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Multidimensional Screening and Methodology Development for Condensations Involving Complex 1,2-Diketones

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Abstract

Multidimensional reaction screening employing complex 1,2-cycloheptanediones is described. The studies have enabled the discovery of regioselective, Lewis acid-mediated condensations with substituted ureas and a diastereoselective hydrogenation process which proceeds *via* an interesting allylpalladium hydride isomerization.

Keywords

reaction discovery; regioselective condensation; Lewis acids; diastereoselective hydrogenation

Multidimensional reaction screening^{1,2} is an efficient high-throughput approach for the discovery of new synthetic methodologies and complex chemotypes.^{3,4} Previous reaction screening efforts utilizing bicyclo [3.2.1]octanoids led to the discovery of a retro-Dieckmann-type fragmentation which afforded highly functionalized cycloheptenones.⁴ We were interested in using the cycloheptenone scaffolds as substrates for additional reaction discovery projects focused on condensations. Condensations of 1,2-dicarbonyls allow facile access to heterocyclic and hetero-polycyclic compounds generating chemotypes with even greater complexity. In the current study, we evaluated a wide range of condensation partners^{5–14} with complex 1,2- cycloheptanediones. Herein, we report our initial screening results and subsequent development of regioselective condensations to afford novel heterocyclic frameworks.

As shown in Scheme 1, the synthesis of the target screening scaffolds originated from [5+2] cycloaddition of quinone monoketal **1** and β -*trans*-methylstyrene to afford bicyclo[3.2.1]octanoid **2**. Retro-Dieckmann-type ring-opening of **2** afforded the corresponding cycloheptenones **3**.^{4,15} Subsequent acid-mediated *O*-demethylation of α -methoxyenone **4** afforded 1,2-diketone **5**. Interestingly, *O*-demethylation of secondary amide **6** afforded α -hydroxyketone **7**.

Preliminary efforts to probe the reactivity of scaffolds **5** and **7** were carried out using known imidazole-forming conditions. While reaction with scaffold **5** afforded the desired imidazole

8, reaction with scaffold **7** unexpectedly afforded oxazoline **9** with high diastereoselectivity (Scheme 1). The major diastereomer of oxazoline **9** was confirmed by X-ray crystallographic analysis.^{16,17}

Having established preliminary reactivity, we carried out a comprehensive multidimensional reaction screen utilizing scaffolds **5** and **7b** (Figure 1). For this screen, 18 condensation partners were selected using both ethanol and acetonitrile as solvents (80 °C, 24 h) in the presence of either pyridinium *p*-toluenesulfonate (PPTS), diisopropylethylamine (DIEA), or without additive.

Each reaction was performed using 3 μmol of substrate (approx. 1 mg scale) with 1.0 equiv of both reaction partner and additive (total reaction volume of 60 μL, 0.05 M). Reaction partners that were used as hydrochloride salts required use of 2.0 equiv of base. Each reaction was prepared in 1 mL oven-dried glass vials with minimal exposure to air from corresponding reagent stock solutions prepared in both EtOH and CH₃CN. The reactions were capped with silicon rubber septa and placed in a heated reaction block (80 °C) fastened to an orbital shaker and agitated for 24 hours. The reactions were diluted to 1 mL and analyzed using UPLC/MS/ELSD.¹⁸ Reactions affording >20 % conversion to a major product were subsequently scaled up and reaction products were isolated for characterization.

As anticipated, 1,2-diketone scaffold **5** underwent a number of reactions to afford new products (Figure 2). Condensation with 1,2-phenylenediamine and (1*S*,2*S*)-(+)-diaminocyclohexane afforded pyrazines **10** and **11**, respectively.⁶ Reactions with 2-aminothiophenol⁷ and 6-amino-*m*-cresol⁸ also resulted in the formation of adducts, but as complex mixtures that were unstable to isolation. Reaction with *S*-methylsemicarbazide hydroiodide under acid conditions resulted in the formation of triazines **12a** and **12b** (2:1 mixture of regioisomers).⁹ Although the two regioisomers were isolated, the structures could not be assigned based on standard NMR analysis. Condensation with 2-aminobenzaldehyde gave rise to a mixture of four quinoline products (**13a-d**). Interestingly, these quinoline products were obtained under acidic conditions which is in contrast to typical Friedländer condensation conditions (KOH, EtOH, reflux).¹⁰ Additionally, acid-catalyzed condensations using urea,¹¹ guanidine hydrochloride,¹² and benzamidine hydrochloride¹³ afforded the cycloheptadiene products **14**, **15**, and **16a**, respectively. In the case of the reaction with urea, alkenyl imidazolone **16a** readily oxidized to the corresponding cycloheptatriene **16b** upon exposure to ambient atmosphere.

Although screening with the α-hydroxyketone **7b** substrate indicated successful conversion to new products, we found that these products were generally unstable to purification. This suggests that while initial imine formation was taking place, subsequent cyclizations were not occurring due to unexpected stability of the *N*-acylhemiaminal. However, we did observe reaction of **7b** with isocyanates¹⁴ (DIEA, CH₃CN, 80 °C, 24 h) to afford the unusual alkenyl oxazolidinones **17** and **18** (Figure 2). Surprisingly, **17** and **18** were remarkably stable under both acidic and basic conditions.

We next selected the condensation of 1,2-diketone **5** with *S*-methylsemicarbazide hydroiodide for initial follow-up with the goal of developing a regioselective condensation. Although there are numerous reports of reactions with 1,2-dicarbonyls, there are a limited number of studies that address the issue of regioselectivity when non-symmetric substrates were utilized.¹⁹ In general, regioselectivity is a direct result of inherent reactivity of the carbonyls.^{19c,e} Despite modest advancements, obtaining regioselectivity with scaffolds of greater complexity remains a significant challenge. Accordingly, we conducted a series of triazene-forming reactions utilizing various catalysts and conditions (Table 1).

Generally, it was observed that replacement of EtOH with 2,2,2-trifluoroethanol (TFE) or CH₃CN enhanced the regioselectivity 3-fold. Conversely, use of THF:H₂O (9:1) resulted in a reduction of regioselectivity (Table 1, entry 2). These results suggest that the presence of a nucleophilic solvent such as EtOH or H₂O leads to the formation of a derived hemiketal or hydrate, respectively, with the slightly more electrophilic ketone thus decreasing regioselectivity. Unexpectedly, addition of Sc(OTf)₃ resulted in an inversion of regioselectivity (Table 1, entry 3). While the addition of 4 Å MS resulted in a slight enhancement of inversion, additional enhancement was achieved by conducting the reaction at 0 °C for 16 h and by using extensively dried *S*-methylsemicarbazide hydroiodide (Table 1, entry 7). The conversion was ultimately improved by using two equivalents of *S*-methylsemicarbazide (Table 1, entry 11). To the best of our knowledge, this study represents the first use of a Lewis acid to invert the regioselectivity of a 1,2-dicarbonyl condensation.

Although two regioisomers were isolated, we were unable to assign the structures of **12a** and **12b** using standard NMR analysis due to the overlapping of several key proton resonances. Attempts to grow suitable crystals for X-ray analysis were also unsuccessful. We therefore sought to synthesize an alternative substrate with fewer more defined proton resonances. Previous work had demonstrated that bicyclo[3.2.1]octanoid **2** undergoes a retro-Dieckmann-type ring opening with pyrrolidine in the presence of TBD.⁴ Unfortunately, this methodology was limited in scope of the secondary amine reagent. Thus, a revised route to the cycloheptenone scaffold was developed that would allow for greater variability of the tertiary amide. We found that performing the fragmentation reaction with water in the presence of DBU afforded the corresponding carboxylic acid **19** as a viable functional handle (Scheme 2). HATU coupling with dimethylamine afforded the desired cycloheptenone **20** in 65 % yield over two steps. Subsequent *O*-demethylation, followed by condensation with *S*-methylsemicarbazide, afforded triazines **22a** and **22b**.

With triazines **22a** and **22b** in hand, we were able to determine their regiochemistries using ¹⁵N-HMBC NMR analysis²⁰ (Scheme 2).¹⁷ Based on these experiments, we postulated that the inherently more reactive ketone is *beta* to the phenyl group (C-1) and that the Lewis acid may preferentially activate the ketone *beta* to the amide group (C-2).

To further understand the mechanism leading to regioselectivity we turned our attention to condensations with urea, which was also identified in the initial screen. Our first objective, however, was to control the oxidative process occurring during the course of the reaction. It was found that degassing the reaction with argon significantly prevented the oxidative process (Table 2, entry 2) while purging the reaction with O₂ increased the degree of

oxidation (Table 2, entry 3). With a viable method for controlling oxidation, the next step was to attempt the condensation with the non-symmetrical *N*-ethylurea. As anticipated, condensation with 1,2-diketone **5** gave rise to a mixture of regioisomers **23a** and **23b** (Scheme 3). Regiochemical assignments were confirmed by 1D NOE analysis.¹⁷ As the unsubstituted urea nitrogen is expected to be more reactive, we anticipated that the initial condensation may occur with the slightly more electrophilic C-1 ketone as observed for condensation with *S*-methylsemicarbazide (*cf.* Scheme 2).

We next conducted a Lewis acid screen to determine if regiochemical control would be possible with substituted ureas. Generally, substituted ureas were found to be substantially less reactive than *S*-methylsemicarbazide which required alternative conditions to obtain regioselectivity. As indicated in Table 3, all Lewis acids investigated resulted in the inversion of regioselectivity with Zn(OTf)₂ being the most effective catalyst. Thus, the incorporation of a Lewis acid in place of a Brønsted acid ultimately rendered the C-2 ketone to be more reactive similar to the regioselective synthesis of triazines **12** and **22**.

To gain insight into the role of the Lewis acid, mechanistic studies were initiated utilizing ¹H and ¹³C NMR analyses of substrate **5** in the presence of Zn(OTf)₂ (Figure 4 and 5). We observed a downfield shift of all the 1,2-cycloheptanedione ring protons except the α-phenyl methine proton (D) which shifted slightly upfield (Figure 4). The addition of Zn(OTf)₂ did not significantly alter coupling constants indicating that the 1,2-cycloheptanedione ring conformation was not significantly altered. ¹³C NMR spectra revealed selective broadening of the two ketone resonances at 196 ppm and 197 ppm. Given that Zn(II) is diamagnetic, we did not anticipate the observed resonance broadening. We propose that Fe(II), a common impurity (1-20 ppm) in Zn(OTf)₂, is likely responsible for the resonance broadening suggesting that Fe(II) or Zn(II) may chelate the 1,2-diketone and not the more Lewis basic amide functionality. Since Fe(OTf)₂ also induces significant inversion of regioselectivity, it is expected that these Lewis acids share a common metal coordination site.

Based primarily on the ¹H and ¹³C NMR studies, we propose a mechanism for the regioselective condensation (Figure 6). Using conformational analysis followed by energy minimization,²¹ we determined that, in the absence of Zn(OTf)₂, the oxygen lone pair on the amide carbonyl is positioned in close proximity to the α-phenyl methine altering its electronic environment. We believe that chelation of Zn(OTf)₂ to the 1,2-diketone lowers the LUMO for both carbonyls triggering rotation of the amide carbonyl forming a stabilizing *n*-π* interaction with the C-1 ketone. The C-2 ketone is unable to undergo a similar *n*-π* interaction due to significant steric clash upon further rotation of the amide. It is also notable that replacement of the pyrrolidine with *N*-methylcyclohexylamine resulted in complete loss of regioselectivity likely due to greater steric interactions inhibiting amide rotation.

We next probed additional substituted ureas (Table 4). It was found that the Zn(OTf)₂-mediated reaction maintained reasonable regioselectivity over a wide range of functionality. However, a slight reduction in selectivity was observed with increasing steric bulk of the ureas substitution (Table 4, entries 1-4). Additionally, we observed that greater electron deficiency was accompanied with a slight decrease in yield (Table 4, entries 8-10). In the

case of *N*-acetylurea, no reaction was observed. Condensations with 1,3-disubstituted ureas, such as 1-methyl-3-phenylurea and 1-ethyl-3-phenylurea, indicated that the phenyl substituted nitrogen is more nucleophilic (Table 4, entries 12 and 13). Reactions with a Brønsted acid catalyst (CSA) were also carried out in select cases. While both allylurea and *p*-chlorophenylurea resulted in similar regioselectivity as ethylurea, 1-ethyl,3-phenylurea gave similar results as the Zn(OTf)₂ mediated reaction. The Zn(OTf)₂-mediated regioselective condensation was also applied to a substituted thiourea with good results. However, in this instance a stoichiometric amount of Zn(OTf)₂ was required to achieve comparable regioselectivity (Table 4, entry 14).

Due to the oxidative instability of the alkenyl imidazolones, we sought to determine the oxidation/reduction potential of these interesting ring systems with the intent of increasing stability. We first carried out oxidation of alkenyl imidazolone **23a** using DDQ (1.2 equiv) which afforded the desired cycloheptatriene **37** along with the *pseudo*-aromatic cycloheptimidazolone (2-hydroxy-1,3-diazaazulene)²² **38** (Scheme 4). Acylation of the urea prevented over oxidation and afforded exclusively cycloheptatriene **39** in moderate yield over two steps.

Diastereoselective hydrogenation of alkenyl imidazolone **23a** with 10 % Pd/C (H-Cube, 50 bar, 50 °C) afforded cycloheptene **40** as a single diastereomer (Scheme 5). The stereochemical assignment was confirmed by 1D NOE analysis.¹⁷ Diastereoselectivity is likely achieved through steric interaction imparted by the *pseudo*-axial methyl effectively blocking the *re*-face (Scheme 5). Unfortunately, reduction of the styrenyl olefin did not result in an appreciable decrease in oxidative decomposition.

Interestingly, *N*-acylation of cycloheptene **40** resulted in only a slight increase in stability which suggests that the electronics of the imidazolone ring plays a significant role in oxidative decomposition. It should be noted that imidazolone rings with greater electron density, such as disubstituted urea condensates **33-35**, underwent decomposition more readily. Initial attempts to fully reduce alkenyl imidazolone **23a** with 10 % Pd/C using extremely harsh conditions (H-Cube, 90 bar, 80 °C) still afforded cycloheptene **40** as the major product as well as some reduction of the phenyl ring. However, full reduction of **23a** was achieved with Raney Ni (H-Cube, 90 bar, 80 °C) to afford imidazolidinone **41** as a 1:1 mixture of diastereomers (Scheme 6). Hydrogenation of the imidazolone olefin effectively eliminated the occurrence of oxidative decomposition.

Unfortunately, hydrogenation with Raney Ni using harsh H-Cube conditions was highly variable due to variability in catalyst cartridge batches. As a result, an alternative more reliable approach for reducing the imidazolone olefin was required. Remarkably, it was discovered that full reduction of the acetylated alkenyl imidazolone **42** with 10 % Pd/C under considerably milder conditions (H-Cube, 30 bar, 90 °C) afforded imidazolidinone **43** as a single diastereomer (Scheme 6). We also observed full reduction of the acetylated alkenyl imidazolone **44** to afford imidazolidinone **45** as a single diastereomer albeit requiring slightly harsher conditions.

As previously described, we propose that the styrenyl olefin undergoes diastereoselective hydrogenation first *via* the well established Horiuti-Polanyi half-hydrogenation mechanism²³ affording the allylpalladiumhydride intermediate **46** (Figure 7). Subsequent isomerization occurs with retention of stereo-chemistry to afford intermediate **47** which may in part be favored due to stabilization by coordination of the amide acetyl oxygen.²⁴ Subsequent reductive elimination of palladium provides the net 1,4-addition product **48** as a single diastereomer. We were also able to isolate intermediate **48** under milder conditions (H-Cube, 10 bar, 40 °C). Stereochemical assignments for **48** were confirmed by 1D NOE analysis.¹⁷ Diastereoselective hydrogenation of the resulting enamine affords the fully reduced product **43**. Diastereoselectivity of the final reduction is due to blocking of the *re*-face by the flanking phenyl and *N*-acylurea. Further evidence for the allylpalladium hydride isomerization mechanism was provided by a failed attempt to reduce the acetylated imidazolone **49** (H-Cube, 10 bar 40 °C) (Scheme 7).

We were also able to isolate enamine **48** upon treatment of **49** with acetic acid (Scheme 7). The selectivity of the acid-mediated isomerization suggests that the observed *syn*-diastereomer is thermodynamically favored. Accordingly, computational studies²¹ for imidazolone **49** and both the *syn*- and *anti*-diastereomers from isomerization were performed. As indicated in Figure 8, the ground-state energy of the *syn*-diastereomer **48** is 1 Kcal lower in energy than the parent imidazolone **49** and 4.8 Kcal lower in energy than the *anti*-diastereomer **50**. These results confirm that the *syn*-diastereomer **48** is thermodynamically favored.

Interesting, similar calculations performed on imidazolone **40**, which lacks the *N*-acetyl, revealed isomerization to either the *syn*- or *anti*-diastereomer is not favored with ground-states energies of +5.6 Kcal and +8.4 Kcal, respectively (Figure 8). These findings, in part, help explain the results obtained for the Raney Ni hydrogenation in which diastereoselective reduction of imidazolone **40** was not observed. Without isomerization to afford bulky functionality flanking the olefin, hydrogenation occurs equally from both the *si*- and *re*-face.

In summary, multidimensional screening of condensations reactions enabled the discovery of regioselective Lewis acid-mediated condensations with a densely functionalized 1,2-diketone scaffold. We determined that regioselective condensations may be conducted using Lewis acid chelation with the 1,2-diketone leading to a proposed *n*- π^* interaction with a pendant amide carbon-yl. This unique approach to achieving regioselectivity apparently relies on a presence of the proximal amide which may form a stabilizing *n*- π^* interaction with the nearest neighboring carbonyl. Regioselective condensations with substituted ureas led to the ultimate discovery of a novel diastereoselective hydrogenation which proceeds *via* an interesting allylpalladium hydride isomerization. Taken together, these discoveries provide a regioselective and diastereoselective route to a number of densely functionalized cycloheptane urea scaffolds. Application of the methodology developed to chemical library synthesis is currently underway and will be reported in due course.

General Information

¹H NMR spectra were recorded at 400 MHz at ambient temperature unless otherwise stated. ¹³C NMR spectra were recorded at 100.0 MHz at ambient temperature unless otherwise stated. Chemical shifts are reported in parts per million relative to CDCl₃ (¹H, δ 7.27; ¹³C, δ 77.0) and CD₃OD (¹H, δ 3.31; ¹³C, δ 49.0). Data for ¹H NMR are reported as follows: chemical shift, integration, multiplicity (ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet) and coupling constants are reported as values in hertz. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Waters Q-TOF mass spectrometer. Analytical LC was performed on a Waters Acquity UPLC with PDA, ELS and SQ detectors. An Acquity UPLC BEH 2.1 × 50 mm 1.7 μM C18 column was used for analytical LC. Analytical thin-layer chromatography was performed using 0.25 mm silica gel 60-F plates. Otherwise, flash chromatography was performed using 200-400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Acetonitrile, THF, and CH₂Cl₂ were purified by passing through two packed columns of neutral alumina. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. Chemical names were generated using MDL AutoNom 2000. The Arthur™ Suite Reaction Planner was used for experimental procedure planning.

General procedure for the synthesis of diketone 5, diketone 21, and α-hydroxyketone 7a/b

To a 20 mL vial was added cycloheptenone **4** (170 mg, 0.52 mmol) followed by DMSO (10 mL). Once fully dissolved, 1.2 M HCl (10 mL) was added. The reaction was heated to 100 °C and stirred for 4 h. The reaction was cooled, diluted with water (25 mL) and partitioned into CH₂Cl₂ (20 mL × 3). The organic layer was washed with brine (25 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* and the crude material purified by flash chromatography (SiO₂, 9:1 CH₂Cl₂:EtOAc) to afford **5** (76 %, 124 mg, 0.40 mmol).

Diketone 5

¹H NMR (400 MHz, CD₃CN) δ 0.73 (d, *J* = 7.0 Hz, 3 H), 1.79 - 1.87 (m, 2 H), 1.88 - 1.94 (m, 2 H), 2.40 - 2.49 (m, 1 H), 2.55 (dd, *J* = 13.3, 1.6 Hz, 1 H), 2.88 (dd, *J* = 16.0, 7.0 Hz, 1 H), 3.00 - 3.07 (m, 1 H), 3.11 (dd, *J* = 16.0, 2.0 Hz, 1 H), 3.29 (d, *J* = 13.3, 12.0 Hz, 1 H), 3.32 - 3.38 (m, 2 H), 3.43 - 3.51 (m, 2 H), 3.54 - 3.62 (m, 1 H), 7.22 - 7.28 (m, 3 H), 7.32 - 7.38 (m, 2 H).

¹³C NMR (100 MHz, CD₃CN) δ 19.9, 25.4, 27.2, 44.4, 45.1, 47.0, 48.3, 48.9, 50.6, 128.0, 128.4, 130.2, 147.5, 172.4, 195.6, 197.0.

IR (thin film) ν_{max} 2973, 1710, 1701, 1653, 1635, 1616, 1559, 1465, 1457, 703 cm⁻¹.

HRMS calculated for C₁₉H₂₄NO₃: 314.1756, found: 314.1751 (M+H).

α -Hydroxyketone 7a. (99 %, 38 mg, 0.11 mmol)

^1H NMR (400 MHz, CDCl_3) δ 0.91 (d, $J = 7.0$ Hz, 3 H), 2.08 - 2.17 (m, 1 H), 2.20 (d, $J = 13.6$ Hz, 1 H), 2.33 (d, $J = 18.2$ Hz, 1 H), 2.39 (t, $J = 11.7$ Hz, 1 H), 2.51 (dd, $J = 13.6, 8.7$ Hz, 1 H), 2.75 (dd, $J = 18.2, 11.7$ Hz, 1 H), 2.89 (d, $J = 8.7$ Hz, 1 H), 4.15 (d, $J = 14.7$ Hz, 1 H), 4.72 (d, $J = 14.7$ Hz, 1 H), 4.88 (s, 1 H), 6.88 (d, $J = 7.8$ Hz, 2 H), 7.17 - 7.22 (m, 1 H), 7.22 - 7.29 (m, 3 H), 7.32 (t, $J = 7.2$ Hz, 2 H), 7.36 - 7.40 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3) δ 19.7, 39.0, 42.0, 43.7, 44.6, 47.0, 47.6, 89.1, 126.6, 126.8, 128.0, 128.5, 128.9, 129.8, 136.4, 144.2, 173.5, 205.9.

IR (thin film) ν_{max} 3415, 2935, 1690, 1454, 1401, 1380, 1348, 1138, 1117, 702 cm^{-1} .

HRMS calculated for $\text{C}_{22}\text{H}_{24}\text{NO}_3$: 350.1756, found: 350.1764 (M+H).

 α -Hydroxyketone 7b. (97 %, 37 mg, 0.098 mmol)

^1H NMR (400 MHz, CDCl_3) δ 0.90 (d, $J = 7.0$ Hz, 3 H), 2.08 - 2.16 (m, 1 H), 2.18 (d, $J = 13.7$ Hz, 1 H), 2.33 (dd, $J = 18.2, 2.0$ Hz, 1 H), 2.37 (td, $J = 12.0, 2.0$ Hz, 1 H), 2.49 (dd, $J = 13.7, 8.6$ Hz, 1 H), 2.74 (dd, $J = 18.2, 12.0$ Hz, 1 H), 2.87 (dd, $J = 8.6, 2.0$ Hz, 1 H), 3.77 (s, 3 H), 4.06 (d, $J = 14.7$ Hz, 1 H), 4.70 (d, $J = 14.7$ Hz, 1 H), 4.90 (s, 1 H), 6.83 (d, $J = 8.8$ Hz, 2 H), 6.89 (d, $J = 7.0$ Hz, 2 H), 7.15 - 7.21 (m, 1 H), 7.22 - 7.28 (m, 2 H), 7.30 (d, $J = 8.8$ Hz, 2 H).

^{13}C NMR (100 MHz, CDCl_3) δ 19.7, 39.0, 41.2, 43.6, 44.4, 46.9, 47.6, 55.2, 89.1, 113.6, 126.6, 126.8, 128.8, 128.5, 131.2, 144.2, 159.2, 173.4, 206.1.

IR (thin film) ν_{max} 3425, 2935, 1690, 1513, 1247, 1177, 1138, 1112, 1032, 703, 668 cm^{-1} .

HRMS calculated for $\text{C}_{23}\text{H}_{26}\text{NO}_4$: 380.1862, found: 380.1867 (M+H).

Diketone 21. (73 %, 60 mg, 0.21 mmol)

^1H NMR (400 MHz, CD_3CN) δ 0.71 (d, $J = 6.6$ Hz, 3 H), 2.41 - 2.50 (m, 1 H), 2.55 (dd, $J = 13.3, 1.6$ Hz, 1 H), 2.83 (dd, $J = 16.0, 7.4$ Hz, 1 H), 2.89 (s, 3 H), 2.95 - 3.02 (m, 1 H), 3.09 (s, 3 H), 3.10 (dd, $J = 16.0, 2.0$ Hz, 1 H), 3.29 (dd, $J = 13.3, 12.0$ Hz, 1 H), 3.67 - 3.75 (m, 1 H), 7.21 - 7.29 (m, 3 H), 7.32 - 7.38 (m, 2 H).

^{13}C NMR (100 MHz, CD_3CN) δ 19.7, 36.2, 39.4, 44.5, 45.1, 46.1, 48.2, 50.5, 128.0, 128.4, 130.1, 147.4, 174.1, 195.8, 197.0.

IR (thin film) ν_{max} 2960, 1709, 1684, 1653, 1635, 1617, 1559, 1506, 1457, 1419, 704 cm^{-1} .

HRMS calculated for $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{Na}$: 310.1419, found: 310.1407 (M+Na).

General procedure for the synthesis of imidazole 8 and oxazoline 9a-b

To an oven-dried vial was added diketone **5** (40 mg, 0.13 mmol) and ammonium acetate (40 mg, 0.52 mmol) followed by anhydrous ethanol (1 mL) and benzaldehyde (15 μL , 0.14

mmol). The reaction vial was sealed with a Teflon-lined cap and heated to 80 °C for 3 h with continuous stirring. The reaction was cooled, concentrated *in vacuo* and purified by flash chromatography (SiO₂, gradient 30:1 CH₂Cl₂:MeOH to 10:1 CH₂Cl₂:MeOH) to afford **8** (36 %, 18 mg, 0.046 mmol).

Imidazole **8**

¹H NMR (400 MHz, CD₃OD) δ 1.12 (d, *J* = 7.0 Hz, 3 H), 1.73 - 1.82 (m, 4 H), 2.40 (t, *J* = 6.8 Hz, 1 H), 2.76 (d, *J* = 14.5 Hz, 1 H), 2.88 - 2.98 (m, 1 H), 2.98 - 3.07 (ovrlp m, 1 H), 3.02 - 3.10 (ovrlp m, 1 H), 3.05 - 3.12 (ovrlp m, 1 H), 3.13 - 3.20 (ovrlp m, 1 H), 3.13 - 3.23 (ovrlp m, 1 H), 3.17 - 3.25 (ovrlp m, 1 H), 3.25 - 3.32 (m, 1 H), 3.32 - 3.40 (m, 1 H), 7.15 - 7.22 (m, 1 H), 7.22 - 7.31 (m, 4 H), 7.35 - 7.42 (m, 1 H), 7.42 - 7.49 (m, 2 H), 7.84 (d, *J* = 8.2 Hz, 2 H).

¹³C NMR (100 MHz, CD₃OD) δ 14.7, 24.0, 25.0, 26.9, 29.3, 41.4, 43.2, 47.1, 47.2, 126.3, 127.6, 129.2, 129.5, 129.9, 130.1, 130.2, 132.0, 133.2, 144.9, 147.0, 175.2.

IR (thin film) ν_{max} 3057, 2971, 2877, 1635, 1493, 1437, 1380, 1265, 773, 734, 702 cm⁻¹.

HRMS calculated for C₂₆H₃₀N₃O: 400.2389, found: 400.2389 (M+H).

Oxazoline **9a**. Purified by flash chromatography (SiO₂, 6:3:1 petroleum ether:CH₂Cl₂:EtOAc) (72 %, 26 mg, 0.058 mmol)

¹H NMR (400 MHz, CDCl₃) δ 0.88 (d, *J* = 6.6 Hz, 3 H), 2.09 - 2.16 (ddq, *J* = 10.9, 6.6, 1.8 Hz, 1 H), 2.21 (d, *J* = 12.9 Hz, 1 H), 2.40 (ddd, *J* = 12.9, 10.9, 2.3 Hz, 1 H), 2.67 (dd, *J* = 19.0, 2.3 Hz, 1 H), 2.69 (dd, *J* = 12.9, 8.6 Hz, 1 H), 2.80 (ddd, *J* = 19.0, 12.9, 3.1 Hz, 1 H), 2.82 (dd, *J* = 8.6, 1.8 Hz, 1 H), 4.40 (d, *J* = 14.9 Hz, 1 H), 4.60 (d, *J* = 14.9 Hz, 1 H), 6.82 (d, *J* = 3.1 Hz, 1 H), 6.92 (d, *J* = 7.4 Hz, 2 H), 7.14 - 7.22 (m, 1 H), 7.23 - 7.29 (m, 3 H), 7.34 - 7.40 (m, 7 H), 7.49 (d, *J* = 7.0 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃) δ 20.6, 37.4, 39.5, 43.2, 44.2, 44.4, 47.7, 103.1, 105.5, 126.1, 126.7, 126.8, 127.9, 128.5, 128.6, 128.8, 128.9, 129.0, 136.9, 138.4, 144.7, 170.9, 173.1.

IR (thin film) ν_{max} 3030, 2965, 2936, 1698, 1494, 1454, 1395, 1153, 1044, 1017, 736, 699, 668 cm⁻¹.

HRMS calculated for C₂₉H₂₉N₂O₂: 437.2229, found: 437.2236 (M+H).

Oxazoline **9b**. Purified by flash chromatography (SiO₂, 6:3:1 petroleum ether:CH₂Cl₂:EtOAc) (61 %, 22 mg, 0.048 mmol)

¹H NMR (400 MHz, CDCl₃) δ 0.86 (d, *J* = 6.6 Hz, 3 H), 2.06 - 2.15 (ddq, *J* = 10.9, 6.6, 1.8 Hz, 1 H), 2.18 (d, *J* = 12.5 Hz, 1 H), 2.35 (ddd, *J* = 12.5, 10.9, 2.3 Hz, 1 H), 2.64 (dd, *J* = 19.0, 2.3 Hz, 1 H), 2.66 (dd, *J* = 12.5, 8.1 Hz, 1 H), 2.78 (ddd, *J* = 19.0, 12.5, 3.3 Hz, 1 H), 2.79 (dd, *J* = 8.1, 1.8 Hz, 1 H), 3.79 (s, 3 H), 4.27 (d, *J* = 14.8 Hz, 1 H), 4.61 (d, *J* = 14.8 Hz, 1 H), 6.82 - 6.93 (m, 5 H), 7.13 - 7.21 (m, 1 H), 7.22 - 7.28 (m, 2 H), 7.34 - 7.44 (m, 7 H).

^{13}C NMR (100 MHz, CDCl_3) δ 20.5, 37.4, 39.5, 42.6, 44.1, 44.4, 47.7, 55.3, 103.1, 105.5, 113.8, 126.1, 126.6, 126.7, 128.6, 128.7, 128.9, 129.1, 130.5, 138.4, 144.8, 159.2, 171.1, 173.0.

IR (thin film) ν_{max} 3029, 2936, 2836, 1696, 1513, 1395, 1278, 1248, 1178, 1036, 736, 699 cm^{-1} .

HRMS calculated for $\text{C}_{30}\text{H}_{31}\text{N}_2\text{O}_3$: 467.2335, found: 467.2323 (M+H).

General procedure for the synthesis of Triazine 12a/b and 22a/b

To an oven-dried vial was added diketone **5** (40 mg, 0.13 mmol) followed by anhydrous EtOH (1 mL). Next, *S*-methylsemicarbazide hydroiodide (91 mg, 0.39 mmol) was added and the reaction was stirred for 6 h at rt. The reaction was concentrated *in vacuo* and purified by flash chromatography (SiO_2 , gradient 9:1 CH_2Cl_2 :EtOAc to 3:1 CH_2Cl_2 :EtOAc) to afford **12a** (38 %, 19 mg, 0.050 mmol) and **12b** (19 %, 9 mg, 0.025 mmol).

Triazine 12a. $R_f=0.55$ (CH_2Cl_2 :MeOH, 20:1)

^1H NMR (400 MHz, CDCl_3) δ 0.69 (d, $J = 7.0$ Hz, 3 H), 1.72 - 1.83 (m, 2 H), 1.85 - 1.94 (m, 2 H), 2.11 - 2.25 (m, 1 H), 2.58 (s, 3 H), 3.08 (dd, $J = 15.2$, 7.8 Hz, 1 H), 3.18 - 3.27 (m, 3 H), 3.28 - 3.44 (m, 6 H), 7.10 - 7.18 (m, 3 H), 7.21 - 7.28 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 18.7, 24.3, 26.3, 37.5, 41.0, 43.5, 44.1, 45.0, 45.6, 47.0, 126.4, 128.7, 145.9, 156.6, 160.6, 170.2, 170.6.

IR (thin film) ν_{max} 2953, 2927, 2873, 1628, 1445, 1376, 1343, 1265, 1165, 734, 702 cm^{-1} .

HRMS calculated for $\text{C}_{21}\text{H}_{27}\text{N}_4\text{OS}$: 383.1906, found: 383.1893 (M+H).

Triazine 12b. $R_f=0.33$ (CH_2Cl_2 :MeOH, 20:1)

^1H NMR (400 MHz, CDCl_3) δ 0.74 (d, $J = 6.6$ Hz, 3 H), 1.76 - 1.89 (m, 2 H), 1.91 - 2.02 (m, 2 H), 2.23 (m, 1 H), 2.60 (s, 3 H), 3.07 (dd, $J = 14.1$, 2.0 Hz, 1 H), 3.19 - 3.29 (m, 2 H), 3.33 (m, 2 H), 3.40 (dd, $J = 14.9$, 2.7 Hz, 1 H), 3.45 - 3.52 (m, 2 H), 3.53 - 3.62 (m, 2 H), 7.15 - 7.23 (m, 3 H), 7.27 - 7.33 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 19.4, 24.3, 26.3, 35.2, 44.0, 44.2, 44.4, 44.5, 45.5, 46.9, 126.5, 128.7, 145.8, 155.2, 161.4, 170.4, 171.3.

IR (thin film) ν_{max} 2972, 2873, 1630, 1443, 1376, 1295, 1262, 734, 702 cm^{-1} .

HRMS calculated for $\text{C}_{21}\text{H}_{27}\text{N}_4\text{OS}$: 383.1906, found: 383.1915 (M+H).

Triazine 22a. (30 %, 14 mg, 0.039 mmol), $R_f=0.52$ (CH_2Cl_2 :MeOH, 20:1)

^1H NMR (400 MHz, CDCl_3) δ 0.68 (d, $J = 6.9$ Hz, 3 H), 2.14 - 2.24 (m, 1 H), 2.57 (s, 3 H), 2.79 (s, 3 H), 3.01 (s, 3 H), 3.06 (dd, $J = 15.0$, 7.6 Hz, 1 H), 3.20 (dd, $J = 15.0$, 2.8 Hz, 1 H),

3.26 - 3.33 (m, 2 H), 3.33 - 3.39 (m, 1 H), 3.39 - 3.43 (m, 1 H), 7.10 - 7.17 (m, 3 H), 7.21 - 7.26 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 18.4, 35.7, 37.3, 37.9, 40.7, 41.3, 43.6, 45.1, 126.5, 128.7, 145.7, 156.5, 160.5, 170.7, 171.9.

IR (thin film) ν_{max} 2928, 1634, 1493, 1376, 1341, 1261, 1132, 734, 703 cm^{-1} .

HRMS calculated for $\text{C}_{19}\text{H}_{25}\text{N}_4\text{OS}$: 357.1749, found: 357.1757 (M+H).

Triazine 22b. (19 %, 9 mg, 0.025 mmol), $R_f=0.29$ (CH_2Cl_2 :MeOH, 20:1)

^1H NMR (400 MHz, CDCl_3) δ 0.67 (d, $J = 6.9$ Hz, 3 H), 2.16 - 2.25 (m, 1 H), 2.54 (s, 3 H), 2.77 (s, 3 H), 3.02 (dd, $J = 14.2, 2.0$ Hz, 1 H), 3.07 (s, 3 H), 3.22 (dd, $J = 14.2, 11.0$ Hz, 1 H), 3.36 - 3.44 (m, 3 H), 3.44 - 3.50 (m, 1 H), 7.09 - 7.18 (m, 3 H), 7.21 - 7.27 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 19.0, 35.7, 37.9, 41.8, 44.1, 44.6, 126.6, 128.7, 145.6, 155.1, 161.6, 171.4, 172.2.

IR (thin film) ν_{max} 2929, 1635, 1517, 1492, 1375, 1296, 1261, 1155, 1133, 729, 702 cm^{-1} .

HRMS calculated for $\text{C}_{19}\text{H}_{25}\text{N}_4\text{OS}$: 357.1749, found: 357.1745 (M+H).

Cycloheptenone 19

To a vial was added bicyclo[3.2.1]octanoid **2** (40 mg, 0.16 mmol) followed by CH_3CN (1 mL) and H_2O (100 μL). Next, DBU (24 μL , 0.16 mmol) was added and the reaction was stirred at rt for 4 h. The reaction was diluted with H_2O (1 mL), rendered acidic (approx. pH 3) with the addition of 1 N HCl, and extracted with CH_2Cl_2 (10 mL $\times$ 3). The organic layer was washed with brine (25 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo*. The crude material was purified by flash chromatography (SiO_2 , 20:1 CH_2Cl_2 :MeOH) to afford **19** (98 %, 43 mg, 0.16 mmol). $R_f=0.30$ (CH_2Cl_2 :MeOH, 20:1).

^1H NMR (400 MHz, CDCl_3) δ 0.87 (d, $J = 6.3$ Hz, 3 H), 2.53 - 2.60 (m, 2 H), 2.80 (d, $J = 17.4$ Hz, 1 H), 3.05 (dd, $J = 17.4, 11.9$ Hz, 1 H), 3.71 (s, 3 H), 3.95 (t, $J = 5.2$ Hz, 1 H), 5.97 (d, $J = 6.1$ Hz, 1 H), 7.15 - 7.20 (m, 2 H), 7.20 - 7.26 (m, 1 H), 7.27 - 7.34 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3) δ 15.4, 41.4, 44.2, 45.8, 48.3, 55.5, 106.1, 127.0, 127.7, 128.8, 143.5, 153.1, 178.0, 197.0.

IR (thin film) ν_{max} 3063, 2964, 2933, 1734, 1684, 1653, 1456, 1203, 1175, 1145, 735, 703 cm^{-1} .

HRMS calculated for $\text{C}_{16}\text{H}_{19}\text{O}_4$: 275.1283, found: 275.1291 (M+H).

Cycloheptenone 20

To a vial was added cycloheptenone **19** (40 mg, 0.15 mmol) followed by CH_2Cl_2 (1 mL). Next was added 2.0 M N,N-dimethylamine in THF (0.38 mL, 0.75 mmol), DIEA (31 μL ,

0.18 mmol), and HATU (63 mg, 0.17 mmol). The reaction was stirred at rt for 6 h. The reaction was evaporated *in vacuo* and resulting residue purified by flash chromatography (SiO₂, 20:1CH₂Cl₂:MeOH) to afford **20** (66 %, 30 mg, 0.10 mmol).

¹H NMR (400 MHz, CD₃OD) δ 0.76 (d, *J* = 6.6 Hz, 3 H), 2.21 - 2.34 (m, 1 H), 2.53 (dd, *J* = 12.2, 9.2 Hz, 1 H), 2.59 (d, *J* = 17.6 Hz, 1 H), 2.98 (s, 3 H), 3.21 (s, 3 H), 3.42 (dd, *J* = 17.6, 12.2 Hz, 1 H), 3.66 (s, 3 H), 4.39 (t, *J* = 5.5 Hz, 1 H), 6.24 (d, *J* = 5.5 Hz, 1 H), 7.19 - 7.27 (m, 3 H), 7.29 - 7.35 (m, 2 H).

¹³C NMR (100 MHz, CDCl₃) δ 15.4, 36.2, 37.4, 40.5, 40.8, 46.0, 48.0, 55.5, 109.4, 126.9, 127.6, 128.8, 144.1, 152.5, 171.4, 197.3.

IR (thin film) ν_{max} 2962, 2932, 1683, 1646, 1495, 1456, 1399, 1209, 1142, 731, 703 cm⁻¹.

HRMS calculated for C₁₈H₂₃NO₃Na: 324.1576, found: 324.1594 (M+Na).

Imidazolones **16a** and **16b**

To a vial was added diketone **5** (40 mg, 0.13 mmol), urea (10 mg, 0.17 mmol), and CSA (30 mg, 0.13 mmol) followed by absolute ethanol (1 mL). The reaction mixture was heated to 80 °C, and stirred for 20 h. The reaction was concentrated *in vacuo* and purified by flash chromatography (SiO₂, 1:1, CH₂Cl₂:acetone) to afford diene **16a** (48 %, 21 mg, 0.062 mmol) and triene **16b** (32 %, 14 mg, 0.042 mmol).

Imidazolone **16a**. R_f=0.1 (CH₂Cl₂:acetone, 1:1)

¹H NMR (400 MHz, CD₃OD) δ 1.16 (d, *J* = 7.0 Hz, 3 H), 1.78 - 1.90 (m, 4 H), 2.62 (dd, *J* = 17.5, 2.4 Hz, 1 H), 2.97 (dd, *J* = 12.7, 2.4 Hz, 1 H), 3.09 (dd, *J* = 17.5, 12.7 Hz, 1 H), 3.15 - 3.25 (m, 2 H), 3.33 - 3.48 (m, 3 H), 6.31 (s, 1 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.43 (d, *J* = 7.4 Hz, 2 H).

¹³C NMR (100 MHz, CD₃OD) δ 12.8, 24.4, 25.2, 26.9, 40.3, 41.3, 47.2, 47.9, 115.0, 118.5, 121.1, 126.5, 128.3, 129.7, 143.8, 145.0, 155.8, 175.2.

IR (thin film) ν_{max} 2971, 2874, 1700, 1684, 1653, 1635, 1437, 1373, 1040, 734, 698 cm⁻¹.

HRMS calculated for C₂₀H₂₄N₃O₂: 338.1869, found: 338.1870 (M+H).

Imidazolone **16b**. R_f=0.15 (CH₂Cl₂:acetone, 1:1)

¹H NMR (400 MHz, CD₃OD) δ 1.06 (d, *J* = 7.4 Hz, 3 H), 1.65 - 1.95 (m, 4 H), 3.17 - 3.26 (m, 1 H), 3.37 - 3.48 (m, 3 H), 4.02 (q, *J* = 7.4 Hz, 1 H), 6.61 (s, 1 H), 6.65 (s, 1 H), 7.25 - 7.32 (m, 1 H), 7.32 - 7.39 (m, 2 H), 7.54 (d, *J* = 7.8 Hz, 2 H).

¹³C NMR (100 MHz, CD₃OD) δ 14.2, 24.7, 27.1, 39.4, 47.2, 51.3, 114.3, 118.0, 122.1, 126.3, 126.9, 128.3, 128.9, 129.7, 136.6, 143.5, 155.9, 172.7.

IR (thin film) ν_{max} 2970, 1699, 1684, 1653, 1576, 1559, 1436, 1419, 723, 697 cm⁻¹.

HRMS calculated for $C_{20}H_{22}N_3O_2$: 336.1712, found: 366.1706 (M+H).

General procedure for the synthesis of alkenyl imidazolone 23-35 and alkenyl imidazolthione 36

To a oven-dried vial was added activated 4 Å molecular sieves (approx. 25 mg), diketone **5** (40 mg, 0.13 mmol), *N*-ethylurea (12 mg, 0.14 mmol), and $Zn(OTf)_2$ (10 mg, 0.026 mmol) followed by anhydrous CH_3CN (1 mL). The reaction mixture was then degassed by bubbling argon through the solution for 15 min. Finally, the vial was sealed with a Teflon-lined cap, heated to 100 °C, and stirred for 5 h. The reaction was cooled and filtered through Celite to remove the sieves. The resulting filtrate was concentrated *in vacuo* and purified by flash chromatography (SiO_2 , gradient 50:1 CH_2Cl_2 :MeOH to 20:1 CH_2Cl_2 :MeOH) to afford **23a** (71 %, 33 mg, 0.090 mmol) and **23b** (21 %, 10 mg, 0.027 mmol).

N-Ethylimidazolone 23a. $R_f=0.20$ (CH_2Cl_2 :MeOH, 20:1)

1H NMR (400 MHz, CD_3OD) δ 1.17 (d, $J = 7.2$ Hz, 3 H), 1.20 (t, $J = 7.0$ Hz, 3 H), 1.80 - 1.90 (m, 4 H), 2.64 (dd, $J = 17.9$, 3.5 Hz, 1 H), 2.99 (dd, $J = 12.9$, 3.5 Hz, 1 H), 3.12 (dd, $J = 17.9$, 12.9 Hz, 1 H), 3.18 - 3.25 (m, 2 H), 3.34 - 3.49 (m, 3 H), 3.71 - 3.84 (m, 2 H), 6.36 (s, 1 H), 7.26 (t, $J = 7.3$ Hz, 1 H), 7.36 (t, $J = 7.6$ Hz, 2 H), 7.46 (d, $J = 8.0$ Hz, 2 H).

NOED (400 MHz, CD_3OD) irradiation. δ 6.36 (*beta*-phenyl, CH) 9 % enhancement at 3.77 (*alpha*-urea, CH_2).

^{13}C NMR (100 MHz, CD_3OD) δ 12.5, 15.2, 24.6, 25.1, 26.9, 35.9, 40.5, 41.0, 47.2, 47.9, 113.3, 118.4, 121.0, 126.7, 128.4, 129.8, 144.3, 145.5, 154.5, 175.0.

IR (thin film) ν_{max} 3164, 2973, 2873, 1700, 1697, 1684, 1653, 1635, 1617, 1437, 759, 733, 699 cm^{-1} .

HRMS calculated for $C_{22}H_{28}N_3O_2$: 366.2182, found: 366.2189 (M+H).

N-Ethylimidazolone 23b. $R_f=0.29$ (CH_2Cl_2 :MeOH, 20:1)

1H NMR (400 MHz, CD_2Cl_2 : CD_3OD , 1:5.2) δ 1.17 (d, $J = 7.0$ Hz, 3 H), 1.26 (t, $J = 7.1$ Hz, 3 H), 1.80 - 1.92 (m, 4 H), 2.69 (dd, $J = 17.5$, 3.2 Hz, 1 H), 2.97 (dd, $J = 12.7$, 3.2 Hz, 1 H), 3.12 (dd, $J = 17.5$, 12.7 Hz, 1 H), 3.17 - 3.26 (m, 2 H), 3.36 - 3.51 (m, 3 H), 3.61 - 3.83 (m, 2 H), 6.31 (s, 1 H), 7.24 (t, $J = 7.43$ Hz, 1 H), 7.33 (t, $J = 7.24$ Hz, 2 H), 7.43 (d, $J = 8.02$ Hz, 2 H).

NOED (400 MHz, CD_3OD) irradiation. δ 2.69 (*beta*-amide, CH_2) 6 % enhancement at 3.72 (*alpha*-urea, CH_2).

^{13}C NMR (100 MHz, CD_2Cl_2 : CD_3OD , 1:5.2) δ 12.7, 15.1, 23.7, 24.9, 26.7, 36.5, 39.8, 41.2, 46.9, 47.7, 114.7, 117.2, 121.1, 126.2, 128.0, 129.4, 143.3, 144.6, 154.0, 174.7.

IR (thin film) ν_{max} 2973, 2874, 1700, 1696, 1684, 1653, 1635, 1617, 1437, 1374, 765, 732, 698 cm^{-1} .

HRMS calculated for $C_{22}H_{28}N_3O_2$: 366.2182, found: 366.2189 (M+H).

N-tert-Butylimidazolone 26a

26a: (57 %, 29 mg, 0.074 mmol), $R_f=0.15$ (CH_2Cl_2 :MeOH, 20:1). **26b:** (31 %, 16 mg, 0.040 mmol), $R_f=0.26$ (CH_2Cl_2 :MeOH, 20:1).

1H NMR (400 MHz, CD_2Cl_2 : CD_3OD , 1:9.4) δ 1.20 (d, $J = 7.0$ Hz, 3 H), 1.67 (s, 9 H), 1.76 - 1.89 (m, 4 H), 2.59 (dd, $J = 18.1$, 4.0 Hz, 1 H), 2.92 (dd, $J = 13.1$, 4.0 Hz, 1 H), 3.10 (dd, $J = 18.1$, 13.1 Hz, 1 H), 3.13 - 3.20 (m, 2 H), 3.33 - 3.48 (m, 3 H), 6.70 (s, 1 H), 7.21 - 7.30 (m, 1 H), 7.32 - 7.42 (m, 4 H).

^{13}C NMR (100 MHz, CD_2Cl_2 : CD_3OD , 1:9.4) δ 11.9, 24.6, 25.0, 26.7, 31.4, 40.0, 40.6, 47.0, 47.7, 58.1, 117.3, 119.3, 122.0, 126.5, 128.0, 129.6, 142.5, 144.9, 154.8, 174.5.

IR (thin film) ν_{max} 2970, 1675, 1635, 1591, 1430, 1128, 1032, 766, 698 cm^{-1} .

HRMS calculated for $C_{24}H_{32}N_3O_2$: 394.2495, found: 394.2505 (M+H).

N-Propargylimidazolone 28a

28a: (74 %, 36 mg, 0.096 mmol), $R_f=0.17$ (CH_2Cl_2 :MeOH, 20:1). **28b:** (17 %, 8 mg, 0.022 mmol), $R_f=0.22$ (CH_2Cl_2 :MeOH, 20:1).

1H NMR (400 MHz, CD_3OD) δ 1.17 (d, $J = 7.0$ Hz, 3 H), 1.78 - 1.96 (m, 16 H), 2.63 (dd, $J = 18.1$, 3.0 Hz, 4 H), 2.70 (t, $J = 2.5$ Hz, 4 H), 2.98 (dd, $J = 12.9$, 3.0 Hz, 4 H), 3.12 (dd, $J = 18.1$, 12.9 Hz, 4 H), 3.18 - 3.28 (m, 8 H), 3.38 - 3.50 (m, 3 H), 4.45 (dd, $J = 18.4$, 2.5 Hz, 1 H), 4.61 (dd, $J = 18.4$, 2.5 Hz, 1 H), 6.53 (s, 1 H), 7.27 (t, $J = 7.3$ Hz, 1 H), 7.36 (t, $J = 7.8$ Hz, 2 H), 7.47 (d, $J = 7.4$ Hz, 2 H).

^{13}C NMR (100 MHz, CD_3OD) δ 12.6, 24.4, 25.0, 26.8, 30.4, 40.2, 40.8, 47.1, 47.8, 73.5, 79.2, 113.4, 118.4, 121.1, 126.6, 128.3, 129.6, 143.9, 145.2, 154.0, 174.8.

IR (thin film) ν_{max} 2971, 2874, 1685, 1635, 1593, 1431, 1387, 734, 700, 633 cm^{-1} .

HRMS calculated for $C_{23}H_{26}N_3O_2$: 376.2025, found: 376.2018 (M+H).

N-Phenylimidazolone 28a

28a: (76 %, 41 mg, 0.099 mmol), $R_f=0.17$ (CH_2Cl_2 :MeOH, 20:1). **28b:** (23 %, 12 mg, 0.030 mmol), $R_f=0.24$ (CH_2Cl_2 :MeOH, 20:1).

1H NMR (400 MHz, CD_2Cl_2 : CD_3OD , 1:6.8) δ 1.23 (d, $J = 7.03$ Hz, 3 H), 1.75 - 1.94 (m, 4 H), 2.71 (dd, $J = 18.4$, 3.1 Hz, 1 H), 3.00 (dd, $J = 12.9$, 3.1 Hz, 1 H), 3.19 - 3.24 (m, 2 H), 3.21 (ovrlp dd, $J = 18.4$, 12.9 Hz, 1 H), 3.36 - 3.50 (m, 3 H), 5.98 (s, 1 H), 7.14 - 7.22 (m, 1 H), 7.23 - 7.27 (m, 4 H), 7.31 (d, $J = 7.42$ Hz, 2 H), 7.38 - 7.43 (m, 1 H), 7.47 - 7.52 (m, 2 H).

^{13}C NMR (100 MHz, $\text{CD}_2\text{Cl}_2:\text{CD}_3\text{OD}$, 1:6.8) δ 12.7, 24.4, 25.0, 26.8, 40.1, 40.8, 47.0, 47.8, 113.9, 119.4, 121.2, 126.3, 128.1, 129.2, 129.3, 129.4, 130.3, 135.3, 143.7, 144.7, 154.2, 174.7.

IR (thin film) ν_{max} 2972, 2875, 1700, 1696, 1684, 1635, 1595, 1499, 1437, 1379, 757, 732, 700, 668 cm^{-1} .

HRMS calculated for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_2$: 414.2182, found: 414.2183 (M+H).

***N*-Phenyl, *N'*-ethylimidazolone 35a**

35a: (77 %, 44 mg, 0.10 mmol), $R_f=0.36$ ($\text{CH}_2\text{Cl}_2:\text{MeOH}$, 20:1). **35b:** (22 %, 13 mg, 0.029 mmol), $R_f=0.29$ ($\text{CH}_2\text{Cl}_2:\text{MeOH}$, 20:1).

^1H NMR (400 MHz, CD_3OD) δ 1.22 (d, $J = 7.0$ Hz, 3 H), 1.27 (t, $J = 7.2$ Hz, 3 H), 1.75 - 1.90 (m, 4 H), 2.36 (d, $J = 15.2$ Hz, 1 H), 2.91 - 3.07 (m, 2 H), 3.16 - 3.28 (m, 2 H), 3.32 - 3.44 (m, 3 H), 3.83 - 3.95 (m, 2 H), 6.48 (s, 1 H), 7.23 - 7.32 (m, 1 H), 7.34 - 7.41 (m, 4 H), 7.47 (d, $J = 7.4$ Hz, 1 H), 7.49 - 7.58 (m, 4 H).

NOED (400 MHz, CD_3OD) irradi. δ 6.48 (*beta*-phenyl, CH) 9 % enhancement at 3.90 (*alpha*-urea, CH_2).

^{13}C NMR (100 MHz, CD_3OD) δ 12.6, 15.2, 25.1, 26.9, 36.6, 40.4, 41.1, 47.1, 47.8, 112.8, 118.4, 122.0, 126.8, 128.6, 129.2, 129.8, 129.8, 130.6, 135.7, 144.1, 146.7, 153.4, 174.9.

IR (thin film) ν_{max} 2972, 2873, 1695, 1636, 1419, 1387, 764, 721, 696 cm^{-1} .

HRMS calculated for $\text{C}_{28}\text{H}_{31}\text{N}_3\text{O}_2$: 442.2495, found: 442.2494 (M+H).

***N*-Ethylimidazolthione 36a**

36a: (79 %, 39 mg, 0.10 mmol), $R_f=0.31$ ($\text{CH}_2\text{Cl}_2:\text{MeOH}$, 20:1). **36b:** (20 %, 10 mg, 0.026 mmol), $R_f=0.40$ ($\text{CH}_2\text{Cl}_2:\text{MeOH}$, 20:1).

^1H NMR (400 MHz, $\text{CD}_2\text{Cl}_2:\text{CD}_3\text{OD}$, 1:4.1) δ 1.16 (d, $J = 7.0$ Hz, 3 H), 1.26 (t, $J = 7.2$ Hz, 3 H), 1.86 (m, 4 H), 2.74 (dd, $J = 17.9$, 3.4 Hz, 1 H), 2.97 (dd, $J = 13.1$, 3.4 Hz, 1 H), 3.19 (ovrlp dd, $J = 17.9$, 13.1 Hz, 1 H), 3.19 - 3.27 (m, 2 H), 3.34 - 3.49 (m, 3 H), 4.08 - 4.29 (m, 2 H), 6.40 (s, 1 H), 7.27 - 7.33 (m, 1 H), 7.38 (t, $J = 7.6$ Hz, 2 H), 7.46 (d, $J = 7.4$ Hz, 2 H).

^{13}C NMR (100 MHz, $\text{CD}_2\text{Cl}_2:\text{CD}_3\text{OD}$, 1:4.1) δ 11.9, 13.4, 22.9, 23.9, 25.7, 38.7, 39.3, 45.9, 46.7, 111.9, 123.4, 125.5, 125.6, 127.5, 128.5, 142.7, 146.0, 158.7, 173.2.

IR (thin film) ν_{max} 3174, 3055, 2971, 2933, 2873, 1636, 1608, 1476, 1448, 1414, 1378, 1276, 1210, 1137, 758, 733, 698 cm^{-1} .

HRMS calculated for $\text{C}_{22}\text{H}_{28}\text{N}_3\text{OS}$: 382.1953, found: 382.1947 (M+H).

General procedure for the synthesis of cycloheptatriene 37, 38, and 39

To a oven-dried vial was added *N*-ethylimidazolone **20a** (40 mg, 0.13 mmol) followed by anhydrous CH₂Cl₂ (1 mL). Next DDQ (36 mg, 0.16 mmol) was added and the reaction was stirred at rt for 2 h. The reaction was diluted with CH₂Cl₂ (10 mL) and washed with sat. NaHCO₃ (10 mL × 2) and brine (10 mL). The organic portion was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO₂, gradient 50:1 CH₂Cl₂:MeOH to 20:1 CH₂Cl₂:MeOH) to afford **37** (71 %, 33 mg, 0.090 mmol) and **38** (21 %, 10 mg, 0.027 mmol).

Cycloheptatriene 37

¹H NMR (400 MHz, CD₂Cl₂:CD₃OD, 1:6) δ 1.04 (d, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.61 - 1.94 (m, 4 H), 3.15 - 3.24 (m, 1 H), 3.33 - 3.47 (m, 3 H), 3.73 - 3.95 (m, 2 H), 3.99 - 4.09 (m, 1 H), 6.64 (s, 1 H), 6.65 (s, 1 H), 7.26 - 7.33 (m, 1 H), 7.34 - 7.40 (m, 2 H), 7.56 (d, *J* = 7.8 Hz, 2 H).

¹³C NMR (100 MHz, CD₂Cl₂:CD₃OD, 1:6) δ 12.7, 13.7, 24.0, 25.8, 35.4, 38.0, 45.9, 49.5, 111.7, 116.5, 120.1, 125.0, 127.1, 127.3, 127.6, 128.3, 135.2, 142.2, 153.0, 171.1

IR (thin film) ν_{max} 3172, 2974, 2874, 1700, 1596, 1443, 1405, 1378, 750, 732, 698 cm⁻¹.

HRMS calculated for C₂₂H₂₆N₃O: 364.2025, found: 364.2024 (M+H).

Cycloheptimidazolone 38

¹H NMR (400 MHz, CD₃OD) δ 1.28 (t, *J* = 7.2 Hz, 3 H), 1.96 - 2.08 (m, 4 H), 2.24 (s, 3 H), 3.15 - 3.24 (m, 1 H), 3.32 - 3.41 (m, 1 H), 3.56 - 3.66 (m, 1 H), 3.66 - 3.74 (m, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 7.40 (d, *J* = 7.4 Hz, 2 H), 7.47 - 7.52 (m, 1 H), 7.52 - 7.59 (m, 2 H), 7.64 (s, 1 H), 7.86 (s, 1 H).

¹³C NMR (100 MHz, CD₃OD) δ 13.8, 23.8, 25.3, 26.9, 37.1, 47.0, 49.7, 120.5, 125.8, 129.1, 129.6, 130.1, 139.1, 145.2, 146.5, 151.4, 155.0, 163.7, 167.2, 170.4.

IR (thin film) ν_{max} 2958, 2924, 2852, 1701, 1635, 1616, 1653, 1447, 1418, 1078, 731, 703 cm⁻¹.

HRMS calculated for C₂₂H₃₄N₃O₂: 362.1869, found: 362.1873 (M+H).

Cycloheptatriene 39. (50 %, 22 mg, 0.055 mmol)

¹H NMR (400 MHz, CD₃OD) δ 1.00 (d, *J* = 7.0 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.80 - 1.98 (m, 4 H), 2.68 (s, 3 H), 3.37 - 3.57 (m, 3 H), 3.57 - 3.67 (m, 1 H), 3.77 - 3.98 (m, 2 H), 4.03 - 4.10 (m, 1 H), 6.65 (s, 1 H), 7.30 - 7.36 (m, 1 H), 7.36 - 7.41 (m, 3 H), 7.68 (d, *J* = 7.0 Hz, 2 H).

¹³C NMR (100 MHz, CD₃OD) δ 13.1, 14.2, 25.3, 26.0, 27.2, 37.1, 39.4, 47.3, 51.3, 111.6, 120.0, 120.5, 127.4, 128.2, 128.7, 129.2, 129.6, 143.2, 152.4, 172.1, 173.8.

IR (thin film) ν_{max} 2973, 2875, 1724, 1621, 1603, 1409, 1372, 1358, 1317, 1276, 749, 731, 700 cm^{-1} .

HRMS calculated for $\text{C}_{24}\text{H}_{28}\text{N}_3\text{O}_3$: 406.2131, found: 406.2128 (M+H).

Cycloheptene 40

Imidazolone **23a** (40 mg, 0.11 mmol) was dissolved in MeOH (10 mL) and flowed (0.5 mL/min) through a 10 % Pd/C cartridge at 50 bar and 50 °C using the H-Cube. The collected reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2 , gradient 50:1 CH_2Cl_2 :MeOH to 20:1 CH_2Cl_2 :MeOH) to afford **40** (99 %, 40 mg, 0.11 mmol).

^1H NMR (400 MHz, CD_3OD) δ 0.93 (d, J = 7.0 Hz, 3 H), 1.15 (t, J = 7.2 Hz, 3 H), 1.81 - 1.93 (m, 2 H), 1.96 - 2.07 (m, 2 H), 2.11 - 2.21 (m, 1 H), 2.40 (dd, J = 16.4, 3.5 Hz, 1 H), 2.62 (dd, J = 15.0, 2.1 Hz, 1 H), 2.93 - 3.05 (m, 1 H), 3.06 - 3.25 (m, 3 H), 3.32 - 3.37 (m, 1 H), 3.45 (dt, J = 11.8, 7.2 Hz, 1 H), 3.55 (dt, J = 10.2, 7.0 Hz, 1 H), 3.62 - 3.70 (m, 2 H), 3.76 (dt, J = 10.4, 6.5 Hz, 1 H), 7.18 - 7.28 (m, 1 H), 7.32 - 7.36 (m, 4 H).

NOED (400 MHz, CD_3OD) irradiation. δ 0.93 (CH_3) 3 % enhancement at 3.00 (β -NH, CH), 4 % at 3.14 (β -NEt, CH).

^{13}C NMR (100 MHz, CD_3OD) δ 6.6, 15.4, 23.7, 25.1, 25.2, 27.1, 36.2, 42.2, 47.2, 48.0, 48.7, 50.0, 117.3, 118.9, 127.7, 128.4, 129.6, 147.0, 154.4, 175.0.

IR (thin film) ν_{max} 3049, 2973, 1699, 1684, 1653, 1635, 1457, 1437, 1419, 736, 701 cm^{-1} .

HRMS calculated for $\text{C}_{22}\text{H}_{30}\text{N}_3\text{O}_2$: 368.2338, found: 368.2346 (M+H).

Imidazolidinone 41

Imidazolone **23a** (40 mg, 0.11 mmol) was dissolved in MeOH (10 mL) and flowed (0.5 mL/min) through a Raney Ni cartridge at 90 bar and 80 °C using the H-Cube hydrogenator. The collected reaction mixture was concentrated *in vacuo* and the resulting residue was purified by preparative HPLC to afford **41a** (50 %, 20 mg, 0.054 mmol) and **41b** (49 %, 20 mg, 0.054 mmol).

Imidazolidinone 41a

^1H NMR (400 MHz, CD_3OD) δ 0.76 (d, J = 6.6 Hz, 3 H), 0.96 (t, J = 7.2 Hz, 3 H), 1.78 (dd, J = 16.0, 4.3 Hz, 1 H), 1.86 (dq, J = 7.0, 6.5 Hz, 2 H), 1.95 - 2.05 (m, 3 H), 2.07 - 2.17 (m, 2 H), 2.38 (ddd, J = 15.8, 11.3, 1.8 Hz, 1 H), 2.76 (dq, J = 14.0, 7.0 Hz, 1 H), 3.06 (dd, J = 11.1, 3.3 Hz, 1 H), 3.12 (dd, J = 10.2, 2.7 Hz, 1 H), 3.25 - 3.35 (m, 1 H), 3.35 - 3.46 (m, 2 H), 3.55 (dt, J = 10.2, 6.8 Hz, 1 H), 3.68 (dt, J = 10.2, 6.6 Hz, 1 H), 4.12 (ddd, J = 10.9, 3.9, 2.3 Hz, 1 H), 4.20 (ddd, J = 10.9, 4.7, 1.6 Hz, 1 H), 7.16 - 7.22 (m, 3 H), 7.26 - 7.32 (m, 2 H).

^{13}C NMR (100 MHz, CD_3OD) δ 7.6, 12.6, 25.2, 27.2, 27.2, 28.3, 36.5, 39.8, 43.6, 45.0, 47.2, 48.0, 53.0, 58.1, 127.3, 129.1, 129.3, 147.2, 163.9, 176.1.

IR (thin film) ν_{max} 2971, 2928, 2874, 1700, 1684, 1676, 1653, 1635, 1617, 1457, 1437, 1379, 1276, 731, 703 cm^{-1} .

HRMS calculated for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_2$: 370.2495, found: 370.2500 (M+H).

Imidazolidinone 41b

^1H NMR (400 MHz, CD_3OD) δ 0.73 (d, J = 7.0 Hz, 3 H), 1.06 (t, J = 7.2 Hz, 3 H), 1.81 (dd, J = 14.8, 3.9 Hz, 1 H), 1.84 - 1.90 (m, 2 H), 1.94 - 2.08 (m, 4 H), 2.11 - 2.26 (m, 2 H), 2.95 (dd, J = 10.2, 3.1 Hz, 1 H), 2.99 - 3.09 (m, 2 H), 3.26 - 3.34 (m, 1 H), 3.37 - 3.46 (m, 2 H), 3.53 (dt, J = 10.2, 7.0 Hz, 1 H), 3.72 (dt, J = 10.5, 6.6 Hz, 1 H), 3.95 (ddd, J = 11.3, 9.8, 3.91 Hz, 1 H), 4.02 (ddd, J = 11.3, 9.8, 4.3 Hz, 1 H), 7.15 - 7.25 (m, 3 H), 7.27 - 7.35 (m, 2 H).

NOED (400 MHz, CD_3OD) irradiation. δ 3.95 (α -NH, CH) 4 % enhancement at 2.95 (α -amide, CH), and 1 % at 1.81 (β -amide, CH_2); irradiation. δ 4.02 (α -NEt, CH) 6 % enhancement at 3.01 (α -phenyl, CH), 2 % at 1.06 (CH_3).

^{13}C NMR (100 MHz, CD_3OD) δ 8.0, 13.2, 25.1, 27.2, 28.2, 28.8, 36.2, 40.1, 47.2, 47.6, 47.9, 48.0, 55.2, 59.9, 127.2, 128.9, 129.3, 147.6, 162.9, 175.6.

IR (thin film) ν_{max} 2971, 2873, 1689, 1631, 1436, 1375, 1272, 732, 702 cm^{-1} .

HRMS calculated for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{O}_2$: 370.2495, found: 370.2494 (M+H).

Imidazolidinone 43

Imidazolone **42** (40 mg, 0.098 mmol) was dissolved in EtOAc (10 mL) and flowed (0.5 mL/min) through a 10 % Pd/C cartridge at 30 bar and 90 °C using the H-Cube. The collected reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2 , gradient 50:1 CH_2Cl_2 :MeOH to 20:1 CH_2Cl_2 :MeOH) to afford **43** (99 %, 40 mg, 0.098 mmol).

$R_f=0.39$ (CH_2Cl_2 :MeOH, 20:1)

^1H NMR (400 MHz, CD_3OD) δ 0.74 (d, J = 6.8 Hz, 3 H), 1.10 (t, J = 7.2 Hz, 3 H), 1.79 - 1.92 (m, 2 H), 1.93 - 2.06 (m, 4 H), 2.12 - 2.25 (m, 3 H), 2.45 (s, 3 H), 3.00 - 3.12 (m, 2 H), 3.22 (dq, J = 14.5, 7.5 Hz, 1 H), 3.28 - 3.35 (m, 1 H), 3.40 - 3.57 (m, 3 H), 3.78 (dt, J = 10.2, 6.4 Hz, 1 H), 4.03 (td, J = 9.9, 6.3 Hz, 1 H), 4.42 - 4.54 (m, 1 H), 7.13 - 7.26 (m, 3 H), 7.27 - 7.35 (m, 2 H).

NOED (400 MHz, CD_3OD) irradiation. δ 4.03 (α -NEt, CH) 3 % enhancement at 3.01 (α -phenyl/ α -amide, CH), 5 % at 4.48 (α -NAc, CH); irradiation. δ 4.48 (α -NAc, CH) 6 % enhancement at 3.01 (α -amide/ α -phenyl, CH), 5 % at 4.03 (α -NEt, CH).

^{13}C NMR (100 MHz, CD_3OD) δ 8.0, 12.6, 24.2, 25.1, 25.4, 27.2, 28.3, 36.8, 39.7, 46.0, 47.2, 47.9, 56.0, 57.4, 127.3, 128.9, 129.3, 147.6, 155.8, 172.2, 175.2.

IR (thin film) ν_{max} 2972, 2875, 1726, 1679, 1634, 1426, 1377, 1351, 1270, 726, 703, 617 cm^{-1} .

HRMS calculated for $\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_3$: 412.2600, found: 412.2582 (M+H).

Imidazolidinone 45

Imidazolone **44** (40 mg, 0.098 mmol) was dissolved in EtOAc (10 mL) and flowed (0.5 mL/min) through a 10 % Pd/C cartridge at 50 bar and 50 °C using the H-Cube. The collected reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2 , gradient 50:1 CH_2Cl_2 :MeOH to 20:1 CH_2Cl_2 :MeOH) to afford **45** (99%, 40 mg, 0.098 mmol).

$R_f=0.41$ (CH_2Cl_2 :MeOH, 20:1)

^1H NMR (400 MHz, CD_3OD) δ 0.66 (d, $J = 6.8$ Hz, 3 H), 1.14 (t, $J = 7.1$ Hz, 3 H), 1.79 - 1.92 (m, 3 H), 1.95 - 2.09 (m, 3 H), 2.16 - 2.31 (m, 3 H), 2.43 (s, 3 H), 2.94 (dd, $J = 9.3, 2.0$ Hz, 1 H), 3.15 (dd, $J = 11.1, 3.7$ Hz, 1 H), 3.21 (dq, $J = 14.5, 7.0$ Hz, 1 H), 3.34 (s, 1 H), 3.41 - 3.62 (m, 3 H), 3.73 (dt, $J = 10.2, 6.5$ Hz, 1 H), 4.01 (ddd, $J = 11.6, 8.80, 6.0$ Hz, 1 H), 4.45 - 4.56 (m, 1 H), 7.13 - 7.20 (m, 3 H), 7.23 - 7.31 (m, 2 H).

NOED (400 MHz, CD_3OD) irradiated. δ 4.01 (α -NEt, CH) 2 % enhancement at 1.14 (NEt, CH_3), 3 % at 2.22 (CH), 3 % at 2.94 (α -amide, CH), 5 % at 4.51 (α -NAc, CH); irradiated. δ 4.51 (α -NAc, CH) 7 % enhancement at 3.15 (α -phenyl, CH), 5 % at 4.01 (α -NEt, CH).

^{13}C NMR (100 MHz, CD_3OD) δ 8.3, 12.6, 24.2, 25.2, 25.4, 27.2, 27.7, 36.8, 39.9, 45.2, 47.3, 48.0, 49.9, 55.6, 58.2, 127.2, 128.7, 129.2, 146.5, 155.9, 172.0, 175.5.

IR (thin film) ν_{max} 2971, 2874, 1727, 1678, 1634, 1426, 1377, 1352, 1323, 1270, 733, 715, 701, 615 cm^{-1} .

HRMS calculated for $\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_3$: 412.2600, found: 412.2582 (M+H).

Cycloheptene 48

Imidazolone **42** (30 mg, 0.074 mmol) was dissolved in EtOAc (7.5 mL) and flowed (0.5 mL/min) through a 10 % Pd/C cartridge at 10 bar and 40 °C using the H-Cube. The collected reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2 , gradient 50:1 CH_2Cl_2 :MeOH to 20:1 CH_2Cl_2 :MeOH) to afford **48** (79 %, 24 mg, 0.058 mmol).

^1H NMR (500 MHz, CD_3OD , 45 °C) δ 0.86 (d, $J = 6.8$ Hz, 3 H), 1.20 (t, $J = 7.2$ Hz, 3 H), 1.72 - 1.80 (m, 1 H), 1.81 - 1.93 (m, 2 H), 1.95 - 2.04 (m, 2 H), 2.06 - 2.11 (m, 1 H), 2.14 (d, $J = 13.4$ Hz, 1 H), 2.49 (s, 3 H), 3.27 - 3.31 (m, 1 H), 3.33 - 3.37 (m, 1 H), 3.41 - 3.47 (m, 1 H), 3.47 - 3.54 (m, 1 H), 3.54 - 3.61 (m, 1 H), 3.61 - 3.69 (m, 1 H), 3.75 - 3.84 (m, 1 H), 3.95 (d, $J = 5.1$ Hz, 1 H), 4.97 (d, $J = 11.2$ Hz, 1 H), 5.10 (d, $J = 5.6$ Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.32 - 7.41 (m, 4 H).

NOED (400 MHz, CD₃OD) irradiation. δ 3.95 (α -phenyl, CH) 8 % enhancement at 3.35 (α -amide, CH), 6 % at 4.97 (α -NAc, CH); irradiation. δ 4.97 (α -NAc, CH) 7 % enhancement at 3.35 (α -amide, CH), 7 % at 3.95 (α -phenyl).

¹³C NMR (125 MHz, CD₃OD, 45 °C) δ 8.7, 12.0, 24.3, 25.0, 26.1, 27.1, 36.2, 39.9, 47.1, 47.8, 50.6, 57.5, 98.8, 127.6, 128.7, 129.6, 138.7, 145.9, 154.6, 171.7, 174.4.

IR (thin film) ν_{max} 2971, 2932, 2875, 1740, 1734, 1695, 1684, 1635, 1419, 1374, 1232, 703, 626, 603 cm⁻¹.

HRMS calculated for C₂₄H₃₂N₃O₃: 410.2444, found: 410.2438 (M+H).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. See the Supporting Information for representative characterization data for compounds 22a, 22b, 23a, 41a, 41b, 48 and X-ray crystal structure data for compound 9a. This information is available via the internet at www.thiemeconnect.com/ejournals/toc/synthesis.
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Scheme 1.
Scaffold synthesis and preliminary results.

Figure 1.
Multidimensional screening parameters.

Figure 2.
Representative Condensation products.

Scheme 2.
Synthesis of alternative triazines.

Scheme 3.
Condensation with ethylurea.

Figure 4.
 ^1H NMR evidence for mechanism (in CD_3CN).

Figure 5.
 ^{13}C NMR evidence for chelation (in CD_3CN).

Figure 6.
Proposed stereoelectronic effects leading to condensation regioselectivity.²¹

Scheme 4.
Further transformations of cycloheptadiene **23a**

Scheme 5.
Diastereoselective reduction of alkenyl imidazolone **23a**.²¹

Scheme 6.
Hydrogenations of alkenyl imidazolone **23a**.

Figure 7.
Proposed mechanism for diastereoselective hydrogenation.

Scheme 7.
Reduction/isomerization of an *N*-acetylimidazolone.

Figure 8.
Ground-state energetics of imidazolone isomerizations.²¹

Table 1

Optimization of triazine regioselectivity

entry	Solvent	temp/time	catalyst ^a	additive	12a:12b	% conv ^b
1	EtOH	rt, 4h	-	-	2 : 1	100
2	THF/H ₂ O (9:1)	rt, 4h	-	-	1 : 1	100
3	THF/H ₂ O (9:1)	rt, 2h	Sc(OTf) ₃	-	1 : 2	100
4	TFE	rt, 2h	-	-	6 : 1	79
5	TFE	rt, 2h	Sc(OTf) ₃	-	5 : 1	51
6	TFE	rt, 2h	Sc(OTf) ₃	4 Å MS	1 : 3	30
7	TFE	0 °C, 16h	Sc(OTf) ₃	4 Å MS	1 : 14	68
8	TFE	0 °C, 16h	La(OTf) ₃	4 Å MS	1 : 10	85
9	TFE	0 °C, 16h	Zn(OTf) ₂	4 Å MS	1 : 1	50
10	CH ₃ CN	0 °C, 16h	Sc(OTf) ₃	4 Å MS	1 : 17	57
11	CH ₃ CN	0 °C, 16h	Sc(OTf) ₃	4 Å MS	1 : 24 ^c	70

^a Lewis Acid (1 equiv).^b Calculated from UPLC/ELS percent conversions.^c Semicarbazide (2 equiv).

Table 2Oxidation during urea condensation.^a

Entry	atm	16a : 16b
1	air	1 : 1
2	argon	32 : 1
3	oxygen	1 : 3

^aCalculated from UPLC/ELS percent conversions.

Table 3Lewis acid screening results.^a

entry	catalyst	23a : 23b
1	CSA ^b	2 : 1
2	Sc(OTf) ₃	1 : 2
3	Yb(OTf) ₃	1 : 2
4	Y(OTf) ₃	1 : 2
5	La(OTf) ₃	1 : 2
6	Mg(OTf) ₂	1 : 4
7	Fe(OTf) ₂	1 : 4
8	Mn(OTf) ₂	1 : 8
9	Zn(OTf) ₂	1 : 9

^a Calculated from UPLC/ELS percent conversions.^b CSA (1 equiv).

Table 4

Scope of urea condensation regioselectivity.

entry	urea	X	R ₁	R ₂	Yield ^{a,b}	rr	product
1		O	H	ethyl	92 % (99 %) ^b	77:23 (47:53) ^b	23a/23b
2		O	H	methyl	99 %	66:34	24a/24b
3		O	H	isopropyl	99 %	71:29	25a/25b
4		O	H	tert-butyl	88 %	65:35	26a/26b
5		O	H	allyl	98 % (96 %) ^b	82:18 (46:54) ^b	27a/27b
6		O	Et	propargyl	91 %	81:19	28a/28b
7		O	H	benzyl	98 %	82:18	29a/29b
8		O	H	phenyl	99 %	77:23	30a/30b
9		O	H	4-chlorophenyl	85 % (96 %) ^b	85:15 (46:54) ^b	31a/31b

entry	urea	X	R ₁	R ₂	Yield ^{a,b}	rr	product
10		O	H	4-bromophenyl	80 %	76:24	32a/32b
11		O	Et	ethyl	93 %	-	33
12		O	Ph	methyl	98 %	76:24	34a/34b
13		O	Ph	ethyl	99 % (99 %) ^b	78:22 (64:36) ^b	35a/35b
14		S	H	ethyl	99 %	80:20 ^c	36a/36b

^a Combined isolated yield using Zn(OTf)₂ (0.2 equiv) with 4 Å MS.

^b Combined isolated yield using CSA (1.0 equiv).

^c Required Zn(OTf)₂ (1.0 equiv) with 4 Å MS.