Catalytic Formal Homo-Nazarov Cyclization

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Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT

The first catalytic method for the cyclization of vinyl-cyclopropyl ketones (formal homo-Nazarov reaction) is reported. Starting from activated cyclopropanes, heterocyclic and carbocyclic compounds were obtained under mild conditions using Brønsted acid catalysts. Preliminary investigation of the reaction mechanism indicated a stepwise process.

Carbocyclic and heterocyclic scaffolds occupy a privileged position in both natural products and pharmaceuticals. Consequently, the development of cyclization and cycloaddition reactions for the efficient formation of cyclic structures is a very important goal in organic chemistry. In this respect, the development of new, highly stereoselective catalytic methods is crucial to allow a more efficient and environmentally friendly access to polycyclic molecules.

One classical approach towards the construction of cyclopentenone rings is the Nazarov reaction, which is the electrocyclic ring closure of a pentadienyl cation, followed by proton transfer (A, Scheme 1). The potential of the Nazarov cyclization was recognized at an early stage in organic synthesis. Solutions to control the termination of the reaction were devised several decades ago, but the necessity of using a stoichiometric amount of strong Lewis or Brønsted acids has limited the use of this reaction. However, in the last five years the first examples of catalytic Nazarov reactions using milder Lewis or Brønsted acids were reported, together with the first examples of asymmetric induction.

cyclopropanation, followed by addition of a lithiated nucleophile to afford 2a in good yield (Scheme 2).

With our model substrate in hand, we began our studies by examining the most frequently used procedure for homo-Nazarov cyclization: stoichiometric SnCl₄. Using these conditions, complete polymerization of the sensitive substrate was observed.

As most Lewis acid led to extensive polymerization, we then turned towards Bronsted acid catalysts. The pKₐ value of the catalyst had a strong influence on the outcome of the reaction: Sulfuric and toluenesulfonic acids were optimal. Stronger acids led to decomposition of the starting material and no full conversion could be achieved with weaker acids. Examination of solvent effects showed that the reaction was faster in non-coordinating solvents, like dichloromethane, but polymerization was also difficult to suppress. Acetonitrile finally offered the best compromise, with sufficient reactivity but less pronounced polymerization. The cyclization of 2a in acetonitrile with 20 mol % toluenesulfonic acid at room temperature led to the formation of the desired cyclohexenone 3a in 70% isolated yield (Scheme 2).

The scope of the reaction was examined next (Table 1). Variation of the aromatic substituent on the cyclopropane confirmed the importance of its electron-donating ability: whereas no reaction was observed with a simple phenyl group (entry 2), a quantitative yield was observed with a 3,4- or 2,4- dimethoxyphenyl group (entries 3 and 4). This result is noteworthy, as electron-rich aromatic substituents are well represented in bioactive natural products and are easily oxidized to the corresponding carboxylic acids. A furan group was also tolerated at this position, although the yield was moderate due to partial polymerization (entry 5).

Finally, the influence of a methyl group α to the ketone was examined. Interestingly, a strong accelerating effect

(8) Oligomerization, then polymerization was apparent in ¹H NMR via formation of broad signals in several regions of the spectra, see Supporting Information (Figure S5).
was observed and cyclohexenone 3f was obtained in quantitative yield after only 15 min (entry 6).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>isolated yield</th>
<th>reaction time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>3a</td>
<td>70%</td>
<td>18 h</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>-</td>
<td>No Reaction</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>3c</td>
<td>quant</td>
<td>5 h</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>3d</td>
<td>quant</td>
<td>15 min</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>3e</td>
<td>50%</td>
<td>3h</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>3f</td>
<td>quant (dr = 5:1)</td>
<td>2 h</td>
</tr>
<tr>
<td>7</td>
<td>4e</td>
<td>5a</td>
<td>15%</td>
<td>36 h</td>
</tr>
<tr>
<td>8</td>
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<td>quant</td>
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<td>quant</td>
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</tr>
<tr>
<td>10</td>
<td>8</td>
<td>-</td>
<td>Polymerization</td>
<td></td>
</tr>
</tbody>
</table>

A plausible explanation would be a faster ring-opening of the cyclopropane ring due to sterical strain release and the higher stability of the formed enol intermediate.\(^\text{(11)}\) Importantly, this accelerating effect on the formal homo-Nazarov cyclization has never been reported before.

We then examined variation of the electron-rich side of the ketone. A dihydrofuran group proved to be more prone to polymerization and the desired product was isolated only in low yield with a 4-methoxyphenyl group on the cyclopropane (entry 7). The stronger stabilizing effect of the 2,4-dimethoxyphenyl substituent allowed the isolation of the desired 5-6 ring system in quantitative yield (entry 8). Replacing the dihydropyran group with an electron-rich N-methylindole heterocycle lead to an efficient cyclization in quantitative yield (entry 9), but only polymerization was observed with a benzoferan ring (entry 10). Interestingly, similar results were obtained in the related Nazarov cyclization.\(^\text{(31)}\)

In order to further increase the versatility of the formal homo-Nazarov process, it would be important to diminish the strong electronic constraints which limit the number of structures that can be synthesized. The use of substrates lacking an electron-donating hetero atom on the double-bond is highly desirable. Based on the seminal work of Denmark on silyl group-directed Nazarov reactions,\(^\text{(3b,12)}\) we decided to use an allyl silane group to enhance the nucleophilicity of the double bond and favorize cyclization (Scheme 3).

Gratifyingly, submitting vinyl-cyclopropyl ketone 11 to the optimized reaction conditions led to the formation of bicyclic ketone 12 in 30 min and 55% yield. The regioselectivity of the double bond formation was completely controlled by the elimination of the silyl group. Interestingly, only one diastereoisomer of 12 was isolated. The structure of 12 was tentatively assigned by NMR experiments (COSY, HSQC, NOESY).\(^\text{(13)}\) This preliminary result held promises for the application of the method in the synthesis of carbocyclic compounds.

The strong influence of electron-donating groups and acid strength on the reaction rate led us to propose a

\(^\text{(11)}\) As an alternative explanation, a higher fraction of the more stable enol tautomer could be envisaged to favor cyclization.


\(^\text{(13)}\) The obtained 2D NMR data strongly support the proposed structure assignment for 12. Further confirmation of the structure will be attempted by X-rays analysis of the corresponding thiosemicarbazone, a procedure developed by Denmark.\(^\text{(12)}\)

\(^\text{a}\) Reaction conditions: 0.4 mmol substrate in 8 mL CH\(_3\)CN with 20 mol % TsOH at 23°C.
tentative stepwise mechanism for the reaction with cyclopropane opening as rate-limiting (Scheme 4).

**Scheme 4. Postulated Mechanism**

In order to further support this mechanism, the following experiments were performed (Scheme 5): (1) The reaction kinetic was followed via 1H NMR spectroscopy, and the reaction was found to be first order in tosic acid for substrate 2a. (2) The use of stoichiometric deuterated tosic acid resulted in a mixture of non-deuterated, mono and bis-deuterated products at the α position to the ketone. A control experiment showed that no deuterium exchange was observed for the isolated cyclization product in the presence of deuterated tosic acid. A possible explanation for this surprising results would be the intramolecular attack of the oxygen atom of intermediates 1a or 1b to form an oxonium intermediate IIIa. From IIIa, proton-deuterium exchange should be easy via dihydrofuran IIIb. Dihydrofuran products have indeed been isolated in the related stoichiometric reaction of aryl vinyl ketones.6c Alternatively, proton exchange could be more rapid on cyclized intermediate IIb and Ia. Proton loss form IIb, or proton lost followed by tautomerization from IIa would then lead to the cyclohexene product. Additionally, a weak kinetic isotope effect (1.15) was observed using 40 mol % deuterated tosic acid, but this result is difficult to interpret due to fast proton exchange between substrate and catalyst. (3) Attempts were made to trap the proposed intermediates (enol and carbocation) of the catalytic cycle.14 With substrate 2a, all nucleophilic (water, allyl silane, butyl vinyl ether) and electrophilic (benzaldehyde, ethyl glyoxalate, acetic anhydride, ethyl acrylate) trapping agents tested so far were not successful. With cyclohexene derivative 15, however, alcohol 16 was obtained in 31% yield when the reaction was conducted in the presence of water.

All the data collected so far are in agreement with a rate-determining cyclopropane opening, followed by a fast cyclization. In the case were the cyclization is too slow (as with 15), polymerization can occur instead of the desired process. We speculate that key for catalysis is the fast tautomerization of the enol intermediates, which contrasts with the strong binding of stoichiometric reagents like SnCl₄, which prevent catalytic turnover.

**Scheme 5. Mechanism Investigation: (1) Van’t Hoff Plot and Reaction Order (2) Deuterium and (3) Trapping Experiments**

In summary, we have reported the first catalytic formal homo-Nazarov process. We have demonstrated that principles successful in the corresponding Nazarov reaction could also be applied to vinyl-cyclopropyl ketones, which allow the first high-yielding cyclization reaction for this class of substrates under mild conditions. First investigations of the reaction mechanism seem to indicate a stepwise mechanism with a rate-limiting cyclopropane ring opening: consequently, the reaction is mechanistically different from the classical Nazarov cyclization. Our future work will focus on the development of asymmetric variations as well as on applications in the synthesis of natural products and their analogs.

**Acknowledgment** The EPFL is acknowledged for financial support. We thank Prof. K. Gademann, Dr. T. Woods and Dr. H. Jessen from the Chemical Synthesis Laboratory at the EPFL for proofreading this manuscript.

**Supporting Information Available** Experimental procedures, spectroscopic information for new compounds, and detailed thermodynamic data are provided in the Supporting Information.
compounds and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org
Supporting information

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1 General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et₂O, CH₃CN, toluene, hexane and CH₂Cl₂ were dried by passage over activated alumina under nitrogen atmosphere (H₂O content < 10 ppm, Karl-Fischer titration). NEt₃ and pyridine were distilled under nitrogen from KOH. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F₂₅₄ TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ¹H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-d₆ or CD₃OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration; interpretation). ¹³C-NMR spectra were recorded with ¹H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, DMSO-d₆ or CD₃OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm⁻¹ (w = weak, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatograph and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAK IC column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used.

2 General Procedures

General procedure 1: formation of Weinreb’s amides

Following the reported procedure¹ N-methylmorpholine (1.1 equiv) was added to a solution of acid (1.0 equiv) in DMF (1 m) at 0 °C. After 25 min, isobutylchloroformate (1.1 equiv) was added dropwise at 0 °C. After 10 min, N,O-dimethylhydroxylamine hydrochloride (1.1 equiv) was added, followed by N-methylmorpholine (1.3 equiv) and the reaction mixture was warmed to 23°C. After 6 h, the reaction was quenched with 0.5 m HCl (2 mL/mmol of acid) and extracted with CH₂Cl₂ (3x2 mL/mmol of acid). The combined organic layers were washed with 0.5 m NaOH (2x2 mL/mmol of acid), brine (2 mL/mmol of acid), dried over MgSO₄ and the solvent was removed under reduced pressure. After 30 min in high vacuum, the residues were dissolved in Et₂O (6 mL/mmol of acid) and washed with brine (2x3 mL/mmol of acid).

dried over MgSO₄ and the solvent was removed under reduced pressure to give the Weinreb amide which was used directly without purification.

**General procedure 2: formation of Corey-Chaykovsky ylide**

\( n\text{BuLi} \ (2.5 \text{ M}, 1.0 \text{ equiv}) \) was added dropwise to a solution of trimethylsulfoxonium iodide (1.1 equiv) in anhydrous THF (0.75 M) at 0°C. The solution was allowed to warm to RT and stirring was continued under nitrogen for 1 hour. A solution 0.54 M of ylide was obtained.

**General procedure 3: Cyclopropanation 1 (Corey-Chaykovsky)**

A solution of ylide (1.1 equiv) in anhydrous THF (0.54 M) was added dropwise to a solution of the alkene derivative (1.0 equiv) in anhydrous THF (0.10 M) at RT under nitrogen. The mixture was stirred at the indicated temperature during the indicated time. The reaction was quenched with NaHCO₃ (10 mL/mmol) and extracted with Et₂O (3x10 mL/mmol). The combined organic layers were washed with brine (2x10 mL/mmol), dried over MgSO₄ and the solvent was removed under reduced pressure.

**General procedure 4: formation of ketone from Weinreb’s amide**

Following a slight modification of a reported procedure,\(^2\) \( t\text{BuLi} \ (2.0 \text{ equiv}) \) was added dropwise in a solution of alkene derivative (2.2 equiv) in THF (0.10 M) at -78°C. The flask was transferred in a bath of ice. After the indicated time the reaction was cooled to -78°C and a solution of amide (1.0 equiv) in THF (0.20 M) was added slowly dropwise. The reaction was stirred at -78°C during the indicated time and controlled via TLC. The solution was finally warmed at 0°C and quenched with saturate solution of NH₄Cl (5 mL/mmol). The product was extracted with Et₂O (10 mL/mmol of amide) and washed with brine (2x6 mL/mmol of amide), dried over MgSO₄ and concentrated under reduced pressure.

**General procedure 5: cyclization**

Toluenesulphonic acid (15 mg, 80 μmol, 0.20 equiv) was added to a solution of a vinyl cyclopropyl ketone derivative (0.40 mmol, 1.0 equiv) in anhydrous CH₃CN (10 mL) at room temperature. The reaction was stirred during the indicated time. The solution was quenched with NaHCO₃ (10 mL) and extracted with Et₂O (3x10 mL). The combined organic layers were washed with brine (2x10 mL), dried over MgSO₄ and the solvent was removed under reduced pressure.

### 3 Substrates synthesis

**2-Acetyl-5,6-dihydro-4H-pyran (17)**

![Diagram of 2-Acetyl-5,6-dihydro-4H-pyran (17)]

Following a reported procedure,\(^2\) a 1.5 M solution of \( t\text{BuLi} \) in pentane (16 mL, 24 mmol 1.0 equiv) was added dropwise to a solution of 5,6-dihydro-4H-pyran (2.2 mL, 24 mmol, 1.0 equiv) in THF (15 mL) at -78°C. The reaction mixture was warmed to 0°C and stirred during 30 min then cooled to -78°C. A solution

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of dimethylacetamide (2.9 mL, 32 mmol, 1.3 equiv) in THF (2.0 mL) was added dropwise during 5 min and the reaction was allowed to warm slowly to RT. After 2 h the reaction was quenched with an aqueous saturated solution of NH₄Cl (10 mL) and extracted with Et₂O (20×2 mL). The organic layers were combined and washed with sat NaCl, dried on MgSO₄ and evaporated under reduced pression. The crude product was purified by flash column chromatography (PET/AcOEt 3:1) to yield ketone 17 (2.4 g, 19 mmol, 80%) as yellow oil. 

\[ \text{Rf } 0.60 \text{ (DCM/AcOEt 16:1, Anisaldehyde).} \]

\[ \text{1H NMR (CDCl₃, 400 MHz) } \delta \text{ 5.93 (t, } J = 4.2 \text{ Hz, 1H; CH-alkene), 4.04 (t, } J = 4.9 \text{ Hz, 2H; CH₂O), 2.21 (s, 3H; CH₃), 2.17 (app dd, } J = 6.3, 10.7 \text{ Hz, 2H; CH₂pyran), 1.80 (app dt, } J = 6.1, 12.0 \text{ Hz, 2H; CH₂pyran).} \]

\[ \text{1H NMR spectra corresponded to the literature values.} \]

\( \text{2} \)

Following a slight modification of the reported procedure,³ NaOH (0.4 mL, 2.5 M) was added to a solution of 17 (0.50 g, 4.0 mmol, 1.0 equiv) in EtOH (8 mL) at RT. The reaction was stirred for 5 min then \( p \)-anisaldehyde 18 (0.50 mL, 4.0 mmol, 1.0 equiv) was added dropwise. The solution was quenched after 1 h and 30 min with water (10 mL) and extracted with Et₂O (20×2 mL). The organic layer was washed with brine, dried over MgSO₄, concentrated and the crude product was purified by flash column chromatography (PET/AcOEt 4:1) to yield 19 (40 mg, 0.14 mmol, 50%) as yellow oil. 

\[ \text{Rf } 0.70 \text{ (PET/AcOEt 4:1, Anisaldehyde).} \]

\[ \text{1H NMR (CDCl₃, 400 MHz) } \delta \text{ 7.72 (d, } J = 15.8 \text{ Hz, 1H; CH-Ar), 7.56 (d, } J = 8.7 \text{ Hz, 2H; Ar-H), 6.09 (t, } J = 4.2 \text{ Hz, 1H; alken}-} \]

\[ \text{H), 4.15 (t, } J = 5.2 \text{ Hz, 2H; CH₂O), 3.84 (s, 3H; OCH₃), 2.26 (app dd, } J = 6.3, 10.7 \text{ Hz, 2H; CH₂pyran), 1.96 – 1.85 (m, 2H; CH₂pyran).} \]

\[ \text{13C NMR (CDCl₃, 100 MHz) } \delta \text{ 184.7, 161.2, 151.6, 143.3, 130.0, 127.3, 117.8, 114.0, 109.9, 66.0, 55.0, 21.3, 20.6. IR } ν \text{ 2953 (w), 2934 (w), 2837 (w), 1660 (w), 1627 (m), 1589 (s), 1570 (s), 1510 (s), 1423 (m), 1327 (m), 1295 (m), 1281 (m), 1253 (s), 1200 (m), 1171 (s), 1090 (m), 1059 (s), 1027 (s), 986 (m), 918 (s), 829 (s), 800 (m), 773 (m), 714 (m). HRMS(ESI) calcd for } C_{15}H_{16}O_3^{+} (M+H) 245.1172, \text{ found 245.1178.} \]

\( \text{3} \)

\( \text{(E)-N-Methoxy-N-methyl-3-(4-methoxyphenyl)-acrylamide (1) and N-methoxy-N-methyl-1-[2-(4-}

\text{methoxyphenyl)-cyclopropan-1-yl]-formamide (21)} \)

Following general procedure 1, the acid 20 (2.00 g, 11.2 mmol, 1.00 equiv) gave the Weinreb amide 1 which was used directly without purification. Using general procedure 3, a solution of ylide (12.2 mL, 6.58 mmol, 1.20 eq) was added to a solution of amide 1 (1.21 g, 5.47 mmol, 1.00 equiv) in THF (45 mL). The reaction was stirred at 40°C during 2 h then quenched. Purification by flash column chromatography (PET/AcOEt, 7:3) afforded 21 (824 mg, 3.50 mmol, 64 %) over 2 steps as oil. 

\[ \text{Rf } 0.35 \text{ (PET/AcOEt 7:3, Anisaldehyde).} \]

\[ \text{1H NMR (CDCl₃, 400 MHz) } \delta \text{ 7.06 (d, } J = 8.6 \text{ Hz, 2H; Ar-H), 6.83 (d, } J = 8.7 \text{ Hz, 2H; Ar-} \]

\[ \text{H), 3.78 (s, 3H; OCH₃), 3.69 (s, 3H; OCH₃), 3.23 (s, 3H; NCH₃), 2.50 – 2.42 (m, 1H; cyclopropane CH),} \]

\[ \text{2} \]

2.33 (m, 1H; cyclopropane CH), 1.65 – 1.55 (m, 1H; cyclopropane CH₂), 1.30 – 1.22 (m, 1H; cyclopropane CH₂). ¹H NMR spectra corresponded to the literature values.¹

(E)-2-[2-(4-Methoxyphenyl)-1-cyclopropanecarbonyl]-5,6-dihydro-4H-pyran (2a)

Following general procedure 3, a solution of sulphoxonium ylide (2.90 mL, 1.57 mmol, 1.20 equiv) was added to a solution of alkene 19 (0.35 g, 1.4 mmol, 1.0 equiv) in THF (15 mL). The reaction was stirred at RT during 3 h and 30 min then quenched. Purification by flash column chromatography (PET/AcOEt 4:1) gave 2a (0.2 g, 0.8 mmol, 55%) as yellow oil.

General procedure 4 was followed using dihydropyran (0.14 mL, 1.5 mmol, 2.2 equiv) and amide 21 (0.16 g, 0.68 mmol, 1.0 equiv). The deprotonation time was 30 min at 0°C and the reaction was quenched after 2 h and 15 min to give 2a (105 mg, 410 μmol, 60%) after purification via flash chromatography (PET/AcOEt, 7:3) as yellow oil. R₇ 0.70 (PET/AcOEt 7:3, Anisaldehyde). ¹H NMR (CDCl₃, 400 MHz) δ 7.06 (d, J = 8.6 Hz, 2H; Ar H), 6.83 (d, J = 8.7 Hz, 2H; Ar-H), 6.01 (t, J = 4.2 Hz, 1H; alkene-H), 4.14 – 4.06 (m, 2H; CH₂O), 3.79 (s, 3H; OCH₃), 2.71 – 2.59 (m, 1H; CH cyclopropane), 2.54 (ddd, J = 4.1, 6.6, 10.5 Hz, 1H; CH cyclopropane), 2.22 (dd, J = 6.3, 10.7 Hz, 2H; CH₂ dihydropyran), 1.92 – 1.81 (m, 2H; CH₂ dihydropyran), 1.76 – 1.67 (m, 1H; CH₂ cyclopropane), 1.37 (ddd, J = 4.0, 6.8, 8.0 Hz, 1H; CH₂ cyclopropane). ¹³C NMR (CDCl₃, 100 MHz) δ 194.6, 158.2, 151.4, 132.5, 127.2, 113.8, 109.5, 66.3, 55.2, 29.3, 27.30, 21.4, 20.7, 19.2. IR ν 3036 (w), 2950 (w), 2934 (w), 2836 (w), 1681 (m), 1667 (m), 1625 (s), 1516 (s), 1440 (m), 1393 (m), 1311 (m), 1286 (s), 1248 (s), 1237 (m), 1201 (w), 1180 (s), 1091 (m), 1061 (s), 1032 (s), 999 (m), 917 (s), 822 (s), 751 (s). HRMS(ESI) calcd for C₁₆H₁₈O₃⁺ (M+H) 259.1329, found 259.1335.

(E)-2-[2-(Phenyl)-1-ethylenecarbonyl]-5,6-dihydro-4H-pyran (22)

Following a slight modification of the reported procedure⁴ iBuOK (44 mg, 0.40 mmol, 0.10 equiv) was added to a solution of 17 (0.50 g, 4.0 mmol, 1.0 equiv) in THF (40 mL) at 0°C. The reaction was stirred at 0°C for 5 min then benzaldehyde (0.60 mL, 6.0 mmol, 1.5 equiv) was added dropwise. The solution was quenched after 30 min with water (10 mL) and extracted with Et₂O (2×20 mL). The organic layer was washed with brine, dried over MgSO₄, concentrated and separated by flash column chromatography (PET/AcOEt 4:1) to yield 22 (39 mg, 0.14 mmol, 40%) as yellow oil. R₇ 0.40 (PET/AcOEt 6:1,

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Anisaldehyde). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.75 (d, $J = 15.8$ Hz, 1H; alkene-H), 7.60 (dd, $J = 2.9$, 6.6 Hz, 2H; Ph-H), 7.41 – 7.37 (m, 3H; Ph-H), 7.33 (d, $J = 15.8$ Hz, 1H; alkene-H), 6.12 (t, $J = 4.3$ Hz, 1H; alkene-H), 4.25 – 4.08 (m, 2H; CH$_2$O), 2.27 (dd, $J = 6.3$, 10.7 Hz, 2H; CH$_2$ pyran), 1.98 – 1.82 (m, 2H; CH$_2$ pyran). $^1$H NMR spectra corresponded to the literature values.$^5$

$^2$-(2-(Phenyl)-1-cyclopropanecarbonyl)-5,6-dihydro-4$^H$-pyran (2b)

Following general procedure 3, a solution of sulphoxonium ylide (1.1 mL, 0.58 mmol, 1.2 equiv) was added to a solution of alkene 22 (0.104 mg, 0.485 mmol, 1.00 equiv) in THF (5 mL). The reaction was stirred at RT during 15 min then quenched. Purification by flash column chromatography (PET/AcOEt 4:1) gave 2b (204 mg, 0.790 mmol, 50%) as colorless oil. $R_f$ 0.80 (PET/AcOEt 7:3, Anisaldehyde). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.28 (dd, $J = 4.7$, 12.4 Hz, 2H; Ph-H), 7.20 (t, $J = 7.3$ Hz, 1H; Ph-H), 7.12 (d, $J = 7.2$ Hz, 2H; Ph-H), 6.02 (t, $J = 4.2$ Hz, 1H; H-alkene), 4.16 – 4.04 (m, 2H; CH$_2$O), 2.80 – 2.67 (m, 1H; CH cyclopropane), 2.62 – 2.51 (m, 1H; CH cyclopropane), 2.22 (dd, $J = 6.3$, 10.7 Hz, 2H; CH$_2$ dihydropyran), 1.93 – 1.80 (m, 2H; CH$_2$ dihydropyran), 1.75 (dddd, $J = 4.1$, 5.2, 9.2 Hz, 1H; CH$_2$ cyclopropane), 1.42 (dddd, $J = 4.0$, 6.6, 8.1 Hz, 1H; CH$_2$ cyclopropane). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 194.5, 151.3, 140.4, 128.3, 126.3, 126.1, 109.7, 66.3, 29.7, 27.3, 21.44, 20.7, 19.6. IR $\nu$ 2958 (s), 2928 (s), 1737 (w), 1666 (m), 1627 (s), 1510 (m), 1497 (m), 1458 (m), 1398 (m), 1341 (m), 1287 (s), 1261 (m), 1237 (m), 1205 (m), 1182 (s), 1159 (m), 1081 (s), 1061 (s), 1030 (s), 1007 (s), 919 (s), 756 (s), 699 (s). HRMS(ESI) calcd for C$_{15}$H$_{16}$O$_2$ $^+$ (M+H) 251.1042, found 251.1037.

(E)-N-Methoxy-N-methyl-3-(3,4-dimethoxyphenyl)-acylamide (24) and N-methoxy-N-methyl-1-[2-(3,4-dimethoxyphenyl)-cyclopropan-1-yl]-formamide (25)

Following general procedure 1, the acid 23 (1.74 g, 8.36 mmol, 1.00 equiv) gave the Weinreb amide 24 which was used directly without purification. Using general procedure 3, a solution of ylide (16.5 mL, 8.91 mmol, 1.20 eq) was added to a solution of amide 24 (1.85 g, 7.36 mmol, 1.00 equiv) in THF (75 mL). The reaction was stirred at room temperature during 3 h then quenched. Purification by flash column chromatography (PET/ AcOEt, 3/2) afforded 25 (918 mg, 3.45 mmol, 47%) over 2 steps as colorless oil. $R_f$ 0.30 (PET/AcOEt 7:3, Anisaldehyde). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.79 (d, $J = 8.2$ Hz, 1H; Ar-H), 6.73 – 6.64 (m, 2H; Ar-H), 3.87 (s, 3H; OCH$_3$), 3.85 (s, 3H; OCH$_3$), 3.70 (s, 3H; OCH$_3$), 3.24 (s, 3H; NCH$_3$), 2.55 – 2.41 (m, 1H; CH cyclopropane), 2.33 (s, 1H; CH cyclopropane), 1.59 (dt, $J = 4.8$, 9.3 Hz, 1H; CH$_2$ cyclopropane), 1.27 (dddd, $J = 5.7$, 8.8, 17.5 Hz, 1H; CH$_2$ cyclopropane). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 173.0, 148.8, 147.5, 133.2, 117.9, 111.2, 110.2, 61.6, 55.8, 55.7, 32.4, 25.6, 21.3, 15.9. IR $\nu$ 3006 (w), 2963 (w), 2938 (w), 2837 (w), 1645 (w), 1518 (m), 1464 (m), 1441 (w), 1420 (w), 1392 (w), 1254 (m), 1235 (m), 1141 (m), 1028 (m), 1004 (w), 907 (s), 805 (w), 726 (s), 648 (m). HRMS(ESI) calcd for C$_{14}$H$_{19}$NO$_4$ $^+$ (M+H) 266.1387, found 266.1385.

2-[2-(3,4-Methoxyphenyl)-1-cyclopropanecarbonyl]-5,6-dihydro-4H-pyran (2c)

Following general procedure 4, dihydropyran (344 μL, 3.77 mmol, 2.20 equiv) and amide 25 (450 mg, 1.71 mmol, 1.00 equiv) were reacted together. The deprotonation time was 45 min at 0°C and the reaction was quenched after 45 min. Purification by flash chromatography (PET/AcOEt, 7:3) afforded 2c (158 mg, 0.550 mmol, 32 %) as colorless oil. Rf 0.40 (PET/AcOEt 7:3, Anisaldehyde). 1H NMR (CDCl3, 400 MHz) δ 6.79 (d, J = 8.8 Hz, 1H; Ar-H), 6.67 (d, J = 6.2 Hz, 2H; Ar-H), 6.02 (t, J = 4.2 Hz, 1H; alkene-H), 4.17 – 4.07 (m, 2H; CH2O), 3.87 (s, 3H; OCH3), 3.85 (s, 3H; OCH3), 2.70 – 2.61 (m, 1H; cyclopropane CH), 2.54 (ddd, J = 4.1, 6.7, 10.6 Hz, 1H; cyclopropane CH), 2.22 (dd, J = 6.3, 10.7 Hz, 2H; dihydropyran CH2), 1.92 – 1.81 (m, 2H; dihydropyran CH2), 1.71 (ddd, J = 4.2, 5.1, 9.1 Hz, 1H; cyclopropane CH2), 1.39 (ddd, J = 4.0, 6.7, 8.1 Hz, 1H; cyclopropane CH2). 13C NMR (CDCl3, 100 MHz) δ 194.7, 151.4, 148.8, 147.7, 133.1, 117.9, 111.2, 110.0, 109.6, 66.3, 55.9, 55.8, 29.6, 27.5, 21.5, 20.7, 19.2. IR ν 3002 (w), 2935 (w), 2836 (w), 2252 (w), 1663 (m), 1590 (w), 1518 (s), 1464 (m), 1439 (w), 1389 (m), 1331 (m), 1287 (m), 1255 (m), 1181 (m), 1141 (m), 1091 (m), 1062 (m), 1027 (s), 913 (s), 806 (m), 729 (s). HRMS(ESI) calcd for C17H20O4+ (M+H) 289.1424, found 289.1434.

(E)-2,4-Dimetoxy-cis-cinnamic acid (27)

Following a reported procedure, a solution of aldehyde 27 (11.0 g, 66.7 mmol, 1.00 equiv), malonic acid (17.5 g, 168 mmol, 2.50 equiv) and β-alanine (1.0 g, 89 mmol, 0.20 equiv) in pyridine (3 mL) was stirred under reflux for 90 min. After cooling to RT, the flask was transferred in an ice bath and a concentrated solution of HCl (8 mL) was added dropwise. The precipitate was filtered, washed with cold water (2x10mL) and dried without further purification to give 27 as light yellow solid (12.5 g, 60.0 mmol, 90%). 1H NMR (DMSO-d6, 400 MHz) δ 12.11 (s, 1H; OH), 7.75 (d, J = 16.1 Hz, 1H; CH-Ar), 7.61 (d, J = 8.6 Hz, 1H; Ar-H), 6.64 – 6.54 (m, 2H; Ar-H), 6.37 (d, J = 16.1 Hz, 1H; CHCO), 3.86 (s, 3H; OCH3), 3.81 (s, 3H; OCH3). 1H NMR spectra corresponded to the literature values.

(E)-N-Methoxy-N-methyl-3-(2,4-dimethoxyphenyl)-acrylamide (28) and N-methoxy-N-methyl-1-[2-(2,4-dimethoxyphenyl)-cyclopropan-1-yl]-formamide (9)

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Following general procedure 1, the acid 27 (12.47 g, 59.89 mmol, 1.000 equiv) gave the Weinreb amide 28 which was used directly without purification. Using general procedure 3, a solution of ylide (53.4 mL, 28.8 mmol, 1.20 eq) was added to a solution of amide 28 (6.00 g, 23.9 mmol, 1.00 equiv) in THF (240 mL). The reaction was stirred at RT overnight then quenched. Purification by flash column chromatography (PET/AcOEt, 3:2) gave 9 (3.93 g, 14.8 mmol, 62%) over 2 steps as white solid. \( R_f \) 0.35 (PET/AcOEt, 3:2, Anisaldehyde). Mp 58 -59 °C. \( ^1H \) NMR (CDCl 3, 400 MHz) \( \delta \) 6.88 (d, \( J = 8.3 \) Hz, 1H; Ar-H), 6.46 – 6.37 (m, 2H; Ar-H), 3.80 (s, 3H; OCH 3), 3.79 (s, 3H; OCH 3), 3.24 (s, 3H; NCH 3), 2.64 – 2.51 (m, 1H; CH cyclopropane), 2.25 (s, 1H; CH cyclopropane), 1.57 – 1.49 (m, 1H; CH 2 cyclopropane), 1.30 – 1.20 (m, 1H; CH 2 cyclopropane). \( ^13C \) NMR (CDCl 3, 100 MHz) \( \delta \) 173.6, 159.4, 159.2, 126.6, 121.2, 103.7, 98.3, 61.3, 55.2, 32.5, 20.7, 19.8, 14.3. IR \( \nu \) 3002 (w), 2960 (w), 2938 (w), 2837 (w), 1650 (s), 1614 (m), 1585 (m), 1510 (s), 1461 (s), 1438 (s), 1417 (s), 1394 (m), 1364 (m), 1321 (w), 1289 (s), 1263 (m), 1208 (s), 1176 (s), 1159 (s), 1155 (s), 1127 (s), 1096 (m), 1033 (s), 933 (m), 920 (w), 874 (w), 834 (s), 800 (w), 775 (w), 729 (w). HRMS(ESI) calced for C14H19NO4+ (M+H) 266.1387, found 266.1381.

2-[2-(2,4-Dimethoxyphenyl)-1-cyclopropanecarbonyl]-5,6-dihydro-4H-pyran (2d)

Following general procedure 4, a solution of amide 9 (400 mg, 1.51 mmol, 1.00 equiv) was added to a solution of dihydropyran (345 \( \mu \)L, 3.77 mmol, 2.50 equiv). The deprotonation time was 30 min at 0°C and the reaction was quenched after 2 h and 15 mins to give 2d (305 mg, 1.01 mmol, 70%) as yellow oil after purification via flash chromatography (PET/AcOEt, 7:3). \( R_f \) 0.55 (PET/ AcOEt 7:3, Anisaldehyde). \( ^1H \) NMR (CDCl 3, 400 MHz) \( \delta \) 6.87 (d, \( J = 8.2 \) Hz, 1H; Ar-H), 6.41 (dd, \( J = 2.3 \), 10.6 Hz, 2H; Ar-H), 4.60 – 4.08 (m, 2H; CH 2O), 3.79 (s, 3H; OCH 3), 2.74 – 2.62 (m, 1H; cyclopropane CH), 2.57 (dt, \( J = 4.8 \), 9.3 Hz, 1H; alkene-H), 2.22 (dd, \( J = 4.3 \), 10.7 Hz, 2H; dihydropyran CH 2), 1.92 – 1.81 (m, 2H; dihydropyran CH 2), 1.71 – 1.63 (m, 1H; cyclopropane CH 2), 1.36 (td, \( J = 3.8 \), 7.6 Hz, 1H; cyclopropane CH 2). \( ^13C \) NMR (CDCl 3, 100 MHz) \( \delta \) 195.2, 159.4, 159.2, 151.5, 126.5, 121.4, 109.4, 103.8, 98.3, 66.23, 55.3, 25.9, 24.7, 21.5, 20.7, 17.8. IR \( \nu \) 3010 (w), 2957 (w), 2936 (w), 2837 (w), 1681 (m), 1666 (m), 1625 (s), 1586 (m), 1510 (m), 1464 (m), 1436 (m), 1397 (m), 1333 (m), 1289 (s), 1265 (w), 1237 (w), 1209 (s), 1182 (m), 1160 (m), 1124 (w), 1092 (w), 1063 (s), 1034 (s), 1002 (w), 954 (w), 918 (m), 837 (w). HRMS(ESI) caled for C17H20O4+ (M+H) 289.1434, found 289.1412.

(E)-N-Methoxy-N-methyl-3-(2-furanyl)-acrylamide (30) and N-methoxy-N-methyl-1-[2-(2-furanyl)\[2\]-cyclopropan-1-yl]-formamide (31)

Following general procedure 1, the acid 29 (1.55 g, 11.2 mmol, 1.00 equiv) gave the Weinreb amide 30 which was used directly without purification. Using the general procedure 3, a solution of ylide (10 mL, 5.4 mmol, 1.2 eq) was added to a solution of amide 31 (810 g, 4.47 mmol, 1.00 equiv) in THF (46 mL). The reaction was warmed to 40°C and stirred during 3 h before quenching. Purification by flash column chromatography (PET/AcOEt, 7:3) gave 28 (436 mg, 2.24 mmol, 50%) over two steps as colorless oil. \( R_f \) 0.50 (PET/AcOEt 7:3, Anisaldehyde). \( ^1H \) NMR (CDCl 3, 400 MHz) \( \delta \) 7.27 – 7.25 (m, 1H; furan-H), 6.28
(dd, J = 1.9, 3.0 Hz, 1H; furan-H), 6.07 (d, J = 3.1 Hz, 1H; furan-H), 3.73 (s, 3H; OCH₃), 3.23 (s, 3H; NCH₃), 2.58 – 2.40 (m, 2H; 2xCH cyclopropane), 1.59 – 1.50 (m, 1H; CH₂ cyclopropane), 1.44 – 1.32 (m, 1H; CH₂ cyclopropane). ¹³C NMR (CDCl₃, 100 MHz) δ 172.6, 153.7, 140.8, 110.3, 105.0, 61.5, 32.4, 19.2, 18.9, 14.0. IR ν 3522 (w), 2938 (w), 1648 (s), 1509 (m), 1462 (m), 1440 (s), 1423 (s), 1389 (m), 1354 (m), 1176 (m), 1148 (m), 1115 (m), 1098 (m), 995 (s), 952 (m), 914 (m), 801 (m), 733 (s).

HRMS(ESI) calcd for C₁₀H₁₃NO₃⁺ (M+H) 196.0968, found 196.0975.

2-[2-(Furan-2-yl)-1-cyclopropanecarbonyl]-5,6-dihydro-4H-pyran (2e)

Following general procedure 4, dihydropyran (400 μL, 4.40 mmol, 2.00 equiv) and amide 31 (430 mg, 2.20 mmol, 1.00 equiv) were reacted together. The deprotonation time was 30 min at 0°C and the reaction was quenched after 1 h. Purification by flash chromatography (PET/AcOEt, 9:1) afforded 2e (300 mg, 1.38 mmol, 63%) as a yellow oil. Rf 0.25 (PET/AcOEt, Anisaldehyde). ¹H NMR (CDCl₃, 400 MHz) δ = 7.26 (m, 1H; Ar-H), 6.29 (s, 1H; Ar-H), 6.08 (s, 1H; Ar-H), 6.04 (t, J = 3.9 Hz, 1H; alkene-H), 4.16 – 4.07 (m, 2H; CH₂O), 2.89 – 2.73 (m, 1H; cyclopropane CH), 2.57 (t, J = 9.6 Hz, 1H; cyclopropane CH), 2.23 (dd, J = 5.8, 10.6 Hz, 2H; dihydropyran CH₂), 1.87 (dd, J = 5.6, 10.8 Hz, 2H; dihydropyran CH₂), 1.67 – 1.58 (m, 1H; cyclopropane CH₂), 1.47 (t, J = 9.0 Hz, 1H; cyclopropane CH₂). ¹³C NMR (CDCl₃, 100 MHz) δ 193.6, 153.4, 150.9, 140.6, 110.1, 109.7, 104.9, 65.9, 24.6, 22.1, 21.1, 20.4, 16.8. IR ν 3118 (w), 2932 (w), 2873 (w), 1683 (m), 1683 (m), 1668 (m), 1626 (s), 1509 (w), 1445 (w), 1431 (w), 1385 (m), 1350 (w), 1314 (w), 1287 (m), 1246 (m), 1236 (m), 1202 (m), 1180 (m), 1149 (w), 1091 (m), 1061 (s), 1034 (m), 1008 (m), 991 (m), 955 (w), 916 (s), 886 (w), 797 (m), 789 (m), 730 (s). HRMS(ESI) calcd for C₁₃H₁₄O₃⁺ (M+H) 219.1016, found 219.1011.

(E)-3-(4-Methoxyphenyl)-2-methyl-acrylic acid (32)

Following a reported procedure, a mixture of anisaldehyde 18 (10 mL, 82 mmol, 1.0 equiv), propionic anhydride (19 mL, 0.16 mol, 2.0 equiv) and sodium propionate (7.9 g, 82 mmol, 1.0 equiv) was heated at 150 °C for 12 h. After cooling to 23 °C, 4 M NaOH solution (60 mL) was added and the mixture was washed with Et₂O (2x20 mL). The water layer was acidified to pH = 1 with conc. HCl and the precipitated colorless solid was washed with water and dried in high vacuo to give 32 as a colorless solid (10.0 g, 52.1 mmol, 63%). Mp 154-157 °C, Lit: 152-155 °C. ¹H NMR (CDCl₃, 400 MHz) δ 7.79 (br s, 1H; alkene-H), 7.43 (d, J = 8.6 Hz, 2H; Ar-H), 6.95 (d, J = 9.0 Hz, 2H; Ar-H), 3.85 (s, 3H; OCH₃), 2.16 (d, J = 1.6 Hz, 3H; CHCH₃). ¹³C NMR (CDCl₃, 75 MHz) δ 174.5, 160.0, 140.8, 131.7, 128.2, 125.2, 113.9, 55.3, 13.7. IR ν 2939 (w), 2838 (w), 2634 (w), 2512 (w), 1661 (m), 1600 (m), 1569 (m), 1511 (m), 1424 (m), 1320 (m), 1275 (s), 1253 (s), 1180 (m), 1130 (m), 1030 (m), 912 (s), 829 (s), 808 (s), 746 (s), 693 (m), 652 (w). ¹H NMR and IR spectra corresponded to the literature values. ⁸

(E)-N-Methoxy-N-methyl-3-(4-methoxyphenyl)-2-methyl-acrylamide (33) and N-methoxy-N-methyl-1-[2-(4-methoxyphenyl)-cyclopropan-1-methyl-1-yl]-formamide (34)

Following general procedure 1, the acid 32 (3.00 g, 15.6 mmol, 1.00 equiv) gave the Weinreb amide 33 which was used directly without purification. A suspension of copper(I) chloride (1.5 g, 15 mmol, 5.0 equiv, purified via precipitation from a solution in conc. HCl, washed with water, EtOH, Et2O and dried in HV) and Zinc dust (activated with 1% HCl, washed with water, EtOH, Et2O and dried in HV, 1.0 g, 15 mmol, 5.0 equiv) in Et2O (7 mL) was refluxed for 30 min. The reaction mixture was cooled to 23 °C and a solution of Weinreb amide 33 (0.71 g, 3.0 mmol, 1.0 equiv) in Et2O (2 mL) was added. After refluxing for 72 h, the reaction mixture was cooled to 23 °C and quenched with sat. NH4Cl (5 mL). Water (5 mL) was added and the reaction mixture was extracted with Et2O (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 5:1-4:1) to yield cyclopropane 34 (0.15 g, 0.61 mmol, 20%, 61% brsm) as a colorless oil as well as recovered starting material 33 (0.47 g, 2.0 mmol, 66%).

IR ν 2934 (w), 1646 (m), 1515 (s), 1463 (m), 1247 (s), 1176 (m), 1029 (m), 911 (s), 837 (m), 730 (s), 647 (w). HRMS(ESI) calcd for C14H19NO3+ (M+Na) 272.1257, found 272.1259.

2-[2-(4-Methoxyphenyl)-1-methyl-1-cyclopropanecarbonyl]-5,6-dihydro-4H-pyran (2f)

Following general procedure 4, dihydropyran (44 mL, 0.48 mmol, 2.0 equiv) and amide 34 (59 mg, 0.24 mmol, 1.0 equiv) were reacted together. The deprotonation time was 30 min at 0°C and the reaction was quenched after 30 min. Purification by flash chromatography (PET/AcOEt 10:1-5:1) afforded 2f (39 mg, 0.14 mmol, 60%) as colorless oil. IR ν 2956 (w), 2930 (w), 1669 (w), 1624 (m), 1515 (s), 1463 (w), 1444 (w), 1382 (w), 1290 (w), 1061 (w), 1036 (m), 916 (s), 836 (m), 732 (s), 648 (w). HRMS(ESI) calced for C17H20O3+ (M-H) 271.1329, found 271.1333.
The reaction was carried out following general procedure 4 from dihydrofuran (353 μL, 4.67 mmol, 2.20 equiv) and amide 21 (500 mg, 2.12 mmol, 1.00 equiv). The deprotonation time was 30 min at 0°C and the reaction was quenched after 1 hour. Purification by flash chromatography (PET/AcOEt, 7:3) afforded 4a (517 mg, 2.12 mmol, 100%) as colorless oil. 

\[ R_{f} \text{0.55 (PET/AcOEt 7:3, Anisaldehyde).} \]

\[ \delta \text{1H NMR (CDCl}_3\text,) \]

\[ \text{δ} 7.05 (d, J = 8.7 Hz, 2H; Ar-H), 6.83 (d, J = 8.6 Hz, 2H; Ar-H), 5.99 (t, J = 3.1 Hz, 1H; alkene-H), 4.49 (t, J = 9.8 Hz, 2H; CH}_2\text{O), 3.79 (s, 3H; OCH}_3\text{), 2.84 (td, J = 3.1, 9.8 Hz, 2H; dihydrofuran CH}_2\text{), 2.63–2.54 (m, 1H; cyclopropane CH), 2.52–2.44 (m, 1H; cyclopropane CH), 1.79–1.72 (m, 1H; cyclopropane CH), 1.44–1.37 (m, 1H; cyclopropane CH).} \]

\[ \delta \text{13C NMR (CDCl}_3\text,) \]

\[ \delta 190.7, 158.4, 155.8, 132.2, 127.3, 113.9, 111.3, 70.3, 55.3, 30.7, 29.4, 29.4, 19.0. \]

\[ \text{IR } \nu \text{3004 (w), 2936 (w), 2836 (w), 1649 (s), 1614 (m), 1516 (s), 1462 (m), 1442 (m), 1421 (m), 1394 (w), 1367 (w), 1303 (w), 1289 (w), 1248 (s), 1177 (m), 1122 (m), 1097 (m), 1035 (m), 1097 (m), 1035 (m), 942 (w), 824 (m), 809 (m), 767 (w), 743 (w).} \]

\[ \text{HRMS(ESI) calcd for C}_{15}\text{H}_{16}\text{O}_5^+ (M+H) 245.1172, found 245.1178.} \]

2-[2-(2,4-Methoxy-phenyl)-1-cyclopropanecarbonyl]-4,5-dihydro-furan (4b)

Amide 9 (400 mg, 1.51 mmol, 1.00 equiv) was added to dihydrofuran (285 μL, 3.77 mmol, 2.50 equiv), following general procedure 4. The deprotonation time was 30 min at 0°C and the reaction was quenched after 45 min to give 4b (414 mg, 1.51 mmol, 100%) as white solid without further purification. 

\[ R_{f} \text{0.45 (PET/AcOEt 7:3, Anisaldehyde).} \]

\[ \text{MP 100-102 °C.} \]

\[ \delta \text{1H NMR (CDCl}_3\text,) \]

\[ \delta 6.87 (d, J = 8.2 Hz, 1H; Ar-H), 6.41 (dt, J = 2.3, 8.3 Hz, 2H; Ar-H), 5.98 (t, J = 3.1 Hz, 1H; alkene-H), 4.57–4.41 (m, 2H; CH}_2\text{O), 3.79 (s, 3H; OCH}_3\text{), 3.78 (s, 3H; OCH}_3\text{), 2.84 (td, J = 3.1, 9.8 Hz, 2H; dihydrofuran CH}_2\text{), 2.70 (ddd, J = 4.2, 7.1, 9.0 Hz, 1H; cyclopropane CH), 2.41 (dt, J = 4.9, 8.1 Hz, 1H; cyclopropane CH), 1.79–1.65 (m, 1H; cyclopropane CH), 1.41 (td, J = 3.9, 7.6 Hz, 1H; cyclopropane CH).} \]

\[ \delta \text{13C NMR (CDCl}_3\text,) \]

\[ \delta 191.2, 159.6, 159.3, 156.0, 126.7, 121.0, 111.0, 103.8, 98.4, 70.2, 55.3, 30.7, 28.0, 25.0, 17.5.} \]

\[ \text{IR } \nu \text{3103 (w), 3000 (w), 2959 (w), 2936 (w), 2836 (w), 1663 (m), 1613 (s), 1585 (m), 1509 (m), 1466 (m), 1456 (m), 1436 (m), 1410 (m), 1342 (w), 1291 (m), 1264 (m), 1209 (s), 1175 (m), 1160 (m), 1060 (m), 1044 (s), 1013 (m), 940 (m), 905 (w), 838 (m), 799 (w), 729 (w).} \]

\[ \text{HRMS(ESI) calcd for C}_{16}\text{H}_{18}\text{O}_4^+ (M+H) 275.1278, found 275.1240.} \]

2-[2-(4-Methoxyphenyl)-1-cyclopropanecarbonyl]-1-methylindole (6)

Following general procedure 4, N-methylindole (192 μL, 1.50 mmol, 2.20 equiv) was added to amide 21 (160 mg, 0.680 mmol, 1.00 equiv). The deprotonation time was 15 min at 0°C and the reaction was quenched after 1 h. Purification by flash chromatography (PET/AcOEt, 7:3) afforded 8 (105 mg, 0.340
mmol, 50%) as white crystals. R_f 0.80 (PET/AcOEt 7:3, Anisaldehyde). Mp 103-105 °C. ^1^H NMR (CDCl_3, 400 MHz) δ 7.68 (d, J = 8.0 Hz, 1H; Ar-H), 7.41 – 7.35 (m, 3H; Ar-H), 7.19 – 7.09 (m, 3H; Ar-H), 6.86 (d, J = 8.7 Hz, 2H; Ar-H), 4.10 (s, 3H; NCH_3), 3.81 (s, 3H; OCH_3), 2.91 – 2.78 (m, 1H; cyclopropane CH), 2.65 (ddd, J = 4.1, 6.7, 10.4 Hz, 1H; cyclopropane CH), 1.91 – 1.80 (m, 1H; cyclopropane CH_2). 13C NMR (CDCl_3, 100 MHz) δ 191.6, 158.4, 140.1, 135.6, 132.6, 127.5, 125.9, 123.4, 120.6, 114.0, 111.5, 110.3, 55.3, 32.2, 30.6, 28.7, 22.9. IR ν 3002 (w), 2961 (w), 2937 (w), 2835 (w), 1648 (s), 1614 (m), 1515 (s), 1466 (m), 1439 (w), 1428 (w), 1404 (m), 1380 (w), 1323 (w), 1293 (w), 1250 (s), 1195 (m), 1163 (w), 1152 (w), 1129 (w), 1032 (m), 991 (m), 913 (w), 824 (w), 748 (m). HRMS(ESI) calcd for C_{20}H_{19}NO_2^+ (M+H) 306.1489, found 306.1475.

(E)-2-[2-(4-Methoxyphenyl)-1-ethylenecarbonyl]-benzofurane (36)

Following a slight modification of the reported procedure,^3 NaOH (4.4 mL, 2.5 M) was added to a solution of 35 (2.50 g, 15.6 mmol, 1.00 equiv) in EtOH (40 mL) at RT. The reaction was stirred for 5 min then p-anisaldehyde 18 (1.90 mL, 15.6 mmol, 1.00 equiv) was added dropwise. The solution was quenched after 30 min with water (20 mL) and extracted with Et_2O (40x2 mL). The organic layer was washed with brine, dried over MgSO_4, concentrated and purified by flash column chromatography (PET/AcOEt 9:1) to yield 36 (1.74 g, 6.25 mmol, 40%) as yellow oil. R_f 0.70 (PET/AcOEt 7:3, Anisaldehyde). Mp 125-127 °C. ^1^H NMR (CDCl_3, 400 MHz) δ 7.93 (d, J = 15.7, 1H; CH-Ar), 7.73 (d, J = 7.8 Hz, 1H; Ar-H), 7.66 (d, J = 8.7 Hz, 2H; Ar-H), 7.63 (d, J = 6.7 Hz, 2H; Ar-H), 7.45 (m, 1H; Ar-H), 7.45 (d, J = 15.7 Hz, 1H; CHCO), 7.33 (t, J = 7.5 Hz, 1H; Ar-H), 6.96 (d, J = 8.7 Hz, 2H; Ar-H), 3.87 (s, 3H; OCH_3). 13C NMR (CDCl_3, 100 MHz) δ 179.6, 161.9, 155.6, 153.8, 144.4, 130.5, 128.0, 127.3, 123.8, 123.1, 118.7, 114.4, 112.7, 112.3, 112.3, 55.2. IR ν 3137 (w), 3065 (w), 2844 (w), 1652 (s), 1589 (s), 1571 (s), 1557 (s), 1510 (s), 1475 (m), 1447 (m), 1424 (s), 1361 (w), 1348 (m), 1295 (s), 1262 (s), 1248 (s), 1194 (m), 1177 (s), 1160 (s), 1139 (s), 1036 (s), 1024 (s), 983 (s), 934 (s), 910 (s), 880 (s), 855 (m), 819 (s), 784 (s), 735 (s). HRMS(ESI) calcd for C_{18}H_{14}O_3^+ (M+H) 279.0999.

2-[2-(4-Methoxyphenyl)-1-cyclopropanecarbonyl]-benzofurane (8)

Following general procedure 3, a solution of sulphoxonium ylide (5.9 mL) was added to a solution of alkene 36 (800 mg, 2.90 mmol, 1.00 equiv) in THF (30 mL). The reaction was stirred at RT during 45 min then quenched. Purification by flash column chromatography (PET/AcOEt 4:1) gave 8 (384 mg, 1.31 mmol, 45%) as white crystals. R_f 0.80 (PET/AcOEt 7:3, Anisaldehyde). Mp 115-117 °C. ^1^H NMR (CDCl_3, 400 MHz) δ 7.70 (d, J = 7.9 Hz, 1H; Ar-H), 7.61 – 7.52 (m, 2H; Ar-H), 7.47 (dd, J = 4.1, 11.4 Hz, 1H; Ar-H), 7.31 (t, J = 7.5 Hz, 1H; Ar-H), 7.13 (d, J = 8.6 Hz, 2H; Ar-H), 6.87 (d, J = 8.7 Hz, 2H; Ar-H), 3.81 (s, 3H; OCH_3), 3.00 – 2.84 (m, 1H; CH cyclopropane), 2.76 (dd, J = 4.0, 6.8, 10.6 Hz, 1H; CH cyclopropane), 1.99 – 1.87 (m, 1H; CH cyclopropane), 1.62 – 1.53 (m, 1H; CH_2 cyclopropane). 13C NMR (CDCl_3, 100 MHz) δ 189.1, 158.4, 155.6, 153.0, 132.0, 128.0, 127.4, 127.1, 123.8, 123.2, 114.0, 112.4, 112.4, 55.2, 29.8,
29.5, 19.2. IR ν 3004 (w), 2935 (w), 2835 (w), 1659 (s), 1516 (s), 1440 (m), 1397 (s), 1337 (m), 1294 (m), 1248 (s), 1180 (s), 1158 (s), 1140 (s), 1034 (s), 1001 (s), 932 (m), 888 (m), 830 (s), 801 (s), 749 (s), 688 (m). HRMS(ESI) calcd for C_{19}H_{16}O_{3}^+ (M+H) 293.1172, found 293.1172.

(2-Bromo-cyclohex-2-enyl)-trimethyl-silane (10)

Following a reported procedure,⁹ bromoform (12 mL, 0.14 mmol, 1.0 equiv) was added to a thick slurry of potassium tert-butoxide (17 g, 0.15 mmol, 1.1 equiv) and cyclopentene (13 mL, 0.15 mmol, 1.1 equiv) in dry hexane (65 mL) over 30 min at 0 °C. The resulting yellow-brown suspension was warmed to 23 °C over 3 h and poured onto 300 g of ice. The mixture was extracted with PET (3x200 mL). The combined organic layers were washed with water (3x200 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. Distillation (bp = 35-40 °C, p = 0.3 mbar) gave cyclopropane 38 (23 g, 96 mmol, 69%) instead of the expected vinyl bromide 39 as a colorless oil. Quantitative conversion of 38 to the desired product 39 as a slightly brown oil was obtained by heating at 130 °C for 45 min. ¹H NMR (CDCl₃, 400 MHz) δ 6.19 (m, 1H; alkene-H), 4.78 (m, 1H; CHBr), 2.09-2.38 (m, 6H; CH₂), 2.00 (m, 1H; CH₂), 1.76 (m, 1H; CH₂). ¹³C NMR (CDCl₃, 100 MHz) δ 133.7, 122.2, 53.9, 33.6, 27.4, 16.3. IR ν 2953 (w), 2935 (w), 2832 (w), 1634 (w), 1437 (w), 1319 (w), 1191 (m), 996 (w), 943 (w), 907 (s), 889 (m), 847 (w), 730 (s), 638 (m). ¹H NMR, ¹³C NMR corresponded to the literature values.¹⁰

Following a reported procedure,¹¹ trichlorosilane (1.1 mL, 11 mmol, 1.1 equiv) was added to a solution of allyl bromide 39 (2.4 g, 10 mmol, 1.0 equiv), triethylamine (dist. over KOH, 1.4 mL, 10 mmol, 1.0 equiv) and CuCl (49 mg, 0.50 mmol, 0.050 equiv) in Et₂O (5 mL) at 15 °C. The resulting thick suspension was stirred at 23 °C for 4 h and filtered under nitrogen. The filter cake was washed with Et₂O (2x5 mL), the combined filtrates were cooled to 0 °C and MeMgBr (3 M in Et₂O, 13.3 mL, 40.0 mmol, 4.00 equiv) was added dropwise. The resulting red-green suspension was stirred for 1 h at 23 °C and poured onto sat. NH₄Cl solution (50 mL) at 0 °C. The mixture was extracted with Et₂O (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET) to yield allylsilane 10 (0.85 g, 3.7 mmol, 37%) contaminated by the corresponding methyl addition product 40 (0.45 g, 2.6 mmol, 26%) as colorless oils. Allyl silane 10 of 93% purity (0.71 g, 3.1 mmol, 31%) was obtained after stirring 1 h in HV (0.3 mbar). ¹H NMR (CDCl₃, 400 MHz) δ 5.92 (td, J = 3.8, 1.6 Hz, 1H; alkene-H), 1.95-2.20 (m, 3H; CH₂), 1.82-1.94 (m, 1H; CH₂), 1.67-1.80 (m, 1H; CH₂), 1.47-1.64 (m, 2H; CH₂), 0.14 (s, 9 H, SiCH₃). ¹³C NMR (CDCl₃, 100 MHz) δ 126.1, 125.4, 35.3, 27.4, 27.3, 20.6, -1.0. IR ν 2953 (m), 2858 (w), 1637 (w), 1451 (w), 1249 (s), 1055 (w), 1031 (w), 986 (m), 940 (w), 919 (w), 836 (s), 798 (m), 733 (m), 692 (w), 615 (w). ¹H NMR, ¹³C NMR corresponded to the literature values.¹²

2-[2-(2,4-Dimethoxyphenyl)-1-cyclopropanecarbonyl]-3-trimethylsilyl-cyclohex-2-ene (11)

Amide 9 (363 mg, 1.37 mmol, 1.00 equiv) was added to vinyl bromide 10 (320 mg, 1.37 mmol, 1.00 equiv), following general procedure 4. The deprotonation time was 30 min at -78°C and the reaction was quenched after 1 h to give 11 (250 mg, 0.70 mmol, 51%) as colorless oil without further purification. Rf 0.25 (PET/AcOEt 15:1, Anisaldehyde). ¹H NMR (CDCl₃, 400 MHz) δ 6.89 (m, 1H; Ar-H), 6.82 (m, 1H; Ar-H), 6.42 (m, 1H; Ar-H), 6.39 (m, 1H; alkene-H), 3.79 (s, 3H; OCH₃), 3.75 (s, 3H; OCH₃), 2.59 (t, J = 9.8 Hz, 1H; CH cyclopropane), 2.45 – 2.32 (m, 2H; CH cyclopropane), 2.22 (m, 2H; CH₂ cyclohexene), 1.87 (m, 1H; CH₂ cyclopropane), 1.64–1.49 (m, 5H, CH₂ cyclohexene), 1.37 (td, J = 3.9, 7.4 Hz, 0.7H; CH₂ cyclopropane, Diastereoisomer A), 1.33 – 1.24 (m, 0.3H; CH₂ cyclopropane, Diastereoisomer B), 0.94 – 0.76 (m, 1H, CHSi), 0.01 (s, 7H, SiCH₃ Diastereoisomer A), -0.02 (s, 2H; SiCH₃ Diastereoisomer B). From 0 ppm to 2.6 ppm we found several overlaps due to presence of 2 diastereoisomers. ¹³C NMR (CDCl₃, 75 MHz) δ 200.0, 159.5, 143.6, 135.8, 135.3, 126.8, 126.7, 121.6, 103.5, 103.8, 98.4, 98.3, 55.4, 55.1, 26.8, 26.5, 25.7, 25.7, 24.1, 24.0, 23.9, 23.8, 23.2, 23.2, 20.6, 16.8, 16.1, 11.1. The excess of signals is due to presence of 2 diastereoisomers. IR ν 3003 (w), 2937 (w), 2836 (w), 1648 (m), 1614 (m), 1585 (w), 1509 (m), 1456 (w), 1436 (w), 1402 (m), 1291 (m), 1248 (m), 1208 (s), 1186 (m), 1159 (m), 1123 (w), 1034 (m), 990 (w), 955 (m), 920 (w), 835 (s), 796 (w), 752 (w), 731 (w). HRMS(ESI) calcd for C₂₁H₃₀O₃Si+(M+H) 359.2037, found 359.2044.

1-Bromocyclohexene (42)

Following a reported procedure,¹³ a mixture of cyclohexenone (distilled, 0.50 g, 5.1 mmol, 1.0 equiv), triphenylphosphine (3.2 g, 12 mmol, 2.4 equiv) and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (4.9 g, 12 mmol, 2.4 equiv) was refluxed in CH₂Cl₂ (15 mL) for 18 h. The crude mixture was filtered over SiO₂, washed with CH₂Cl₂ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/Et₂O 100:1) to yield 1-bromocyclohexene (42) (354 mg, 90% pure by ¹H NMR, 1.98 mmol, 39%). Rf 0.80 PET/Et₂O 100:1, KMnO₄). ¹H NMR (CDCl₃, 400 MHz) δ 6.03 (m, 1H, alkene H), 2.36-2.48 (m, 2 H, CH₂), 2.02-2.12 (m, 2 H, CH₂), 1.68-1.79 (m, 2 H, CH₂), 1.54-1.67 (m, 2 H, CH₂). ¹³C NMR (CDCl₃, 100 MHz) δ 128.9, 122.3, 35.2, 27.4, 24.5, 21.1. ¹H NMR, ¹³C NMR corresponded to the literature values.¹³

Cyclohex-1-enyl-[2-(4-methoxy-phenyl)-cyclopropyl]-methanone (15)

Amide 21 (445 mg, 1.68 mmol, 1.00 equiv) was added to vinyl bromide 42 (300 mg, 90% pure, 1.68 mmol, 1.00 equiv), following general procedure 4. The deprotonation time was 30 min at -78°C and the reaction was quenched after 2 h to give 15 (275 mg, 1.07 mmol, 64%) as a colorless solid after purification on column chromatography (PET/AcOEt 10:1). \( R_f \) 0.25 (PET/AcOEt 15:1, Anisaldehyde). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.05 (d, \( J = 8.8 \) Hz, 2 H, Ar H), 6.99 (br m, 1 H, alkene H), 6.83 (d, \( J = 8.8 \) Hz, 2 H, Ar H), 3.79 (s, 3 H, OCH\(_3\)), 2.51 (m, 1 H, cyclopropane H), 2.45 (m, 1 H, cyclopropane H), 2.21-2.33 (m, 4 H, cyclohexene CH\(_2\)), 1.57-1.73 (m, 5 H, Cyclohexene and cyclopropane CH\(_2\)), 1.30 (dd, \( J = 8.1, 6.5, 4.0 \) Hz, 1 H, cyclopropane CH\(_2\)). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta \) 199.1, 158.2, 139.8, 139.7, 132.9, 127.2, 113.8, 55.3, 28.3, 27.5, 26.1, 23.5, 21.9, 21.6, 18.2. IR \( \nu \) 3004 (w), 2935 (m), 2934 (m), 2863 (w), 2862 (w), 2836 (w), 2835 (w), 1650 (s), 1649 (s), 1517 (s), 1405 (m), 1329 (m), 1250 (s), 1205 (m), 1037 (w), 1031 (w), 917 (w), 837 (w), 741 (w), 736 (w). HRMS(ESI) calcd for C\(_{17}\)H\(_{21}\)O\(_2\)+ (M+H) 257.1536, found 257.1543.

4 Cyclization

5-(4-Methoxyphenyl)-3,4,6,7-tetrahydro-2H-chromen-8(5H)-one (3a)

The reaction was carried out following general procedure 5, starting from cyclopropane 2a (103 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 18 h. Purification by flash chromatography (PET/AcOEt, 4:1) afforded 3a (72 mg, 0.28 mmol, 70 %) as yellow oil. \( R_f \) 0.35 (PET/AcOEt 1:1, Anisaldehyde). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.12 (d, \( J = 8.6 \) Hz, 2H; Ar-H), 6.88 (d, \( J = 8.6 \) Hz, 2H; Ar-H), 4.20 – 3.99 (m, 2H; CH\(_2\)O), 3.81 (s, 3H, OCH\(_3\)), 3.58 (t, \( J = 5.2 \) Hz, 1H; CH-Ar), 2.59 – 2.47 (m, 1H; CH\(_2\)), 2.45 – 2.27 (m, 2H; CH\(_2\)), 2.03 – 1.90 (m, 3H; CH\(_2\)), 1.85 (d, \( J = 6.0 \) Hz, 2H; CH\(_2\)). \(^1\)H NMR (benzene-d\(_6\), 400 MHz) \( \delta \) 6.83-6.77 (m, 2H, Ar-H), 6.76-6.70 (m, 2H; Ar-H), 3.75-3.57 (m, 2H; CH\(_2\)O), 3.33 (s, 3H, OCH\(_3\)), 3.02 (dd, \( J = 6.00, 5.29 \) Hz, 1H; CH-Ar), 2.37 (ddd, \( J = 16.61, 9.59, 4.50 \) Hz, 1H, CH\(_2\)-ketone), 2.14 (ddd, \( J = 16.58, 8.04, 4.49 \) Hz, 1H, CH\(_2\)-ketone), 1.85 (tdd, \( J = 13.29, 9.57, 4.65 \) Hz, 1H, CH\(_2\)), 1.62-1.49 (m, 2H, CH\(_2\)), 1.45-1.35 (m, 1H, CH\(_2\)), 1.32-1.20 (m, 2H, CH\(_2\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 193.2, 158.5, 146.8, 133.3, 132.1, 128.9, 114.1, 65.8, 55.2, 45.0, 34.9, 30.9, 25.1, 21.8. IR \( \nu \) 2934 (m), 2870 (w), 1683 (s), 1612 (w), 1511 (s), 1463 (w), 1385 (w), 1293 (w), 1247 (s), 1180 (m), 1154 (m), 1085 (w), 1035 (m), 986 (w), 926 (w), 833(m). HRMS(ESI) calcd for C\(_{16}\)H\(_{18}\)O\(_3\)+ (M+H) 259.1329, found 259.1323.

Deuterium Labeling Experiment
The reaction was carried out following general procedure 5, starting from cyclopropane 2a (33 mg, 0.13 mmol, 1.0 equiv) and deuterated tosic acid monohydrate (23 mg, 0.13 mmol, 1.0 equiv). The reaction was quenched after 1 h. Purification by flash chromatography (PET/AcOEt, 4:1) afforded a mixture of 3a, 13 and 14 (20 mg, 0.078 mmol, 61 %) as yellow oil. Rf 0.35 (PET/AcOEt 1:1, Anisaldehyde). 1H NMR (benzene- d6, 400 MHz) δ 6.83-6.77 (m, 2H, Ar-H), 6.76-6.70 (m, 2H; Ar-H), 3.75-3.57 (m, 2H; CH2O), 3.33 (s, 3H, OCH3), 3.02 (m, 1H, CH-Ar), 2.37 (ddd, J = 16.61, 9.59, 4.50 Hz, 0.6H, CH2-ketone), 2.14 (ddd, J = 16.58, 8.04, 4.49 Hz, 0.6H, CH2-ketone), 1.85 (m, 1H, CH2), 1.62-1.49 (m, 2H, CH2), 1.45-1.35 (m, 1H, CH2), 1.32-1.20 (m, 2H, CH2). 13C NMR (CDCl3, 100 MHz) δ 193.33, 193.29, 193.24, 158.6, 146.8, 133.36, 133.331, 133.30, 133.26, 132.16, 132.13, 129.0, 114.1, 65.9, 55.3, 45.06, 45.03, 45.00, 44.97, 34.9, 34.5 (t, J = 19.5 Hz), 30.91, 30.85, 30.81, 30.74, 29.7, 25.1, 21.8. HRMS(ESI) calcd for C16H18NaO3+ (M+Na) 281.1148, found 281.1141 (87%), calcd for C16H17DNaO3+ (MD+Na) 282.1211, found 282.1205 (100%), calcd for C16H16D2NaO3+ (MD2+Na) 283.1274, found 283.1278 (70%).

5-(3,4-Dimethoxyphenyl)-3,4,6,7-tetrahydro-2H-chromen-8(5H)-one (3c)

The reaction was performed following general procedure 5, starting from cyclopropane 2c (115 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 5 h to give 3c (115 mg, 0.400 mmol, 100 %) as yellow oil without further purification. Rf 0.25 (PET/AcOEt 1:1, Anisaldehyde). 1H NMR (CDCl3, 400 MHz) δ 6.82 (d, J = 8.2 Hz, 1H; Ar-H), 6.76 – 6.68 (m, 2H; Ar-H), 4.17 – 4.02 (m, 2H; CH2O), 3.87 (s, 3H; OCH3), 3.86 (s, 3H; OCH3), 3.57 (t, J = 5.3 Hz, 1H; CH Ar) 2.54 (ddd, J = 4.3, 9.5, 16.2 Hz, 1H; CH2), 2.46 – 2.28 (m, 2H; CH2), 2.03 – 1.92 (m, 3H; CH2), 1.91 – 1.78 (m, 2H; CH2). 13C NMR (CDCl3, 100 MHz) δ 193.1, 149.1, 146.7, 144.9, 133.7, 131.9, 119.8, 111.1, 65.8, 55.8, 45.3, 34.9, 30.7, 25.0, 21.7. IR ν 2936 (w), 2871 (w), 2835 (w), 1731 (w), 1678 (s), 1629 (w), 1592 (w), 1515 (s), 1464 (m), 1450 (w), 1418 (w), 1385 (w), 1279 (w), 1265 (m), 1248 (m), 1233 (m), 1182 (m), 1139 (s), 1085 (w), 1026 (s), 987 (m), 913 (m), 851 (w), 812 (w), 728 (s). HRMS(ESI) calcd for C17H20O4+ (M+H) 289.1434, found 289.1420.

5-(2,4-Dimethoxyphenyl)-3,4,6,7-tetrahydro-2H-chromen-8(5H)-one (3d)

The cyclization was achieved following general procedure 5, starting from cyclopropane 2d (115 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 10 min to give 3d (115 mg, 0.400 mmol, 100 %) as yellow oil without further purification. Rf 0.40 (PET/AcOEt 1:1, Anisaldehyde). 1H NMR (CDCl3, 400 MHz) δ 6.82 (d, J = 8.2 Hz, 1H; Ar-H), 6.77 – 6.68 (m, 2H; Ar-H), 4.19 – 4.01 (m, 2H; CH2O), 3.87 (s, 3H; OCH3), 3.86 (s, 3H; OCH3), 3.57 (t, J = 5.3 Hz, 1H;
5-(Furan-2-yl)-3,4,6,7-tetrahydro-2H-chromen-8(5H)-one (3e)

The cyclization was achieved following general procedure 6, starting from cyclopropane 2e (87.3 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 2 h. Purification by flash chromatography (PET/AcOEt, 2:8) afforded 3 (44 mg, 0.20 mmol, 50 %) as yellow oil. Rf 0.10 (PET/AcOEt 8:2, Anisaldehyde). 1H NMR (CDCl3, 400 MHz) δ 7.35 (s, 1H; Ar-H), 6.36 – 6.26 (m, 1H; Ar-H), 6.07 (d, J = 3.1 Hz, 1H; Ar-H), 4.13 – 4.01 (m, 2H; CH2O), 3.68 (t, J = 4.9 Hz, 1H; CH Ar), 2.68 – 2.51 (m, 1H; CH2), 2.47 – 2.35 (m, 1H; CH2), 2.32 – 2.13 (m, 2H; CH2), 2.10 (t, J = 6.4 Hz, 2H; CH2), 1.86 (dq, J = 3.6, 6.6 Hz, 2H; CH2). 13C NMR (CDCl3, 100 MHz) δ 192.8, 154.4, 146.5, 142.0, 130.0, 110.2, 106.7, 65.9, 39.2, 35.1, 29.6, 24.8, 21.8. IR ν 2933 (w), 2874 (w), 1685 (m), 1635 (w), 1505 (w), 1385 (w), 1289 (m), 1146 (w), 1087 (w), 1043 (w), 1009 (w), 985 (w), 911 (m), 854 (w), 810 (w), 730 (s). HRMS(ESI) calcd for C13H14O3 + (M+H) 219.1016, found 219.1007.

5-(4-Methoxyphenyl)-7-methyl-3,4,6,7-tetrahydro-2H-chromen-8(5H)-one (3f)

The reaction was carried out following general procedure 5, starting from cyclopropane 2f (64.0 mg, 0.235 mmol, 1.00 equiv) and tosic acid (9.0 mg, 0.047 mmol, 0.20 equiv). The reaction was quenched after 1 h. Purification by flash chromatography (PET/AcOEt, 8:2) afforded 3f (64.0 mg, 0.235 mmol, 100 %, 5:1 mixture of diastereoisomers) as yellow oil. Rf 0.15 (PET/AcOEt 8:2, Anisaldehyde). 1H NMR (CDCl3, 400 MHz) (Major diastereoisomer) δ 7.10 (d, J = 8.4 Hz, 2H; Ar-H), 6.86 (d, J = 8.5 Hz, 2H; Ar-H), 4.26 (d, J = 8.8 Hz, 1H; CH2O), 3.95 – 3.81 (m, 1H; CH2O), 3.79 (s, 3H; OCH3), 3.55 (d, J = 7.3 Hz, 1H; CH Ar), 2.64 – 2.40 (m, 1H; CH2), 2.14 (m, 1H; CH2), 1.79 (m, 4H; CH2), 1.15 (m, 3H; CH3). 13C NMR (CDCl3, 100 MHz) δ 195.4, 158.4, 146.3 135.1, 131.6, 129.0, 128.5 114.0, 113.6, 65.7, 55.2, 46.0, 41.3, 40.3, 25.0, 21.7, 14.9. IR ν 2961 (w), 2932 (w), 2870 (w), 2836 (w), 1729 (w), 1682 (s), 1623 (m), 1611 (w), 1584 (w), 1512 (s), 1458 (w), 1444 (w), 1385 (w), 1272 (m), 1250 (s), 1178 (m), 1149 (s), 1093 (w), 1079 (w), 1035 (m), 990 (m), 919 (w), 855 (w), 833 (m), 732 (m). HRMS(ESI) calcd for C17H20O3 + (M+H) 273.1485, found 273.1490.

4-(4-Methoxyphenyl)-2,3,5,6-tetrahydrobenzofuran-7(4H)-one (5a)

CH Ar), 2.54 (ddd, J = 4.3, 9.5, 16.2 Hz, 1H; CH2), 2.46 – 2.28 (m, 2H; CH2), 2.04 – 1.92 (m, 3H; CH2), 1.91 – 1.77 (m, 2H; CH2). 13C NMR (CDCl3, 100 MHz) δ 193.8, 159.8, 158.3, 147.0, 132.8, 128.4, 120.9, 103.7, 98.8, 65.8, 55.3, 55.2, 38.3, 34.9, 28.2, 24.9, 21.9. IR ν 2961 (w), 2937 (w), 2837 (w), 1674 (m), 1612 (w), 1587 (w), 1505 (w), 1465 (w), 1438 (w), 1419 (w), 1388 (w), 1293 (w), 1259 (w), 1208 (m), 1158 (m), 1115 (w), 1087 (w), 1036 (w), 986 (w), 907 (s), 838 (w), 827 (w), 726 (s), 648 (m). HRMS(ESI) calcd for C17H20O4 + (M+H) 289.1434, found 289.1444.
The reaction was performed following general procedure 5, starting from cyclopropane derivate 4a (98 mg, 0.40 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 36 h. Purification by flash chromatography (PET/AcOEt, 7:3) afforded 5a (15 mg, 0.060 mmol, 15 %) as yellow oil. Rf 0.40 (PET/AcOEt 7:3, Anisaldehyde). $^1$H NMR (CDCl3, 400 MHz) $\delta$ 7.12 (d, $J = 8.5$ Hz, 2H; Ar-H), 6.89 (d, $J = 8.5$ Hz, 2H; Ar-H), 4.50 – 4.37 (m, 2H; CH 2O), 3.81 (s, 3H; OCH 3), 3.75 (m, 1H; CH Ar), 2.65 (t, $J = 9.6$ Hz, 2H; CH 2), 2.59 – 2.50 (m, 1H; CH 2), 2.49 – 2.31 (m, 2H; CH 2), 2.11 – 1.98 (m, 1H; CH 2). $^{13}$C NMR (CDCl3, 100 MHz) $\delta$ 190.3, 158.7, 150.2, 136.9, 133.1, 128.6, 114.2, 69.3, 55.3, 41.2, 36.5, 33.1, 32.8. IR $\nu$ 2951 (w), 2934 (w), 2838 (w), 1767 (w), 1676 (s), 1641 (w), 1611 (m), 1512 (s), 1463 (w), 1443 (w), 1395 (w), 1340 (w), 1302 (w), 1178 (m), 1148 (w), 1102 (s), 1033 (m), 1003 (m), 935 (w), 874 (w), 834 (m), 771 (w), 736 (w). HRMS(ESI) calcd for C15H16O3 $^+$(M+H) 245.1172, found 245.1171.

$\textbf{4-(2,4-Dimethoxyphenyl)-2,3,5,6-tetrahydrobenzofuran-7(4H)-one (5b)}$

The reaction was carried out following general procedure 6 from cyclopropane 4b (110 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 15 min to give 5b (104 mg, 0.380 mmol, 95 %) without further purification as yellow oil. Rf 0.30 (PET/AcOEt 7:3, Anisaldehyde). $^1$H NMR (CDCl3, 400 MHz) $\delta$ 6.95 (d, $J = 8.3$ Hz, 1H; Ar-H), 6.49 (s, 1H; Ar-H), 6.45 (d, $J = 8.3$ Hz, 1H; Ar-H), 4.42 (td, $J = 3.0$, 9.6 Hz, 2H; CH 2O), 4.13 (dd, $J = 5.2$, 6.4 Hz, 1H; CH Ar), 3.82 (s, 3H; OCH 3), 3.80 (s, 3H; OCH 3), 2.67 (t, $J = 9.6$ Hz, 2H; CH 2), 2.53 – 2.34 (m, 2H; CH 2), 2.27 (d, $J = 4.9$ Hz, 1H; CH 2), 2.08 (d, $J = 6.7$ Hz, 1H; CH 2). $^{13}$C NMR (CDCl3, 100 MHz) $\delta$ 191.1, 160.3, 158.4, 150.8, 138.1, 128.8, 121.2, 104.4, 99.3, 69.6, 55.7, 55.7, 36.7, 34.9, 33.2, 31.1. IR $\nu$ 2958 (w), 2838 (w), 1674 (m), 1612 (m), 1587 (m), 1506 (m), 1466 (m), 1439 (m), 1419 (m), 1293 (m), 1262 (m), 1159 (m), 1102 (m), 1035 (m), 906 (s), 839 (m), 726 (s), 648 (m). HRMS(ESI) calcd for C16H18O4 $^+$(M+H) 275.1278, found 275.1292.

$\textbf{4-(4-Methoxyphenyl)-9-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (7)}$

Following general procedure 5, tosic acid (15 mg, 0.08 mmol, 0.2 equiv) was added to a cyclopropane 6 (122 mg, 0.400 mmol, 1.00 equiv). The reaction was quenched after 3 h and 30 min to give 7 (122 mg, 0.400
mmol, 100%) as a yellow oil without further purification. $R_f$ 0.30 (PET/AcOEt 8:2, Anisaldehyde). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.38 – 7.30 (m, 2H; Ar-H), 7.13 (d, $J = 8.6$ Hz, 2H; Ar-H), 7.00 – 6.90 (m, 2H; Ar-H), 6.84 (d, $J = 8.6$ Hz, 2H; Ar-H), 4.45 (dd, $J = 4.9$, 7.5 Hz, 1H; CH Ar), 4.13 (s, 3H; NCH$_3$), 3.80 (s, 3H; OCH$_3$), 2.76 – 2.56 (m, 2H; CH$_2$), 2.51 (ddd, $J = 4.6$, 9.2, 12.3 Hz, 1H; CH$_2$), 2.25 (ddd, $J = 4.5$, 11.1, 17.4 Hz, 1H; CH$_2$). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 192.7, 158.8, 140.3, 135.9, 131.1, 131.0, 129.5, 126.9, 124.9, 122.9, 120.5, 114.3, 55.7, 40.1, 38.4, 35.2, 32.0. IR $\nu$ 3058 (w), 2938 (w), 2833 (w), 1654 (s), 1612 (m), 1510 (s), 1471 (m), 1429 (w), 1410 (w), 1375 (w), 1347 (w), 1243 (s), 1203 (w), 1176 (m), 1072 (w), 1035 (m), 909 (m), 833 (m), 730 (s), 648 (w). HRMS(ESI) calcd for C$_{20}$H$_{19}$NO$_2$ $^+$ (M+H) 306.1489, found 306.1478.

4-(2,4-Dimethoxyphenyl)-3,4,4a,5,6,7-hexahydronaphthalen-1(2H)-one (12)

The reaction was performed following general procedure 6, starting from cyclopropane 11 (143 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 25 minutes. Purification by flash chromatography (PET/AcOEt, 8:2) afforded 12 (63 mg, 0.22 mmol, 55%) as colorless oil. $R_f$ 0.30 (PET/AcOEt 8:2, Anisaldehyde). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.06 (d, $J = 8.0$ Hz, 1H; H$^n$), 6.79 (br s, 1H; H$^i$), 6.48 (d, $J = 7.7$ Hz, 2H; H$^l$ and H$^m$), 3.81 (s, 3H; H$^o$ or H$^i$), 3.80 (s, 3H; H$^o$ or H$^i$), 3.03 (m, 1H; H$^d$), 2.74 – 2.60 (m, 1H; H$^o$), 2.61 – 2.54 (m, 1H; H$^o$), 2.54 – 2.40 (m, 1H; H$^b$), 2.20 (m, 2H; H$^b$), 2.04 (m, 1H; H$^c$), 2.01 – 1.90 (m, 1H; H$^c$), 1.67 (m, 1H; H$^{e1}$), 1.61 – 1.47 (m, 1H; H$^{e2}$), 1.36 (m, 1H; H$^{e1}$), 1.10 (m, 1H; H$^{e1}$). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 201.1 (a), 159.0 (r), 158.2 (p), 139.7 (l), 136.8 (i), 127.5 (n), 124.8 (m), 104.3 (o), 98.5 (q), 55.4 (s or t), 55.4 (s or t), 42.4 (d), 40.4 (e), 39.2 (b), 29.9 (c), 27.8 (f), 26.2 (h), 21.4 (g). IR $\nu$ 3000 (w), 2935 (m), 2861 (w), 2836 (w), 1686 (s), 1613 (s), 1587 (m), 1507 (s), 1465 (m), 1456 (m), 1420 (w), 1328 (w), 1296 (m), 1268 (m), 1209 (s), 1158 (m), 1036 (m), 927 (w), 836 (w), 737 (w). HRMS(ESI) calcd for C$_{18}$H$_{22}$O$_3$ $^+$ (M+H) 287.1647, found 287.1636.

Further analytical data: COESY, NOESY and HSQC.

Important signal for NOESY : H$^e$-H$^d$(s); H$^e$-H$^f$(m); H$^d$-H$^c$(s).

1-Cyclohex-1-enyl-4-hydroxy-4-(4-methoxy-phenyl)-butan-1-one (16)
A solution of cyclopropane 15 (81 mg, 0.32 mmol, 1.0 equiv) and tosic acid monohydrate (59 mg, 0.32 mmol, 1.0 equiv) in acetonitrile (8 mL) and water (0.4 mL) was stirred at RT for 36 h. The solution was quenched with NaHCO₃ (10 mL) and extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. Purification by flash chromatography (PET/AcOEt, 4:1-2:1) afforded 16 (27 mg, 0.099 mmol, 32 %) as yellow oil. (Rf 0.20 (PET/AcOEt 4:1, Anisaldehyde). ¹H NMR (CDCl₃, 400 MHz) δ 7.25-7.30 (m, 2 H, Ar-H), 6.83-6.92 (m, 3 H, Ar-H and alkene-H), 4.69 (br m, 1 H, CHOH), 3.80 (s, 3 H, OCH₃), 2.57 (td, J = 7.0, 1.0 Hz, 2 H, ketone-CH₂), 2.47 (br s, 1 H, OH), 2.17-2.29 (m, 4 H, cyclohexene-CH₂), 2.05 (q, J = 6.9 Hz, 2 H, CH₂CHOH), 1.54-1.68 (m, 4 H, cyclohexene-CH₂). ¹³C NMR (CDCl₃, 100 MHz) δ 201.7, 158.9, 140.3, 139.0, 136.6, 126.9, 113.8, 73.40, 55.3, 33.4, 33.3., 26.1, 23.1, 21.9, 21.5. IR ν 3447 (br w), 2932 (m), 2860 (w), 1663 (m), 1614 (m), 1514 (s), 1458 (w), 1302 (w), 1247 (s), 1175 (m), 1034 (s), 914 (w), 832 (m), 734 (w). HRMS(ESI) calcd for C₁₇H₂₂NaO₃⁺ (M+Na) 297.1461, found 297.1452.

5. Kinetic Measurements

5.1 Methods and Formula

NMR-Method for the Monitoring of the Formal Homo-Nazarov Cyclization

Substrate 2a (6.00 mg, 0.00232 mmol, 1.00equiv) was dissolved in CD₃CN (0.5 mL) at 23 °C under nitrogen in a NMR tube. A solution of the desired amount of tosic acid in CD₃CN (0.15 mL) was then added and the tube put in the spectrometer as fast as possible (time set to zero at this point). The reaction was monitored by ¹H-NMR at 400 MHz. The reaction was examined with 0.1, 0.2, 0.3 and 0.4 equiv tosic acid and 0.4 equiv deuterated tosic acid. The decrease of the concentration of 2a was monitored via the decrease of the integral of the alkene proton peak between 6.0383 and 6.0022 ppm, using the internal CH₃CN signal as standard. The concentration of product 3a was monitored via the increase of the integral of the benzylic proton between 6.0383 and 6.0022 ppm, using the internal CH₃CN signal as standard. The concentration of product 3a was monitored via the increase of the integral of the benzylic proton between 3.6454 and 3.6050 ppm. This signal was increase further by a factor 1.33 (part of the signal was dropped in the integration due to impurity interference, the correction factor was obtained by integrating the missing area on a pure sample) and 1.09 (difference of integration between the two observed signal for a separately prepared 1:1 solution). Better results were obtained with the alkene proton, as the baseline was more stable in this region of the spectra. Spectra were taken every 36.5 s with one single scan.

Statistical Methods and Formula

Reaction Rate

The initial rates r of the reactions were determined using standard linear regression programs (Excel) applied on the linear region of the concentration curves (4.25 min). The standard deviation and the confidence interval of the data were calculated using following formula:

Standard deviation of the rate:

\[ s_r^2 = \frac{n}{n \cdot \sum_{i=1}^{n} t_i^2 - (\sum_{i=1}^{n} t_i)^2} \cdot \frac{1}{n-2} \cdot \sum_{i=1}^{n} (c_i - I - r \cdot t_i)^2 \]

Confidence interval (95%) of the rate:

\[ v_r = t_s \cdot \frac{s_r}{\sqrt{n}} \]

Whereas \( n \) is the amount of data points measured, \( t \) is the time of measurement after the addition of acid, \( c \) is the measured concentration of \( 2a \), \( r \) is the calculated reaction rate, \( I \) is the calculated intercept of the curve, \( t_s \) is the student-t factor corresponding to 95% probability and a degree of freedom of \( n-2 \).

**Van't Hoff Equation**

Van't Hoff Equation: \( y = \log r = O \cdot \log c + I = a \cdot \log c + b \),

Standard deviation, confidence interval for \( y \) values:

\[ s_{yi} = \frac{s_{ri}}{Ln(10) \cdot r_i} \]

\[ v_{yi} = \frac{v_{ri}}{Ln(10) \cdot r_i} \]

Standard deviation of the reaction order:

\[ s_O = s_a = \frac{1}{m} \sum_{i=1}^{m} \frac{1}{s_{yi}} \cdot x_i = \log c_i \]

Confidence interval (95%) of the reaction order:

\[ v_O = v_a = t_s \cdot \frac{s_a}{\sqrt{m}} \]

Correlation factor \( R \):

\[ \sqrt{\frac{\sum_{i=1}^{m} \frac{1}{s_{yi}} \sum_{i=1}^{m} x_i y_i - \left( \sum_{i=1}^{m} x_i \right) \left( \sum_{i=1}^{m} y_i \right)}{\sum_{i=1}^{m} \frac{1}{s_{yi}} \sum_{i=1}^{m} x_i^2 - \left( \sum_{i=1}^{m} x_i \right)^2} \cdot \frac{\sum_{i=1}^{m} \frac{1}{s_{yi}} \sum_{i=1}^{m} y_i^2 - \left( \sum_{i=1}^{m} y_i \right)^2}{m \cdot \sum_{i=1}^{m} \frac{1}{s_{yi}}}} \]

Whereas \( r \) is the calculated reaction rate with standard deviation \( s_r \) and confidence interval \( v_r \), \( O \) is the reaction order with standard deviation \( s_O \) and confidence interval \( v_O \), \( c \) is the concentration of the examined reagent, \( m \) is the amount of data points measured, \( R \) is the correlation factor, \( t_s \) is the student-t factor corresponding to 95% probability and a degree of freedom of \( n-2 \).

**5.2 Graphical Representation of the Data**
**Figure S1.** Influence of the concentration of tosic acid on the reaction rate of the starting material 2a.

**Figure S2.** Influence of the concentration of tosic acid on the formation of product 3a.
**Figure S3.** Comparison of tosic acid and deuterated tosic acid: kinetic isotope effect?

![Graph showing kinetic isotope effect with apparent kinetic isotope effect: 1.15](image)

**Figure S4.** Determination of the rate order using Van’t Hoff plot.

\[ y = 1.0023 \pm 0.0013 \times -0.5383 \]

\[ R^2 = 0.9955 \]
6.1 Important Spectra for Analysis of the Reaction

Figure S5. Comparison of the crude NMR of the reaction of 2a with SnCl₄ and TsOH.
Figure S6 $^1$H NMR spectra in benzene-$d_6$ of cyclization product 3a obtained using TsOH (top) and TsOD (bottom).
Figure S7  $^{13}$C NMR spectra in CDCl$_3$ of cyclization product 3a obtained using TsOD.
6.2 Spectra of New Compounds