High-Pressure promoted Nazarov-like electrocyclization enables access to *trans*-4,5-Diamino-Cyclopent-2-enones bearing Electron-Poor Anilines

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High pressure, Nazarov-type electrocyclization, Furfural, *trans*-4,5-Diamino cyclopent-2-enones

ABSTRACT: Unlike secondary alkyl amines and electron-rich anilines, secondary electron-poor anilines are challenging amine sources to explore the chemical space of Lewis acid-catalyzed condensation-based transformations with furfural. In this work is reported the efficient synthesis of *trans*-4,5--diamino cyclopentenones (DCP) using a high-pressure promoted Nazarov-like electrocyclization of Stenhouse salts arising from the Sc(III)-catalyzed condensation of furfural with secondary electron-poor anilines. The reaction enables access to otherwise difficultly accessible DCP and compatibility with a large scope of alkyl and aryl secondary amines. A 2 to 18-fold increase in yields for electron-poor anilines was highlighted by the use of this approach in the synthesis of a pharmacologically active compound.

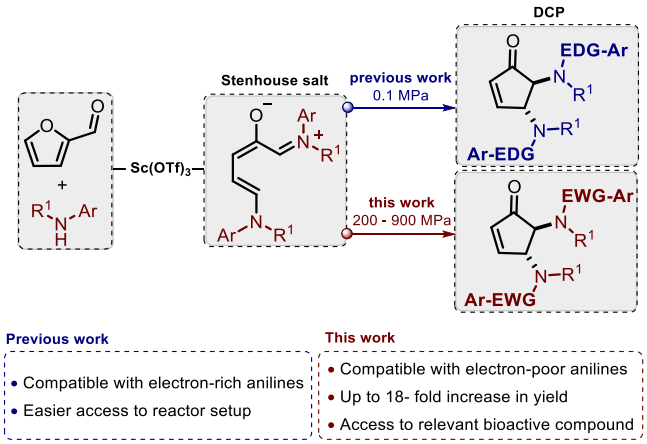
INTRODUCTION

Trans-4,5-diamino-cyclopent-2-enones (DCP), synthesized from the Lewis acid-catalyzed condensation of furfural with amines are versatile motifs in the preparation of several natural occurring products and other bioactive scaffolds.[1] Since the early report on the use of lanthanides(III) in dry acetonitrile to access DCP,[2] alternative methods have employed ionic liquid 1-methylimidazolium tetrafluoroborate,[3] aluminum(III) chloride,[4] Dy(III)/Ni(III) based heteronuclear clusters,[5, 6] erbium(III) chloride in ethyl acetate,[7] and microwave irradiation in water, for being less time consuming, using cheaper catalysts and/or greener solvents.[8] Additionally, a tosylamine-based method has allowed for a metal free variant.[9]

More recently, convenient silica immobilized a erbium(III) reusable catalyst,[10] and a Cu(II) method to afford DCP in water in minute-scale, excellent yields have emerged without the need for chromatography.[11] The demand for reaction scale-up while avoiding formation of secondary products (such as the 2,4-regioisomer), resulted in the use of silica-supported copper catalysts under continuous flow conditions to obtain larger amounts of DCP.[12]

The reaction mechanism involves the formation of a Stenhouse salt which undergoes a Nazarov-like electrocyclization to afford the corresponding DCP.[13] The reported literature tolerates only secondary alkyl and electron-rich anilines. However, primary anilines substituted with electron-withdrawing groups (i.e. F or CF_3) afforded only the Stenhouse salt product.[5, 6] To the best of our knowledge, the use of secondary electron-poor anilines in the generation of DCP was only firstly reported in a recent work by Afonso and co-workers, yet with significantly lower yields.[14]

Scheme 1. Lewis acid-catalyzed condensation of furfural with secondary amines bearing electron-poor anilines under atmospheric pressure or high pressure conditions.



When controlling reactivity, chemists have generally looked at temperature as a central variable given its ease of control. However, the role of pressure in modulating chemical reactivity has been scrutinized, particularly in the second half of the 20th century.

Cycloadditions undergo negative volume change of the reaction system from reactant to transition state - volume of activation - ($\Delta^{\ddagger}V$) which is further complemented by a typically negative reaction volume (ΔV) - corresponding to the volume change from reactant to product. In practice, reaction with negative $\Delta^{\ddagger}V$ are expected to be accelerated under pressure as the associated volume contraction works in favor of the compression. [15-19]

While extensive body of literature exists for pressure accelerated Diels–Alder cycloadditions, a single example on ring-closure electrocyclic reactions promoted by high

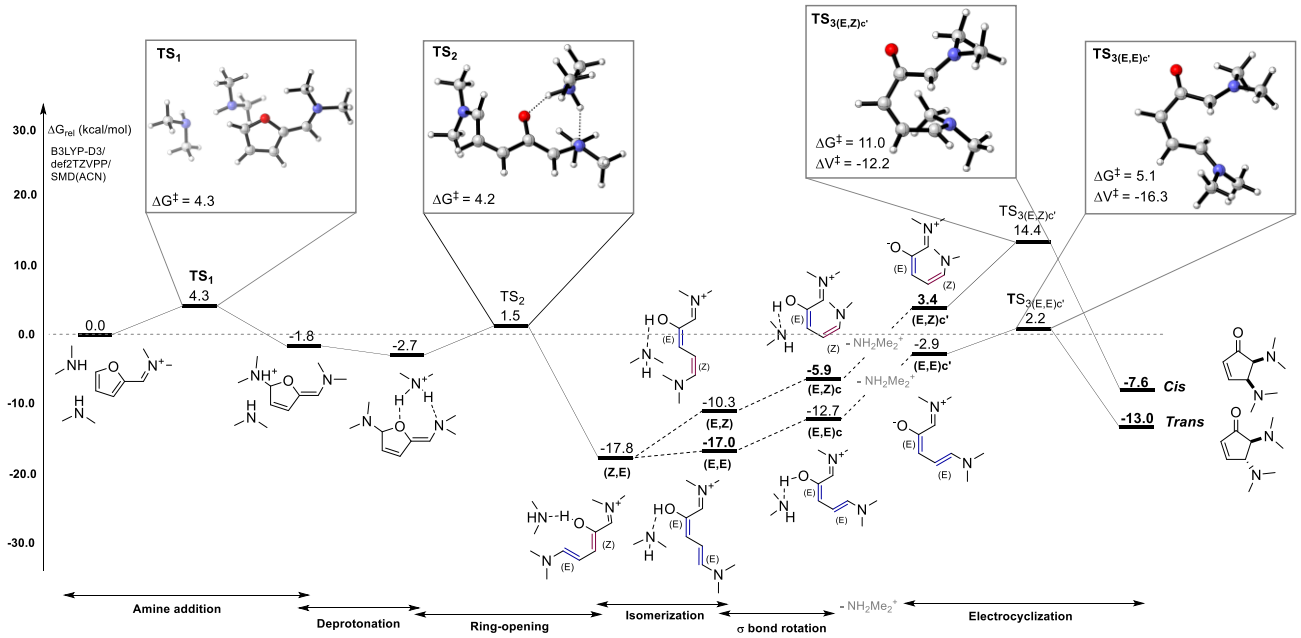
pressure is reported – the transformation of (*Z*)-1,3,5-hexatriene into 1,3-cyclohexadiene.[20, 21]

Inspired by these previous reports, we wondered whether it was possible to increase the competitiveness of DCP - limited by the often negligible conversions using electron-poor anilines in current methods - by capitalizing on the negative $\Delta^{\ddagger}V$ of the key limiting electrocyclization step. In this sense, herein we report that DCP derivatives containing electron-poor anilines can be easily accessed by operating the condensation of furfural and those anilines, and the consecutive Nazarov-type electrocyclization at high-pressure conditions (Scheme 1).

RESULTS AND DISCUSSION

To understand the effect of high pressure on this transformation, we started our studies by performing DFT calculations. We modelled the reaction of model *N*-(furan-2-ylmethylene)-*N*-methylmethanaminium with dimethylamine at the B3LYP-D3/def2TZVPP/SMD(ACN) level of theory using geometries optimized by B3LYO/6-31G(d) as implemented by Gaussian 09.[22] The Nazarov-like electrocyclization was identified as the rate-limiting step with a $\Delta G^{\ddagger}$ = 5.1 kcal mol^{-1} for the *E,E* intermediate - which affords the more thermodynamically stable *trans*-DCP product - and over 2-fold higher $\Delta G^{\ddagger}$ for the *E,Z*-isomer, in accordance with the report of Batey and coworkers.[2] Negative volumes of activation ($\Delta^{\ddagger}V$= −16.3 cm^3 mol^{-1} for the *E,E* – isomer vs $\Delta^{\ddagger}V$= −12.2 cm^3 mol^{-1} for the *E,Z* – isomer) suggest this rate-determining step could be highly accelerated in high-pressure conditions. Additionally, the reaction volume is also negative, consistent with bond formation and decrease of the molar volume occupied by the DCP products. [15-19]

Scheme 2. Free energy profiles for the complete DFT study. DFT calculations were performed at the B3LYP-D3/defTZVPP/SMD(ACN) level of theory using geometries optimized by B3LYP/6-31G(d). The distances shown are in Å, energies are in kcal mol^{-1} and volumes in cm^3 mol^{-1}.



We proceeded our studies by evaluating the electronic features of anilines in the formation of DCP in atmospheric and higher pressures employing $Sc(OTf)_3$ as catalyst in acetonitrile. This choice allowed us to perform the reaction under high pressure and low temperature without the risk of solvent freezing and is well suited for anilines.[2] Examples of electron-poor anilines, including 4-CF_3 and 4-Cl substituted *N*-methyl anilines, were reacted with furfural (Scheme 3). To evaluate the effect of the pressure the reactions were performed at 200 MPa and 900 MPa. To increase the pressure of the reaction to 200 MPa, a metal reactor with water was immersed in an acetone bath at −20 ºC, causing water freezing phenomena responsible for pressure induction to 200 MPa as described by Hayashi.[23-25] To reach 900 MPa a liquid piston vessel LV30/16 in a laboratory hydraulic press U101 was used at ambient temperature.

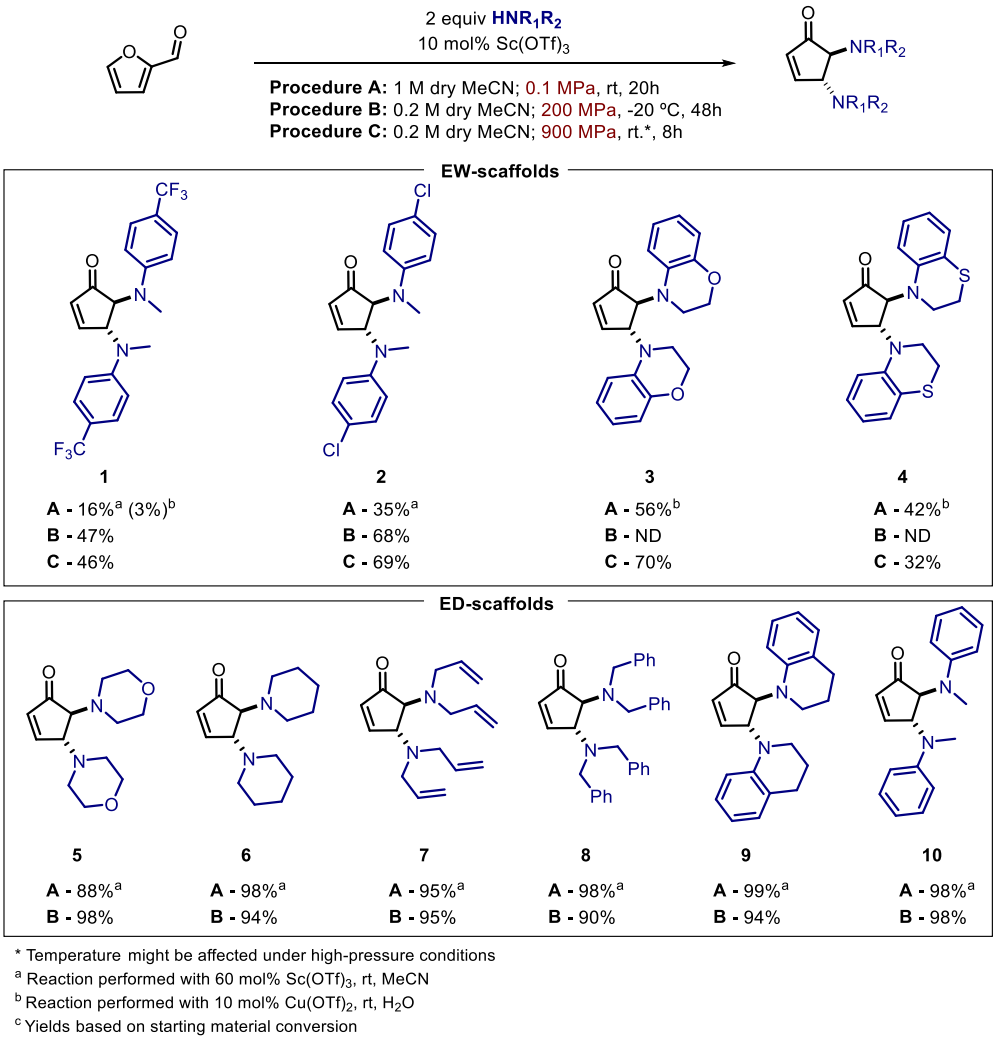
A slight increase to 16% yield of **1** was observed when $Sc(OTf)_3$ was used instead of only 3 % yield using $Cu(OTf)_2$. The less electron-withdrawing 4-Cl DCP derivative **2** was obtained in 35% yield using $Sc(OTf)_3$ as catalyst. The dehydro-benzoxazine and dehydro-benzothiazine moieties **3** and **4**, were obtained in low yields of 56% and 42% respectively, using the methodology of $Cu(OTf)_2$ in water (Scheme 3).

By transposing those reaction conditions at atmospheric pressure to the technology using 200 MPa at −20 ºC, the conversion towards **1** using $Sc(OTf)_3$ was significantly improved 3-fold from 16 to 47% isolated yield (Scheme 3). Similarly, the yield obtained for **2** was improved almost 2-fold (68% vs 35%). Employing amines with higher nucleophilicity such as morpholine, piperidine, diallylamine, dibenzylamine, tetrahydroquinoline and *N*-methyl aniline, DCP **5-10** were obtained in good to excellent yields com-

parable in both 200 MPa and atmospheric pressure using $Sc(OTf)_3$.

Interestingly, working at high-pressure conditions (900 MPa) did not improve the yield significantly on most of these substrates when comparing to the 200 MPa (Scheme 3). Such highlights that easily accessible home-made 200 MPa reactors may suffice in many simples EW-scaffolds, thus bypassing the low accessibility of the hydraulic reactors. Given this limited benefit and ease of availability, reaction at 900 MPa was not conducted for ED-amines.

Scheme 3. Scope of DCP obtained under atmospheric *vs* high pressure conditions



* Temperature might be affected under high-pressure conditions

[a] Reaction performed with 60 mol% $Sc(OTf)_3$, rt, MeCN

[b] Reaction performed with 10 mol% $Cu(OTf)_2$, rt, H_2O

[c] Yields based on starting material conversion

We then aimed at the preparation of a 3-NO_2 substituted dehydro-benzoxazine α-enaminone derivative, known as ATP-sensitive potassium channel modulator **11**.[26] Surprisingly, the synthesis of DCP **11** under classical conditions at atmospheric pressure, namely 10 mol% $Cu(OTf)_2$ in water[11] and 10 mol% $Sc(OTf)_3$ in acetonitrile[2] failed to afford any product at all. Solely by increasing $Sc(OTf)_3$ to 60 mol% allowed the isolation of DCP **11** in only 5% yield (see SInfo, Table S1).

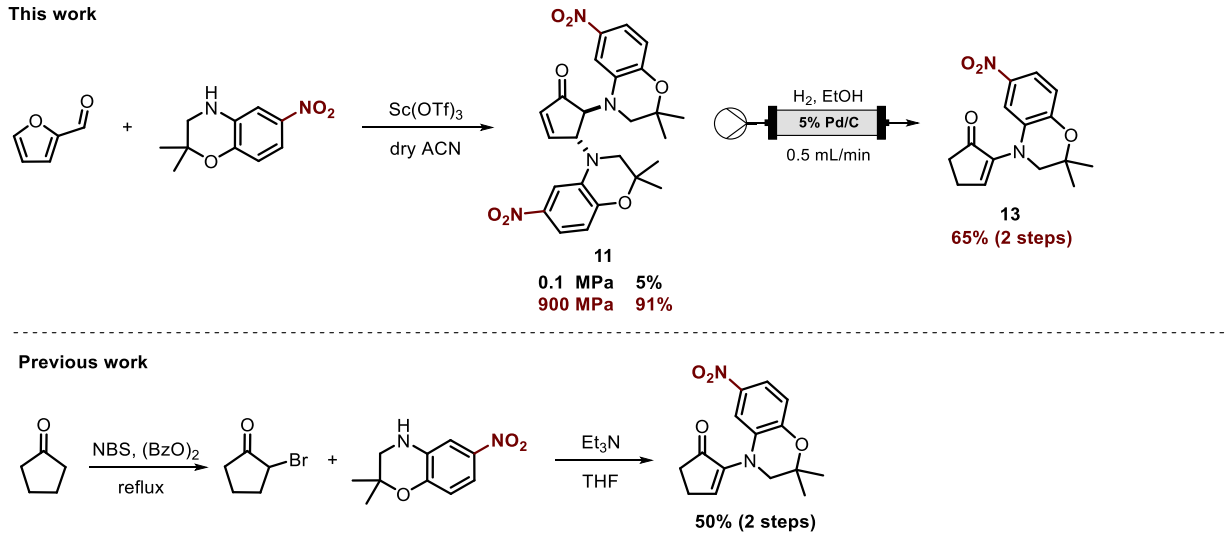
Interestingly, contrary to previous EW-amines, reaction of 3-NO_2 substituted dehydro-benzoxazine did not proceed at 200 MPa using Cu(II) or Sc(III) catalysis. On the other hand, the use of 10 mol% $Sc(OTf)_3$ at 900 MPa afforded **11** in 23% yield with minor formation of aminal **12** at 5 hours of reaction (see SInfo, Table S1). The poor yield led us to test other catalysts, although $Sc(OTf)_3$ remained the best choice. While 10 $Dy(OTf)_3$ afforded only 15% yield of **11**, $Cu(OTf)_2$ provided only the undesired aminal **12** in 19% yield. This is in accordance to our previous findings where

$Cu(OTf)_2$ promote the formation of aminals and thioaminals.[27, 28]

Furthermore, the use of 10 mol% $Sc(OTf)_3$ and extension of reaction time from 5 to 8h allowed to access isolated yields of 87% of **11,** which could be further improved to 91% by increasing reaction concentration 18-fold (see SInfo, Table S1).

This method enables the competitive preparation of 2-(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one 13, a known ATP-sensitive potassium channel modulator, comparing with reported method.[26] While previous work allows the preparation of 13 in 50% yield from cyclopentanone, the combination of this work with previous reported continuous flow hydrogenation of DCP enables the synthesis of 13 in increased yield of 65% from furfural (Scheme 4).[14] The new approach overcomes price, raw material availability (cyclopentenone is prepared from furfural upon Piancatelli rearrangement and hydrogenation)[29, 30] and potentially more sustainable, not only by the use of biorenewable furfural but also due to catalyst reuse in the continuous flow step.

Scheme 4. Synthesis of 3-NO_2 substituted dehydro-benzoxazine α-enaminone derivative - ATP-sensitive potassium channel agonist.



CONCLUSIONS

A series of DCP were synthesized at high pressure conditions in reactors operating at 900 MPa at room temperature and 200 MPa at −20 °C. Particular highlight is given to the reactions involving anilines with electron-withdrawing groups, whose DCP were prepared with more than 2-fold increase in yield compared with literature methods at atmospheric pressure, including the precursor for bioactive 2-(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one, a known ATP-sensitive potassium channel modulator, which was prepared with an increase in yield compared with previous method, providing a cheaper and more sustainable process.

The benefit of high pressure was guided by DFT calculations, which corroborate the positive effect of high pressure in the Nazarov-like electrocyclization step, identified as the rate limiting step and associated with a negative volume of activation ($\Delta^{\ddagger}V$) of −16.3 $cm^3\ mol^{-1}$.

EXPERIMENTAL SECTION

All solvents were of analytical grade and distilled prior to use. Unless otherwise stated, all reagents were used as received from commercial suppliers. Reactions at 900 MPa were conducted in a liquid piston vessel LV30/16 in a laboratory hydraulic press U101, Polish Academy of Sciences. NMR spectra were recorded in a Bruker Fourier 300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). Chemical shifts are reported in ppm (δ), and the center of the residual solvent signal was used as the internal standard which was related to TMS with δ 7.26 ppm (^1H in $CDCl_3$), δ 77.16 ppm (^{13}C in $CDCl_3$). The multiplicity of the signals is reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Spin–spin coupling constants (J) are given in hertz. High Resolution Mass Spectrometry (HRMS) results were recorded in a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo Scientific™ Q Exactive™ Plus) connected to Dionex Ultimate 3000 UHPLC+ system equipped with a Multiple-Wavelength detector, using an imChem Surf C18 TriF 100A 3 µm 100x2.1 mm column. Infrared spectra were recorded in a Bruker Alpha II FT-IR spectrometer.

General procedure A for the synthesis of DCP at 900 MPa. Furfural (1 equiv) was dissolved in dry MeCN (0.2 M) and placed in a Teflon vial containing $Sc(OTf)_3$ (10 mol%) and 4Å MS. Amine (2.1 equiv) was added and the reaction placed in a reactor operating at 900 MPa and room temperature for 8 h. Pure DCP was obtained after column chromatography in *n*-hexane/EtOAc (4:1) then (3:2).

General procedure B for the synthesis at 200 MPa. Furfural (1 equiv) was dissolved in dry MeCN (0.2 M) and

placed in a Teflon vial containing Sc(OTf)3 (10 mol%) and 4Å MS. Amine (2.1 equiv) was added and the reaction placed in a reactor operating at 200 MPa and −20ºC for 48h. The reaction crude was filtered through a pipette with low amount of silica. The yields were calculated from crude ^{1}H NMR analysis in $CDCl_3$ using 1,3,5-trimethoxybenzene as internal standard.

General procedure C for the synthesis of DCP using Cu(OTf)$_2$ at 0.1 MPa. To a solution of Sc(OTf)$_3$ (10 or 60 mol%) in MeCN (1 M) were added amine (2 equiv) and furfural (1 equiv) placed in a previously dried and Ar degassed round bottom flask containing 4Å MS. The reaction was allowed to stir vigorously at room temperature for 20 hours. Then the reaction mixture was diluted with water (1 mL) and extracted with EtOAc (3 × 2 mL). The organic phase was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR. If necessary, additional chromatographic purification was performed (n-hexane/EtOAc) to yield pure DCP.

General procedure D for the synthesis of DCP using Sc(OTf)$_3$ at 0.1 MPa. To a solution of Cu(OTf)$_2$ (10 mol%) in water (1 M) were added amine (2 equiv) and furfural (1 equiv). The reaction was allowed to stir vigorously at room temperature for 5 minutes. Then the reaction mixture was diluted with water (1 mL) and extracted with EtOAc (3 × 2 mL). The organic phase was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR. If necessary, additional chromatographic purification was performed (n-hexane/EtOAc) to yield pure DCP.

*Trans-4,5-bis(methyl(4-(trifluoromethyl)phenyl)amino)cyclopent-2-en-1-one **1**.* DCP **1** was obtained as a yellow solid following general procedure A (46% yield, 79 mg). R$_f$ = 0.43 (*n*-hexane/EtOAc – 3:2). m. p. = 115-120ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, J = 6.3, 2.0 Hz, 1H, H2), 7.40 – 7.33 (m, 4H, H12, H14, H20, H22), 6.72 – 6.66 (m, 2H, H19, H23), 6.57 – 6.50 (m, 3H, H1, H11, H15), 5.25 (dt, J = 4.1, 2.2 Hz, 1H, H3), 4.36 (d, J = 3.8 Hz, 1H, H4), 2.91 (s, 3H, H18), 2.86 (s, 3H, H10) ppm. ^{13}C NMR (75 MHz, $CDCl_3$)*: δ 200.7 (C5), 160.5 (C2), 151.2 (C17), 150.9 (C9), 135.3 (C1), 131.4 (C16, C24), 126.8-126.6 (C12, C14, C20, C22), 112.9 (C19, C23), 112.7 (C11, C15), 111.1 (C13, C21), 69.7 (C4), 62.0 (C3), 36.8 (C10), 33.5 (C18) ppm (see ESI for assignments). *Carbon spectrum presented as APT. HRMS calcd for $C_{21}H_{18}F_6N_2O$ $[M+H]^+$ = 429.14109 *m/z*, found 429.14016 *m/z*. FT-IR: 1705 cm^{-1} (C=O stretching); 1105 cm^{-1} and 1066 cm^{-1} (C-F stretching).

*Trans-4,5-bis((4-chlorophenyl)(methyl)amino)cyclopent-2-en-1-one **2**.* DCP **2** was isolated as a brown oil following general procedure A (69% yield, 99.8 mg). R*f* = 0.49 (*n*-hexane/EtOAc – 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 6.3, 2.0 Hz, 1H, H2), 7.17 – 6.98 (m, 4H, H14, H16, H19, H21), 6.61 – 6.56 (m, 2H, H13, H17), 6.47 – 6.41 (m, 3H, H1, H18, H22), 5.07 (dd, *J* = 3.9, 2.0 Hz, 1H, H3), 4.23 (d, *J* = 3.7 Hz, 1H, H4), 2.79 (s, 3H, H12), 2.74 (s, 3H, H10) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5 (C5), 161.0 (C2), 147.6 (C11), 147.4 (C9), 134.8 (C1), 129.1 (C14, C16), 129.0 (C19, C21), 123.6 (C20), 123.2 (C15), 115.3 (C18, C22), 114.9 (C13, C17), 69.8 (C4), 62.5 (C3), 36.7 (C10), 33.7 (C12) ppm (see ESI for assignments). HRMS calcd for $C_{19}H_{18}Cl_2N_2O$ $[M+Na]^+$ = 383.06939 *m/z*; found 383.101661 *m/z*.

*Trans-4,5-bis(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one **3**.* DCP **3** was isolated as a yellow solid following general procedure A (70% yield, 60.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 6.3, 2.1 Hz, 1H), 6.86-6.78 (m, 2H), 6.72-6.63 (m, 4H), 6.61-6.57 (m, 1H), 6.54 (dd, *J* = 6.3, 2.2 Hz, 1H), 6.17-6.06 (m, 1H), 5.29 (dt, *J* = 3.9, 2.1 Hz, 1H), 4.33-4.11 (m, 6H), 3.45-3.15 (m, 5H) ppm.[11]

*Trans-4,5-bis(2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)cyclopent-2-en-1-one **4**.* DCP **4** was isolated as a yellow solid following general procedure A (32% yield, 29.9 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 6.3, 2.1 Hz, 1H), 7.08 (ddd, *J* = 7.7, 5.8, 1.6 Hz, 2H), 6.92-6.82 (m, 2H), 6.75-6.63 (m, 3H), 6.52 (dd, *J* = 6.3, 2.1 Hz, 1H), 6.29 (dd, *J* = 8.3, 1.2 Hz, 1H), 5.18 (dt, *J* = 4.0, 2.1 Hz, 1H), 4.25 (d, *J* = 3.7 Hz, 1H), 3.68-3.39 (m, 5H), 3.21-2.96 (m, 5H) ppm.[11]

*Trans-4,5-dimorpholinocyclopent-2-en-1-one **5**.* DCP **5** was isolated as a yellow oil following general procedure B (98% yield, 25 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 6.2, 2.2 Hz, 1H), 6.23 (dd, *J* = 6.2, 1.8 Hz, 1H), 3.83-3.76 (m, 1H), 3.70 (dt, *J* = 11.9, 4.7 Hz, 8H), 3.28 (d, *J* = 3.0 Hz, 1H), 2.87-2.75 (m, 2H), 2.70-2.56 (m, 6H) ppm.[11]

*Trans-4,5-di(piperidin-1-yl)cyclopent-2-en-1-one **6**.* DCP **6** was isolated as a yellow oil following general procedure B (94% yield, 24 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 6.2, 2.2 Hz, 1H), 6.09 (dd, *J* = 6.2, 1.9 Hz, 1H), 3.72 (q, *J* = 2.3 Hz, 1H), 3.20 (d, *J* = 2.8 Hz, 1H), 2.71-2.64 (m, 2H), 2.51-2.44 (m, 6H), 1.55-1.44 (m, 9H), 1.41-1.35 (m, 3H) ppm.[11]

*Trans-4,5-bis(diallylamino)cyclopent-2-en-1-one **7**.* DCP **7** was isolated as a yellow oil following general procedure B (95% yield, 27 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 6.2, 2.1 Hz, 1H), 6.14 (dd, *J* = 6.2, 2.0 Hz, 1H), 5.87-5.77 (m, 4H), 5.25-5.07 (m, 8H), 4.08 (dt, *J* = 3.3, 2.1 Hz, 1H), 3.57 (d, *J* = 3.3 Hz, 1H), 3.36-3.12 (m, 8H) ppm.[11]

*Trans-4,5-bis(dibenzylamino)cyclopent-2-en-1-one **8**.* DCP **8** was isolated as a yellow oil following general procedure B (90% yield, 44 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 6.2, 2.1 Hz, 1H), 7.24-7.14 (m, 20H), 6.13 (dd, *J* = 6.2, 1.9 Hz, 1H), 3.97 (q, *J* = 2.4 Hz, 1H), 3.74 (d, *J* = 13.2 Hz, 3H), 3.53 (d, *J* = 2.9 Hz, 1H), 3.46 (d, *J* = 13.2 Hz, 2H), 3.30 (s, 4H) ppm.[11]

*Trans-4,5-bis(3,4-dihydroquinolin-1-(2H)-yl)cyclopent-2-en-1-one **9**.* DCP **9** was isolated as a yellow oil following general procedure B (94% yield, 34 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 6.3, 2.0 Hz, 1H), 6.89 (d, *J* = 7.3 Hz, 2H), 6.83-6.77 (m, 2H), 6.56-6.50 (m, 2H), 6.45-6.41 (m, 2H), 6.00 (d, *J* = 8.2 Hz, 1H), 5.29 (br s, 1H), 4.24 (br s, 1H), 3.25-3.05 (m, 4H), 2.71-2.61 (m, 4H), 1.92-1.80 (m, 4H) ppm.[11]

*Trans-4,5-4,5-bis(methyl(phenyl)amino)cyclopent-2-en-1-one **10**.* DCP **10** was isolated as a yellow oil following general procedure B (98% yield, 30 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 6.3, 2.0 Hz, 1H), 7.20-7.13 (m, 4H), 6.79-6.70 (m, 4H), 6.56 (dd, *J* = 8.8, 1.0 Hz), 6.49 (dd, *J* = 6.3, 2.1 Hz, 1H), 5.20 (dt, *J* = 4.0, 2.2 Hz, 1H), 4.33 (d, *J* = 3.6 Hz, 1H), 2.86 (s, 3H), 2.82 (s, 3H) ppm.[11]

Trans-4,5-trans-4,5-bis(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one ***11***. DCP **11** was obtained as an orange solid following general procedure A (91% yield, 111.8 mg). R_f = 0.33 (*n*-hexane/EtOAc – 3:2). m. p. = 222-224°C ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 6.3, 2.1 Hz, 1H, H2), 7.50 (dd, *J* = 8.7, 2.4 Hz, 2H, H20, H25), 7.41 (d, *J* = 2.5 Hz, 1H, H23), 7.21-7.11 (m, 1H, H22), 6.77 (d, *J* = 8.8 Hz, 2H, H19, H26), 6.65 (dd, *J* = 6.4, 2.0 Hz, 1H, H3), 5.40 (s, 1H, H1), 4.51 (s, 1H, H4), 3.15 (dd, *J* = 12.2, 8.6 Hz, 2H, H9), 3.01 (dd, *J* = 11.3, 7.4 Hz, 2H, H18), 1.48-1.33 (m, 12H, H29, H30, H27, H28) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1 (C5), 149.8 (C2), 149.4 (C2), 149.1 (C15), 141.3 (C21), 141.2 (C25), 136.7 (C1), 131.7 (C13, C14), 117.5 (C19, C26), 115.8 (C20, C25), 107.0 (C23), 106.3 (C22), 74.3 (C10, C17), 59.5 (C3, C4), 50.9 (C9, C18), 25.8 (C27, C28), 25.0 (C29, C30) ppm (see ESI for assignments). HRMS calcd for $C_{25}H_{26}N_4O_7$ $[M+H]^+$ = 495.18797 *m/z*, found 495.18764 *m/z*. FT-IR: 1709 cm^{-1} (C=O stretching); 1503 cm^{-1} (N-O stretching).

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge at. It contains additional procedures for the preparation of starting materials, additional experimental work and the NMR spectra of the compounds.

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ABBREVIATIONS

DCP, *trans*-4,5-diamino cyclopentenones; HP, high pressure; ED, electron-donating; EW, electron-withdrawing

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