitrosobenzene.

After these works, no other amine organocatalysts able to perform this amination reaction have been reported in the literature. However, new catalytic systems have been developed more recently where the C3-amination of oxindoles with diethyl azodicarboxylate can be organocatalysed by resin-supported cinchona alkaloids, obtaining high enantioselections with a very high recycling ability.[16]

2.2. Hydrogen Bonding Catalysis

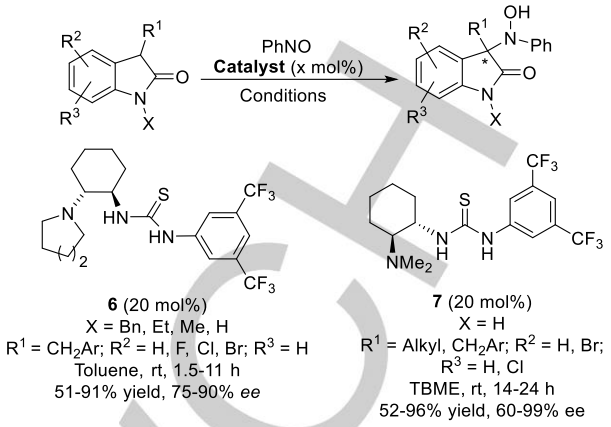
The irruption in the last years of hydrogen bonding catalysis led to the publication of several works concerning the asymmetric electrophilic amination of oxindoles using this type of catalysts. Thus, in 2011, the direct amination of 3-aryl and 3-alkyl oxindoles

with di-*tert*-butyl azodicarboxylate using a bifunctional quinine-derived thiourea **5** as an organocatalyst was described, giving rise to good yields and enantioselectivities of the corresponding aminated products (Scheme 5).[17]



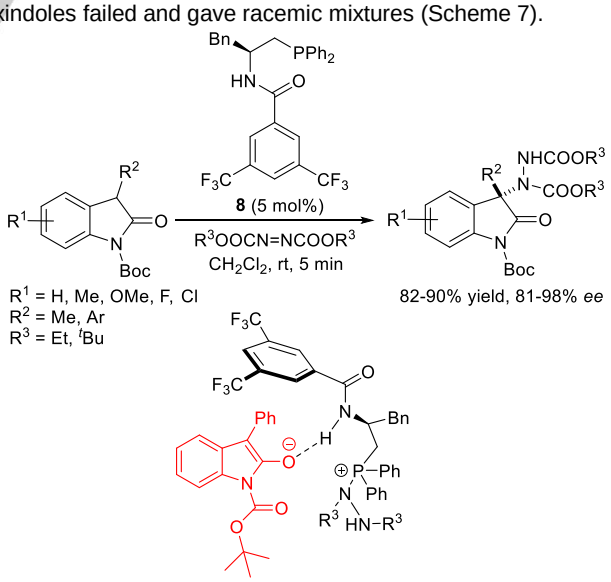
Scheme 5: Amination of oxindoles using thiourea-cinchona alkaloid catalyst **5**.

After this seminal work, two articles appeared concurrently describing the asymmetric hydroxyamination of oxindoles with nitrosobenzene using thiourea-based organocatalysts. Thus, catalyst **6** was efficiently used for the amination of both *N*-protected and unprotected oxindoles, affording the corresponding products with high yields and enantioselectivities.[18] The same authors have recently used organocatalyst **6** for the construction of chiral spirooxindoles with good yields and high enantioselectivities (up to 95% *ee*), performing the same reaction using C3 alkyl ester-substituted oxindoles as starting materials.[19] On the other hand, Takemoto's thiourea catalyst **7** turned out to be slightly more selective in the enantioselective hydroxyamination reaction of oxindoles with nitrosobenzene, starting from unprotected oxindoles (Scheme 6).[20] In both articles, the proposed transition state suggests a bifunctional role of the catalysts, activating the reaction through tertiary amine and hydrogen bonding catalysis. In the case of using Takemoto´s catalyst **7**, it was also found that the regiochemical outcome of the reaction was dependent on the starting oxindole. Thus, if the oxindole was *N*-benzyl protected, an aminoxylation reaction occurs instead of an oxyamination reaction, contrary to the results observed when using catalyst **6**. It is hypothesized that this change is due to an intermolecular hydrogen bonding of the enolate oxygen in the unprotected 3-substituted oxindoles.



Scheme 6: Amination of oxindoles with nitrosobenzene using thiourea-tertiary amine organocatalysts.

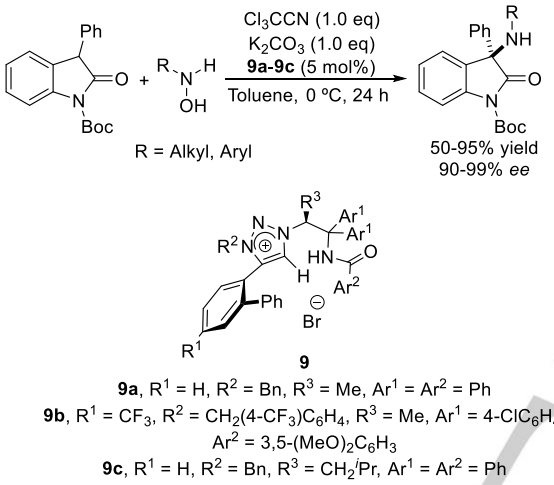
An efficient method of achieving the enantioselective amination of 3-aryl-substituted *N*-Boc protected oxindoles with azodicarboxylates, using an amino acid-derived chiral phosphine organocatalyst **8** has been recently reported (Scheme 7).[21] The process gives rise to a very effective methodology, as the reaction can reach completion in only 5 minutes, achieving high yields and enantioselectivities by using an organocatalyst loading of only 5 mol%. The suggested transition state model justifying the final results was based on the ^{31}P NMR spectra. Thus, the researchers hypothesize that the mechanism of the reaction involves addition of the organocatalyst, containing a tertiary phosphine, to the electrophile, generating *in situ* a zwitterionic species which can act as a Brønsted base deprotonating the oxindole. The resultant enolate would be coordinated with the catalyst via hydrogen bonding and static interactions. However, alkyl 3-substituted oxindoles failed and gave racemic mixtures (Scheme 7).



Scheme 7: Amination of using organocatalyst **8.**

2.3 Phase-Transfer Catalysis

Surprisingly, it was not until recently that a phase-transfer catalyst was employed for the amination of oxindoles, using a completely different approach than previously published. Thus, the report by Ooi and co-workers, describes that the electrophilic asymmetric C3-amination of oxindoles can be achieved using chiral 1,2,3-triazolium salts **9** as catalysts after an *in situ* activation of readily available hydroxylamines with trichloroacetonitrile, forming electrophilic *O*-imino hydroxylamines as amination species (Scheme 8).[22] The reaction is very effective and straightforward and the scope is very diverse as a wide array of alkyl and aryl substituents on the amine nitrogen source can be used. With this strategy, different 3-aryl and 3-alkyl-substituted oxindoles were C3-aminated in good yields and excellent enantioselectivities.



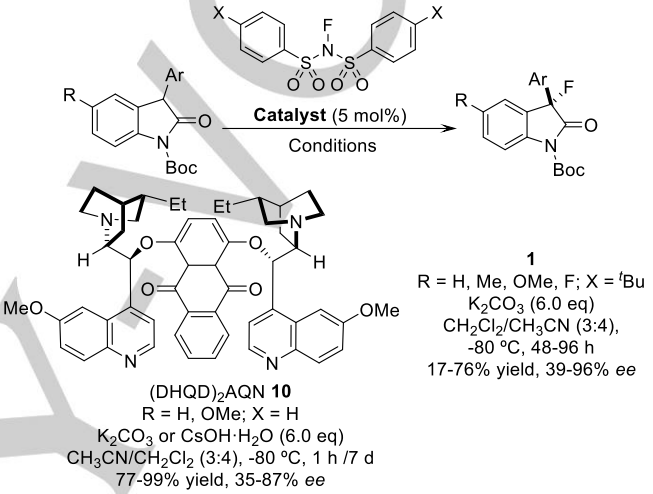
Scheme 7: Amination of oxindoles using organocatalyst **9**.

3. Halogenation

The exchange of the 3-hydrogen of oxindoles by halogens is an interesting way of improving the biological activity of these molecules for pharmaceutical applications. Thus, nowadays widespread popularity of fluorinated drugs is attributed to their advantageous bioavailability, metabolic stability, and other pharmacological properties that often compare favorably to those of the nonfluorinated parents.[23] 3-Substituted 3-fluorooxindoles have shown an interesting medicinal potential,[24] and, additionally, the substitution for chlorine can also be beneficial for similar reasons.

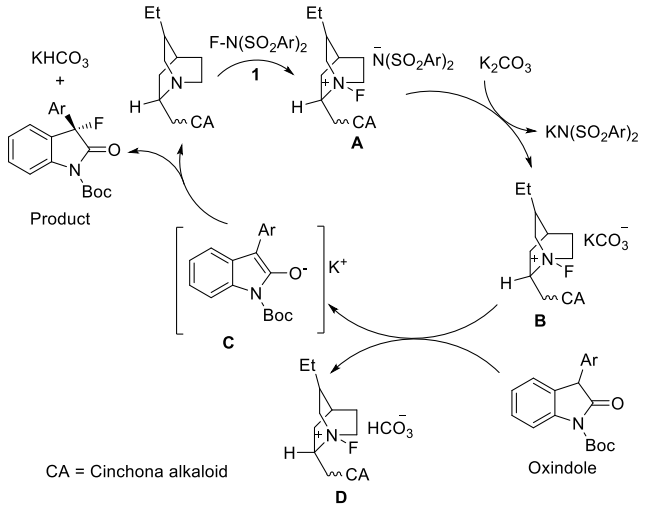
3.1 Fluorination

At the beginning of this century, a pioneering work by Shibata and co-workers described a new method for the asymmetric enantioselective C3-fluorination of oxindoles. The procedure used a stoichiometric combination of various cinchona alkaloid derivatives and Selectfluor®, improving previous studies that employed unstable fluorine sources leading to multistep procedures.[25] However, it was not until some years later when the same group established a successful procedure for the organocatalytic enantioselective C3-fluorination of oxindoles, by using a catalytic amount of bis-cinchona-derived alkaloid $(DHQD)_2AQN$ (**10**) and *N*-fluorobenzenesulfonimide (NFSI) as electrophilic fluorine (Scheme 9).[26] Some years later, another work was reported in which $(DHQD)_2PHAL$ (**1**) was used as an organocatalyst instead. The authors now could slightly increase the previous reported enantioselectivities by using some substituted NFSI analogues. Among them, those bearing *tert*-butyl groups at the *para*-position of the phenyl rings produced the highest enantioselectivities (Scheme 9).[27]



Scheme 9: Organocatalysed fluorination of oxindoles.

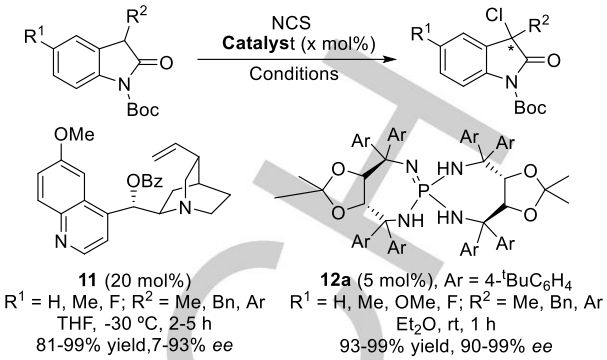
In both articles, a similar catalytic cycle for this reaction was proposed (Scheme 10). The researches hypothesize that the NFSI analogues react with the quinuclidine ring of the cinchona-derived organocatalyst to afford intermediate **A**. This species moves the inorganic base to the organic phase by acting as phase-transfer catalyst, affording intermediate **B**, which then promotes the enolization of the oxindole to form enolate **C** and intermediate **D**. Then either intermediates **A** or **B** or NFSI, can fluorinate the enolate generating the final product.



Scheme 10. Proposed catalytic cycle for the catalytic asymmetric organocatalysed fluorination of oxindoles.

3.2 Chlorination

The organocatalytic asymmetric chlorination of oxindoles is a rare reaction.[28] There are very few examples, mainly based on the use of Brønsted bases as organocatalysts. One example is the enantioselective C3-chlorination of 3-aryloxindoles using the cinchona alkaloid derivative **11** as an organocatalyst and *N*-chlorosuccinimide (NCS) as the chlorine source (Scheme 11).[29] The procedure gave rise to the corresponding 3-aryl-3-chlorooxindoles in high yields and moderate to high enantioselectivities under mild reaction conditions. However, the use of 3-alkyl and 3-benzyl-substituted oxindoles rendered the chlorination product in low optical purity. In addition, a similar chlorination procedure has been performed, but using an iminophosphorane base organocatalysts **12a** (Scheme 11).[30] Despite that the synthesis of the catalyst is much more complicated, this organocatalytic procedure has advantages over the previous one. Thus, it uses considerably lower catalyst loadings and higher conversions and enantioselectivities were achieved after a short reaction time at room temperature. Furthermore, alkyl and benzyl substituents at C3 were well tolerated and excellent results were also achieved. Finally, it is worth mentioning that the catalyst could be recycled up to six times after chromatographic purification with almost no decrease in efficiency.

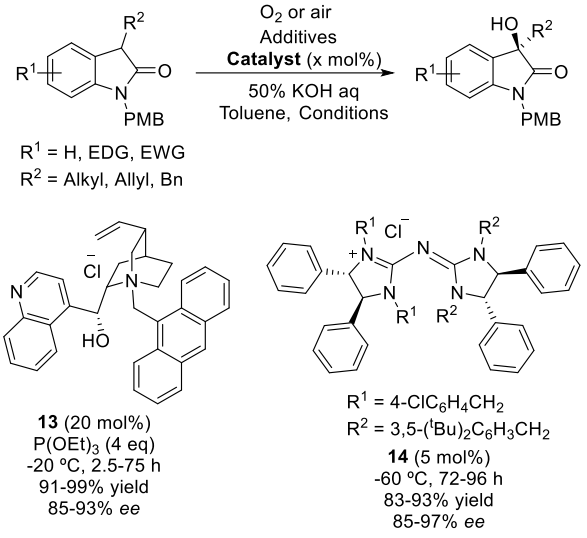


Scheme 11: Organocatalytic chlorination of oxindoles with NCS.

4. Hydroxylation

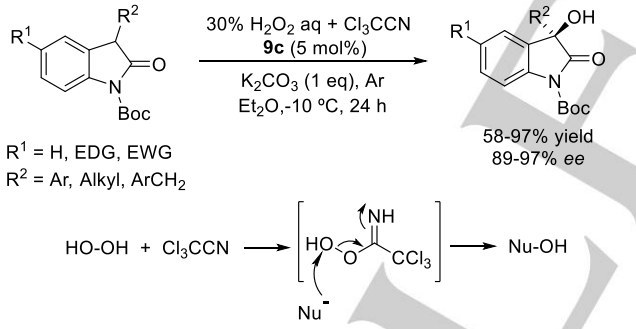
3-Hydroxyoxindole-containing compounds have recently received extensive attention due to their diverse biological activities in medicinal chemistry,[31] the asymmetric C3-hydroxylation of oxindoles being therefore considered of high interest.[32] Only phase-transfer catalysis has been used to achieve the asymmetric electrophilic hydroxylation of oxindoles.

The organocatalytic enantioselective hydroxylation of 3-substituted oxindoles with molecular oxygen, using cinchonidine-derived phase-transfer catalyst **13** was developed in 2008 by Itoh's group (Scheme 12).[33] This reaction is very effective and simple, as the use of air as the oxygen source is inexpensive and eco-friendly. However, the use of 4 equivalents of $(EtO)_3P$ as reducing agent turned out to be crucial for achieving high yields when *N*-*p*-methoxybenzyl (PMB)-protected oxindoles were employed, obtaining also high enantioselectivities. In subsequent studies, pentanidium-based phase-transfer catalyst **14** was employed for the enantioselective hydroxylation of oxindoles using molecular oxygen, the results being, in terms of enantioselectivity, slightly better than in the previous case (Scheme 12).[34] What is significant about this procedure is that there is no need for an additional reducing agent. According to the authors, this reaction proceeds via a kinetic resolution of the hydroperoxyl oxindole intermediate by means of its reduction by the *in situ* generated enolate of the 3-substituted oxindole. In further studies by the same research group, different tests were conducted to verify the proposed reaction pathway. In addition, by adjusting reaction conditions, they were able to obtain the hydroperoxyl oxindole as the major product, which is also an interesting compound for medical purposes.[35]



Scheme 12: Hydroxylation of oxindoles using various phase-transfer catalysts.

More recently, a new and practical method for the hydroxylation of C3-substituted oxindoles was developed using the *in situ* generation of an electrophilic oxygenating agent created from hydrogen peroxide and trichloroacetonitrile as activator, and the presence of a chiral phase- transfer organocatalyst **9c** (Scheme 13).[36] Using *N*-Boc protected oxindoles, excellent yields and enantioselectivities were obtained independently of the substitution pattern at 3-position.



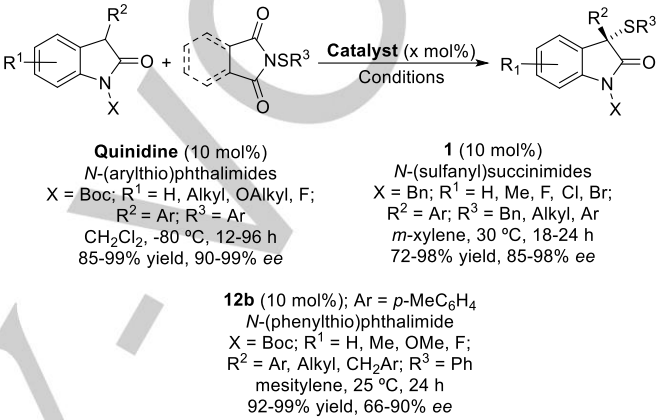
Scheme 13: Hydroxylation of oxindoles with organocatalyst **9c** and activation of hydrogen peroxide by trichloroacetonitrile.

5. Sulfenylation

Anticancer, antifungal, and antitubercular activities have been found in many oxindoles with a sulfur-containing group at the chiral C3 centre.[37] Therefore, methods to obtain 3-sulfenyl-2-oxindoles are the subject of much research and various ways of preparing them organocatalytically have been reported.

5.1 Brønsted Base Catalysis

In 2012, two different papers described almost simultaneously that the asymmetric electrophilic sulfenylation of 3-aryloxindoles could be achieved by using cinchona-derived alkaloids. (Scheme 14). In the first report, the use of *N*-(phenylthio)phthalimide and 10 mol% of quinidine as catalyst allowed the sulfenylation of *N*-Boc protected 3-aryloxindoles with excellent yields and enantioselectivities.[38] Similar results were observed shortly after when $(DHQD)_2PHAL$ (**1**) was employed as an organocatalyst for the electrophilic amination reaction of *N*-benzyl protected oxindoles, using *N*-(sulfanyl)succinimides as sulfenylation reagents. In this case, the methodology was applicable to a broader scope of 3-substituted oxindoles, since substrates with 3-alkyl and 3-benzyl substituents were successfully employed.[39]

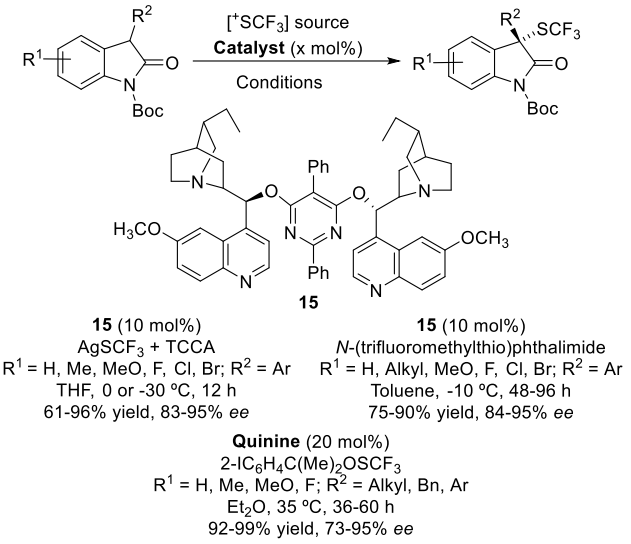


Scheme 14: Sulfenylation of oxindoles using Brønsted base catalysts.

More recent research has been focused on the asymmetric sulfenylation of 3-CF_3-oxindoles[40] and 3-pyrrolyloxindoles,[41] by following the already described methodologies using quinidine-derived and cinchonidine as catalysts, respectively.

Finally, it has been very recently described that the sulfenylation of 3-substituted oxindoles can also be achieved by using chiral tartaric acid derived iminophophoranes **12b** as organocatalysts, using *N*-(phenylthio)phthalimide as the electrophilic sulfur source (Scheme 14).[42] The reaction afforded high yields and enantioselectivities, showing a wide scope. Notably, 3-aryl and 3-methyl-substituted oxindoles gave rise to the (*S*)-enantiomer, while 3-aryldiene and 3-isobutyl substituents gave the opposite (*R*)-enantiomer.

The presence of a trifluoromethylthio (SCF_3) group in the structure of biologically active compounds gives rise to some useful properties, such as a higher electron-withdrawing ability and higher lipophilicity, which enhances their transmembrane permeation improving their bioavailability.[43] Therefore, the addition of SCF_3 to oxindoles may lead to interesting developments for pharmacological applications. The trifluoromethylthiolation of oxindoles can be carried out by using Brønsted base catalysts, particularly cinchona alkaloid-derived organocatalysts (Scheme 15).

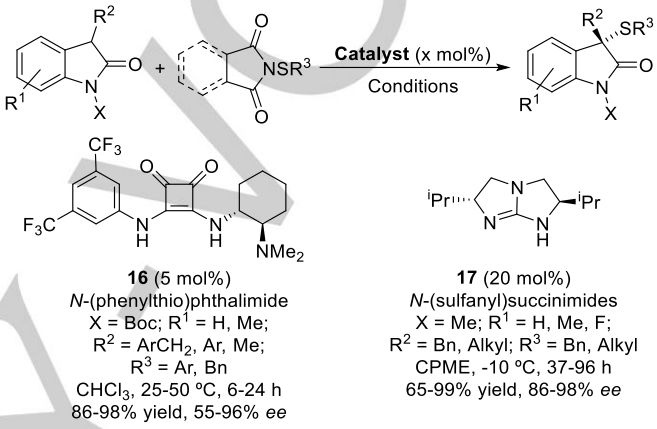


Scheme 15: Trifluoromethylation of oxindoles using Brønsted base catalysts.

Thus, in 2014 it was established that the asymmetric trifluoromethylthiolation of 3-arylated oxindoles could be achieved via *in situ* generation of an active electrophilic triofluoromethylthio species from $AgSCF_3$ and trichloroisocyanuric acid (TCCA) (Scheme 15).[44] While screening for the optimal reaction conditions, it was observed that bifunctional catalysts with a hydrogen bonding component had an undesirable effect into enantioselectivity. However, it was found that dimeric cinchona alkaloid organocatalysts such as $(DHQD)_2PYR$ (**15**), were ideal for this reaction. The scope of this reaction is broad as both electron-donating and electron-withdrawing substituents on the oxindole can afford high yields and enantioselectivities of the final products. The main advantage of this procedure is the fact that the starting materials are cheap and there is no need for the isolation of the SCF_3 reagent, saving time and money. In addition, the same organocatalyst can be used for the enantioselective synthesis of 3-aryl-3-SCF_3-substituted oxindoles using *N*-(trifluoromethylthio)phthalimide with good results (Scheme 15).[45] Moreover, the asymmetric trifluoromethylthiolation of oxindoles was carried out using trifluoromethyl-substituted thioperoxide as the electrophilic reagent and quinine as organocatalysts, affording 3-substituted-3-SCF_3 oxindoles (Scheme 15).[46] When exploring the scope of this reaction, an exchange of the *N*-protecting group from Boc to less hindered groups, caused any noticeable change in the enantioselectivity. It was also observed that the 3-trifluoromethylthiolated reaction products from 3-arylated oxindoles had lower optical purity than those from 3-alkylated ones.

5.2 Hydrogen Bonding Catalysis

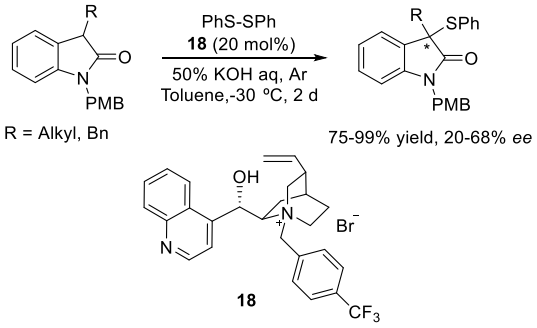
In 2012, Enders' group reported the use of squaramide **16** as an effective hydrogen-bond organocatalyst for the sulfenylation of *N*-Boc-protected oxindoles, obtaining high yields and enantioselectivities of the final products, especially when 3-aryl-substituted oxindoles were employed as substrates (Scheme 16).[47] More recently, a highly enantioselective sulfenylation reaction of 3-benzyl/alkyl oxindoles with *N*-(sulfanyl)succinimides was developed, using chiral bicyclic guanidine **17** as a bifunctional hydrogen-bond-based organocatalyst in the highly hydrophobic cyclopentilmethyl ether (CPME) as solvent (Scheme 16).[48] This procedure was found to be applicable to a large variety of substituted oxindoles never used before, even 3-oxofuranones being sulfenylated with good results. The authors proposed a transition state in which the bifunctional role of the catalyst is shown, acting both as a superbase and a hydrogen-bond-forming catalyst.



Scheme 16: Sulfenylation of oxindoles using hydrogen bonding organocatalysts.

5.3 Phase-Transfer Catalysis

The asymmetric sulfenylation of 3-substituted oxindoles can also be achieved by using phase-transfer catalysts. Thus, it has been reported that this reaction can be organocatalysed by cinchonidine-derived phase-transfer catalyst **18**, using readily available diphenyl disulphide as sulfenylation reagent (Scheme 17).[49] The reaction had a broad scope, although only moderate enantioselectivities were obtained. In addition, phenyl-substituted oxindoles afforded the sulfenylated product as racemic mixtures. The researchers also conducted experiments to investigate the mechanism and it was found that the reaction apparently proceeds via a radical pathway.



Scheme 17: Sulfenylation of oxindoles with diphenyl disulphide.

6. Conclusions

The introduction of a heteroatom at the C3-position of oxindoles in an enantioselective manner can be considered as an important methodology for the preparation of new chiral entities with potential use as drug-candidates or as synthetic intermediates in the synthesis of molecules with biological activity. Among the different strategies developed for such purpose, the enantioselective organocatalytic electrophilic hetero-functionalization of 3-substituted oxindoles can be envisioned as the easiest and most straightforward one. This fact is reflected in the good amount of work done in this field in the last ten years, which has been shown in this review. Thus, amination, halogenation, hydroxylation and sulfenylation reactions have been reported so far using Brønsted base catalysis, hydrogen-bond catalysis and chiral phase-transfer catalysis. However, despite all the work already done, there is still plenty of room for improvement, since some limitations still need to be overcome. Thus, more research is needed for achieving the heterofunctionalization of unprotected oxindoles, since most of the developments employ *N*-protected starting materials. Another point, which should be improved, is the use of readily available or easy-to-obtain electrophilic reagents, since most of them are expensive or require several steps for their preparation. Finally, a better understanding of the reaction mechanisms would be desirable for many of the transformations herein presented. There are no doubts that further and interesting developments in this area will appear in next future.

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Keywords Oxindoles • Asymmetric Catalysis • Organocatalysis• Electrophilic Heterofunctionalization • Quaternary Stereocentres

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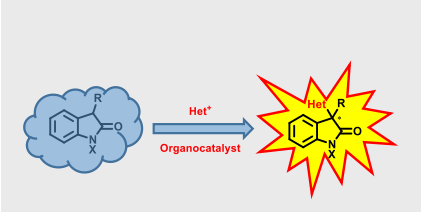
REVIEW



The organocatalyzed asymmetric electrophilic heterofunctionalization of 3-substituted oxindoles allows stablishing a new quaternary stereocenters bearing an heteroatom, which resulted in the formation of highly-valuable intermediates in organic synthesis. This strategy has experienced a significant grown in the last decade. Herein, the state of the art of the topic is gathered, presenting those successful examples and the limitations that must be overcome.

Megan Freckleton, Alejandro Baeza, Llorenç Benavent, Rafael Chinchilla**

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