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Revisão

RECENT ADVANCES IN CYANATION REACTIONS†

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Transformations involving structurally complex molecules, natural products and representative molecules are extremely important to obtain key reaction intermediates, in addition to accessing molecules with bioactive properties. The development of cyanation methodologies in those molecules becomes important, because nitriles are versatile and important building blocks in organic synthesis. They can be converted into other organic functions, including amines, alcohols, α-amino acids and various carbonyl compounds and can therefore become relevant synthetic intermediates. Recent studies show new and intriguing asymmetric cyanation protocols or reagents as those that use electrophilic cyanide source, metal- and oxidant-free or avoid the use of toxic cyanide reagents. Photoredox catalysis emerges as a relevant approach from the point of view of green and sustainable chemistry; usually provides access to the versatile skeleton of α-aminonitriles that among their various modes of reactivity and provide access to reactive iminium ion. Thus, this perspective aims to highlight these impressive advances as well as to show their main advantages and applications.

Keywords: cyanation; photoredox; complex molecules; natural products; drug-like molecule.

INTRODUCTION

Organic compounds containing the cyano group, also known as nitriles, are highly versatile and useful building blocks in organic synthesis, as this moiety can be easily converted to other organic functions. According to the molecule structure and the reaction conditions, the nitrile moiety can be converted into amines, tetrazoles, alcohols, α-amino acids, diamines, besides various carbonyl compounds such as ketones, aldehydes, amides, among others.[1,2]

Such versatility can be understood by analyzing the general reactivity of this function. Nitriles may contain, at least, one hydrogen atom in the Cα. Thus, its reactivity summary allows access to a range of addition products to the C≡N bond in the presence of varied nucleophiles or generate nitrile anions by reaction with bases, via Hα abstraction (pKa around 25-30 in DMSO), as shown in Figure 1. Furthermore, the presence of the lone pair in the nitrogen atom allows these substances to act as Brønsted and Lewis bases, according to the reaction conditions.[3]

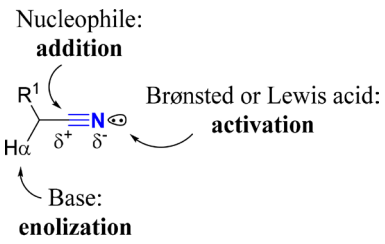

Figure 1. *General reactivity of the cyano group*

This range of possibilities makes these cyano derivatives widely used as synthetic intermediates. In particular, structurally complex molecules and cyanated natural products are widely used for this purpose, as they allow access to greater structural diversity and bioactive products.

As an example of such synthetic potential, Zhang and co-workers recently reported the synthesis of several biaryls through cyanated 2,2'-biphenols, described in Scheme 1.[4] The main cyanated substrate was scaled up to gram-scale and, from this, various functionalizations were made in different reaction conditions, allowing to access different organic functions such as aldehyde, ketone, amide, oxazoline, benzofuran, among other derivatives.

Besides allowing access a great structural diversity from cyanated intermediates, the maintenance of the cyano moiety in the final product is interesting regarding the synthesis of biologically active compounds. A current example can be observed in the synthesis of Remdesivir, an important antiviral drug originally evaluated against the Ebola outbreak in 2014. Nowadays, it is used against SARS-Cov-2, the viral pathogen that caused the global pandemic in 2020.[5,6] One of the steps in its synthesis (of a total of 6) consists of the stereoselective addition of the cyano group in the presence of triflic acid at cryogenic temperatures. After its implementation, the cyano moiety remains intact throughout the synthesis, until the target drug is obtained.[7] Thinking about the large-scale production which requires the use of hazardous reagents and extreme conditions, Vieira and co-workers have recently reported both batch and continuous flow mode cyanation of glycoside **1** under milder conditions, with high diastereoselectivity (Scheme 2).[8]

In addition to Remdesivir, several drugs containing the cyano group are currently used in different treatments. For example, BMS-214662, which is a farnesyltransferase inhibitor that entered clinical studies for chronic myeloid leukemia , Vildagliptin, which is used in the treatment of type 2 diabetes and Neratinib, which is adopted to treat HER2-positive breast cancer, shown in Figure 2.[9] Due to the remarkable number of bioactive nitrile derivatives, researchers have been evaluating the modes of interaction between the nitriles and bioactive receptors, in order to better understand the mechanism of action of such drugs. Several compounds of natural origin also have this important organic function in their scaffold, such as the marine compound (+)-Calyculin A and Borrelidin, which is extracted from the bacterium *Streptomyces rochei*, also shown in Figure 2.[10,11]

Traditionally, besides the hydrocyanation of unactived alkenes, cyanated compounds are obtained from the addition of cyanide to electrophiles such as carbonyl compounds, imines and electron-deficient

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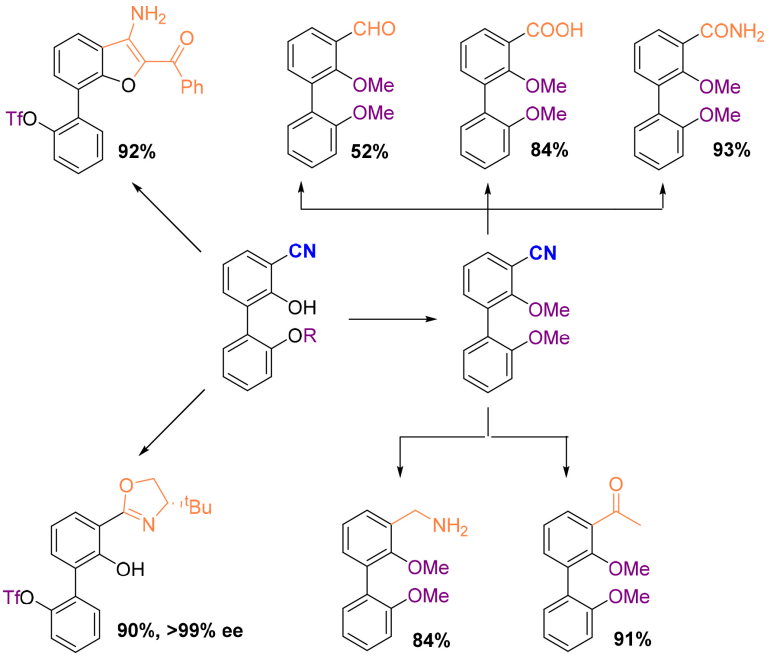
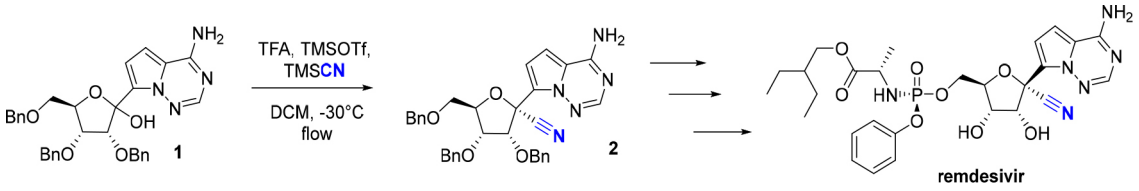
†Dedicated to Prof. Rodrigo B. Andrade from Temple University who passed away very early in Philadelphia, USA.



Scheme 1. *Examples of functionalization of cyanated compounds*



Scheme 2. *Cyanation of the glycosidic intermediate for Remdesivir's synthesis*

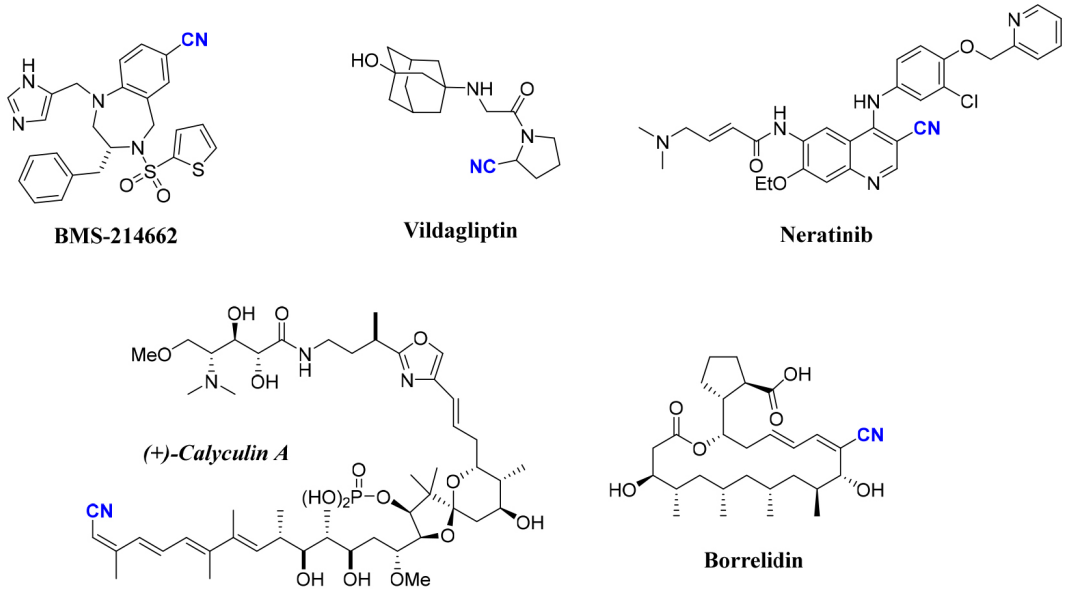


Figure 2. *Natural and bioactive compounds containing the cyano group*

olefins. Due to the synthetic versatility of cyanation reactions and because it is one of the most important C-C bond formation reactions, over the past 30 years, enantioselective approaches of these reactions have been intensively studied. As research advances, intriguing asymmetric cyanation protocols have been developed, such as the cyanofunctionalization of alkenes, cyanation via C-H functionalization, cyanide free protocols as well as the development of bifunctional cyanating reagent; all of them with the intention to avoid the use of highly toxic and volatile cyanation reagents.[12]

In this review, we will address methodologies developed over the last 20 years that employ cyano group insertion in the preparation of complex molecules, whether of natural or synthetic origin, as well as in bioactive molecules. In addition, discussions about reactivity, the generality of the methods through the representative scope and their applications will be detailed. As an emerging tool, we will approach the recent works that use photoredox catalysis for the homologation of the cyano group, both in simple structures, as in complex molecules and reaction intermediates.

METAL-CATALYZED METHODOLOGIES

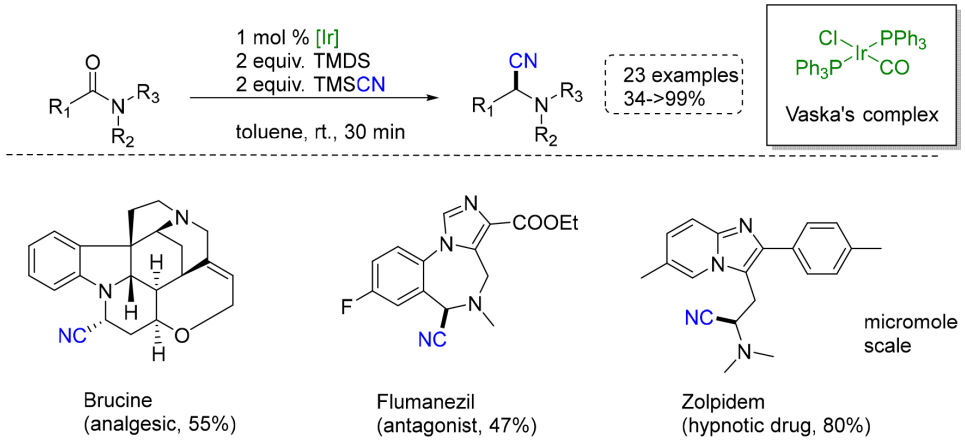
Nucleophilic cyanide sources

Metal catalysis is a widely used tool in the development of efficient methodologies for the cyanation of complex structures. For instance, Dixon and co-workers have reported the use of iridium as a catalyst in the reductive cyanation of amides and lactams.[13] To overcome the low electrophilicity of the amides and lactams carbonyl group and achieve the desired reactivity, Vaska's complex in the presence of tetramethyldisiloxane (TMDS) was used, instead of either most likely used metal hydride reducing agents or strong electrophiles. The reductive cyanation reaction shown in Scheme 3 was applied to alkaloids and drugs possessing either tertiary amide or lactam residues. The reaction proved to be diastereoselective for alkaloids containing multiple stereogenic centers. Considering the methodology, several heterocycles were well tolerated. Additionally, olefin and ester proved to be inert under the reaction conditions. The reaction was also successful on the micromole scale, with moderate to good yields in all cases.

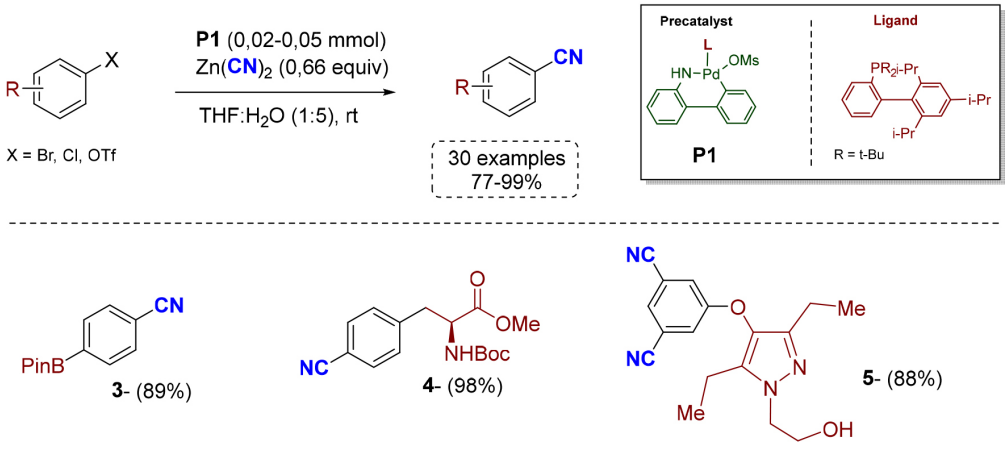
In 2015, Buchwald and co-workers described the palladium-catalyzed cyanation of aryl and heteroaryl halides and triflates as shown in Scheme 4, using lower temperatures than those commonly required in previously described methodologies.[14-17] In the optimization process, cyanide was assumed to act as an ideal base in activating the precatalyst, since the absence of base has resulted in a higher level of conversion. Furthermore, based on previous studies, THF:H_2O solvent mixture provided the slowest diffusion of the cyanide to the organic phase, allowing a moderate rate for the transmetallation step without deactivation of the palladium catalyst. A variety of aryl halides containing both electron-donating and electron-withdrawing substituents were well tolerated under the optimized reaction conditions, and 5- and 6-membered heteroaryl halides as well. It is worth noting that the boronate ester **3** was compatible with the protocol, with no homocoupling product formation. Natural product derivatives were also appropriate, obtaining the cyanated products in excellent yields and without epimerization of the stereocenter, as in the case of product **4**. In order to demonstrate the practicality and robustness of the method in the pharmaceutical/medicinal field, the protocol was applied in the cyanation of the final intermediate of lersivirine **5**, a reverse transcriptase inhibitor.

Also using palladium catalysis, Leahy and co-workers reported an efficient methodology for the synthesis of the structurally similar compounds BMS-763534 **6** and BMS-764459 **7**, corticotropin-releasing factor (CRF) antagonists which are potential clinical candidates to the treatment of neurological disorders such as depression and anxiety.[18] The key step in this synthesis was the conversion of **6** to **7** via palladium-catalyzed aryl chloride cyanation (Scheme 5). Although high temperature is required, this approach can be considered efficient due to the low reactivity of 5-chloropyrazinones **6**, which makes palladium-catalyzed cross-coupling difficult.

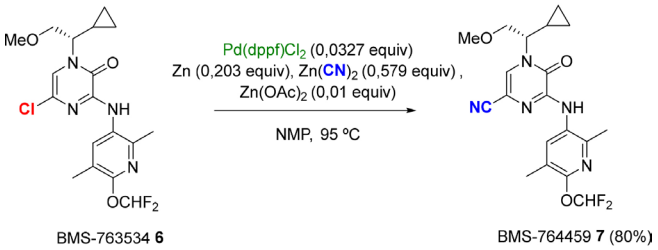
The use of catalysis by copper salts has also emerged as a strategy of choice in cyano group homologation in the synthesis of structurally complex molecules. In this context, Okamoto and co-workers reported the direct copper-catalyzed cyanation of terminal alkynes using cyanogen iodide as the cyanide source, 10 mol% of the copper triflate complex (CuOTf-toluene) and 2,2,6,6- tetramethylpiperidine (TMP)



Scheme 3. *Reductive cyanation of alkaloids and drugs*



Scheme 4. *Palladium-catalyzed cyanation of aryl halides*

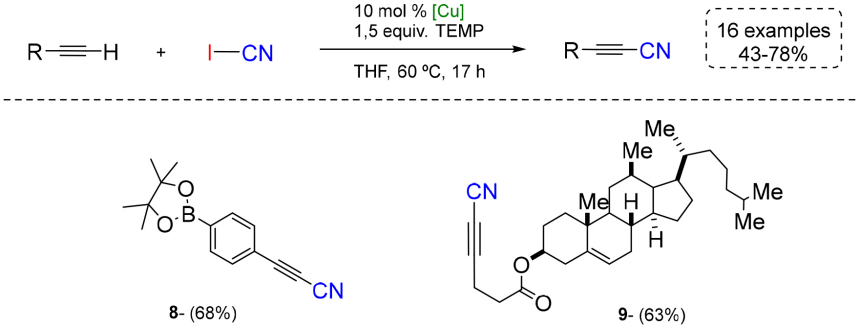


Scheme 5. *Antagonist BMS-763534 cyanation*

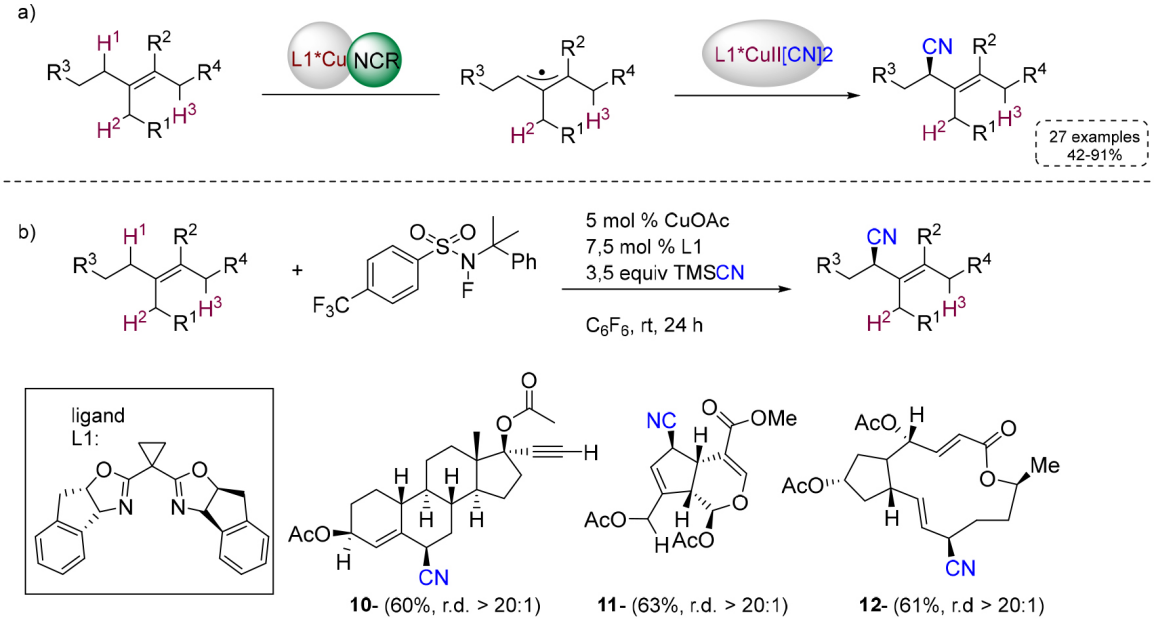
as a bulky base (Scheme 6).[19] The reaction was efficient for alkynes containing a variety of substituents, such as alkyl groups, thiophene, silylacetylene, *para*-substituted aromatic acetylenes, among others. It is interesting to highlight the tolerance of the boronic pinacolester moiety **8**, despite its susceptibility to the transmetallation reaction. The desired product was obtained in 68% yield, which allowed the final product to undergo further transformations, such as Suzuki-Miyaura cross-coupling. The presence of substituents at the *meta*- and *ortho*-positions was not evaluated in this substrate scope. The method was also efficient for more structurally complex molecule, such as cholesterol, allowing access to product **9** with 63% yield. Mechanistic studies suggest that the reaction pathway go through the formation of alquinyl iodide and a salt of cyanide with base (TMP·HCN) as the cyanation agent. This consists of alternative pathway from the usual approaches, which typically occur via copper acetylate formation.

Liu and co-workers also reported the use of copper catalyst in the site- and enantioselective allylic C-H cyanation of functionalized alkenes (Scheme 7).[20] In the methodology, the copper complex with bidentate ligand associated with a (*N*)-centered radical species (NCR) were active in the hydrogen atom transfer (HAT) process, increasing the site-selectivity between allylic C-H bonds by enhancing ΔΔG. After this process, the allylic radical was captured in a highly selective manner by the L1*$Cu^{II}(CN)_2$ species, leading to the formation of the desired product (Scheme 7.a). Importantly, the enantioselective process of interception of the allylic radical is independent of the HAT step, since similar results were obtained with different NCR precursors. A wide variety of alkenes was compatible with the protocol, such as di-, tri-, and even tetrasubstituted alkenes, including those having as part of the structure, stereogenic centers. It is worth noting that the method was applied in a highly selective functionalization of compounds with biological importance. For example, from Norethisterone diacetate, the formation of the unique isomer **10** was observed with 60% yield, keeping the terminal alkyne intact. Genipin and Brefeldin A diacetates led to the formation of products **11** and **12** respectively, with excellent site- and diastereoselectivity (d.r. > 20:1), even in the presence of hydrogen with certain lability, such as those alpha to alkoxy carbonyl groups.

In one of the steps of the asymmetric total synthesis of Mycoleptodiscin A, Li and co-workers used indium (III) chloride in the cyanation reaction of intermediate **13** (Scheme 8).[21] A series of reaction conditions for the benzylic cyanation of **13** were evaluated by varying parameters such as Lewis's acid and solvent. As the



Scheme 6. *Copper-catalyzed cyanation of terminal alkynes*



Scheme 7. *a) Formation of allylic radical b) Diastereoselective cyanation of olefinic compounds*

optimal reaction condition, the cyanation step was performed using TMSBr, $InCl_3$ as Lewis acid and TMSCN as cyanation reagent. The desired product **14** was obtained as a single diastereomer in 89% yield. According to X-ray analyses, the cyano group installed in structure **14** has pseudo-equatorial position. Indolosesquiterpenoids have attracted much attention in the fields of chemical synthesis and biosynthesis due to their cytotoxic activities against cancer cell lines, thus the development of their total syntheses becomes important.

Electrophilic cyanide sources

Although widely used reagents provide the CN^- anion as nucleophile in cyanation reactions, reagents that transfer this group in its electrophilic form (CN^+) have become a versatile complementary strategy in the synthesis of cyanated compounds. This reversal of the inherent reactivity of the cyano group allows the cyanation of classical pro-nucleophiles, such as enolates, for example, in addition to access to important structures that would be more difficult to access by other approaches.[22]

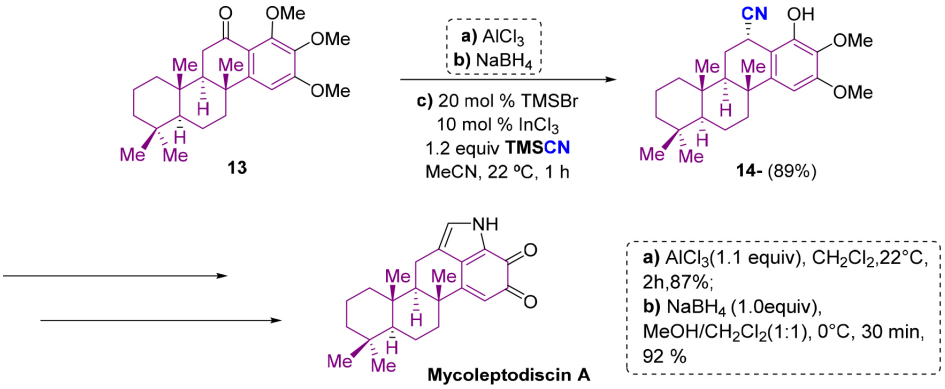
In 2016, Morrill and co-workers reported the one-pot synthesis of cyanamides from secondary amines using trichloroacetonitrile as an electrophilic cyanide source (Scheme 9).[23] A good variety of substrates, both cyclic and acyclic **15**, proved to be suitable for the protocol, including structures containing more than one nucleophilic nitrogen atom **16**, which demonstrates the selectivity of the method. This is interesting from a synthetic point of view, especially with regard to the use of complex systems containing more than one reactive site. However, the approach is limited to the use of less nucleophilic secondary amines, since these did not lead to the formation of the desired product. Such result can be justified by the lower reactivity of trichloroacetonitrile compared to the commonly used cyanogen bromide (BrCN). The selectivity profile of both reagents was evaluated against substrates containing two nucleophilic atoms. Possibly due to its higher reactivity, BrCN led to the formation of dicyanamide **19**, while trichloroacetonitrile, to the monocyanate product **18**.

As an application to the synthesis of cyanamides, the *N*-cyanation of the Rolipram-derived pyrrolidine **17** was performed, resulting in a higher yield than that obtained by the reported approach using BrCN.[24]

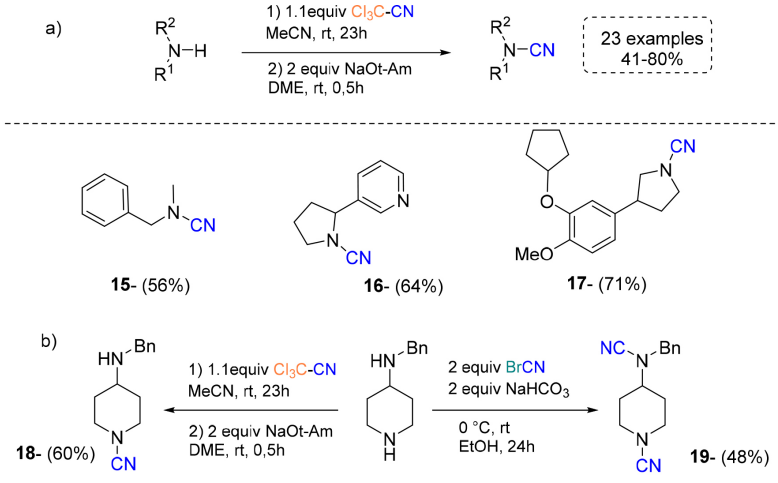
It is interesting to note that the direct cyanation of primary, secondary or tertiary amines is usually performed using cyanogen halides, mainly cyanogen bromide (BrCN). These halides have high electrophilicity in their CN subunit, which gives them great efficiency as reagents in this type of reaction with amines. However, the use of cyanogen halides presents some disadvantages that make their handling dangerous, their high toxicity, sensitivity to humidity (causing release of toxic HCN), and unfavorable physical properties (in particular, their low melting and boiling points).[25]

Cyanogen halides are also widely used in the synthesis of cyanamides, being important from both industrial and synthetic point of view, since these structures are present in both pharmaceuticals and agrochemicals. In addition, they have been commonly chosen as intermediates in the synthesis of biologically active compounds, as in the case of Verubecestat, which was evaluated in the treatment of Alzheimer's disease.

In 2019, Cohen and co-workers developed a one-pot synthesis of cyanamides from primary and secondary amines using $Zn(CN)_2$ as an alternative to the use of the highly toxic cyanogen halides (Scheme 10).[26] Control experiments demonstrate that the amine is instantly oxidized to the corresponding *N*-chloroamine after



Scheme 8. *Cyanation step in the synthesis of Mycoleptodiscin A*



Scheme 9. *a) Synthesis of cyanamides from secondary amines. b) Comparison of cyanation reagents*

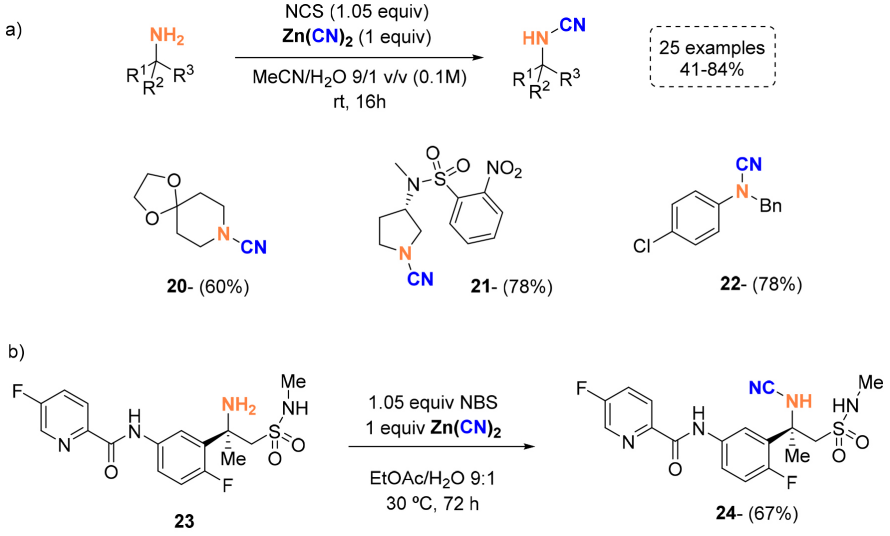
N-chlorosuccinimide addition. Different amines such as piperidine derivatives **20**, pyrrolidine **21** and aniline **22** were well tolerated. Importantly, the methodology was successfully applied to the cyanation of the intermediate amine **23** in the route of obtaining Verubecestat. Upon adjusting the optimized reaction conditions, amine **23** resulted in the desired product **24** in 67% yield.

Fu and co-workers have reported the direct cyanation of the C-H bond in arenes, using as cyanide source, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS). It is less toxic and easily available cyanide source (Scheme 11).[27] The protocol was well tolerated by a wide range of substituents such as halogens, glycoconjugates, boronic acid derivatives **25**, among others, allowing further functionalizations. It is worth noting the efficiency of the approach when applied to substrate containing the epoxide group **26**, since few reactions catalyzed by transition metals are compatible with this group. Other directing groups and heteroaromatic compounds were also well tolerated. In particular, despite the presence of the cyclic thioether subunit, the method was efficient in the cyanation of Zaltoprofen derivative, leading to the cyanated product **27** in 74% yield.

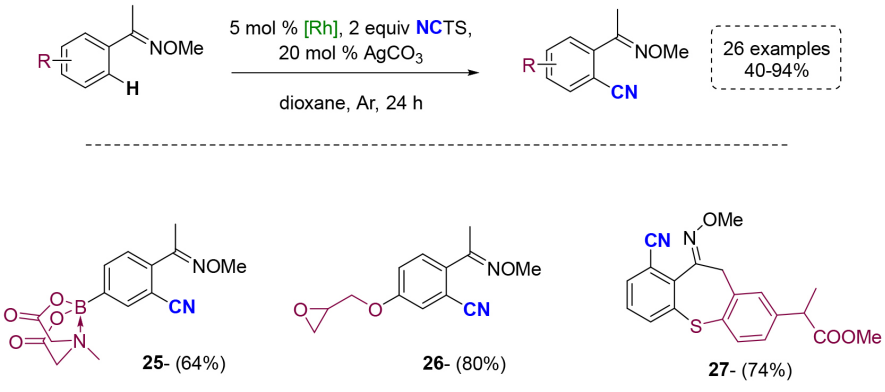
The highly regioselective monocyanation of *N*-aryl-7-azaindoles was described by Deb and co-workers, using *N*-cyano-*N*-phenyl-*p*-toluene sulfonamide (NCTS) as the cyano source (Scheme 12).[28] The methodology required 5 mol % of the catalyst $[RuCl_2(p\text{-cymene})]_2$, which is relatively cheaper than the rhodium catalyst, and showed good results for a variety of substituted and unsubstituted azaindoles (**28**, **29**, and **30**). Importantly, no bis-cyanated product formation was observed. Based on the control experiments, the proposed mechanism suggests the formation of a cationic ruthenium complex in the presence of AgOTf and NaOAC, followed by the reversible insertion of the metal into the C-H bond and subsequent coordination of the cyanation reagent.

The use of nickel catalysis was reported by Watson and co-workers in the deaminative cyanation of Katritzky pyridinium salts, allowing the conversion of alkyl amines into alkyl nitriles.[29] In this work, the alkylamine is condensed with the commercial pyridinium salt **34**, leading to the formation of pyridinium salt as an intermediate, which goes to the alkyl nitriles via nickel-catalyzed cyanation process (Scheme 13). $Zn(CN)_2$ was used as a less toxic cyanide source and Xantphos as a ligand. Unlike the alkyl halides, the alkyl amines are more flexible with regard to synthetic strategy, since they can be functionalized early or with adequate protection. Furthermore, amines are present in readily available, simple starting materials and in a variety of complex pharmaceutical intermediates. Various functional groups were well tolerated, including the incorporation of nitrile into heterocycles. The generality of the method was highlighted in the functionalization of pyridine salts, leading to important intermediates in the synthesis of pharmaceutical products, such as Agomelatine (**35**), Lipitor (**36**), and Mosapride (**37**). The method importance has been also demonstrated in the efficient one-carbon homologation of the protected primary amine. In this case, the desired product **38** was synthesized in 53% yield.

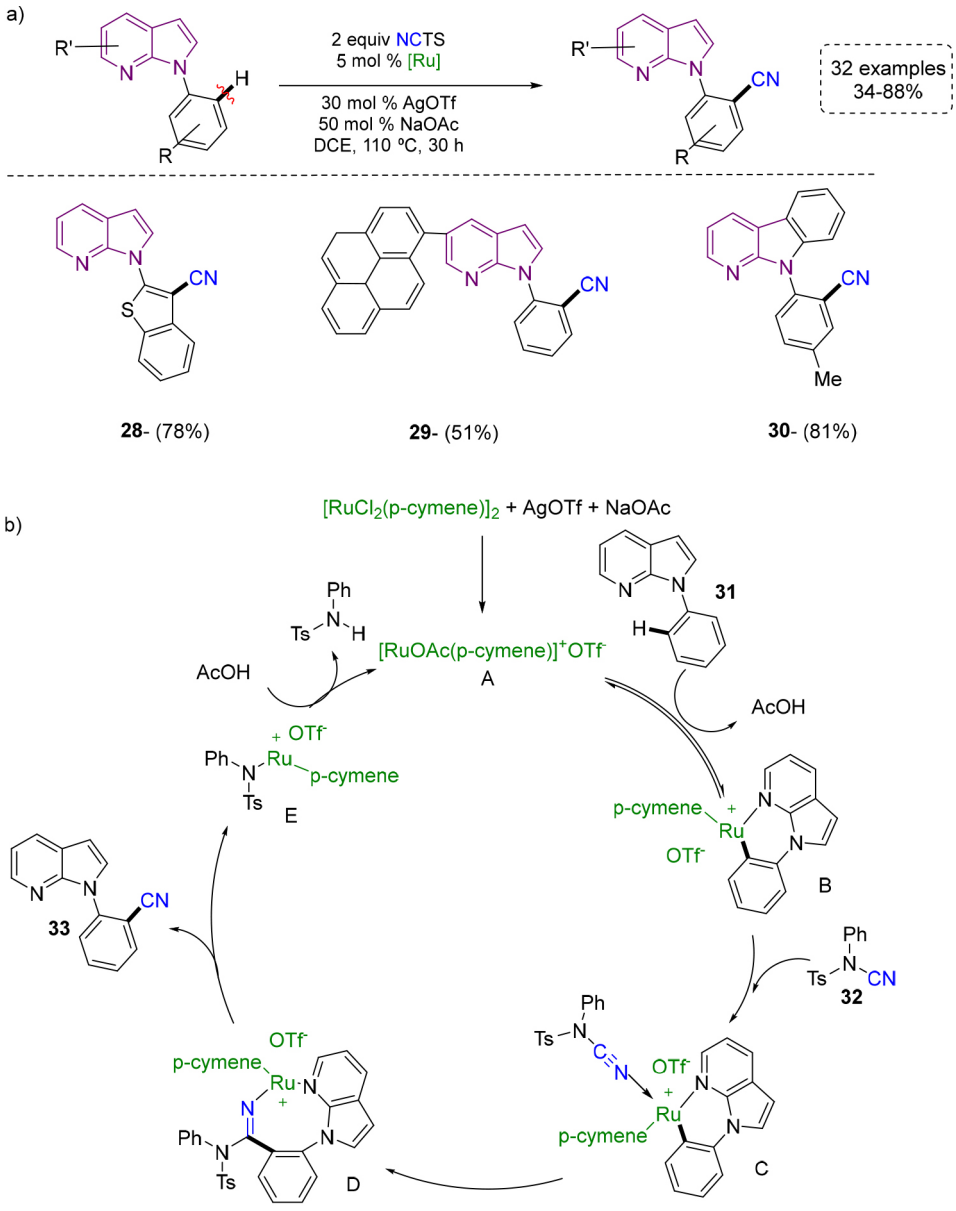
In view of their versatility and wide application, the development of new electrophilic cyanation reagents has been the subject of research in recent years. Alcarazo and co-workers have recently reported the synthesis of 5-(cyano)dibenzothiophenium triflate **39** and its reactivity as an electrophilic cyanation reagent (Scheme 14).[30]



Scheme 10. *a) Cyanation of primary and secondary amines using $Zn(CN)_2$ b) Cyanation of the intermediate amine en route to Verubecestat*



Scheme 11. *Rhodium-catalyzed directed C-H cyanation of arenes*



Scheme 12. *a) Cyanation of N-aryl-7-azaindoles b) Mechanistic proposal*

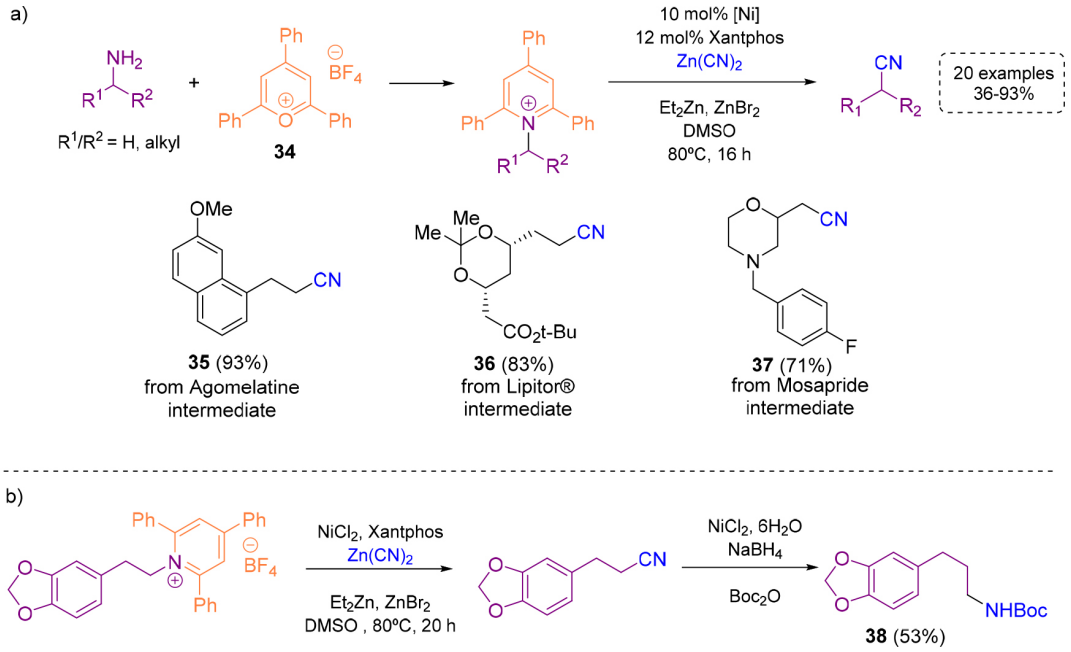
A variety of compounds containing nucleophilic N, S, and C atoms were used to evaluate the efficiency of the reagent, obtaining the respective cyanated compounds in yields ranging from 27 to 99% (Scheme 14.a). In order to evaluate the generality and efficiency of the new reagent in more complex transformations, indole derivatives containing an internal nucleophilic group were evaluated in the intramolecular cyanofunctionalization reaction (Scheme 14.b). Substrates containing N, O and C as nucleophilic atoms were well tolerated, with the formation of only one diastereomer, with the exception of compound **44**, due to the additional chiral center. The reagent was also efficient in the cascade process of cyanation followed by [4+2] Povarov-type cyclization, leading to the desired tetracyclic skeletons with good yields (67-85%) and high diastereoselectivity.

TRANSITION METAL-FREE METHODOLOGIES

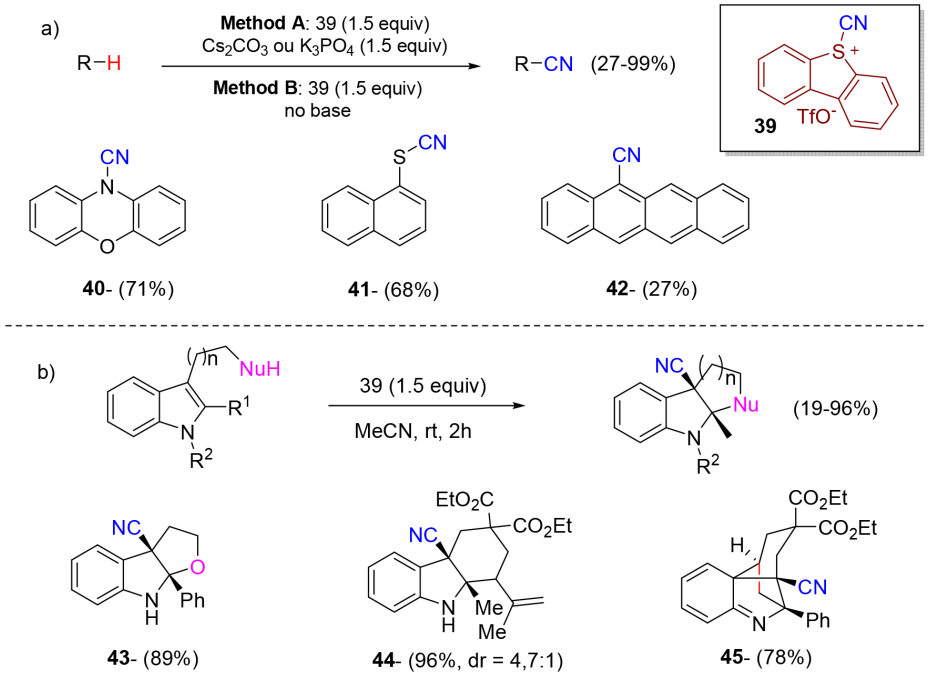
Metal- and oxidant-free cyanation processes have also attracted the attention of several researchers, as for example in the work of Wang and co-workers, who reported the use of electrochemistry in the synthesis of cyanated *N*-heterocycles.[31] Starting from simple and easily available substrates, a good variety of cyanated *N*-heterocyclic quinoline derivatives could be accessed (Scheme 15). Different alkylamines, considering both aromatic **46** and aliphatic **47** moieties, were compatible with the optimized reaction conditions. In both substrate scope, electron-rich substituents showed better results than electron-deficient ones. In addition, despite the good reactivity, bulky substituents on quinoline scaffold showed an important influence in the reaction yield, as shown in the preparation of **48**.

Due to their bifunctional nature, α-aminonitriles are versatile building blocks for a wide range of nitrogen heterocycles. The first report of their synthesis dates back to 1850, when Strecker performed a three-component reaction between aldehydes, amines, and hydrogen cyanide. Since then, this reaction has been intensively studied, resulting in several protocols derived from the pioneering reaction, including stereoselective versions.[32-34]

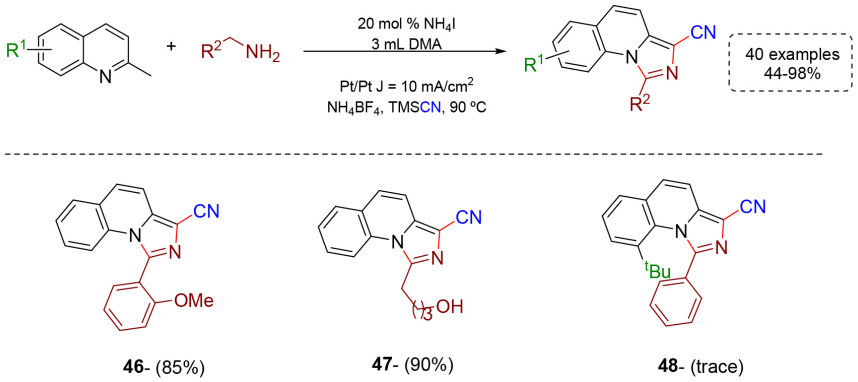
In 2019, Liu and co-workers reported the first asymmetric total synthesis of (+) Winchinine B **50**, an alkaloid containing a rare cyano group, from the commercially available 2-ethylcyclohexanone.[35] As the last step of the total synthesis, the imine cyanation reaction



Scheme 13. *a) Deaminative cyanation of Katritzky pyridinium salts b) One-carbon homologation*

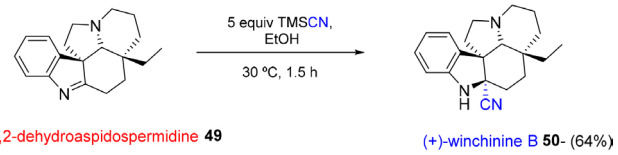


Scheme 14. *a) Electrophilic cyanation using **44** b) Electrophilic cyanation-Povarov cascade of indole derivatives*



Scheme 15. *Synthesis and functionalization of N-heterocycles fused to imidazoles*

of (+)-1,2-dehydroaspidospermidine **49** using TMSCN lead to the formation of the desired product in 64% yield (Scheme 16). The desired cyanated alkaloid was accessed only in the presence of a protic solvent, as it was assumed that hydrogen-bonding activation accelerated the addition of the cyano group in the molecule.



Scheme 16. *Cyanation step of the total synthesis of (+)-winchinin B*

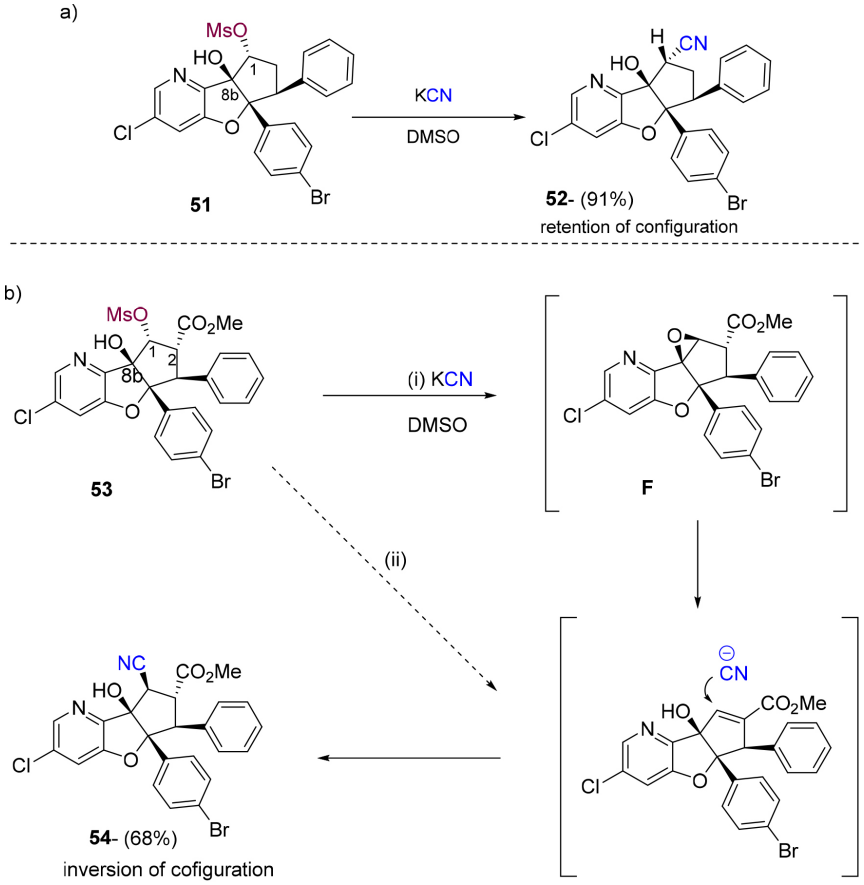
Rocaglamides and other flavaglin analogues, in addition to other biological activities, are natural products with remarkable anticarcinogenic activity through inhibition of eukaryotic initiation factor 4A (eIF4A). In order to develop diastereoselective strategies for new flavaglin analogues, Reich and co-workers have reported the functionalization at the C1 position of aza-rocaglamides via cyanation reactions (Scheme 17).[36] Interestingly, cyanation of the mesylated aza-rocaglamide **16** led to the formation of product **52** with retention of the C1 position configuration. Mechanistic studies suggest the regioselective opening of the epoxide, formed by the assistance of the hydroxyl of carbon C8b. In contrast, in the presence of substituent group at C2 (**53**), the nucleophilic substitution reaction occurs with opposite configuration. In addition to the epoxide formation pathway (i), mechanistic studies suggest the possibility of an additional pathway (ii), through direct elimination of the mesyl group. This methodology allows access to the desired aza-rocaglamide derivative **54** with the opposite configuration to that observed by removing the substituent at C1.

Corey and co-workers used cyanation functionalization in one of the steps in the synthesis of the carbocyclic core of cortistatin **57**.[37] The cyanation of compound **55** using TMSCN as the cyanide source and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as oxidant, yielded compound **56** in 95% yield (Scheme 18.a). During reaction optimization, when the cyanide reagent concentration was at least 3 mol L^{-1}, the product formed was the desired benzyl cyanide C9 **58**; however, when this concentration was less than 3 mol L^{-1}, the cyanation product of C12 **59** was predominant (Scheme 24.b). These results indicate that the benzyl cation C9 formed could undergo rapid proton loss and then oxidation by DDQ at low concentrations of cyano source reagents.

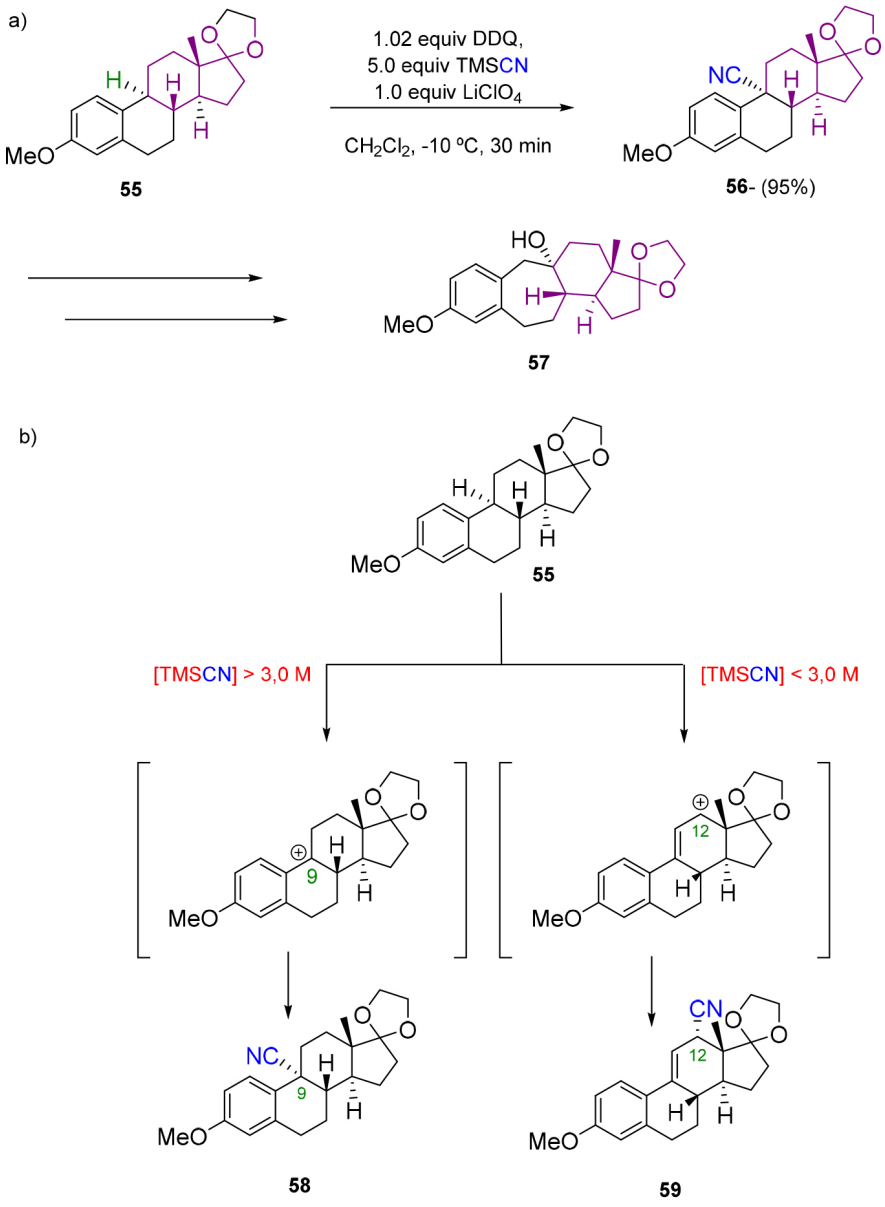
In addition to the development of cyanation processes, important tools in organic synthesis such as photoredox catalysis have been recently employed in order to develop cleaner and more efficient protocols for cyano group insertion into representative molecules. Next section is dedicated to recent examples of this strategy.

LIGHT-DRIVEN STEREOSELECTIVE CYANATION

In the last decades there has been a growing concern of several renowned research groups in the development of methodologies that combine efficiency and sustainability. In this context, mild and efficient methods for the redox manipulation of complex organic molecules are extremely valuable from a synthetic point of view. The use of sunlight is interesting because it is an abundant, inexpensive, non-polluting and endlessly source of clean energy, in addition to several other advantages.[38] Since most organic molecules do not have the ability to absorb visible wavelengths of light and transform it into chemical energy, photoredox catalysis has emerged as an interesting alternative to address this issue.



Scheme 17. *a) Stereoselective cyanation of a monomesylated diol b) Stereoinvertive C1 displacement in* ***54***



Scheme 18. *a) Synthesis of the cortistatin derivatives b) Benzylic vs allylic cyanation studies*

In the process of photoredox catalysis, the photocatalyst, usually a metal complex or an organic dye, reaches its excited state by absorbing radiation in the visible region. From this excited state, the photocatalyst then activates the organic molecule through either energy or electron transfer. In the latter, the electron transfer between the photocatalyst and the organic molecule can occur either by oxidative or reductive quenching cycle or through redox neutral reactions.[39,40]

Although in recent decades photoredox catalysis has been employed as an enabling methodology for small molecules, the use of this tool in the synthesis of natural products as well as complex substrates are comparatively limited. One of the first report on the use of light in the cyanation process of complex amines dates back to 1977, when Santamaria and co-workers reported the photocyanation of complex alkaloids, such as vincadiformin and tabersonine using the organic dye rose Bengal irradiated by visible light.[41] Since then, aspects such as the structure/regioselectivity relationship have been studied, besides the development of different protocols, such as the use of singlet oxygen in the single electron transfer (SET) process.[42-44]

In the few works reported so far using the photochemical approach, bioactive compounds and natural products are usually used as substrates when it comes to evaluate the generality of the methodology on structurally complex molecules. Generally, cyanation of alkaloids allows access to the versatile α-aminonitriles motif. Among their various modes of reactivity, these structures possess latent iminium ion reactivity, which can be generated by spontaneous or induced loss of the cyanide ion. This masked reactivity allows access to a wide structural diversity, reacting with various nucleophiles. Besides, this effect can lead enamines through deprotonation or even to carbonyl compounds after hydrolysis.[45]

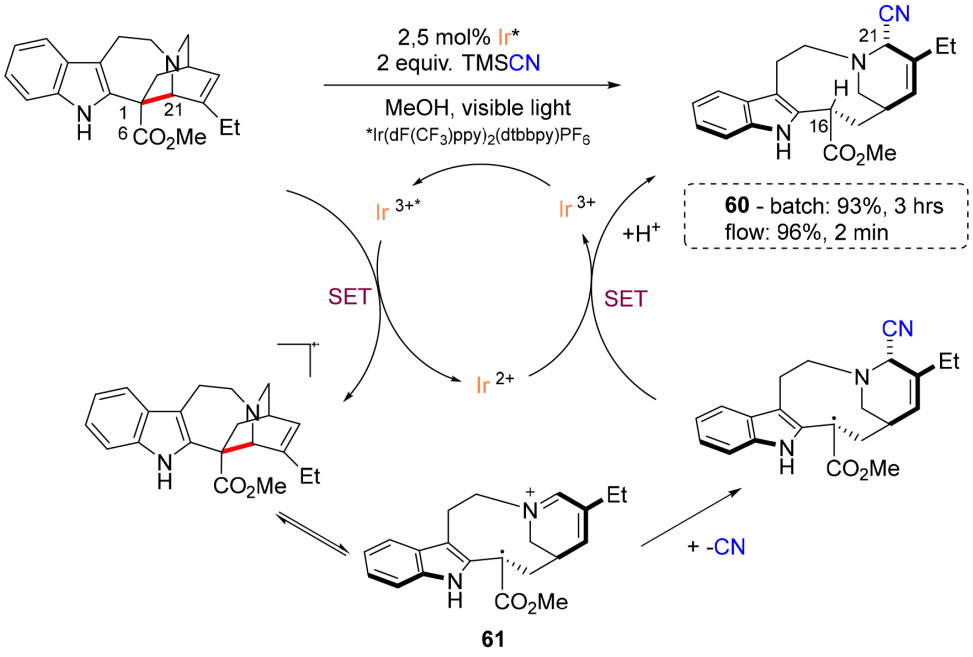
Beatty and Stephenson reported the photoredox cyanation of (+)-catharanthine catalyzed by iridium complex in order to access structurally related alkaloids through a common α-aminonitrile intermediate (Scheme 19).[46] In one hand, the fragmentation product containing the cyano group **60** was obtained in 93% yield after 3 hours in batch mode; on the other hand, in 96% using the flow photochemical reactor after only 2 minutes. In the proposed catalytic cycle, the starting material is oxidized, leading to the formation of a radical cation. This, in turn, undergoes C16-C21 bond fragmentation, leading to the formation of the cationic ring-opening radical **61**, which is stereoselectively trapped by the cyanide. The generality

of the methodology was evaluated using hydrogenated analogues of (+)-catharanthine. Energetic analysis of C16-C21 bond cleavage showed that hydrogenation of the alkene attenuates ring strain as a driving force in the fragmentation of catharanthine.

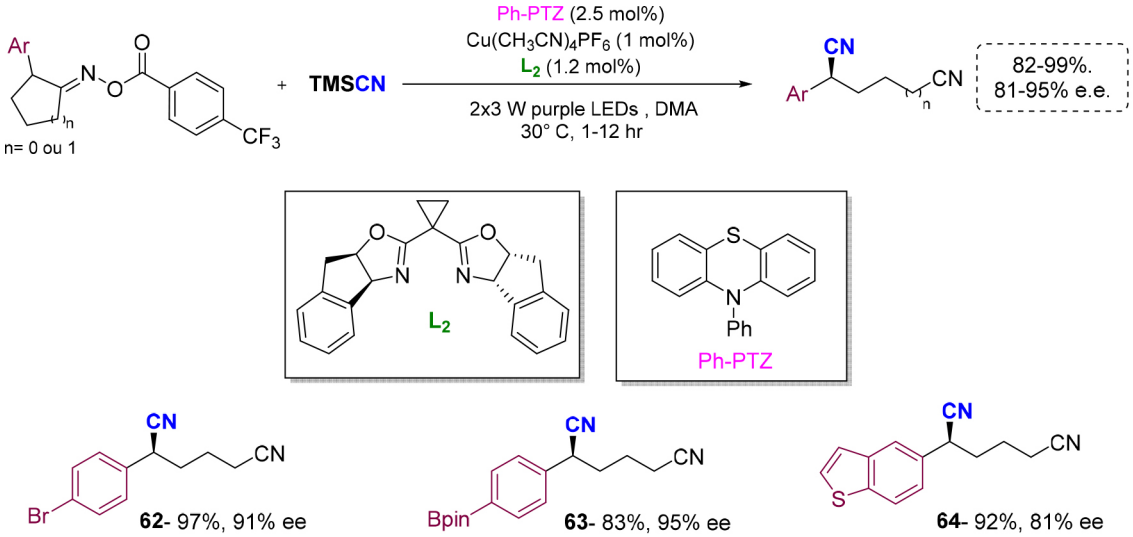
Chen and co-workers reported, for the first time, the enantioselective radical ring-opening cyanation of redox-active oxime esters by merging copper catalysis with photoredox catalysis (Scheme 20).[47] From the optimized reaction conditions, a broad substrate scope could be accessed, including halide-containing substrates and the aryl boronic ester (Bpin) functionality. It is worth noting that the methodology could also be employed in a three-component enantioselective version through the addition of *para*-phenyl-substituted styrene, leading to the formation of the desired dinitrile compounds (**62**-**64**) with up to 99% yield and 95% e.e. In terms of mechanism, the redox-active oxime ester engages in a SET with the photocatalyst, generating an iminyl radical upon decarboxylation of the substrate, while the copper cycle was responsible for the transfer of the cyano group to the radical formed after cleavage of the C-C bond of the iminyl radical.

Due to the high reactivity of radical species, the development of asymmetric protocols involving such intermediates becomes considerably hampered. In this context, Liu and co-workers reported the asymmetric radical decarboxylative cyanation from racemic carboxylic acids via cooperative catalysis between chiral copper catalyst and photoredox catalysis.[48] From this enantioselective radical cyanation protocol, several α-aryl nitriles could be reached. Racemic *N*-hydroxy-phtalimide (NHP) ester derived (**65**-**67**) from bioactive compounds such as pranoprofen, carprofen and zaltoprofen were suitable to this asymmetric cyanation, with yields ranging from 59 to 98% and good enantiomeric excess (82-92% e.e.) (Scheme 21.a). In the proposed mechanism, the photocatalyst reduces the NHP, which will undergo decarboxylation generating the benzylic radical that will be captured, thereafter, by the copper catalyst in an enantioselective fashion (Scheme 21.b).

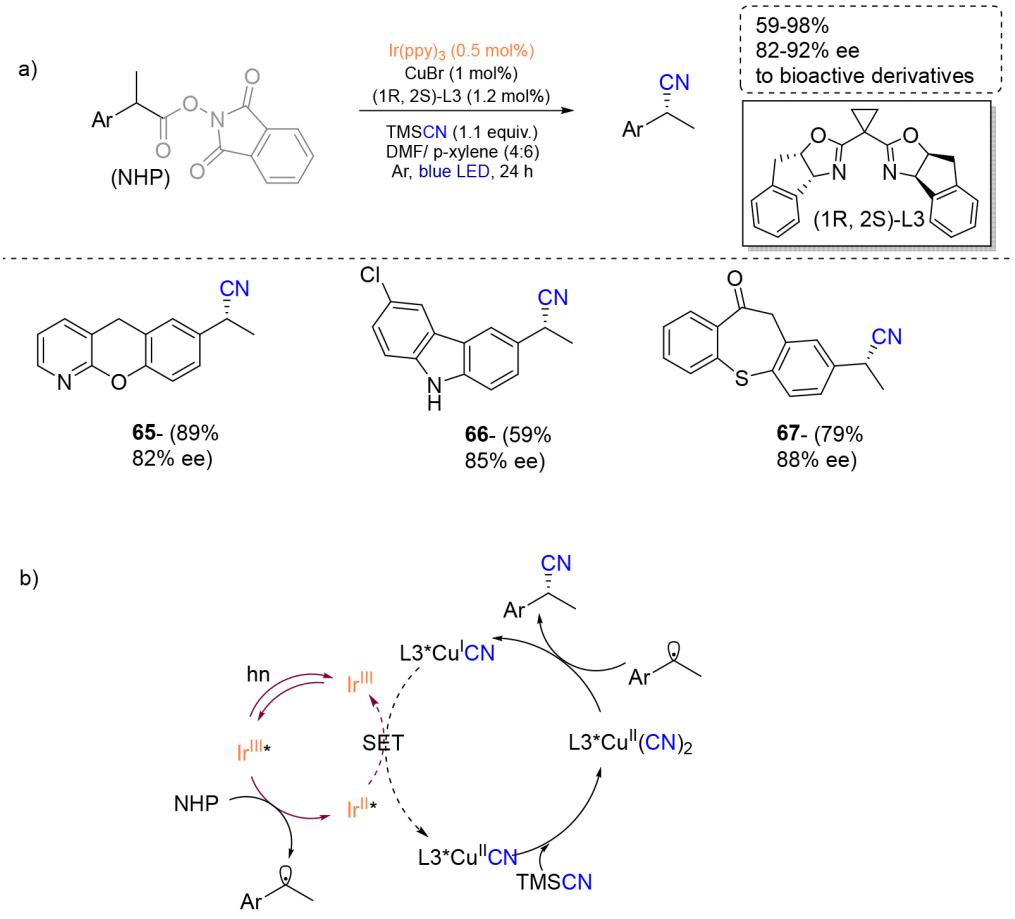
Also using chiral copper complexes, Xu and co-workers have recently reported an interesting protocol for the cyanofluoroalkylation of alkenes, where the same copper catalyst acted in both photochemical and enantioselective cross-coupling cycles (Scheme 22).[49] Estrone



Scheme 19. *Photoredox cyanation of (+)-catharanthine*



Scheme 20. *Enantioselective radical ring-opening cyanation of redox-active oxime ester*

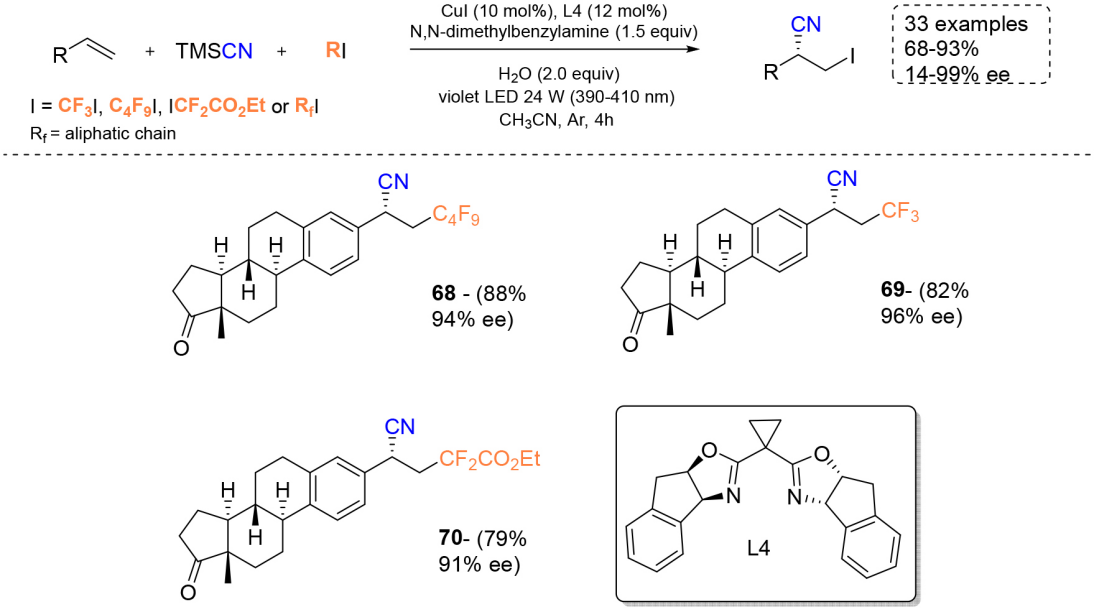


Scheme 21. *a) Cooperative catalysis in the photocyanation of N-hydroxy-phtalimide esters b) Mechanistic proposal*

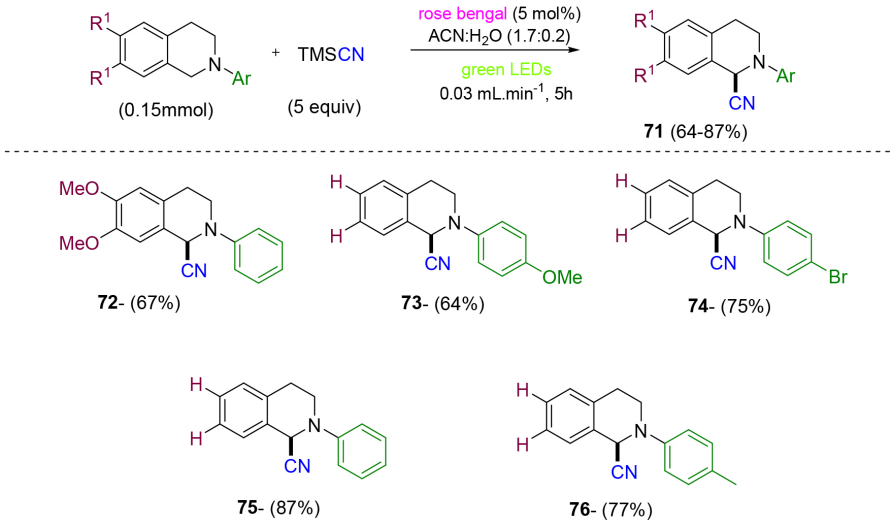
derivatives were employed with the variety of fluoroalkyl iodides, with good yields and high enantioselectivities. Despite these great findings, some drawbacks such as the evaluation of both electronic and steric effects on the double bond and the use of other complex molecules were not contemplated in this work.

Rueping and co-workers reported a simple protocol for the oxidative photocyanation of tetrahydroisoquinoline derivatives using iridium photocatalyst and acetic acid as co-catalyst, which proved to be essential for attained the desired product.[50] In general, combination of photocatalysis with transition metals are widely used in photoredox methodologies. However, due to the high cost and potential toxicity of this combination, the use of organic dyes has emerged as a more economical and environmentally alternative.[51]

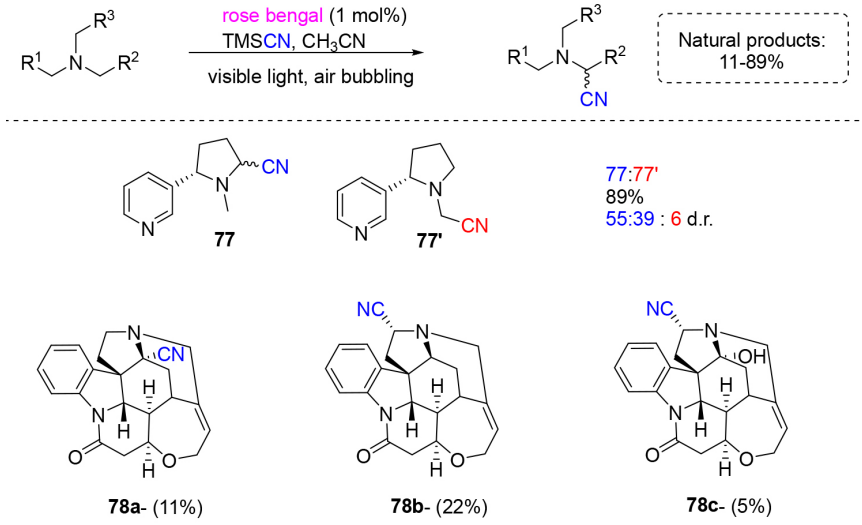
In 2013, the same author reported the α-functionalization



Scheme 22. *Dual functionality of chiral copper complex in the photocyanation of alkenes*



Scheme 23. *Photocyanation of tetrahydroisoquinoline derivatives using continuous flow system*

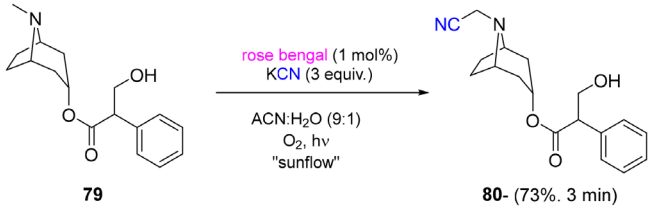


Scheme 24. *Photocyanation of natural products*

of aforementioned derivatives with different nucleophiles under continuous flow technique, using the organic dye rose bengal instead of the metal photocatalyst (Scheme 23).[52] The method was suitable for the five designed substrates, with yields ranging from 64 to 87%. Although direct comparison is not possible due to the structural differences, this method seems to be limited in terms of substrate scope. By and large, the α-cyanation was more efficient in terms of reaction time in a continuous flow mode when compared to the batch process.

Also taking advantage of the organic dye rose bengal, in 2016, Opatz's group reported the photocyanation of tertiary amines using 1 mol% of the photocatalyst irradiated by compact fluorescent lamp (CFL) (Scheme 24).[53] This method was applicable to aliphatic amines, which typically act as an electron reservoir in photocatalytic cycles. In the reaction scope, it was possible to perform the photocyanation of some alkaloids, with yields ranging from 11 to 89%. In the case of nicotine, besides the formation of the main product **77**, there was found the formation of the cyanated regioisomer in the methyl portion **77'**. The proposed methodology was not very efficient to complex alkaloids such as strychnine. Besides the long reaction time, the reaction with those substrates lead to the mixture of regioisomers **78a** and **78b** and to the formation of the hydroxylated product **78c**.

As another approach to the aforementioned work, in 2017, Opatz and co-workers reported the α-cyanation of tertiary amines **81** using microcapillary flow reactor, which was named as "sunflow" (Scheme 25).[54] The reaction using atropine as substrate was more effective compared to other protocols in batch mode, leading to **82** in 73% yield, after only 3 minutes of reaction. Moreover, protection of the hydroxyl group was not required. The decrease in the chemical yield at longer reaction times was justified by the decomposition of the formed α-aminonitriles.



Scheme 25. *Photocyanation of atropine in continuous flow mode*

One year later, the same group developed a titanium dioxide (TiO_2) nanoparticle photocatalyst with the redox-active chromophore DHMIQ, which has broad absorption in the visible spectrum, extending into the near infrared region (Scheme 26).[55] Despite this

advent, the studied reaction was more efficient when the photocatalyst was irradiated in the blue and green region. The method applied to the protected atropine **81** was efficient, they observed relatively long reaction time, though. In the case of nicotine, a less likely reported selectivity was observed, which is interesting from a synthetic point of view **82**.

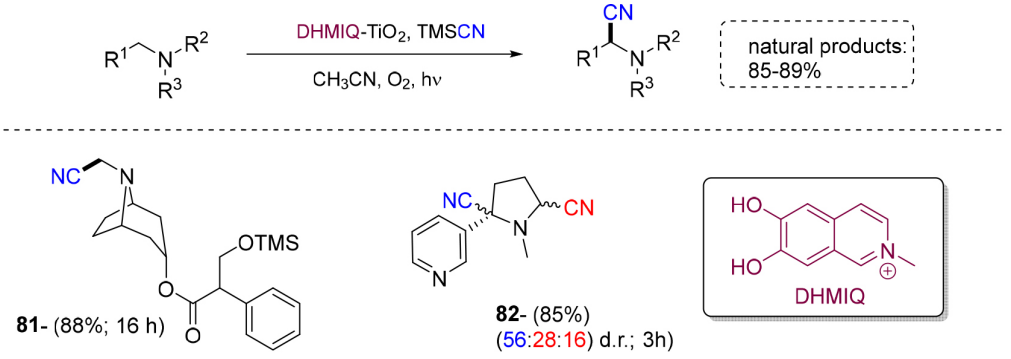
In comparison to the previous work, despite the low selectivity, there was observed an unprecedented formation of the cyanated product on the more sterically hindered benzylic position. This result can be justified by the size of the nanoparticle, which allows easier access to the reaction site in question. Unlike the result obtained with the organic dye, the formation of the cyanated product was not observed in the methyl portion, which makes the protocol an interesting alternative in terms of organic synthesis.

Considering the scarcity of simple methodologies for the direct cyanation of aromatic compounds, McManus and Nicewicz reported the direct C-H functionalization of arenes through photoredox catalysis to reach aromatic nitriles (Scheme 27).[56] The protocol was well employed for the four complex bioactive molecules tested, including polycyclic and heteroaromatic structures, with moderate to good yields. Importantly, the obtained selectivity in fenopren methyl ester was noteworthy, where cyanation occurred solely in to the more electron-rich ring. Different from other examples, the proposed methodology was highly regioselective in all tested bioactive molecules, with only one regioisomer being isolated.

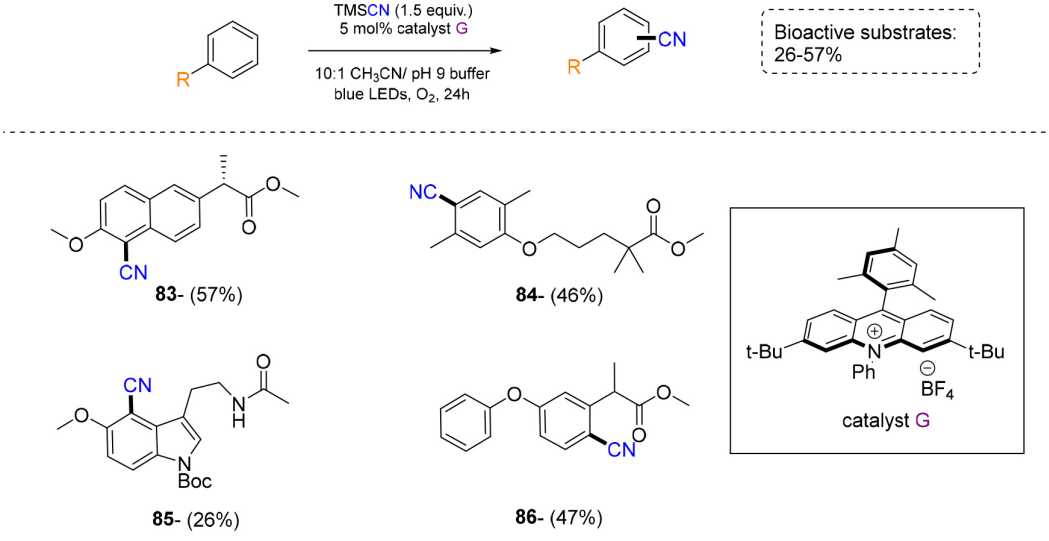
Through an even more sustainable approach, König and co-workers have recently reported the photocatalytic ammoxidation of methylarenes in a completely metal- and cyanide-free methodology, allowing access to higher value-added products (Scheme 28).[57] Taking the optimized reaction conditions, steric and electronic effects could be evaluated in the C(sp_3)-H functionalization of a wide range of methylarenes. Several biologically active molecules and drug analogues were selectively cyanated, including compounds that were more sensitive under photochemical conditions due to the presence of multiple oxygen atoms **87**. It is worth noting that the anti-inflammatory drug Celecoxib led to the formation of the desired product **89** in gram-scale, with 60% yield. Alcohols, aldehydes and aromatic oximes were also suitable functionalities for this protocol.

Based on both kinetic and spectroscopic investigations, the proposed catalytic cycle suggested that the photocatalyst acted in two steps in a synergistic manner: in the first one, the catalytic cycle led to the formation of an oxime as the key intermediate to render the desired cyanoarene. In the second, based on the observation that the presence of NH_4Br was crucial to achieve a satisfactory yield, the photocatalyst acted in the generation of the bromide radical. This, in fact, is engaged with a HAT process, converging then to the same reaction pathway leading to the desired aromatic nitrile.

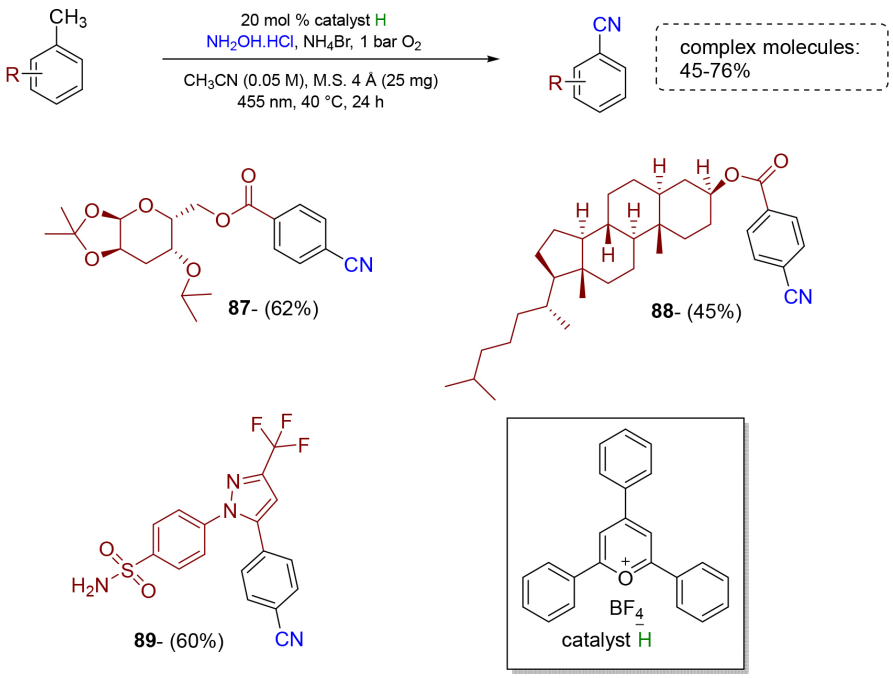
In 2021, Gevorgyan and colleagues developed a Pd-catalyzed, visible-light-induced three-component protocol for the functionalization of 1,2-alkyl using alkenes, alkyl iodides, and isocyanides.[58] (Scheme 29) In this methodology, a reactive intermediate, ketenimine **90** is formed which undergoes several one-pot transformations leading to compounds such as amides, tetrazoles, amidines, and nitriles. Obtaining nitrile compounds was possible due to the cleavage of the N-C bond in ketenimine by $BF_3{\cdot}Et_2O$, tolerating several functional groups, leading to the formation of products such as benzyl nitriles with primary and secondary alkyl substituents on



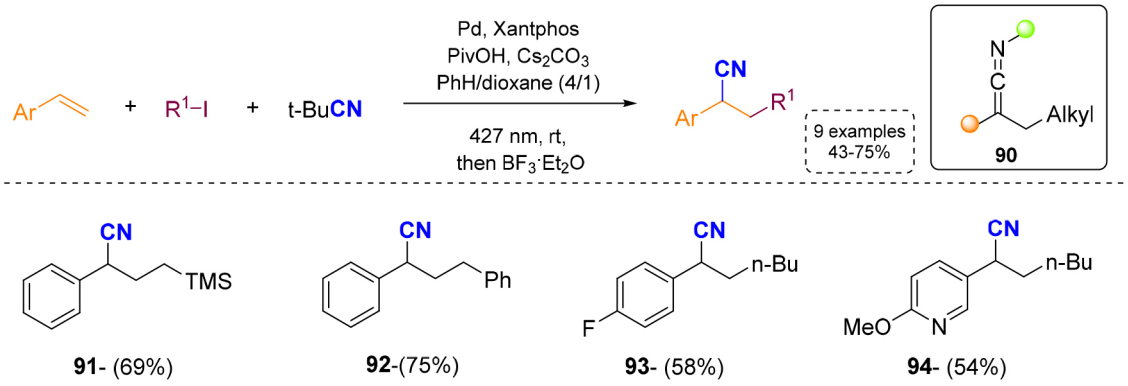
Scheme 26. *Photocyanation using TiO_2 nanoparticle photocatalyst*



Scheme 27. *Direct photocyanation of aromatic compounds*



Scheme 28. *Ammoxidation of methylarenes*



Scheme 29. *Alkyl cyanation of alkenes*

one side of the chain, substituted styrenes, and *m*-vinyl pyridine, with yields ranging from 43 to 75%

CONCLUSIONS

In this review, the advances in cyanation methodologies of complex molecules, including asymmetric and late-stage functionalization methods are evaluated. These consist of great challenges in the preparation of complex bioactive molecules. On one hand, the homologation of the cyano group is important in terms of advanced synthetic intermediates preparation, with subsequent functionalization of this group; on the other hand, maintaining its structure important, since many bioactive molecules have this functionality in their structure. In this particular case, it can be noticed the antiretroviral Remdesivir, currently adopted against SARS-CoV-2, the viral pathogen causing the pandemic in 2020.

In contrast to the most widely employed metal catalysis-assisted cyanation and reagents that provided the CN^- anion, some recent protocols have come out with new chemicals with the cyano group in its electrophilic form (CN^+), being a complementary strategy to the usual pathway, allowing, for instance, the cyanation of pro-nucleophilic compounds.

From an environmental point of view, effective methods that use non-toxic cyanide sources such as *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS), and those that do not use metals or oxidants in their processes are particularly prominent. Within this context, photoredox catalysis emerges as a softer tool to reach either different structures or reactivities, difficultly accessed by other routes. Despite large advances, there are few reports on the use of this tool in cyanation of particularly complex molecules. All in all, the work reported so far shows the potential of this form of activation to achieve complex nitrile derivatives, making it a promising tool for the development of new cyanation methods, including asymmetric versions.

ACKNOWLEDGMENTS

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