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Catalyst-free microwave-assisted azo-Povarov reaction of *N*-carbonyl aryldiazenes with *trans*-cyclooctene to access ring-fused cinnoline derivatives†

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A previously unprecedented azo-Povarov reaction between *N*-carbonyl aryldiazenes and *trans*-cyclooctene derivatives has been developed. The participation of these aryldiazenes in the uncatalyzed [4 + 2] cycloaddition reaction has enabled the construction of a variety of appealing fused cinnoline derivatives, with yields ranging from 34% to 91% across a broad substrate scope. The starting materials are cost-effective and readily accessible, while the reaction conditions and procedures are straightforward, requiring no external catalysts. Moreover, the synthetic significance of this methodology has been demonstrated through a gram-scale azo-Povarov reaction and further derivatizations of the resulting *N*-containing heterocycles.

Introduction

Cinnolines exhibit a broad range of pharmacological activities, including antitumor, anti-inflammatory, analgesic, antibacterial, anticonvulsant, antihypertensive and antifungal properties.[1] Representative drug candidates featuring cinnoline scaffolds are outlined in Fig. 1. For instance, compounds **I** and **II** can act as selective $GABA_A$ receptors allosteric modulators for the treatment of anxiety and other psychiatric disorders.[2] Meanwhile, the cinnoline-isoxazole hybrid compound **III** presents greater *in vitro* antibacterial potency against both Gram-positive and Gram-negative bacteria compared to the standard drug norfloxacin.[3] Alternatively, cinnoline derivatives have been designed as promising candidates for anticancer drugs. In this context, cinnoline derivative **IV**, an inhibitor of colony-stimulating factor 1 receptor (CSF-1R) tyrosine kinase, plays a significant role in both inflammation processes and cancer.[4] Whereas, ARC-31 **V** exhibits a greater ability to trigger DNA cleavage in the presence of Topoisomerase I (TOP1).[5] In addition, cinnoline carboxamide **VI** is a highly potent and selective ataxia telangiectasia mutated (ATM) kinase inhibitor, has demonstrated tumor regression in a colorectal cancer cell line and is currently undergoing preclinical evaluation.[6]

As a result, considerable focus has been directed to the efficient construction of the cinnoline scaffold. Despite this, the conventional methods for accessing cinnoline derivatives, such as intermolecular annulation reactions requiring prefunctionalization of nitriles,[2] aryl hydrazines,[7] and aryl hydrazones,[8] or cyclization of phenyldiazonium ions with highly active triazenes *ortho* to a terminal phenylacetylene,[9] generally exhibit a limited synthetic applicability and involve complex multi-step reaction sequences, making them unsuitable as general synthetic approaches. Moreover, other improved methods previously described for the synthesis of heterocycles,

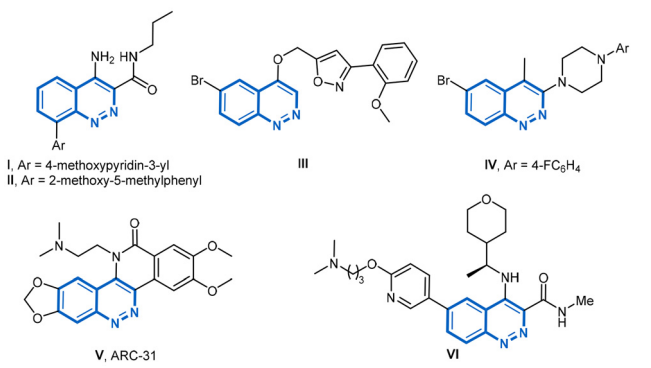

Fig. 1 Selected examples of cinnoline derivatives with high potential for therapeutic applications.

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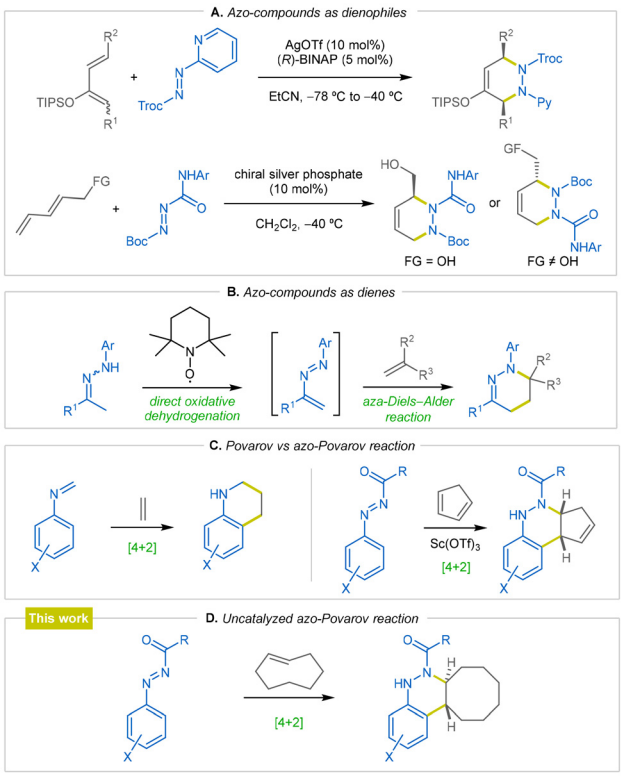
particularly those involving transition-metal-catalyzed C–H bond activation,[10] have emerged as a powerful tool for constructing the valuable cinnoline skeleton. In recent years, C–H activation and functionalization reactions catalyzed by stable rhodium(III) complexes have experienced a rapid development. The Rh-catalyzed cascade annulation reaction of azobenzenes with terminal alkynes for the preparation of indolo[1,2-*b*]cinnolines, developed by Yuan *et al.*;[11] the annulation of *N*-phenylindazoles and diazo compounds for the synthesis of indazolo[2,1-*a*]cinnolines;[12] and the construction of pyrazolo[1,2-*a*]cinnolines through Rh-catalyzed annulation of pyrazoline derivatives with sulfoxonium ylides, improved by Liu, Wang *et al.*,[13] are only a few representative examples that have been recently reported.[14] Iridium is another noble metal used with success in metal-catalyzed C–H activation reactions for the synthesis of cinnoline derivatives.[14c,15] However, alternative cost-effective transition metals, such as Pd[16] or Ru,[12,17] have emerged as appealing catalysts for C–H bond activation to construct the cinnoline backbone.

Additionally, azo compounds have found extensive applications in cycloaddition reactions with diverse partners for the preparation of a number of nitrogen-containing heterocyclic compounds. For instance, in 2006, Yamamoto *et al.* reported a highly regio-, diastereo- and enantioselective azo-Diels–Alder reaction as an efficient synthetic route to a series of chiral 1,4-diamines (Scheme 1A).[18] Similarly, chiral silver phosphate species effectively catalyze a highly regio- and enantioselective azo hetero-Diels–Alder reaction of diazenes, affording high product yields with excellent *ee* values (Scheme 1A).[19] Furthermore, azo compounds have been also widely used as dienes in [4 + 2] cycloaddition reactions. Accordingly, the synthesis of tetrahydropyridazines has been achieved *via* azo-Diels–Alder reaction of olefins with azoalkenes, which were previously generated through the direct oxidative dehydrogenation of ketohydrazones using TEMPO (Scheme 1B).[20] In this research field, in the past, we have demonstrated the value of phosphorus-substituted azoalkenes in the synthesis of functionalized mercapto diketones,[21] α-amino phosphonates,[22] and various hetereocyclic compounds, such as pyrazine derivatives[23,24] and quinoxalines.[24]

On the other hand, the Povarov reaction[25] between aldimines and an olefinic or acetylenic component represents a powerful approach for the construction of substances containing N-heterocyclic frameworks, providing access to tetrahydroquinolines, quinolines and julolidines in a single step (Scheme 1C). Despite the typical advantages offered by C–H bond activation reactions for the preparation of cinnoline scaffolds,[11–17] such as a high regioselectivity, atom economy, and fewer reaction steps, we have recently accomplished the first azo-version of the Povarov reaction (azo-Povarov reaction). This involves a $Sc(OTf)_3$-catalyzed [4 + 2] cycloaddition reaction of cyclopentadiene with *N*-carbonyl aryldiazenes, that act as 4π-electron donors[26] (Scheme 1C).

Inspired by our previous studies on the chemistry of azoalkenes, herein we report a practical, microwave-assisted, and catalyst-free method for synthesizing cinnoline scaffolds. More precisely, our novel method consists of a [4 + 2] cycloaddition reaction (azo-Povarov reaction) between *N*-carbonyl aryldiazenes and *trans*-cyclooctene derivatives (Scheme 1D).



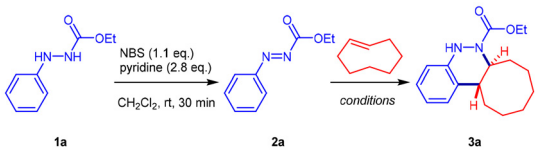
Scheme 1 Conceptualization of this work.

Results and discussion

Following our first example using cyclopendadiene as the dienophile component, we attempted to expand the scope of the azo-Povarov reaction using a broader variety of alkenes. However, substrates such as cyclopentene, indene, styrene, norbornene, phenylacetylene, buta-1,3-diene, enamines, enol ethers, and *cis*-cyclooctene all failed to deliver the desired cinnoline derivatives when reacted with aryldiazenes under catalyzed azo-Povarov conditions.[26] Consequently, strained alkenes were selected as dienophiles for the azo-Provarov reaction.

Our initial efforts were focused on optimizing the reaction conditions, using aryldiazene carboxylate **2a** and *trans*-cyclooctene as model substrates (Table 1). The starting aryldiazene carboxylates **2** can be straightforwardly synthesized through the selective oxidation of aromatic hydrazines **1** using *N*-bromosuccinimide (NBS)/Py.[27] According to our previous work,[26] we began our studies by exploring the [4 + 2] cycloaddition reaction of **2a** (0.5 mmol) with *trans*-cyclooctene (0.75 mmol) in the presence of $Sc(OTf)_3$ (1.2 equiv.) in chloroform at room temperature. To our delight, after 0.5 h, octahydrocycloocta[*c*]cinnoline **3a** was isolated in 56% yield (Table 1, entry 1). As previously reported for the $Sc(OTf)_3$-catalyzed [4 +

Table 1 Optimization of the reaction conditions



Entry[a]	Solvent	Conditions	Time (h)	Yield[b] (%)
1	$CHCl_3$	$Sc(OTf)_3$ (1.2 equiv.), rt	0.5	56
2	$CHCl_3$	$Sc(OTf)_3$ (0.2 equiv.), rt	72	19
3	$CHCl_3$	61 °C	240	98
4	$CHCl_3$	86 °C, MW	16	89
5	**$CHCl_3$**	**111 °C, MW**	**4**	**84**
6	DCE	133 °C, MW	2	74[c]
7	H_2O	150 °C, MW	1.5	26
8	H_2O	125 °C, MW, TBAB (0.1 mol%)	2.5	72
9	H_2O	40 °C, TBAB (0.1 mol%)	216	48[c]
10	PBS	40 °C	408	44[c]

[a] Unless otherwise noted, reactions were conducted on a 0.5 mmol scale and 3 mL of the corresponding solvent. [b] Isolated yields. [c] Some starting materials were observed in the crude reaction.

2] cycloaddition of aryldiazene carboxylates with cyclopentadiene,[26] when exploring the catalyst loading, the use of 1.2 equiv. of the catalyst appeared to be essential in the current reaction. A catalyst loading of 20 mol% led to a significant decrease in the reaction yield and required a longer reaction time (Table 1, entry 2). Considering the high reactivity expected in the strained alkene bond of *trans*-cyclooctene, we then directed our efforts towards the uncatalyzed version of the azo-Povarov reaction, which has not been described thus far. However, no reaction occurred when aryldiazene **2a** was treated with *trans*-cyclooctene at room temperature. Interestingly, when using refluxing chloroform as the solvent, cinnoline derivative **3a** was achieved in very high yield (98%), although a time-consuming reaction of 10 days was required for full conversion (Table 1, entry 3).

Microwave-assisted synthesis has emerged as an important tool for the synthesis of heterocycles in an eco-friendly and energy-efficient manner.[28] It offers several advantages, such as mild reaction conditions, short reaction times, high yields, homogeneous heat distribution leading to lower side reaction, better control of reaction temperature, and good functional group tolerance. Recently, significant progress has been made in the use of microwaves for the synthesis of heterocycles.[29] For this reason, we next explored the uncatalyzed-azo-Povarov reaction assisted by microwaves. A mixture of *N*-carbonyl aryldiazene **2a** and *trans*-cyclooctene was subjected to microwave heating at 86 °C (200 W) and, after 16 h, a very good yield (89%) of compound **3a** was obtained under moderate reaction conditions (Table 1, entry 4). In view of the acceleration observed under microwave irradiation, we then optimized the diverse reaction parameters using microwaves. Notably, by increasing the temperature to 111 °C, we reduced the reaction time from 16 h to 4 h, while maintaining a similar chemical yield (84%) of **3a**, as shown in Entry 5.

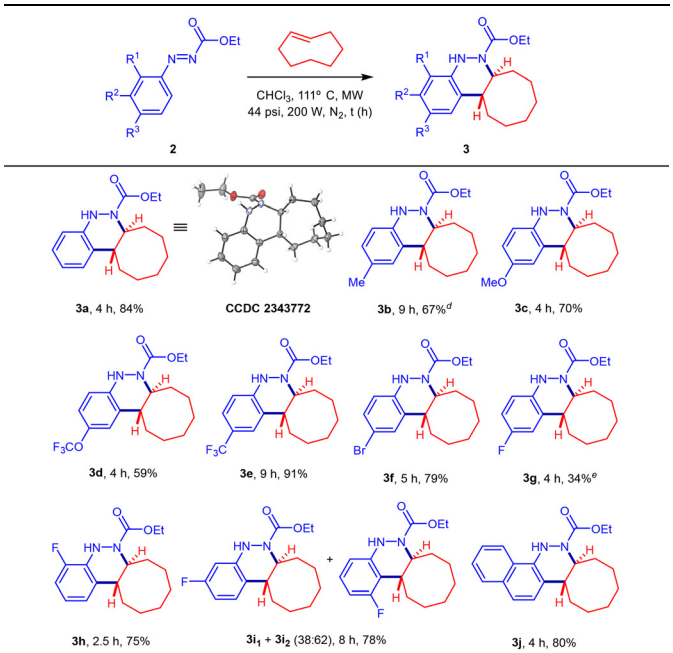
Next, we investigated the influence of different solvents and the reaction temperatures on the reaction yield. It was observed that compound **3a** was attained with a slightly lower yield (74%) when 1,2-dichloroethane (DCE) was used as the solvent under microwave irradiation at 133 °C during the cycloaddition reaction (Table 1, entry 6).

The use of environmentally friendly solvents in organic reactions is highly desirable.[30] For this reason, we next tested water as the solvent in the model [4 + 2] cycloaddition reaction. However, the use of water at 150 °C reduced the reaction time but led to a significant decrease in the chemical yield (see entry 7). Nevertheless, the addition of tetrabutylammonium bromide (TBAB, 0.1 mol%) as an additive in water promoted the azo-Povarov process, yielding **3a** in 72% with a reduced reaction time of 2.5 h (Table 1, entry 8). It should be noted that under identical reaction conditions without microwave irradiation, a considerable increase in the reaction time was required, obtaining only a 48% yield of **3a** (see entry 9), thus demonstrating the benefits of using microwaves in this process.

In addition, bioorthogonal chemistry encompasses a class of highly efficient chemical reactions that occur rapidly and selectively in biological environments, without interfering with endogenous functional groups through side reactions.[31] In this context, we attempted to evaluate the tolerance of this procedure in biological media. As reported in Table 1, entry 10, we were pleased to observe that under phosphate-buffered saline medium (PBS, pH = 7.2), the azo-Povarov reaction of aryldiazene **2a** and *trans*-cyclooctene at 40 °C was moderately efficient, yielding 44% of **3a** after 17 days.

Considering that the preliminary studies suggested chloroform as the optimal solvent and 111 °C as the ideal temperature for the microwave-assisted [4 + 2] cycloaddition, we adopted these reaction conditions for further investigations. Accordingly, the substrate scope of aryldiazene carboxylates was studied as shown in Table 2. *N*-Aryldiazenes bearing activating groups (Me, OMe, OCF_3, **2b–2d**), deactivating groups (CF_3, **2e**), or halogen-substituted groups (Br, F, **2f–2g**) at the *para* position of the phenyl ring produced the target cinnoline derivatives **3b–3g** in yields ranging from 34% to 91%. The 4-trifluoromethyl-substituted derivative **3e** was achieved with the highest yield (91%). In terms of electronic and steric effects, no significant influence was observed in the case of *ortho*- or *meta*-substituted compounds. For example, compound **2h** bearing a fluorine atom at the *ortho*-position of the phenyl ring (R^1 = F, R^2 = R^3 = H), reacted with *trans*-cyclooctene to afford substrate **3h** in good yield (Table 2). In addition, a separable mixture of cinnoline derivatives **3i$_1$** (30% yield) and **3i$_2$** (48% yield) was obtained in the cycloaddition reaction of *meta*-F-substituted *N*-aryldiazene **2i** with *trans*-cyclooctene. As evidenced from the scope of the reaction, halogen substituents were found to be suitable, making the synthetic approach useful in organic synthesis due to the potential modifications at the halogenated positions. Finally, the use of 1-naphthyl derived *N*-aryldiazene **2j** was also well tolerated in this transformation, affording the corresponding octahydrocycloocta[*c*]cinnoline **3j** in good yield (Table 2). These results showed that

Table 2 Substrate scope of aromatic ring in aryldiazene carboxylates **2**[a,b,c,d,e]



[a] Reaction conditions: **2** (0.5 mmol), *trans*-cyclooctene (0.75 mmol) in $CHCl_3$ (1 mL) at 111 °C and 200 W, under microwave irradiation. [b] Isolated yield. [c] See ESI† for experimental details. [d] Some starting material **2b** was observed in the crude reaction. [e] Some reduced starting material (functionalized hydrazine **1g**) was observed in the crude reaction.

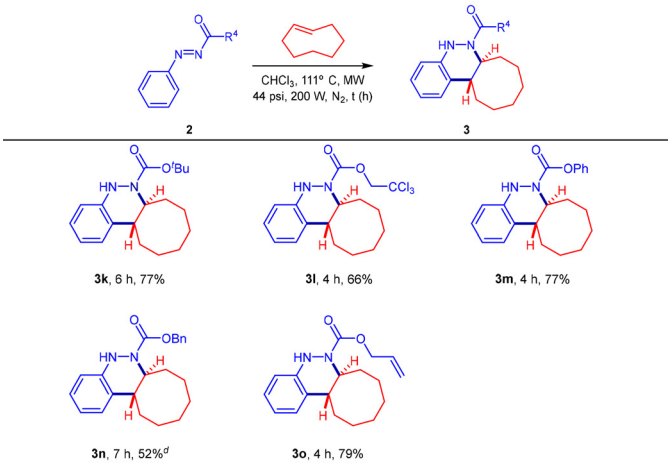
the electron density of substituents or their position on the benzene ring (2-, 3-, or 4-position) does not significantly influence the efficiency of this reaction.

Cinnoline derivatives **3**, resulting from the [4 + 2] cycloaddition reaction, were characterized based on their spectroscopic data and HRMS (see ESI† for details). The most characteristic chemical shifts for compound **3a** in the ^{1}H NMR spectrum are the two well-resolved double triplets at δ_H = 4.52 and 2.84 ppm, corresponding to H6a and H12a, respectively, with a reciprocal coupling constant of $^3J_{HH}$ = 11.4 Hz, characteristic of a *trans*-fused ring. The NH group of the ring in **3a** appears as broad singlet at δ_H = 6.31 ppm and, as expected, it exchanges with D_2O. In the ^{13}C NMR spectrum, the formation of **3a** is evident from the presence of two signals corresponding to the tertiary carbons of the ring junctions, C6a and C12a, which appear at δ_C = 55.8 and 34.9 ppm, respectively. The carbonyl group shows a chemical shift at δ_C = 155.6 ppm, while the quaternary carbon corresponding to C4a resonates at δ_C = 146.2 ppm. The multiplicity of all the signals in the ^{13}C NMR spectrum were confirmed by DEPT experiments. Moreover, the structure of **3a** has been unequivocally established through X-ray crystallography. The CIF data is provided in ESI,† and the ORTEP drawing of **3a** is depicted in Table 2.

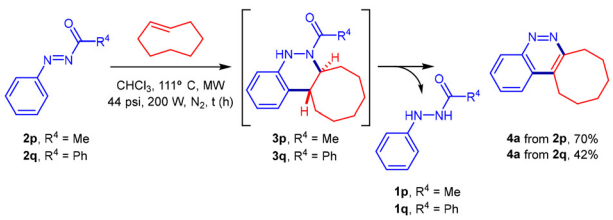
Motivated by the aforementioned results obtained in the uncatalyzed [4 + 2] cycloaddition reaction between aryldiazene carboxylates **2** and *trans*-cyclooctene, we next proceeded to explore the substrate scope by varying the functional group (R^4) at the nitrogen atom of the aryldiazene **2** (Table 3). In this regard, a selection of several protecting groups at the nitrogen atom of the *N*-aryldiazene was well tolerated in this transformation, affording the corresponding octahydrocycloocta[*c*]cinnolines (**3k–3o**) in good yields. For instance, using microwave irradiation under the optimized reaction conditions, the [4 + 2] cycloaddition reaction of *N*-Boc aryldiazene **2k** (R^4 = O^{t}Bu) with *trans*-cyclooctene afforded cycloadduct **3k** in 77% yield. However, a slight drop in the reaction yield was observed for *N*-Troc-derivative **3l** (66%) or *N*-Cbz-cinnoline derivative **3n** (52%) when using aryldiazene carboxylates **2l** or **2n**, bearing R^4 = 2,2,2-trichloro-ethoxy or OBn, respectively. Furthermore, the cycloaddition reactions of other aryldiazene carboxylates (**2m**, **2o**) with functional groups such as R^4 = OPh and Oallyl (*N*-Alloc) were also successful, yielding cinnoline derivatives **3m** and **3o** in good yields (Table 3).

In addition, we also examined the scope of the reaction using *N*-carbonyl aryldiazenes **2p** (R^4 = Me) and **2q** (R^4 = Ph) as substrates, as shown in Scheme 2. Under microwave irradiation and adopting similar reaction conditions as before, *N*-acetyl aryldiazene **2p** (R^4 = Me), derived from *N*′-phenylaceto-

Table 3 Azo-Povarov reaction with different groups (R^4) at the nitrogen atom of *N*-aryldiazene carboxylates **2**[a,b,c,d]



[a] Reaction conditions: **2** (0.5 mmol), *trans*-cyclooctene (0.75 mmol) in $CHCl_3$ (1 mL) at 111 °C and 200 W, under N_2 and microwave irradiation. [b] Isolated yield. [c] See ESI† for experimental details. [d] For a full conversion 3 equivalents of *trans*-cyclooctene were needed.



Scheme 2 Azo-Povarov reaction using *N*-acyl or *N*-benzoyl aryldiazenes.

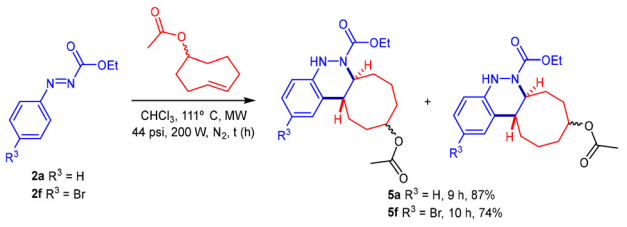
hydrazide, reacted with *trans*-cyclooctene to afford, in only 0.5 h, hexahydrocycloocta[*c*]cinnoline **4a** in 70% yield (based in the amount of compound **4a** formed and the functionalized hydrazine **1p** recovered). The oxidation of octahydrocycloocta[*c*]cinnoline **3p** to yield the cinnoline derivative **4a** was accompanied by the formation of some *N*′-phenylacetohydrazide **1p**, resulting from the reduction of the starting *N*-acetyl aryldiazene **2p**. The same behavior was observed when *N*-benzoyl aryldiazene **2q** (R^4 = Ph), derived from *N*′-phenylbenzohydrazide, was used in the reaction, yielding the same product **4a** in 42% yield (Scheme 2). When the reaction was performed using conventional heating (refluxing chloroform for 30 h), 98% of **4a** was obtained after treatment of diazene **2p** with *trans*-cyclooctene.

Encouraged by the satisfactory results using *trans*-cyclooctene, we attempted to extend the substrate scope to other *trans*-cyclooctene derivatives. The optimal reaction conditions were applied to the uncatalyzed [4 + 2] cycloaddition reaction between aryldiazene carboxylates **2** and 5-acetyl-substituted *trans*-cyclooctene, as shown in Scheme 3. In the case of aryldiazene carboxylate **2a**, 87% yield of cinnoline derivative **5a** was obtained. However, the cycloaddition reaction was not regioselective, leading to a mixture of two regioisomers of **5a**. Additionally, for each regioisomer, two different diastereoisomers were formed, distinguished by the stereochemistry of the acetyl substituent in *trans*-cyclooctene. The formation of these diastereoisomers in the final product highlights the complexity of the reaction, resulting from the lack of regioselectivity and the formation of multiple diastereoisomers. Notably, the bromo group demonstrates good tolerance, as compound **5f** can be obtained in 74% yield as a mixture of regio- and diastereoisomers.

In order to investigate whether other *trans*-cyclooctene derivatives could also undergo this azo-Povarov reaction with aryldiazenes **2**, we explored a range of *trans*-cyclooctene derivatives (Fig. 2). To our disappointment, our studies revealed that (1*E*,5*E*)-cycloocta-1,5-diene or (1*Z*,3*E*)-cycloocta-1,3-diene failed to deliver the desired cinnoline derivative when reacted with aryldiazene **2a**. Only the starting material and the functionalized hydrazine **1a**, resulting from the reduction of the aryldiazene carboxylate **2a**, were observed. Additionally, the more sterically hindered methyl-substituted *trans*-cyclooctene, featuring a methyl substituent at the double bond, was also tested in this reaction, but no conversion was observed at all. As in the previous cases, only a mixture of diazene **2a** and functionalized hydrazine **1a** was recovered.

Finally, to explore if the new procedure could be extended to strained dienophiles beyond *trans*-cyclooctene, we examined cyclooctyne as substrate in the uncatalyzed [4 + 2] cycloaddition reaction (Scheme 4). Therefore, under microwave irradiation and applying the previously established reaction conditions, aryldiazene carboxylate **2a** reacted with cyclooctyne, yielding in this case a mixture of tetrahydrocycloocta[*c*]cinnoline **6a**, cinnoline derivative **4a**, and functionalized hydrazine **1a** in 24%, 30% and 30% yields, respectively, after 8 h. A similar outcome was obtained when employing aryldiazene carboxylate **2e** in the reaction. This led to the formation of a mixture of products **6e**/**4e**/**1e** in 18%, 33% and 36% yields, respectively (Scheme 4). Conversely, *N*-acetyl aryldiazene **2p** (R^4 = Me) reacted with cyclooctyne to afford, after 2.5 h, compound **4a** in 26% yield together with *N*′-phenylacetohydrazide **1p**.

As outlined in Scheme 5, the process is proposed to begin with an uncatalyzed [4 + 2] cycloaddition reaction of *N*-carbonyl aryldiazenes **2**, serving as 4π-electron donors, and cyclooctyne. The resulting [4 + 2] intermediate **VII** can follow two possible pathways: (1) undergoing hydrogen loss to yield tetrahydrocycloocta[*c*]cinnoline **6** (green pathway), or (2)



Scheme 3 Azo-Povarov reaction using 5-acetyl-substituted *trans*-cyclooctene.

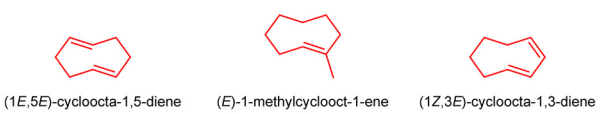
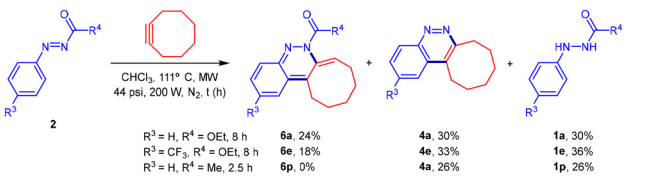
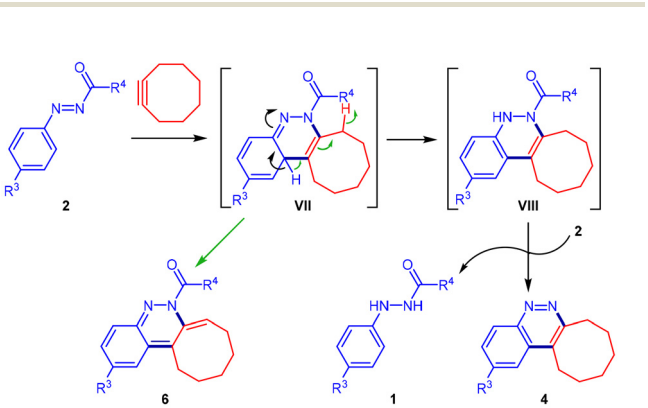


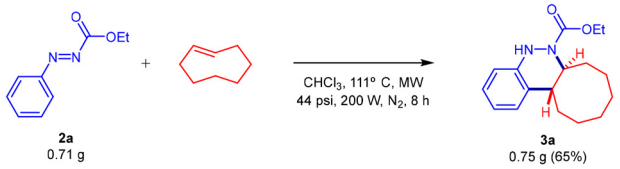
Fig. 2 Representative *trans*-cyclooctene derivatives used in the azo-Povarov reaction.



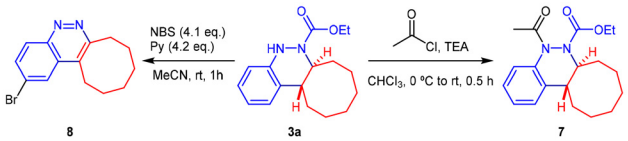
Scheme 4 Azo-Povarov reaction between *N*-carbonyl aryldiazenes and cyclooctyne.



Scheme 5 Postulated mechanism for the azo-Povarov reaction between *N*-carbonyl aryldiazenes and cyclooctyne.



Scheme 6 Gram-scale synthesis of **3a**.



Scheme 7 Synthetic applications of cinnoline **3a**.

undergoing oxidation of intermediate **VIII**, leading to the formation of aromatic cinnoline derivative **4** along with compound **1** (black pathway).

Currently, there is an ongoing discussion about the intricacies of the Povarov reaction mechanism. While some authors suggest a concerted aza-Diels–Alder [4 + 2] cycloaddition process,[32] many others assert evidences supporting an ionic mechanism consisting of a Mannich-type addition of an electron-rich alkene to an activated imine, followed by a subsequent cyclization *via* an intramolecular Friedel–Crafts reaction (stepwise mechanism).[33] However, in recent years, the ionic mechanism has gained greater acceptance for the Povarov reaction. This shift is supported by significant experimental evidence favoring a stepwise process rather than a concerted aza-Diels–Alder reaction. Conversely, the *trans*-stereochemistry detected in isolated cinnoline derivatives **3** strongly supports the idea of a concerted mechanism in the uncatalyzed synthesis of cinnoline derivatives *via* the azo-Povarov reaction, effectively supporting a concerted process.

To highlight the applicability and robustness of this methodology, a gram-scale experiment was performed using *N*-aryldiazene **2a** (0.71 g, 4 mmol) and *trans*-cyclooctene, yielding 0.75 g of **3a** in 65% yield (Scheme 6).

In order to demonstrate the practical value of the substrates obtained through the microwave-assisted azo-Povarov reaction, we next focused our efforts on some potential synthetic modifications of compounds **3** (Scheme 7). In particular, *N*-acetyl cinnoline carboxylate **7** was obtained in 81% yield when compound **3a** reacted with acetyl chloride in the presence of a base (TEA) in chloroform. Additionally, NBS-mediated bromination/dehydrogenation[34] with the concomitant deprotection of the *N*-protecting group in compound **3a** under mild reaction conditions afforded product **8** in 43% yield.

Conclusions

A direct method for the construction of cinnoline derivatives has been developed through a catalyst-free, microwave-assisted [4 + 2] cycloaddition reaction of *N*-carbonyl aryldiazenes with *trans*-cyclooctene derivatives or cyclooctyne. *N*-Aryldiazenes bearing activating groups (Me, OMe, OCF_3), deactivating groups (CF_3), or even halogen-substituted groups (Br, F) at the *para* position of the phenyl ring are well tolerated and produce cycloocta[*c*]cinnolines selectively in moderate to excellent yields by using microwave irradiation under the optimized reaction conditions. The electron density of substituents or the position of substitutions on the benzene ring (2-, 3-, or 4-position) did not significantly influence the efficiency of this reaction, providing a general synthetic methodology for the construction of the cinnoline scafold. This example, together with the previous contributions of other authors in this field, may contribute to shed some light into the understanding of the real mechanisms involved on the azo-Povarov reaction. Although previous results suggest a stepwise mechanism, in our case, the use of a non-activated 2π system and the total stereoselectivity of the bonds formed, point to a concerted [4 + 2] mechanism. The concrete machinery of the process seems to be dependent of the electronic nature of the substrates and, probably, both options, stepwise and concerted, are implicated when nucleophilic 2π-systems are employed, while an exclusive concerted mechanism is the driving force if non-activated alkenes are used as 2π-partners. As far as we are concerned, this report represents the first example of an uncatalyzed-azo-Povarov reaction.

Author contributions

X. J.-A.: formal analysis, investigation, methodology, visualization, writing – review and editing. G. P.: formal analysis, investigation. J. V.: funding acquisition, project administration, resources, supervision, visualization, writing – review and editing. J. M. S.: funding acquisition, methodology, project administration, resources, supervision, visualization, writing – original draft, writing – review and editing.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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