UNIVERSIDADE DE SÃO PAULO

FACULDADE DE CIÊNCIAS FARMACÊUTICAS DE RIBEIRÃO PRETO

Development of new selective synthetic methods en route to privileged scaffolds of pharmaceutical relevance

Desenvolvimento de novos métodos sintéticos seletivos visando estruturas privilegiadas de relevância farmacêutica

Thiago dos Santos

Ribeirão Preto
2022

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Concentration Area: Natural and synthetic products.

Supervisor: Prof. Dr. Giuliano Cesar Clososki

Co-supervisor: Prof. Dr. Till Opatz

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1. Nitriles. 2. Metalation. 3. Building blocks. 4. Glucose. 5. 2,3-dihydroquinazolin-4(1*H*)-ones.

APPROVAL PAGE

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Examiners

Prof. Dr. _____

Institution: _____ Signature:_____

Prof. Dr. _____

Institution: _____ Signature:_____

Prof. Dr. _____

Institution: _____ Signature:_____

Prof. Dr. _____

Institution: _____ Signature:_____

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RESUMO

DOS SANTOS, T. **Desenvolvimento de novos métodos sintéticos seletivos visando estruturas privilegiadas de relevância farmacêutica**. 2021. 262f. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2021.

Desde os pioneiros trabalhos de Gilman e Bebb, e Wittig e Furhmann seguidos por importantes contribuições incluindo Snieckus, a metalação *orto*-dirigida (D*o*M) tem sido empregada na funcionalização de diversos sistemas. Particularmente, os amidetos de 2,2,6,6-tetrametilpiperidil de Knochel e colaboradores apresentam excelente solubilidade em THF e tolerância a grupos funcionais além de boa estabilidade térmica. O grupo ciano é de grande interesse em D*o*Ms seguido do fluoro como destacado no trabalho de Schlosser. Considerando a viabilidade do emprego das bases de Knochel em D*o*Ms e a potencial aplicação de nitrilas fluoradas como blocos construtores, o primeiro projeto compreendeu a metalação regiosseletiva e funcionalização de diversas nitrilas fluoradas e posterior aplicação no preparo de 4-aminoquinazolinas. Cerca de 47 nitrilas funcionalizadas (45-90%) foram preparadas via TMPMgCl·LiCl ou $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ com a exploração de novos e insuficientemente estudados sítios de metalação. Adicionalmente, uma estratégia de difuncionalização foi possível e os blocos construtores funcionalizados aplicados na síntese de relevantes heterociclos. A 2,3-diidroquinazolin-4(1*H*)-ona (DHQ) é uma estrutura privilegiada e presente em várias moléculas bioativas incluindo fármacos e candidatos a fármacos. A glicose, como um recurso renovável, pode ser facilmente obtida de biomassa lignocelulósica e empregada em processos redutivos sob condições alcalinas. O único método direto disponível para a obtenção de DHQs a partir de 2-nitrobenzonitrila demanda excesso de ácido borônico e cobre como catalizador. Assim, o segundo projeto visou o uso de glicose como um agente redutor sustentável em solução aquosa de carbonato de potássio para a síntese de DHQs derivadas da 2-nitrobenzonitrila de maneira *one-pot*. Um protocolo *one-pot* baseado em ciano-hidratação, nitro redução, formação de imina e ciclização empregando glicose em meio aquoso alcalino foi estabelecido fornecendo DHQs em rendimentos de 18-90%. A competição entre a função aldeído da glicose com o carbonílico adicionado não foi verificada e as DHQs podem ser convertidas em suas respectivas quinazolinonas encontrando mais ampla aplicação em química medicinal. Adicionalmente, um estudo de reposicionamento do fármaco Tenofovir foi efetuado.

Palavras-chave: Regiosseletividade; Metalação; TMP-bases; Nitrilas; 4-aminoquinazolinas; Glicose; 2,3-diidroquinazolin-4(1*H*)-ona; Eco-friendly; Química Verde.

ABSTRACT

DOS SANTOS, T. **Development of new selective synthetic methods en route to privileged scaffolds of pharmaceutical relevance**. 2021. 262p. Thesis (Doctoral). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2021.

Since the pioneering works of Gilman and Bebb, and Wittig and Furhmann accompanied by important contributions including Snieckus, directed *ortho*-metalation reactions (D*o*M) have found great application in the functionalization of diverse systems. Particularly, the 2,2,6,6-tetramethylpiperidyl bases by Knochel and co-workers show excellent solubility in THF, functional group tolerance, and great stability at room and higher temperatures. The cyano group is of great interest in *Do*Ms followed by fluoro as highlighted by the work of Schlosser. Therefore, considering the feasibility of Knochel bases in D*o*Ms and the potential application of fluorinated nitriles as building blocks, the first project comprised the regioselective metalation-functionalization of diverse fluorinated nitriles and their application in the synthesis of 4-aminoquinazolines. About 47 diverse functionalized nitriles (45-90%) with the exploration of new and scarcely investigated metalation sites were prepared by metalation with TMPMgCl·LiCl or $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$. Besides, a difunctionalization strategy was possible and the building blocks were applied to construct relevant heterocycles. The 2,3-dihydroquinazolin-4(1*H*)-one (DHQ) is a privileged scaffold in a multitude of biologically active molecules including marketed pharmaceuticals and potential drug candidates. Glucose, as a renewable source, can be easily obtained from lignocellulosic biomass and applied in reduction processes under alkaline conditions. The only available method to directly access DHQs from 2-nitrobenzonitrile requires an excess of diboronic acid and copper as a catalyst in a water/methanol mixture. Thus, the second project envisioned the use of glucose as an eco-friendly reductant in an aqueous solution of potassium carbonate for the synthesis of DHQs from 2-nitrobenzonitrile in a one-pot fashion. A one-pot protocol based on nitrile hydration, nitro-reduction, imine formation, and cyclization with glucose in alkaline water was successfully established affording DHQs in yields 18-90%. No competition of the aldehyde from glucose with the externally added carbonyl compound was verified, and the synthesized DHQs in this work can be further converted to the corresponding quinazolinones finding even wider application in Medicinal Chemistry. Additionally, a study on the repositioning of the drug Tenofovir was performed.

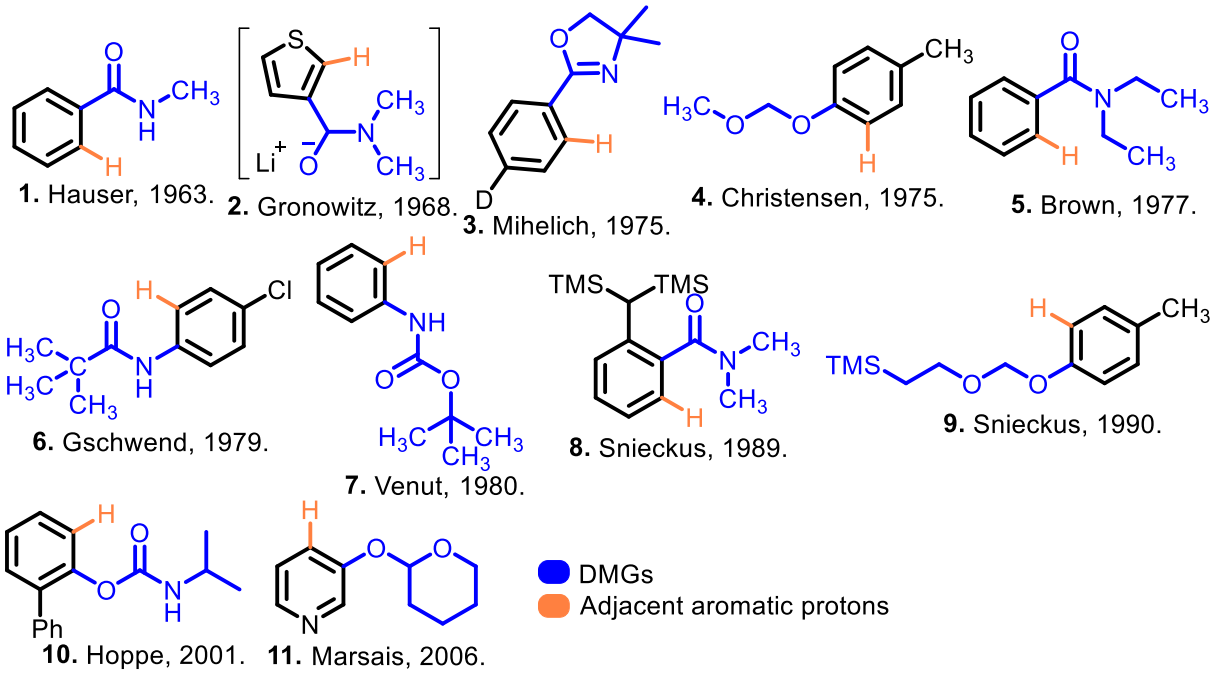
Keywords: Regioselectivity; Metalation; TMP-bases; Nitriles; 4-aminoquinazoline; Glucose; 2,3-dihydroquinazolin-4(1*H*)-one; Eco-friendly; Green Chemistry.

1. INTRODUCTION

1.1 DIRECTED *ORTHO*-METALATION

The first reports of directed *ortho*-metalation reactions (DoM) come from Gilman and Bebb[1] in 1939 and Wittig and Furhmann[2] in 1940, the *ortho*-lithiation of methoxy-bearing substrates such as 2-methoxydibenzofuran and anisole with *n*-Butyllithium or phenyl lithium, respectively. The scope of directed *ortho* metalation groups (DMGs) was later expanded[3] including the work of Hauser,[4] Gronowitz,[5] Gschwend,[6] Mihelich,[7] Brown,[8] Snieckus,[9] Christensen,[10] Venut,[11] Hoppe,[12] Marsais,[13] and their co-workers (**Figure 1**).

Figure 1. Some DMGs explored in the literature.



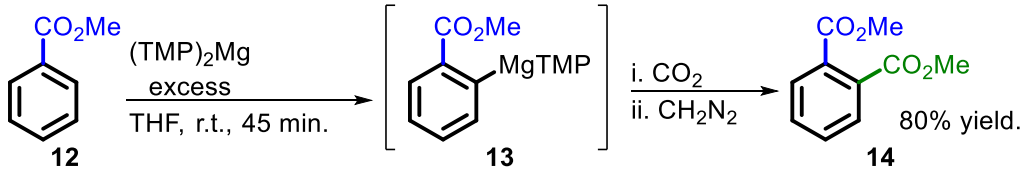
Source: GREEN; CHAUDER; SNIECKUS, 1999;[3b] MIAH *et al*., 2018.[3d]

The *ortho*-directing properties of DMGs can either relate to the establishment of a complex-induced proximity effect (CIPE) with the coordination of a heteroatom to the metal of a base with simultaneous proton transfer (e.g., Lithium in the case of LDA - Lithium diisopropylamide)[14] or the reduction in pK_a for the adjacent aromatic protons through inductive effect.[15]

Although lithium bases have been extensively applied to the deprotometalation of aromatic and heteroaromatic systems via D*o*Ms, there are important drawbacks: they normally demand low temperatures or the *in-situ* generation before metalation, and the organolithium intermediates are highly reactive and may lead to side products in the presence of some sensitive groups such as esters.[16]

As alternative methods, Hauser and co-workers developed diethyl- and diisopropylaminomagnesium bromides to promote the self-condensation of esters in the synthesis of β-keto esters.[17] In 1989, Eaton, Lee, and Xiong prepared the sterically hindered TMP-bases (2,2,6,6-tetramethylpiperidyl), TMPMgBr, and $(TMP)_2Mg$, for the *ortho*-magnesiation of aromatics as depicted in **Scheme 1**.[18] Later, Mulzer and co-workers reported the synthesis of TMPMgCl with the regioselective metalation of pyridinylcarbamates and pyridinecarboxamides.[19]

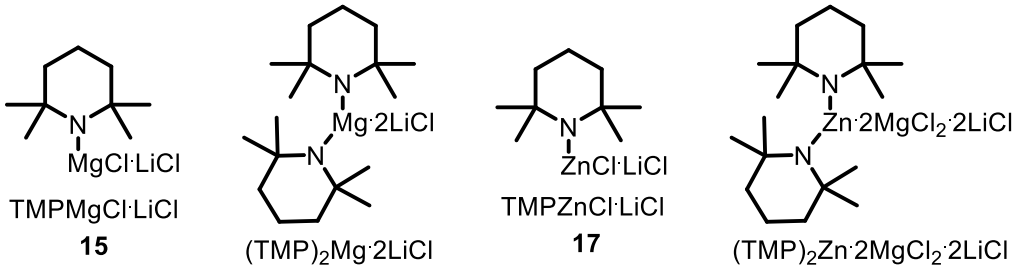
Scheme 1. The regioselective magnesiation of methyl benzoate with $(TMP)_2Mg$.



Source: EATON; LEE; XIONG, 1989.[18]

However, these magnesium-based bases displayed low solubility in common solvents and needed to be employed in excess (2-12 Equiv.)[20] in order to achieve great substrate conversions. To solve such problems, Knochel and co-workers developed the mixed Mg/Li, Zn/Li, and Zn/Mg/Li amides TMPMgCl·LiCl,[20] $(TMP)_2Mg{\cdot}2LiCl$,[21] TMPZnCl·LiCl,[22] $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[23] (**Figure 2**) with excellent solubility in THF and functional group tolerance, and great stability at room and higher temperatures. These TMP-bases have been successfully employed for the regioselective magnesiation and zincation of diverse heteroaromatic and aromatic systems, such as 1,5-naphthyridine scaffold,[24] quinolines,[25] indolizines,[26] oxazolines,[16b,27] 1,3,4-oxadiazoles and 1,2,4-triazoles,[28] 2-pyridones and 2,7-naphthyridones,[29] pyrazolo[1,5-*a*]pyridines,[30] 2- and 4-pyrones,[31], pyridines,[32] and 1*H*-imidazo[1,2-*b*]pyrazoles.[33]

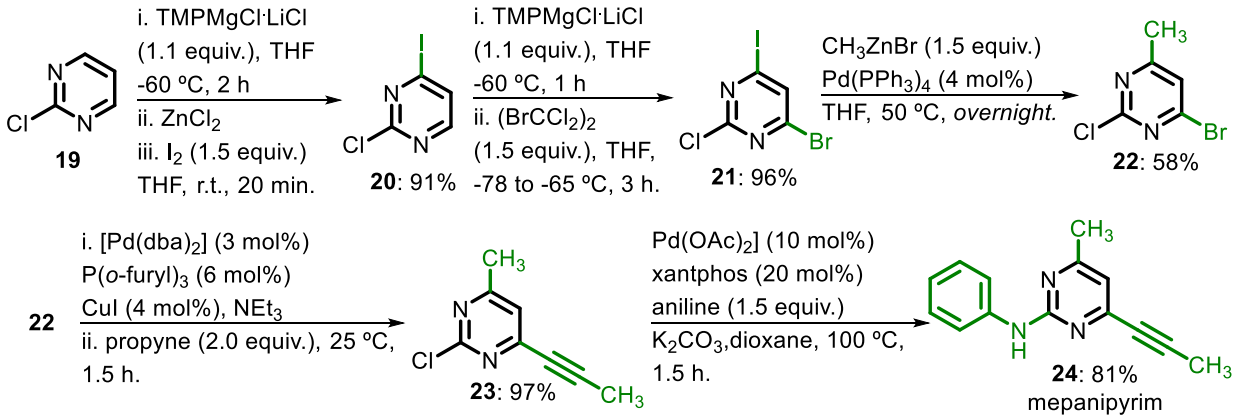
Figure 2. Developed TMP-bases by Knochel and co-workers.



Source: KRASOVSKIY; KRASOVSKAYA; KNOCHEL, 2006;[20] CLOSOSKI; ROHBOGNER; KNOCHEL, 2007;[21] UNSINN; FORD; KNOCHEL, 2013;[22] WUNDERLICH; KNOCHEL, 2007.[23]

Furthermore, the Knochel bases find direct application in the synthesis of valuable building blocks for the construction of natural products and drugs.[34] For example, Mosrin and Knochel obtained the fungicide mepanipyrim (**24**) in 40% overall yield from 2-chloropyrimidine **19** after two consecutive magnesiations with TMPMgCl·LiCl, followed by a Negishi cross-coupling with CH_3ZnBr, a Sonogashira reaction with propyne, and a Buchwald-Hartwig amination with aniline (**Scheme 2**).[35]

Scheme 2. Employment of TMPMgCl·LiCl in the synthesis of Mepanipyrim.

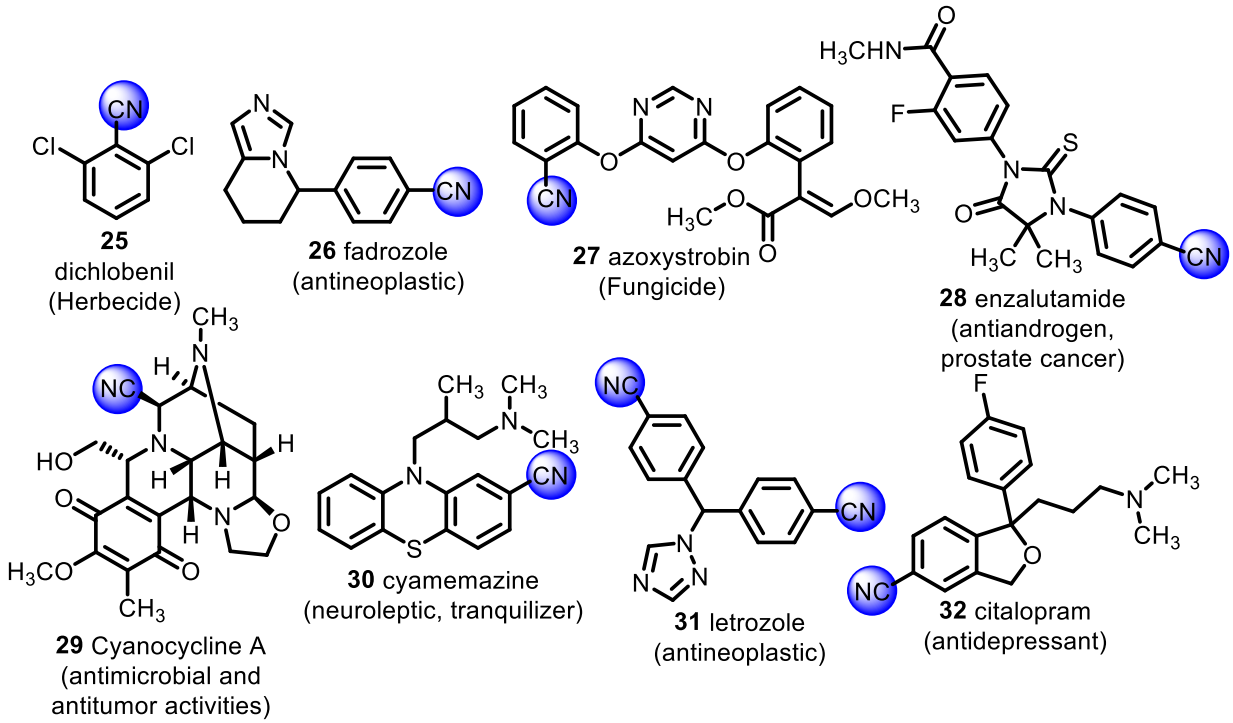


Source: MOSRIN; KNOCHEL, 2009.[35]

1.2 CYANO AND FLUORINE AS DIRECTING GROUPS

The cyano group is of great interest in organic synthesis and can be easily converted into various functional moieties, such as amines, aldehydes, amides, acids, esters, tetrazoles, triazoles, oxazoles, and thiazoles.[36] It is also present in agrochemicals, pharmaceuticals, and natural products as illustrated in **figure 3**.[37]

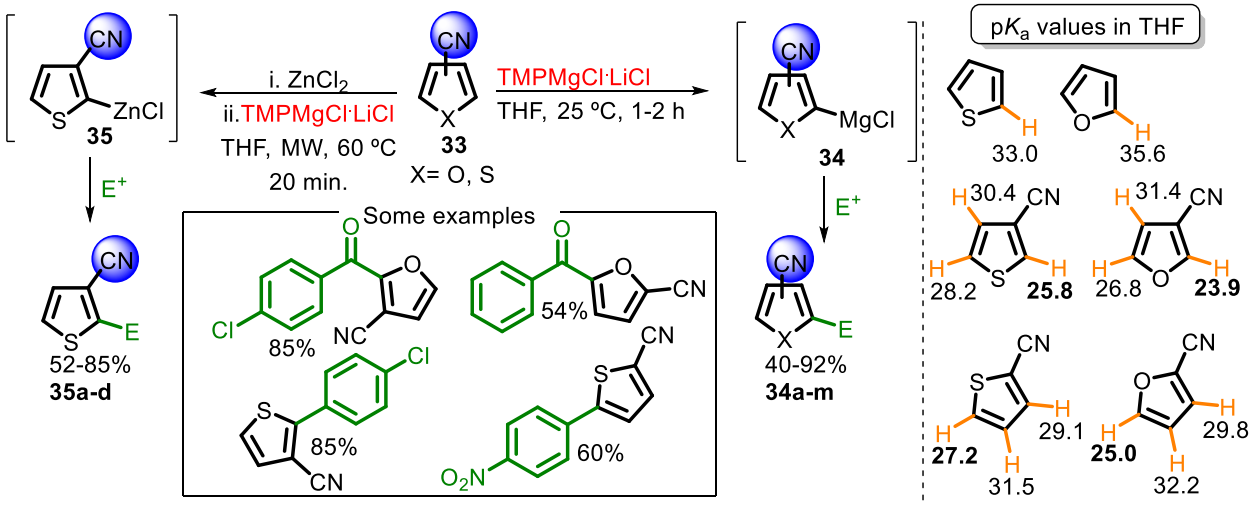
Figure 3. Some bioactive molecules bearing the cyano group.



Source: ANBARASAN; SCHAREINA; BELLER, 2011;[37a] CHAITANYA; ANBARASAN, 2018;[37b] GRUNDKE; VIERENGEL; OPATZ, 2020.[37c]

Given the importance of nitriles, DoMs involving the cyano as a directing group (electron-withdrawing effect and coordination properties)[38] has become an interesting strategy to access functionalized nitrile-based systems. Our research group has performed the directed metalation of cyano-substituted thiophenes and furans with TMPMgCl·LiCl (**Scheme 3**).[39] The cyano group led to a decrease in pK_a[40] for C2-H or C5-H in all the studied substrates favoring the deprotometalations at these positions. However, the regioselectivity control for thiophene-3-carbonitrile (**35**) was more challenging requiring a pre-complexation with $ZnCl_2$ followed by the magnesiation at 60 ºC in a microwave reactor to avoid a mixture of products, regioisomers, and difunctionalized ones.

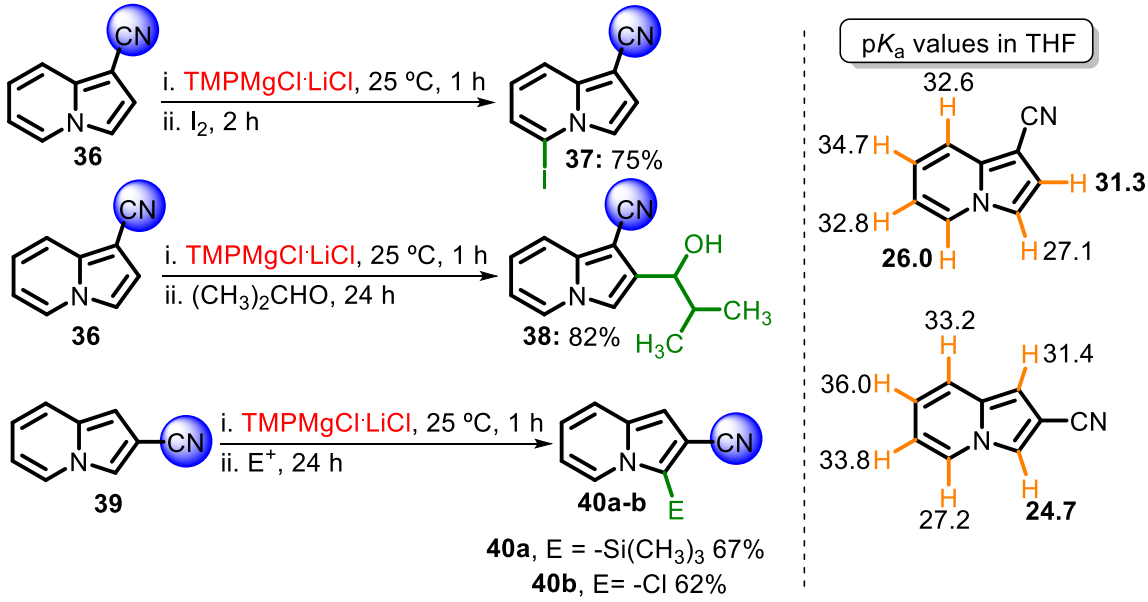
Scheme 3. Directed functionalization of cyano-substituted furans and thiophenes plus pK_a values.



Source: DOS SANTOS *et al*., 2015;[39] FRASER; MANSOUR; SAVARD, 1985.[40]

Additionally, TMPMgCl·LiCl allowed us to access position C2 for 1-cyanoindolizine **36** with isobutyraldehyde and C5 with iodine as the electrophiles, respectively (**Scheme 4**).[26b] It is expected that the observed regioselectivity for the latter electrophile relies on the disruption of a base-cyano chelate by the generated iodide leading to anion isomerization, C2 to C5. In the case of 2-cyanoindolizine **39**, the metalation took place at C3, the most acidic site.

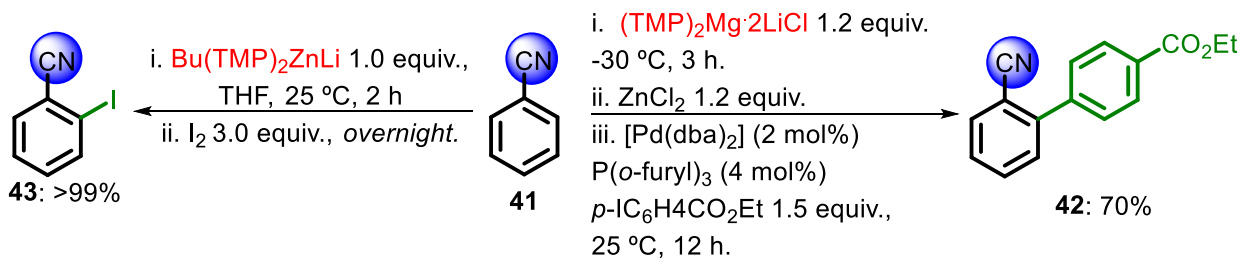
Scheme 4. Regioselective functionalization of cyano-substituted indolizines **36** and **39** and pK_a values.



Source: BERTALLO *et al*., 2019.[26b]

Knochel and co-workers have reported the direct magnesiation of benzonitrile (**41**) with the bisamide **16** $(TMP)_2Mg{\cdot}2LiCl$ at -30 ºC for 3 hours with further transmetalation with $ZnCl_2$, and a Pd-catalyzed Negishi cross-coupling reaction to afford biaryl **42** in 70%.[21] The same position, C2, was explored by Mongin and co-workers upon the use of a mixture of $ZnCl_2{\cdot}$TMEDA (TMEDA=*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), LiTMP (Lithium 2,2,6,6-tetramethylpiperidide), and *n*-BuLi (Butyllithium) to putatively obtain $Bu(TMP)_2ZnLi$ in the synthesis of aromatic **43** (**Scheme 5**).[41]

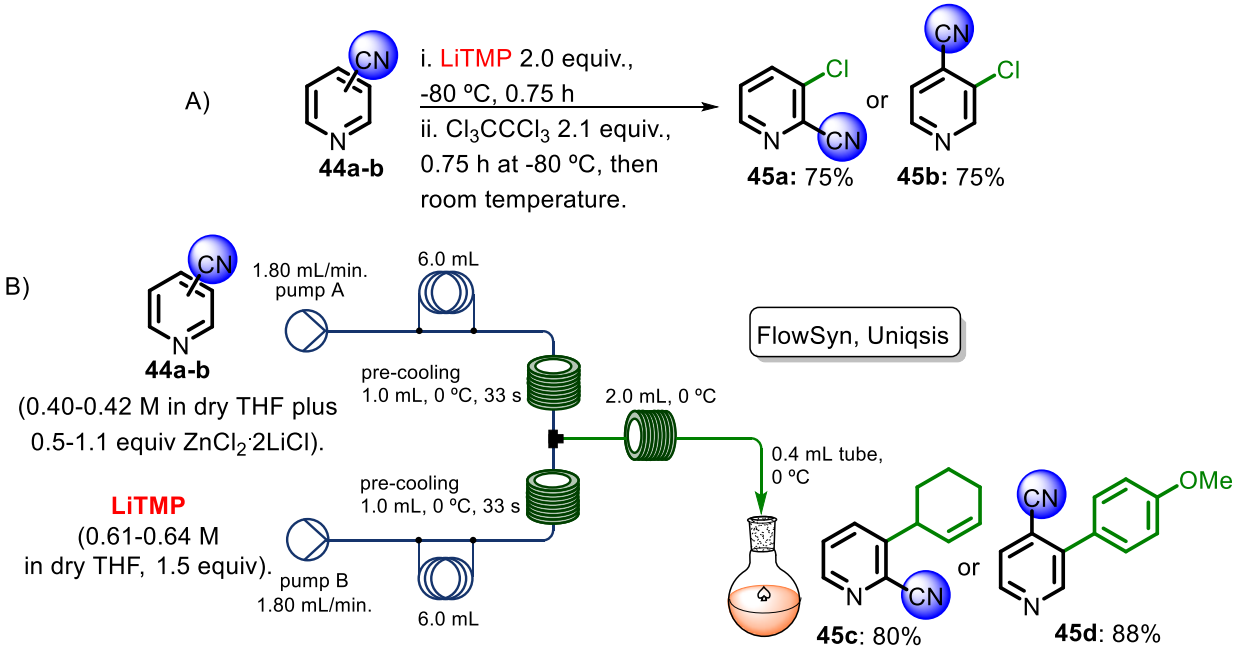
Scheme 5. Metalation and functionalization of benzonitrile.



Source: CLOSOSKI; ROHBOGNER; KNOCHEL, 2007; SNÉGAROFF *et al*., 2010.[41]

Regarding the regioselective metalation of cyano-substituted pyridines, such as 2-cyanopyridine (**44a**) and 4-cyanopyridine (**44b**), Mongin and co-workers applied a mixed lithium-cadmium base, $(TMP)_3CdLi$, but mixtures of di-, tri-, and four-substituted pyridines were obtained.[42] LiTMP, differently, can be considered for the regiocontrolled-lithiation under a low temperature of the same substrates affording **45a** and **45b** in 75% yield after reaction with hexachloroethane (**Scheme 6A**).[43] Besides, a wise approach developed by Knochel and co-workers, an *in situ* trapping transmetalation via $ZnCl_2$, allowed the metalation of **44a-b** to take place at 0 ºC (40 s) under flow conditions with the same base resulting in the disubstituted pyridines **45c** and **45d** in great yields (**Scheme 6B**). [44]

Scheme 6. Regioselective lithiation of pyridines **44a-b** and their functionalization.



In situ trapping conditions (flask)

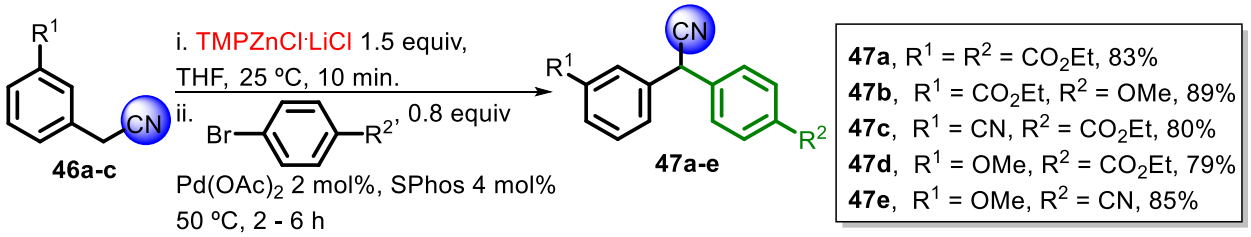
45c: 3-bromocyclohexene (0.8 equiv), CuCN·2LiCl 10 mol% in THF, 1.5 h at 0 ºC.
45d: 4-iodoanisole (0.8 equiv), $Pd(dba)_2$ 2 mol%, tris(2-furanyl)phosphine (tfp) 4 mol% in THF, 2 h at 25 ºC.

Source: CAILLY; FABIS; RAULT, 2006;[43] BECKER; KNOCHEL, 2015.[44]

Expanding the scope of functionalized nitriles via deprotometalation, TMPZnCl·LiCl was remarkably suitable for the mono-α-arylation of benzylic nitriles at room temperature

even in the presence of *ortho*-directing groups, such as methoxy, cyano, and ethyl ester in the aromatic moiety (**Scheme 7**).[45]

Scheme 7. The α-arylation of benzylic nitriles **46a-c** with TMPZnCl·LiCl.

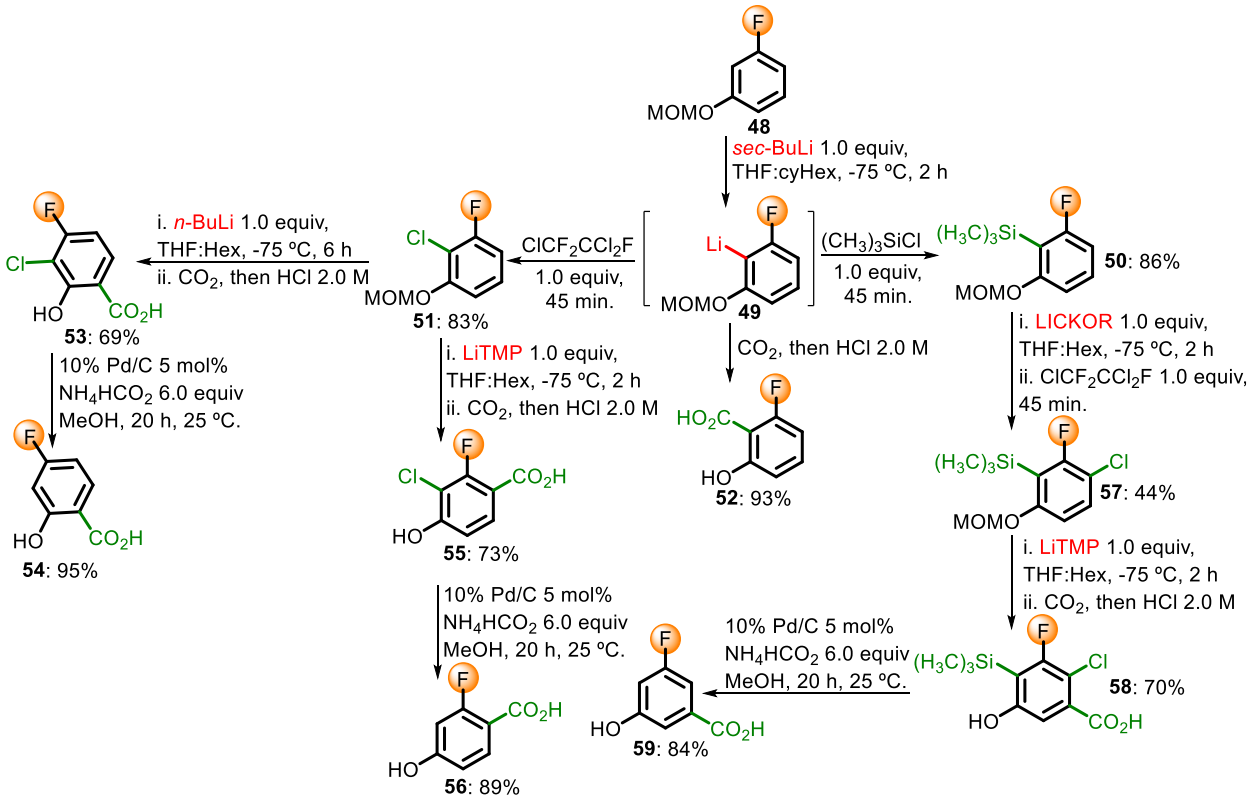


Source: DUEZ *et al.*, 2011.[45]

The fluoro group has been of great importance as an *ortho*-directing group in aromatic and heteroaromatic metalations due to its electron-withdrawing properties.[15] Prof. Dr. Manfred Schlosser has made a huge contribution in this area with the concept of regiochemically exhaustive functionalization of readily available organofluorines to furnish valuable building blocks. For instance, the treatment of the *O*-methoxymethyl-protected 3-fluorophenol **48** with sec-Butyllithium afforded the lithiated species **49** which were further reacted with 1,2,2-trichloro-1,2,2-trifluoroethane to obtain **51** (83%), carbon dioxide to synthesize **52** (92%), and chlorotrimethylsilane to prepare **50** (86%) (**Scheme 8**).[46] Regioselective lithiation of the tri-substituted aromatic **51** by *n*-Butyllithium (position C4) and subsequent carboxylation with deprotection of the phenolic methoxymethyl (MOM) ether under acidic conditions furnished the 3-chloro-4-fluoro-2-hydroxybenzoic acid **53** in 69% yield. Blocking the acidic position C2 in **50** and **51** favored the regioselective metalation with LiTMP and LICKOR at C6 in the synthesis of 3-chloro-2-fluoro-4-hydroxybenzoic acid **55** in 73% and (3-chloro-2-fluoro-6-(methoxymethoxy)phenyl)trimethylsilane **57** in 44%, respectively. LICKOR, also known as Schlosser's base, is comprised of *n*-butyllithium and potassium *tert*-butoxide in a one-to-one ratio. Furthermore, LiTMP was useful to promote the *ortho*-deprotometalation to the chlorine group in **57** giving **58** in 70% after treatment with an excess of carbon dioxide followed by acidic conditions. Therefore, using chlorine and trimethylsilyl groups to switch off metalation positions or considering directed lithiation with *sec*-BuLi for the MOM ether **48**, all the available functionalization sites were accessed: after removal of

trimethylsilyl group with tetra-butylammonium fluoride and chlorine by catalytic hydrogenation, carboxylic acids derived from 3-fluorophenol, **52**, **54**, **56**, and **59**, were prepared.

Scheme 8. The regiochemically exhaustive functionalization of 3-fluorophenol by Schlosser and co-workers.

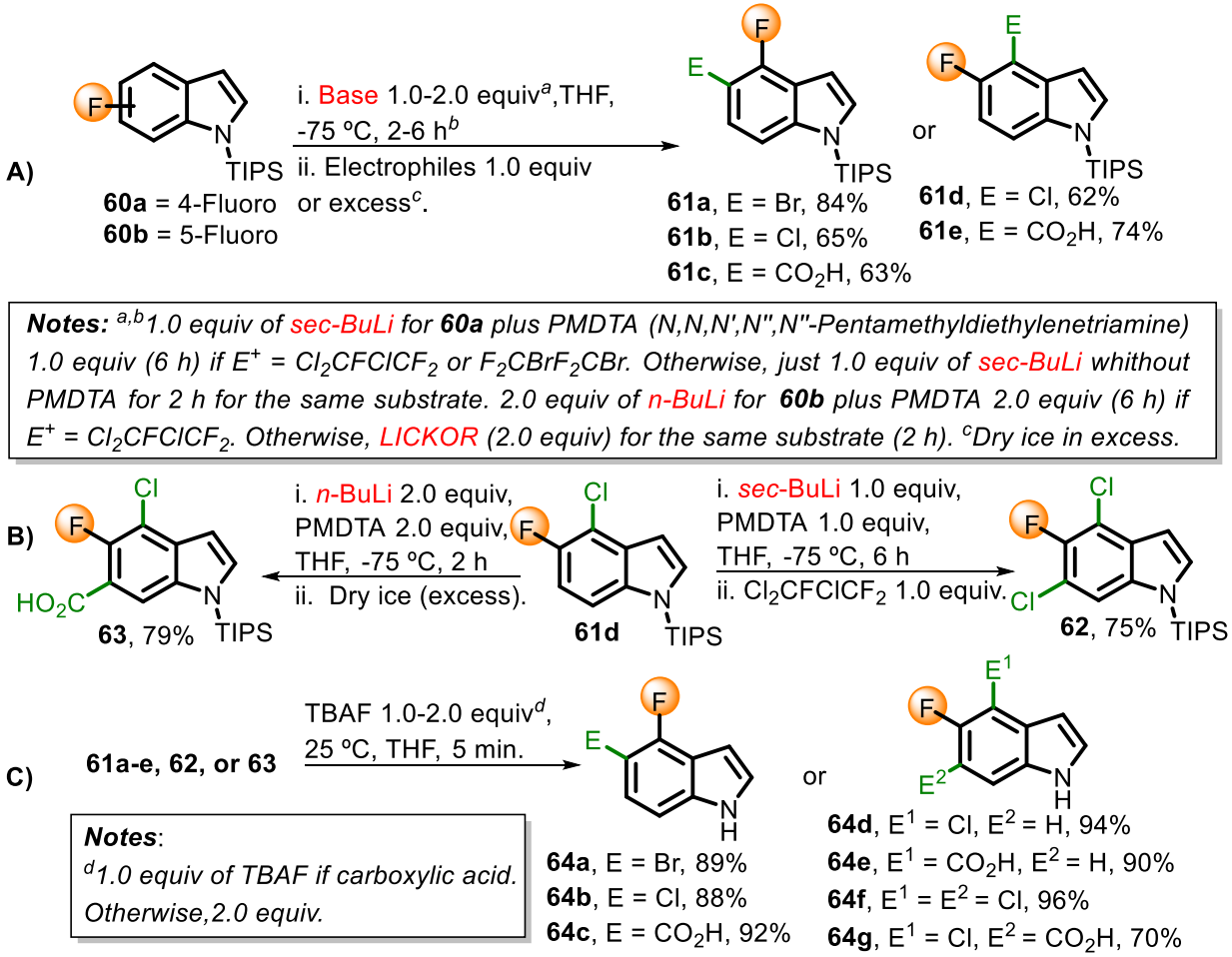


Source: MARZI *et al.*, 2005.[46]

In a similar manner, Schlosser an co-workers have explored the functionalization of fluorinated pyridines (3-fluoropyridine,[46,47] 2-fluoropyridine, 2,3-difluoropyridine, and 2,5-difluoropyridine,[47,48] 2,4-difluoropyridine and 2,4,6-trifluoropyridine,[47,49] 2,6-difluoropyridine,[47,50] 2,3,5-trifluoropyridine and 3,5-difluoropyridine[47,51]), phenols (2,4-difluorophenol, 2,5-difluorophenol, 2,3-difluorophenol, 3,5-difluorophenol, 3,4-difluorophenol, 2,4,5-trifluorophenol, and 2,3,4-trifluorophenol),[52] and indoles.[53] For the latter substrate, an interesting strategy was devised in order to avoid metalation at position C2 of the indole system: its nitrogen was protected with a bulky group, triisopropylsilyl (TIPS). The treatment of 4-fluoro-1-(triisopropylsilyl)indole **60a** with *sec*-

BuLi at -75 ºC and subsequent trapping with 1,2-dibromo-1,1,2,2-tetrafluoroethane, 1,1,2-trichloro-1,2,2-trifluoroethane or carbon dioxide led to C5-functionalized indoles **61a-c** with yields up to 84%. For 5-fluoro-1-(triisopropylsilyl)indole **60b**, *n*-BuLi and LICKOR were suitable to functionalize C4 position affording **61d** (62%) and **61e** (74%) after chlorination and carboxylation, respectively (**Scheme 9A**). Interestingly, **61d** was subjected to a second metalation with *n*-BuLi or *sec*-BuLi to obtain the tri-substituted indoles **62** and **63** in great yields (**Scheme 9B**). Tetrabutylammonium fluoride was successfully applied to all substrates at 25 ºC for 5 minutes to remove the TIPS groups (**Scheme 9C**).[53]

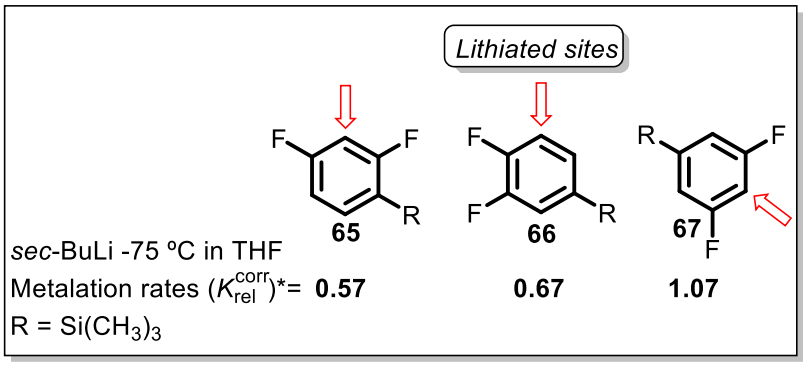
Scheme 9. The metalation and functionalization of 5-fluoro and 4-fluoro -1-(triisopropylsilyl)indoles with lithium bases.



Source: SCHLOSSER; GINANNESCHI; LEROUX, 2006.[53]

Complementing the study of the influence of a bulky alkyl-silyl group on metalation selectivity for fluorinated compounds, it was found that trimethylsilyl group (TMS) can affect kinetic acidity due to a buttressing effect when occupying a fluoro-neighboring position, and therefore, deprotometalation rates (**Figure 4**). The steric pressure exerted by TMS as pointed by Schlosser is less pronounced in **67** at position C4 because of the *meta* disposition of both fluoro groups. On the other hand, the *meta* position to TMS is available in both **66** and **65** favoring the transmission of the buttressing effect that is greatly enhanced by an adjacent fluoro group in the latter scenario.[54]

Figure 4. Metalation rates (2,4-difluorophenyl)- **65**, (3,4-difluorophenyl)- **66**, and (3,5-difluorophenyl)trimethylsilane **67.**



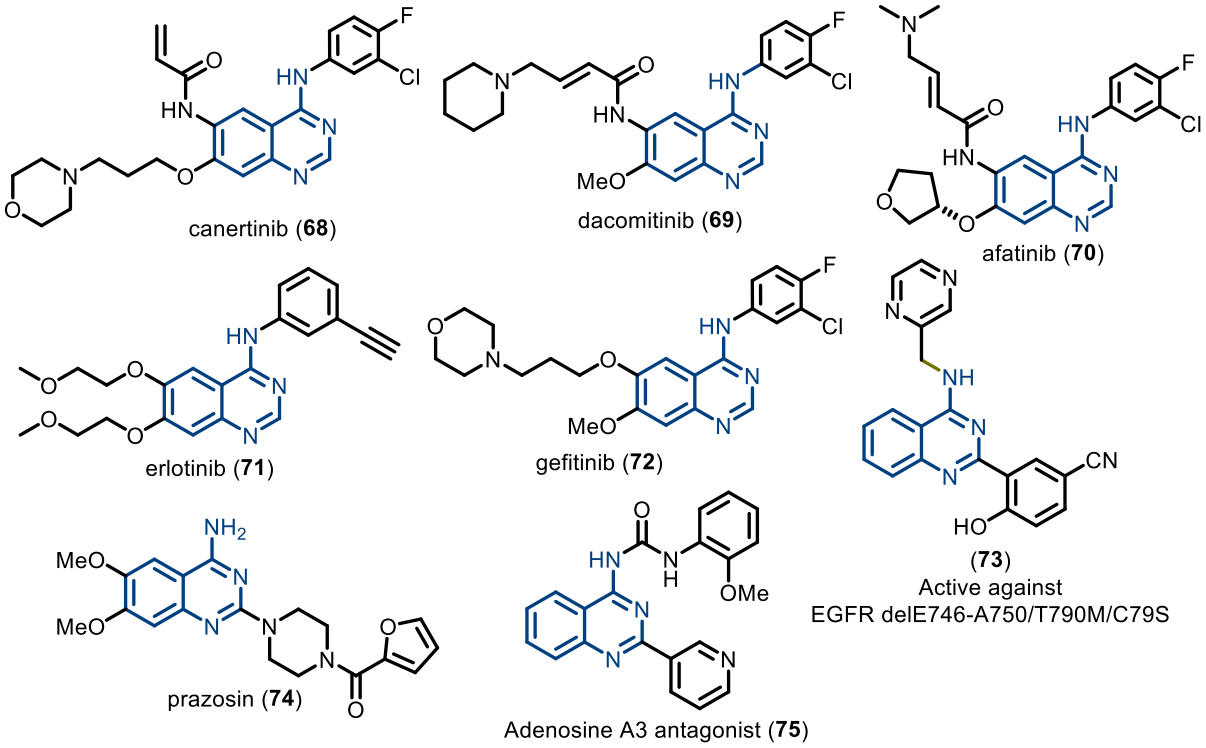
*(K_{rel}^{corr})(= $K^{R = Si(CH3)3}/K^{R = H}$).

Source: HEISS *et al*., 2007.[54]

1.3 4-AMINOQUINAZOLINES: BIOLOGICAL IMPORTANCE AND SYNTHESIS

Heterocyclic systems account for more than 85% of bioactive molecules with special mention to *N*-heterocyclic rings which represent more than 75% of the drugs approved by the FDA (The Food and Drug Administration).[55] Among them, 4-aminoquinazoline is a privileged scaffold present in bioactive molecules of high pharmaceutical importance, such as the epidermal growth factor receptor (EGFR) inhibitors **68**-**73**, the antihypertensive agent prazosin **74**, and the human adenosine A_3 receptor antagonist **75** (**Figure 5**).[56]

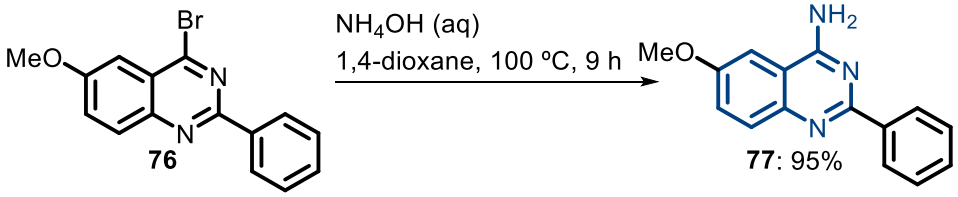
Figure 5. Some bioactive 4-aminoquinazolines.



Source: JIA *et al*., 2015; CHEN *et al*., 2018.[56]

Because of their great relevance, preparation protocols to access diverse 4-aminoquinazolines are a prevailing demand. A common method involves the nucleophilic aromatic substitution of 4-haloquinazolines[57] as verified for the synthesis of **77** in 95% by Ahmad, Hill, and Movassaghi (**Scheme 10**).[58]

Scheme 10. The synthesis of 6-methoxy-2-phenylquinazolin-4-amine **77**.

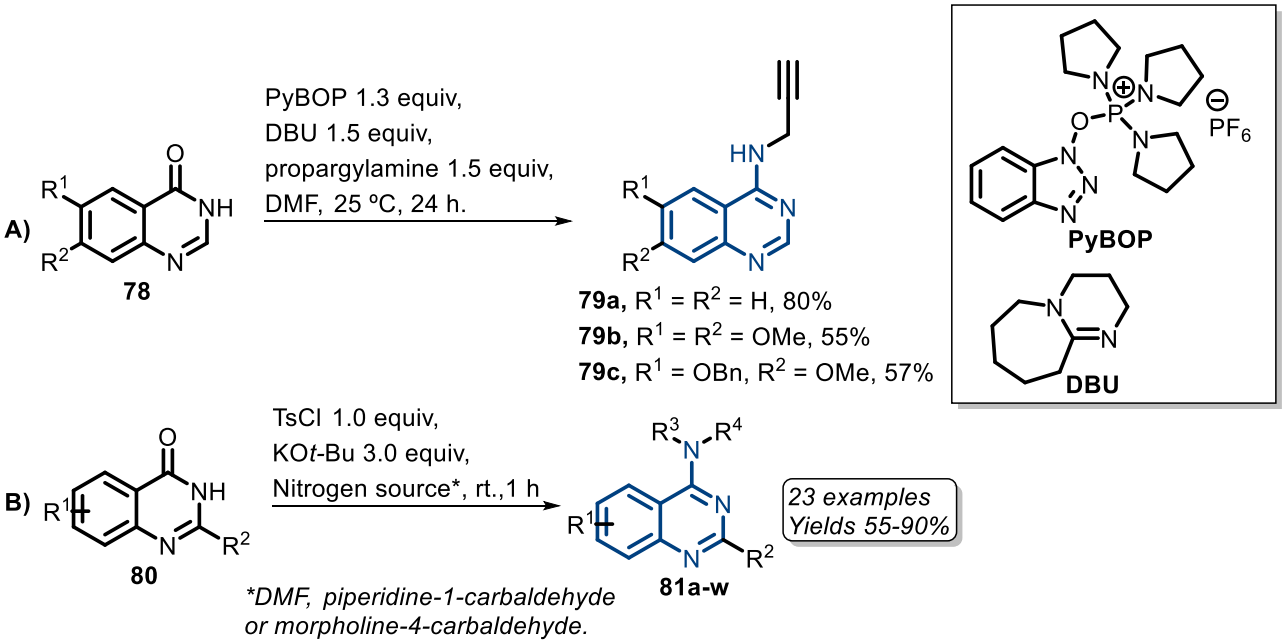


Source: AHMAD; HILL; MOVASSAGHI, 2009.[58]

PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) in the presence of DBU (2,3,4,6,7,8,9,10-octahydropyrimidol[1,2-*a*]azepine) can be

employed for the *in situ* activation of the carbonyl group of quinazolinones[59] as in **78** with further substitution by propargylamine in DMF in the synthesis of **79a-c** (**Scheme 11A**).[60] Another strategy by Peng and co-workers employed 4-toluenesulfonyl chloride in conjunction with potassium *tert*-butoxide in DMF to generate a tosylate intermediate prone to substitution affording 4-dimethylaminoquinazolines **81a-w** (**Scheme 11B**).[61]

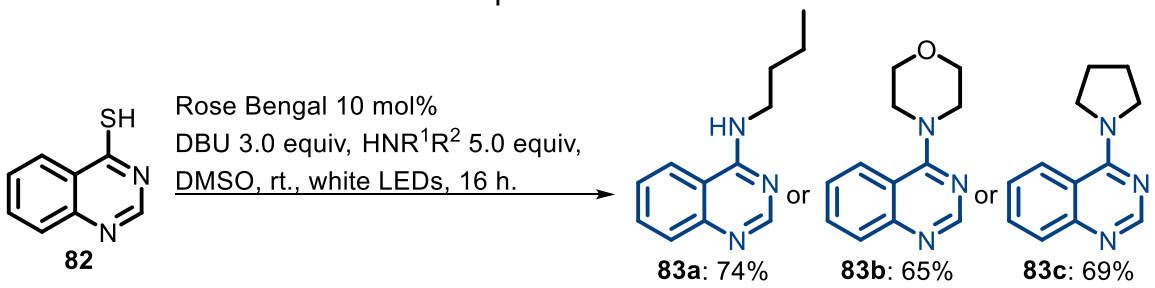
Scheme 11. Some protocols for the synthesis of 4-aminoquinazolines from quinazolinones.



Source: NUNES *et al*., 2021;[60] CHEN *et al.*, 2015.[61]

In addition to the S_NAr-based protocols, the organic dye Rose Bengal under irradiation of visible light enabled the amination of 4-mercaptoquinazoline **82** with different amines leading to **83a-c** in good yields (**Scheme 12**).[62]

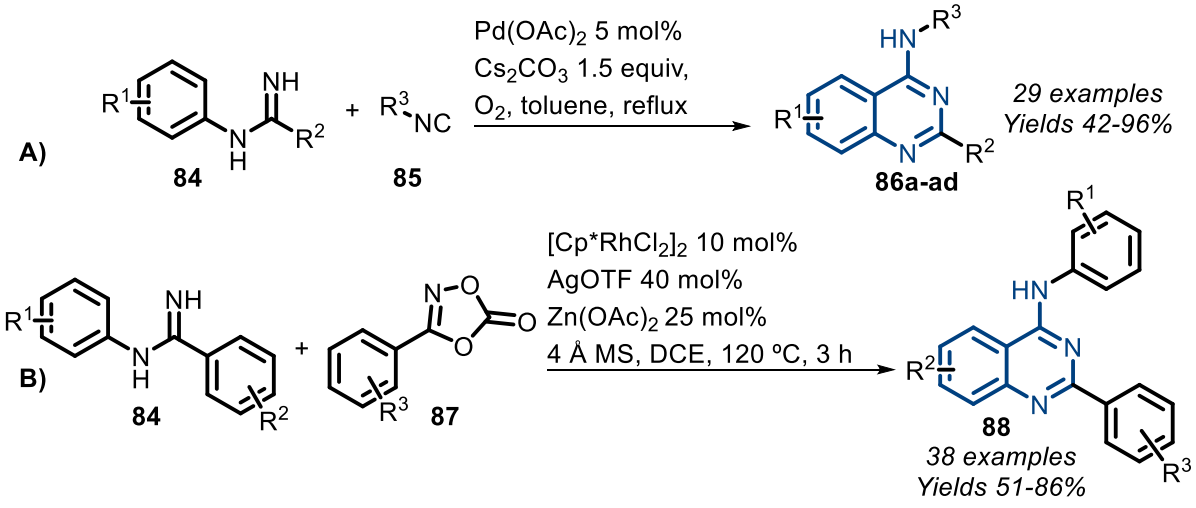
Scheme 12. Visible light enabled S_NAr of 4-mercaptoquinazoline **82** to afford 4-aminoquinazolines **83a-c**.



Source: RATTANANGKOOL; SUKWATTANASINITT; WACHARASINDHU, 2017.[62]

About the cyclization reactions based on a specific C(sp^2)-H activation bond to access 4-aminoquinazolines, palladium(II) and rhodium(III) have found application in intramolecular C-H amidinations involving isonitrile and 1,4,2-dioxazol-5-ones migratory insertion, respectively. $Pd(OAc)_2$ with Cs_2CO_3 in toluene under aerobic and reflux conditions catalyzed the conversion of *N*-arylamidines in quinazolines **86a-ad** with yields up to 96% (**Scheme 13A**).[63] For the rhodium-catalyzed annulation, $[Cp^*RhCl_2]_2$ (pentamethylcyclopentadienyl rhodium dichloride dimer) was used with AgOTf and $Zn(OAc)_2$ as additives in dichloroethane (DCE) at 120 ºC for 3 hours (**Scheme 13B**).[64]

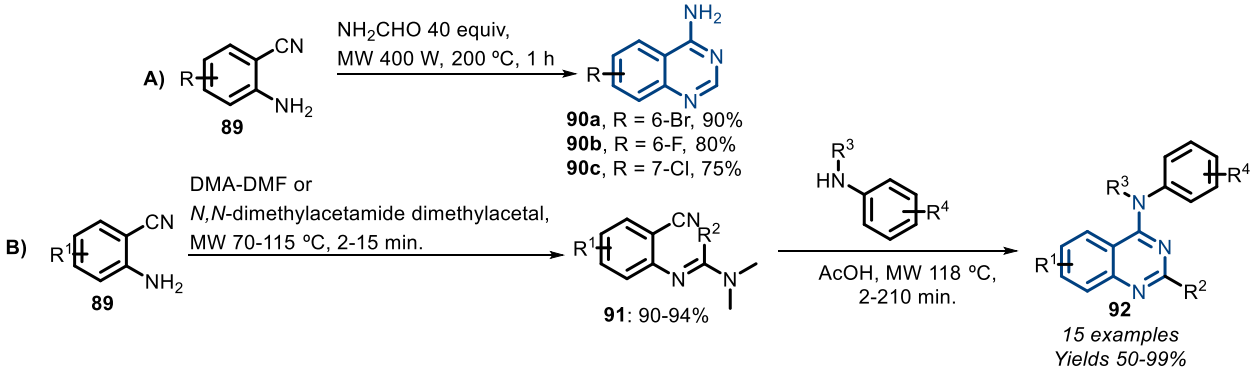
Scheme 13. Metal-catalyzed synthesis of 4-aminoquinazolines from *N*-arylamidines.



Source: WANG *et al.*, 2011;[63] REN *et al.*, 2021.[64]

Some other annulation protocols include the use of anthranilonitriles. Loidreau and Besson have applied formamide as an NH_3 and CO source under thermal decomposition in the presence of halogenated anthranilonitriles **89** for the preparation of 4-aminoquinazolines of type **90a-c** in good yields (**Scheme 14A**).[65] Moreover, anthranilonitriles can be converted into formamidines **91** which under acidic and microwave irradiation conditions react with amines through Dimroth rearrangement to afford 4-aminoquinazolines of type **92** (**Scheme 14B**).[66]

Scheme 14. Preparation of 4-aminoquinazolines from anthranilonitriles.

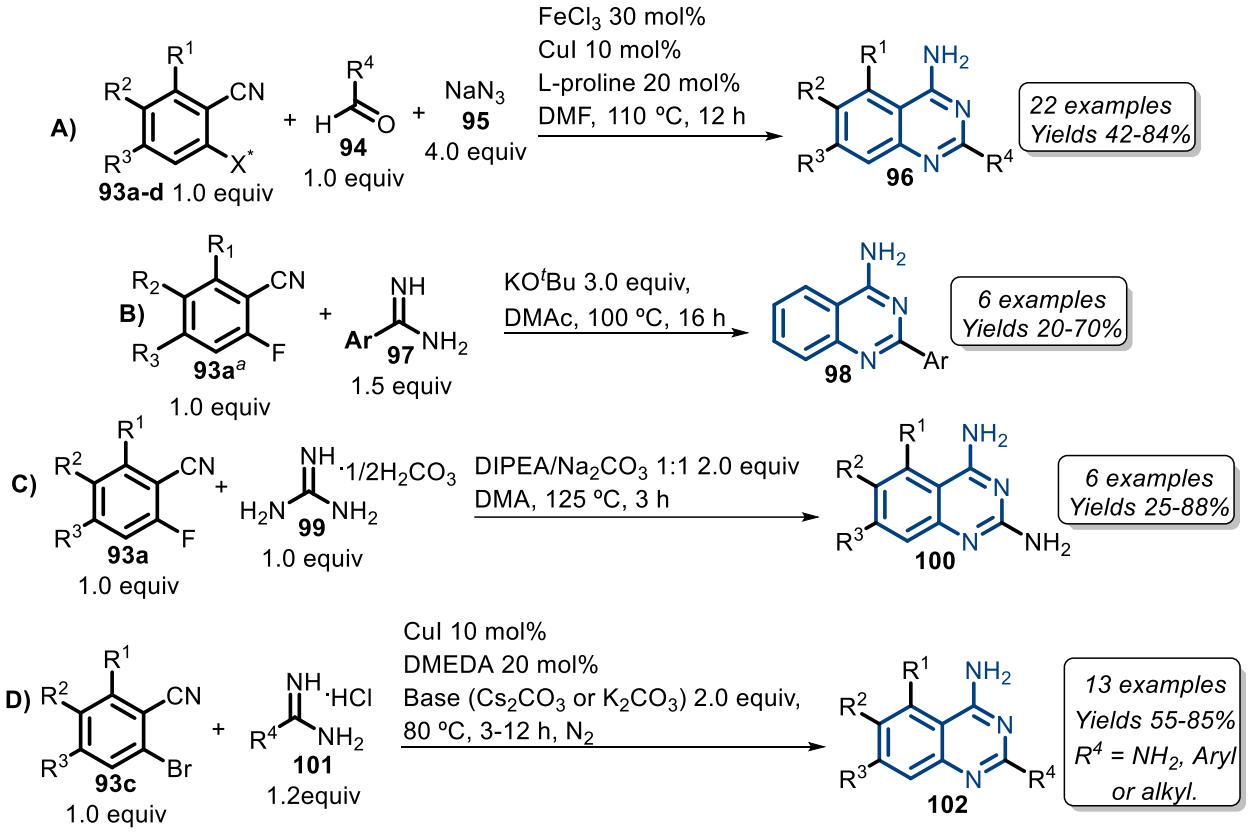


Source: LOIDREAU; BESSON, 2011;[65] FOUCOURT *et al.*, 2010.[66]

Concerning the use of *ortho*-halogenated benzonitriles, distinct protocols have been developed towards the synthesis of 2-substituted 4-aminoquinazolines. For instance, Wu and co-workers devised a domino strategy with consecutive iron-mediated [3+2] cycloaddition, copper-catalyzed S_NAr, reduction, cyclization, oxidation, and copper-catalyzed denitrogenation processes for 2-F-, 2-Cl-, 2-Br-, and 2-I-substituted benzonitriles with varied aldehydes and sodium azide as the nitrogen source (**Scheme 15A**).[56e] Another procedure includes the reaction of amidines with 2-flurobenzonitriles in the presence of potassium *t*-butoxide at 100 ºC for 16 hours by a base-assisted S_NAr followed by the attack of the amino group to the cyano carbon (**Scheme 15B**).[67] Furthermore, under basic conditions, guanidine salts cyclize well with 2-fluorobenzonitriles at 125 ºC in *N,N*-dimethylacetamide (DMAc) (**Scheme 15C**)[68] and CuI plus *N,N'*-dimethylethylenediamine (DMEDA) is suitable for the Ullmann-type

coupling of 2-bromobenzonitriles with amidine or guanidine salts in DMF at 80 ºC (**Scheme 15D**).[69]

Scheme 15. Synthesis of 4-aminoquinazolines from *ortho*-halogenated benzonitriles.



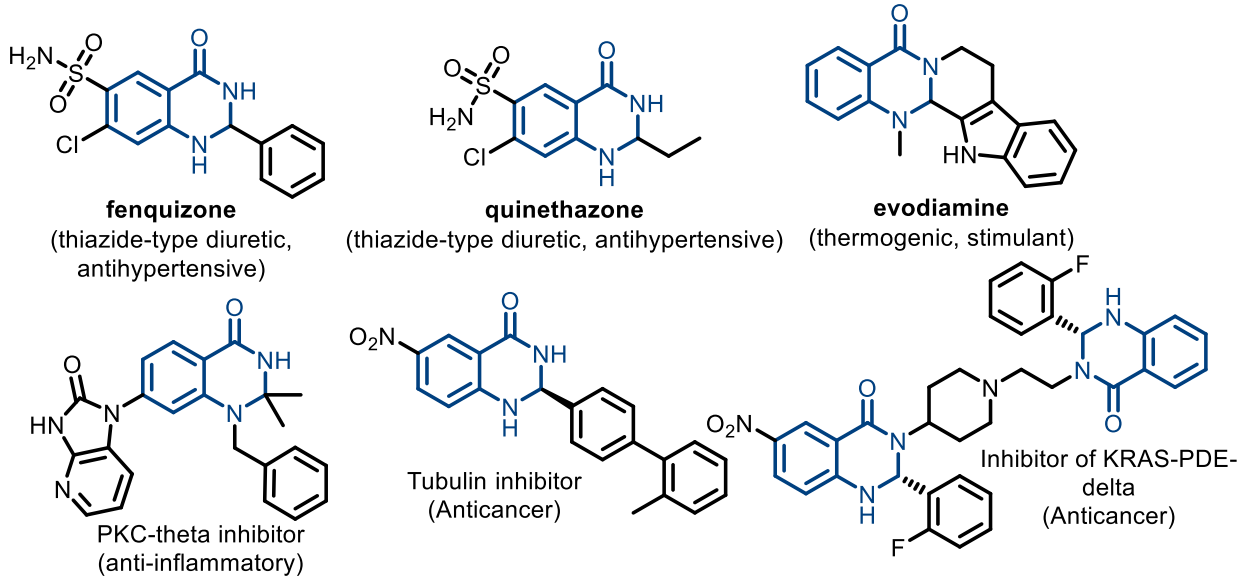
X group: **93a* = F, **93b** = Cl, **93c** = Br, or **93d** = I. [a]R^1=R^2=R^3 = H*

Source JIA *et al*., 2015;[56e] FENG; WU, 2015;[67] SHELKE *et al*., 2015;[68] YANG *et al*., 2010.[69]

1.4 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES: BIOLOGICAL IMPORTANCE AND SYNTHESIS

The 2,3-dihydroquinazolin-4(1*H*)-one (DHQ), a nitrogen-based heterocycle and a privileged scaffold, is present in a multitude of biologically active molecules including marketed pharmaceuticals and potential drug candidates as depicted in **figure 6**.[70] Hence, its synthesis mainly targeting 2-substituted derivatives has aroused great interest, and a vast number of synthetic protocols has been reported in the literature.

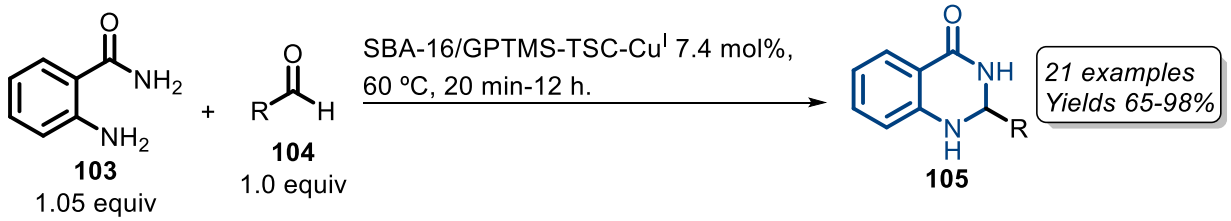
Figure 6. Some bioactive molecules containing the DHQ core.



Source: BADOLATO; AIELLO; NEAMATI, 2018;[70a] JIANG *et al*., 2017;[70d] CHINIGO *et al*., 2008.[70b]

The most common synthetic protocols comprise the use of 2-aminobenzamides to construct the central bicyclic ring system.[71] For example, a recent approach by Ghodsinia and co-workers reported the use of the heterogenous catalyst SBA-16/GPTMS-TSC-Cu^{I} to promote the cyclocondensation of 2-aminobenzamide **103** with aldehydes under solvent-free conditions furnishing twenty-one 2,3-dihydroquinazolin-4(1*H*)-ones in great to excellent yields (**Scheme 16**). For such, mesoporous silica SBA-16 was functionalized by aminated 3-glycidyloxypropyltrimethoxysilane with thiosemicarbazide and further treated with Cu^{I}.[71a]

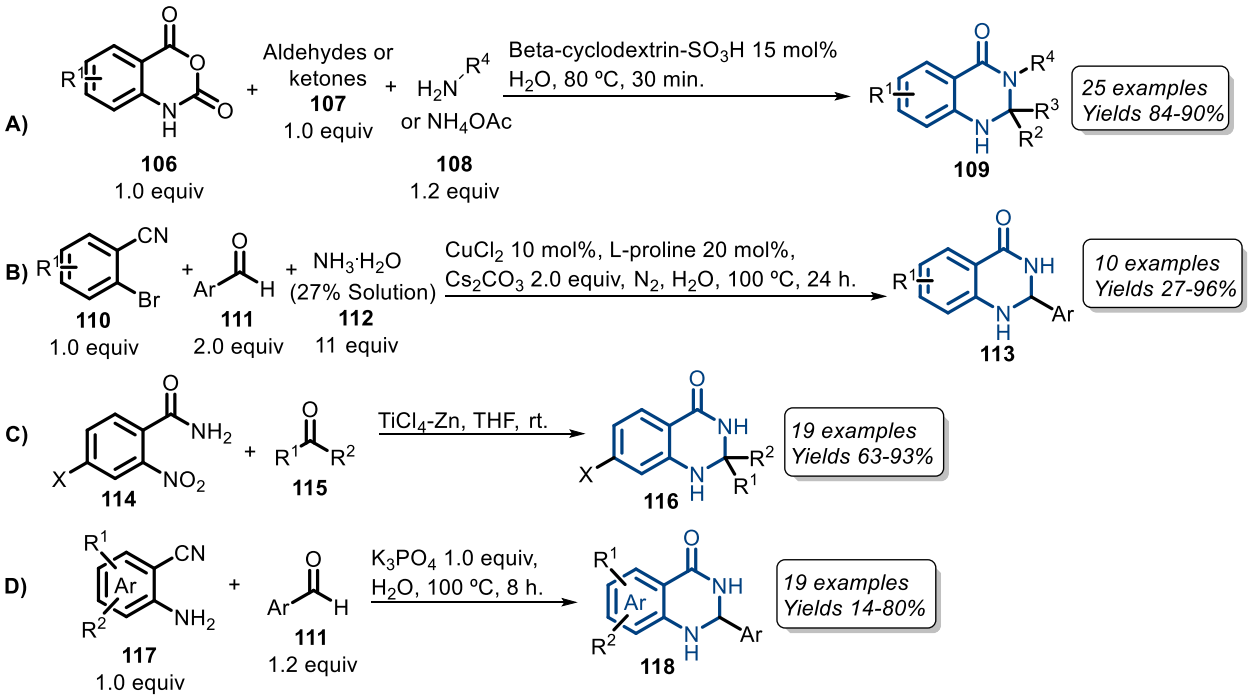
Scheme 16. Catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by SBA-16/GPTMS-TSC-Cu^{I} catalyst.



Source: ERFAN; AKHLAGHINIA; GHODSINIA, 2020.[71a]

Other suitable substrates for the synthesis of this scaffold are isatoic anhydrides,[72] *o*-bromobenzonitriles,[73] 2-nitrobenzamides,[74] and 2-aminobenzonitriles or 2-aminonicotinonitrile.[75] β-cyclodextrin-SO_3H, a recyclable acid catalyst, applied to the one-pot condensation of isatoic anhydrides **106** with primary amines or ammonium acetate and aldehydes or ketones **107** in aqueous media at 80 ºC. Twenty-five 2,3-dihydroquinazolin-4(1*H*)-ones were obtained with yields varying from 84 to 90% (**Scheme 17A**).[72a] In the case of 2-bromobenzonitriles **110**, their treatment with benzaldehydes and aqueous ammonia under copper catalysis, nitrogen, and basic aqueous conditions gave 2,3-dihydro-2-aryl quinazolin-4(1*H*)-ones with yields up to 96% (**Scheme17B**).[73] Besides, *o*-nitrobenzamides **114** undergo reductive cyclization in the presence of carbonyl compounds with the aid of $TiCl_4$/Zn in dry THF (**Scheme 17C**),[74] and 2-aminobenzonitriles **117** favorably react with aromatic aldehydes in K_3PO_4 aqueous solution (**Scheme 17D**).[75]

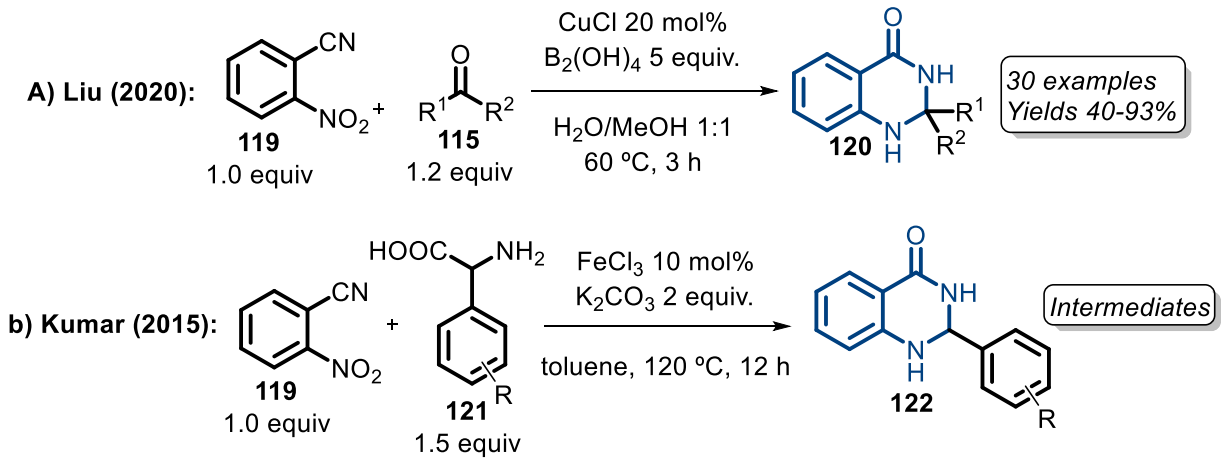
Scheme 17. Synthesis of DHQs from isatoic anhydrides, *o*-bromobenzonitriles, 2-nitrobenzamides, and 2-amino- benzonitriles or nicotinonitrile.



Source: WU *et al*., 2014;[72a] LIU *et al.*, 2018;[73] SHI *et al.*, 2003;[74] WU *et al*., 2014.[75]

Regarding the use of 2-nitrobenzonitrile as a precursor of DHQs, Liu and co-workers have recently reported a combined reduction/hydration/cyclocondensation approach requiring an excess of diboronic acid and copper as a catalyst in a water/methanol mixture.[76] DHQs were also observed by Kumar and co-workers from the reaction of the same substrate with phenylglycine in the presence of $FeCl_3$ and K_2CO_3 but only as intermediates.[77]

Scheme 18. Synthetic procedures for the synthesis of DHQs from 2-nitrobenzonitrile.



Source: LIU *et al*., 2020;[76] KUMAR *et al*., 2015.[77]

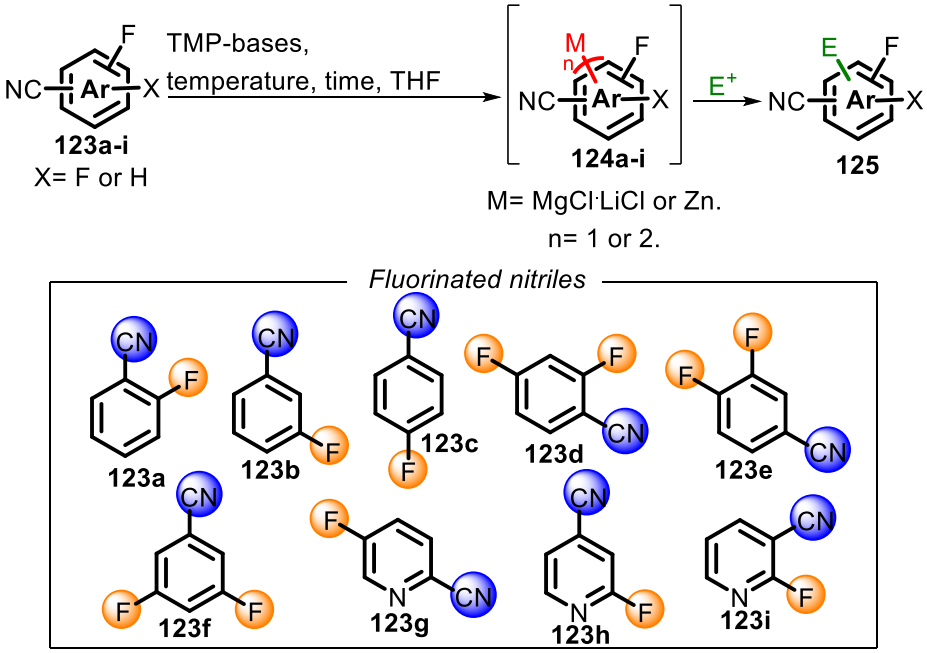
2. OBJECTIVES

In the first project, it was aimed at the regioselective metalation of fluorinated nitriles with 2,2,6,6-tetramethylpiperidyl bases (TMP-bases) to explore new and scarcely investigated metalation positions (**Scheme 19**). The subsequent trapping of the generated aromatic and heteroaromatic organometallic species with diverse electrophiles was investigated to afford functionalized building blocks. Besides, the following specific goals were settled:

- to reproduce the metalation with a TMP-base and further functionalization at gram scale for at least one substrate;
- to study sequential difunctionalization to achieve tetrasubstituted derivatives;

- to exemplify the potential of the functionalized fluorinated nitriles as building blocks in the synthesis of 4-aminoquinazolines and other heterocycles of pharmaceutical importance as synthetic applications.

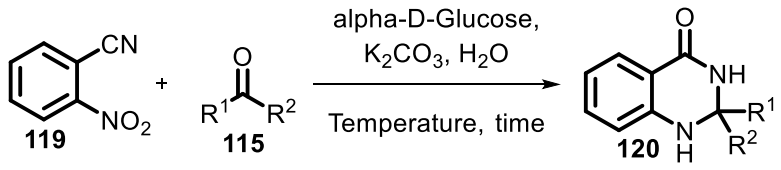
Scheme 19. The main goal from the first project and chosen substrates for study.



Source: The author.

In the second project, it was envisioned the use of glucose as an eco-friendly reductant with an aqueous solution of potassium carbonate for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-nitrobenzonitrile in a one-pot manner (**Scheme 20**). In this scenario, the study of optimal conditions including time and temperature variation, the influence of concentration on reaction outcome, and the scope of carbonyl compounds were planned.

Scheme 20. Synthesis of DHQs with glucose as an eco-friendly reductant.



Source: The author.

6. CONCLUSIONS

About 47 diverse functionalized nitriles with the exploration of new and scarcely investigated metalation sites were prepared in yields ranging from 48 to 95% by metalation with the TMP-bases TMPMgCl·LiCl or $(TMP)_2Zn.2MgCl_2·2LiCl$. In the case of known metalation positions, this study has greatly contributed to the establishment of shorter metalation times at milder temperatures with a better exploration of reactivity towards varied electrophiles. Favorably, the devised methods proved to be scalable as illustrated by the synthesis of **125f** at a 5.5 mmol scale (91% isolated yield, 1.21 g). The suitability of TMPMgCl·LiCl in the difunctionalization of **123c** to access tetrasubstituted derivatives **126a-b** can be viewed as a blueprint for the development of exhaustive functionalization protocols with TMP-bases as wisely explored by prof. Manfred Schlosser with lithium-based bases.

The obtained functionalized fluorinated nitriles can be employed as building blocks in the construction of heterocyclic systems of great pharmaceutical importance as exemplified by the synthesis of 4-aminoquinazolines **134** and **135**, 1*H*-indazole **137**, and dibenzoxazepinamine **138**. Furthermore, the prepared building blocks may find application in the synthesis of other diverse important heterocycles since fluorinated nitriles have been also successfully used to access spiro[indazolo[3,2-*b*]quinazoline-7,3'-indolines,[116] indazolo-quinazolinones,[117] cyanodibenzo[1,4]dioxines,[118] dibenzo[*b,f*][1,4]oxazepines,[119] oxazepinones,[120] 11H-pyrido[2,1-b]quinazolin-11-ones,[121] and benzo[d]imidazo[2,1-b]thiazoles.[122]

In the second work, an environmentally friendly one-pot protocol based on nitrile hydration, nitro-reduction, imine formation, and cyclization with glucose in alkaline water was successfully established affording DHQs in yields 18-90%. As a transition metal-free method, it represents a great and fast alternative to access 2,3-dihydroquinazolin-4(1*H*)-ones from 2-nitrobenzonitrile. Moreover, it may ignite the general interest of the research community in applying glucose as a green reductant in the synthesis of other important heterocyclic systems.

Speaking of sustainability, glucose is a relevant renewable resource easily accessible from lignocellulosic biomass through well-established technology and was favorably

employed in water as the solvent with potassium carbonate (“potash”, available from plant ashes) as the base. Also important, no competition of the aldehyde from glucose with the externally added carbonyl compound was verified, and the synthesized DHQs in this work can be easily oxidized under eco-friendly conditions to the corresponding quinazolinones[123] finding even wider application in medicinal chemistry.

8. References

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