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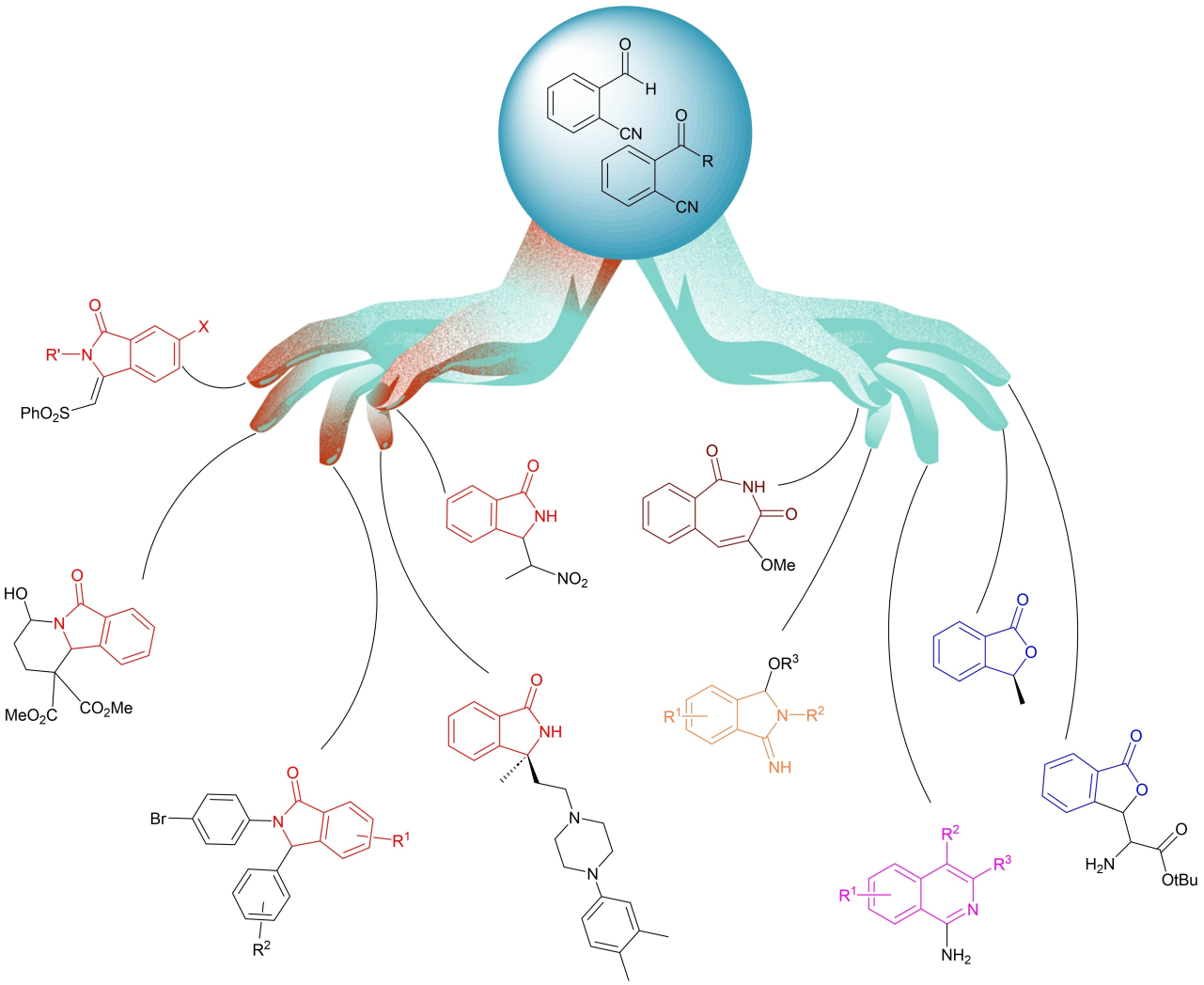
# Multifaceted Behavior of 2-Cyanobenzaldehyde and 2-Acylbenzonitriles in the Synthesis of Isoindolinones, Phthalides and Related Heterocycles

Mohammad Sadeq Mousavi,[a] Antonia Di Mola,[a] and Antonio Massa*[a]



2-Cyanobenzaldehye (also called 2-formylbenzonitrile) and related 2-acylbenzonitriles belong to a class of bifunctional aromatic compounds that emerged as useful starting materials in developing efficient cascade-type reactions leading to different heterocyclic compounds. The variety of sometimes unpredictable mechanisms that rise from these structurally simple starting materials renders this class of compounds unique to afford, through divergent cascade reactions, heterocycles like isoindolinones, phthalides (also known with the name of isobenzofuranones), imidates, and in less extent isoindolin-1-imine, six- and seven-membered heterocycles, porphyrins, also in asymmetric way exploiting different organocatalytic activation modes. To give a picture, this chemistry can be associated to Goldberg variations which stem from a common motive in a pressing and surprising way. In this Review, emphasis is also given to the synthetic methods for the access to substituted 2-cyanobenzaldehydes and 2-acylbenzonitriles which allowed to enlarge the scope of the described cascade reactions.

## 1. Introduction

"Unusual" is often the reaction of colleagues when they hear for the first time about the chemistry of 2-cyanobenzaldehyde (also called 2-formylbenzonitrile) and related 2-acylbenzonitriles. This is a human reaction to what usually is not thoroughly comprehensible, but what is unusual is that the potential applications of this chemistry have been neglected for a long time, since these starting materials can be efficiently used in the synthesis of a wide range of important heterocyclic compounds like isoindolinones,[1–2] phthalides[3] (also known with the name of isobenzofuranones), imidates,[1] and in less extent isoindolin-1-imine, six- and seven-membered heterocycles, porphyrins.[4]

Isoindolinones and phthalides are heterocycles of great interest in the scientific community because of the variety of biological activities of both natural products as hericenone B **1**, taliscanine **3**, nuevamine **7** and so on (Figure 1), and synthetic bioactive compounds as Pazinaclone **8**, (*S*)-PD17293818 **11** (Figure 2), or unsaturated derivatives (Figure 3), known as 3-methylene isoindolinones, that include fumaridine extracted from vegetable sources, compound **17** that has local anesthetic activity superior to that of procaine, compound **18** with mechanochromic properties, muscarinic receptor ligand **19**.[2] In these examples, it is possible to distinguish 3-unsubstituted, 3-substituted and 3,3-disubstituted derivatives.

Phthalides are also particularly popular. They are found in natural products as isopestacin **21**, vermistatin **22** with an important compound as (*S*)-3-butyl phthalide **20** showing a range of different of biological activities and in synthetic bioactive compounds (Figure 4).

However, the aim of this Review is not an analysis of the chemistry and the properties of these heterocyclic compounds, but it is a comprehensive critical discussion of the main applications of 2-cyanobenzaldehyde and 2-acylbenzonitriles in the synthesis of heterocycles, also focusing on asymmetric synthesis and mechanistic insights, ranging from the previous publications till the most recent applications. The synthetic methodologies for the obtaining of 2-cyanobenzaldehydes and 2-acylbenzonitriles are also described.

## 2. Synthesis of 3-substituted isoindolinones

The most relevant results about the use of 2-cyanobenzaldehyde regard the synthesis of 3-substituted isoindolinones. To our knowledge, the first article was reported by Sato and coworkers in 1984 in the synthesis of 3-amino substituted isoindolinones **28**, obtained in quantitative yields in most of the

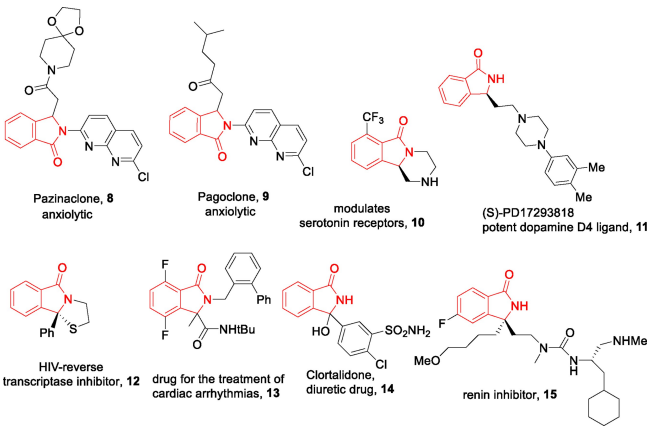



**Figure 1.** Isoindolinones natural products.

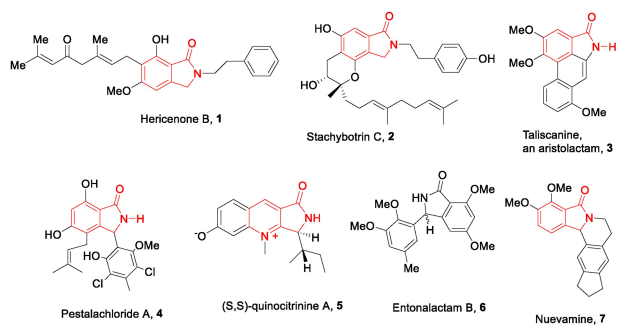



**Figure 2.** Synthetic bioactive isoindolinones.

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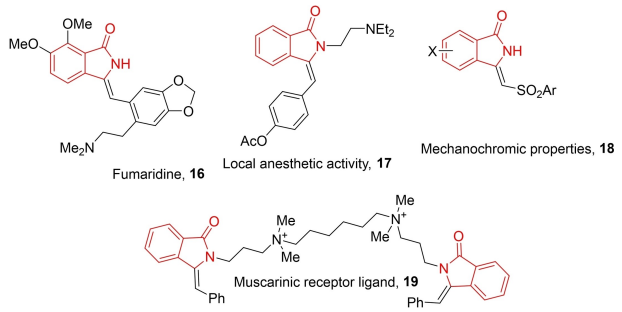



**Figure 3.** 3-methylene isoindolinones.

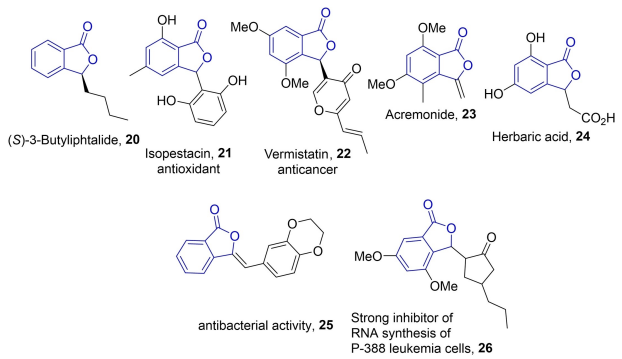
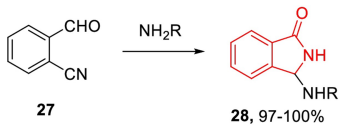



**Figure 4.** Phthalides natural products.

cases, treating 2-cyanobenzaldehyde with primary amines (Scheme 1).[5]




**Scheme 1.** Reaction with amines.

The authors also proposed a mechanism reporting a rearrangement from imidate **B** to isoindolinone **28** without any other details (Scheme 2).

In 1988 the same authors investigated the reaction of 2-cyanobenzahdeyde with alcohols obtaining mixtures of the respective imidates **29** or isoindolinones **30** in variable yields depending on the used base (Scheme 3).[6] They also reported the synthesis of 3-hydroxyisoindolinone (**30a**, R=H), by base promoted hydrolysis of **27**, whose mechanism was then investigated by Bowden and co-workers in 1997.[7]

In 2003 Lee and co-workers described an elegant use of 2-cyanobenzaldehyde in an application of Morita-Baylis-Hillman methodology in the synthesis of new 3-substituted isoindolinones **34** with a series of electron-poor alkenes **31** like methyl vinyl ketone, vinyl sulphones, ethyl acrylate in the presence of DABCO from low to moderate yields (Scheme 4).[8]

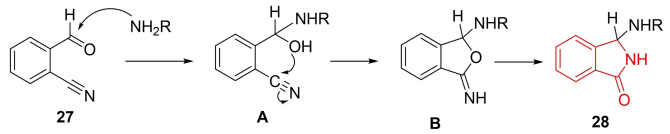
The authors also detailed the mechanism of the rearrangement, proposing a ring opening followed by an intramolecular aza-Michael reaction of a neutral amide intermediate **B** (Scheme 5).

In 2008, Ramström and co-workers reported a new application of 2-cyanobenzaldehyde with nitroethane leading to **36** in high yield and good diastereoselectivity (Scheme 6).[9,10]

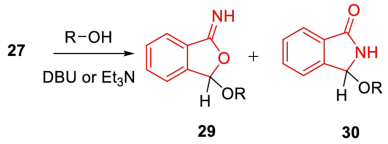
Mohammad Sadeq Mousavi was born in Iran, Tehran, in 1996. He obtained his B.Sc. degree in chemistry from K. N. Toosi University of Technology, in 2019 and his M.Sc. degree in Organic Chemistry working on the cyclization of 2-alkynylbenzaldoximes and graduated from K. N. Toosi University of Technology in 2021. He is currently pursuing his doctoral research under the supervision of Prof. Massa at University of Salerno. His research interests include devising novel routes towards the synthesis of heterocyclic compounds.

Antonia Di Mola was born in 1978 in Italy. She studied Medicinal Chemistry at the University of Bari. She obtained her doctorate in 2007 on the topic of synthesis of novel angiotensin AT1 receptor ligands at University of Bari. Afterwards she spent a year as a postdoctoral fellow at the SCRIPPS, La Jolla, California, with Prof. K. Janda. Since the end of 2011, she joined the research group of Prof. Massa, where she is mainly involved in the synthesis and applications of nitrogen-based heterocyclic compounds. She has founded the spin-off 4AChem.

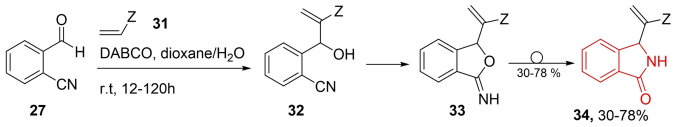
Antonio Massa was born in Cava dei Tirreni, Italy in 1971. After obtaining his MSc degree in chemistry at University of Salerno (Italy) in 1996, he worked for three years in R&D in the company Montefibre. In 2003 he obtained his PhD in organic chemistry in Salerno (supervisor prof. Scettri). After post-doc, in 2004 he became assistant professor at University of Salerno. In 2002 he was visiting investigator at University of Glasgow (UK) in prof. Kočovsky's lab and in 2008 at the SCRIPPS Research Institute in San Diego (USA) with a Fulbright scholarship in prof. Barbas III's lab. Since 2015 he is currently associate professor and in 2017 he obtained habilitation as full professor. His main research interests are on the development of new synthetic methodologies and scale-up, asymmetric catalysis an the synthesis of bioactive compounds. He is involved in several collaborations and is consultant of pharma companies.



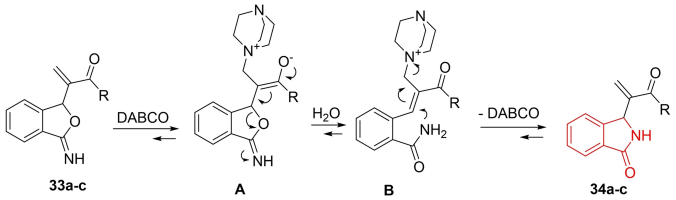
**Scheme 2.** Mechanism of reaction with amines.



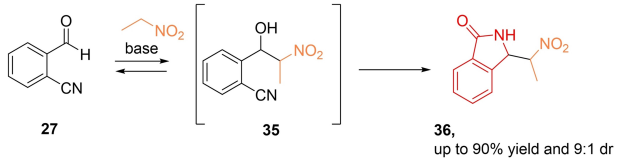
**Scheme 3.** Reaction with alcohols.



**Scheme 4.** Cascade reaction based on Baylis-Hillman methodology.



**Scheme 5.** Mechanism of Baylis-Hillman cascade reaction.

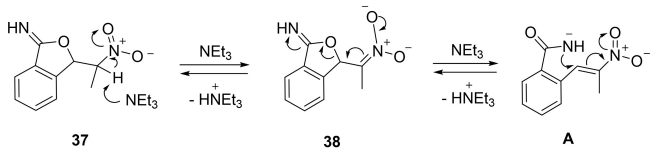


**Scheme 6.** Reaction with nitroethane.

The mechanism of this reaction was further analyzed by the same authors by DTF calculations, proposing the formation of an anionic amide intermediate **A** after ring opening, followed by an intramolecular aza-Michael reaction, in agreement with a Dimroth type rearrangement (Scheme 7).[9,10]

Interestingly, nitromethane cannot be used in this reaction since it gives a complex mixture of products.[11] Only more recently, our group developed a different approach to produce 3-nitromethyl isoindolinones, using α-amidosulfones derived from 2-formyl benzoates as electrophiles in a cascade aza-Henry/lactamization reaction reaching very high enantioselectivities.[11]

We started the investigation of the reactivity of 2-cyanobenzaldehyde by chance, ignoring these publications.[5-10]

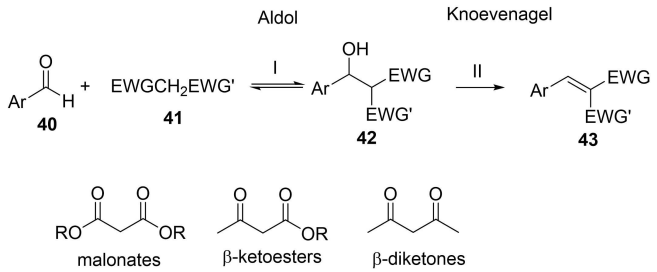


**Scheme 7.** Mechanism of reaction with nitroethane.

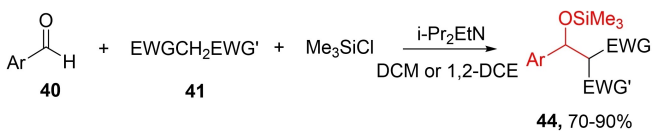
At that time, we were analyzing the scope of aldol reaction of double activated methylene compounds **41** like dimethylmalonate (Scheme 8).[12,13] Cross aldol reaction of dimethylmalonate with aromatic aldehydes **40** is very challenging, because the reaction is reversible, and the aldol product **42** is not stable.[12,13] When the reaction is forced, the Knoevenagel condensation product **43** is obtained (Scheme 8).[12]

At that time, we tackled this issue using an entrapping reagent which traps the obtained aldol intermediate, driving the aldol addition to the completion. To this purpose the use of chlorotrimethylsilane in the presence of a weak base like *i*-$Pr_2EtN$ (DIPEA) led to the easy isolation of the protected aldol products **44** in high efficiency, in a one-pot multicomponent process (Scheme 9).[12,13] The isolated protected aldol products were also utilized in different transformations to afford useful synthons.[12,13]

During the analysis of the scope of this multicomponent reaction, we performed control experiments in deuterated solvent just mixing the aldehyde **40**, dimethylmalonate and the base, observing very low conversion at NMR analysis, with one



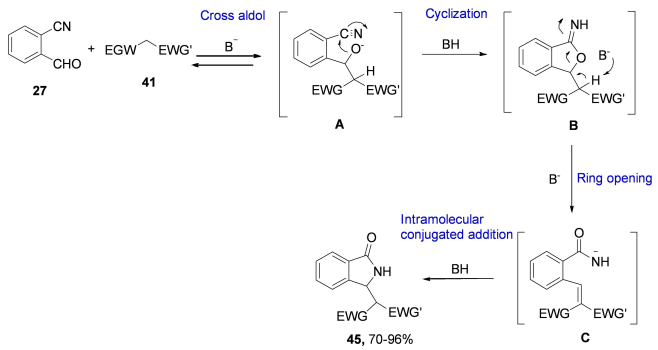
**Scheme 8.** Destiny of cross aldol reaction of aromatic aldehydes with double activated methylene compounds.



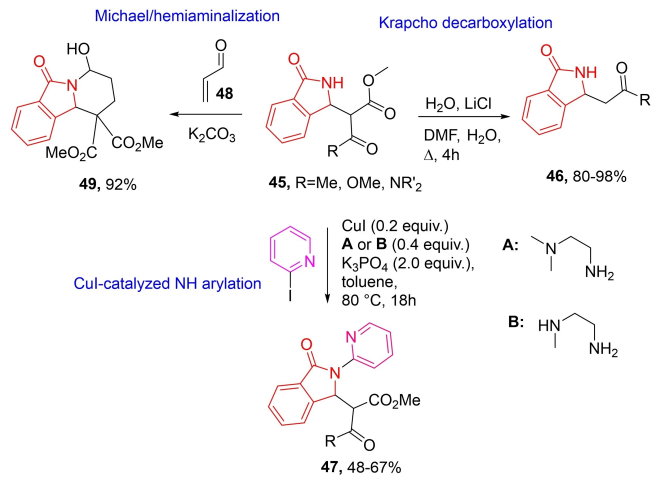
**Scheme 9.** Trapping of unstable aldol products.

exception, with 2-cyanobenzaldehyde. The experiment involving 2-cyanobenzaldehyde gave an unexpected result, which led us to investigate the reactivity of this electrophile in combination with a series of readily available nucleophiles (Scheme 10).[14] The presence of cyano group in 2-position favors the aldol addition step through cyclization of **A** to give **B**. This step can be considered a sort of intramolecular entrapping of the unstable aldol intermediate **A**, driving the aldol addition to completion. When an acidic proton is present in α position of the obtained imidate intermediate **B**, a rearrangement occurs leading to 3-substituted isoindolinones **45** from good to very high yields. When the acidic proton is not present, the reaction stops at the imidate stage **B**. These type of imidates can sometimes be isolated and hydrolyzed to ester group, affording another type of important heterocycles, the phthalides (See section 7).

The reaction can also be promoted by a catalytic amount of an inorganic base such as $K_2CO_3$ and the obtained products can be used in further transformations to afford more complex structures (Scheme 11).[15] In particular, Krapcho decarboxylation affords **46**, Cu(I) catalyzed arylation of the NH gives **47**, sequential Michael/hemiaminalization with acrolein **48** leads to benzoindolizidine **49**.[15]




**Scheme 10.** Reaction with double-activated methylene compounds.



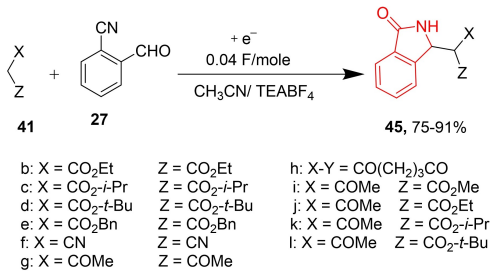

**Scheme 11.** Krapcho decarboxylation, Cul-catalyzed NH arylation, sequential Michael/hemiaminalization with acrolein.

The cascade reaction can also be induced electrochemically in the presence of a large number of double activated methylene compounds as described in the following scheme (Scheme 12).[16]

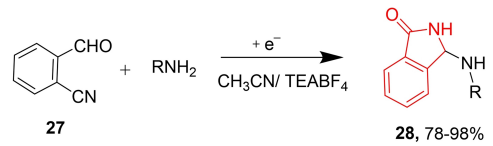
Electrochemical activation was also used in reactions with primary amines in aminal formation according to scheme 13.[17,18]

Exploring this mechanistic pathway, in 2014 the use of glycine Schiff base **50** as nucleophile allowed to develop the synthesis of α-amino acid fused alternatively with phthalides **52** or isoindolinones **54** (Scheme 14). This preference was tuned by the use of the base: $K_2CO_3$ led to the isolation of the imidate **51** (see also section 6), while the rearrangement was possible only in the presence of KOH leading first to the Schiff base **53** and after hydrolysis to the α-amino ester **54**.[19]

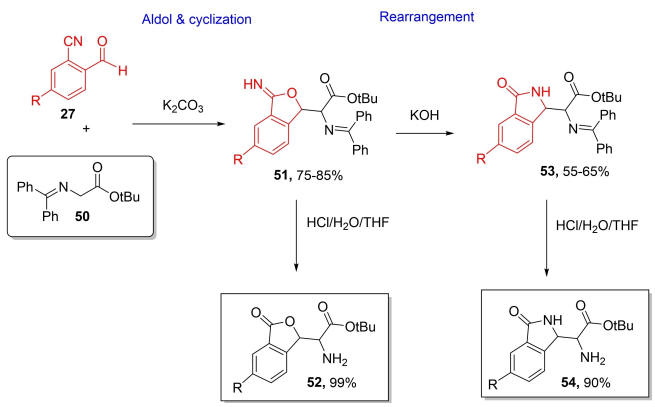
In 2015 Soloshonok and co-workers reported a related NaOMe-catalyzed stereoselective reaction between the nickel complex of chiral glycine Schiff base (*S*)-**55** with 2-cyanobenzaldehyde to provide a convenient preparation of the novel α-(1-oxoisoindolin-3-yl)glycine **57** of high pharmaceutical potential




**Scheme 12.** Electrochemically induced cascade reaction of double activated methylene compounds.



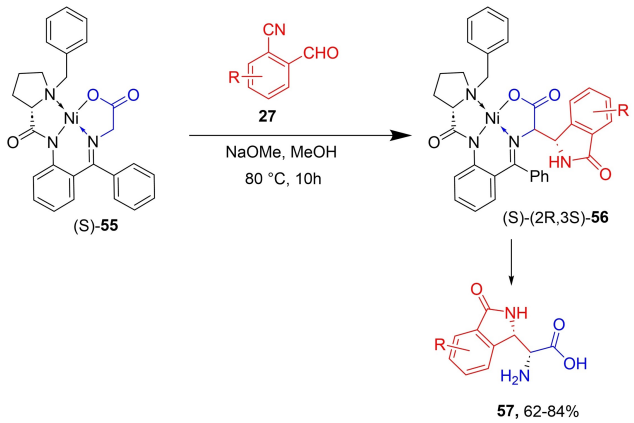

**Scheme 13.** Electrochemically induced cascade reaction of amines.



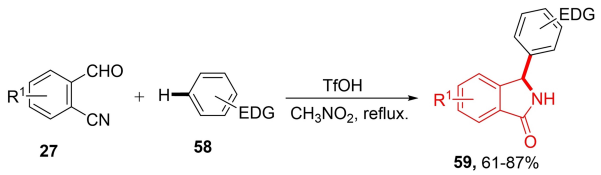

**Scheme 14.** Reaction with glycine Schiff base.

(Scheme 15) reporting a similar mechanistic pathway as described in the previous schemes.[20]

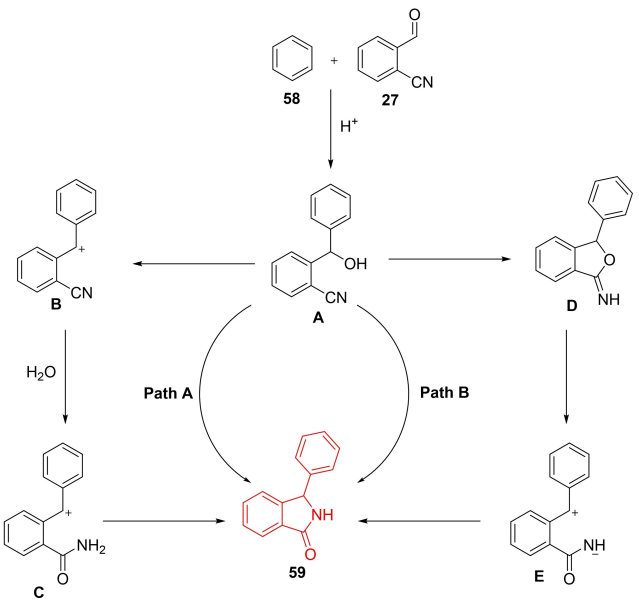
In 2014 Zhang, Zheng and co-workers reported a convenient metal-free method for the synthesis of 3-aryl isoindolinones via TfOH catalyzed aromatic C–H functionalization of electron-rich arenes **58** for the synthesis of isoindolinone derivatives **59** in good to high yields and regioselectivities (Scheme 16).[21]




**Scheme 15.** Reaction with nickel complex of chiral glycine Schiff base.




**Scheme 16.** TfOH catalyzed aromatic C–H functionalization.




**Scheme 17.** Proposed mechanism of TfOH catalyzed aromatic C–H functionalization.

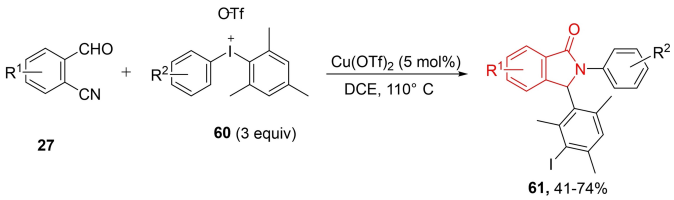
In the proposed reaction mechanism, arenes first couple with the aldehyde groups through the Friedel–Crafts reaction to generate alcohols **A**, which would then undergo dehydration to afford intermediate carbocations **B** (Scheme 17). The cyano group is subsequently converted into an amide group through the hydrolysis under strong acidic conditions. Finally, an intramolecular addition process occurs to produce the isoindolinone framework (path A); alternatively, intermediate alcohols can also be converted to imidates **D** through an intramolecular cyclization, imidates are then converted to amides **E** after rearrangement, the final products are finally generated through cyclization (path B).

In 2017 Miao, Li and co-workers described copper-catalyzed divergent cyclizations of 2-formylbenzonitrile **27** and diaryliodonium salts **60** to give aryl-substituted isoindolinones (Schemes 18 and 19). The process proceeds through a copper-catalyzed tandem C–H/N–H arylation, producing two different isoindolinone derivatives **61** and **62** under different reaction conditions, using Cu(II) or Cu(I) catalysts respectively.[22]

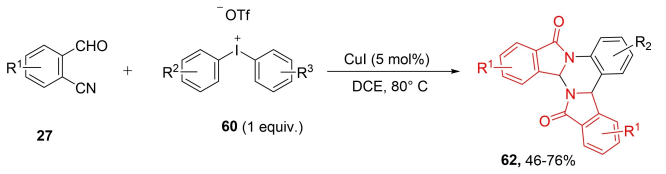
New versions of this reaction from the same authors allowed to develop a three-component cascade cyclization using 2-formylbenzonitrile, arenes **58**, and diaryliodonium salts **60** to give 3-aryl isoindolinones **63** (Scheme 20).[23]

Mechanistic insights were also given, postulating the formation of a cationic isoindolinone intermediate **C** in all the cases, which will react with arenes in Friedel–Crafts manner to give **D** and then **63** (Scheme 21).

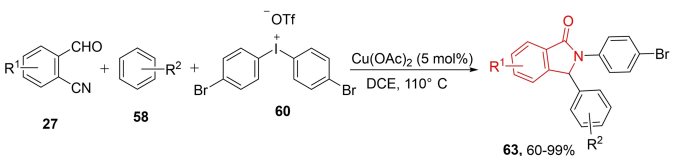
Fused polycyclic isoindolinones **65** were obtained with Cu-catalyzed three-component cascade cyclization among 2-for-



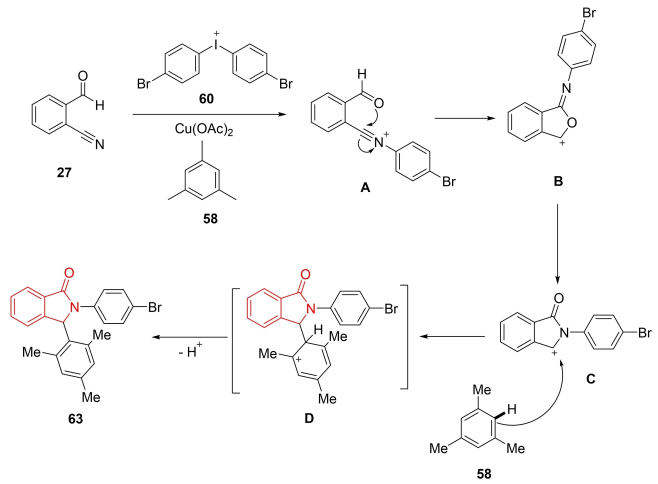

**Scheme 18.** Cu(II)-catalyzed reaction with diaryliodonium salts.




**Scheme 19.** Cu(I)-catalyzed reaction with diaryliodonium salts.



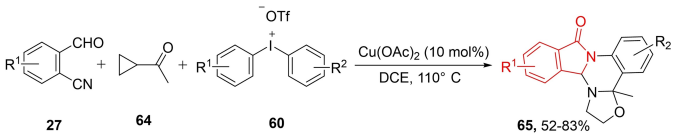

**Scheme 20.** Cu(II)-catalyzed reaction with arene and diaryliodonium salts.



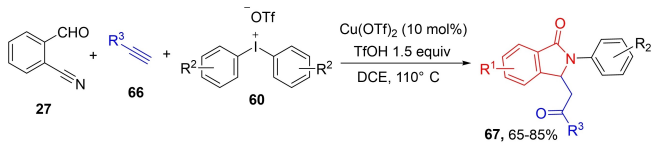

**Scheme 21.** Mechanism of Cu(II)-catalyzed reaction with arene and diaryliodonium salts.

mylbenzonitrile, cyclopropyl ketones and diaryliodonium in moderate to good yields. The proposed mechanism involved a ring expansion of cyclopropyl ketones/formation of *N*-acyliminium/hetero-[4 + 2]-cycloaddition process (Scheme 22).[24]

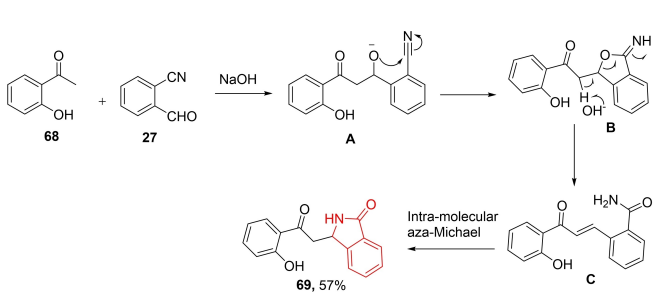
In 2022 Li and co-workers described a copper-catalyzed multicomponent cascade cyclization using 2-formylbenzonitriles, phenylacetylenes **66**, and diaryliodonium salts **60**




**Scheme 22.** Cu(II)-catalyzed reaction with cyclopropyl ketones and diaryliodonium salts.




**Scheme 23.** Cu(II)-catalyzed reaction with phenylacetylenes and diaryliodonium salts.




**Scheme 24.** Claisen–Schmidt reaction intermediate under basic conditions.

(Scheme 23). A broad reaction scope was presented with good functional group compatibility, giving rise to a range of 3-(2-oxopropyl)-2-arylisoindolinones **67** in moderate to good yields.[25]

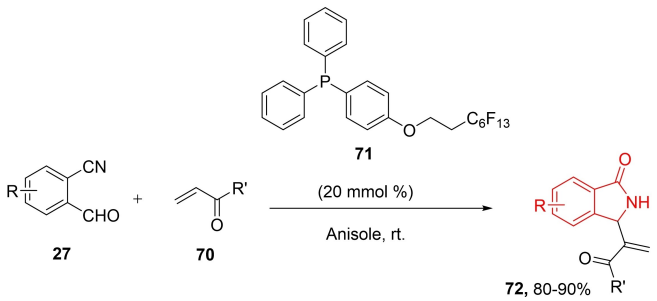
In 2019 Chen and co-workers reported an efficient one-pot synthesis method for multiple heterocyclic scaffolds based on the cyano-containing amphiphilic Claisen–Schmidt reaction intermediate under basic conditions (Scheme 24).[26] Ring opening of imidate **B** can be ascribed to base-promoted deprotonation of the enolizable ketone.

Environmentally benign access to isoindolinones was reported by Chai, Zhang and co-workers via a tandem reaction of 2-cyanobenzaldehydes and α,β-unsaturated ketones/esters based on Morita-Baylis-Hillman protocol (Scheme 25). In the presence of catalytic amount of the organocatalyst **71** based on a fluorinated phosphine, in green solvents at rt, a variety of isoindolinones **72** was obtained (see also Scheme 4).[27]

## 3. Asymmetric synthesis of 3-substituted isoindolinones

In the course of the years, the interest in the asymmetric synthesis of 3-substituted isoindolinones increased enormously. Until 2010, most of the strategies was based on the resolution of racemates and the use of chiral auxiliaries, showing low yields and low efficiency.[1] Only more recently a good number of more convenient enantioselective catalytic methodologies has been developed using chiral metal complexes and organocatalysts.[1]

In this context, in 2012 our group developed one of the first organocatalytic asymmetric synthesis of 3-substituted isoindolinones, by the organocatalytic control of the rearrangement in the cascade reaction of 2-cyanobenzaldehyde with dimethylmalonate **42**.[28] To this purpose, several chiral tertiary amines as simple Cinchona alkaloids, thiourea derived *epi*-quinine, or combinations of chiral ammonium salts with an inorganic base under phase transfer conditions were used (Scheme 26).[29–30] In particular, the 3-substituted isoindolinone **73** was obtained in very high yields and in good enantioselectivities, up to 74% ee with thiourea derived *epi*-quinine **74**[28,29] and 78% ee with the chiral bifunctional phase transfer catalyst (PTC) **75** derived from trans-1,2-diaminocyclohexane developed by Waser et. al..[30,31]




**Scheme 25.** Green protocol for Morita-Baylis-Hillman type cascade reaction.

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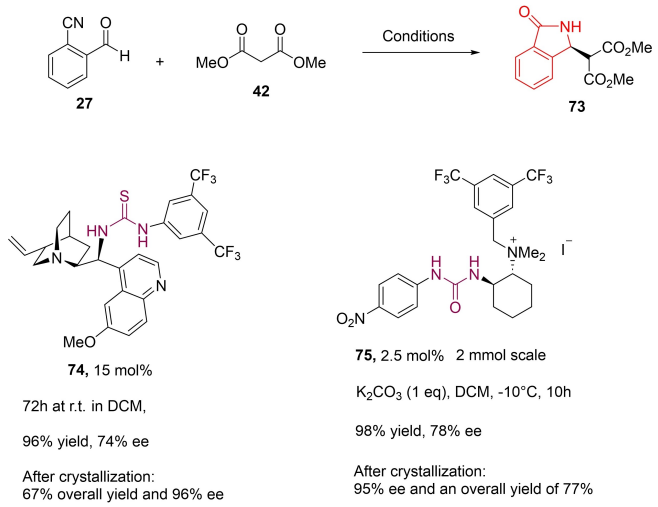
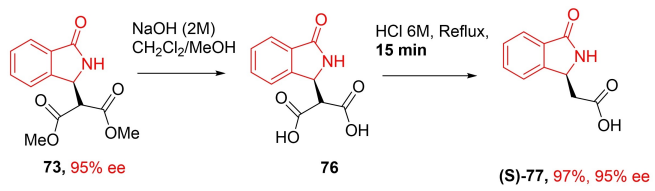


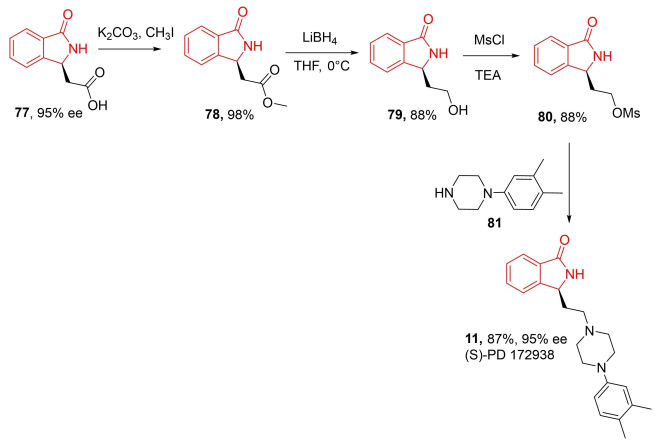

**Scheme 26.** Organocatalytic asymmetric reaction with dimethylmalonate.

The scope of the reaction was also enlarged with 2-cyanobenzaldehydes substituted on the aromatic ring and different malonate diesters, reaching enantioselectivities up to 86% ee.[29]

An heterochiral crystallization (the isoindolinone **73** crystallizes as racemate) led to an improvement of the enantiopurity up to 95–98% ee in good overall yields. The use of readily available chiral PTC **75** also gave the possibility to scale up the reaction at 2 mmol scale using only 2.5 mol% of the catalyst.[31]




**Scheme 27.** Transformation of the enantioenriched product **73** into a chiral key building block.




**Scheme 28.** Transformation of the chiral building block (***S***)**-77** into (*S*)-PD172938.

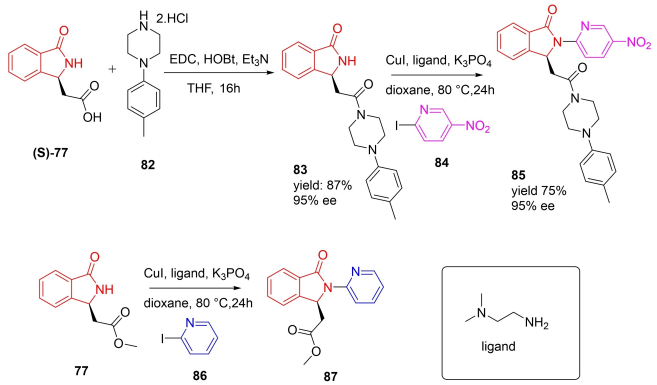
This allowed to develop the first asymmetric total synthesis of important bioactive isoindolinones based on a catalytic methodology (Schemes 27 and 28). Determination of absolute configuration of **73** by VCD measurements was also achieved.[32]

Instead of Krapcho decarboxylation which led to racemization, the two-step procedure, as described in Scheme 27, saponification followed by HCl decarboxylation, allowed to obtain the chiral isoindolinone acetic acid **(*S*)-77** in high yield and most importantly with unchanged enantiomeric purity.[31]

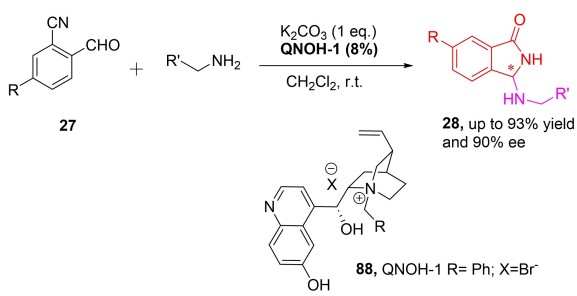
This building block was used to synthesize the (*S*)-PD172938 **11** in good overall yield and unchanged enantiopurity of 95% ee, after methylation, chemoselective reduction of ester **78** with $LiBH_4$, mesylation and displacement with the arylpiperazine **81** (Scheme 28).[31]

In addition, amidation of **(*S*)-77** promoted by EDC/HOBt activation of the carboxylic acid, in the presence of arylpiperazine **82**, followed by Cu(I) catalyzed NH arylation led to the synthesis of **85** and **87**, analogues of hypnotic sedative drugs with unchanged 95% ee in good overall yield (Scheme 29).

Asymmetric versions of the cascade reaction were also developed in the presence of primary amines. The best results up to 93% yield and 90% ee were obtained under phase transfer conditions in the presence of chiral ammonium salt derived from cupreine **88** (Scheme 30).[33]




**Scheme 29.** Transformation of the chiral building block **77** into analogues of hypnotic sedative drugs.




**Scheme 30.** Organocatalytic asymmetric reaction with amines.

## 4. Synthesis of 3-methylene isoindolinones

In 2010, another pioneering paper was reported by Kobayashi and co-workers about a convenient synthesis of 3-methylideneisoindol-1-ones **89** by reaction of 2-cyanobenzaldehyde with dimethyloxosulfonium methylide (Scheme 31).[34]

Basically, the proposed mechanism is a little more complicated since a further 1,2-elimination step at the end of the entire process occurs (Scheme 32). What is particularly interesting is that instead of Corey–Chaykovsky epoxide **B** formation, dimethylsulfoxide was eliminated in the last step of the process giving the methylene isoindolinone **89**.

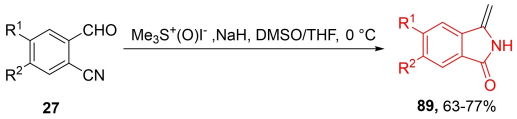
After the Kobayashi's work, the possibility to use 2-cyanobenzaldehyde in the synthesis of 3-methylene isoindolinones was neglected for a long time until 2021. In particular, when it was reacted with ((chloromethyl)sulfonyl)benzenes **90**, it led to a series of 3-(sulfonyl-methylene)isoindolin-1-ones **18** in quantitative yields in most of the cases (Scheme 33).[35] The obtained compounds are particularly interesting since some of them were already synthesized and reported to show mechanochromic properties (Figure 3).[2b]

As reported by Kobayashi in the reactions with dimethyloxosulfonium methylide (Scheme 32), the epoxide **B** is not observed. Instead of Darzens pathway a, cyclization at cyano group is favored, followed by rearrangement of **C** till the stereoselective *Z* HCl elimination in **D** in the last step favored by hydrogen bond (Path. b). DFT calculations and control experiments confirmed the proposed pathway in agreement with Ramstrom mechanism, identifying the intermediates and excluding the Darzens pathway a (Scheme 34).[35]

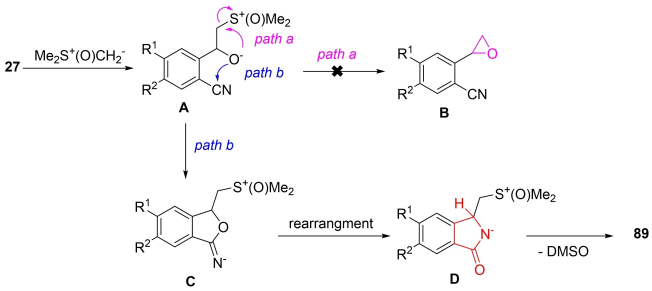
It was also possible to combine a further sequential alkylation of the NH group just using 2 equiv. of $K_2CO_3$ to afford compounds **91** useful for the synthesis of aristolactams (Scheme 35).[35] Both NH-free and N-alkylated 3-(sulfonyl-methylene)isoindolin-1-ones **18** and **91** were previously synthesized by a less convenient oxidative cyclization of aromatic nitriles with arylvinylsulfones catalyzed by Ru(II)/Ag(I)catalysis in the presence of an excess of Cu(II) salts.[2b,c]

In contrast with what is described in Scheme 26,[26] in 2022 Goel and co-workers reported a one-pot synthesis of 3-methylene isoindolinones **93** and related bis(isoindolinone)ethane derivatives **94** by the reacting 2-cyanobenzaldehyde and methyl ketones **92** in the presence of KOH or $K_2CO_3$ respectively (Scheme 36) reporting from low to moderate yields.[36]

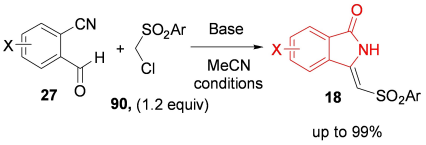
It was observed that 2-cyanobenzaldeydes **27a** having amine moiety adjacent to cyano group in aryl system facilitated



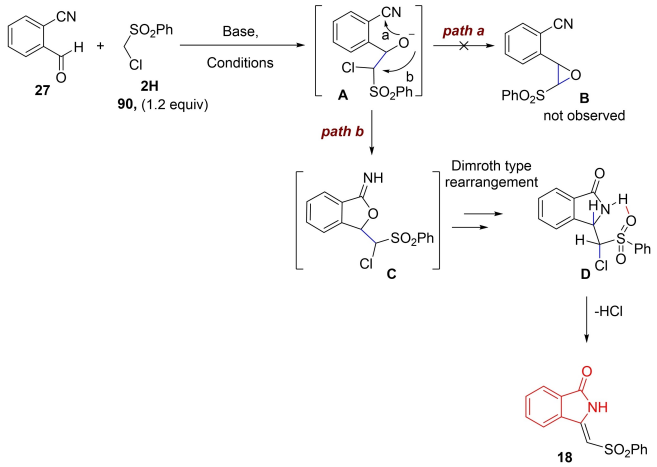

**Scheme 31.** Reaction with dimethyloxosulfonium methylide.



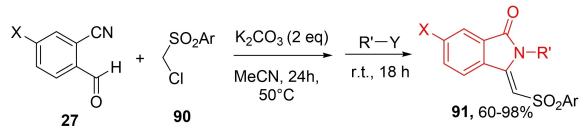

**Scheme 32.** Mechanism of reaction with dimethyloxosulfonium methylide.



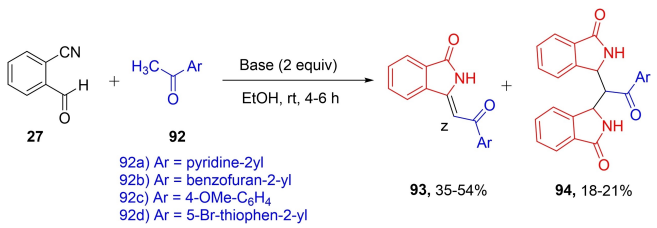

**Scheme 33.** Reaction with((chloromethyl)sulfonyl)benzenes.




**Scheme 34.** Mechanism of reaction with ((chloromethyl)sulfonyl)benzenes.




**Scheme 35.** Sequential reaction with ((chloromethyl)sulfonyl)benzenes/alkylation.




**Scheme 36.** Reaction with methyl ketones.

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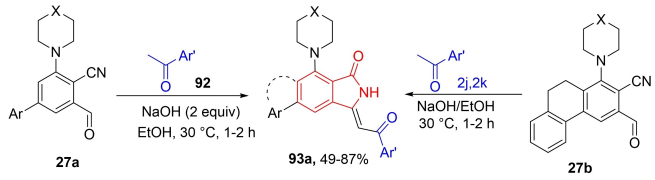
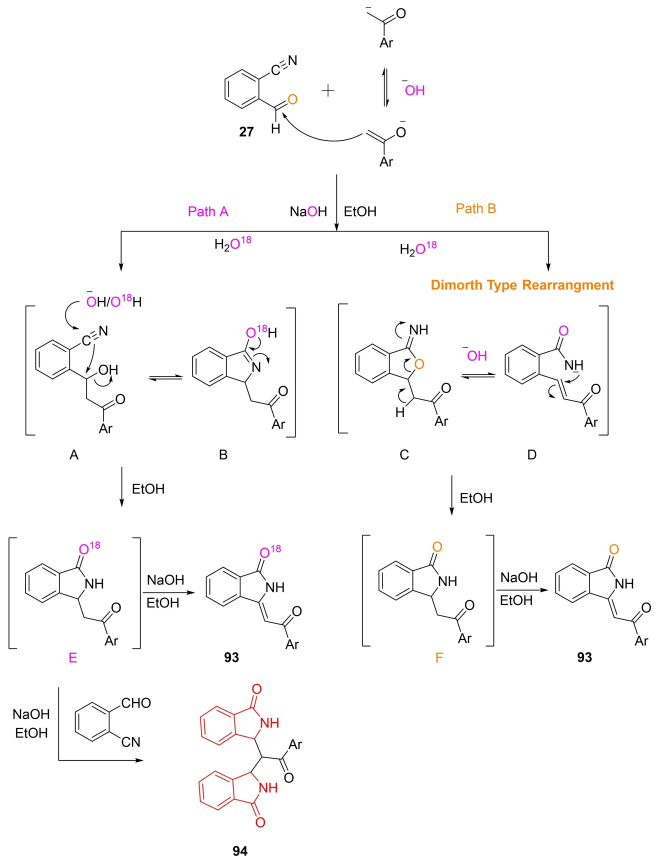



**Scheme 37.** Reaction of substituted 2-cyanobenzaldehydes methyl ketones.

the reaction and afforded **93 a** analogues only, more quickly (1–2 h) and in better yields (Scheme 37).

Mechanistic investigations were also described by the authors, based on labeled $H_2O^{18}$ exchanges (Scheme 38), comparing two possible pathways, one involving hydrolysis of the cyano group and the other based on the classical Dimroth type rearrangement (Scheme 38). Both the mechanisms propose an unusual 1,2-elimination step (**E**→**93** or **F**→**93** in Scheme 38) to afford the alkene moiety, but further details about this uncommon hydride elimination/oxidation step have not been given.[36]



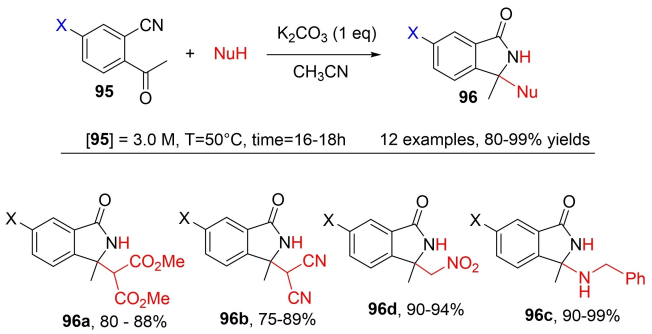

**Scheme 38.** Proposed mechanisms.

## 5. 2-Acylbenzonitriles in the synthesis of 3,3-disubstituted isoindolinones

During the last years the interest of our group was also devoted to more challenging nucleophilic additions to related ketones, 2-acetylbenzonitriles **95**, in order to develop a convenient tandem synthesis of isoindolinones with a tetrasubstituted carbon in 3-position (Scheme 39).[37] Only one application of 2-acetylbenzonitriles **95** was reported in literature, particularly in the synthesis of benzyl alcohols and phthalides.[38]

We were mainly attracted by the fact that nucleophilic addition to ketones has always been a major challenge in organic synthesis because of the poor electrophilic character of this carbonyl group and competitive enolization. Surprisingly, 2-acetylbenzonitriles **95** reacted under very mild conditions, similar to 2-cyanobenzaldehyde, leading reasonably through the same pathway to novel isoindolinones **96** bearing a tetrasubstituted stereocenter (Schemes 39–42). Using 1 equiv. of the $K_2CO_3$, several carbon- and hetero-nucleophiles NuH were reacted such as dimethylmalonate, malononitrile, nitromethane, primary amines and water in very high yields.[37] The products were also characterized by X-ray crystallography. The product with dimethylmalonate was useful in the synthesis of 3-methylated analogues of bioactive isoindolinones as pazinaclone and PD172938 (See below).

Hydration of 2-acetylbenzonitriles **95** in the presence of only 0.3 eqv. of KOH was also a particularly interesting reaction since afforded known and novel 3-hydroxy-3-methyl isoindolinones **97** (Scheme 40).[37] These are important compounds known for their biological activity as clortalidone (see Figure 1). They are also used as starting materials in the synthesis of other




**Scheme 39.** Reaction of acetylbenzonitriles with carbon- and hetero-nucleophiles.


**Scheme 40.** Reaction of acetylbenzonitriles with water.

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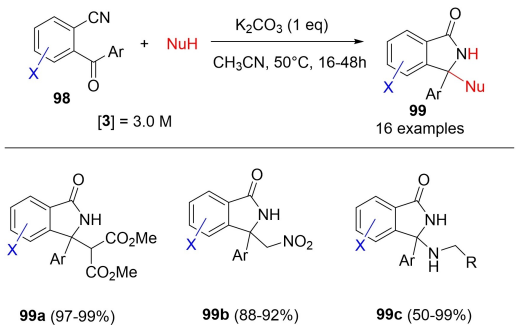
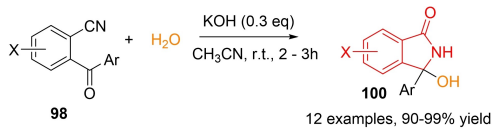



**Scheme 41.** Reaction of 2-cyanobenzophenones with carbon- and hetero-nucleophiles.



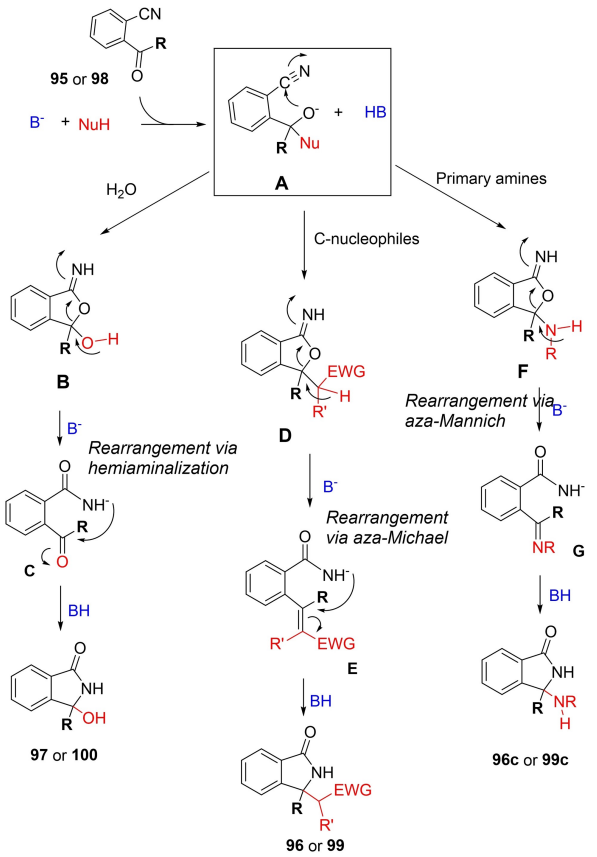

**Scheme 42.** Reaction of 2-cyanobenzophenones with water.

3,3-disubstituted isoindolinones under organocatalytic conditions.[37] However, only one methodology has been reported for the synthesis of **97**, by nucleophilic addition of Grignard $CH_3MgBr$[39] or methyl lithium[40] to phthalimide. In comparison, the methodology described in scheme 40 is more convenient since, according to the literature, the addition of organometallic reagents to phthalimides substituted on the aromatic ring, leads to mixtures of regioisomers.[39,40]

The more hindered aromatic ketones 2-cyanobenzophenones **98** attracted also the attention of our group. Under similar conditions, 2-cyanobenzophenones reacted to give 3,3-disubstituted isoindolinones **99** in high yields with several carbon and heteronucleophiles as dimethylmalonate, malononitrile, nitromethane, primary amines and water (Schemes 41 and 42).[41]

The hydration of these ketones with water in the presence of 0.3 eqv of KOH led to 3-aryl-3-hydroxyisoindolinones **100** in very high yields as well (Scheme 42), overcoming the same issues as previously described regarding the addition of organometallic reagents to substituted phthalimides.[41]

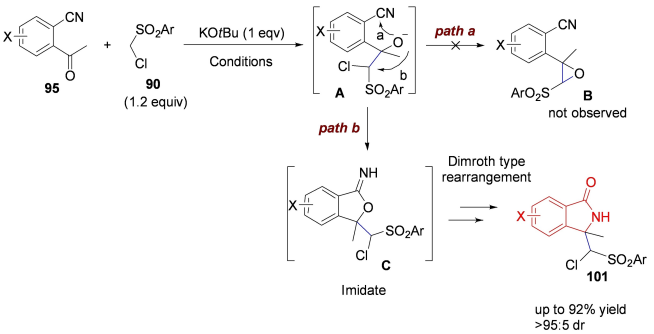
Control experiments performed on benzophenone and acetophenone in the presence of the used nucleophiles under the same reaction conditions did not lead to any reaction, emphasizing the importance of the cyano group in 2-position to drive the addition to completion through cyclization. Therefore, as for 2-cyanobenzaldehyde **27** a similar cascade mechanism was proposed for both these two classes of 2-acylbenzonitriles (Scheme 43). The mechanism can be grouped in the following scheme for both carbon- and hetero-nucleophiles and in all the cases it is base-catalyzed and proceeds with a rearrangement via hemiaminalization of **C**, via aza-Michael of **E** or via aza-Mannich of **F**. Ring opening for **B**, **D** and **F**, was possible thanks to the presence of an additional hydrogen atom in the side chains.



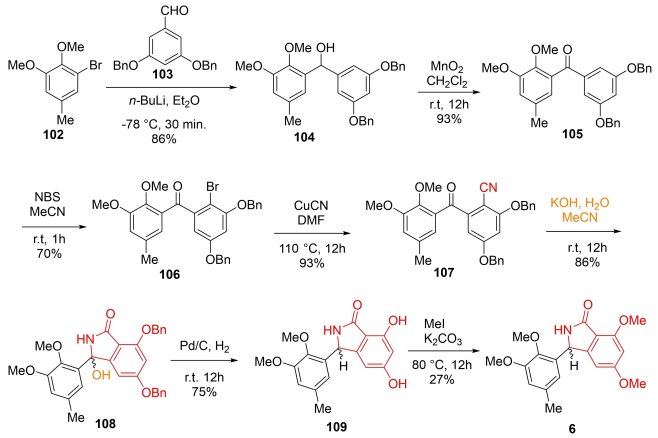

**Scheme 43.** Mechanism of reactions of acylbenzonitriles with carbon- and hetero-nucleophiles.

The use of ((chloromethyl)sulfonyl)benzene-derived carbanions **90** carrying a leaving group (LG) in the α-position, led to the isoindolinone **101**, demonstrating that cyclization via nucleophilic attack at the cyano group (path b) is preferred to cyclization with formation of epoxides (Darzens reaction, path a), since epoxide **B** was not detected (Scheme 44).[35] In this case, the obtaining of 3,3-disubstitued isoindolinones **101** with a α-chlorosulfonyl side chain was possible.

Recently, Kamauchi and co-workers reported the first total synthesis of isoindolinone (±)-entonalactams A, B and C,




**Scheme 44.** Reaction of acetylbenzonitriles with ((chloromethyl)sulfonyl)benzene.



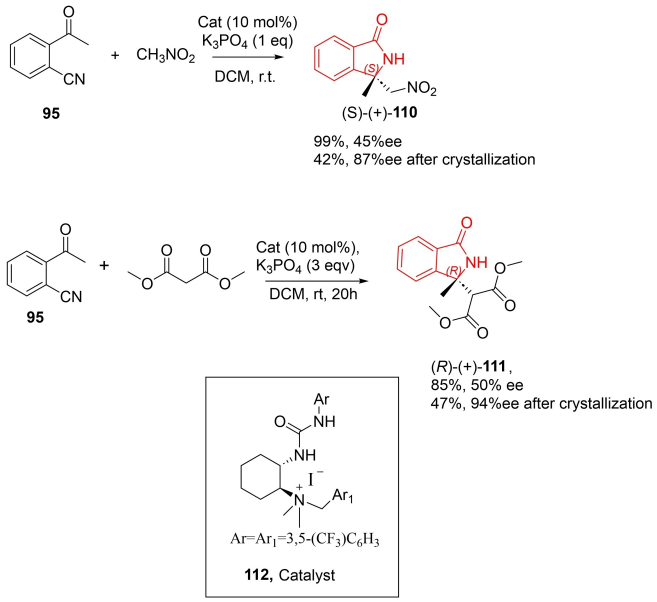

**Scheme 45.** Synthesis of the Isomer of entonalactam B from 2-cyanobenzophenones.

originally isolated from the fungus *Entonaema sp.* The synthesis was achieved in 7 to 14 steps from commercially available 5-bromovanillin **102** via 2-cyanobenzophenone intermediates synthesis **107**, according to the Scheme 45.[42] Cyanation of **106** was carried out by the use of CuCN, while cyclization of **107** was achieved under KOH promoted conditions similar to those of Scheme 42. Isoindolinone, phthalide, and benzophenone analogues of natural products were also synthesized in this work.[42]

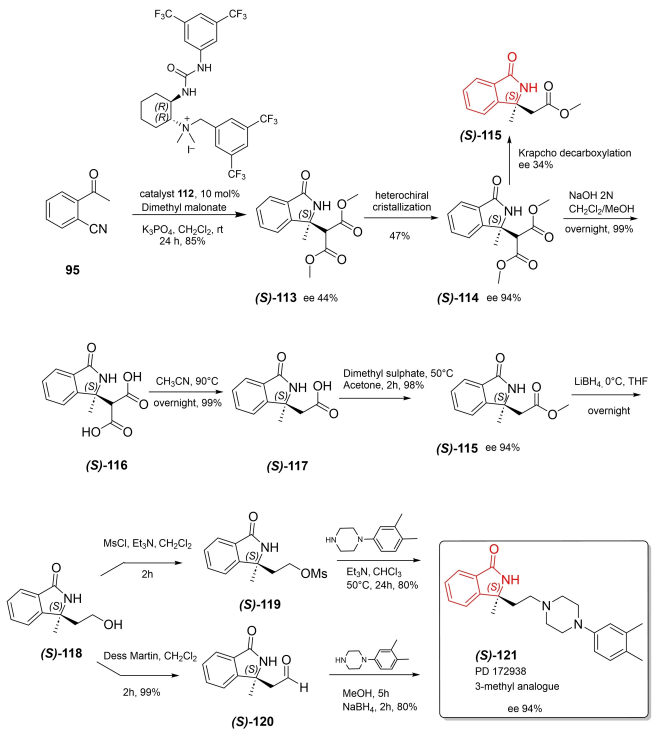
## 6. 2-Acetylbenzonitriles in the asymmetric synthesis of 3,3-disubstituted isoindolinones

Asymmetric versions of acetylbenzonitrile reactions were also investigated in the presence of nitromethane and dimethylmalonate (Scheme 46). The best results were obtained using chiral bifunctional ammonium salts derived from trans-1,2-diaminecyclohexane **112** developed by Waser et al., utilized under phase transfer conditions. Even though moderate enantioselectivities were obtained, an efficient process of heterochiral crystallization led to the increase of the enantiomeric purity in acceptable yields for **110** and **111**.[43,44]

The easy access to the catalyst **112** in high scale led to scale-up the asymmetric process with dimethylmalonate. This allowed the asymmetric synthesis of 3-methylated analogue of (*S*)-PD172938 **121** in very high enantiomeric purity (Scheme 47).[45] Also, in this case the key step of the route was the decarboxylation, performed simply heating in acetonitrile the dicarboxylic acid **116**, without decrease of the enantiopurity with respect to Krapcho decarboxylation that led to racemization. Then, $LiBH_4$ reduction of **115**, led to the alcohol **118** which was converted into **121** by two complementary pathways: displacement on **119** with piperazine or reductive amination of the aldehyde **120** without decreasing of the enantiomeric purity.

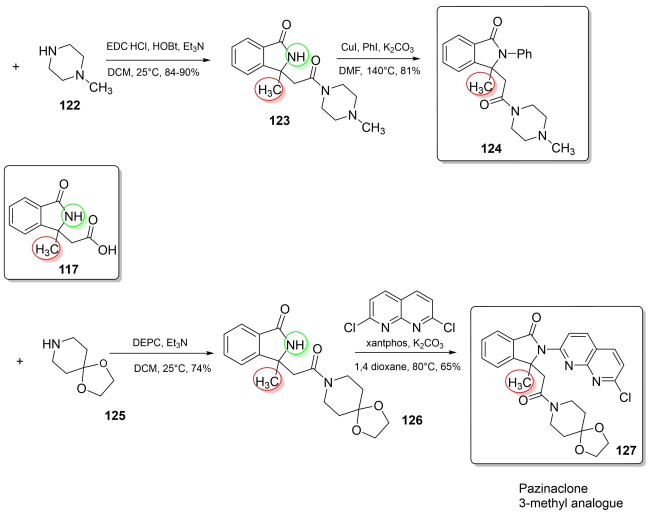



**Scheme 46.** Organocatalytic asymmetric reaction of acetylbenzonitriles with nitromethane and dimethylmalonate.




**Scheme 47.** Asymmetric synthesis of 3-methylated analogue of (*S*)-PD172938.

The synthesis of **124** and of 3-methylated pazinaclone **127** were carried out as racemate, respectively by CuI or palladium-xantphos catalyzed arylation of the NH lactam group of **123** and **126** (Scheme 48).[45]



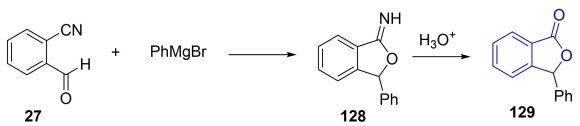

**Scheme 48.** Synthesis of 3-methylated pazinaclone.

## 7. Synthesis of phthalides and imidates

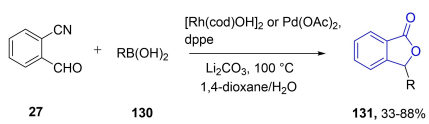
### 7.1. Use of 2-cyanobenzaldehyde

2-Cyanobenzaldehyde has been used several times in the synthesis of imidates and phthalides. The cascade reaction stops at imidate stage when its side chain cannot give rearrangement through deprotonation. In these cases, the imidates can be isolated and eventually hydrolyzed. In this context, to our knowledge, the first article mentioning 2-cyanobenzaldehyde was reported by Patelski et al. in 1936, in which the treatment with phenylmagnesium bromide led to the cyclic imidate **128** and then hydrolyzed to the phthalide **129** (Scheme 49).[46]

In 2011 Chen, Cheng and co-workers developed a rhodium or palladium-catalyzed addition of boronic acids to 2-cyanobenzaldehyde, followed by an intramolecular lactonization of cyano and hydrolysis. This procedure gave the access to 3-substituted aryl phthalides **131**, bearing a series of functional groups, such as methoxy, fluoro, chloro, and vinyl groups (Scheme 50).[47]




**Scheme 49.** First attempt of reaction with Grignard reagent dated 1936.

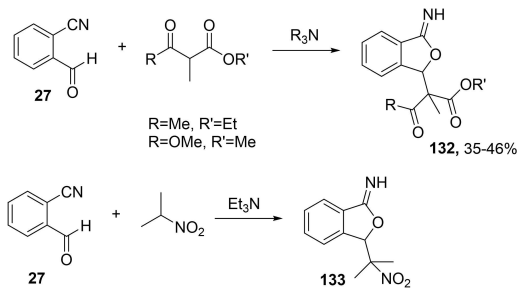



**Scheme 50.** Rhodium or palladium-catalyzed addition of boronic acids.

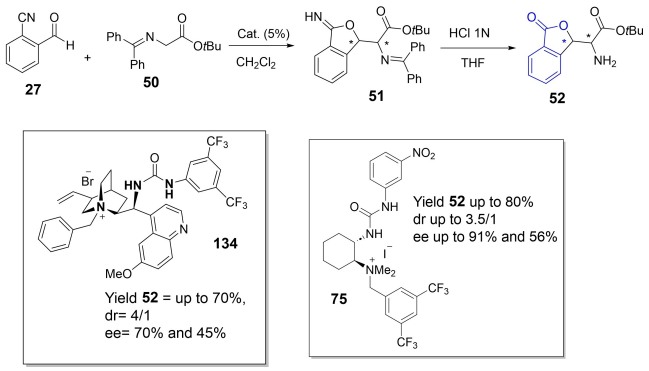
The use of 2-methyl dimethylmalonate, 2-methyl ethylacetoacetate and 2-nitropropane, compounds without a further acidic hydrogen in α position, was useful to demonstrate that it is possible to isolate the imidate **132** and **133**, confirming experimentally the cascade mechanism (Scheme 51).[10,14]

In the presence of *t*-butyl glycine Schiff base **50**, the imidate **51** does not rearrange under $K_2CO_3$ conditions and in this case, it can be isolated (Scheme 14). On the other hand, when treated with KOH rearrangement occurs leading to the isoindolinone **53** (see Scheme 14). The imidate **51** was subjected to hydrolysis to afford interesting unnatural α-amino acids **52** containing a phthalide in the side chain (Scheme 14).[19] Asymmetric versions of this reaction were also investigated. High enantioselectivity was achieved employing new designed chiral ammonium salts derived from trans-1,2-diaminecyclohexane **75** developed by Waser et al. In the presence of $K_2CO_3$ under phase transfer conditions this catalyst leads to the imidates **51** and after hydrolysis the respective α-aminoacid phthalides **52** with ee up to 91 % (Scheme 52). A similar reaction was not developed for the isoindolinone analog since the asymmetric rearrangement from **53** to **54** of Scheme 14 proved to be particularly challenging. Other chiral PTCs like **134** were also tested but proved to be less effective (Scheme 52).[19,48]

New heterocyclic hybrids were synthesized combining 2-cyanobenzaldehyde with nucleophilic isoindolinones **135** and isoxazolidin-5-ones **139** both bearing activated methine groups. Also, in these cases asymmetric versions were developed under

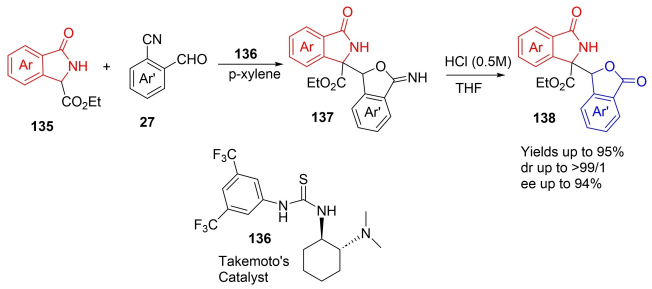



**Scheme 51.** Reaction with 2-methyl dimethylmalonate, 2-methyl ethylacetoacetate and 2-nitropropane.

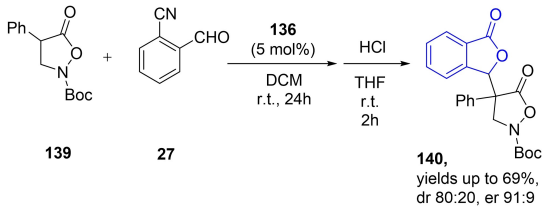



**Scheme 52.** Organocatalytic asymmetric reaction with *t*-butyl glycine Schiff base.

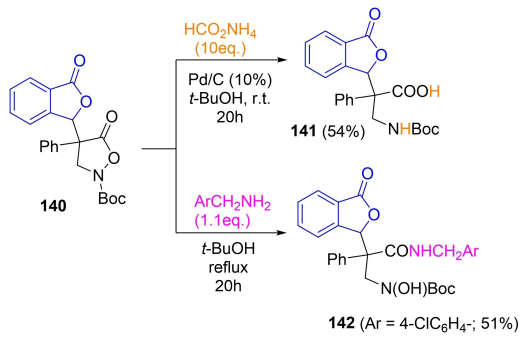
organocatalytic conditions employing Takemoto's catalyst **136**. Hydrolysis of the imidates intermediate afforded heterocyclic hybrids isoindolinones-phthalides **138** or isoxazolidinones-phthalides **140** with contiguous tertiary and quaternary stereocenters in very high and good diastereo- and enantioselectivities respectively (Schemes 53 and 54).[49,50]



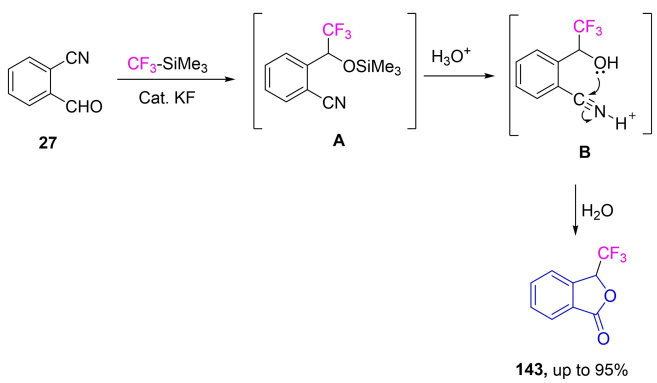

**Scheme 53.** Organocatalytic asymmetric reaction with nucleophilic isoindolinones.




**Scheme 54.** Organocatalytic asymmetric reaction with nucleophilic isoxazolidin-5-ones.




**Scheme 55.** Further elaboration of the isoxazolidin-5-one nucleus.




**Scheme 56.** Reaction with (perfluoroalkyl)trimethylsilanes.

The isoxazolidin-5-one nucleus **140** was further elaborated to give $\beta^2$-amino acid phthalide hybrids **141** and **142** (Scheme 55).[50]

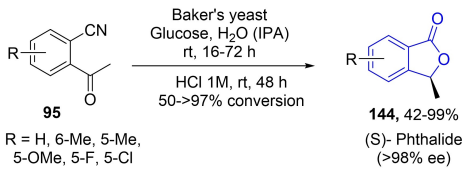
In 2018 Amii and co-workers described a versatile and practical method for the synthesis of C3 perfluoroalkyl-substituted phthalides **143** upon the treatment of 2-cyanobenzaldehyde with (perfluoroalkyl)trimethylsilanes, as $CF_3SiMe_3$, in the presence of KF or triethylamine as catalysts. The reaction proceeds via nucleophilic addition and subsequent intramolecular cyclization of **B** in high yields (Scheme 56).[51]

### 7.2. Use of 2-acetylbenzonitriles

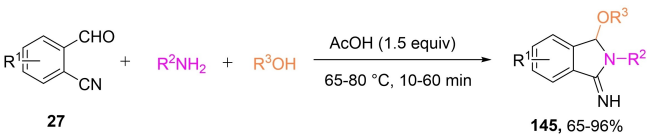
To our knowledge the first article about the use of 2-acylbenzonitrile was reported by Gotor, Fernandez and co-workers in 2012, reporting a straightforward synthesis of (*S*)-3-methylphthalides **144**.[38] The key asymmetric step was the bio-reduction of 2-acetylbenzonitriles **95** using Baker's yeast under acidic pH, which was found to be the best biocatalyst acting in a highly stereoselective fashion. The simple treatment of the reaction crudes with aqueous HCl provided access to enantiopure (*S*)-3-methylphthalides **144** in moderate to excellent yields and very high enantiopurity (Scheme 57).[38] To our knowledge other works about the use of acylbenzonitriles **95** or **98** in the synthesis of imidates and phthalides are not reported.

## 8. Synthesis of isoindolin-1-imine

A one-pot procedure has been developed by Lei and Hu and co-workers in 2012 for the synthesis of 2-substituted 3-alkoxyisoindolin-1-imine derivatives **145** via three-component condensation of 2-cyanobenzaldehyde, amines and alcohols (Scheme 58). The reaction catalyzed by acetic acid provides the corresponding products from various substrates in very good yields (65–96 %).[52]




**Scheme 57.** Asymmetric bio-reduction of 2-acetylbenzonitriles.

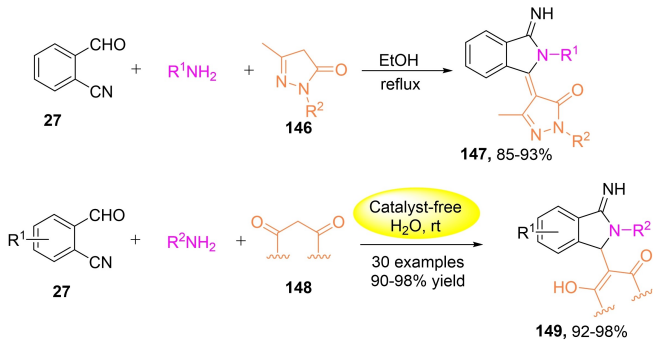



**Scheme 58.** One-pot multicomponent reaction with amines and alcohols.

A related one pot procedure was reported by the same authors in 2013 using, instead of the alcohols, 3-methyl-1H-pyrazol-5(4H)-one, 1,3-dimethyl-1H-pyrazol-5(4H)-one **146** or other active methylene compounds **148** (Scheme 59).[53,54]

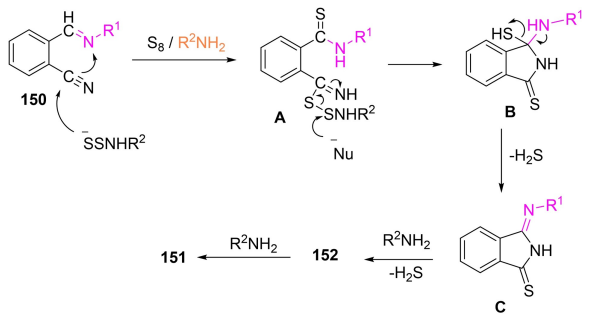
The synthesis of 1,3-diiminoisoindoline **152** was reported by Sato and co-workers in 1985 with reactions of *N*-(2-cyanobenzylidene)aniline **150** obtained from 2-cyanobenzaldeyde, with elemental sulfur in liquid ammonia and amines in moderate yields and variable **151/152** ratios (Scheme 60).[55]

A plausible pathway of this reaction was also proposed, involving two main steps: the oxidation of methine carbon with elemental sulfur in liquid ammonia giving thioamide **A**; the cyclization to **B** that seems to proceed by nucleophilic attack of a thiolate anion toward the nitrile carbon of **A** followed by substitution of the sulfur with ammonia as shown in the Scheme 61. To the best of our knowledge, other studies confirming the proposed reaction mechanism and enlarging the scope of the reaction have not been reported.




**Scheme 59.** One-pot multicomponent reaction with amines and 3-methyl-1H-pyrazol-5(4H)-one or double activated methylene compounds.


**Scheme 60.** Reaction with elemental sulfur in liquid ammonia and amines.




**Scheme 61.** Proposed mechanism of reaction with elemental sulfur in liquid ammonia and amines.

## 9. Miscellaneous

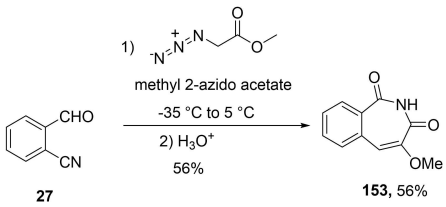
The treatment of 2-cyanobenzaldehyde with methyl azidoacetate in the presence of sodium methoxide furnished azepine derivatives **153** in good 56% yield (Scheme 62).[56]

In the proposed mechanism it was suggested that methoxide anion favors addition to cyano group in the initial product **A**, which is followed by ring closure to furnish intermediate **B**. Then, a nucleophilic displacement of the azide in **B** by methoxide would give the final intermediate **C** and after work-up the final product **153** (Scheme 63).

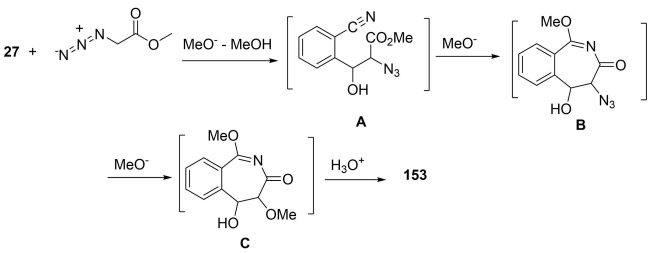
Benzo[4,5]imidazo[2,1-a]isoquinolines **155** and isoquinolino[3,4-b]quinoxalines **156** were obtained via tandem cyclization strategies in reactions with o-phenylenediamines **154** (Scheme 64).[57]

A $Cu(acac)_2$-catalyzed cyclization reaction of 2-cyanobenzaldehydes **27** or 2-acetylbenzonitriles **95** with 2-isocyanoacetates **157** provides an efficient strategy for the synthesis of substituted 1-aminoisoquinolines **158** (Scheme 65). The reaction proceeds smoothly under mild conditions with high efficiency. This can be considered an alternative strategy for the synthesis of 1-aminoisoquinolines.[58]

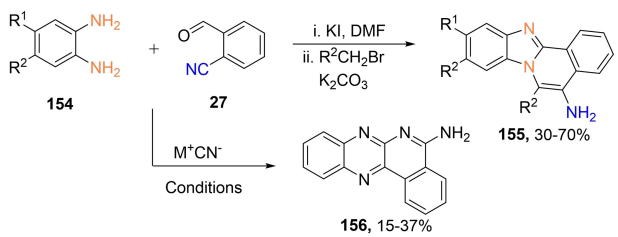
Initially, the nucleophilic addition of **A** to the carbonyl group of **27** or **95** would give, in the presence of a base, the



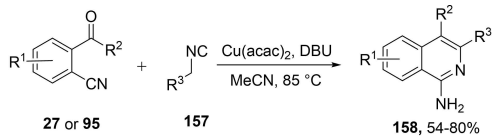

**Scheme 62.** Reaction with methyl azidoacetate.




**Scheme 63.** Mechanism of reaction with methyl azidoacetate.




**Scheme 64.** Reactions with o-phenylenediamines.




**Scheme 65.** $Cu(acac)_2$-catalyzed reaction of 2-cyanobenzaldehydes or 2-acetylbenzonitriles with 2-isocyanoacetates.

intermediate **B**. Next, an intramolecular cyclization of intermediate **B** could afford intermediate **C** containing a dihydrooxazole moiety, which would undergo a ring opening/rearrangement to furnish intermediate **D**. Under the activation of the copper(II) catalyst, a 6-exo cyclization leads to intermediate **E**, followed by decarbonylation–aromatization that would generate the isoquinoline **158** (Scheme 66).

## 10. Synthesis of 2-cyanobenzaldehydes and 2-acylbenzonitriles

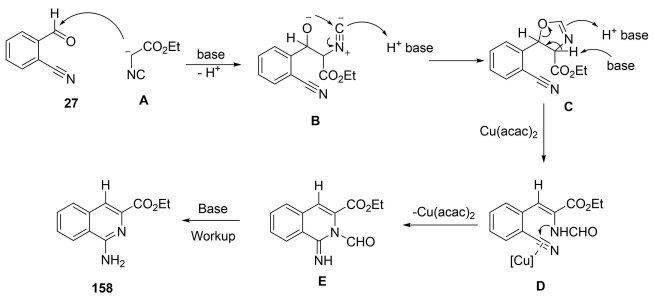
A first synthesis of 2-cyanobenzaldehyde was reported in 1936 by Patelski et al. by reacting 2-cyanobenzal bromide with excess of silver nitrate, in 95% ethanol, albeit low yields were obtained.[46] The necessity to synthesize 2-cyanobenzaldehdyes substituted with further groups on the aromatic ring led our group to develop different pathways based on formylation of substituted benzonitrile **159** or CuCN promoted cyanation of 2-bromo benzaldehyde **160** under microwave conditions (Scheme 67).[28]

However, considering the narrow scope of the reactions described in scheme 67, the method previously reported by Patelski was reconsidered under different conditions,[46] refluxing easily accessible benzal bromides **162** in a mixture of water and dioxane, leading to a series of 2-cyanobenzaldehydes in good to high yields, without using the excess of $AgNO_3$ (Scheme 68).[59]

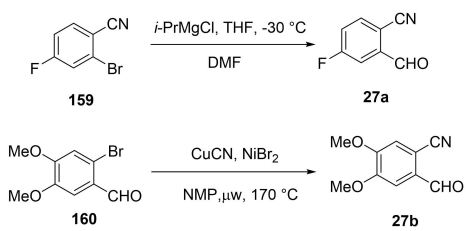
Emphasis was also given to the synthesis of 2-acetylbenzonitrile because it is rather expensive, and because derivatives substituted on the aromatic ring are not easy to synthesize. In 2012 Gotor, Fernandez and co-workers[38] reported a synthetic pathway to 2-acetyl benzonitriles **95**, requiring several steps and employing cyanating agents like NaCN or CuCN in Sandmeyer reactions in rather low yields.

In order to develop a more effective synthesis of **95** from readily available starting materials, a one-pot dibromination/hydrolysis mixing together NBS, AIBN, water in acetonitrile was developed as reported in the following scheme 69, starting from 2-ethylbenzonitrile **163** (X=H).[37] This new method has the advantage to avoid the isolation of the respective gem-dibromide and the use of $CCl_4$ (see Scheme 68 for comparison). In addition, the easy functionalization of 2-ethylbenzonitrile **163** allowed to obtain different 2-acetylbenzonitriles and therefore different substituted isoindolinones.[37]

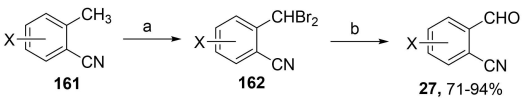
As for 2-acetylbenzonitriles **95**, the synthesis of 2-cyanobenzophenones **98** was carried out by benzylic oxidation of 2-benzylbenzonitriles **166** by one-pot radical dibromination/hydrolysis reactions in a mixture of water and acetonitrile




**Scheme 66.** Proposed mechanism of $Cu(acac)_2$-catalyzed reaction of 2-cyanobenzaldehydes or 2-acetylbenzonitriles with 2-isocyanoacetates.



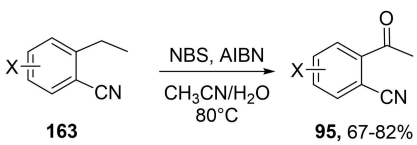

**Scheme 67.** Formylation of substituted benzonitriles or CuCN promoted cyanation of 2-bromo benzaldehydes in the synthesis of 2-cyanobenzaldehydes.



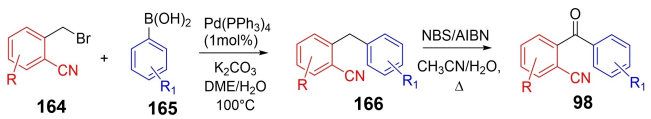

X= H, 5-$NO_2$, 5-Cl, 5-F, 5-Br, 5-I, 5-$OCH_3$, 5-[(3,4-$(CH_3O)_2C_6H_3$], 4-$NO_2$

**Reagents and conditions:** a) *N*-bromosuccinicimide, dibenzoyl, peroxide, $CCl_4$, reflux; b) dioxane/water (1/1), reflux, 24h

**Scheme 68.** Hydrolysis of benzal bromides in the synthesis of 2-cyanobenzaldehydes.




**Scheme 69.** One-pot dibromination/hydrolysis in the synthesis of 2-acetylbenzonitriles.




**Scheme 70.** Sequence of Suzuki–Miyaura cross-coupling reactions and one-pot dibromination/hydrolysis in the synthesis of 2-cyanobenzophenones.

(Scheme 70). The advantage of this approach also relies on the easy synthesis of 2-arylbenzonitriles **166** differently substituted on both the aromatic rings, obtained by Suzuki–Miyaura palladium catalyzed cross-coupling reactions of **164** (Scheme 70).[41]

## 11. Conclusions

In this Review we have described the chemistry of 2-cyanobenzaldehydes and related 2-acylbenzontriles in divergent cascade type reactions, leading to series of interesting classes of fused five membered heterocycles as isoindolinones, phthalides, 1-iminosoindoline, six membered as imidazo[2,1-a]isoquinolines and Isoquinolino[3,4-b]quinoxalines and seven membered as azepine derivatives, also in asymmetric way. Even though this variety of complex chemical reactions based on different cascade pathways has been discovered mainly by serendipity, the knowledge and the comprehension of such complex reaction mechanisms is of paramount importance to develop new processes, to expand the scope leading to new products and to design the synthesis of more complex molecular structures. Therefore, the aim of this Review is also to highlight how important is the proper designing of suitable multifunctional starting materials to develop target-oriented cascade synthesis of complex molecular structures and new products.

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## *Conflict of Interests*

The authors declare no conflict of interest.

**Keywords:** asymmetric catalysis · cascade reactions · heterocyclic compounds · one-pot reactions · organocatalysis

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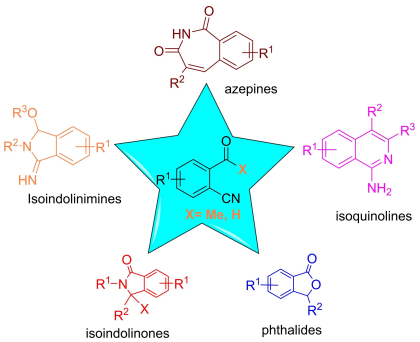
# REVIEW

Easy access to several classes of heterocyclic compounds is provided by reacting 2-cyanobenzaldehyde or 2-acylbenzonitriles with a range of nucleophiles under mild conditions through divergent cascade reactions in an asymmetric way.

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