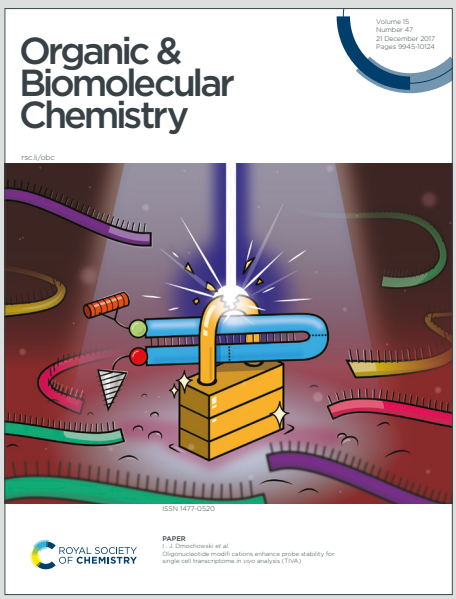
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Jimenez-Aberasturi, X. del Corte, J. M. de los Santos and J. Vicario, *Org. Biomol. Chem.*, 2026, DOI: 10.1039/D6OB00771F.



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Review

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DOI: 10.1039/D6OB00771F

Azo Compounds as Key Intermediates in the Synthesis of Cinnolines. Recent Advances

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Over the past decades, azo compounds have emerged as versatile and efficient building blocks for the construction of cinnoline frameworks due to their ready availability, structural diversity, and unique reactivity profiles. This review provides a comprehensive overview of recent advances in the use of azo compounds for cinnoline synthesis, highlighting transition-metal-catalyzed C–H activation modern strategies, cycloaddition reactions and classical methods (von-Richter, Widman–Stoermer or Borsche–Herbert).

1. Introduction

Nitrogen-containing heterocycles occupy a central position in modern drug discovery, forming the core of many clinically relevant small molecules.[1] Among them, cinnolines (benzo[*c*]pyridazines)[2] are an important class of bicyclic diazines that have emerged as versatile and pharmacologically valuable scaffolds. Structurally, they are 1,2-diaza analogues of naphthalene and are related to other heterocyclic systems, which enables diverse chemical functionalization and precise modulation of biological interactions across multiple therapeutic areas.[3]

Although naturally occurring cinnolines are rare,[4] synthetic derivatives have revealed a broad spectrum of biological activities. Over the past decades, the cinnoline scaffold has emerged as a privileged structure in drug discovery due to its capacity to interact with diverse biological targets. Cinnoline derivatives have shown anti-inflammatory, analgesic, and antimicrobial properties, including phosphodiesterase 4 (PDE4) inhibition,[5] transient receptor potential vanilloid 1 (TRPV1) antagonism (Fig. 1),[6] as well as activity against Gram-positive and Gram-negative bacteria, mycobacteria and fungi. However, cinoxacin (Fig. 1)[7] remains the only marketed drug with cinnoline core and is commonly used to treat urinary tract infections. Structural modifications, such as sulfonamide conjugation[8] leading to interesting cinnolinone nucleoside analogues for the treatment of tuberculosis have further expanded their therapeutic potential (Fig. 1).

The intrinsic cytotoxic profile of certain cinnoline derivatives has further positioned this scaffold at the forefront of anticancer research. Indeed, cinnoline-based compounds have shown compelling activity as topoisomerase inhibitors,[9] receptor tyrosine kinase modulators (including c-Met and CSF-1R),[10] and regulators of additional oncogenic signaling pathways (Fig. 1). Such target diversity underscores the scaffold's capacity to engage both enzymatic and receptor-mediated systems with high specificity.

Beyond oncology, they have shown promise in central nervous system disorders, acting as modulators of $GABA_A$ receptors,[11] phosphodiesterase inhibitors,[12] and histamine receptor antagonists,[13] highlighting their relevance in neuropsychiatric and neurodegenerative diseases. Particularly, AstraZeneca's patented drug AZD7325[14] has undergone clinical trial (phases I and II) for the treatment of anxiety and autism (Fig. 1).

In addition to their pharmacological applications, cinnoline derivatives have been explored in agrochemistry[15] as herbicides and molluscicides (see Fig. 1). They also present interesting opportunities in materials science, particularly in cell imaging[16] and semiconductor technologies,[17] owing to their tuneable optical properties and potential as fluorescent probes[18] (Fig. 1).

The synthesis of the cinnoline core has attracted sustained interest since the late nineteenth century, driving the continuous evolution of methodologies that enable access to structurally diverse derivatives. These advances have not only facilitated the efficient preparation of increasingly complex molecular architectures but have also expanded opportunities for structure–activity relationship studies, ultimately enabling more rational approaches to the design of cinnoline-based compounds with tailored properties.

Early approaches to cinnoline synthesis rely primarily on diazonium chemistry, intramolecular cyclizations, and hydrazine-based strategies. The seminal Richter reaction[19] marked the beginning of this field, establishing the utility of *ortho*-substituted arenediazonium salts in electrophilic annulation reactions (Scheme 1a). Building on this reactivity, related transformations such as the Widman–Stoermer[20] (Scheme 1b) and Borsche–Herbert (or Borsche-Koelsch)[21] reactions (Scheme 1c) expanded the scope of accessible cinnoline frameworks through variations in cyclization pathways, thereby enriching structural diversity.

In parallel, methodologies based on arylhydrazines and hydrazones introduced complementary strategies, enabling annulation through diazotization–reduction sequences and subsequent cyclization steps (Scheme 1d).[22] Hydrazone-based methodologies, including acid-promoted[23] and Friedel–Crafts-type processes,[24] (Scheme 1e) further broadened the synthetic landscape and provided versatile routes to functionalized cinnoline derivatives.

The synthesis of more complex systems, such as benzo[*c*]cinnolines, a subclass of particular pharmacological

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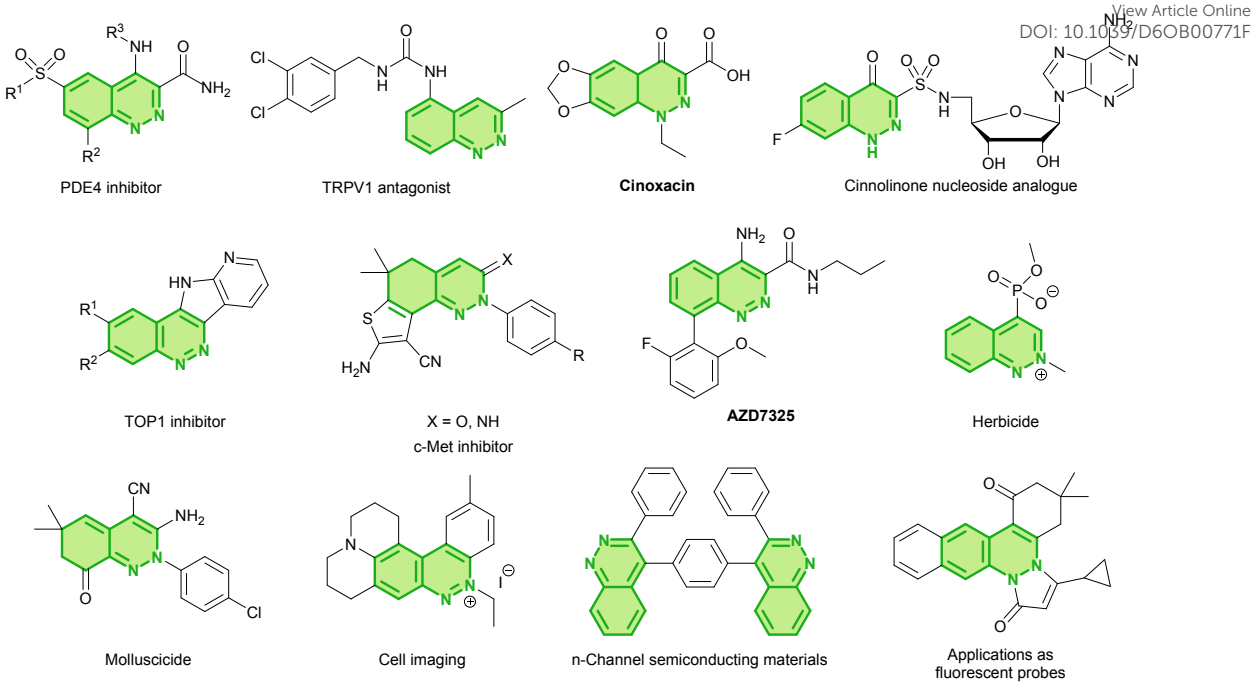
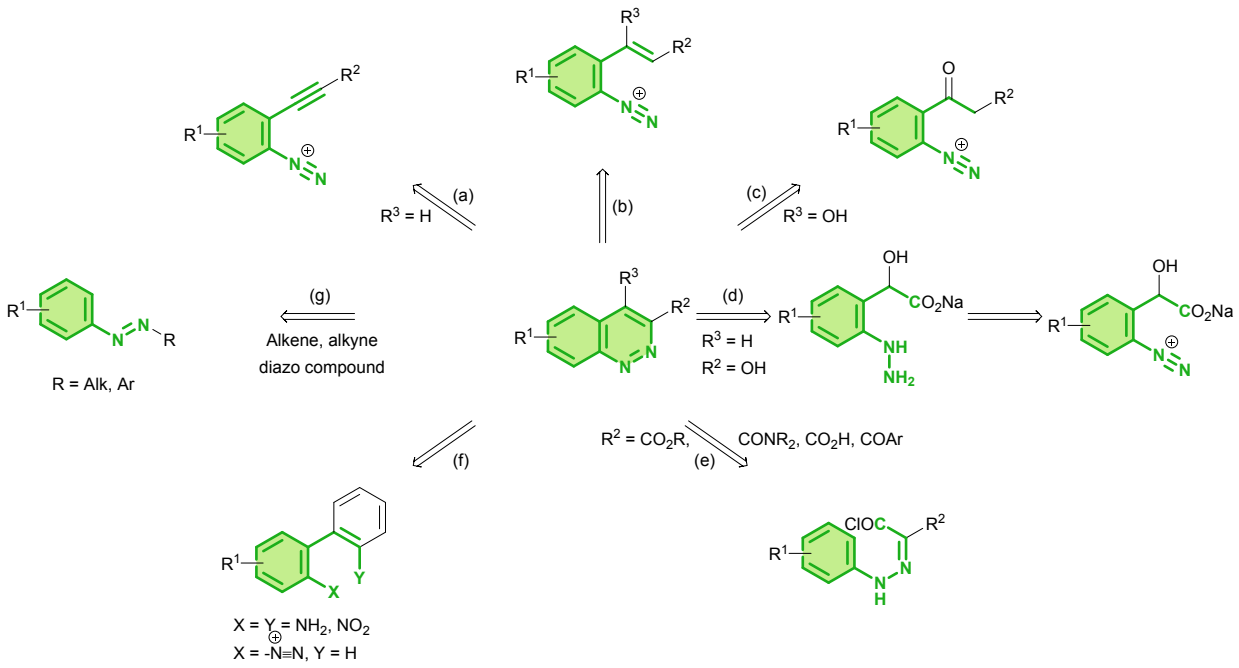


Fig. 1 Representative bioactive molecules and functional materials with cinnoline core.

interest, has traditionally relied on functionalized biaryl precursors, with transformations involving azo coupling,[25] reductive processes,[26] or oxidative bond formation[27] (Scheme 1f). Overall, these classical methodologies have defined the key reactivity patterns underlying cinnoline construction, despite inherent limitations in substrate scope and the frequent need for prefunctionalized starting materials.

More recently, the field has shifted toward the development of more efficient and sustainable strategies. In particular, transition-metal-catalyzed C–H activation has emerged as a powerful approach, enabling the streamlined and atom-economical construction of cinnoline[28] and cinnoline-fused heterocyclic frameworks,[29] while offering improved functional group tolerance and synthetic flexibility.

Several reviews have addressed the synthesis of cinnoline scaffolds, either specifically[30] or within the broader context of nitrogen-containing heterocycles.[31] Building on these contributions, this review critically is focused on recent



Scheme 1 Different approaches for cinnoline synthesis.

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advances in the chemistry of azo derivatives for the synthesis of cinnoline derivatives, highlighting key trends and future perspectives relevant to their development as pharmacologically important scaffolds.

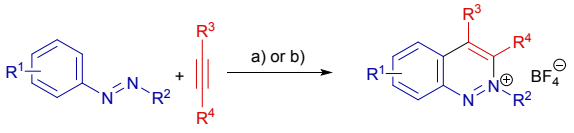
The review is organized into two main sections covering annulation (Scheme 1g) and intramolecular cyclization processes of azo derivatives (Scheme 1a, 1b and 1c). Emphasis is placed on methodological developments reported since 2008, with particular attention to emerging strategies and advances in this field.

2. Synthesis of cinnolines through annulation reactions involving azo compounds

As previously stated, azo compounds have demonstrated wide utility in traditional methods for the synthesis of cinnoline derivatives. Nonetheless, more recently, they have also shown significant potential for the preparation of cinnolines through modern procedures, especially through C–H activation-based reactions. In fact, C–H functionalization has emerged as one of the most powerful tools for constructing the cinnoline core through simple, fast and efficient protocols.

In this context, the groups of Cheng and You, independently, disclosed the reaction between azobenzenes **1** and alkynes **2** catalyzed by $(RhCp^*Cl_2)_2$, which in the presence of Cu^{II} afforded cinolinnium salts **3** (Scheme 2).[32,33] In both cases, the reaction accepted a broad spectrum of substituents both in the aryldiazene and in the alkyne obtaining adducts **3** in high to excellent yields.

Regarding the mechanism of the reaction, the authors propose a catalytic cycle starting with the coordination and subsequent



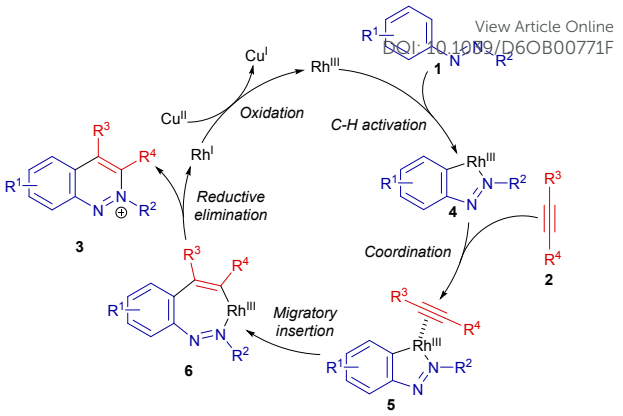
a) $(RhCp^*Cl_2)_2$ (1 mol%), $Cu(BF_4)\cdot 6H_2O$ (0.5 equiv.), ^{t}BuOH, 70 °C, air, 16 h (Ref 32)

R^1 = H, 4-Me, 4-OMe, 4-^{t}Bu, 4-^{n}Bu, 4-F, 4-Br, 4-CO_2Et, 2-Et, 3,4-$(OMe)_2$
R^2 = Me, ^{n}Pr, ^{c}Hex, Ph, 4-MeC_6H_4, 4-OMeC_6H_4, 4-^{t}BuC_6H_4, 4-^{n}BuC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-CO_2EtC_6H_4, 2-EtC_6H_4, 3,4-$(OMe)_2C_6H_3$
R^3 = Ph, 4-MeC_6H_4, 4-OMeC_6H_4, 4-BrC_6H_4, Me, ^{n}Pr, CH_2OMe, Et, CO_2Et, COMe
R^4 = Ph, 4-MeC_6H_4, 4-OMeC_6H_4, 4-BrC_6H_4, Me, ^{n}Pr, CH_2OMe

b) $(RhCp^*Cl_2)_2$ (2 mol%), $Cu(OAc)_2$ (2 equiv.), Ag_2CO_3 (10 mol%), $NaBF_4$ (2 equiv.), ^{t}AmylOH, 110 °C, 16 h (Ref. 33)

R^1 = H, 3-Me, 4-OMe, 2-OMe, 3,5-$(OMe)_2$, 2-Br, 4-COMe, 4-CO_2Et, 4-Br
R^2 = Me, Ph, 3-MeC_6H_4, 4-OMeC_6H_4, 3,5-$(OMe)_2C_6H_3$, 2-BrC_6H_4, 4-(COMe)C_6H_4, 4-(CO_2Et)C_6H_4, 4-OHC_6H_4
R^3 = H, Ph, 2-OMeC_6H_4, 4-OMeC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 2-C_4H_3S, ^{n}Pr, CH_2OMe, Me, ^{n}Hex
R^4 = Ph, 3-FC_6H_4, 2-OMeC_6H_4, 4-OMeC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 2-Thiophenyl, ^{n}Pr, CH_2OMe, CO_2Et, (*E*)-CH=CH-^{n}Hex, ^{n}Hex

Scheme 2 Rh-catalyzed annulation between azobenzenes **1** and alkynes **2**.

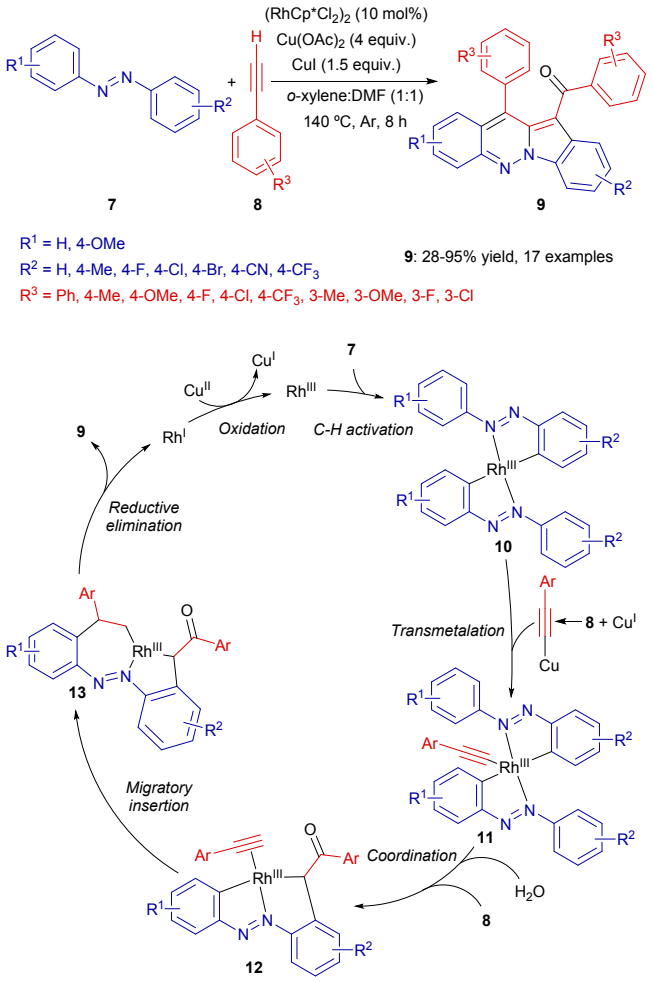


Scheme 3 Catalytic cycle for the formation of cinnolinium salts **3**.

C–H activation of the aromatic ring in azo derivative **1** directed by the nitrogen atom through species **4**. Then, the coordination of the alkyne **2** with Rh^{III} as shown in species **5**, and subsequent insertion of the olefin **2** forms metalacyclic intermediate **6** whose reductive elimination provides the final nitrogenated heterocycle **3** (Scheme 3). The last step of the catalytic cycle consists of the reduction of Cu^{II} to Cu^{I}, thus releasing the Rh^{III} catalyst. This step requires stoichiometric amounts of the oxidant to perform the reaction. In this respect, the utility of electricity as a "green reagent" was demonstrated by the group of Zhang in 2021.[34] In this work the authors describe an electrochemical reaction using a carbon felt anode and a platinum electrode cathode to obtain cinnolinium derivatives **3** in good yields ranging from 60% to 88% in the absence of any oxidant.

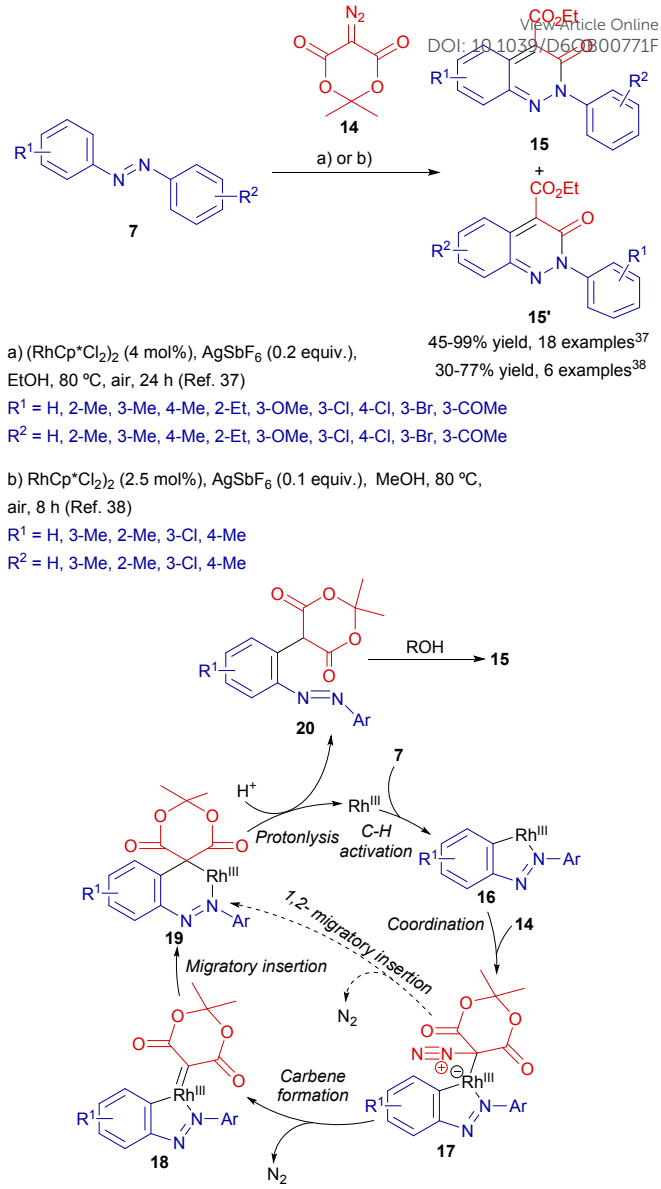
Interestingly, the annulation between azobenzenes **1** and alkynes **2** was extended to the use of cobalt as catalyst by Cheng and coworkers.[35] In this case, the C–H functionalization catalyzed by $CoCp^*(CO)I_2$ gave cinnolinium salts **3** in high yields, comparable to those obtained under rhodium catalysis in the aforementioned studies. The reaction worked over a wide variety of starting substrates, observing a slight increase in the chemical yield when electron-donating substituents were present at the structure of aryldiazene **1** (i.e. 4-Me, 4-^{n}Bu, 2-Me or 2-Et).

Following a similar approach under rhodium catalysis, the group of Yuang also studied the reactivity of aromatic azo compounds toward alkynes in annulation reactions implying C–H activation.[36] In this case, they utilized terminal alkynes **8** as starting materials for the cyclization reaction and, in contrast to the previous investigations, they isolated indolo[1,2-*b*]cinnolines **9** (Scheme 4). The proposed mechanism starts with the C–H activation that affords dimer **10**, followed by transmetalation that forms species **11**. Remarkably, the authors demonstrated that the presence of residual water in the solvent or in the copper salts used in the reaction mixture seemed crucial for the reaction, serving as the oxygen source for the formation of the carbonyl group present in the structure of the intermediate **12**. Finally, migratory insertion leads to the formation of metalacycle **13** and the reductive elimination releases final adduct **9**.



Scheme 4 Synthesis of indolo[1,2-*b*]cinnolines **9** through C–H functionalization.

In 2015, the groups of Lee and Kim, separately, described the use of the diazo derivative of Meldrum's acid **14** as 2π-electron system for its annulation towards various azobenzenes **7**.[37,38] In both reports they employed the widely used $(RhCp^*Cl_2)_2$ as the catalyst, obtaining cinnoline-3(2*H*)-ones **15** over a broad scope of symmetrical and asymmetrical aryldiazenes **7**, including electron-withdrawing and electron-donating functional groups (Scheme 5). It should be noted that the use of non-symmetrical starting substrates **7** led to the formation of two different regioisomers (**15** and **15'**) in different ratios. The process would presumably be initiated by the C–H activation of **7** delivering metallacycle **16** whose coordination toward diazo compound **14** would afford intermediate **17**. Then, direct 1,2-migratory insertion (dashed pathway) or carbene formation followed by migratory insertion (through species **18**), would form intermediate **19**. Finally, protonolysis of **19** would lead to the construction of open adduct **20**, which in the presence of an alcohol would be converted into final substrate **15** (Scheme 5). Similarly, the potential of $IrCp^*Cl_2$ as the catalyst in C–H activation was proven by Patel and Borah in 2019.[39] In this research cinnoline-3(2*H*)-ones **15** were isolated after 10 hours under mild reaction conditions, with similar chemical yields to those obtained with Rh^{III}.



Scheme 5 Use of diazotized Meldrum's acid **14** as 2π-electron system for C–H functionalization.

Lin *et al.* extended the use of diazo compounds beyond the diazotized Meldrum's acid for the construction of cinnolines through the C–H functionalization of aromatic azo derivatives.[40] In the current investigation *N*-Boc-protected aryldiazenes **21** and different diazo compounds **22**, bearing an electron-withdrawing group, reacted to provide aromatic cinnoline derivatives **23** under Rh^{III} catalysis (Scheme 6a). In contrast, the reaction of these diazo derivatives **22** with aryldiazenes **1** (lacking Boc protecting group) catalyzed by Rh^{III}, led to the formation of cinnolinium salts **24** instead of neutral cinnoline derivatives **23** as it was reported by Li *et al.* in 2018 (Scheme 6b).[41]

In addition, vinylene carbonate (**25**) has also shown applicability for the synthesis of cinnoline derivatives *via* C–H functionalization. In this regard, Kim and coworkers studied the competition between the [4 + 2] and [4 + 1] annulations of

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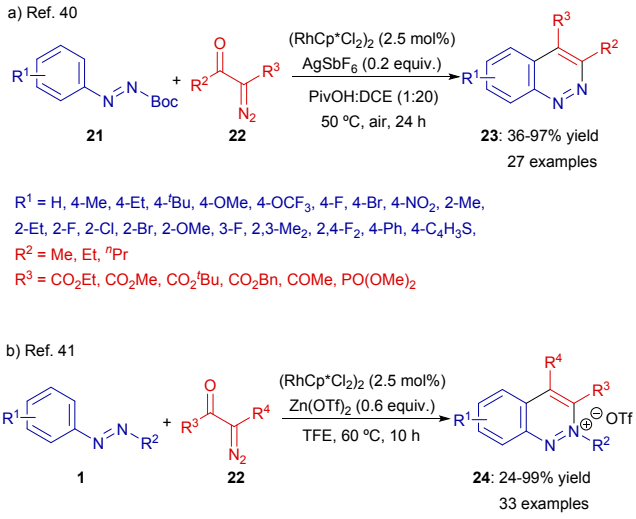
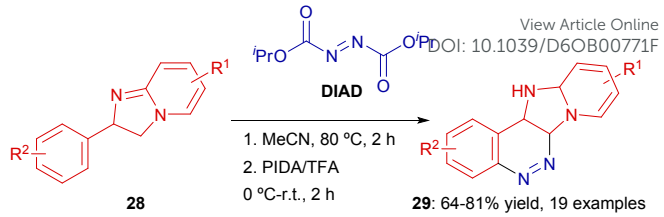


Scheme 6 Diazo compounds **22** as starting substrates for the construction of cinnolines **23** and cinnolinium salts **24**.

azobenzenes **7** and vinylene carbonate **25** in the presence of Rh^{III} catalysts.[42] In this research, the electron density of azobenzene species **7** turned out to be the key aspect for the selectivity of the process. While electron-rich diazenes **7** bearing electron-donating substituents led to the formation of (2*H*)-indazoles **27** ([4 + 1] cycloaddition), electron-withdrawing groups at the structure of azobenzene **7** favored the formation of 2,3-dihydrocinnolin-4-ones **26** ([4 + 2] cycloaddition). Interestingly, unsubstituted diphenyldiazene **7** (R^1 = R^2 = H) provided a mixture of both products **26** and **27** in a 3:2 ratio favoring the construction of the cinnolone derivative **26** (Scheme 7).

Furthermore, azo compounds have also been used as 2π electron systems for the preparation of cinnoline derivatives *via* C–H functionalization. In fact, Sabitha and Kandimalla reported the diisopropyl azodicarboxylate (DIAD) as the nitrogen source for the synthesis of polycyclic fused cinnoline derivatives **29** upon annulation towards 2-arylimidazo[1,2-*a*]pyridines **28**.[43] This protocol provided efficiently a large library of pyrido-



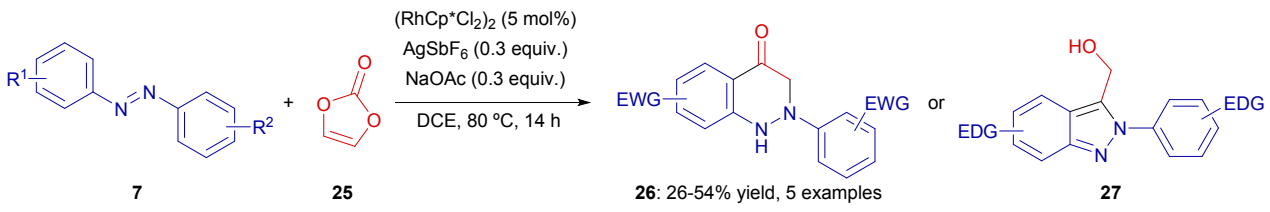
Scheme 8 Azo derivatives as 2π-systems for the preparation of tetracyclic fused cinnolines **29**.

imidazo-cinnolines **29** after two subsequent reaction steps, which were successfully conducted in a one-pot procedure under metal-free conditions (Scheme 8).

As an alternative to C–H activation, the use of halobenzenes is a very convenient strategy for annulation reactions leading to cinnolines. In this regard, the synthesis of cinnolines **31** has been reported through a Pd-catalyzed annulation reaction of *o*-iodophenyltriazenes **30** with alkynes **2** (Scheme 9).[44] In general, the synthetic procedure provides better yields when electron donating substituents are used either at the aromatic ring or at the alkyne substrate. The authors propose two possible mechanisms for the reaction, which are represented in scheme 9. The first part of the pathway, shared by both proposed mechanisms, implies an initial oxidative addition of *o*-iodoaryltriazene **30** to Pd(0) leading to arylpalladium intermediate **32**, which subsequently undergoes the addition of the alkyne to form a vinylpalladium iodide complex **33**.

In one plausible pathway, species **33** undergoes an addition to the N=N bond leading to aminopalladium intermediate **34**, whereas an alternative 6π-electron cyclization furnishes aminopalladium intermediate **34'**. Next, β-amino elimination from either intermediate yields the target cinnoline **31** along with (diethylamino)palladium(II) iodide (**35**), which subsequently undergoes β-hydride elimination followed by base-assisted HI elimination to release the Pd(0) catalyst.

In a second alternative pathway, coordination of the pendant triazene to the vinylic palladium centre affords a seven-membered palladacycle **36**, which subsequently undergoes reductive elimination to generate iminoimmonium salt **37**, regenerating the Pd(0) species. Intermediate **37** furnishes cinnolines **31** in the presence of $^nBu_3N$ (Scheme 9).



Scheme 7 [4 + 1] *versus* [4 + 2] annulations between azo compounds **7** and vinylene carbonate (**25**).

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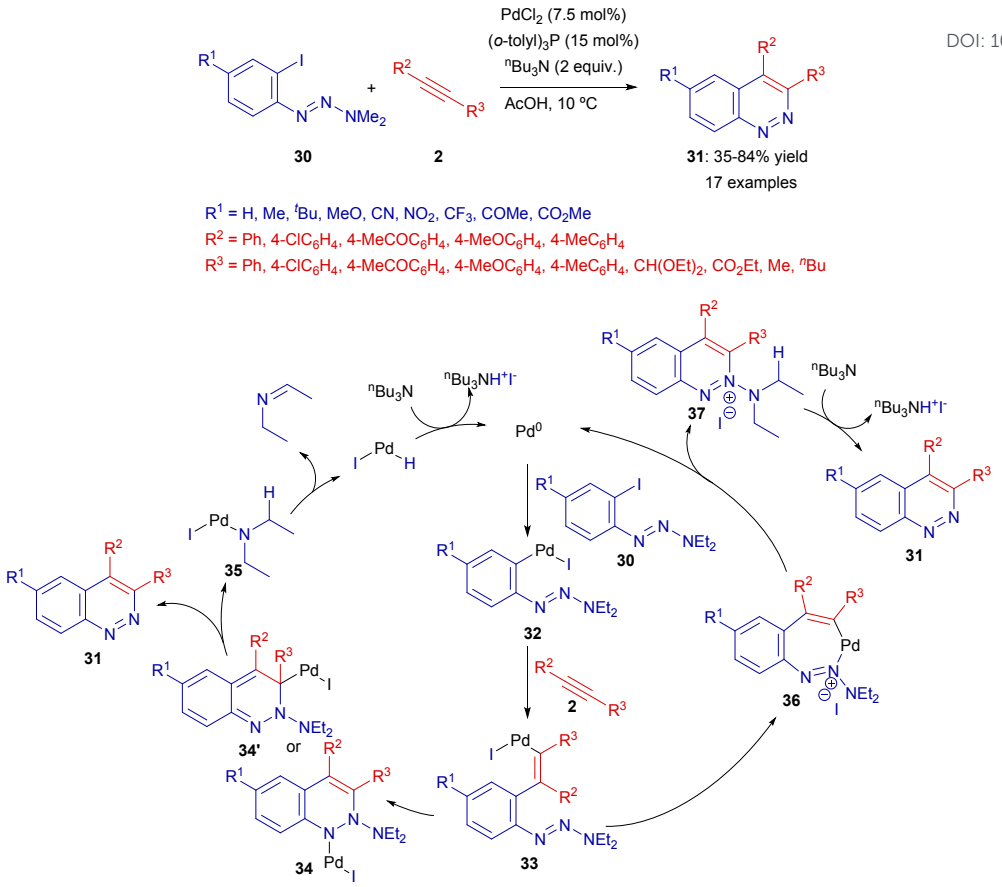
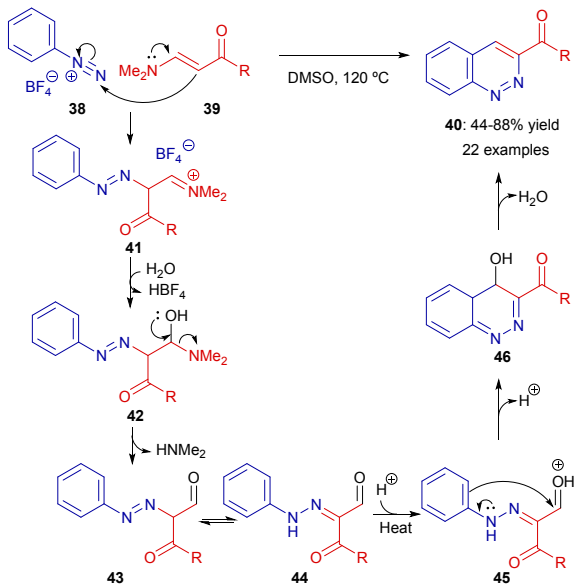


Scheme 9 Pd-catalyzed annulation of *ortho*-iodophenyltriazenes **30** with alkynes **2**.

Without the need of C–H activation, normally using transition metal catalysts, a catalyst-free cascade annulation of aryl diazonium tetrafluoroboronates **38** and enaminones **39** for the synthesis of acyl cinnolines **40** was reported in 2023 (Scheme 10).[45] The reaction proceeds in better yields when activated aromatic substituents are used in the enaminone structure. However, the authors do not provide any example using alkyl-substituted enaminones **39**, which suggests that those substrates are not appropriate for this reaction.

As proposed by the authors, based on control experiments and literature data, the transformation is assumed to start with the nucleophilic attack of the enaminone substrate **39** to the aryl diazonium ion **38**, resulting in the formation of azo-iminium intermediate **41**. This initial coupling step establishes the key N–N-linkage and activates the intermediate for the subsequent transformation. In the presence of trace quantities of water in the reaction media, intermediate **41** undergoes hydrolytic modification to generate N,O-acetal intermediate **42**. This hydrolysis step stabilizes the reactive centre and prepares the molecule for further structural rearrangement.

Following the formation of intermediate **42**, elimination of dimethylamine takes place, leading to the generation of aldehyde **43**. This elimination step is crucial, as it creates a more conjugated framework that enables the next mechanistic event. Intermediate **43** subsequently undergoes a 1,3-hydrogen atom transfer, producing hydrazone derivative **44**. This hydrogen transfer step contributes to the stabilization of the molecular structure and facilitates the progression toward cyclization. Upon increasing the reaction temperature, protonation of the oxygen atom occurs, giving rise to oxonium intermediate **45**.

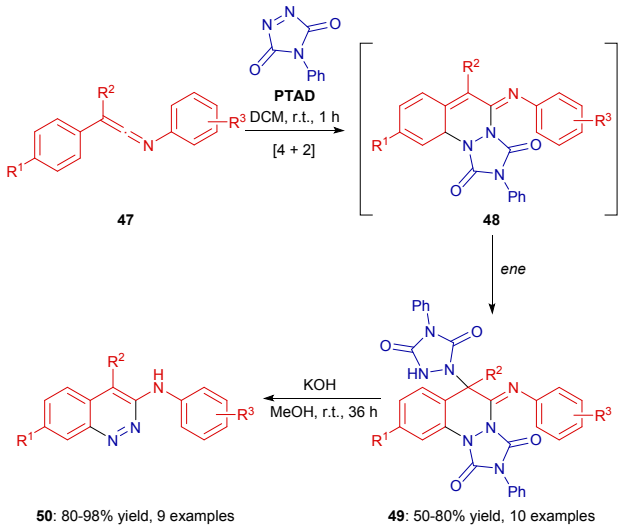


Scheme 10 Synthesis of cinnolines **40** through annulation of aryl-diazonium salts **38** and enaminones **39**.

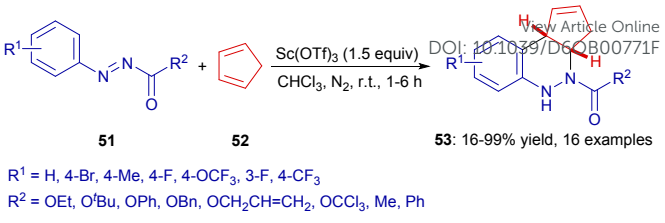
The formation of this positively charged species significantly enhances the electrophilicity of the system and promotes intramolecular nucleophilic attack. Therefore, a cyclization process takes place, leading to the formation of the dihydrocinnoline intermediate **46** through ring closure. This step represents the key structural assembly responsible for constructing the heterocyclic framework. Finally, intermediate **46** undergoes dehydration, implying aromatization, to furnish the thermodynamically stable cinnolines **40**. The loss of water and subsequent development of aromatic stabilization drive the reaction to completion, yielding the desired heteroaromatic compound as the final product. Noticeably, acyl-cinnolines **40** have shown activity as potential anti-inflammatory drugs.

Along with C–H activation and related strategies, [4 + 2] cycloadditions constitute an effective and straightforward route for the synthesis of cinnolines. In this scenario, azo compounds have demonstrated a valuable potential as both the dienophile and the diene of the annulation process. Regarding their use as dienophiles, Vidal *et al.* described the cycloaddition between 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) and *C*-aryl ketenimines **47**, which followed by an ene reaction afforded triazolocinnoline derivatives **49** through intermediate **48**. Cinnoline derivatives **49** are easily converted into aromatic 3-aminocinnolines **50** after treatment under basic media (Scheme 11).[46]

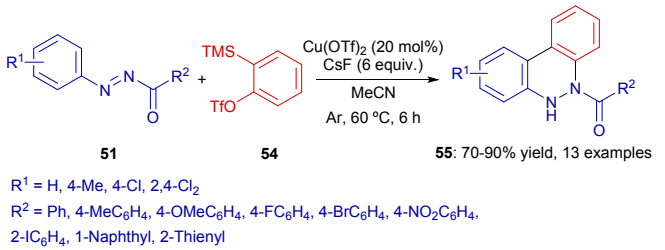
On the other hand, the use of azo derivatives as dienes in a [4 + 2] cycloaddition reaction was reported for the first time in 2022 by our group.[47] In this work, *N*-carbonyl protected aryldiazenes **51** served as 4π-systems for their cyclization with cyclopentadiene (**52**) as the dienophile. This Sc^{III}-mediated process afforded tricyclic fused cinnoline derivatives **53** in a regio- and diastereoselective way after short reaction times, offering a rapid procedure for the preparation of cinnoline derivatives with full atom economy (Scheme 12).



Scheme 11 PTAD as dienophile for the formation cinnoline derivatives **49** and **50**.



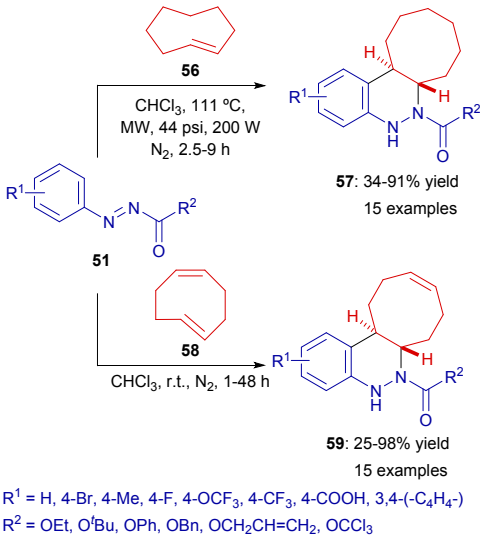
Scheme 12 The first example of an azo-Povarov reaction.



Scheme 13 Azo-Povarov annulation with benzyne precursor **54** as the dienophile.

This azo-Povarov reaction was further studied by the group of Das,[48] who extended the cycloaddition process of aryldiazenes **51** using in this case benzyne precursor **54** as the dienophile partner. The optimization of the reaction conditions led to the use of $Cu(OTf)_2$ as the catalyst, delivering various cinnoline derivatives **55** with high chemical yields after 6 h at 60 °C (Scheme 13).

In more recent dates, our group studied the reactivity of strained cyclic olefins as dienophiles for their cycloaddition toward aromatic diazenes **51**. In this context, we examined *trans*-cyclooctene (**56**) as the 2π-system, where the ring strain enabled the formation of the target azo-Povarov cycloadducts **57** in a metal-free procedure, promoting the reaction through microwave irradiation. The reaction afforded cinnolines **57** over a broad scope of azo-compounds **51** maintaining the diastereoselectivity of the process observed in our previous work (Scheme 14).[49]



Scheme 14 *Trans*-cyclooctene (**56**) and *cis,trans*-cyclocta-1,5-diene (**58**) used as cyclic olefins in an azo-Povarov cyclization.

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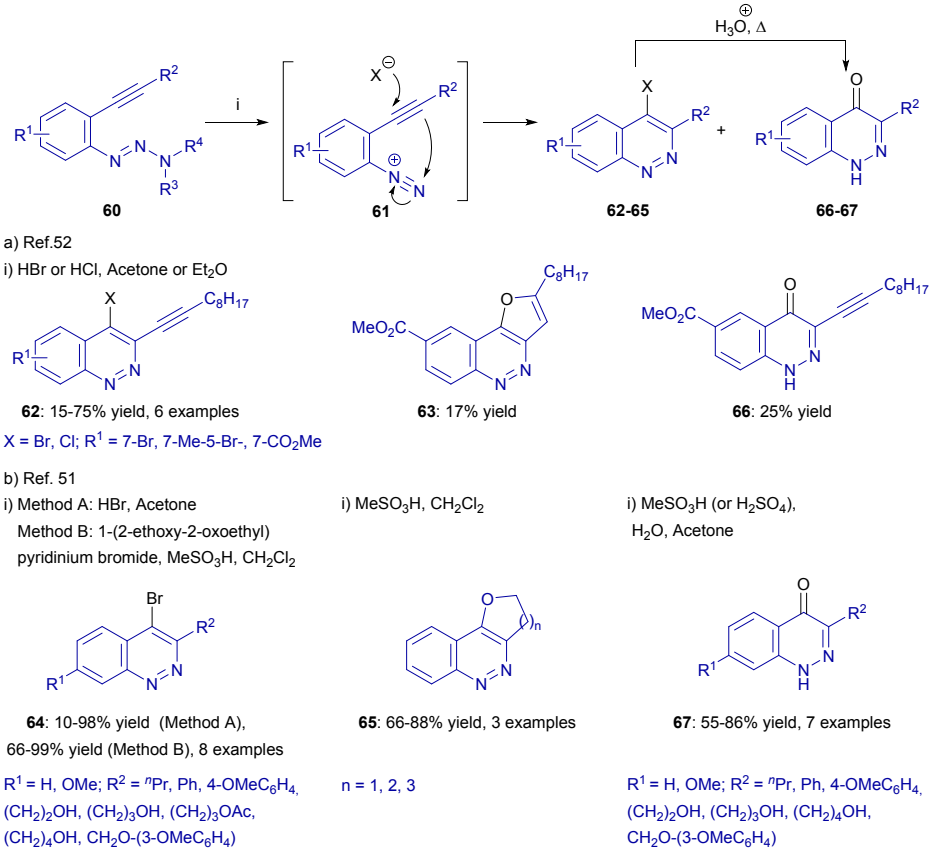
Taking into account the significant results obtained due to the use of strained olefins in the azo-Povarov cycloaddition, we further investigated the importance of the ring strain shown by *trans*-cyclooctene (**56**).[50] To this end, we studied the effect of *cis,trans*-cyclocta-1,5-diene (**58**), whose unstable configuration served as driving force to promote the reaction at room temperature in the absence of any activating Lewis acid. In this way, we reported a fast and simple protocol for the diastereoselective preparation of cinnoline derivatives **59** with full atom economy (Scheme 14). Considering the nature of the reagents and the stereochemistry of the obtained cinnoline substrates, both reactions are likely to proceed through a concerted [4 + 2] mechanism.

As far as we are concern, this work constitutes the first click reaction reported for the synthesis of cinnoline derivatives. Moreover, the applicability of this click cycloaddition was extended to a novel fluorogenic reaction where azo-fluorophore adducts (quenched due to the presence of the N=N bond) were activated through the addiction of *cis,trans*-cyclocta-1,5-diene (**58**) affording turn-on ratios of up to 881-fold.

3. Synthesis of cinnolines through intramolecular cyclizations of azo compounds.

One of the simplest and most straightforward methodologies for accessing cinnolines *via* intramolecular cyclization is the Richter reaction.[19] The key diazonium intermediate **61** for this transformation can be generally generated through the treatment of (2-alkynylphenyl)triazenes **60** with aqueous HBr or HCl (Scheme 15). The diazonium ion **61** subsequently undergoes intramolecular cyclization to afford cinnolines **62-65** or cinnolinones **66-67** upon nucleophilic attack, typically by a halide (or water). In addition, as originally described by Richter, heating the reaction conditions promotes the hydrolysis of cinnolines **62** or **64**, leading to the formation of cinnolinones **66** or **67**, respectively.[51]

In 2009, Balova and co-workers reported the Richter reaction of triazenes **60** (R^2 = –C≡C–C_8H_{17}; R^3 = Et; R^4 = Ph) bearing two acetylene moieties, which required strong acidic conditions to afford cinnoline derivatives **62** (Scheme 15a).[52] The use of concentrated HBr proved more effective than HCl, leading to shorter cyclization times and significantly improved yields. However, a different behavior was observed for triazenes containing an electron-withdrawing group on the aromatic ring. Due to the strongly acidic medium, the methoxycarbonyl substituent at the aromatic ring activates the hydrolysis of 4-halocinnolines under the standard reaction conditions, resulting in the additional formation of furo[3,2-*c*]cinnoline **63** and cinnolinone **66**. This protocol has been later applied to TMS-protected alkynyl triazene **60** (R^1 = H; R^2 = –C≡C–TMS; R^3 = R^4 = Et), and the resulting 3-alkynyl cinnoline was used as an excellent precursor in the synthesis of a cinnoline-fused 10-membered ring enediynes, which proved to be inducers of single-stranded DNA scission.[53] Moreover, following the same procedure, the same authors have prepared 4-bromo cinnolines



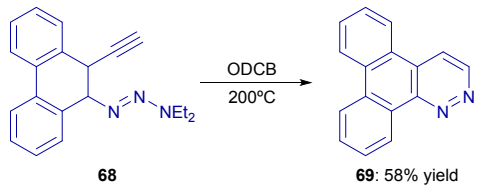
Scheme 15 Richter cyclization for the synthesis of cinnolines **62-65** and/or cinnolinones **66-67**.

as precursors of cinnoline-containing poly(aryleneethynylene)s, that were evaluated for their remarkable photochemical properties and Pd^{+2} sensing ability.[54]

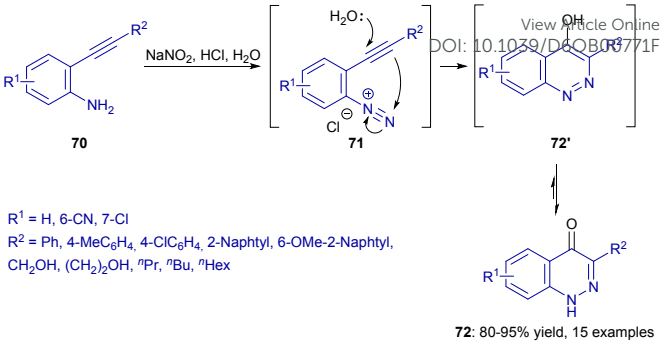
In addition, Flynn and co-workers reported in 2010 an efficient methodology for the synthesis of cinnolines **64**-**65** and cinnolinones, **67** using aryltriazenes **60** as masked diazonium ions (Scheme 15b).[51] Unmasking diazonium ions **61** from triazenes **60** in the presence of aqueous HBr resulted in cyclization, proving to be an effective synthetic protocol for the synthesis of a wide range 4-bromocinnoline derivatives **64** in good yields. However, if an electron-donating group is present at the alkyne **60** (R^2 = 4-$MeOC_6H_4$), the target product is formed in low yield, as the reaction preferentially proceeds *via* exo-cyclization to give the corresponding indazole as the major product. In contrast, when 4-methoxy-phenoxymethyl alkynes **60** (R^2 = CH_2O-(3-$OMeC_6H_4$)) are used, a significant amount of the corresponding cinnolinones **67** are formed. To address these limitations, an alternative set of conditions was explored using the commercially 1-(2-ethoxy-2-oxoethyl) pyridinium bromide salt, in combination with methanosulfonic acid, providing 4-bromocinnolines **64** with improved yields and enhanced selectivity. Under similar reaction conditions hydroxyalkyl substituted alkynes **60** (R^2 = $(CH_2)_nOH$) afford the corresponding co-cyclized cinnolines **65**. Additionally, the authors employed the same 2-alkynylaryldiazenes **60** for the selective synthesis of cinnolinones **67** in good to excellent yields by using water as the nucleophile under strong acidic conditions.

Remarkably, there is in the literature a single example of a Richter reaction without the need of a nucleophilic reagent, described by Herges and Haley.[55] In this case, dibenzo[*f*,*h*]cinnoline **69** is formed through the thermolysis of triazene **68** by heating the reaction in *o*-dichlorobenzene (ODCB) to 200 °C (Scheme 16).

An alternative methodology to the use of aryldiazenes for generating the key aryldiazonium intermediates in a Richter reaction involves the diazotization of 2-alkynylanilines **70**. Following this approach, Ranu reported a simple method for accessing cinnolinones **72**, starting from 2-alkynylanilines **70** as starting materials and using $NaNO_2$ in aqueous acidic medium.[56] The fact that the diazotizing reagent, HNO_2, is generated under aqueous media provides water as the nucleophile, leading to the formation of 4-hydroxy cinnolines **72'**, which after tautomeric equilibrium provide cinnolinones **72** (Scheme 17). Excellent yields are obtained in all examples, particularly when the substituent at the alkyne moiety (R^2) is aromatic rather than aliphatic. In the latter case, due to the initial formation of a tautomeric mixture, longer reaction times are required in order to provide cinnolinones as exclusive products.



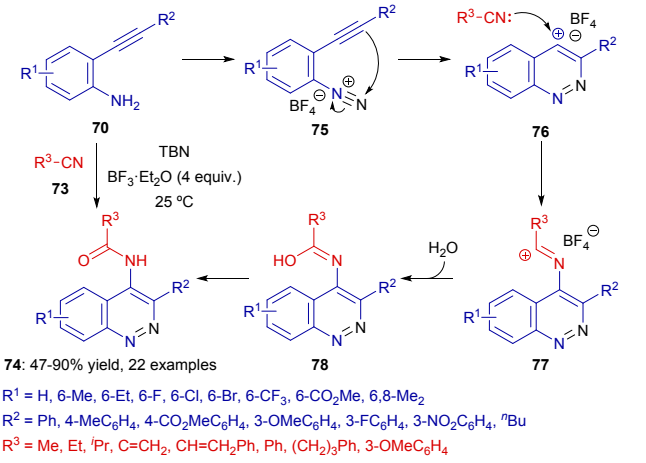
Scheme 16 Thermolysis of triazene **68** for the formation of dibenzo[*f*,*h*]cinnoline **69**.



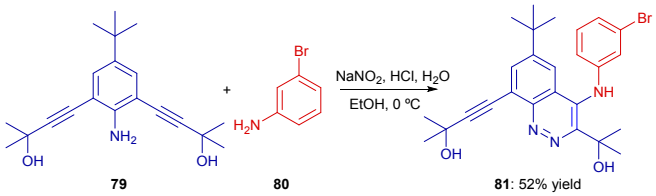
Scheme 17 Richter cyclization for the synthesis of cinnolinones **72**.

Following a similar approach, in 2022, Balova's group reported the selective synthesis of cinnolinones **72**, using in this case aqueous H_2SO_4 as the acidic source.[57] More recently, Goswamy reported an alternative methodology for the synthesis of cinnolinones **72** in which again water also acts as the nucleophile, using $BF_3{\cdot}OEt_2$ and TBN as diazotizing reagents.[58] This method showed a broad substrate scope, accommodating a variety of substituents on both the terminal alkyne and the aniline ring, and affording the corresponding products in good to excellent yields.

Additionally, the literature reports several examples of the Richter reaction with the participation of other different nucleophiles. Among nitrogen-based nucleophiles, Wang and co-workers described a BF_3-promoted cascade reaction of 2-alkynylanilines **70** with nitriles **73** (Scheme 18).[59] This process involves an initial diazotization, promoted by *tert*-butyl nitrite TBN), followed by addition of the alkyne to the corresponding diazonium moiety in species **75**. Next, the nitrile that acts as solvent and nucleophile, undergoes an addition to the cationic intermediate **76**, leading to iminium species **77**. Hydration of **77** leads to the formation of imidic acid **78**, which upon tautomerization yields the final 4-amido-cinnolines **74**. Overall, the reaction exhibits broad functional group tolerance. However, slower reaction rates were observed when electron-withdrawing substituents were present at the alkyne or the aromatic ring (R^1 or R^2), and the reaction was unsuccessful with nitriles bearing electron-withdrawing groups (R^3).



Scheme 18 BF_3-promoted cascade reaction of 2-alkynylanilines **70** with nitriles **73**.

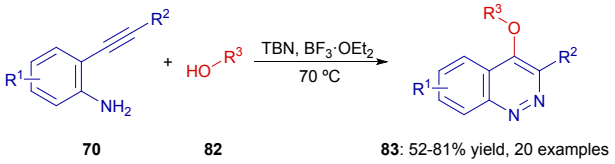


Scheme 19 Richter cyclization using 3-bromoaniline (**80**) as the nucleophilic partner.

Another example of the Richter reaction that involves the participation of nitrogen nucleophiles was reported by Feng in 2017, in this case employing an amine (Scheme 19).[60] The reaction comprises the diazotization of 2-alkynylaniline **79** with nitrous acid, generated in situ from $NaNO_2$ and HCl, in the presence of 3-bromoaniline (**80**), affording cinnoline **81** in moderate yield. However, one single example is provided in this report.

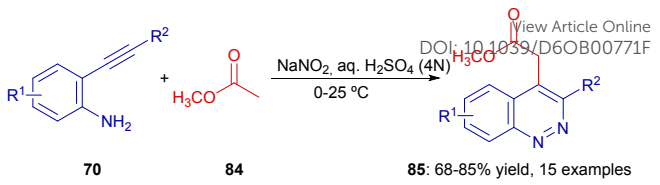
Following a similar approach, in 2024 Goswami's group reported several examples of the Richter reaction employing alcohols **82** as nucleophiles.[58] The synthetic procedure consists of the diazotization of 2-alkynylanilines **70** in alcoholic media using TBN and $BF_3{\cdot}OEt_2$, obtaining 4-oxycinnolines **83** in moderate to good yields (Scheme 20). Similarly to Wang's example, in this case the role of alcohols **82** is dual, behaving as a solvent and as a nucleophile. The reaction showed limitations when sterically demanding aromatic groups were introduced at the alkyne position. Similarly, the incorporation of a *tert*-butyl group led to a mixture of products including the corresponding cinnolinone due to the addition of water, as the participation of the alcoholic nucleophile is almost completely inhibited. Regarding the nucleophilic species, both aliphatic and aromatic alcohols were successfully employed; however, in the case of aromatic alcohols, the reaction proceeded smoothly only when weak-to-moderate electron-donating or electron-withdrawing substituents were present.

The use of enols as the nucleophilic source in a Richter cyclization was described in 2023 (Scheme 21).[61] Presumably, the reaction starts with the typical diazotization of 2-alkynylanilines **70** with $NaNO_2$ under aqueous acidic media. Under such acidic media, a nucleophilic enol species is generated from methyl acetate (**84**). In the presence of the enol nucleophile, the cyclization between the alkyne and diazonium moiety takes place, affording the corresponding cinnolines **85**. In general, the reaction shows comparable efficiency with both aromatic and aliphatic substituents at the R^2 position of 2-alkynylanilines **70**. However, a higher yield is observed when an



R^1 = H, 6-F, 6-Cl, 6-Me, 7-Me
R^2 = Ph, 3-MeC_6H_4, 4-BrC_6H_4, 3-FC_6H_4, 4-$CF_3C_6H_4$, ^{t}Bu
R^3 = CH_2CF_3, 2-BrC_6H_4, 3-$CF_3C_6H_4$, 4-MeC_6H_4, 2-IC_6H_4

Scheme 20 Richter cyclization using alcohols **82** as nucleophiles.



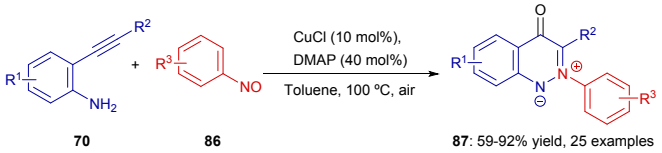
R^1 = H, 6-OMe, 7-F, 7-Cl
R^2 = Ph, 4-ClC_6H_4, 2,5-$Me_2C_6H_3$, 3-OHC_6H_4, 2-$CO_2HC_6H_4$, 2-Naphthyl, 2-Pyrimidyl, Me, Et, Pr, ^{i}Bu

Scheme 21 Richter cyclization using an enol as the nucleophile.

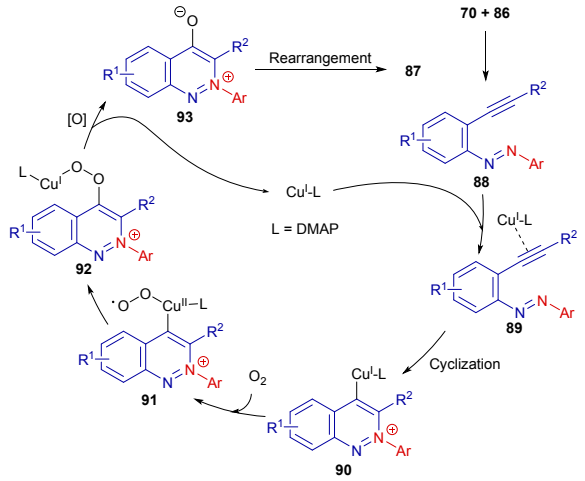
electron-donating group (R^1 = 6-OMe) is present on the aromatic ring.

In 2021, Wang and Yu reported an efficient Cu(I)/DMAP/air system for the one-pot synthesis of 4-oxo-4*H*-cinnolin-2-ium-1-ides **87** from 2-alkynylanilines **70** and nitrosobenzenes **86** (Scheme 22).[62] The reaction begins with the condensation of the starting materials to form diazene **88**, which forms a complex with Cu(I) and DMAP yielding species **89**. Subsequent intramolecular cyclization forms intermediate **90**, which is oxidized by oxygen from air to give peroxycopper species **91**. Subsequent isomerization affords a new peroxide **92**, and the O–O bond cleavage leads to intermediate **93**. Finally, rearrangement of **93** delivers the target cinnoline derivatives **87**. Although the mechanism proposed by the authors does not involve the generation of a diazonium intermediate species, this reaction can be considered as a Richter-type cyclization.

The procedure works efficiently with aryl, heteroaryl, and alkyl substituents at the alkyne position (R^2), irrespective of the electronic properties of the substituent. However, steric effects



R^1 = H, 6-Me, 6-F, 6-Br, 6-NO_2, 6-CN, 6-CO_2Me, 7-Cl, 5-Cl, 6,8-Cl_2
R^2 = Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-PhC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 4-$CO_2MeC_6H_4$, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 2-Thiophenyl, 3-Py, ^{c}Pr
R^3 = H, 4-Me, 2-Me, 4-OMe, 2-OMe, 4-Cl, 4-Br



Scheme 22 Copper-catalyzed aerobic oxidative cyclization of 2-alkynylanilines **70**.

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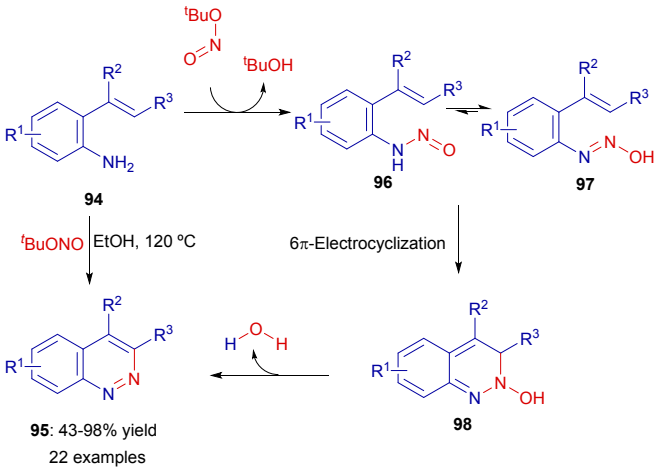
of the substituents either in 2-alkynylanilines **70** or nitrosobenzenes **86** had some impact on the reaction, with diminished yields observed when aromatic rings are *ortho*-substituted.

In addition to the Richter reaction, other approaches based on intramolecular cyclizations of *ortho*-substituted arenediazonium salts have also been reported. The Widman-Stoermer annulation involves an intramolecular attack of a carbon-carbon double bond in *ortho*-vinylarenediazonium derivatives. [20]

In 2017 Yan and col. reported *tert*-butyl nitrite as the nitrogen source for the synthesis of cinnolines **95** from *ortho*-vinylanilines **94** in moderate to excellent yields (Scheme 23).[63] Based on computational studies and some control experiments, the authors propose a plausible mechanism in which nitrosamine species **96** would be firstly generated from aniline **94** through the decomposition of TBN. The computational calculations indicate that nitrosamine **96** would be in equilibrium with its hydroxydiazene tautomer **97**, in which the 6π-electrocyclization reaction is substantially favoured, leading to *N*-hydroxy-cinnoline derivative **98**. Finally, a spontaneous dehydration, driven by the formation of an aromatic structure bearing 10π electrons yields cinnolines **95**. Although such reaction does not strictly proceed through a diazonium species, it can be classified as a variant of a Widman-Stoermer annulation reaction. However, although there is not an acidic source in the media which may lead to the generation of nitrous acid, the classical course of this reaction through the diazonium intermediate cannot be ruled out, since it is well known that aromatic amines, in the presence of TBN, are able to provide the aryldiazonium *tert*-butoxides through a radical pathway.[64]

The synthetic protocol is applicable to a wide variety of aromatic amines **94** bearing electron donating groups and halogen atoms at the *ortho* and *para* positions (R^1). However, the reaction fails if anilines bearing strong electron withdrawing substituents are used (i.e. $R^1 = NO_2$). Regarding the vinylic unit, the presence of



R^1 = H, 2-Me, 4-Me, 2,3-Me_2, 2-^{i}Pr, 4-^{i}Pr, 4-^{t}Bu, 4-OMe, 4-Ph, 2-F, 4-F, 2-Cl, 4-Cl, 2-Br, 4-Br
R^2 = Ph, 4-MeC_6H_4, 4-PrC_6H_4, 2-FC_6H_4, 2-ClC_6H_4, Me
R^3 = H, Me

Scheme 23 Synthesis of cinnolines **95** through Widman-Stoermer reaction.

aromatic substituents at the α-carbon (R^2) is well tolerated, while the presence of an aliphatic substituent results in a drastic drop in the yield. In addition, the substitution of the β-carbon (R^3) with an aliphatic substituent still leads to the formation of cinnoline derivative **95** in very good yield, although the placement of an aromatic group at this position prevents the formation of cinnolines **95** and only traces of the target compounds are observed (Scheme 23).

Very recently, the same reaction has been described, using in this case an excess of TBN (3 equiv.) and CH_2Cl_2 at 50 °C as solvent.[65] Besides the substitution pattern described in the previous work, under these conditions the authors are able to obtain cinnolines **95** starting from deactivated anilines **94** (R^1 = NO_2, CO_2Me) in very good to excellent yields.

It is well known that the Widman-Stoermer reaction is facilitated by the presence of electron-donating groups at the α-carbon of the styrene, while the presence of alkyl or (hetero)aryl substituents at the β-carbon complicates the cyclization and electron-withdrawing substituents at any position avoid the reaction. This suggests that electron rich C=C bonds at the *ortho* position of the arenediazonium derivatives are highly desirable. Considering this, *ortho*-byaryldiazonium species, especially those containing electron-donating groups, are excellent precursors of polycyclic cinnolines. Accordingly, *ortho*-biarylamines **99** in the presence of a diazotization agent may be converted into their *ortho*-biaryldiazonium derivatives **100**, which can be sometimes isolated, although in most of the cases they spontaneously evolve to the corresponding polycyclic cinnoline derivatives **101-112** (Scheme 24). Thus, benzofused cinnoline derivatives **101** can be obtained in good to very good yields by the diazotization of *ortho*-biarylamines **99**. The diazonium intermediate **100** can be isolated as the tetrafluoroborate salt (X = BF_4, Scheme 24a) if nitrous acid is generated from sodium nitrite and tetrafluoroboric acid,[66] while if hydrochloric acid is used instead, the reaction yields directly cinnoline derivatives **102-104** (X = Cl, Scheme 24b).[67] Alternatively, *ortho*-biaryldiazonium species **100** can be generated in situ using nitrosyl tetrafluoroborate in acetonitrile affording cinnoline derivatives **105-108** without the isolation of diazonium intermediate **100** (X = BF_4, Scheme 24c).[68] Similarly, anthracene-fused cinnolines **109** are obtained by the diazotization of *ortho*-anthracenyl anilines **99** with sodium nitrite and hydrochloric acid, followed by thermal treatment of the diazonium intermediate in dichloromethane (X = Cl, Scheme 24d).[69] In addition, more complex polycyclic cinnoline derivatives **110-112** are obtained by diazotization of dibenzoisoquinoline-4,6-dione[70] or benzocarbazol[71] derived arylamines **99** with nitrosyl tetrafluoroborate or sodium nitrite in sulphuric acid media, respectively (X = BF_4, SO_4, Scheme 24e,f). Remarkably, cinnolino[3,4-α]carbazoles **112** show a potent cytotoxic activity towards osteosarcoma, hepatocellular carcinoma, lung and colon cancer cells.

It should be noted how all the reported examples of Widman-Stoermer reaction using *ortho*-biaryldiazonium derivatives bear very convenient activating groups at the aromatic ring (Alk, NR_2,

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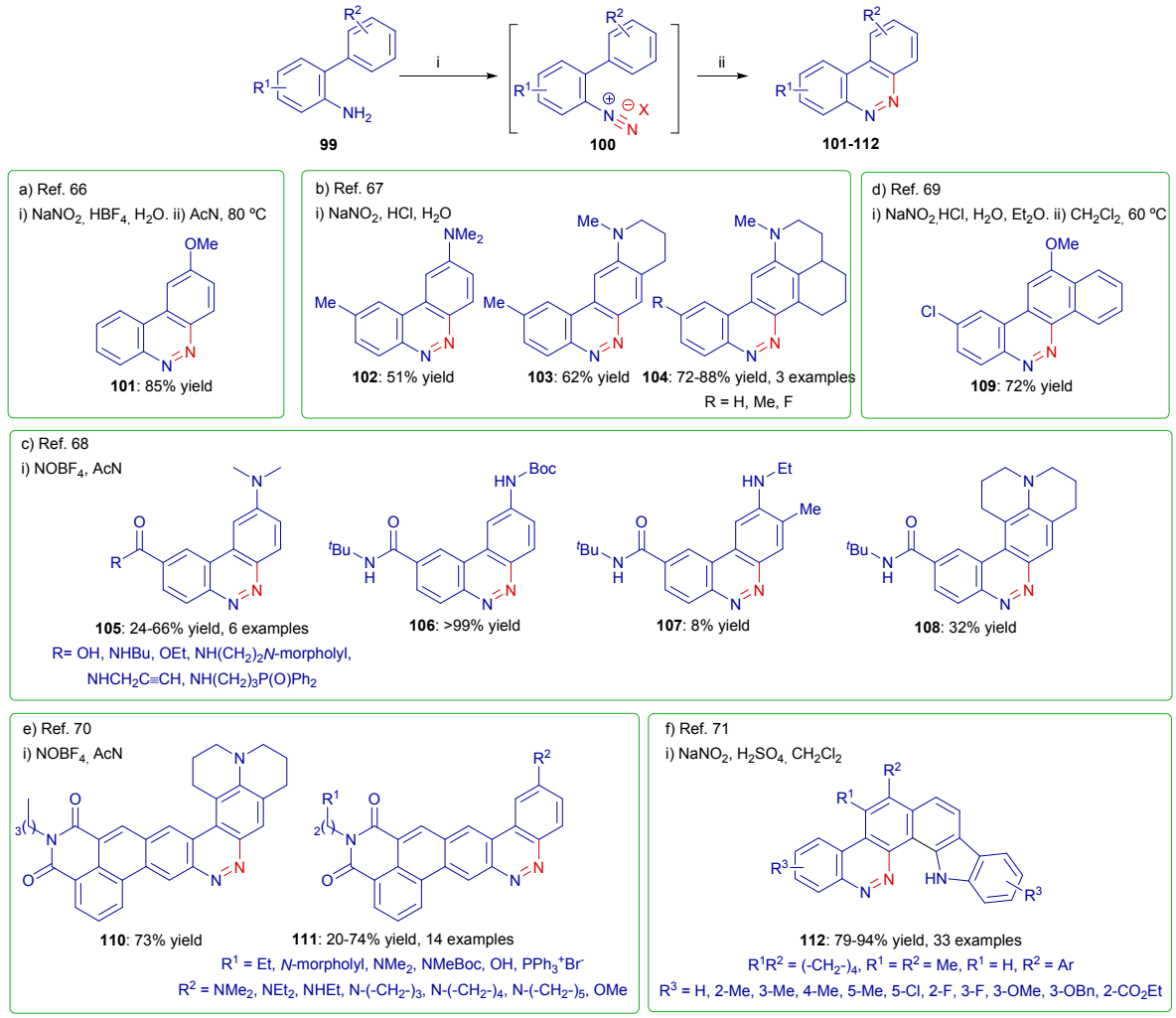
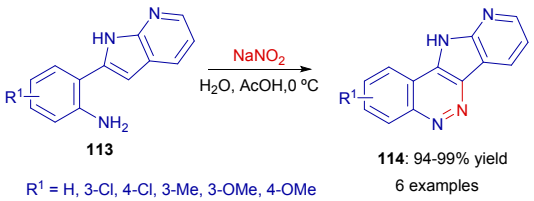
OR), thus providing the required electronic density to the carbon involved in the cyclization process.



Scheme 24 Widman-Stoermer reaction of *ortho*-biarylamines **99**.

Considering that, as it has been mentioned above, a high electron density at the carbon-carbon double bond involved in the electrocyclization process with the diazonium moiety favours the Widman-Stoermer reaction, the use of anilines bearing electron-rich heteroaromatic substituents at the *ortho* position is a very suitable modification for the preparation of heteroaromatic polycyclic cinnolines. Accordingly, the diazotization of 7-azaindole substituted anilines **113** with sodium nitrite in acetic acid media provides 7-azaindole-fused cinnolines **114** in excellent yields (Scheme 25).[72] Remarkably, 11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*c*]cinnolines **114** exhibit nanomolar cytotoxic activity towards several cancer cell lines, showing a particular efficacy against the leukemia subpanel.



Scheme 25 Synthesis of 7-azaindole-fused cinnolines **114**.

Within the preparation of cinnolines through the Widman–Stoermer reaction using electron-rich *ortho*-substituted heteroaromatic aryldiazonium species, complex dimeric cinnolines **116** with a pyrrolo[3,2-*b*]pyrrole core have been prepared through the diazotization of the parent aniline derivatives **115** using TBN as the nitrogen source (Scheme 26).[73] The reaction proceeds in a mixture THF/AcN as solvent, leading to dimeric cinnolines **116** in moderate to good yields.

Closely related to the Widman-Stoermer reaction, the Borsche-Herbert (or Borsche-Koelsch) reaction comprises the diazotization of *ortho*-aminoarylketones.[21] Indeed, the

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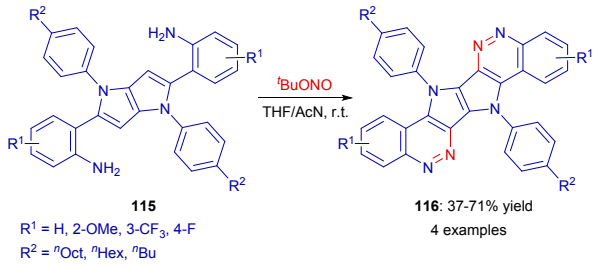
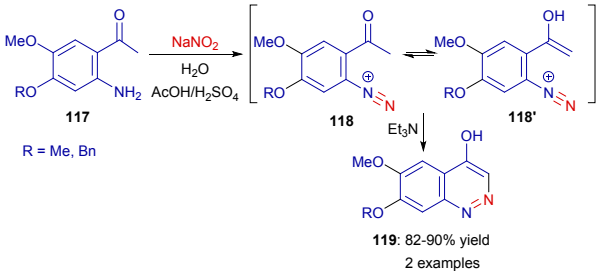


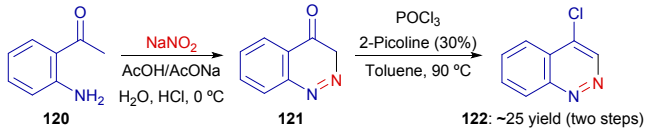
Scheme 26 Synthesis of dimeric pyrrole-fused cinnolines **116**.



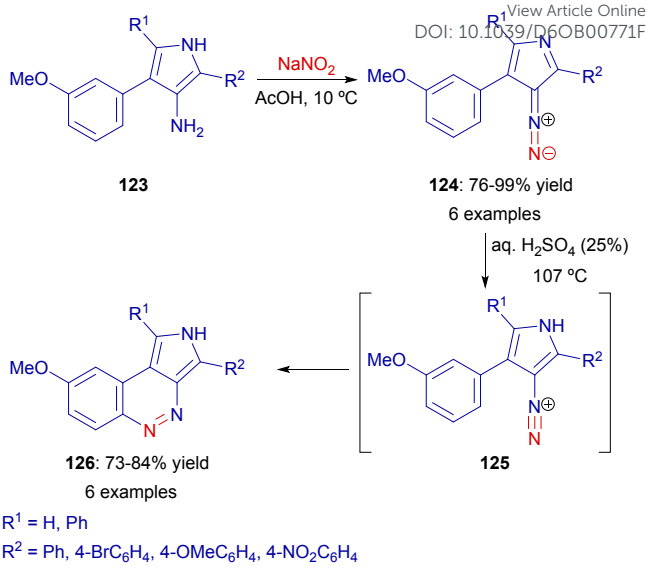
Scheme 27 Synthesis of cinnolines **119** through Borsche-Herbert reaction.

mechanism takes place through the enol species, which is in fact an activated alkene. Following this approach, the diazotization of *ortho*-aminoarylketones **117** with sodium nitrite in a mixture $AcOH/H_2SO_4$, leads to the generation of acetophenone derived diazonium derivative **118** which, through its enol tautomer **118'**, renders 4-hydroxycinnolines **119** (Scheme 27).[74] Noticeably, substrates **119** have been used as intermediates for the preparation of benzimidazole analogues as phosphodiesterase 10A inhibitors.

Another recent example of a Borsche-Herbert reaction is the diazotization of *ortho*-aminoacetophenone (**120**) with sodium nitrite in a mixture AcOH/AcONa, leading to cinnolone **121**. The subsequent treatment of compound **121** with phosphorus oxychloride affords 4-chlorocinnoline **122**, that has been used as intermediate in the synthesis of cinnoline sulfonamides as anticancer agents (Scheme 28).[75] However, in this report the authors do not provide exact yields for their synthesis.



Scheme 28 Synthesis of cinnoline **122** from cinnolone **121** through a Borsche-Herbert approach.



Scheme 29 Synthesis of cinnolines **126**.

A particular reaction involving intramolecular cyclization of azo compounds is the azo coupling of 3-aryldiazopyrroles **124** (Scheme 29).[76] Aminopyrroles **123** are converted into diazopyrroles **124** by the reaction with sodium nitrite in acetic acid. Next, the cyclization of diazopyrroles **124** to pyrrole-fused cinnolines **126** is performed across the formation of their diazonium salt **125** in refluxing aqueous sulfuric acid (25%). The singularity of this reaction lies in the fact that, unlike the Widman-Stoermer and Borsche-Herbert reactions, where the key step consists of the formation of a C–N bond between N2 and C3 of the cinnoline core, this strategy involves the formation of a new bond between N1 and C8a of the aromatic ring.

4. Final Remarks

This review has provided a focused and critical overview of recent advances in the use of azo derivatives as key building blocks for the synthesis of cinnoline derivatives. Some methodologies have been developed and improved for this purpose, offering valuable tools for the efficient construction of these scaffolds. Given the important role of the cinnoline ring in drug discovery, due to its capacity to interact with a wide range of biological targets, access to diverse and reliable synthetic strategies represents a significant advantage for synthetic chemists. Notably, a number of efficient and outstanding methodologies have been highlighted throughout this review. By organizing the discussion around annulation and intramolecular cyclization processes, clear trends in reactivity and strategy development have emerged, particularly among contributions reported since 2008.

The synthesis of cinnoline and cinnoline-fused heterocyclic frameworks has undergone significant evolution, with recent efforts increasingly directed toward more efficient and sustainable methodologies. Among these, transition-metal-catalyzed C–H activation has proven to be a particularly

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powerful and versatile approach, enabling atom-economical transformations, broad functional group compatibility, and enhanced synthetic flexibility. Nevertheless, despite the remarkable progress achieved, several challenges remain that warrant further attention.

Looking forward, continued innovation in catalytic systems, together with improvements in sustainability and the development of more selective and versatile transformations, is expected to further expand the synthetic utility of these approaches. Future research in this field would benefit from a stronger emphasis on broadening substrate scope and deepening mechanistic understanding. In addition, the development of greener and scalable protocols will be crucial for the practical implementation of cinnoline synthesis in industrial and pharmaceutical context. Furthermore, the use of azo derivatives as dienes in [4+2] cycloaddition reactions remains largely underexplored and represents a promising area that deserves greater attention. Such advances are likely to further consolidate the role of cinnoline derivatives as valuable scaffolds in medicinal chemistry and related fields.

Author contributions

All the authors contributed equally.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support PID2024-159921NB-I00 funded by the Ministerio de Ciencia, Innovación y Universidades MICIU/AEI/10.13039/501100011033 and by "ERDF A way of making Europe", and by Gobierno Vasco (GV, IT1701-22; UPV-EHU) is gratefully acknowledged.

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View Article Online
DOI: 10.1039/D6OB00771F

Data availability statement

All data analyzed in this review are included in the published literature cited within the reference lis