



Cite this: *RSC Adv.*, 2024, **14**, 16784

C(sp³)–H cyclizations of 2-(2-vinyl)phenoxy-*tert*-anilines[†]

Petra Dunkel, ^{*a}Dóra Bogdán,^a Ruth Deme,^a Ádám Zimber,^a Veronika Ballayová,^{ab} Eszter Csizmadia,^a Bence Kontra, ^{ac}Eszter Kalydi,^a Attila Bényei, ^dPéter Mátyus^{ae} and Zoltán Mucsi ^{*cfg}

1,5-hydride transfer-triggered cyclization reactions offering a robust method for C(sp³)–C(sp³) coupling and the synthesis of e.g. tetrahydroquinolines have been thoroughly investigated in the literature. Catalysts allowing milder reaction conditions or the development of enantioselective processes were important recent contributions to the field, as well as the studies on substrates with oxygen or sulfur heteroatoms (besides the originally described nitrogen heterocycles). In a series of studies, we focused on expanded, higher order H-transfers/cyclizations by positioning the interacting substituents on distanced rings. Cyclizations of appropriately functionalized biaryl and fused bicyclic systems led to 7–9 membered rings. In the frame of this research, we set out to study the feasibility of the cyclization and the factors affecting it by *in silico* methods. The conclusions drawn from computational studies were complemented by cyclization screens on 2-(2-vinyl)phenoxy-*tert*-anilines and their CH₂-expanded analogues, the results of which are presented here. Besides isolating the expected oxazoline products in several cases, we also observed a unique dimer formation, leading to an interesting 5–6–5 ring system.

Received 31st December 2023
 Accepted 29th April 2024

DOI: 10.1039/d3ra08974f

rsc.li/rsc-advances

Introduction

C(sp³)–H bond functionalization and C(sp³)–C(sp³)-cross coupling reactions (*i.e.* transformations involving inactivated C–H bonds) have long been at the forefront of interest in the field of synthetic organic chemistry. These methods allow access to complex structures, particularly in the field of total synthesis of natural products or medicinal chemistry.^{1–3} For instance, an elegant one-step approach leading to indolizidine derivatives, based on ‘inverse hydride shuttle catalysis’ was recently presented by the Maulide group.⁴ Of the various C–H bond functionalizations of amines,⁵ cyclizations of tertiary anilines with different double bonds in the *ortho* position were historically classified as variants of the ‘*tert*-amino effect’.^{6–9}

^aDepartment of Organic Chemistry, Semmelweis University, Hógyes Endre utca 7, H-1092 Budapest, Hungary. E-mail: dunkel.petra@semmelweis.hu

^bDepartment of Chemical Drugs, Masaryk University, Palackého 1946/1, 612 00 Brno, Czech Republic

^cDepartment of Biological Chemistry, Brain Vision Center, Liliom utca 43–45, H-1094 Budapest, Hungary

^dInstitute of Physical Chemistry, University of Debrecen, Egyetem tér 1, H-4010 Debrecen, Hungary

^eUniversity of Veterinary Medicine, István utca 2, H-1078 Budapest, Hungary

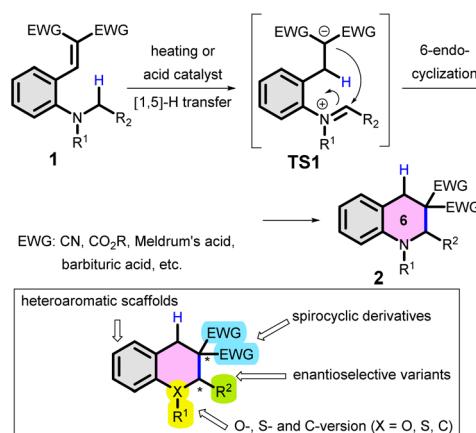
^fDepartment of Chemistry, Femtonics Ltd, Tűzoltó utca 59, H-1094 Budapest, Hungary. E-mail: zmucsi@femtonics.eu

^gInstitute of Chemistry, University of Miskolc, Egyetem út 1, H-3515 Miskolc, Hungary

[†] Electronic supplementary information (ESI) available. CCDC 2253075 and 2253076. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3ra08974f>

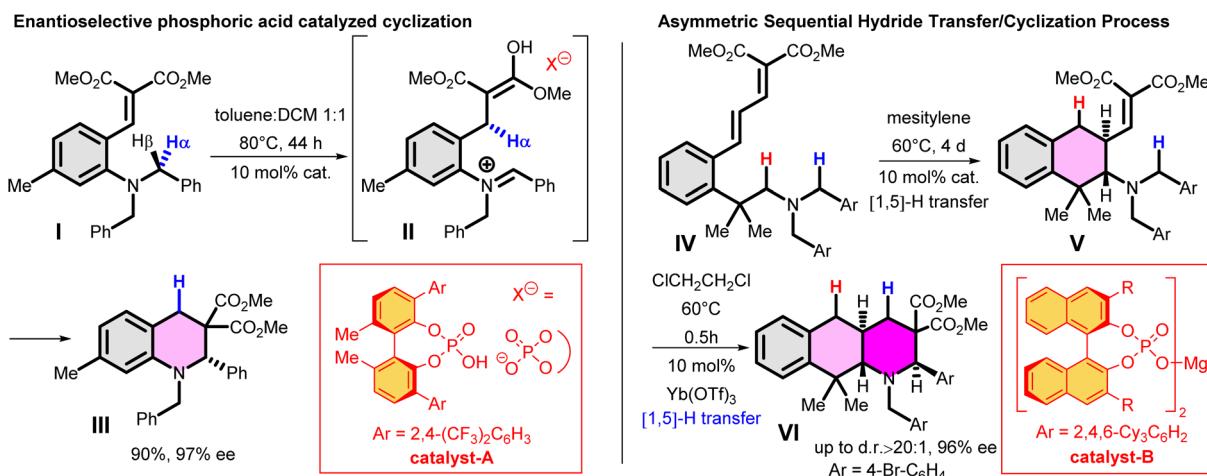
version of these reactions, the internal redox transformations involving [1, *n*]-H transfer and cyclization of tertiary anilines with an *ortho*-vinyl group (**1**) have been addressed in detail by several groups, particularly by Reinhoudt *et al.* (Scheme 1).^{10–15} In these reactions, typically a thermodynamically favoured 6-membered ring (often a tetrahydroquinoline; **2**) is obtained with the formation of a new C–C bond. The reaction proceeds *via* several elementary steps and transition states (*e.g.* **TS1**), without the need for a transition metal catalyst. Consequently, this reaction type is of special interest in the field of synthetic chemistry.^{16–18} Besides detailed synthetic studies, the cyclization was judiciously used in medicinal chemistry as well, for the preparation of antibacterial DNA gyrase inhibitors.¹⁹ Moreover, the synthetic utility of the reaction and its significant potential was recently demonstrated also by the preparation of unsymmetric julolidines from 8-vinyl-tetrahydroquinolines *via* [1,5]-H transfer/cyclization.²⁰ The tricyclic julolidine is a privileged scaffold in the design of fluorescent probes, photoswitches or photolabile protecting groups,^{21–24} therefore these fields could also benefit from straightforward synthetic approaches towards julolidine building blocks. Recently, Lewis- and Bronsted-acid catalysed variants of the cyclization were developed,^{25–27} allowing milder reaction conditions (of note, the first variants used typically higher temperatures). However, both the demand for an electron withdrawing group (EWG) and the preference of the six-member ring product formation limits the synthetic perspectives of this variant.



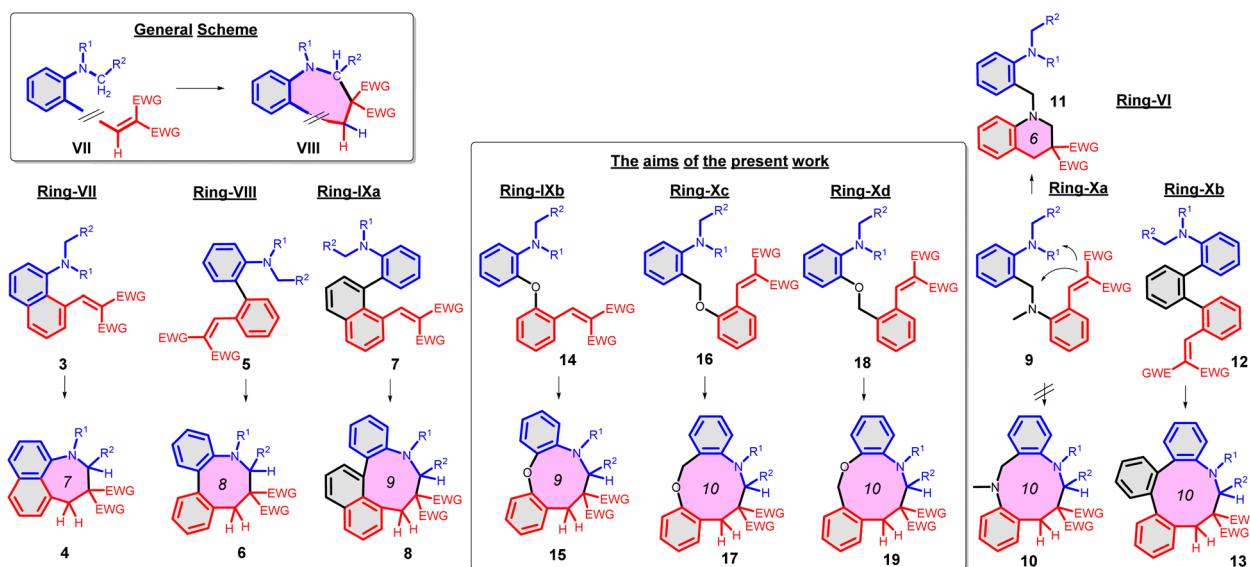


Scheme 1 Typical [1,5]-H transfer/cyclization of 2-vinyl-N,N-dialkylanilines (1; "tert-amino effect") and its potential variants.

As further important developments, highly enantioselective cyclizations (as **I** → **II** → **III**) and sequential hydride transfer/cyclization protocols (as **IV** → **V** → **VI**) were disclosed (Scheme 2).^{27–32} The oxygen version of the reaction (cyclization of *ortho*-vinylaryl alkyl ethers) allows a straightforward access to dihydrobenzopyran derivatives.^{33,34} Of note, the cyclization is operating also with 2-(2-alkylthio)benzylidene)malonates (*i.e.* with a sulphur analogue), leading to thiochromananes.³⁵ Although the heteroatom has an essential role in the stabilization of the carbocation formed by the hydride transfer, recently the carbon version of the reaction was developed. The [1,5]-hydride transfer/cyclization sequences of appropriately substituted aliphatic or benzylic substrates afford various tetrahydronaphthalene systems.^{36–38} Higher order H-transfers/cyclizations (as **VII** → **VIII**) could be envisaged by positioning the interacting substituents on different rings (Scheme 3). Cyclizations of fused



Scheme 2 Examples for enantioselective and sequential [1,5] hydride transfer/cyclization processes.^{31,32}



Scheme 3 Higher order H-transfer/cyclization processes (ring-VII–X), resulting in larger ring sizes.^{39–43}

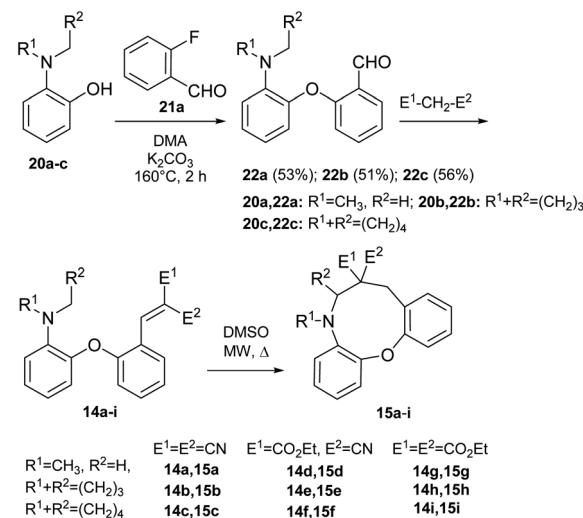
bicyclic (**3** → **4**) and biaryl systems (**5** → **6**, **7** → **8**) with the interacting dialkylamino and vinyl groups in *ortho*, *ortho'* or *ortho* and *peri* positions furnished the respective 7–9 membered rings, besides the formation of novel zwitterionic phenantridium or benzo[*d,e*]quinolinium systems through a Michael type addition in several cases.^{39,40} Starting from triaryl derivatives, 10-membered azecine rings could be attained (**12** → **13**).⁴¹ As examples of nondirectly connected biaryl systems, where a sigmatropic hydrogen transfer could *a priori* be excluded, the cyclization of biphenyl derivatives bridged with a methylamino-*N*-methyl group (**9** → **10**) or an oxygen between the phenyl rings (**14** → **15**) were studied.^{42,43} Although in the former case the formation of a 6-membered ring was observed instead (**9** → **11**), the cyclization of the biaryl-ether provided the 9-membered oxazonine ring (**14** → **15**), the structure of which was confirmed by X-ray crystallography as well. Of note, several of these more complex ring systems have natural analogues and could serve as interesting scaffolds for medicinal chemistry. Therefore, finding novel approaches for their preparation could be also of significant practical value.^{44,45}

The aim of the present work was to study in more detail the synthetic scope of the cyclization of biaryl ethers (**14** → **15**), potentially furnishing oxazonine derivatives *via* hydride transfer from an *N*-alkyl group to an electron-deficient alkene, facilitated in principle by the proximity of the groups and the electron-rich character of the *N*-alkyl group.⁴⁶ To explore the frontiers of the cyclization, the respective CH₂-analogues were tested as well (**16** → **17** and **18** → **19**). Moreover, we wished to gain a better understanding of our experimental results by computational chemistry calculations. We set out to study the influence of the conditions and the structural elements of the substrate **1/VII**, helping to predict the mechanism and the feasibility of the transformation.

Results and discussion

Synthesis of biaryl ethers and the scope of their cyclization

We previously described our first preliminary result for the cyclization of a biaryl ether (**14** → **15**, Scheme 3).⁴² In the present work, for studying the scope of the H-transfer/cyclization among biaryl ethers, a set of 2-(2-vinyl)phenoxy-*tert*-anilines (**14a–i**) were selected, with the most commonly used dialkylamino (dimethylamino, pyrrolidino and piperidino) and vinyl substituents (CN, CO₂Et). These variants represent different reactivity, as shown by experimental data and our theoretical comparison of typical amine and EWG substituents (Scheme 4 and Fig. 5). The **22a–c** aldehydes were prepared from commercially available 2-fluorobenzaldehyde (**21a**) and the corresponding 2-aminophenols^{47,48} (**20a–c**, Scheme 4). The vinyl precursors for the cyclization studies were prepared by the Knoevenagel condensation of **22a–c**, with malononitrile, ethyl cyanoacetate or diethyl malonate as the active methylene agents. In the case of malononitrile and ethyl cyanoacetate, the **14a–f** vinyl products were obtained with good yields under mild conditions. For diethyl malonate, refluxing in toluene was necessary (**14g–i**).



Scheme 4 Preparation and cyclization of 2-(2-vinyl)phenoxy-*tert*-anilines (**14a–i**) to oxazonine products (**15a–i**). Reaction conditions: **14a–c**: CH₂(CN)₂, EtOH, rt; **14d–f**: CNCH₂CO₂Et, EtOH, rt; **14g–i**: CH₂(CO₂Et)₂, toluene, reflux; **14a** (71%); **14b** (65%); **14c** (35%); **14d** (73%); **14e** (86%); **14f** (80%); **14g** (60%); **14h** (65%); **14i** (48%); **15a** (27%); **15b** (21%); **15d** (28%); **15c,e–i** (n.d.).

For the **14d–f** derivatives, judged by the NMR spectra (δ_{H} of vinyl protons in CDCl₃): **14d**: 8.92 ppm, **14e**: 8.89 ppm, **14f**: 8.96 ppm) exclusively the *E* isomers were formed (the less bulkier nitrile group being in *cis* position to the benzene ring), in accordance with former examples reported in the literature.^{12,49–51} Cyclizations of **14a–i** were first attempted in DMSO solution with conventional heating (50/75/100 or 125 °C, 16 h). In the case of **14b,c,e** and **14f**, at higher temperatures complex mixtures were formed. Therefore, only the apparently thermally more stable **14a** and **14d** were subjected to heating at higher temperature in microwave reactor. For the latter, short irradiations (15/30 min) were screened (125, 150 and 175 °C) with LC-MS monitoring. In the dinitrile series, the expected oxazonine products were formed from **14a** and **14b**, albeit only in modest yields. For **14c** no conversion was observed at lower temperatures, while higher temperatures led only to the decomposition of the vinyl precursor. Similar results were obtained for **14e** and **f** from the ester series, having cyclic amine moieties. However, **14d** could be cyclized, but a higher reaction temperature (175 °C) was required for the transformation. Of note, even for the successful attempts, a compromise between full conversion and decomposition was difficult to find, therefore shorter reaction times were selected for isolating the cyclic products. For the diester products (**14g–i**), a series of Lewis acids and catalysts previously tested [Yb(OTf)₃, Gd(OTf)₃, FeCl₃, Mg(ClO₄)₂ and AlCl₃] for cyclizations were first screened in MeCN solvent at 80 °C, 16 h. Heating in DMSO solution was attempted also in this series, without catalyst. Compound **14g** proved inert under the conditions tested. For **14h** and **14i**, oxazonine products were not appearing in significant amount, however, in some cases the aldehyde was formed. Moreover for **14h**, a higher molecular weight species was detected. (A summary of the reaction conditions tested is provided in the ESI†).



As an alternative activation method, we tested the cyclizations under photoirradiation on substrates already known to furnish the tetrahydroquinoline products [1: $R^1=CH_3$, $R^2=H$, $R^1+R^2=(CH_2)_3$ or $(CH_2)_4$.⁵² For the photoirradiation, the respective absorption maximum wavelengths were used in a dedicated PhotoCube instrument. A quick screen of conditions (solvent, irradiation time) showed traces of the products, assigned to thermal effects. Therefore, we did not pursue this direction for our present, more challenging substrates (see the ESI† for further details). Of note, successful photoinduced cyclization of the same substrates was recently reported following a more thorough screening of the conditions, such as significantly longer reaction times not tested by us.⁵³

The structures of **14c** and **15a** were confirmed by X-ray crystallography (structural data of **15b** was reported previously)⁴² (Fig. 1). Studying the position of the interacting groups that might be relevant for cyclization, the distance between the tertiary amine nitrogen and the α vinyl carbon was found to be 4.37 Å in compound **14c**, *i.e.* no closer proximity was observed. With the cyclization of **14b**, a new stereogenic centre is formed. In chiral HPLC experiments, two peaks could be detected in an almost 1 : 1 ratio, presumably due to the formation of the two enantiomers. For **15b**, upon X-ray crystallography, two molecules were observed in the asymmetric unit (*R/S* configuration at the stereogenic carbon, however no isomers resulting from inversion of the pyrrolidino nitrogen).

Further optimization and scale-up studies were run with **14b** (5 mg **14b** in 0.5 mL solvent, NMR monitoring). On the one hand, changing the solvent to toluene, no cyclization was detected (MW, 100 °C, 0–120 min), whereas in *n*-BuOH a similar reaction pattern to that observed in DMSO was recorded.

The cyclization to **15b** could be well monitored by NMR spectroscopy (Fig. 2), by the appearance of the characteristic NMR signals of the methylene hydrogens adjacent to the nitrogen and the carbon bearing the electron-withdrawing groups in the product.

In a more concentrated sample (50 mg **14b** in 0.5 mL solvent), besides the formation of **15b**, two further products were detected. By NMR, the structure of **23** was identified as the result of a dimerization, confirmed also by the 631 Da peak detected in LC-MS (Scheme 5). The relative configuration of the octahydro-dipyrroloquinoline product was determined by the respective NOE interactions. To ascertain that **23** is not formed *via* **15b**, in a control experiment an isolated sample of **15b** was

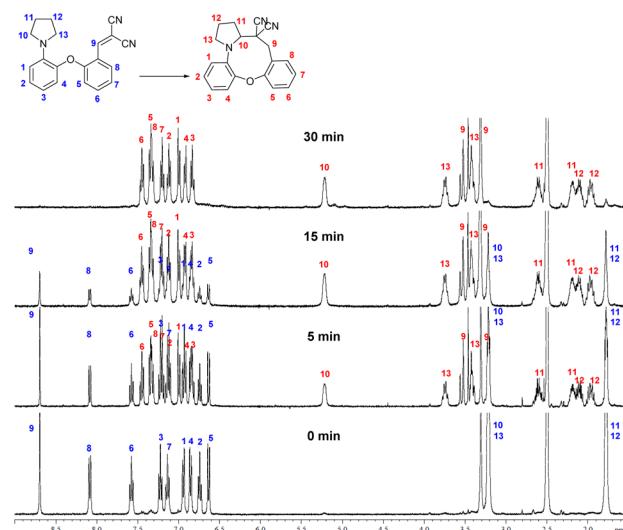
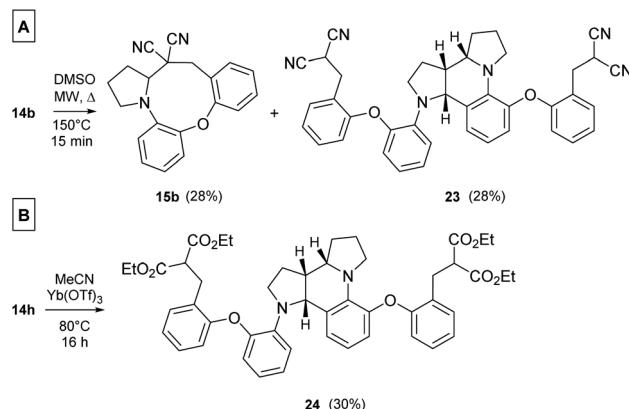


Fig. 2 ^1H NMR monitoring of the cyclization (5 mg **14b** in 0.5 mL DMSO- d_6 , 100 °C, NMR spectra taken at the indicated time points, the 30 min spectrum showing full conversion).



Scheme 5 (A) Products **15b** and **23** formed upon heating a more concentrated (1 g/10 mL) DMSO solution of **14b** (MW, 100 °C, 15 min). (B) Dimer product obtained from **14h**.

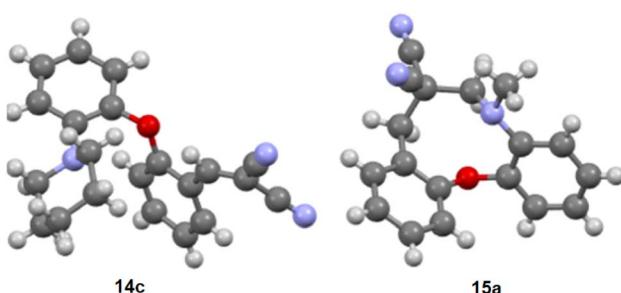
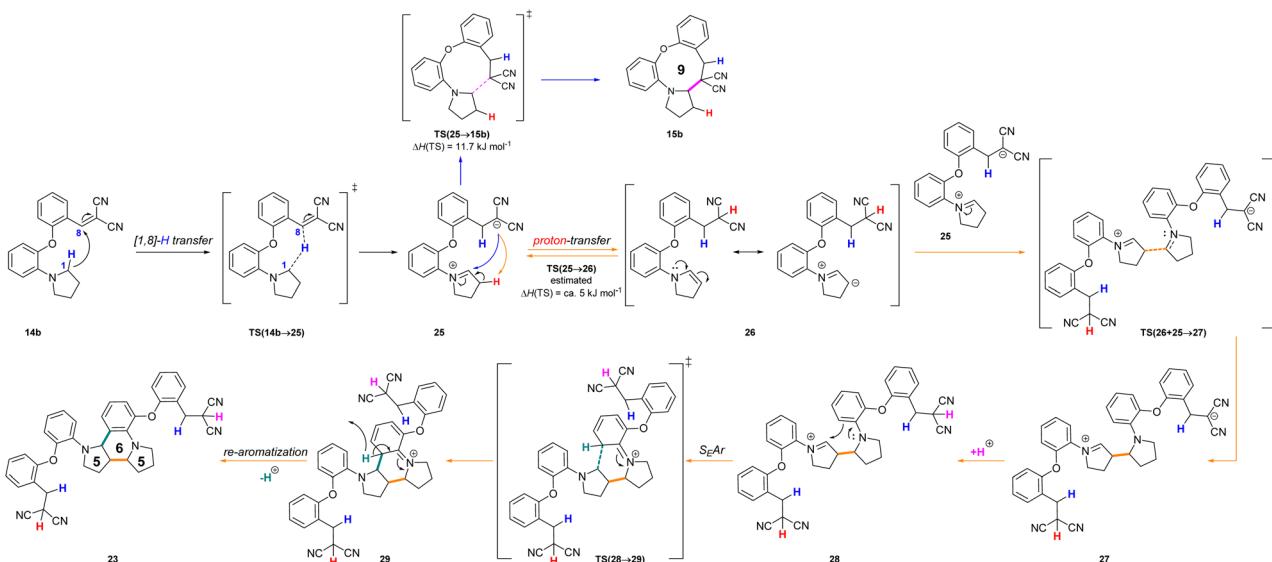


Fig. 1 X-ray structure of **14c** and **15a**.

subjected to 100 °C heating in DMSO, however no change was observed. The NMR studies showed that the higher M_w product (**24**) obtained from **14h** also corresponds to the respective octahydro-dipyrroloquinoline structure. A similar dimerization, leading to octahydro-dipyrroloquinoline derivatives was reported for carbo-analogues.⁵⁴ The cascade mechanism suggested by the authors proceeds *via* dehydration and the formation of a carbocation, inducing a [1,5]-hydride transfer to an iminium cation. The reaction between the iminium cation and an enamine formed with the isomerization of the iminium cation leads to an intermediate suitable for an intramolecular Pictet-Spengler type reaction, the result of which is an octahydro-dipyrroloquinoline derivative. Studying differently substituted diphenylmethanol derivatives, the authors observed, that the preferred reaction pathway is influenced by the electron density of the benzene ring (not carrying the amino group). The second pathway – *via* an intramolecular Pictet-





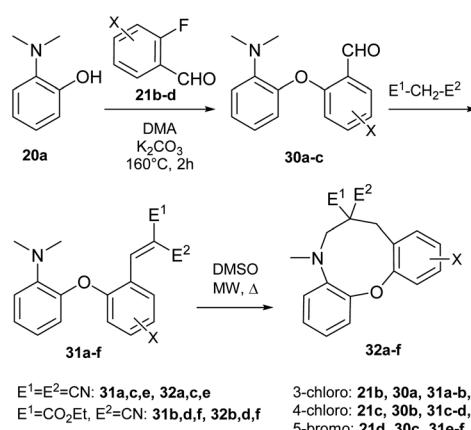
Scheme 6 Reaction mechanism proposed for the formation of the octahydro-dipyrroloquinoline derivative **23** (orange) in comparison with the formation of **15b** (blue) and the calculated enthalpies for the possible reaction pathways (**14b** → **15b** or **14b** → **23**). The related enthalpy values can be seen in Fig. S10.†

Spengler reaction without the dimerization step – affords dihydrodibenzo[*b,e*]azepines in good yields. In our case, a similar process could be envisaged, involving a higher order [1,8]-H transfer, an intramolecular proton transfer, C-C bond formation between two pyrrolidine moieties followed by a S_EAr step and finally a re-aromatization. The two possible reaction pathways (blue or orange), branching from the common **25** intermediate are shown in Scheme 6, while the corresponding calculated enthalpies on Fig. S10.† Interestingly, there is a negligible activation enthalpy difference between the **25** → **15b** and the **25** → **26** steps (11.7 kJ mol^{-1} vs. 5 kJ mol^{-1}). Noteworthy, that the formation of **23** is an exothermic process, in contrast to **15b**.

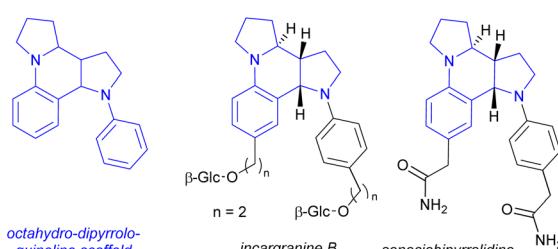
The [5-6-5] tetracyclic octahydro-dipyrroloquinoline scaffold is relatively rare among natural products, however there are some interesting biologically active alkaloids containing it, such as incagranine B and seneciobipyrrolidine (Scheme 7).^{55,56} For preparing the octahydro-dipyrroloquinoline skeleton several strategies were suggested in the literature, as (i) a chiral metal-phosphate-catalyzed asymmetric tandem hydroamination/formal Povarov reaction of aminoalkynes,⁵⁷ (ii) a domino Mannich/electrophilic aromatic substitution

sequence of aniline derivatives,⁵⁸ (iii) oxidative annulation of aryl amines⁵⁹ or a (iv) cycloaddition/arylation sequence of azomethine ylides.⁶⁰ The operationally simple dimerization observed for **14b** and **14h** could serve as an interesting addition to this synthetic toolbox.

To demonstrate the scope of the cyclization yielding oxazoline products, aldehydes **30a–c** were prepared, substituted with halogens on the aryl ring carrying the vinyl moiety. For the cyclization a short series of test reactions were run, with 15/30 min MW irradiations at two temperatures (150/175 °C for the dinitrile or 175/200 °C for the CN-CO₂Et derivatives). Of the six novel vinyl derivatives (**31a–f**), the expected oxazoline products were isolated in five cases (**32a,c–f**), with varying yields (Scheme 8). Although a further set of studies would be necessary

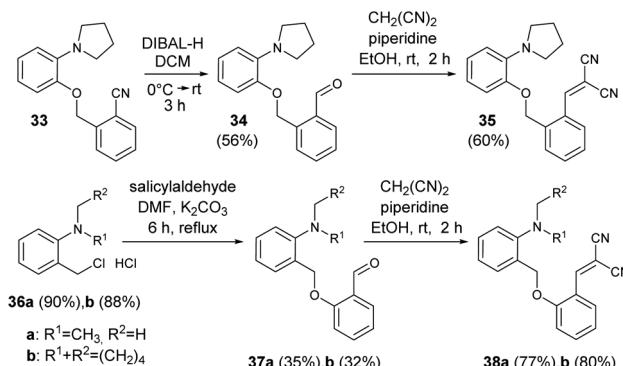


Scheme 8 Preparation and cyclization of halo-substituted 2-(2-vinyl) phenoxy-tert-anilines (**31a–f**) to oxazoline products (**32a–f**). Reaction conditions: **31a,c,e**: $CH_2(CN)_2$, EtOH, rt; **31b,d,f**: $CNCH_2CO_2Et$, EtOH, rt; **31a** (48%); **31b** (46%); **31c** (67%); **31d** (60%); **31e** (72%); **31f** (65%); **32a** (35%); **32b** (n.d.); **32c** (25%); **32d** (30%); **32e** (62%); **32f** (21%).



Scheme 7 Natural products containing an octahydro-dipyrroloquinoline scaffold.





Scheme 9 The synthesis of $-\text{CH}_2-\text{O}-$ bridged vinyl derivatives.⁶¹

to assess the effect of the aryl ring substituents on the cyclization, the halogens in our examples could serve as useful linchpins for further derivatizations of the ring systems.

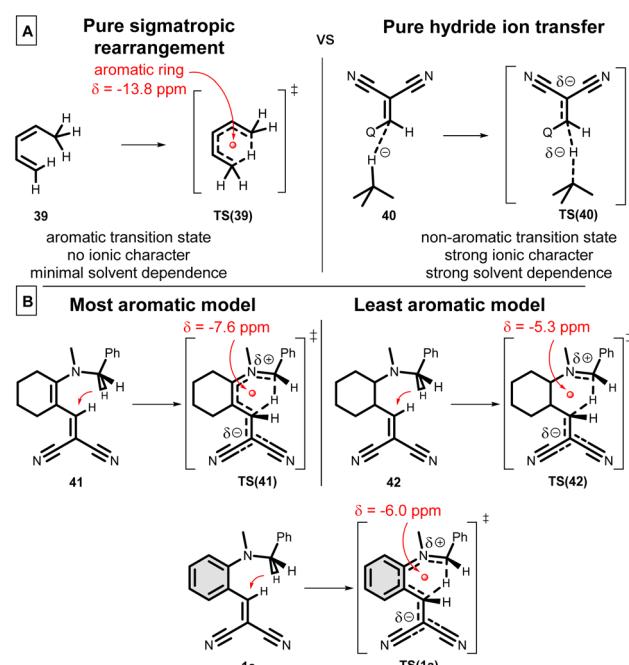
To discern the limits of the cyclization resulting in larger ring sizes, the $-\text{CH}_2-$ extended vinyl derivatives were prepared as well. The key intermediates were obtained by alkylation reactions of the appropriate phenol or benzyl alcohol (Scheme 9).⁶¹ For the cyclization the standard conditions were screened, *i.e.* heating in DMSO solution or in MeCN, in the presence of Lewis acid catalysts (see ESI[†] for a detailed list of the conditions tested).

In the case of **38a,b**, only decomposition was observed and the expected 10-membered rings could not be isolated. Similarly for **35**, mainly decomposition was observed for the different heating scenarios tested. However, in the presence of $\text{Gd}(\text{OTf})_3$ catalyst, the formation of three novel structures were observed by LC-MS, the M_w of which (660, 461, 461 Da) did not confirm the formation of the ten-membered ring. However, based on our previous results, the M_w 660 Da product could correspond to the formation of an octahydro-dipyrroloquinoline scaffold also in this case.

Theoretical investigations, comprehensive theoretical study

To get a better insight about the [1,5]-H transfer/cyclization reaction, we carried out a wide range of theoretical calculations. The first theoretical description dates back to 1988,¹² however, later this direction did not attract too much interest. Therefore, a novel DFT study [B3LYP/6-31G(d,p)//PCM(DMSO)] is appropriate. Here, a comprehensive analysis is reported, involving several aspects. The Nucleus Independent Chemical Shifts (NICS in ppm)⁶² were calculated in the ring centre of TSs to measure the degree of aromaticity by the same level of theory. The classical method is not suitable to measure the aromaticity degree in a **TS1** structure. The question arises, how can we classify this mechanism? Is this mechanism a pure sigmatropic rearrangement, involving a complete aromatic ring in the transition state (TS), or it is rather a hydride ion transfer, where only the H⁻ jumps from the -NCH₂- to the -CH=C- (Scheme 10A)? Or could it be a mixture of the two? The main characteristics of the sigmatropic rearrangement, like **39** → **TS(39)**, are that the process is solvent independent (no ionic character) and involves high aromatic ring current [$\delta(\text{NICS}) = -13.8 \text{ ppm}$]. In the case of

a hydride ion transfer mechanism, like **40** → **TS(40)**, one can observe high solvent dependence and a non-aromatic ring current, with low NICS values. In Scheme 10B, the most (**41** → **TS(41)**) and the least aromatic (**42** → **TS(42)**) models of hydride shift are considered at the theoretical level. In the case of **41**, the highest NICS value [$\delta(\text{NICS}) = -7.6$ ppm] is observed, due to the single aromatic ring forming in the TS. In the case of **42**, there is no chance for any aromatic ring current, but the calculated NICS value is still unexpectedly significant [$\delta(\text{NICS}) = -5.3$ ppm]. As one may expect, the general **1a** → **TS(1a)** reaction exhibits a compromised NICS value of -6.0 ppm, which reveals the fact



Scheme 10 Comparison of sigmatropic rearrangement and ionic reactions

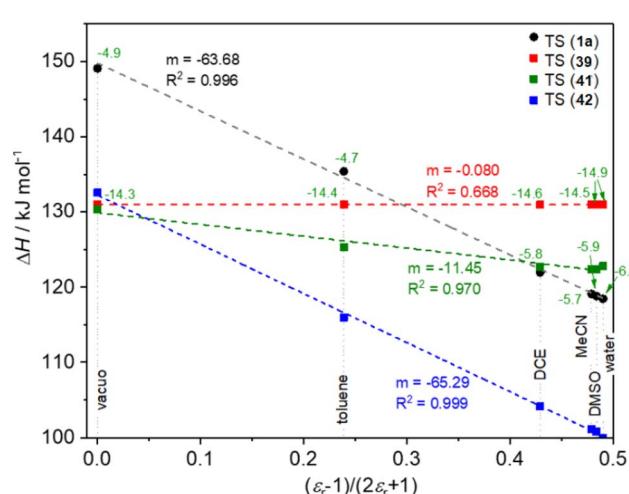


Fig. 3 Calculated solvent dependence of the TSs and the formation of intermediate 43 in various solvents as a function of $(\epsilon - 1)/(2\epsilon + 1)$ at B3LYP/6-31G(d,p)/PCM(solvent) level of theory.

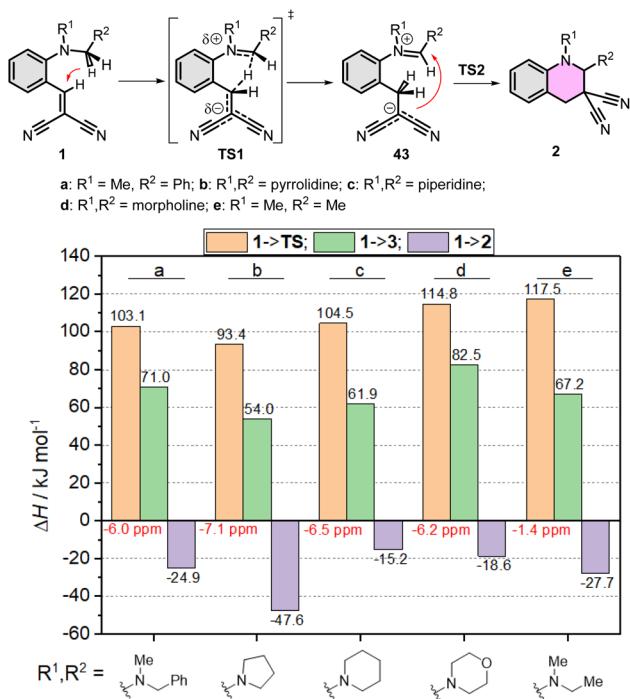


Fig. 4 Simplified reaction mechanism of the cyclization of compounds **1a–e**. Calculated enthalpies of **TS(1a–e)**, the formation of intermediate **43a–e**, and products **2a–e** at B3LYP/6-31G(d,p)//PCM(DMSO) level of theory.

that this hydride shift is between the two sides. The calculated TS enthalpies are not too high, between 100–130 kJ mol⁻¹, which is lowered by the quantum tunnelling effect by even 20 kJ mol⁻¹.

In the 3 next step, we studied the solvent dependence of **1** → **TS(1)** in comparison with **39** → **TS(39)**, **41** → **TS(41)** and **42** → **TS(42)**, by theoretical method *in vacuo* and in five solvents (water, DMSO, MeCN, dichloroethane, toluene). In the diagram in Fig. 3 we considered the $(\epsilon - 1)/(2\epsilon + 1)$ as *x* axis, which gives a linear relationship with the ΔH or ΔG values of the TSs, when the formation of a dipole is the dominant process.⁶³ The pure sigmatropic rearrangement, like model compound **39**, exhibits complete solvent independence, as the horizontal red line in Fig. 3. Model compound **41** (green line) shows only a moderate slope, which represents its high sigmatropic characteristics. In contrast with that, the rather ionic rearrangement of **42** shows the deepest slope (blue), representing a strong dipole involvement in the course of the reaction.

Compound **1a** follows a slightly moderate solvent dependence compared to **41**, but it is rather close to it, referring to a mixed mechanism between the sigmatropic and ionic mechanism.

In the third step, addressing the suitability of our substrates for the cyclization, the reaction parameters and the rate determining step were studied by computational chemistry. Three parameters were considered, the TS and the ΔH values of the intermediates [$\Delta H(1 \rightarrow 43)$] and the products [$\Delta H(1 \rightarrow 2)$]. According to general practise, if the $\Delta H(\text{TS})$ is larger than

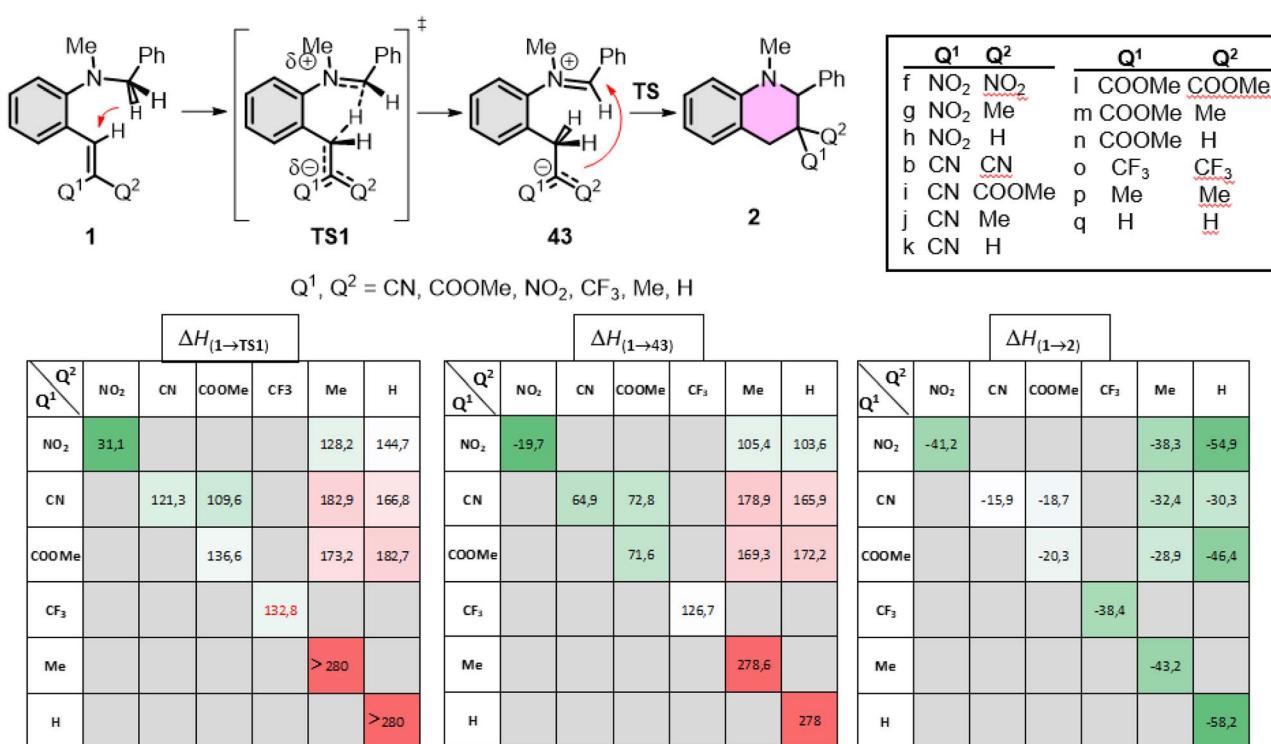


Fig. 5 Calculated enthalpies of **TS(1a)** and **TS(1f–q)**, the formation of intermediate **43a** and **43f–q** as well as **1a** and **1f–q** at B3LYP/6-31G(d,p)//PCM(DMSO) level of theory. The effect of the EWG group on the cyclization [B3LYP/6-31G(d,p)//PCM(DMSO)]. The colour code of the cells illustrates the potential of the reactions. Dark green and green cells are feasible, white cells are in the edge of the feasibility, while light red and red cells refer to the forbidden reactions.

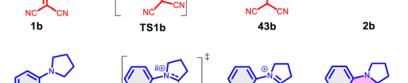
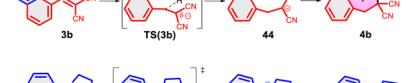
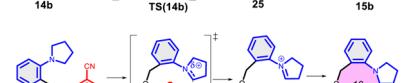


150 kJ mol⁻¹, the reaction is extremely slow even in a MW reactor at high temperature, but above 180 kJ mol⁻¹, the reaction can be considered as an unfeasible option. The negative enthalpy of product formation [$\Delta H(1 \rightarrow 2)$] indicates that the product formation is beneficial. Although in the cases of positive values, the formation is unbeneficial, however, with high temperature, it can provide some energy content ($RT = ca\ 5-10\ kJ\ mol^{-1}$, where R is the universal gas constant and T is the

reaction temperature in K) to invest and proceed the product formation.

First, the amino part was varied with some typical functionalities applied earlier, such as *N*-Me-benzyl, *N*-Me-ethyl, pyrrolidinyl, piperidinyl or morpholinyl, as summarized in Fig. 4. In these series, the lowest gap and the most exothermic pathway belongs to the pyrrolidinyl (**1b**) derivative, but the *N*-Me-benzyl (**1a**) and piperidinyl (**1c**) are close to it. The morpholinyl (**1d**) and *N*-Me-ethyl (**1e**) are the least beneficial amines

Table 1 Summary table about the effect of various sizes of the core scaffold on the cyclization at B3LYP/6-31G(d,p)//PCM(DMSO) level of theory. E = entry, SM = starting material, TS = transition state, INT = intermediate, P = product. The $n(\pi e^-)$ means the number of participating π electrons in the TS, planarity refers to the geometry of the TS structure, NICS means the Nucleus independent chemical shift in ppm^a

General scheme	SM → TS1	SM → intermed		SM → P		Conclusion	
		$n(\pi e^-)$	→ intermed		$\Delta H/kJ\ mol^{-1}$		
			Planarity	$\Delta H/kJ\ mol^{-1}$	$\Delta G/kJ\ mol^{-1}$		
E		$\Delta H/kJ\ mol^{-1}$	$\Delta G/kJ\ mol^{-1}$	$\Delta S/J\ mol^{-1}\ K^{-1}$	δ/ppm	$\Delta S/J\ mol^{-1}\ K^{-1}$	
1		+93.4 +100.1 -22.4	6 π Planar	+54.0 +55.2 -7.0 -4.2	-47.8 -36.8 -27.6		
2		+84.5 +91.7 -22.3	8 π Q-planar	+70.6 +71.7 -1.7 -3.7	-43.4 -30.9 -40.6		
3		+103.7 +111.8 -27.1	8 π Q-planar	+55.6 +57.7 -7.0	-19.0 -4.6 -48.1		
4		+136.5 +144.1 -25.7	8 π Non-planar	+68.4 +70.7 +1.2 -8.0	-2.0 +11.5 -45.2		
5		+114.7 +126.8 -40.9	8 π Q-planar	+54.8 +56.1 +0.6 -4.1	+10.1 +30.2 -67.2		
6		+112.5 +133.0 -68.8	— Q-planar n.a.	+70.7 +68.8 +6.4	+20.2 +40.3 -67.3		
7		+90.7 +105.0 -47.9	— Q-planar n.a.	+48.7 +51.1 -8.0	+6.9 +27.9 -70.3		
8		+104.6 +115.8 -37.5	10 π Non-planar n.a.	+67.8 +68.7 +0.9 -3.2	+27.6 +47.2 -65.7		

^a n.a. not available.



here, in agreement with the experimental findings. The study was extended to the EWG side as well, scanning several common functional groups (CN, COOMe, NO₂, CF₃, H, Me) in several combinations with each other with a constant *N*-Mebenzyl functionality (**1a**, **1f-q**). The calculated enthalpies are collected in Fig. 5. In conclusion, in all the cases the product formations allow the cyclization. However, large differences can be observed in the TS enthalpies. Only two conjugative EWGs, such as CN, COOMe and NO₂ can effectively decrease the energy gap to be close to 100 kJ mol⁻¹. However, only one EWG and one EDG (like H or Me) results in too high energy values, the only exception may be one NO₂ with one Me (**1g**). Two EDG groups do not allow the existence of the zwitterionic structures (**43p,q**), so neither the corresponding TS. Interestingly, the non-conjugative EWG CF₃ (**1o**) has much less beneficial effect on the **TS(1o)** or the intermediate **43o**, despite its strong electron withdrawing effect, indicating, that the conjugative characteristic is essential.

Finally, we studied the effect of the ring size from 6 to 10 members involving several model reactions, listed in Table 1. We analysed the number of participating π electrons, the computed ΔH , ΔG and ΔS values for TS, for the intermediate and the products. In the light of the results, one can understand, which parameters control the reaction, and which structural features may lead to cyclised products. The formation of the 6-member ring (entry 1) is very preferential, as was discussed earlier, however, surprisingly, the 7-member naphthalene product (entry 2) is more advantageous energetically. The aromatic character in the TS is verified exclusively in the first case (**1b**), as in the case of larger rings, the rings in the TSs are typically not planar. Maybe this is the reason that the anti-aromatic π -electron octet in entries 3, 4 and 5 cannot negatively dominate the hydride transfer and somewhat feasible energy gaps are involved in the TS. Consequently, compound **6b**, **8b** and **15b** could be prepared in acceptable yields. As reported in the experimental section, due to the relatively high activation enthalpy, the reaction proceeds only at elevated temperature, which allows the formation of the competitive side product **23**. Interestingly, despite the non-aromatic TS, compounds **17b** and **19b** (entries 6 and 7) exhibit moderate TS enthalpies. The ring closed products could not be isolated, due to the competitive reactions. Although entry **8b** exhibits moderate TS, the formation of the product is quite endothermic. Taking into account the high reaction temperature (over 100 °C), it can perhaps be explained that the product appears, although in low yield.

Conclusions

According to preliminary computational studies, biaryl ethers are less evident substrates for [1,8]-hydride transfer/cyclization reactions. Seeking an experimental verification, a set of biaryl ethers were prepared, with dialkylamino and vinyl substituents in *ortho*, *ortho'* positions. Cyclizations under thermal conditions (MW, DMSO) afforded oxazoline derivatives in several cases. The structure of one vinyl and two oxazoline derivatives were confirmed also by X-ray crystallography. In the diester series, cyclizations were attempted also using Lewis-acid catalysts,

however not resulting in the expected oxazoline products. An interesting dimerization was observed instead, leading to an octahydrodipyrrolo-quinoline derivative. The energy profile of the two possible reaction pathways was compared and a possible mechanism for the unexpected transformation was suggested. Theoretical studies show that the rate determining reaction step is the first hydride shift, which represents a mixed mechanism between the sigmatropic rearrangement and the ionic hydride transfer. Aromaticity of the TS plays an important role only in the formation of six membered products, but the weight of the ionic character is already significant. In the case of larger ring products, the aromatic character vanishes and only the pure ionic hydride transfer dominates the TSs, irrespective to the number of participating π -electrons.

Materials and methods

General information

All reagents and solvents were purchased from commercial sources and were utilized without further purification. Melting points were determined on a Büchi-540 capillary melting point apparatus and are uncorrected. The ¹H and ¹³C NMR spectra were recorded at ambient temperature, in the solvent indicated, with a Varian Mercury Plus spectrometer at a frequency of 400/600 or 100/150 MHz or with a Bruker 400 MHz spectrometer, at a frequency of 400 or 100 MHz, and are reported in ppm. Spectra were recorded at 400 MHz (¹H) or 100 MHz (¹³C), if not indicated otherwise. Chemical shifts are given on the δ -scale relative to tetramethylsilane or the residual solvent signal as an internal reference. For structure elucidation, one-dimensional ¹H, ¹³C, DEPT, two-dimensional ¹H, ¹H-COSY, ¹H, ¹³C-HSQC, ¹H, ¹³C-HMBC measurements were run. Mass spectra utilizing fast atom bombardment ionization were recorded on a VG-ZAB-2SEQ spectrometer. Elemental analyses were performed on a Carlo Erba 1012 apparatus. Microwave (MW) irradiation experiments were carried out in a monomode CEM-Discover MW reactor, using the standard configuration as delivered, including proprietary software.

The experiments were executed either in 10 mL MW process vials or in open-vessel mode, with control of the temperature by infrared detection. After completion of the reaction, the vial/flask was cooled to 50 °C by air jet cooling. Reactions were monitored by a Shimadzu LC-MS 2020 system.

Preparative HPLC was applied for purification in several cases using an Armen SPOT Prep II instrument with UV detector (200–600 nm scan) equipped with a Phenomenex Gemini C18, 250 × 50.00 mm; 10 μ m, 110A column. Gradient elution was employed using 0.08 g NH₄HCO₃ in 1 L water (A) and acetonitrile (B) or 2 mL TFA in 1 L water (A) and acetonitrile (B) as eluent systems, using the gradient method. For flash column chromatography purification, Kieselgel 60 (Merck, 0.040–0.063 mm) was used; for TLC analysis, Silica gel 60 F254 (Merck) plates were applied. Solvent mixtures used for chromatography are always given in a vol/vol ratio. The structures of all compounds were consistent with their analytical and spectroscopic data. Spectroscopic data are provided for compounds described previously but not characterized spectroscopically.



For reporting NMR assignment, an arbitrary numbering was used.

X-ray diffraction studies

A good-looking single crystal of the compound was fixed on the top of a glass fiber using epoxy glue. Data were collected at 293(1) K, Enraf Nonius MACH3 diffractometer (Bruker Nonius, Delft, Netherlands), Mo K α radiation $\lambda = 0.71073$ nm, ω motion. Raw data were evaluated using the XCAD4 software;⁶⁴ the structure was solved using direct methods by the SIR-92 software⁶⁵ and refined on F² using SHELX-97 (ref. 66) program. Refinement was performed anisotropically for nonhydrogen atoms. Hydrogen atoms were placed into geometric position. Figures were prepared with the WINGX-97 suite.⁶⁷ The PLATON program^{68,69} was used for crystallographic calculations.

Deposition Numbers of 2253075 for **14c** and 2253076 for **15a** containing the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Theoretical calculations

Gaussian 16 program package (G16),⁷⁰ using default convergence criteria was used, respectively. Computations were carried out at M06-2X/6-31G(d,p) level of theory.⁷¹ The method and basis sets were chosen for their reliability shown in earlier studies.⁷² The vibrational frequencies were computed at the same levels of theory as used for geometry optimization to properly confirm that all structures reside at minima on their potential energy hypersurfaces (PESSs). Thermodynamic functions, such as energy (U), enthalpy (H), Gibbs free energy (G), and entropy (S) were computed for 398.15 K, using the quantum chemical, rather than the conventional thermodynamic reference state.

General procedure for the synthesis biaryl ethers

To a solution of the appropriate phenol (15.00 mmol, for **22a**, **30a–c**: 2-(dimethylamino)phenol (2.06 g), for **22b**: 2-(pyrrolidin-1-yl)phenol (2.45 g), for **22c**: 2-(piperidin-1-yl)phenol (2.65 g)) in DMA (15 mL), the appropriate 2-fluorobenzaldehyde (for **22a–c**: 2-fluorobenzaldehyde (**21a**, 1.58 mL, 15.00 mmol), for **30a**: 3-chloro-2-fluorobenzaldehyde (**21b**, 1.76 mL, 15.00 mmol), for **30b**: 4-chloro-2-fluorobenzaldehyde (**21c**, 2.38 g, 15.00 mmol), for **30c**: 5-bromo-2-fluorobenzaldehyde (**21d**, 1.78 mL, 15.00 mmol)) and K₂CO₃ (4.15 g, 30.00 mmol) were added. The mixture was heated at 160 °C (oil temperature) under argon atmosphere for 1.5 h. To the cooled reaction mixture EtOAc (20 mL) was added. The organic phase was washed with H₂O (1 × 20 mL) and aq saturated Na₂CO₃ solution (1 × 20 mL). The organic layer was dried (Na₂SO₄), filtered and evaporated to dryness. The crude product obtained was purified by flash column chromatography on silica gel (eluent for **22a**: toluene → toluene : EtOAc 10 : 1 gradient, for **22b,c**: toluene, for **30a–c**: heptane → heptane : EtOAc 4 : 1 gradient).

2-[2-(Dimethylamino)phenoxy]benzaldehyde (22a). Yellow crystals (1.92 g, 53%), mp 100–101 °C, R_f = 0.40 (toluene). ¹H

NMR (CDCl₃) δ (ppm): 10.65 (s, 1H, H-19), 7.91 (dm, $J = 7.6$ Hz, 1H, H-15), 7.44–7.39 (m, 1H, H-13), 7.21–6.89 (m, 5H, H-1,2,3,4,14), 6.68 (dm, $J = 8.0$ Hz, 1H, H-12), 2.79 (s, 3H, H-8,9). ¹³C NMR (CDCl₃) δ (ppm): 190.1 (C-17), 161.1 (C-11), 147.7 (C-5), 146.0 (C-6), 136.4 (C-13), 128.9 (C-15), 126.5 (C-16), 126.4 (C-1/2/3/4), 123.0 (C-14), 122.5 (C-1/2/3/4), 122.5 (C-1/2/3/4), 119.6 (C-1/2/3/4), 117.3 (C-12), 43.6 (C-8,9). Anal. calcd for C₁₅H₁₅NO₂ (241.29): C, 74.67; H, 6.27; N, 5.81. Found: C, 75.07; H, 6.18; N, 5.65.

2-[2-(Pyrrolidin-1-yl)phenoxy]benzaldehyde (22b). Yellow crystals (1.98 g, 51%), mp 82–83 °C, R_f = 0.30 (toluene). ¹H NMR (CDCl₃) δ (ppm): 10.64 (d, $J = 0.7$ Hz, 1H, H-19), 7.90 (dm, $J = 8.0$ Hz, 1H, H-15), 7.45–7.40 (m, 1H, H-13), 7.15–7.04 (m, 2H, H-3,14), 6.94 (dm, $J = 8.0$ Hz, 1H, H-1), 6.82 (dm, $J = 8.0$ Hz, 1H, H-4), 6.74 (tm, $J = 7.6$ Hz, 1H, H-2), 6.69 (dm, $J = 8.0$ Hz, 1H, H-12), 3.36–3.31 (m, 4H, H-8,9), 1.86–1.82 (m, 4H, H-20,21). ¹³C NMR (CDCl₃) δ (ppm): 190.3 (C-17), 162.0 (C-11), 142.9 (C-5), 142.7 (C-6), 136.5 (C-13), 128.9 (C-15), 126.8 (C-3), 126.0 (C-16), 123.5 (C-1), 122.4 (C-14), 118.5 (C-2), 116.7 (C-12), 116.3 (C-4), 50.7 (C-8,9), 26.0 (C-20,21). Anal. calcd for C₁₇H₁₇NO₂ (267.32): C, 76.38; H, 6.41; N, 5.24. Found: C, 77.19; H, 6.51; N, 5.02.

2-[2-(Piperidin-1-yl)phenoxy]benzaldehyde (22c). Yellow oil (2.38 g, 56%), R_f = 0.30 (toluene). ¹H NMR (CDCl₃) δ (ppm): 10.69 (s, 1H, H-19), 7.90 (dm, $J = 7.6$ Hz, 1H, H-15), 7.38 (dm, $J = 7.6$ Hz, 1H, H-13), 7.23–6.97 (m, 5H, H-1,2,3,4,14), 6.63 (dm, $J = 7.6$ Hz, 1H, H-12), 3.01–2.89 (m, 4H, H-8,9), 1.45–1.31 (m, 6H, H-20,21,22). ¹³C NMR (CDCl₃) δ (ppm): 190.2 (C-17), 161.4 (C-11), 148.0 (C-6/5), 146.4 (C-6/5), 136.0 (C-13), 128.6 (C-15), 126.7 (C-1/2/3/4), 125.8 (C-16), 123.3 (C-1/2/3/4), 123.1 (C-1/2/3/4), 122.5 (C-14), 120.9 (C-1/2/3/4), 116.6 (C-12), 52.7 (C-8,9), 26.8 (C-20,22), 24.8 (C-21). Anal. calcd for C₁₈H₁₉NO₂ (281.35): C, 76.84; H, 6.81; N, 4.98. Found: C, 75.57; H, 6.91; N, 5.80.

3-Chloro-2-[2-(dimethylamino)phenoxy]benzaldehyde (30a). Orange solid (3.71 g, 90%). ¹H NMR (CDCl₃) δ (ppm): 10.12 (s, 1H, H-19), 7.89 (dd, $J = 7.8$, 1.7 Hz, 1H, H-10), 7.74 (dd, $J = 7.9$, 1.7 Hz, 1H, H-12), 7.33 (t, $J = 7.9$ Hz, 1H, H-11), 7.07 (dd, $J = 8.0$, 1.7 Hz, 1H, H-4), 7.01 (td, $J = 7.8$, 1.7 Hz, 1H, H-3), 6.80 (td, $J = 7.7$, 1.7 Hz, 1H, H-2), 6.32 (dd, $J = 8.1$, 1.4 Hz, 1H, H-1), 2.95 (s, 6H, H-15,16). ¹³C NMR (CDCl₃) δ (ppm): 188.9 (C-18), 154.1 (C-8), 151.7 (C-6), 142.2 (C-5), 136.7 (C-10), 131.3 (C-9), 129.4 (C-13), 127.2 (C-12), 126.4 (C-11), 123.5 (C-3), 122.4 (C-2), 119.5 (C-4), 114.2 (C-1), 43.7 (C-15,16). MS (ESI) *m/z* 276 (M⁺).

4-Chloro-2-[2-(dimethylamino)phenoxy]benzaldehyde (30b). Yellow solid (3.14 g, 76%). ¹H NMR (CDCl₃) δ (ppm): 10.60 (s, 1H, H-18), 7.85 (d, $J = 8.4$ Hz, 1H, H-12), 7.22 (ddd, $J = 8.6$, 6.3, 2.6 Hz, 1H, H-2), 7.09–7.04 (m, 2H, H-1,4), 7.03–6.96 (m, 2H, H-3,11), 6.61 (d, $J = 1.9$ Hz, 1H, H-9), 2.77 (s, 6H, H-15,16). ¹³C NMR (CDCl₃) δ (ppm): 188.5 (C-17), 161.0 (C-8), 146.0 (C-5), 145.5 (C-6), 141.9 (C-10), 129.5 (C-12), 126.6 (C-2), 124.1 (C-13), 122.9 (C-4), 122.5 (C-3), 122.2 (C-1), 119.3 (C-11), 116.5 (C-9), 43.1 (C-15,16). MS (ESI) *m/z* 276 (M⁺).

5-Bromo-2-[2-(dimethylamino)phenoxy]benzaldehyde (30c). Yellow solid (3.65 g, 76%). ¹H NMR (CDCl₃) δ (ppm): 10.58 (s, 1H, H-18), 8.01 (d, $J = 2.6$ Hz, 1H, H-12), 7.49 (dd, $J = 8.9$, 2.6 Hz, 1H, H-10), 7.20 (dt, $J = 8.6$, 4.5 Hz, 1H, H-2), 7.06 (br s, 1H, H-1), 6.98 (br d, 2H, H-3,4), 6.54 (d, $J = 8.9$ Hz, 1H, H-9), 2.77 (s, 6H, H-15–16). ¹³C NMR (CDCl₃) δ (ppm): 188.1 (H-17), 159.5 (C-8), 146.5



(C-5), 138.3 (C-10), 130.9 (C-12), 126.8 (C-13), 126.4 (C-2), 122.2 (C-3,4), 119.2 (C-1), 118.4 (C-9), 115.1 (C-11), 43.1 (C-15,16). MS (ESI) m/z 320,322 ($M+1$)⁺.

Synthesis of 14a-f and 31a-f biaryl vinyl compounds via Knoevenagel condensation

To a solution of the aldehyde (22a-c, 30a-c) (2.00 mmol) in EtOH (2.50 mL), malononitrile (for 14a-c, 31a,c,e: 132 mg, 2.00 mmol) or ethyl cyanoacetate (for 14d-f, 31b,d,f: 0.21 mL, 2.00 mmol), and a few drops of piperidine were added. The mixture was stirred at room temperature until the starting material had been consumed (monitored by TLC, reaction time: 2–3 h). Work-up: (i) the reaction mixture was evaporated to dryness and the crude product obtained was purified by flash column chromatography on silica gel with toluene or heptane/EtOAc eluent (14a, 31a,b,c,f) or (ii) the precipitated crystals were filtered off and washed with 5 × 1 mL EtOH to afford the analytically pure product (14b-f, 31d,e).

{2-[Dimethylamino]phenoxy}benzylidene}propane-dinitrile (14a). Orange crystals (411 mg, 71%), mp 76–78 °C, R_f = 0.35 (hexane : EtOAc 9 : 1). ¹H NMR (CDCl₃) δ (ppm): 8.50 (s, 1H, H-23), 8.28 (dm, J = 8.0 Hz, 1H, H-15), 7.46–7.40 (m, 1H, H-13), 7.22–7.11 (m, 2H, H-2,14), 7.04 (dm, J = 8.0 Hz, 1H, H-1), 6.98–6.93 (m, 1H, H-3), 6.91 (dm, J = 8.0 Hz, 1H, H-4), 6.66 (dm, J = 8.0 Hz, 1H, H-12), 2.75 (s, 6H, H-8,9). ¹³C NMR (CDCl₃) δ (ppm): 158.4 (C-11), 154.8 (C-17), 147.0 (C-5), 146.0 (C-6), 136.8 (C-13), 129.2 (C-15), 127.0 (C-2), 123.3 (C-14), 122.8 (C-4), 122.7 (C-3), 121.5 (C-16), 119.8 (C-1), 116.9 (C-12), 114.9 (C-19/21), 113.6 (C-19/21), 82.8 (C-18), 43.6 (C-8,9). Anal. calcd for C₁₈H₁₉NO₂ (289.33): C, 74.72; H, 5.23; N, 14.52. Found: C, 74.82; H, 4.59; N, 13.86.

{2-[Pyrrolidin-1-yl]phenoxy}benzylidene}propanedinitrile (14b). Orange crystals (410 mg, 65%), mp 92–93 °C, R_f = 0.60 (toluene). ¹H NMR (CDCl₃) δ (ppm): 8.46 (s, 1H, H-19), 8.29 (dm, J = 8.0 Hz, 1H, H-17), 7.48–7.41 (m, 1H, H-15), 7.18–7.09 (m, 2H, H-3,16), 6.86 (dm, J = 8.0 Hz, 1H, H-1), 6.83 (dm, J = 8.0 Hz, 1H, H-4), 6.78–6.71 (m, 1H, H-2), 6.70 (dm, J = 8.0 Hz, 1H, H-14), 3.32–3.23 (m, 4H, H-9,12), 1.92–1.83 (m, 4H, H-10,11). ¹³C NMR (CDCl₃) δ (ppm): 159.2 (C-13), 154.8 (C-19), 142.8 (C-5), 142.3 (C-6), 137.0 (C-15), 129.2 (C-17), 127.3 (C-3), 123.4 (C-1), 123.0 (C-16), 121.2 (C-18), 118.8 (C-2), 116.6 (C-4), 116.6 (C-14), 114.9 (C-21/22), 113.6 (C-21/22), 82.7 (C-20), 50.7 (C-9,12), 26.0 (C-10,11). Anal. calcd for C₂₀H₁₇N₃O (315.37): C, 76.17; H, 5.43; N, 13.32. Found: C, 76.60; H, 5.80; N, 12.52.

{2-[Piperidin-1-yl]phenoxy}benzylidene}propanedinitrile (14c). Yellow crystals (231 mg, 35%), mp 128–130 °C, R_f = 0.50 (hexane : EtOAc 10 : 1). ¹H NMR (CDCl₃) δ (ppm): 8.53 (s, 1H, H-26), 8.26 (dm, J = 8.0 Hz, 1H, H-15), 7.43–7.38 (m, 1H, H-13), 7.23–7.18 (m, 1H, H-1/2/3/4), 7.14–7.09 (m, 1H, H-14), 7.08–7.04 (m, 1H, H-1/2/3/4), 7.03–7.00 (m, 2H, H-1/2/3/4), 6.63 (dm, J = 8.4 Hz, 1H, H-12), 2.92–2.87 (m, 4H, H-8,9), 1.45–1.32 (m, 6H, H-19,20,21). ¹³C NMR (CDCl₃) δ (ppm): 158.7 (C-11), 154.8 (C-17), 147.6 (C-5/6), 146.2 (C-5/6), 136.5 (C-13), 128.9 (C-15), 127.2 (C-1/2/3/4), 123.7 (C-1/2/3/4), 123.0 (C-1/2/3/4), 121.2 (C-1/2/3/4), 121.0 (C-16), 116.5 (C-12), 114.9 (C-22/24), 113.7 (C-22/24), 82.4 (C-18), 52.7 (C-8,9), 26.8 (C-19,21), 24.7 (C-20).

Anal. calcd for C₂₁H₁₉N₃O (329.40): C, 76.57; H, 5.81; N, 12.76. Found: C, 76.33; H, 5.47; N, 12.22.

Ethyl 2-cyano-3-[2-(dimethylamino)phenoxy]phenyl}prop-2-enoate (14d). Pale yellow crystals (488 mg, 73%), mp 104–106 °C, R_f = 0.45 (hexane : EtOAc 5 : 1). ¹H NMR (CDCl₃) δ (ppm): 8.92 (s, 1H, H-25), 8.38 (dm, J = 8.0 Hz, 1H, H-13), 7.40–7.35 (m, 1H, H-11), 7.19–7.10 (m, 2H, H-1/2/3/4,12), 7.04–7.01 (m, 1H, H-1/2/3/4), 6.96–6.89 (m, 2H, H-1/2/3/4), 6.65 (dm, J = 8.4 Hz, 1H, H-10), 4.37 (q, J = 7.2 Hz, 2H, H-19), 2.76 (s, 6H, H-21,22), 1.39 (t, J = 7.2 Hz, 3H, H-20). ¹³C NMR (CDCl₃) δ (ppm): 163.3 (C-17), 158.6 (C-9), 150.1 (C-15), 147.5 (C-5), 146.0 (C-6), 135.3 (C-11), 129.8 (C-13), 126.5 (C-1/2/3/4), 123.2 (C-12), 122.7 (C-1/2/3/4), 122.5 (C-1/2/3/4), 122.2 (C-14), 119.6 (C-1/2/3/4), 116.7 (C-10), 116.5 (C-23), 103.7 (C-16), 63.2 (C-19), 43.6 (C-21,22), 14.8 (C-20). Anal. calcd for C₂₀H₂₀N₂O₃ (336.38): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.31; H, 5.62; N, 8.28.

Ethyl 2-cyano-3-[2-(pyrrolidin-1-yl)phenoxy]phenyl}prop-2-enoate (14e). Yellow crystals (620 mg, 86%), mp 111–112 °C, R_f = 0.36 (toluene). ¹H NMR (CDCl₃) δ (ppm): 8.89 (s, 1H, H-27), 8.39 (dm, J = 8.0 Hz, 1H, H-13), 7.42–7.35 (m, 1H, H-11), 7.15–7.07 (m, 2H, H-3,12), 6.87 (dm, J = 8.0 Hz, 1H, H-1), 6.80 (dm, J = 8.0 Hz, 1H, H-4), 6.75–6.71 (m, 1H, H-2), 6.67 (dm, J = 8.0 Hz, 1H, H-10), 4.38 (q, J = 7.2 Hz, 2H, H-19), 3.32–3.25 (m, 4H, H-21,22), 1.87–1.81 (m, 4H, H-23,24), 1.40 (t, J = 7.2 Hz, 3H, H-20). ¹³C NMR (CDCl₃) δ (ppm): 163.4 (C-17), 159.5 (C-9), 150.1 (C-15), 142.8 (C-5), 142.7 (C-6), 135.5 (C-11), 129.8 (C-13), 126.9 (C-3), 123.5 (C-1), 122.7 (C-12), 121.8 (C-14), 118.5 (C-2), 116.6 (C-25), 116.4 (C-10), 116.3 (C-4), 103.6 (C-16), 63.2 (C-19), 50.7 (C-21,22), 26.1 (C-23,24), 14.9 (C-20). Anal. calcd for C₂₂H₂₂N₂O₃ (362.42): C, 72.91; H, 6.12; N, 7.73. Found: C, 73.17; H, 6.25; N, 7.41.

Ethyl 2-cyano-3-[2-(piperidin-1-yl)phenoxy]prop-2-enoate (14f). Pale yellow crystals (600 mg, 80%), mp 60–62 °C, R_f = 0.33 (toluene). ¹H NMR (CDCl₃) δ (ppm): 8.96 (s, 1H, H-15), 8.37 (dm, J = 8.0 Hz, 1H, H-13), 7.36–7.31 (m, 1H, H-11), 7.21–7.15 (m, 1H, H-1/2/3/4), 7.12–6.98 (m, 4H, H-1/2/3/4,12), 6.61 (dm, J = 8.4 Hz, 1H, H-10), 4.38 (q, J = 7.2 Hz, 2H, H-19), 2.94–2.89 (m, 4H, H-21,22), 1.42–1.31 (6H, H-23,24,25), 1.39 (t, J = 7.2 Hz, 3H, H-20). ¹³C NMR (CDCl₃) δ (ppm): 163.4 (C-17), 158.9 (C-9), 150.1 (C-15), 147.8 (C-5/6), 146.3 (C-5/6), 135.0 (C-11), 129.5 (C-13), 126.8 (C-1/2/3/4), 123.4 (C-1/2/3/4), 123.2 (C-1/2/3/4), 122.7 (C-12), 121.5 (C-14), 120.9 (C-1/2/3/4), 116.6 (C-26), 116.1 (C-10), 103.2 (C-16), 63.2 (C-19), 52.7 (C-21,22), 26.8 (C-23,25), 24.8 (C-24), 14.9 (C-20). Anal. calcd for C₂₃H₂₄N₂O₃ (376.45): C, 73.38; H, 6.43; N, 7.44. Found: C, 72.90; H, 6.68; N, 7.36.

{3-Chloro-2-[2-(dimethylamino)phenoxy]phenyl}methylidene propanedinitrile (31a). Orange oil (0.31 g, 48%). ¹H NMR (CDCl₃) δ (ppm): 8.15 (dd, J = 8.0, 1.5 Hz, 1H, H-12), 8.11 (s, 1H, H-19), 7.73 (dd, J = 8.1, 1.5 Hz, 1H, H-10), 7.34 (t, J = 8.1 Hz, 1H, H-11), 7.11–7.04 (m, 2H, H-1,2), 6.87–6.78 (m, 1H, H-3), 6.35 (d, J = 8.1 Hz, 1H, H-4), 2.95 (s, 6H, H-15,16). ¹³C NMR (CDCl₃) δ (ppm): 155.1 (C-18), 152.5 (C-8), 151.3 (C-5), 142.7 (C-6), 136.2 (C-10), 129.8 (C-9), 127.5 (C-12), 127.1 (C-13), 126.5 (C-11), 124.5 (C-2), 122.5 (C-3), 119.6 (C-1), 115.9 (C-4), 113.5 (C-23), 112.2 (C-21), 85.1 (C-20), 43.7 (C-15,16). MS (ESI) m/z 324 ($M+1$)⁺.



Ethyl (2E)-3-[3-chloro-2-[2-(dimethylamino)phenoxy]phenyl]-2-cyanoprop-2-enoate (31b). Orange oil (0.34 g, 46%). ^1H NMR (CDCl_3) δ (ppm): 8.36 (s, 1H, H-19), 8.25 (dd, J = 8.0, 1.5 Hz, 1H, H-12), 7.66 (dd, J = 8.1, 1.5 Hz, 1H, H-10), 7.33 (t, J = 8.0 Hz, 1H, H-11), 7.05 (d, J = 7.3 Hz, 1H, H-1), 7.00 (t, J = 7.3 Hz, 1H, H-2), 6.79 (t, J = 7.6 Hz, 1H, H-3), 6.27 (dd, J = 8.1, 1.4 Hz, 1H, H-4), 4.28 (q, J = 7.2 Hz, 2H, H-24), 2.94 (s, 6H, H-15,16), 1.31 (t, J = 7.1 Hz, 3H, H-25). ^{13}C NMR (CDCl_3) δ (ppm): 161.7 (C-21), 151.6 (C-8), 151.1 (C-5), 149.1 (C-18), 142.6 (C-6), 135.1 (C-10), 129.3 (C-9), 128.1 (C-12), 127.8 (C-13), 126.3 (C-11), 123.6 (C-2), 122.3 (C-3), 119.5 (C-1), 115.1 (C-26), 114.6 (C-4), 106.0 (C-20), 62.9 (C-24), 43.7 (C-15,16), 14.2 (C-25). MS (ESI) m/z 371 (M+1)⁺.

({4-Chloro-2-[2-(dimethylamino)phenoxy]phenyl}methylidene) propanedinitrile (31c). Orange oil (0.43 g, 67%). ^1H NMR (CDCl_3) δ (ppm): 8.43 (s, 1H, H-18), 8.23 (d, J = 8.6 Hz, 1H, H-12), 7.24 (ddd, J = 8.2, 7.1, 2.1 Hz, 1H, H-2), 7.11 (dd, J = 8.4, 1.8 Hz, 1H, H-11), 7.08 (dm, J = 8.2 Hz, 1H, H-1), 7.00 (td, J = 7.6, 1.5 Hz, 1H, H-3), 6.95 (dd, J = 7.9, 1.8 Hz, 1H, H-4), 6.60 (d, J = 2.0 Hz, 1H, H-9), 2.73 (s, 6H, H-15,16). ^{13}C NMR (CDCl_3) δ (ppm): 158.4 (C-8), 152.9 (C-17), 145.4 (C-5), 145.3 (C-6), 142.5 (C-10), 129.4 (C-12), 127.2 (C-2), 123.3 (C-11), 122.5 (C-3,4), 119.5 (C-1), 119.1 (C-13), 116.3 (C-9), 114.2 (C-21,23), 112.9 (C-19), 43.1 (C-15,16). MS (ESI) m/z 324 (M+1)⁺.

Ethyl (2E)-3-[4-chloro-2-[2-(dimethylamino)phenoxy]phenyl]-2-cyanoprop-2-enoate (31d). Yellow solid (0.44 g, 60%). ^1H NMR (CDCl_3) δ (ppm): 8.87 (s, 1H, H-18), 8.33 (d, J = 8.6 Hz, 1H, H-12), 7.24–7.17 (m, 1H, H-2), 7.09 (d, J = 8.6 Hz, 1H, H-11), 7.05 (d, J = 12.0 Hz, 1H, H-1), 7.01–6.93 (m, 2H, H-3,4), 6.58 (s, 1H, H-9), 4.38 (q, J = 7.2 Hz, 2H, H-23), 2.74 (s, 6H, H-15,16), 1.39 (t, J = 7.2 Hz, 3H, H-24). ^{13}C NMR (CDCl_3) δ (ppm): 162.6 (C-20), 158.6 (C-8), 148.2 (C-17), 145.9 (C-5), 145.5 (C-6), 140.7 (C-10), 129.9 (C-12), 126.7 (C-2), 122.9 (C-11), 122.5 (C-4), 122.2 (C-3), 119.7 (C-13), 119.3 (C-1), 116.0 (C-9), 115.8 (C-26), 103.2 (C-19), 62.8 (C-23), 43.0 (C-15,16), 14.3 (C-24). MS (ESI) m/z 371 (M+1)⁺.

({5-Bromo-2-[2-(dimethylamino)phenoxy]phenyl}methylidene) propanedinitrile (31e). Orange crystals (0.53 g, 72%). ^1H NMR (CDCl_3) δ (ppm): 8.40 (s, 1H, H-18), 8.34 (d, J = 2.4 Hz, 1H, H-12), 7.50 (dd, J = 9.0, 2.4 Hz, 1H, H-10), 7.22 (ddd, J = 8.5, 7.1, 1.7 Hz, 1H, H-2), 7.06 (d, J = 8.0 Hz, 1H, H-1), 6.98 (td, J = 7.6, 1.5 Hz, 1H, H-3), 6.93 (dd, J = 8.0, 1.7 Hz, 1H, H-4), 6.52 (d, J = 9.0 Hz, 1H, H-9), 2.73 (s, 6H, H-15,16). ^{13}C NMR (CDCl_3) δ (ppm): 156.9 (C-8), 152.7 (C-17), 145.9 (C-5), 145.4 (C-6), 138.6 (C-10), 130.8 (C-12), 126.9 (C-2), 122.4 (C-3,4), 122.1 (C-11), 119.4 (C-1), 117.8 (C-9), 115.0 (C-13), 113.4 (C-21), 112.4 (C-23), 83.7 (C-19), 43.0 (C-15,16). MS (ESI) m/z 368,370 (M+1)⁺.

Ethyl (2E)-3-[5-bromo-2-[2-(dimethylamino)phenoxy]phenyl]-2-cyanoprop-2-enoate (31f). Yellow solid (0.54 g, 65%). ^1H NMR (CDCl_3) δ (ppm): 8.82 (s, 1H, H-18), 8.43 (d, J = 2.4 Hz, 1H, H-12), 7.44 (dd, J = 9.0, 2.4 Hz, 1H, H-10), 7.19 (ddd, J = 8.5, 6.7, 2.2 Hz, 1H, H-2), 7.03 (d, J = 8.1 Hz, 1H, H-1), 7.00–6.90 (m, 2H, H-3,4), 6.50 (d, J = 8.9 Hz, 1H, H-9), 4.38 (q, J = 7.1 Hz, 2H, H-23), 2.73 (s, 6H, H-15,16), 1.39 (t, J = 7.1 Hz, 3H, H-24). ^{13}C NMR (CDCl_3) δ (ppm): 162.3 (C-20), 157.0 (C-8), 147.8 (C-17), 146.3 (C-5), 145.5 (C-6), 137.2 (C-10), 131.4 (C-12), 126.5 (C-2,12), 122.9 (C-13), 122.4 (C-3), 122.1 (C-4), 119.2 (C-1), 119.1 (C-9), 114.8 (C-26), 114.5 (C-11), 104.5 (C-19), 62.9 (C-23), 43.0 (C-15,16), 14.3 (C-24). MS (ESI) m/z 415,417 (M+1)⁺.

Synthesis of biaryl vinyl compounds *via* Knoevenagel condensation 2

To a solution of the aldehyde (22a–c) (2.00 mmol) in toluene (5.0 mL), diethyl malonate (0.46 mL, 3.00 mmol) and a few drops of piperidine were added. The mixture was heated to reflux overnight. The reaction mixture was evaporated to dryness and the crude product obtained was purified by flash column chromatography on silica gel with hexane/ethyl acetate eluent (14h) or preparative HPLC (14g, 14i).

Diethyl 2-(2-(dimethylamino)phenoxy)benzylidene)malonate TFA salt (14g). Yellow oil (426 mg, 60%). R_f = 0.40 (hexane/EtOAc 9 : 1). ^1H NMR (400 MHz, CDCl_3) δ 7.89 (s, 1H, H-17), 7.74 (d, J = 8.0 Hz, 1H, H-1), 7.55 (d, J = 7.8 Hz, 1H, H-12), 7.43 (t, J = 7.6 Hz, 1H, H-10), 7.33 (t, J = 8.0 Hz, 1H, H-3), 7.24 (t, J = 7.7 Hz, 1H, H-11), 7.19 (t, J = 7.7 Hz, 1H, H-2), 7.00 (d, J = 8.2 Hz, 1H, H-9), 6.84 (d, J = 8.3 Hz, 1H, H-4), 4.26 (q, J = 7.1 Hz, 2H, H-27), 4.25 (q, J = 7.1 Hz, 2H, H-23), 3.32 (s, 6H, H-15,16), 1.28 (t, J = 7.2 Hz, 3H, H-24), 1.24 (t, J = 7.5 Hz, 3H, H-28). ^{13}C NMR (100 MHz, CDCl_3) δ 165.8 (C-20), 163.5 (C-19), 153.0 (C-8), 150.3 (C-5), 136.2 (C-17), 133.2 (C-6), 132.2 (C-10), 130.5 (C-3), 129.7 (C-11), 128.9 (C-18), 125.9 (C-13), 125.5 (C-1), 124.6 (C-2), 123.5 (C-1), 119.4 (C-9), 119.0 (C-4), 61.9 (C-23/27), 61.7 (C-23/27), 44.8 (C-15,16), 14.0 (C-24), 13.9 (C-28). (ESI) m/z 384 (M+1)⁺.

Diethyl 2-(2-(pyrrolidin-1-yl)phenoxy)benzylidene)malonate (14h). Pale yellow crystals (532 mg, 65%), mp 73–76 °C, R_f = 0.35 (hexane/EtOAc 9 : 1). ^1H NMR (400 MHz, CDCl_3) δ 8.22 (s, 1H, H-15), 7.45 (dm, J = 7.8 Hz, 1H, H-13), 7.22 (tm, J = 8.7 Hz, 1H, H-11), 7.08 (tm, J = 8.5 Hz, 1H, H-3), 6.94 (tm, J = 7.6 Hz, 1H, H-12), 6.88 (dm, J = 7.9, 1H, H-1), 6.77 (dm, J = 8.2 Hz, 1H, H-4), 6.70 (tm, J = 7.6 Hz, 1H, H-2), 6.63 (dm, J = 8.4 Hz, 1H, H-10), 4.30 (q, J = 6.1 Hz, 2H, H-21), 4.28 (q, J = 7.0 Hz, 2H, H-26), 3.33–3.22 (m, 4H, H-22,23), 2.04–1.67 (m, 4H, H-29,30), 1.32 (t, J = 7.2 Hz, 3H, H-27), 1.23 (t, J = 7.2 Hz, 3H, H-28). ^{13}C NMR (100 MHz, CDCl_3) δ 166.6 (C-18), 164.1 (C-17), 157.4 (C-9), 142.1 (C-6), 142.0 (C-5), 137.8 (C-15), 131.7 (C-11), 128.9 (C-13), 126.6 (C-16), 125.6 (C-3), 122.7 (C-1), 122.7 (C-14), 121.4 (C-12), 117.5 (C-2), 115.3 (C-4), 115.3 (C-10), 61.4 (C-21), 61.3 (C-26), 49.7 (C-22,23), 25.2 (C-29,30), 14.0 (C-27), 13.7 (C-28). (ESI) m/z 410 (M+1)⁺.

Diethyl 2-(2-(piperidin-1-yl)phenoxy)benzylidene)malonate TFA salt (14i). Yellow oil (516 mg, 48%). R_f = 0.40 (hexane/EtOAc 9 : 1). ^1H NMR (400 MHz, CDCl_3) δ 7.93 (s, 1H, H-15), 7.78 (d, J = 8.0 Hz, 1H, H-1), 7.53 (d, J = 7.8 Hz, 1H, H-13), 7.40 (t, J = 7.8 Hz, 1H, H-11), 7.30 (t, J = 7.8 Hz, 1H, H-3), 7.23–7.15 (m, 2H, H-2,12), 6.95 (d, J = 8.1 Hz, 1H, H-10), 6.87 (d, J = 8.3 Hz, 1H, H-4), 4.26 (q, J = 7.1 Hz, 4H, H-21,29), 3.74–3.61 (m, 4H, H-22,23), 2.08–1.94 (m, 4H, H-24,26), 1.70–1.58 (m, 2H, H-25), 1.28 (t, J = 7.1 Hz, 3H, H-31), 1.24 (t, J = 7.2 Hz, 3H, H-30). ^{13}C NMR (100 MHz, CDCl_3) δ 165.9 (C-18), 163.6 (C-17), 153.4 (C-9), 149.8 (C-5), 136.5 (C-15), 133.5 (C-6), 132.2 (C-11), 130.0 (C-3), 129.5 (C-13), 128.7 (C-16), 125.4 (C-14), 125.0 (C-2,12), 124.1 (C-1), 119.8 (C-4), 118.8 (C-10), 61.8 (C-29), 61.7



(C-21), 54.4 (C-22,23), 23.5 (C-24,26), 21.7 (C-25), 14.0 (C-31), 13.9 (C-30). (ESI) m/z 424 ($M+1$)⁺.

MW-assisted isomerization of the biaryl vinyl compounds in DMSO

A solution of the vinyl precursor (**14a,b,d, 31a-f**) (2.00 mmol) in 1 mL dry DMSO was irradiated in a 10 mL MW process vial at the temperature and for the reaction time as indicated below. The reaction mixture was subsequently cooled to ambient temperature and poured into CH_2Cl_2 (15 mL). The organic layer was washed with H_2O (3 \times 15 mL), dried (MgSO_4), filtered and evaporated to dryness. The residue obtained was purified by flash column chromatography on silica gel with hexane : EtOAc 4 : 1 eluent or by preparative HPLC.

5-Methyl-5,6-dihydrodibenzo[b,h][1,4]oxazonine-7,7(8H)-dicarbonitrile (15a). Heating: 150 °C, 15 min. Column chromatography: toluene. White crystals, mp 178–180 °C, R_f = 0.34 (hexane : EtOAc 9 : 1). ¹H NMR (CDCl_3) δ (ppm): 7.39–7.33 (m, 2H, H-4,13), 7.24–7.13 (m, 2H, H-2,11), 7.12–7.08 (m, 1H, H-3), 7.05–7.01 (m, 1H, H-1), 6.83–6.78 (m, 1H, H-10), 3.77 (br s, 2H, H-16), 3.69 (br s, 2H, H-15), 2.79 (s, 3H, H-17). ¹³C NMR (CDCl_3) δ (ppm): 157.2 (C-9), 150.3 (C-5), 145.5 (C-6), 131.8 (C-13), 130.6 (C-15), 126.3 (C-4), 124.5 (C-4), 124.5 (C-12), 124.5 (C-14), 123.8 (C-3), 119.9 (C-1), 118.3 (C-10), 115.6 (C-19), 115.6 (C-21), 64.8 (C-18), 40.8 (C-17), 39.3 (C-15), 36.4 (C-16). Anal. calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$ (289.33): C, 74.72; H, 5.23; N, 14.52. Found: C, 75.17; H, 4.66; N, 13.85.

5,6,7,7a-Tetrahydrodibenzo[e,h]pyrrolo[1,2-a]oxazonine-8,8(9H)-dicarbonitrile (15b). Heating: 100 °C, 15 min. White crystals, mp 172–174 °C, R_f = 0.58 (toluene). ¹H NMR (CDCl_3) δ (ppm): 7.43–7.37 (m, 1H, H-11), 7.29 (dm, J = 8.0 Hz, 1H, H-10), 7.18–7.14 (m, 2H, H-12,13), 7.11–7.06 (m, 1H, H-2), 6.92 (dm, J = 8.0 Hz, 1H, H-1), 6.89 (dm, J = 8.0 Hz, 1H, H-4), 6.83–6.78 (m, 1H, H-3), 5.35 (br s, 1H, H-18), 3.95–3.87 (m, 1H, H-17), 3.74 (d, J = 14.8 Hz, 1H, H-15), 3.48–3.41 (m, 1H, H-17), 3.03 (d, J = 14.8 Hz, 1H, H-15), 2.65–2.56 (m, 1H, H-20), 2.36–2.24 (m, 2H, H-19,20), 2.09–1.97 (m, 1H, H-19). ¹³C NMR (CDCl_3) δ (ppm): 156.3 (C-9), 146.1 (C-5), 140.4 (C-6), 135.0 (C-13), 131.4 (C-11), 126.6 (C-2), 125.5 (C-12), 124.1 (C-14), 122.9 (C-14), 122.9 (C-10), 121.3 (C-13), 118.8 (C-1), 116.3 (C-21/23), 114.6 (C-21/23), 62.9 (C-18), 51.9 (C-17), 45.6 (C-16), 38.5 (C-15), 32.7 (C-20), 23.2 (C-19). Anal. calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$ (289.33): C, 76.17; H, 5.43; N, 13.32. Found: C, 75.36; H, 5.00; N, 12.53.

2-(2-(2-(2,2-Dicyanoethyl)phenoxy)-2,3,3a,3b,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a:3',2'-c]quinolin-1-yl)phenoxy)benzyl)malononitrile (23). White crystals, R_f = 0.43 (hexane/EtOAc 5 : 1). ¹H NMR (500 MHz, CDCl_3) δ 7.35 (dm, J = 6.8 Hz, 1H, H-33), 7.34 (dm, J = 7.1 Hz, 1H, H-15), 7.30–7.25 (m, 2H, H-13,31), 7.16 (tm, J = 7.8 Hz, 1H, H-20), 7.10 (td, J = 7.5, 1.2 Hz, 1H, H-32), 7.06 (td, J = 7.5, 1.1 Hz, 1H, H-14), 6.95–6.90 (m, 2H, H-2,19), 6.92 (dd, J = 7.9, 1.7 Hz, 1H, H-22), 6.86 (td, J = 7.6, 1.4 Hz, 1H, H-21), 6.82 (dd, J = 8.3, 1.1 Hz, 1H, H-30), 6.69 (dd, J = 8.4, 1.1 Hz, 1H, H-12), 6.66 (dd, J = 7.9, 1.6 Hz, 1H, H-4), 6.51 (t, J = 7.8 Hz, 1H, H-3), 5.31 (d, J = 7.4 Hz, 1H, H-26), 4.29 (t, J = 8.0 Hz, 1H, H-36), 4.26 (t, J = 8.0 Hz, 1H, H-18), 3.64–3.54 (m, 2H, H-8,9), 3.49–3.40 (m, 3H, H-9,17), 3.38–3.31 (m, 3H, H-

27,35), 3.32–3.21 (m, 1H, H-27), 2.68–2.51 (m, 1H, H-40), 2.00–1.90 (m, 2H, H-37,39), 1.89–1.72 (m, 3H, H-38,39), 1.68–1.57 (m, 1H, H-37). ¹³C NMR (125 MHz, CDCl_3) δ 157.1 (C-11), 156.2 (C-29), 144.5 (C-23), 141.3 (C-24), 141.2 (C-5), 138.9 (C-6), 131.9 (C-33), 131.6 (C-15), 130.5 (C-13), 130.4 (C-31), 127.0 (C-1), 126.0 (C-20), 125.5 (C-2), 123.2 (C-32), 122.7 (C-34), 122.6 (C-14), 122.1 (C-16), 121.6 (C-22), 121.3 (C-4), 119.8 (C-21), 118.5 (C-19), 117.6 (C-3), 117.0 (C-30), 116.3 (C-12), 112.6 (C-41/43/45/47), 59.8 (C-26), 58.7 (C-8), 50.6 (C-9), 49.1 (C-27), 41.0 (C-40), 32.9 (C-35), 32.8 (C-17), 28.8 (C-37), 24.0 (C-38), 22.8 (C-18), 22.7 (C-39), 22.5 (C-36). MS (ESI) m/z 631 ($M+1$)⁺.

Ethyl 7-cyano-5-methyl-5,6,7,8-tetrahydrodibenzo[b,h][1,4]oxazonine-7-carboxylate (15d). White crystals, mp 110–112 °C, R_f = 0.43 (hexane : EtOAc 5 : 1). ¹H NMR (CDCl_3) δ (ppm): 7.37–7.31 (m, 2H, H-8,15), 7.17–7.09 (m, 2H, H-6,13), 7.08–7.02 (m, 2H, H-7,14), 7.00 (dm, J = 8.0 Hz, 1H, H-5), 6.75 (dm, J = 8.0 Hz, 1H, H-12), 4.33 (q, J = 7.2 Hz, 2H, H-21), 4.01 (d, J = 13.2 Hz, 1H, H-17), 3.91 (d, J = 14.8 Hz, 1H, H-2), 3.37 (dd, J = 14.8, 1.8 Hz, 1H, H-2), 3.03 (dd, J = 13.2, 1.8 Hz, 1H, H-17), 2.73 (s, 3H, H-3), 1.37 (t, J = 7.2 Hz, 3H, H-22). ¹³C NMR (CDCl_3) δ (ppm): 168.8 (C-20), 157.3 (C-11), 150.7 (C-9), 146.4 (C-4), 131.7 (C-15), 129.7 (C-13), 126.7 (C-16), 125.9 (C-6), 124.4 (C-8), 124.2 (C-14), 123.0 (C-7), 119.7 (C-5), 118.8 (C-19), 118.1 (C-12), 64.0 (C-2), 63.8 (C-21), 48.7 (C-18), 40.5 (C-3), 38.2 (C-17), 14.7 (C-22). Anal. calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$ (289.33): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.59; H, 5.29; N, 8.23.

Diethyl 2-(2-(2-(2-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)phenoxy)methyl)-2,3,3a,3b,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a:3',2'-c]quinolin-1-yl)benzyl)oxy)benzyl)malonate (24). To a solution of the vinyl precursor (**14h**, 205 mg, 0.50 mmol) in 1 mL dry MeCN 0.1 eq $\text{Yb}(\text{OTf})_3$ catalyst was added and the mixture was stirred at 80 °C for 16 h. The product was isolated by preparative HPLC. White crystals (61 mg, 30%). ¹H NMR (500 MHz, DMSO-d_6) δ 7.21 (dd, J = 7.6, 1.8 Hz, 1H, H-35), 7.18 (dd, J = 7.5, 1.7 Hz, 1H, H-15), 7.16 (dd, J = 7.5, 1.7 Hz, 1H, H-33), 7.11 (td, J = 7.6, 1.8 Hz, 1H, H-13), 7.07 (tm, J = 7.2 Hz, 1H, H-22), 6.97 (tm, J = 7.5 Hz, 1H, H-34), 6.94–6.88 (m, 2H, H-14,21), 6.87 (dm, J = 7.6 Hz, 1H, H-2), 6.83 (dd, J = 8.0, 1.8 Hz, 1H, H-24), 6.78 (tm, J = 7.1 Hz, 1H, H-23), 6.64 (d, J = 8.2 Hz, 1H, H-32), 6.56 (dd, J = 8.0, 1.7 Hz, 1H, H-4), 6.45 (d, J = 8.3 Hz, 1H, H-12), 6.41 (t, J = 7.8 Hz, 1H, H-3), 4.09–3.96 (m, 8H, H-53,55,57,59), 3.91 (t, J = 8.1 Hz, 1H, H-38), 3.84 (t, J = 8.0 Hz, 1H, H-18), 3.55–3.47 (m, 2H, H-8,9), 3.45–3.38 (m, 1H, H-9), 3.32–3.21 (m, 2H, H-29), 3.24–3.14 (m, 4H, H-17,37), 2.54–2.48 (m, 1H, H-44), 1.94–1.83 (m, 2H, H-41,43), 1.83–1.75 (m, 1H, H-42), 1.72–1.63 (m, 2H, H-42,43), 1.60–1.52 (m, 1H, H-41), 1.08 (t, J = 7.1 Hz, 3H, H-56), 1.07 (t, J = 7.2 Hz, 3H, H-54), 1.05 (t, J = 7.1 Hz, 3H, H-58), 1.01 (t, J = 7.0 Hz, 3H, H-60). ¹³C NMR (125 MHz, DMSO-d_6) δ 169.0 (C-40), 168.9 (C-39), 168.8 (C-19), 168.7 (C-20), 157.5 (C-11), 156.1 (C-31), 144.8 (C-25), 141.7 (C-5), 141.4 (C-26), 139.2 (C-6), 131.6 (C-35), 131.4 (C-15), 128.9 (C-33), 128.8 (C-13), 127.5 (C-1), 127.3 (C-38), 127.2 (C-36), 127.2 (C-18), 126.4 (C-16), 125.7 (C-22), 125.2 (C-2), 122.8 (C-34), 122.0 (C-14), 121.5 (C-24), 121.2 (C-4), 119.3 (C-23), 118.1 (C-21), 117.4 (C-3), 116.7 (C-32), 115.6 (C-12), 61.5 (C-53), 61.5 (C-55), 61.4 (C-57), 61.4 (C-59), 59.1 (C-28), 58.4 (C-8), 50.6 (C-9), 48.5 (C-29), 40.7 (C-44), 32.4 (C-37), 31.5 (C-17), 28.8 (C-41), 24.0 (C-42), 22.4 (C-43),



14.3 (C-54), 14.3 (C-56), 14.3 (C-58), 14.2 (C-60). (ESI) m/z 819 (M+1)⁺.

12-Chloro-5-methyl-5,6-dihydridobenzo[b,h][1,4]oxazoline-7,7(8H)-dicarbonitrile (32a). Heating: 175 °C, 30 min. Column chromatography: heptane → heptane : EtOAc 4 : 1 gradient. White crystals. ¹H NMR (CDCl₃) δ (ppm): 7.35 (dd, J = 8.0, 1.7 Hz, 1H, H-10), 7.26 (d, J = 6.1 Hz, 1H, H-4), 7.24 (dd, J = 6.1, 1.4 Hz, 1H, H-12), 7.16–7.07 (m, 2H, H-2,11), 7.05–6.99 (m, 2H, H-1,3), 4.01 (s, 2H, H-16), 3.55 (s, 2H, H-18), 2.91 (s, 3H, H-15). ¹³C NMR (CDCl₃) δ (ppm): 151.8 (C-8), 148.6 (C-5), 142.8 (C-6), 132.1 (C-10), 130.8 (C-12), 127.3 (C-13), 126.6 (C-9), 125.7 (C-2), 125.3 (C-11), 124.4 (C-4), 123.3 (C-3), 119.6 (C-1), 114.8 (C-20,22), 63.4 (C-16), 41.4 (C-15), 37.7 (C-18), 35.9 (C-19). (ESI) m/z 324 (M+1)⁺.

11-Chloro-5-methyl-5,6-dihydridobenzo[b,h][1,4]oxazoline-7,7(8H)-dicarbonitrile (32c). Heating: 150 °C, 30 min. Column chromatography: heptane → heptane : EtOAc 4 : 1 gradient. White crystals. ¹H NMR (CDCl₃) δ (ppm): 7.35 (dd, J = 7.8, 1.6 Hz, 1H, H-4), 7.30 (d, J = 8.1 Hz, 1H, H-12), 7.28 (s, 1H), 7.20 (td, J = 7.7, 1.6 Hz, 1H, H-2), 7.14–7.09 (m, 2H, H-3,11), 7.07 (dd, J = 8.0, 1.6 Hz, 1H, H-1), 6.78 (d, J = 2.1 Hz, 1H, H-9), 3.77 (s, 2H, H-16), 3.67 (s, 2H, H-17), 2.82 (s, 3H, H-15). ¹³C NMR (CDCl₃) δ (ppm): 157.1 (C-8), 149.4 (C-5), 144.8 (C-6), 135.5 (C-10), 131.8 (C-12), 126.2 (C-2), 124.3 (C-11), 123.8 (C-4), 123.6 (C-3), 122.6 (C-13), 119.7 (C-1), 118.5 (C-19), 114.8 (C-20,22), 64.4 (C-16), 40.2 (C-15), 38.4 (C-17), 35.6 (C-18). (ESI) m/z 324 (M+1)⁺.

Ethyl 11-chloro-7-cyano-5-methyl-5,6,7,8-tetrahydridobenzo[b,h][1,4]oxazoline-7-carboxylate (32d). Heating: 200 °C, 30 min. Column chromatography: heptane → heptane : EtOAc 4 : 1 gradient. White crystals. ¹H NMR (CDCl₃) δ (ppm): 7.33 (dd, J = 7.8, 1.6 Hz, 1H, H-4), 7.30 (d, J = 8.2 Hz, 1H, H-12), 7.16 (td, J = 7.7, 1.6 Hz, 1H, H-2), 7.10–7.05 (m, 2H, H-3,11), 7.03 (dd, J = 8.0, 1.7 Hz, 1H, H-1), 6.75 (d, J = 2.1 Hz, 1H, H-9), 4.34 (qd, J = 7.2, 1.3 Hz, 2H, H-23), 3.97 (d, J = 13.5 Hz, 1H, H-17), 3.87 (dd, J = 14.7, 0.9 Hz, 1H, H-16), 3.37 (dd, J = 14.7, 1.9 Hz, 1H, H-16), 3.01 (dd, J = 13.5, 1.9 Hz, 1H, H-17), 2.76 (s, 3H, H-15), 1.38 (t, J = 7.2 Hz, 3H, H-24). ¹³C NMR (CDCl₃) δ (ppm): 168.0 (C-19), 157.2 (C-8), 149.9 (C-5), 145.7 (C-6), 134.4 (C-10), 131.8 (C-12), 125.8 (C-2), 124.9 (C-13), 124.0 (C-11), 123.6 (C-4), 122.8 (C-3), 119.4 (C-1), 118.3 (C-9), 118.1 (C-25), 63.6 (C-16), 63.4 (C-23), 47.9 (C-18), 40.0 (C-15), 14.4 (C-24). (ESI) m/z 371 (M+1)⁺.

10-Bromo-5-methyl-5,6-dihydridobenzo[b,h][1,4]oxazoline-7,7(8H)-dicarbonitrile (32e). Heating: 175 °C, 30 min. Column chromatography: heptane → heptane : EtOAc 4 : 1 gradient. White crystals. ¹H NMR (CDCl₃) δ (ppm): 7.48 (d, J = 2.5 Hz, 1H, H-12), 7.33 (dd, J = 7.7, 1.7 Hz, 1H, H-4), 7.30 (dd, J = 8.7, 2.4 Hz, 1H, H-10), 7.17 (td, J = 7.7, 1.7 Hz, 1H, H-2), 7.10 (dd, J = 7.6, 1.7 Hz, 1H, H-1), 7.05 (td, J = 8.0, 1.7 Hz, 1H, H-3), 6.66 (d, J = 8.7 Hz, 1H, H-9), 3.76 (s, 2H, H-17), 3.69–3.57 (m, 2H, H-16), 2.80 (s, 3H, H-15). ¹³C NMR (CDCl₃) δ (ppm): 155.8 (C-8), 149.4 (C-5), 144.8 (C-6), 133.7 (C-12), 133.0 (C-10), 126.0 (C-2,11), 123.8 (C-4), 123.4 (C-1), 119.5 (C-9), 119.4 (C-3), 116.2 (C-13), 114.7 (C-20,22), 64.3 (C-16), 40.2 (C-15), 38.2 (C-17), 35.5 (C-18). (ESI) m/z 369,371 (M+1)⁺.

Ethyl 10-bromo-7-cyano-5-methyl-5,6,7,8-tetrahydridobenzo[b,h][1,4]oxazoline-7-carboxylate (32f). Heating: 175 °C, 30 min. Purification by preparative HPLC. White crystals. ¹H

NMR (CDCl₃) δ (ppm): 7.48 (d, J = 2.4 Hz, 1H, H-12), 7.31 (dd, J = 7.7, 1.7 Hz, 1H, H-4), 7.24 (dd, J = 9.3, 2.8 Hz, 1H, H-10), 7.13 (td, J = 7.8, 1.7 Hz, 1H, H-2), 7.04 (dd, J = 7.7, 1.8 Hz, 1H, H-1), 7.00 (d, J = 8.2 Hz, 1H, H-3), 6.62 (d, J = 8.6 Hz, 1H, H-9), 4.33 (tt, J = 7.9, 4.0 Hz, 2H, H-22), 3.96 (d, J = 13.4 Hz, 1H, H-17), 3.85 (d, J = 14.8 Hz, 1H, H-16), 3.37 (dd, J = 14.8, 1.9 Hz, 1H, H-16), 2.97 (d, J = 11.5 Hz, 1H, H-17), 2.75 (s, 3H, H-15), 1.37 (t, J = 7.1 Hz, 3H, H-23). ¹³C NMR (CDCl₃) δ (ppm): 167.9 (C-19), 155.9 (C-8), 149.9 (C-5), 145.7 (C-6), 133.7 (C-12), 132.0 (C-10), 128.4 (C-11), 125.6 (C-2), 123.7 (C-4), 122.6 (C-1), 119.3 (C-9), 119.2 (C-3), 118.0 (C-25), 116.0 (C-13), 63.5 (C-22), 47.8 (C-18), 40.0 (C-15), 37.2 (C-17), 14.2 (C-23). (ESI) m/z 415,417 (M+1)⁺.

Synthesis of CH₂-extended analogues

2-[(2-(Pyrrolidin-1-yl)phenoxy)methyl]benzonitrile (33). 2-(Pyrrolidin-1-yl)phenol (0.82 g; 5.00 mmol) was dissolved in anhydrous THF (15 mL) under argon atmosphere, then NaH (0.24 g; 6.00 mmol) was added and the mixture was stirred at rt for 30 min. To the mixture a solution of 2-(bromomethyl)benzonitrile (28, 0.98 g; 5.00 mmol) in THF (5 mL) was added dropwise under inert conditions, then the mixture was stirred at rt overnight. The following day the reaction mixture was poured onto water (100 mL) and extracted with DCM (3 × 50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel with hexane : EtOAc 4 : 1 eluent. Pale pink oil (0.97 g, 70%), R_f = 0.43 (hexane/EtOAc 4 : 1). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.74–7.68 (m, 2H, H-15,18), 7.63 (t, J = 7.7 Hz, 1H, H-16), 7.43 (t, J = 7.6 Hz, 1H, H-17), 6.97–6.91 (m, 2H, H-3,5), 6.83–6.76 (m, 2H, H-2,4), 5.26 (s, 2H, H-13), 3.36–3.31 (m, 4H, H-9,12), 2.02–1.83 (m, 4H, H-10,11). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 148.5 (C-6), 141.1 (C-14), 140.6 (C-1), 133.0 (C-16), 132.8 (C-18), 128.6 (C-15), 128.2 (C-17), 122.5 (C-3), 119.1 (C-4), 117.1 (C-20), 115.6 (C-2), 114.6 (C-5), 111.1 (C-19), 68.8 (C-13), 50.5 (C-9,12), 25.0 (C-10,11). MS (ESI) m/z 279 (M+1)⁺.

2-[(2-(Pyrrolidin-1-yl)phenoxy)methyl]benzaldehyde (34). 2-[(2-(Pyrrolidin-1-yl)phenoxy)methyl]benzonitrile (33; 2.28 g; 8.19 mmol) was dissolved in anhydrous DCM (30 mL) under argon atmosphere and the solution was cooled to 0 °C. Diisobutylaluminium hydride (1.2 M; 7.50 mL; 9.00 mmol) was added dropwise and the mixture was stirred at rt for 3 h. The reaction mixture was poured onto water (150 mL) and extracted with DCM (3 × 50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel with hexane : EtOAc 4 : 1 eluent. Pale yellow oil (1.28 g, 56%), R_f = 0.43 (hexane/EtOAc 4 : 1). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.23 (s, 1H, H-20), 7.91 (d, J = 7.5 Hz, 1H, H-18), 7.79 (d, J = 7.7 Hz, 1H, H-15), 7.63 (t, J = 7.5 Hz, 1H, H-16), 7.52 (t, J = 7.5 Hz, 1H, H-17), 6.95–6.90 (m, 2H, H-3,5), 6.83–6.75 (m, 2H, H-2,4), 5.53 (s, 2H, H-13), 3.36–3.30 (m, 4H, H-9,12), 1.94–1.88 (m, 4H, H-10,11). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 193.0 (C-20), 148.9 (C-6), 140.4 (C-1), 140.1 (C-14), 134.0 (C-16), 133.3 (C-18),



133.0 (C-19), 128.0 (C-15), 127.8 (C-17), 122.0 (C-3), 119.2 (C-4), 115.6 (C-2), 114.3 (C-5), 68.8 (C-13), 50.6 (C-9,12), 24.9 (C-10,11). MS (ESI) m/z 282 (M+1)⁺.

2-(2-[2-(Pyrrolidin-1-yl)phenoxy]methyl)benzylidene malonitrile (35). To a mixture of 2-[2-(pyrrolidin-1-yl)phenoxy]methylbenzaldehyde (34; 0.40 g; 1.42 mmol) in anhydrous EtOH (5 mL), malononitrile (0.11 g; 1.70 mmol) and a few drops of piperidine were added. The mixture was stirred at rt for 2 h, then evaporated to dryness. The crude product was purified by flash column chromatography on silica gel with hexane : EtOAc 4 : 1 eluent. Orange crystals (0.28 g, 60%), R_f = 0.43 (hexane/EtOAc 4 : 1). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.25 (s, 1H), 8.09 (d, J = 7.7 Hz, 1H), 7.63–7.50 (m, 3H), 6.97 (t, J = 7.2 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.84–6.75 (m, 2H), 5.10 (s, 2H), 3.27–3.21 (m, 4H), 1.94–1.86 (m, 4H). MS (ESI) m/z 330 (M+1)⁺.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

P. D. and Z. M. were recipients of the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (BO/799/21/7, ÚNKP-23-ME4). The research was supported by the TKP2021-NVA-14 and ED-2022-00208. We thank the contribution of Tamás Gáti to expert NMR analyses and the assignment of the NMR spectra, of Gergő Rizsiter and Zoltán Kaleta to LC-MS analyses and of Zoltán Dobi and Gergely Hetényi to the synthetic work. We gratefully acknowledge our reviewer's suggestions for the mechanism in Scheme 6. This research was funded by the National Research, Development and Innovation Office (NKFIH) grant number SNN 135825. On behalf of the 'Development and mechanistic study of DNA dyes' (PI: Ervin Kovács) project we are grateful for the possibility to use ELKH Cloud which helped us achieve the computational results published in this paper.

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