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Formal [8+3]-Annulation between Azaoxyallyl Cations and Tropones

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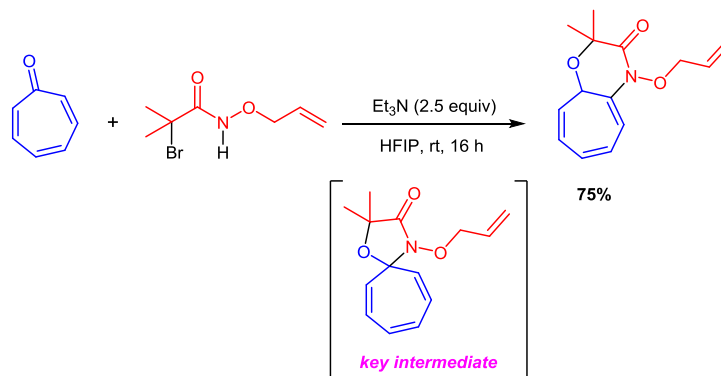
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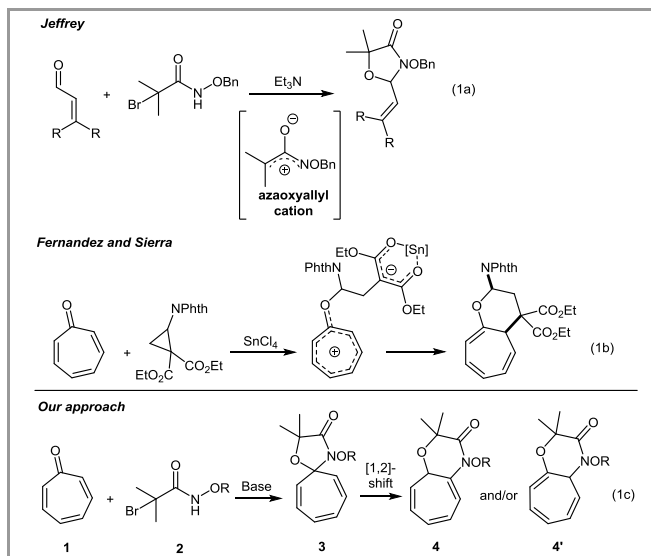
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Abstract For the first time, azaoxyallyl cations were used as cycloaddition partners with tropone derivatives to access nitrogen-containing [7,6]-fused bicycles in a metal-free process under mild reaction conditions. DFT computations have been used to shed light on the selectivities observed during the course of the reaction.

Key words tropone, α -haloamide, azaoxyallyl cation, cycloaddition, DFT computations,

The framework of tropones, which are non-benzenoid aromatic seven-membered rings, can be found in manifold natural and bioactive molecules, triggering substantial efforts towards the synthesis of these motifs.¹ However, it does not represent an end in itself as tropones have also recently emerged as fascinating partners for cycloadditions, notably for high-order cycloadditions (HOC) such as [6+6], [8+3] or [8+2], which still remain clearly underexplored in synthesis.² Besides, tropones are not the only cycloaddition partner to have made a breakthrough in the last decade; we can also cite azaoxyallyl cations that can be easily formed from α -haloamides in the presence of a common base.^{3,4} Azaoxyallyl cations are typically viewed as a zwitterionic 1,3-dipoles even if their structures are in fact closer to an aziridinone or an oxirane-2-imine.^{4a,4j} In this context, our idea was to combine these two entities to access unprecedented [7,6]-fused heterocycles through a formal [8+3]-annulation in a metal-free transformation. Indeed, based on their history, we postulated that azaoxyallyl cations might react differently with tropones than other 1,3-dipoles. For instance, the group of Jeffrey demonstrated that azaoxyallyl cations could react with acroleins to generate the corresponding 4-oxazolidinones with the alkene moiety remaining intact (Scheme 1a).^{4d} On the other hand, Fernandez and Sierra reported a tin(IV)-catalyzed [8+3]-cycloaddition between tropones and donor-acceptor cyclopropanes through a mechanism involving a stepwise sequence (Scheme 1b).^{2e} Thus, we envisioned that a reaction between tropone and an azaoxyallyl cation would lead to the corresponding 4-oxazolidinone 3 and a subsequent [1,2]-shift could provide

either 4 and/or 4' as products (Scheme 1c). Herein, we report our findings on this transformation along with DFT computations to gain insight its mechanism.

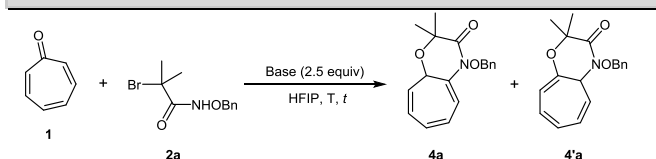


Scheme 1 [8+3] annulation between tropone and azaoxyallyl cation

In our initial studies, we investigated the reactivity of tropone 1 towards α -haloamide 2a in hexafluoroisopropanol (HFIP) at a concentration of 0.2 M (Table 1). Indeed, because of its intrinsic properties such as hydrogen-donor ability combined with a high dielectric constant,⁵ HFIP represents a solvent of choice to stabilize azaoxyallyl cations. As mentioned in the introduction, the formation of azaoxyallyl cations can be easily achieved in the presence of a base, prompting us to screen several common organic and inorganic bases as promoters (Entries 1-8). We were pleased to find that triethylamine could afford the desired products 4a and 4'a in 60% and 8% yields, respectively, within 3 hours (Entry 4). Interestingly, the spiro compound 3a was also detected as a minor product (5%). The structure of the major product 4a was corroborated by X-Ray crystallography (Figure 1). Importantly, the reaction had to be carried out in the

presence of 2 equivalents of **2a**, as the yield of **4a** sharply dropped to 39% with only 1 equivalent because of a competitive hydrolysis of the α -haloamide. It is noteworthy that the concentration of the reaction is a critical factor for its success as decreasing or increasing it derailed the transformation (Entries 9–10), essentially leading to the decomposition of the substrates. The influence of drying agents such as molecular sieves and MgSO_4 was also examined but no significant improvement was observed (Entries 11–12). On the other hand, we noticed that the yields could be slightly improved by conducting the reaction for a longer reaction time so that the complete disappearance of the spiro compound was observed (Entry 13). As a final point, it is important to emphasize that the ratio between **4a** and **4'a** was identical before and after purification by flash column chromatography.

Table 1 Reaction optimization for the reaction between tropone **1** and α -haloamide **2a**



Entry	Base	T [°C]	t [h]	Yield 4a [%]	Yield 4'a [%]
1	K_2CO_3	20	3	33	4
2	Na_2CO_3	20	3	53	10
3	Cs_2CO_3	20	3	40	7
4	Et_3N	20	3	60	8
5 ^[a]	Et_3N	20	3	39	4
6	DABCO	20	3	16	2
7	DIPEA	20	3	44	8
8	DBU	20	3	50	7
9 ^[b]	Et_3N	20	3	13	11
10 ^[c]	Et_3N	20	3	28	2
11 ^[d]	Et_3N	20	3	45	4
12 ^[e]	Et_3N	20	3	59	7
13	Et_3N	20	16	71	9
14	Et_3N	0	16	58	4

Reaction conditions: tropone **1** (1 equiv), α -haloamide **2a** (2 equiv) and base (2.5 equiv) in HFIP (0.2 M) at the indicated temperature for the indicated time. [a] α -haloamide **2a** (1 equiv) and base (1.5 equiv). [b] concentration = 0.4 M. [c] concentration = 0.1 M. [d] in the presence of MgSO_4 . [e] in the presence of 4Å molecular sieves.

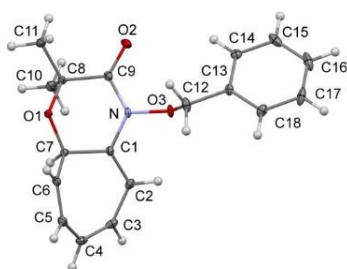
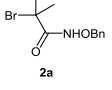
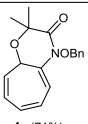
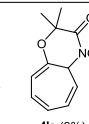
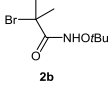
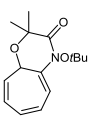
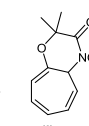
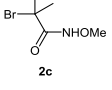
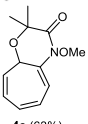
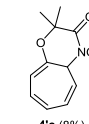
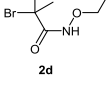
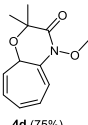
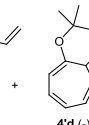
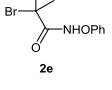
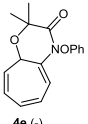
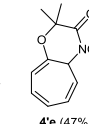
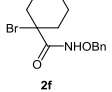
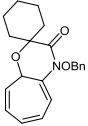
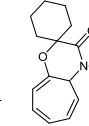
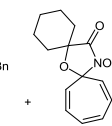
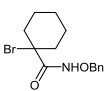
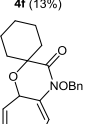
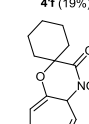
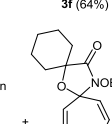
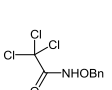
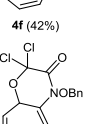
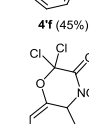
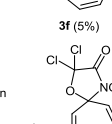
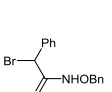
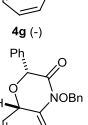
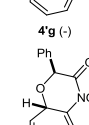
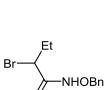
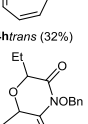
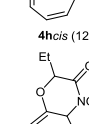


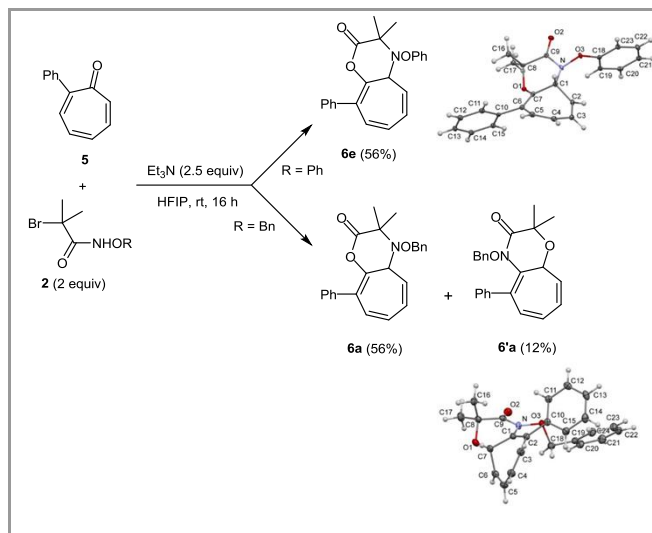
Figure 1 ORTEP drawing of compound **4a**. Thermal ellipsoids are shown at 30% probability level.

Under the optimal reaction conditions, we sought to explore the scope of the reaction, notably the reactivity of tropone **1** with a series of α -haloamides (Table 2). Replacing the benzyl substituent by a methyl, *tert*-butyl or allyl group did not affect the transformation, providing the targeted products in good yields and selectivities (Entries 1–4). Nevertheless, in the latter case, the reaction afforded **4d** in 75% yield with a complete control of the selectivity. To our delight, in the case of **2b**, we succeeded to obtain X-Ray characterizations of both **4b** and **4'b**, confirming unambiguously the structure of the minor compound **4'b**. Surprisingly, with a phenyl substitution, the other isomer **4'e** was isolated as a sole product in 47% yield (Entry 5). On the other hand, in the case of a cyclohexyl tether, the reaction occurred at a slower rate, delivering 4-oxazolidinone **3f** as a major product (64%) after 3 h (Entry 6). By increasing the reaction time (36 h), we succeeded to observe the almost complete transformation of **3f** into compounds **4f** and **4'f**. While the overall yield is excellent, the selectivity remained not satisfying (Entry 7). During our investigations, we also evaluated the reactivity of α -haloamide **2g**, bearing chlorine substituents, which gave exclusively the spiro compound **3g** in 48% without any further transformation (Entry 8). We hypothesized that the electron-withdrawing nature of the substituents precluded any [1,2]-shift and, thus, the reaction was shut down at the first step. In addition, the reaction was also compatible with a secondary bromide such as **2h** to generate the corresponding diastereoisomers **4h**, whose configurations were ascertained by NOESY analysis (see the Supporting Information for details), in 32% and 12% yields, respectively (Entry 9). However, in the case of **2i**, no reaction occurred, as the azaoxyallyl cation formed might be less electrophilic to trigger the transformation (Entry 10).

Gratifyingly, the reaction is not only limited to the simple tropone but could also be applied to 2-phenyltropone **5** (Scheme 2). As an example, in the case of α -haloamide **2e**, the reaction provided compound **6e** in 56% yield. Its structure was confirmed by X-Ray crystallography (Figure 2). On the other hand, the reaction proved to be less selective with α -haloamide **2a** as two products **6a** and **6'a** (X-Ray structure, Figure 3) were isolated in 56% and 12% yields, respectively. Disappointingly, we only observed the decomposition of the tropone derivative when the reaction was conducted in the presence of tropolone and 2-methoxytropone.

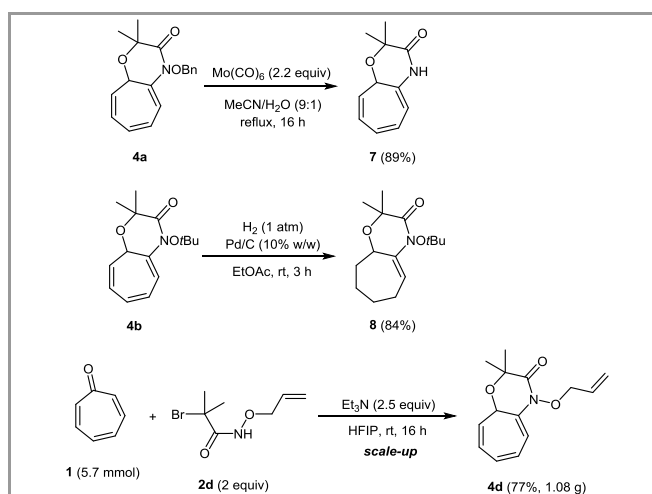
Table 2 Scope of α -haloamide **2a–2i** with tropone **1**. ORTEP drawings of compounds **4b** and **4'b**. Thermal ellipsoids are shown at 30% probability level.

Entry	α -haloamide 2	t [h]	Products (Yield %)
1		16	 4a (71%) +  4'a (9%)
2		16	 4b (72%) +  4'b (8%)
3		3	 4c (63%) +  4'c (8%)
4		16	 4d (75%) +  4'd (-)
5		16	 4e (-) +  4'e (47%)
6		3	 4f (13%) +  4'f (19%) +  3f (64%)
7		36	 4f (42%) +  4'f (45%) +  3f (5%)
8		3	 4g (-) +  4'g (-) +  3g (48%)
9		16	 4htrans (32%) +  4hcis (12%)
10		16	 4i (-) +  4'i (-)



Scheme 2 Influence of tropone substitution on the reactivity. ORTEP drawings of compounds **6e** and **6'a**. Thermal ellipsoids are shown at 30% probability level.

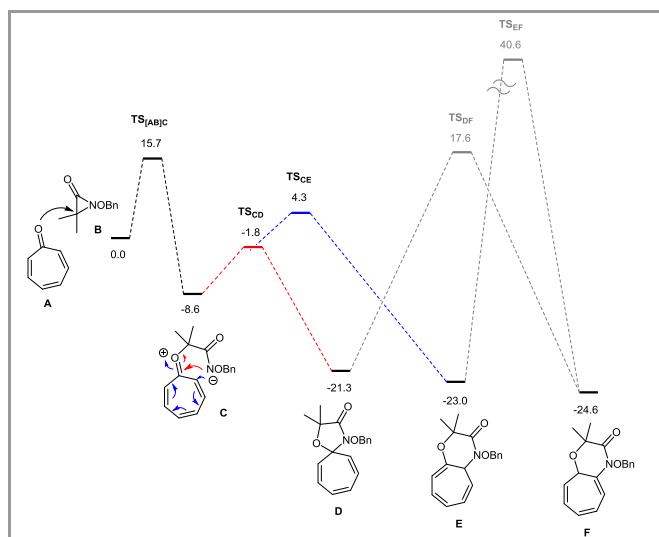
Regarding the practical utility of this transformation (Scheme 3), we succeeded to remove selectively the benzyloxy group on the nitrogen to obtain the corresponding free amide **7** in 89% yield by using $\text{Mo}(\text{CO})_6$ as a promoter. Two of the three double bonds were reduced with H_2 and Pd/C in ethyl acetate to give **8** with the enamide functionality remaining intact. Additionally, the reaction could be performed on a 5.7 mmol scale to produce 1.08 g of compound **4d** without any drop in yield (77%).



Scheme 3 Post-modifications and scale-up

To rationalize the observed selectivity, DFT computations were carried out using the Gaussian 09 software package (see the Supporting Information for details). Minima and transition states were optimized using the M06-2X functional⁶ and the 6-311G(d,p) basis set,⁷ as implemented in Gaussian. Solvent correction was obtained using the SMD model⁸ with the parameters of 2-propanol, adjusting the ϵ value to 16.7.⁹ The values presented are ΔG_{298} in kcal/mol. The first set of computations was carried out with tropone **A** and the benzyloxy-substituted “azaoxyallyl” intermediate **B** which, in agreement with previous computational studies, converged as a 3-membered ring (Scheme 4).^{4k} The capture of intermediate **B** by **A** was modeled through $\text{TS}_{[\text{AB}]C}$, lying 15.7 kcal/mol above the

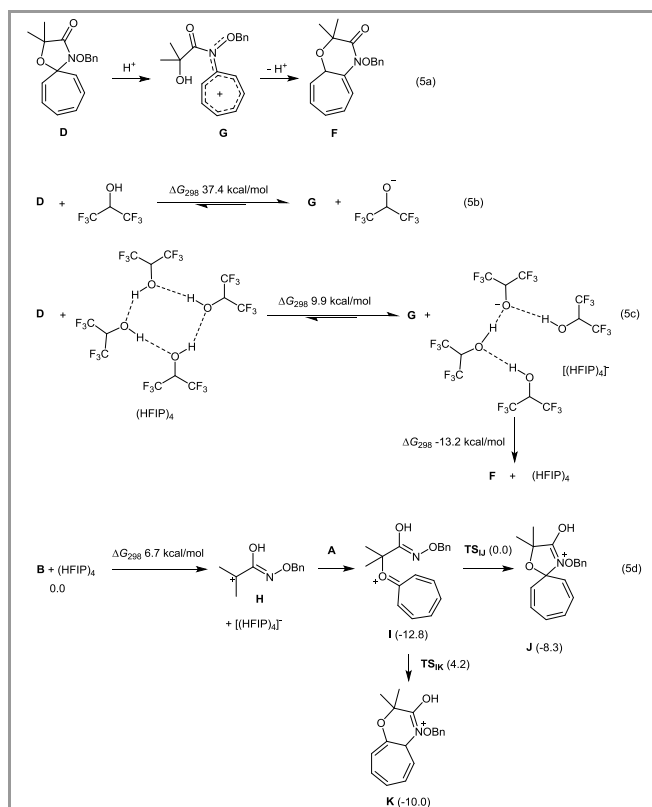
reactants. It leads to the zwitterionic species **C**, located 8.6 kcal/mol below **A** and **B**. Attack of the negatively charged nitrogen atom to the carboxonium center (red pathway, **TS_{CD}**) leads to the spiro intermediate **D**, which was observed experimentally as a trace component of the mixture. Another possibility is the conjugate 1,8-addition (blue pathway, **TS_{CE}**) to give **E**. This compound was also experimentally observed as a minor product. The formation of the spiro compound **D** is clearly kinetically favored over that of **E** (-1.8 vs 4.3 kcal/mol). Due to its symmetry-forbidden nature, it was not possible to locate a [1,7]-sigmatropic nitrogen shift transition state connecting **D** to **E**. On the other hand, the symmetry forbidden [1,7]-sigmatropic oxygen shift transition state could be found, but the transformation of **D** into **F** seems unlikely since the corresponding activation free energy is 38.9 kcal/mol (21.3 + 17.6). Compound **F** is the most stable of the three observed products (**D**, **E**, **F**) and is a tautomeric form of **E**. The direct conversion of **E** into **F** can be modeled, but as it is also a symmetry forbidden shift, the corresponding transition state is not accessible (**TS_{EF}** 40.6 kcal/mol). Thus, similarly to the keto-enol equilibrium, which cannot be an intramolecular process and cannot be computed, the isomerization of **E** into **F** would require an unknown proton shuttle. Since the isomerization of isolated **E** into **F** is relatively longer than the reaction time,¹⁰ we can infer that another way should be possible between **D** and **F**, i.e. something not direct as **TS_{DF}** and not through **E**.



Scheme 4 Computed free energy profile using the benzyl-substituted intermediate **B** (ΔG_{298} , kcal/mol).

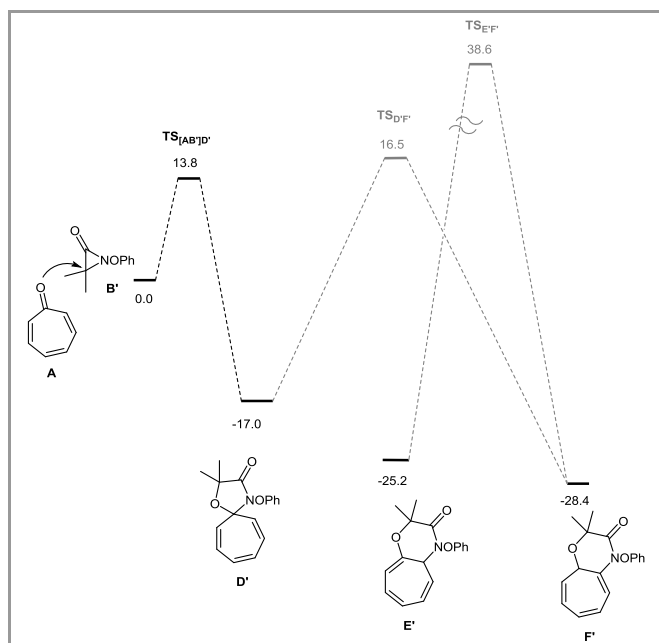
A serious lead was obtained after protonating heterocycles **D**, **E** and **F** at the oxygen atom. While **E** and **F** remained cyclic, the spiro intermediate **D** opened to form the corresponding tropylium **G** (Scheme 5a). It was not possible to form a 6-membered ring from **G**, but removal of a proton and optimization led to **F** spontaneously. This suggests that proton-exchanges can directly connect **D** to the major product **F** in a stepwise fashion. This raises the question of the proton source, the most obvious one being HFIP itself. A single HFIP molecule cannot do this job, as shown by the very large free energy of 37.4 kcal/mol (Scheme 5b). However, it is known that the acidity of alcohols comes from the formation of H-bonded aggregates, a feature that is exceptionally efficient with HFIP.¹¹

Taking for instance a tetramer of HFIP, the free energy of the protonation drops to 9.9 kcal/mol (Scheme 5c). It remains an endergonic reversible process, but the spontaneous formation of **F** by simple deprotonation might funnel this reaction. The possible role of HFIP clusters as proton source prompted us to reconsider a cationic mechanism from the beginning (eq 5d). As previously described, cation **H**, which is the protonated form of **B**, can be optimized as an azaoxyallyl species.^{4b} Its formation was found exergonic by 6.7 kcal/mol. Manifold efforts failed to locate a transition state between **H** and tropone **A**, and the corresponding adduct **I** lying at -12.8 kcal/mol. If formed, **I** can lead to the protonated spiro compound **J**, but the corresponding transition state, located at 0.0 kcal/mol, would be 1.8 kcal/mol higher on the energy surface than **TS_{CD}** and the reaction would be endergonic by 4.5 kcal/mol (from -12.8 to -8.3 kcal/mol). Of note, the open compound **I** is also more stable than **K**, which is the protonated of **E**. Both can be connected via **TS_{IK}**, lying at 4.2 kcal/mol.



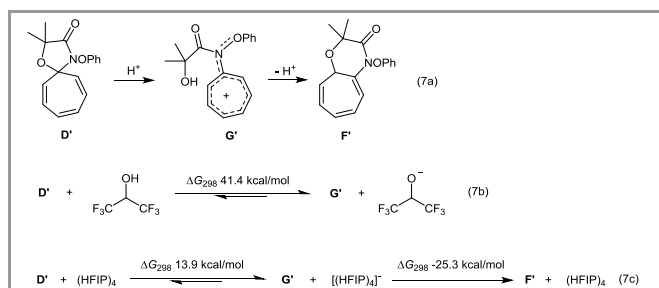
Scheme 5 Computed protonation of intermediates **D** and **B**.

The case of the phenyl-substituted intermediate **B'** was next studied (Scheme 6). The main difference was the absence of the previous zwitterionic intermediate **C** because of a direct collapse of the reactants **A** and **B'** to the spiro compound **D'**. From there, the rest of the energy profile is similar to the one computed in the benzyl series.



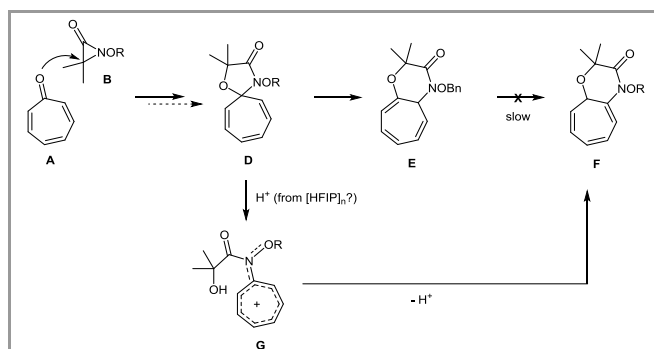
Scheme 6 Computed free energy profile using the phenyl-substituted intermediate **B'** (ΔG_{298} , kcal/mol).

The formation of **F'**, unobserved experimentally, could yet have happened as explained above, by protonation of **D'**, which again promotes its spontaneous opening into **G'**, and spontaneous ring closure upon deprotonation (Scheme 7a). This time though, the formation of **G'** requires a higher free energy (13.9 vs 9.9 kcal/mol, Scheme 7c). This reflects the lower ability of the NOPh group to stabilize the tropylium ion compared to the more basic NOBn group.



Scheme 7 Computed protonation of the spiro intermediate **D'** and deprotonation of **G'**.

Without knowing the exact nature of the proton donor, only trends can be derived from the above calculations. One might propose that each of these reactions circulate through a spiro intermediate, which isomerizes into **F**-type products in a stepwise fashion by protonation/deprotonation when starting from the most basic substrates. With less basic substrates, the spiro intermediate will rather transform in a stepwise fashion into **E**-type products (Scheme 8). The way the substitution pattern at **A** or **B** influences these two pathways seems to obey a subtle balance between steric and electronic effects and is difficult to fully rationalize.



Scheme 8 Plausible mechanism

In conclusion, we have devised a formal [8+3]-annulation between tropones and α -haloamides, enabling the access to new bicyclic nitrogen-containing scaffolds in good yields, whose selectivity can be controlled by the substituents of the α -haloamides. The reaction proceeds under mild conditions by using readily available starting materials and further enriching the synthetic potential of both tropone derivatives and azaoxyallyl cations. The reaction proceeds through a different pathway than the traditional [8+3]-cycloadditions involving tropones as suggested by DFT computations.

Unless otherwise stated, reactions were carried out in oven-dried flasks. Analytical thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF254) using UV light as the visualizing agent and a solution of phosphomolybdic acid in ethanol as the developing agent. Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40–60 mm). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. NMR spectra were recorded at 298 K on AM250, AV300 or AV360 MHz Bruker spectrometer. Mass spectra were recorded on MicroTOFq Bruker spectrometer by electrospray ionization. Melting points were determined using a Reichert melting point apparatus. Infrared spectra were recorded on a FTIR spectrometer (Perkin-Elmer spectrum one, NaCl pellets or Bruker Vertex 70 ATR Pike Germanium) and are reported in cm^{-1} .

General procedure for the cyclization:

To a solution of tropone (1 equiv.) and α -haloamide (2 equiv.) in HFIP (0.2 M) was added triethylamine (2.5 equiv.). The reaction mixture was stirred at room temperature for the indicated time. Then, it was quenched with a saturated solution of NH_4Cl and extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed with rotary evaporation. The crude product was purified by flash column chromatography using gradients of Pentane and EtOAc as eluent.

Following the general procedure, starting from tropone **1** (30 mg, 0.283 mmol, 1 equiv.), *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** (146 mg, 0.566 mmol, 2 equiv.) and triethylamine (98 μ L, 0.707 mmol, 2.5 equiv.) in HFIP (1.4 mL) for 16 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford products **4a** as an orange solid (60 mg, 71%) and **4'a** as an orange solid (8 mg, 9%).

4-(benzyloxy)-2,2-dimethyl-4,9a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (**4a**)

Mp = 63–65 °C.

IR (ATR): 3032, 2982, 2837, 1714, 1698, 1614, 1531, 1455, 1380, 1226, 1112, 1031, 983, 860 cm^{-1} .

1H NMR ($CDCl_3$, 300 MHz): δ = 7.40–7.30 (m, 5H), 6.54 (ddd, J = 16.7, 11.1, 6.2 Hz, 2H), 6.18 (ddd, J = 9.7, 5.7, 1.6 Hz, 1H), 6.00 (dd, J = 6.7, 1.3 Hz, 1H), 5.20 (dd, J = 9.7, 3.7 Hz, 1H), 4.92 (d, J = 9.7 Hz, 1H), 4.81 (d, J = 9.7 Hz, 1H), 3.85 (dt, J = 3.5, 1.7 Hz, 1H), 1.56 (s, 3H), 1.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 91 MHz): δ = 168.7, 133.9, 129.9, 129.1, 128.9, 128.8, 128.5, 127.2, 124.2, 123.1, 100.6, 77.4, 76.4, 70.5, 25.0, 21.4.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₁₈H₂₀NO₃: 298.1438; found: 298.1430.

4-(benzyloxy)-2,2-dimethyl-4,4a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4'a)

Mp = 70–72 °C.

IR (ATR): 2985, 2840, 1710, 1698, 1635, 1455, 1386, 1226, 1050, 998, 865 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 7.49–7.42 (m, 2H), 7.39–7.30 (m, 3H), 6.57–6.42 (m, 2H), 6.24–6.19 (m, 1H), 5.79 (d, *J* = 6.0 Hz, 1H), 5.36 (dd, *J* = 9.4, 4.7 Hz, 1H), 5.07 (s, 2H), 3.52 (d, *J* = 4.4 Hz, 1H), 1.58 (s, 3H), 1.55 (s, 3H).

¹³C NMR (CDCl₃, 101 MHz): δ = 169.4, 140.2, 134.8, 129.7, 129.1, 128.7, 128.1, 127.0, 125.2, 120.9, 105.4, 80.7, 60.4, 25.3, 24.7, one carbon hidden.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₈H₁₉NNaO₃: 320.1257; found: 320.1250.

Following the general procedure, starting from tropone **1** (30 mg, 0.283 mmol, 1 equiv.), 2-bromo-*N*-(tert-butoxy)-2-methylpropanamide **2b** (134 mg, 0.566 mmol, 2 equiv.) and triethylamine (98 μL, 0.707 mmol, 2.5 equiv.) in HFIP (1.4 mL) for 16 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford products **4b** as a white solid (53 mg, 72%) and **4'b** as a white solid (6 mg, 8%).

4-(tert-butoxy)-2,2-dimethyl-4,9a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4b)

Mp = 55–57 °C.

IR (ATR): 2979, 2935, 1715, 1612, 1523, 1464, 1380, 1368, 1281, 1221, 1183, 1115, 1033, 980, 863 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 6.53 (ddd, *J* = 16.7, 11.0, 6.2 Hz, 2H), 6.19 (ddd, *J* = 9.5, 5.7, 1.5 Hz, 1H), 6.01 (d, *J* = 6.7 Hz, 1H), 5.32 (dt, *J* = 9.1, 4.6 Hz, 1H), 3.83–3.78 (m, 1H), 1.59 (s, 3H), 1.37 (s, 3H), 1.19 (s, *J* = 3.8 Hz, 9H).

¹³C NMR (CDCl₃, 91 MHz): δ = 173.1, 132.5, 129.1, 126.8, 124.1, 123.4, 101.4, 86.3, 78.2, 71.3, 27.4, 25.9, 21.2.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₁₅H₂₂NO₃: 264.1594; found: 264.1588.

4-(tert-butoxy)-2,2-dimethyl-4,4a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4'b)

Mp = 88–90 °C.

IR (ATR): 2984, 2840, 1702, 1682, 1578, 1385, 1367, 1284, 1143, 1006, 964, 868 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 6.52–6.45 (m, 2H), 6.24–6.18 (m, 1H), 5.81–5.75 (m, 1H), 5.47 (dd, *J* = 9.5, 4.8 Hz, 1H), 3.80 (d, *J* = 4.8 Hz, 1H), 1.62 (s, 3H), 1.48 (s, 3H), 1.29 (s, 9H).

¹³C NMR (CDCl₃, 101 MHz): δ = 173.1, 141.9, 128.6, 127.1, 125.4, 122.1, 104.5, 84.4, 81.2, 62.4, 27.5, 26.6, 23.6.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₅H₂₁NNaO₃: 286.1414; found: 286.1409.

Following the general procedure, starting from tropone **1** (30 mg, 0.283 mmol, 1 equiv.), 2-bromo-*N*-methoxy-2-methylpropanamide **2c** (111 mg, 0.566 mmol, 2 equiv.) and triethylamine (98 μL, 0.707 mmol, 2.5 equiv.) in HFIP (1.4 mL) for 3 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford products **4c** as an orange oil (39 mg, 63%) and **4'c** as orange oil (5 mg, 8%).

4-methoxy-2,2-dimethyl-4,9a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4c)

IR (ATR): 2987, 2835, 1708 1685, 1436, 1398, 1375, 1284, 1111, 1004, 971, 868 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 6.54 (ddd, *J* = 16.8, 11.1, 6.3 Hz, 2H), 6.21 (ddd, *J* = 10.0, 5.8, 1.7 Hz, 1H), 5.94 (dd, *J* = 6.8, 1.5 Hz, 1H), 5.26 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.88 (dt, *J* = 3.6, 1.8 Hz, 1H), 3.70 (s, 3H), 1.57 (s, 3H), 1.40 (s, 3H).

¹³C NMR (CDCl₃, 91 MHz): δ = 168.2, 128.9, 128.3, 127.3, 124.4, 123.2, 100.2, 77.3, 70.4, 61.9, 25.0, 21.5.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₂H₁₅NNaO₃: 244.0944; found: 244.0934.

4-methoxy-2,2-dimethyl-4,4a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4'c)

IR (ATR): 2985, 2838, 1702, 1682, 1578, 1503, 1385, 1367, 1150, 1008, 970 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 6.59–6.47 (m, 2H), 6.26 (dd, *J* = 9.5, 4.9 Hz, 1H), 5.83 (d, *J* = 5.8 Hz, 1H), 5.41 (dd, *J* = 9.4, 4.7 Hz, 1H), 3.88 (s, 3H), 3.70 (d, *J* = 5.0 Hz, 1H), 1.56 (brs, 6H).

¹³C NMR (CDCl₃, 101 MHz): δ = 169.3, 140.2, 128.2, 127.1, 125.4, 120.9, 105.6, 80.7, 62.4, 59.4, 25.2, 24.7.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₂H₁₅NNaO₃: 244.0944; found: 244.0939.

4-(allyloxy)-2,2-dimethyl-4,9a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4d)

Following the general procedure, starting from tropone **1** (50 mg, 0.471 mmol, 1 equiv.), *N*-(allyloxy)-2-bromo-2-methylpropanamide **2d** (209 mg, 0.942 mmol, 2 equiv.) and triethylamine (164 μL, 1.180 mmol, 2.5 equiv.) in HFIP (2.3 mL) for 16 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford product **4d** as an orange oil (87 mg, 75%).

Scale-up: starting from tropone **1** (606 mg, 5.71 mmol, 1 equiv.), *N*-(allyloxy)-2-bromo-2-methylpropanamide **2d** (2.52 g, 11.43 mmol, 2 equiv.) and triethylamine (2 mL, 14.27 mmol, 2.5 equiv.) in HFIP (28 mL) for 16 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford product **4d** as an orange oil (1.08 g, 77%).

IR (ATR): 2984, 2939, 1872, 1714, 1682, 1613, 1526, 1504, 1382, 1304, 1227, 1172, 1112, 1031, 984, 844 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 6.59 (dd, *J* = 11.1, 6.8 Hz, 1H), 6.48 (dd, *J* = 11.1, 5.7 Hz, 1H), 6.19 (ddd, *J* = 9.7, 5.7, 1.5 Hz, 1H), 5.99–5.83 (m, 2H), 5.30–5.19 (m, 3H), 4.38–4.28 (m, 2H), 3.85 (dt, *J* = 3.5, 1.7 Hz, 1H), 1.55 (s, 3H), 1.39 (s, 3H).

¹³C NMR (CDCl₃, 91 MHz): δ = 168.8, 131.1, 128.9, 128.8, 127.1, 124.1, 123.3, 121.4, 100.4, 77.3, 75.1, 70.5, 25.0, 21.3.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₄H₁₇NNaO₃: 270.1101; found: 270.1094.

2,2-dimethyl-4-phenoxy-4,4a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4'e)

Following the general procedure, starting from tropone **1** (30 mg, 0.283 mmol, 1 equiv.), 2-bromo-2-methyl-*N*-phenoxypropanamide **2e** (146 mg, 0.566 mmol, 2 equiv.) and triethylamine (98 μL, 0.707 mmol, 2.5 equiv.) in HFIP (1.4 mL) for 16 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford product **4'e** as an orange oil (38 mg, 47%).

IR (ATR): 2980, 2835, 1754, 1709, 1591, 1542, 1488, 1381, 1291, 1198, 1168, 1000, 962, 872 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 7.36–7.30 (m, 2H), 7.12–7.02 (m, 3H), 6.54–6.46 (m, 2H), 6.20 (ddd, *J* = 9.3, 3.6, 1.6 Hz, 1H), 5.90 (d, *J* = 5.4 Hz, 1H), 5.43 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.86 (d, *J* = 4.7 Hz, 1H), 1.56 (brs, 6H).

¹³C NMR (CDCl₃, 91 MHz): δ = 170.5, 158.3, 139.9, 129.8, 128.1, 127.4, 125.5, 123.6, 120.3, 113.6, 106.1, 81.3, 60.9, 25.2, 24.9.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₁₇H₁₈NO₃: 284.1281; found: 284.1276.

Following the general procedure, starting from tropone **1** (30 mg, 0.283 mmol, 1 equiv.), *N*-(benzyloxy)-1-bromocyclohexanecarboxamide **2f** (176 mg, 0.566 mmol, 2 equiv.) and triethylamine (98 μL, 0.707 mmol, 2.5 equiv.) in HFIP (1.4 mL) for 36 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford products **4f** as an orange oil (40 mg, 42%), **4'f** as an orange oil (42 mg, 45%) and **3f** as an orange oil (5 mg, 5%).

4-(benzyloxy)-4,9a-dihydro-3H-spiro[cyclohepta[b][1,4]oxazine-2,1'-cyclohexan]-3-one (4f)

IR (ATR): 2933, 2858, 1698, 1611, 1502, 1451, 1272, 1102, 1032, 970, 844 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.42–7.28 (m, 5H), 6.59 (dd, *J* = 11.0, 6.8 Hz, 1H), 6.48 (dd, *J* = 11.0, 5.6 Hz, 1H), 6.18 (ddd, *J* = 9.7, 5.7, 1.5 Hz, 1H), 5.98 (dd, *J* = 6.7, 1.2 Hz, 1H), 5.22 (dd, *J* = 9.7, 3.7 Hz, 1H), 4.91 (d, *J* = 9.7 Hz, 1H), 4.79 (d, *J* = 9.7 Hz, 1H), 3.79 (dt, *J* = 3.3, 1.6 Hz, 1H), 2.20–2.04 (m, 1H), 1.99–1.91 (m, 1H), 1.87–1.26 (m, 8H).

¹³C NMR (CDCl₃, 91 MHz): δ = 169.0, 134.0, 129.9, 129.1, 129.0, 128.9, 128.5, 127.0, 124.1, 123.3, 100.4, 78.4, 76.4, 69.8, 32.4, 28.8, 25.2, 21.0, 20.9.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₂₁H₂₄N₃O₃: 338.1751; found: 338.1740.

4-(benzyloxy)-4,4a-dihydro-3H-spiro[cyclohepta[b][1,4]oxazine-2,1'-cyclohexan]-3-one (4f)

IR (ATR): 2934, 2858, 1683, 1611, 1502, 1449, 1378, 1273, 1241, 1112, 1032, 970, 914 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.47–7.41 (m, 2H), 7.38–7.32 (m, 3H), 6.58–6.41 (m, 2H), 6.26–6.16 (m, 1H), 5.84 (d, *J* = 5.7 Hz, 1H), 5.36 (dd, *J* = 9.5, 4.7 Hz, 1H), 5.06 (s, *J* = 10.3 Hz, 2H), 3.50 (d, *J* = 4.7 Hz, 1H), 2.13–2.01 (m, 1H), 1.99–1.78 (m, 3H), 1.73–1.55 (m, 5H), 1.42–1.24 (m, 1H).

¹³C NMR (CDCl₃, 101 MHz): δ = 169.7, 139.9, 134.8, 129.7, 129.1, 128.6, 127.9, 127.0, 125.1, 121.0, 105.6, 81.6, 60.2, 32.3, 31.5, 24.8, 20.6, 20.5, one carbon hidden.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₂₁H₂₃NNaO₃: 360.1570; found: 360.1556.

15-(benzyloxy)-7-oxa-15-azadispiro[5.1.6⁸.2⁶]hexadeca-9,11,13-trien-16-one (3f)

Product unstable on silica gel.

IR (ATR): 2938, 2860, 1702, 1562, 1398, 1358, 1289, 1241, 1110, 1035, 981, 914 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.43–7.28 (m, 5H), 6.59–6.51 (m, 2H), 6.50–6.40 (m, 2H), 5.66 (d, *J* = 10.8 Hz, 2H), 5.03 (s, 2H), 1.86–1.42 (m, 10H).

¹³C NMR (CDCl₃, 91 MHz): δ = 171.4, 134.7, 130.1, 129.8, 129.0, 128.5, 128.1, 127.0, 89.6, 78.7, 78.2, 35.2, 24.9, 21.2.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₂₁H₂₃NNaO₃: 360.1570; found: 360.1561.

4-(benzyloxy)-2,2-dichloro-1-oxa-4-azaspiro[4.6]undeca-6,8,10-trien-3-one (3g)

Following the general procedure, starting from tropone **1** (30 mg, 0.283 mmol, 1 equiv.), *N*-(benzyloxy)-2,2,2-trichloroacetamide **2g** (151 mg, 0.566 mmol, 2 equiv.) and triethylamine (98 μL, 0.707 mmol, 2.5 equiv.) in HFIP (1.4 mL) for 3 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford product **3g** as an orange oil (46 mg, 48%).

IR (ATR): 2925, 2855, 1641, 1600, 1567, 1453, 1363, 1082, 1041, 1012, 918, 885, 747, 696 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 7.44–7.28 (m, 5H), 6.97–6.87 (m, 1H), 6.44–6.35 (m, 1H), 6.24–6.06 (m, 4H), 5.13 (s, 2H).

¹³C NMR (CDCl₃, 101 MHz): δ = 156.4, 137.9, 134.1, 132.8, 132.0, 130.3, 129.5, 128.4, 128.0, 127.8, 125.8, 76.0, two carbons hidden.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₆H₁₃Cl₂NNaO₃: 360.0165; found: 360.3215.

Following the general procedure, starting from tropone **1** (50 mg, 0.471 mmol, 1 equiv.), *N*-(benzyloxy)-2-bromo-2-phenylacetamide **2h** (300 mg, 0.942 mmol, 2 equiv.) and triethylamine (164 μL, 1.178 mmol, 2.5 equiv.) in HFIP (2.3 mL) for 16 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford the products **4htrans** as an orange oil (52 mg, 32%) and **4hcis** as an orange oil (19 mg, 12%).

4-(benzyloxy)-2-phenyl-4,9a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4htrans)

IR (ATR): 2938, 2879, 1699, 1611, 1541, 1454, 1116, 1037, 918 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 7.44–7.33 (m, 10H), 6.62 (dd, *J* = 11.1, 6.9 Hz, 1H), 6.52 (dd, *J* = 11.1, 5.7 Hz, 1H), 6.22 (ddd, *J* = 9.8, 5.7, 1.6 Hz, 1H), 6.10 (dd, *J* = 7.0, 1.6 Hz, 1H), 5.29 (dd, *J* = 9.9, 3.5 Hz, 1H), 5.07 (s, 1H), 4.96 (d, *J* = 9.9 Hz, 1H), 4.90 (d, *J* = 9.9 Hz, 1H), 4.09 (dt, *J* = 3.3, 1.6 Hz, 1H).

¹³C NMR (CDCl₃, 91 MHz): δ = 165.9, 134.6, 133.9, 130.1, 129.1 (2C), 129.0, 128.7, 128.5, 128.1, 127.5, 124.4, 122.6, 101.7, 78.9, 76.5, 74.6, one carbon hidden.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₂₂H₂₀N₃O₃: 346.1438; found: 346.1425.

4-(benzyloxy)-2-phenyl-4,9a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (4hcis)

IR (ATR): 2938, 2849, 1699, 1611, 1531, 1454, 1362, 1115, 1076, 996 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 7.49–7.41 (m, 2H), 7.38–7.29 (m, 8H), 6.49 (dd, *J* = 11.1, 6.8 Hz, 1H), 6.40 (dd, *J* = 11.1, 5.6 Hz, 1H), 6.17 (ddd, *J* = 9.9, 5.6, 1.6 Hz, 1H), 6.00 (dd, *J* = 6.7, 1.2 Hz, 1H), 5.63 (s, 1H), 5.31 (dd, *J* = 9.8, 3.8 Hz, 1H), 5.04 (d, *J* = 9.6 Hz, 1H), 4.93 (d, *J* = 9.6 Hz, 1H), 3.70–3.68 (m, 1H).

¹³C NMR (CDCl₃, 91 MHz): δ = 164.2, 133.8, 133.2, 130.0, 129.2, 129.1, 129.0, 128.9, 128.6, 128.1, 127.4, 124.5, 122.5, 101.3, 78.7, 76.8, 70.7, one carbon hidden.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₂₂H₂₀N₃O₃: 346.1438; found: 346.1427.

3,3-dimethyl-4-phenoxy-9-phenyl-4,4a-dihydrocyclohepta[b][1,4]oxazin-2(3H)-one (6e)

Following the general procedure, starting from 2-phenylcyclohepta-2,4,6-trienone **5** (43 mg, 0.236 mmol, 1 equiv.), 2-bromo-2-methyl-*N*-phenoxypropanamide **2e** (121 mg, 0.472 mmol, 2 equiv.) and triethylamine (83 μL, 0.590 mmol, 2.5 equiv.) in HFIP (1.2 mL) for 16 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford product **6e** as an orange solid (47 mg, 56%).

Mp = 133–135 °C.

IR (ATR): 2990, 2939, 2875, 1705, 1694, 1591, 1487, 1379, 1362, 1293, 1170, 1154, 1000, 964 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 7.41–7.28 (m, 7H), 7.13–7.07 (m, 3H), 6.74–6.68 (m, 1H), 6.62–6.56 (m, 1H), 6.30 (ddd, *J* = 9.3, 5.3, 1.7 Hz, 1H), 5.66 (dd, *J* = 9.3, 4.9 Hz, 1H), 4.07 (dd, *J* = 5.0, 1.5 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 3H).

¹³C NMR (CDCl₃, 91 MHz): δ = 170.3, 158.0, 137.1, 136.2, 132.5, 129.9, 129.4, 128.1, 127.3, 127.0, 125.5, 123.7, 123.2, 118.8, 113.8, 81.6, 61.0, 25.7, 24.6.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₂₃H₂₂N₃O₃: 360.1594; found: 360.1577.

Following the general procedure, starting from 2-phenylcyclohepta-2,4,6-trienone **5** (80 mg, 0.425 mmol, 1 equiv.), *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** (231 mg, 0.850 mmol, 2 equiv.) and triethylamine (148 μL, 1.060 mmol, 2.5 equiv.) in HFIP (2.1 mL) for 16 h, the crude product was purified by flash column chromatography (100/0 to 95/5 pentane/EtOAc) to afford product **6a** as an orange oil (89 mg, 56%) and **6b** as an orange solid (19 mg, 12%).

4-(benzyloxy)-3,3-dimethyl-9-phenyl-4,4a-dihydrocyclohepta[b][1,4]oxazin-2(3H)-one (6a)

IR (ATR): 2988, 2835, 1687, 1653, 1603, 1455, 1376, 1295, 1150, 1029, 1014, 908 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 7.50–7.42 (m, 2H), 7.40–7.25 (m, 8H), 6.66–6.53 (m, 2H), 6.27 (ddd, *J* = 9.2, 5.0, 1.4 Hz, 1H), 5.52 (dd, *J* = 9.3, 5.1 Hz, 1H), 5.16–5.04 (m, 2H), 3.74 (dd, *J* = 5.1, 1.5 Hz, 1H), 1.56 (s, 3H), 1.50 (s, 3H).

¹³C NMR (CDCl₃, 91 MHz): δ = 169.3, 137.3, 136.4, 134.8, 132.4, 130.5, 129.7, 129.5, 129.1, 128.7, 128.1, 127.1, 126.9, 125.2, 123.8, 117.9, 81.0, 60.6, 25.8, 24.5.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₂₄H₂₄N₃O₃: 374.1751; found: 374.1732.

4-(benzyloxy)-2,2-dimethyl-5-phenyl-4,9a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (6b)

Mp = 110–112 °C.

IR (ATR): 2978, 2936, 2850, 1704, 1595, 1490, 1452, 1382, 1323, 1280, 1224, 1170, 1130, 988 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 7.37–7.31 (m, 2H), 7.28–7.23 (m, 3H), 7.21–7.10 (m, 3H), 6.86–6.78 (m, 2H), 6.77–6.74 (m, 1H), 6.70–6.62 (m, 1H), 6.28 (ddd, *J* = 9.2, 5.5, 1.7 Hz, 1H), 5.27 (dd, *J* = 9.3, 4.4 Hz, 1H), 4.42 (s, 2H), 3.58 (dd, *J* = 4.3, 1.7 Hz, 1H), 1.62 (s, 3H), 1.59 (s, 3H).

¹³C NMR (CDCl₃, 101 MHz): δ = 168.7, 139.1, 134.0, 133.0, 129.6, 129.5, 129.1, 128.5, 128.1, 128.1, 127.4, 126.1, 123.7, 120.7, 117.0, 77.7, 75.0, 72.7, 24.9, 21.1.

HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₂₄H₂₄NO₃: 374.1751; found: 374.1743.

2,2-dimethyl-4,9a-dihydrocyclohepta[b][1,4]oxazin-3(2H)-one (7)

In a round bottom flask were placed compound **4a** (100 mg, 0.337 mmol, 1 equiv.) and [Mo(CO)₆] (195 mg, 0.740 mmol, 2.2 equiv.). A mixture CH₃CN/H₂O (9:1) (3 mL) was added and the reaction mixture was stirred under reflux for 16 h. Then, it was filtered through a short pad of Celite, which was rinsed with dichloromethane. The solution was dried over anhydrous MgSO₄ and filtered. The solvent was removed with rotary evaporation. The crude product was purified by flash column chromatography (60/40 pentane/EtOAc) to afford product **7** as an orange solid (57 mg, 89%).

Mp = 161–163 °C.

IR (ATR): 2934, 2874, 1680, 1631, 1531, 1381, 1263, 1226, 1106, 966 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 8.69 (brs, 1H), 6.55–6.41 (m, 2H), 6.22–6.13 (m, 1H), 5.64 (dd, *J* = 5.6, 1.4 Hz, 1H), 5.25 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.88 (dt, *J* = 3.5, 1.8 Hz, 1H), 1.55 (s, 3H), 1.44 (s, 3H).

¹³C NMR (CDCl₃, 91 MHz): δ = 174.5, 128.9, 128.4, 127.2, 124.0, 123.3, 101.9, 75.8, 69.1, 24.5, 21.6.

HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₁H₁₃NNaO₂: 214.0835; found: 214.0828.

4-(tert-butoxy)-2,2-dimethyl-4,6,7,8,9,9a-hexahydrocyclohepta[b][1,4]oxazin-3(2H)-one (8)

In a round bottom flask were placed compound **4b** (25 mg, 0.095 mmol, 1 equiv.) and Pd/C (3 mg, 10% w/w). EtOAc (5 mL) was added and the reaction mixture was stirred at room temperature for 3 h under H₂ atmosphere. Then, it was filtered through a short pad of Celite, which was rinsed with EtOAc. The solvent was removed with rotary evaporation. The crude product was purified by flash column chromatography (90/10 Pentane/EtOAc) to afford product **8** as an orange oil (21 mg, 84%).

IR (ATR): 2929, 2919, 2876, 1699, 1652, 1541, 1472, 1095, 960 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 5.60 (ddd, *J* = 9.4, 5.8, 2.0 Hz, 1H), 4.61 (d, *J* = 9.9 Hz, 1H), 2.33–2.22 (m, 1H), 2.08–1.92 (m, 2H), 1.74–1.59 (m, 5H), 1.48 (s, 3H), 1.36 (s, 3H), 1.32 (s, 9H).

¹³C NMR (CDCl₃, 91 MHz): δ = 169.3, 138.2, 122.6, 85.5, 78.7, 31.9, 31.3, 30.2, 28.0, 27.2, 26.4, 24.6, 24.2.

HRMS (ESI⁺): *m/z* [(M-^tBuOH)+Na]⁺ calcd for C₁₁H₁₆NNaO₂: 217.1079; found: 217.1069.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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