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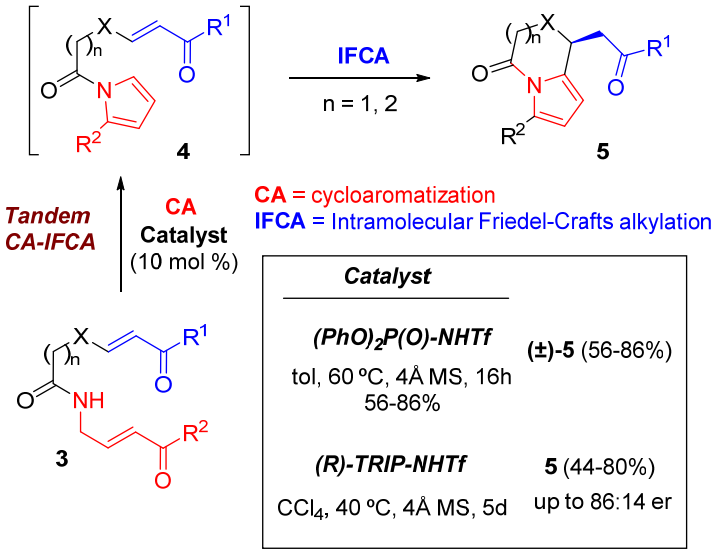
Tandem Organocatalytic Cycloaromatization/ Intramolecular Friedel-Crafts Alkylation Sequence for the Synthesis of Indolizinones and Pyrrolo-azepinone Derivatives

Fernando Rabasa-Alcañiz,[†] María Sánchez-Roselló,[†] Santos Fustero*[,†,‡] and Carlos del Pozo,*[,†]

[†] Departamento de Química Orgánica, Universidad de Valencia, 46100 Burjassot, Spain

[‡] Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, 46012 Valencia, Spain.

E-mail: carlos.pozo@uv.es; santos.fustero@uv.es



ABSTRACT:

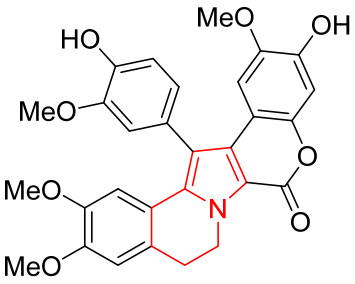
The organocatalytic synthesis of indolizinones and pyrrolo-azepinones has been accomplished in a tandem fashion through a sequence that comprises an initial cycloaromatization followed by an intramolecular Friedel Crafts alkylation. The process takes place under Brønsted acid catalysis giving rise to final products in moderate to good yields. Attempts to carry out the tandem protocol in an enantioselective fashion were performed with chiral (*R*)-BINOL-derived

N-triflyl phosphoramides. After initial optimization, the tandem process took place with moderate levels of enantioselectivity.

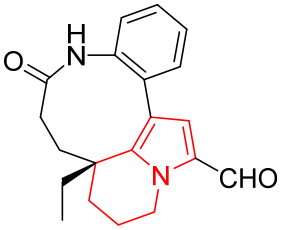
INTRODUCTION

Pyrrole is the fundamental 5-member ring aromatic *N*-heterocycle and a prevalent structural motif in natural and synthetic biologically active compounds, such as natural products, drugs and agrochemicals, as well as in catalysts and advanced materials.[1] Particularly, annulated pyrroles and pyrrolidines are highly represented moieties in clinically useful pharmaceuticals and natural products,[2] as in the lamellarin, indolizidine, stemona or rhazinilam alkaloid families (Figure 1).[3] Anticancer, antileukemia, anticholinergic and antimicrobial properties are among the biological activities displayed by those derivatives.[4] Therefore, these interesting frameworks have attracted high interest in synthetic organic chemistry. Cyclization of *N*-tethered substrates is by far the most common strategy for the preparation of annulated pyrroles.[5] Friedel-Crafts alkylation and acylation (FCA) of these of compounds give access to indolizines and the corresponding pyrrolo-azepines, which are also frequently occurring frameworks in natural products.[6] Syntheses based on asymmetric catalysis (metal and organocatalysis) can also be found in the literature.[7]

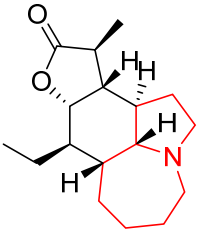
Figure 1. Biologically relevant annulated pyrroles.



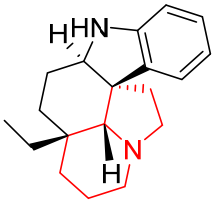
lamellarin D



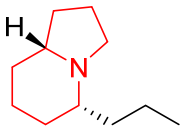
rhazinal



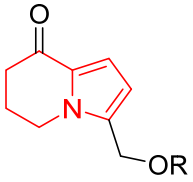
stenine



aspidospermidine



(-)-indolizidine 167B



Polygonatine A, R=H
Polygonatine B, R=Et
Kinganone A, R=*n*-Bu

Given the importance of pyrrole-fused derivatives in pharmaceutical and agricultural development, efficient new methodologies for the construction of the pyrrole core are still needed. The classical Paal-Knorr reaction, involving a primary amine and a 1,4-dicarbonyl compound, remains the cornerstone of pyrrole synthesis from acyclic starting materials. However, olefin metathesis has revealed itself as a powerful alternative of increasing importance for the construction of functionalized heterocycles from acyclic unsaturated precursors.[8] In this sense, Donohoe[9] and Rutjes[10] were pioneers in the application of ring closing metathesis (RCM) to pyrrole synthesis. In their approach, RCM of an appropriate allylamine renders an intermediate pyrroline, which upon acid-catalyzed elimination or oxidation, evolves into the corresponding pyrrole. One-pot protocols of this sequence[11] or processes involving enyne cross-metathesis and subsequent aromatization have also been described.[12]

Donohoe[13] and Grela[14] independently reported the combination of a cross-metathesis reaction with an acid-catalyzed cycloaromatization. In the first step of this sequence, a trans-γ-aminoenone is generated which upon addition of an acid co-catalyst undergoes trans/cis isomerization and subsequent dehydration towards the final pyrrole (Scheme 1A). In this way, indolizidine derivatives have been efficiently synthesized by sequences comprising a cross-metathesis step and a subsequent intramolecular Friedel-Crafts alkylation.[15] In this synthetic

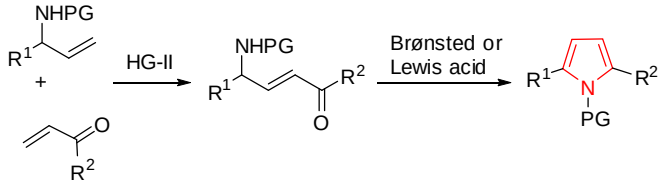
strategy, pyrroles featuring an *N*-tethered olefin are first converted into the corresponding α,β-unsaturated carbonyl compounds, which then undergo intramolecular Michael addition (the intermediate pyrrole being the nucleophile) in a one-pot or sequential fashion. The intramolecular Friedel-Crafts alkylation has been developed in an organocatalytic asymmetric fashion employing chiral secondary amines (for iminium activation of enals)[15b,e-h] or chiral BINOL-phosphoric acids (for hydrogen-bond activation of enones).[15c,d] The latter are compatible with ruthenium metathesis catalysts and they have been combined in a one-pot tandem protocol (Scheme 1B).

In comparison to indoles, for which a myriad of asymmetric procedures involving the FCA have been developed,[16] pyrroles have been relatively less used as nucleophilic counterparts in this reaction. The reasons for the lack of reports on the use of pyrroles in (organocatalytic) FCA reactions might be found in the high intrinsic nucleophilicity of this heterocyclic ring, which renders the enantiofacial discrimination more difficult in comparison to its benzannulated derivative indole.

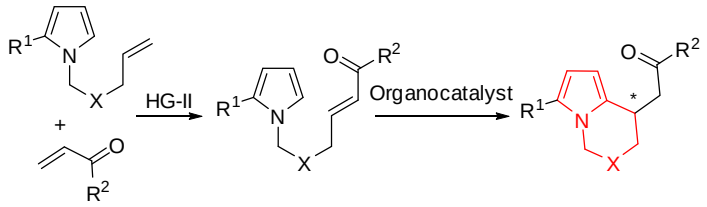
Scheme 1. Synthetic strategies to access pyrrole-derivatives.

Previous work

(A) Cross-metathesis/cycloaromatization approach to pyrroles (Ref. 13 and 14)

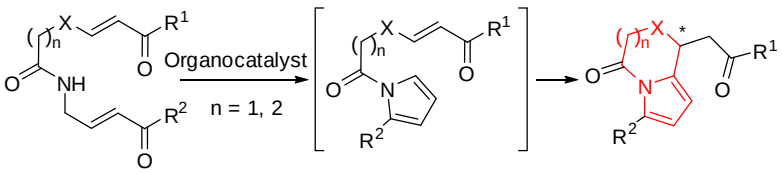


(B) Cross-metathesis/intramolecular Friedel-Crafts alkylation approach to indolizidines and pyrrolo[1,2-a]azepines (Ref. 15)



This work

(C) Tandem organocatalytic cycloaromatization/intramolecular Friedel-Crafts alkylation process to indolizidines and pyrrolo[1,2-a]azepines



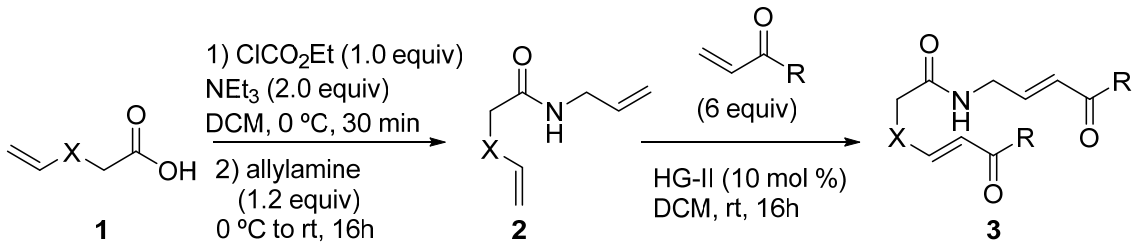
With these precedents in mind, we envisioned the combination of the cycloaromatization of γ-amidoenones, accessible by bidirectional cross-metathesis, and an intramolecular Friedel-Crafts alkylation in a tandem organocatalyzed protocol (Scheme 1C). This intramolecular double cyclization would generate the bicyclic core of indolizidines and pyrrolo[1,2-a]azepines in just one step from simple, acyclic substrates.[17] Furthermore, efforts towards an enantioselective approach will be made.

RESULTS AND DISCUSSION

Our study began with the synthesis of the starting amides **3** (Table 1), which was accomplished in two steps. First, amides **2** were prepared from the corresponding free acid (commercially available or described in the literature) *via* the mixed anhydride. In the case of **2d** and **2f**, a more reactive acid derivative was necessary and, thus, the appropriate acid chloride was used instead. Bidirectional olefin cross-metathesis with the corresponding vinyl ketone and Hoveyda-Grubbs 2nd generation catalyst (HG-II) converted **2** into **3**. All reactions were carried out at room

temperature, except in the case of **3e**, in which the less reactive phenyl vinyl ketone required a higher temperature (40 °C), but nevertheless, the reaction was low-yielding and messy. Compounds **3j**, **3k** and **3l** were obtained along with equimolecular amounts of the corresponding mono-cross-metathesis products (as a non-separable mixture of the two possible isomers).

Table 1. Synthesis of the starting amides 3



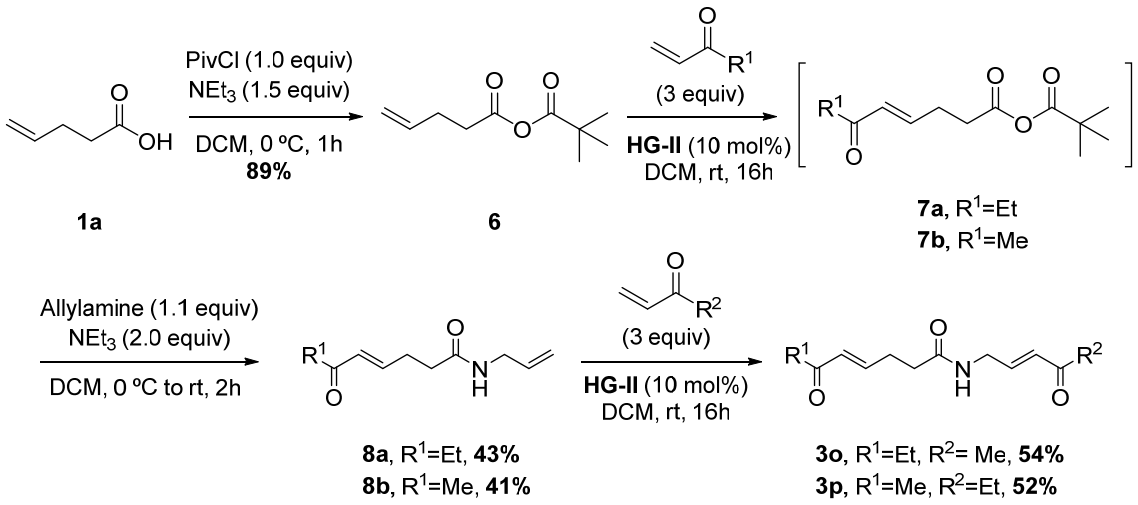
Entry	X	**2**	Yield (%)[a]	R	**3**	Yield (%)[a]
1	CH_2	**2a**	98	Me	**3a**	60
2	CH_2	**2a**		Et	**3b**	56
3	CH_2	**2a**		*n*-Pr	**3c**	36
4	CH_2	**2a**		*n*-Pent	**3d**	18
5	CH_2	**2a**		Ph	**3e**	12[c]
6	$(CH_2)_2$	**2b**	94	Me	**3f**	72
7	$(CH_2)_2$	**2b**		Et	**3g**	74
8	$(CH_2)_2$	**2b**		*n*-Pr	**3h**	51
9	$(CH_2)_2$	**2b**		*n*-Pent	**3i**	26
10	CH_2O	**2c**	36	Me	**3j**	39 (+31)[d]
11	CH_2S	**2d**	63[b]	Me	**3k**	12 (+19)[d]
12	$CH_2N(Boc)$	**2e**	89	Me	**3l**	40 (+41)[d]
13	$CH_2N(Ts)$	**2f**	89[b]	Me	**3m**	39
14	$CH_2C(CO_2Et)_2$	**2g**	34	Me	**3n**	59

[a] Isolated yield after flash column chromatography. [b] A different procedure was used for the amide synthesis. See Supporting Information for details. [c] The reaction was run at reflux. [d] Recovered yields of mono-cross-metathesis products are given in parentheses.

In order to expand the generality of the present methodology, "unsymmetrical" amides **3o** and **3p** were prepared, in which the substituents of each ketone end were different. A stepwise

synthesis was required to install each enone sequentially into the structure of the final product (Scheme 2). Mixed anhydride **6** was prepared and then subjected to cross-metathesis conditions with the vinyl ketone required in the carbon end of the amide. It should be emphasized that the metathesis catalyst is perfectly compatible with the relatively reactive mixed anhydride. The obtained intermediates **7a** and **7b** were not isolated, but directly treated with allylamine to afford **8a** and **8b**, which were then purified by flash chromatography. Finally, a second cross-metathesis reaction with the second vinyl ketone provided access to **3o** and **3p** respectively.

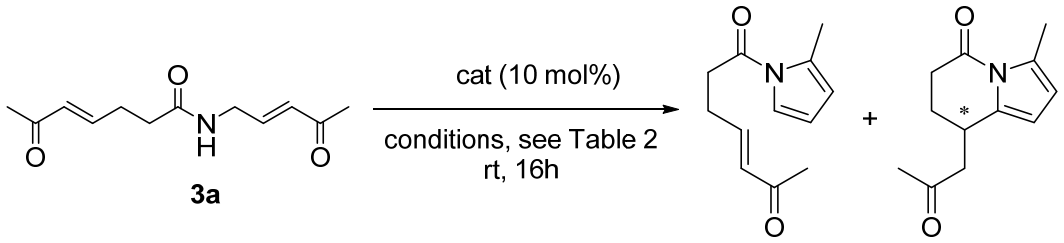
Scheme 2. Synthesis of unsymmetrical substrates 3o,p



With starting amides **3** in hand, their behavior was studied, choosing **3a** as a model substrate (Table 2). Preliminary screening of the reaction conditions revealed that strong Brønsted bases decomposed the starting material (entries 1-3). DABCO and 9-amino-(9-deoxy)epi-hydroquinine (HQN-NH_2) did not promote any reactivity (entries 4 and 5). To our delight, Brønsted and Lewis acids catalyzed the formation of dihydroindolizinone **5a** *via* pyrrole **4a** (entries 6 and 7). The sequence can be understood as a cycloaromatization/intramolecular Friedel-Crafts alkylation process. Aiming at the development of an organocatalytic process, diphenyl phosphate and the corresponding *N*-triflyl phosphoramide were tested. The first catalyst enabled the pyrrole formation, but was insufficiently acidic to efficiently activate the intermediate enone for the intramolecular Friedel-Crafts alkylation (entry 8). Longer reaction

times or higher temperatures did not provide better product ratios. Generally, pyrroles are considered electron-rich heterocycles, but in **3a** the free electron pair of the pyrrole nitrogen belongs at the same time to an amide moiety, which explains the relatively low reactivity in position 2 of the pyrrole ring. In contrast, the more acidic phosphoramide catalyzes the whole process and it is able to drive it to completion when the reaction mixture is heated in toluene at 60 ºC (entries 9 and 10).

Table 2. Preliminary screening of the reaction conditions

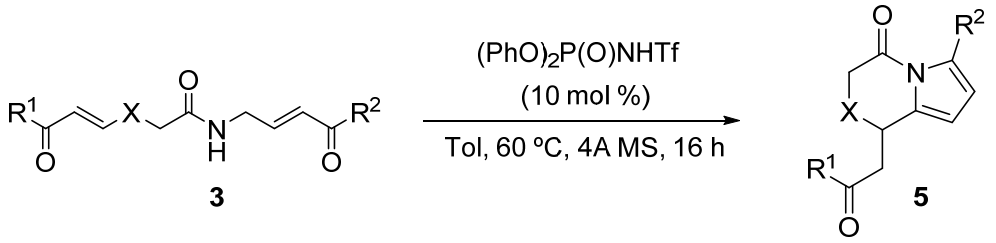


Entry	Catalyst	Solvent	Conversion (%)[a]	Product(s)
1[b]	NaH	THF	decomposition	
2[b]	P_2Et (phosphazene base)	THF	decomposition	
3[b]	*t*-BuOK	THF	decomposition	
4[b]	DABCO	DCM	0	-
5	HQN-NH_2	DCM	0	-
6[b]	$BF_3 \cdot OEt_2$	DCM	>95	**5a**
7[b]	TFA	DCM	>95	**5a**
8	$(PhO)_2P(O)OH$	DCM	>95	**4a**/**5a** (8/1)[c]
9	$(PhO)_2P(O)NHTf$	DCM	>95	**4a**/**5a** (1/1)[c]
10[d]	$(PhO)_2P(O)NHTf$	toluene	>95	**5a** (84%)[e]

[a] Conversion was determined from ^{1}H-NMR of the crude mixture. [b] 100 mol % of the corresponding catalyst was used. [c] Product ratio was determined from ^{1}H-NMR of the crude mixture. [d] The reaction was run at 60 °C. [e] Isolated yield after flash column chromatography.

Having found suitable conditions for the tandem protocol, these were applied to the rest of substrates **3**. Table 3 summarizes the results obtained in the evaluation of the scope of the process.

Table 3. Scope of the tandem cycloaromatization/intramolecular Friedel-Crafts alkylation.



3 **5**

5a (84%) **5b** (80%) **5c** (86%) **5d** (83%) **5e** (60%)

5f (74%) **5g** (72%) **5h** (70%) **5i** (76%) **5j** (70%) **5k** (56%)

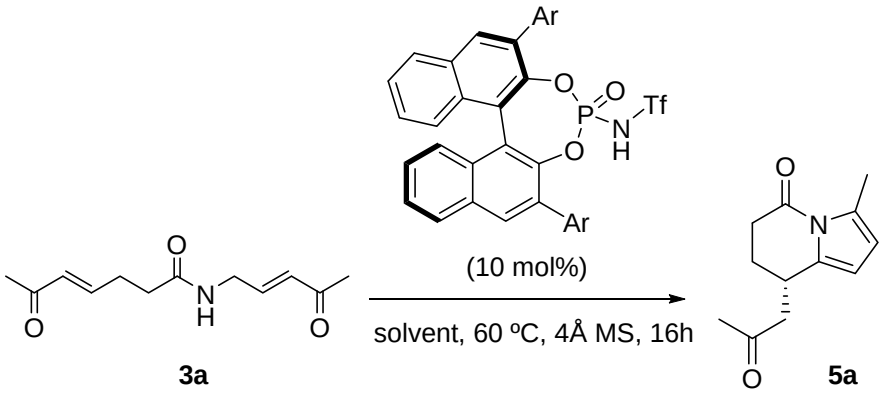
5l (64%) **5m** (82%) **5n** (72%) **5o** (80%) **5p** (82%)

A variety of indolizinone (**5a-e**) and pyrrolo-azepinone (**5f-i**) derivatives was obtained in good yields, either with aliphatic or aromatic substituents at the ketone and at the pyrrole end. This methodology is also amenable to obtain pyrrolo-oxazepinone **5j**, pyrrolo-thiazepinone **5k** and

pyrrolo-diazepinones **5l,m**. Finally, unsymmetrical indolizinones **5o,p** could also be obtained in good yields.[18]

In the hope of developing an enantioselective process, a variety of (R)-BINOL derived *N*-triflyl phosphoramides[19] were screened (Table 4). BINOL-derived organocatalysts bearing the most frequent 3,3' substitution pattern in the literature were synthesized and tested under the screening conditions. Among all the catalysts (Table 4, entries 1-8), the one substituted with the bulky 2,4,6-triisopropylphenyl groups was identified as the best for this transformation in terms of enantioselectivity (Table 4, entry 5). Non-polar, non-coordinating solvents were the best choice for this tandem sequence as one would anticipate for the non-covalent interaction (H-bond) between the catalyst and the substrate in the critical reaction step in which the stereocenter is formed.

Table 4. Preliminary screening of the reaction conditions



3a **5a**

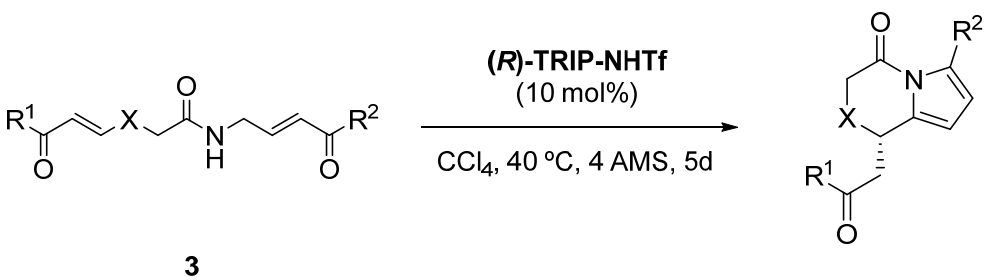
Entry	Ar	Solvent	Conversion (%)	er
1	1-naphthyl	toluene	>95	58:42
2	2-naphthyl	toluene	>95	56:44
3	9-anthryl	toluene	>95	58:42
4	9-phenanthryl	toluene	>95	61:39
5	2,4,6-triisopropyl-phenyl	toluene	>95	73:27
6	2,4,6-tricyclohexyl-phenyl	toluene	>95	70:30
7	4-biphenyl	toluene	>95	52:48
8	3,5-bis-trifluoromethyl-phenyl	toluene	>95	57:43
9[a]	2,4,6-triisopropyl-phenyl	toluene	>95	69:31

10	2,4,6-triisopropyl-phenyl	DCM	>95	70:30
11	2,4,6-triisopropyl-phenyl	DCE	>95	58:42
12	2,4,6-triisopropyl-phenyl	$CHCl_3$	>95	75:25
13	2,4,6-triisopropyl-phenyl	CCl_4	>95	78:22
14[b]	2,4,6-triisopropyl-phenyl	CCl_4	>95 (76%)[c]	80:20

[a] No molecular sieves were used. [b] The reaction was run at 40 °C for 5 days. [c] Isolated yield after flash column chromatography.

A solvent screening was also carried out. It is remarkable how apparently subtle changes in the solvent resulted in dramatic effects on the enantioselectivity, as in the pair DCM/DCE (Table 4, entries 10, 11). Carbon tetrachloride provided the best result in terms of enantioselectivity, if only moderate (Table 4, entry 13). The reaction temperature was adjusted to 40 °C, resulting in a reaction time of 5 days to ensure complete conversion to the final product of the tandem sequence (**5a**). Temperatures lower than 40 ºC invariably resulted in mixtures of **4a** and **5a**, no matter how long the reaction was run. Thus, it was necessary to sacrifice some enantioselectivity in favor of conversion in reasonable reaction times. Therefore, optimized conditions involved the use of (*R*)-BINOL-derived 2,4,6-triisopropylphenyl-substituted *N*-triflyl phosphoramide [(*R*)-TRIP-NH-Tf] in CCl_4 at 40 ºC for five days, in the presence of 4Å MS. Finally, the best reaction conditions were applied to all amides **3** in order to study the scope of the reaction (Table 5).

Table 5. Scope of the enantioselective tandem cycloaromatization/intramolecular Friedel-Crafts alkylation.



3

Entry	**3**	X	R^1	R^2	**5**	Yield (%)[a]	er
1	**3a**	CH_2	Me	Me	**5a**	76 (44)[b]	80:20 (74:26)[b]

2	**3b**	CH_2	Et	Et	**5b**	70	81.5:18.5
3	**3c**	CH_2	*n*-Pr	*n*-Pr	**5c**	80	83:17
4	**3d**	CH_2	*n*-Pent	*n*-Pent	**5d**	63	85:15
5	**3e**	CH_2	Ph	Ph	**5e**	44	86:14
6	**3f**	$(CH_2)_2$	Me	Me	**5f**	70	73.5:26.5
7	**3g**	$(CH_2)_2$	Et	Et	**5g**	71	68:32
8	**3h**	$(CH_2)_2$	*n*-Pr	*n*-Pr	**5h**	63	69:31
9	**3i**	$(CH_2)_2$	*n*-Pent	*n*-Pent	**5i**	79	65:35
10	**3j**	CH_2O	Me	Me	**5j**	70	65:35
11	**3k**	CH_2S	Me	Me	**5k**	47	73:27
12	**3l**	$CH_2N(Boc)$	Me	Me	**5l**	59	76:24
13	**3m**	$CH_2N(Ts)$	Me	Me	**5m**	75	84:16
14	**3n**	$CH_2C(CO_2Et)_2$	Me	Me	**5n**	62	65:35
15	**3o**	CH_2	Et	Me	**5o**	70	84:16
16	**3p**	CH_2	Me	Et	**5p**	62	76:24

[a] Isolated yield of the tandem sequence run at a 0.09 mmol scale after flash column chromatography.

[b] Results of the tandem sequence run at a 2.38 mmol scale. See the Experimental Section.

A variety of indolizine and azepine derivatives was obtained with moderate enantioselectivies (up to 72%) and moderate to good yields for this tandem sequence. Structural variability was introduced *via* the ketone substituents (R^1 and R^2) and the linker chain (X). When the appropriate heteroatom-bearing linker was used, oxa-azepine, thia-azepine and diazepine ring systems were obtained.

The reactions giving rise to the indolizine derivatives show slightly higher levels of enantioselectivity than the reactions producing the pyrrolo-azepinone derivatives, which can be attributed to a higher stereocontrol as a result of the smaller ring size in the transition state. In addition, the bulkier the ketone substituents R^1 and R^2 are in the indolizine derivatives, the higher is the reaction enantioselectivity, while the opposite is more or less true for the azepines. In terms of yield, no trends can clearly be inferred.

The absolute configuration of a recrystallyzed sample of **5a** was determined to be (S) by Vibrational Circular Dichroism (VCD) (See Supporting Information for further details).

SUMMARY

In summary, we have developed a novel tandem organocatalyzed cycloaromatization/intramolecular Friedel-Crafts alkylation sequence leading to the synthesis of a new family of indolizinones and pyrrolo-azepinones in moderate to good yields. The starting amidodienones are accessible by bidirectional or sequential olefin cross-metathesis. An asymmetric approach was developed using an (*R*)-BINOL-derived *N*-triflyl phosphoramide as Brønsted acid catalyst for the whole process, obtaining moderate levels of enantioselectivity. In this sense, further work is currently being carried out in our laboratory.

EXPERIMENTAL SECTION

General Methods. Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and toluene were distilled from sodium, and CH_2Cl_2 was distilled from calcium hydride. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040−0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (J) are given in hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The designation br indicates that the signal is broad. The abbreviations DCM and THF indicate dichloromethane and tetrahydrofuran, respectively. A QTOF mass analyzer system has been used for the HRMS measurements. Enantiomeric excess was determined by means of HPLC using chiral columns and mixtures of hexane and isopropanol as mobile phase.

General procedure for the synthesis of intermediate amides 3.

To a solution of the corresponding carboxylic acid **1** (5 mmol) in DCM (20 mL, 0.25 M) at 0 ºC, TEA (1.39 mL, 10 mmol, 2.0 equiv) and ethyl chloroformate (0.48 mL, 5 mmol, 1.0 equiv)

were sequentially added. After 30 min at the same temperature, allylamine (0.45 mL, 6 mmol, 1.2 equiv) was added dropwise and the resulting mixture was stirred at room temperature for 16h. 20 mL of a saturated NH_4Cl solution were added, the organic phase was separated and the aqueous phase was extracted with DCM (2x20 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The crude amide **2** was used as an intermediate in the synthesis of amide **3** without further purification.

N-Allyl-4-pentenamide **(2a):** Starting from commercially available 4-pentenoic acid and following the procedure described above, **2a** was obtained as a colorless oil in 98% (682 mg). The spectroscopic data matched those from the literature.[20]

N-Allyl-5-hexenamide **(2b):** Starting from commercially available 5-hexenoic acid and following the procedure described above, **2b** was obtained as a colorless oil in 94% (720 mg). The spectroscopic data matched those from the literature.[20]

N-Allyl-2-(allyloxy)acetamide **(2c):** Starting from 2-(allyloxy)acetic acid[21] and following the procedure described above, **2c** was obtained as a light yellow oil in 36% yield (279 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (br s, 1H), 5.96-5.79 (m, 2H), 5.38 – 5.05 (m, 4H), 4.06 (dt, J = 5.7, 1.4 Hz, 2H), 3.97 (s, 2H), 3.94 (tt, J = 5.9, 1.6 Hz, 2H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 169.6, 134.1, 133.6, 118.4, 116.6, 72.5, 69.5, 41.3.

N-Allyl-2-(allylthio)acetamide **(2d):** 2-(Allylthio)acetic acid[22] (500 mg, 3.78 mmol) was dissolved in DCM (15 mL) and cooled down to 0 ºC in an ice bath. To this solution, oxalyl chloride (0.64 mL, 7.56 mmol, 2.0 equiv) and 2 drops of anhydrous DMF were added. The resulting solution was allowed to reach room temperature for 3h. Volatiles were then removed under vacuum and the residue was redissolved in DCM (15 mL) and cooled down to 0 ºC. Allylamine (0.34 mL, 4.54 mmol, 1.2 equiv) and TEA (1.05 mL, 7.56 mmol, 2.0 equiv) were added dropwise and the resulting solution was allowed to reach room temperature for 16h. 20 mL of a saturated NH_4Cl solution were added, the organic phase was separated and the aqueous phase was extracted with DCM (2x20 mL). The combined organic phases were washed with

brine (20 mL) and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. **2d** was obtained as an orange oil in 63% yield (410 mg) and used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (br s, 1H), 5.97–5.63 (m, 2H), 5.33 – 5.06 (m, 4H), 3.92 (tt, *J* = 5.8, 1.5 Hz, 2H), 3.21 (s, 2H), 3.18–3.12 (m, 2H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 168.5, 134.0, 132.7, 119.0, 116.8, 42.2, 35.8, 34.7.

tert-Butyl allyl(2-(allylamino)-2-oxoethyl)carbamate **(2e):** Starting from *N*-allyl-*N*-(*tert*-butoxycarbonyl)glycine[23] and following the procedure described above, **2e** was obtained as a yellow oil in 89% yield (1.13 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92–5.68 (m, 2H), 5.21-5.12 (m, 4H), 3.98–3.75 (m, 6H), 1.46 (s, 9H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 169.6, 165.5, 134.1, 132.8, 118.0, 116.5, 81.2, 51.0, 45.9, 41.7, 28.4 (3xCH_3).

N-Allyl-2-[(*N*-allyl-4-methylphenyl)sulfonamide]acetamide **(2f):** *N*-Allyl-*N*-tosylglycinoyl chloride[23] (535mg, 1.86 mmol) dissolved in DCM (5 mL) was added to a solution of allylamine (0.17 mL, 2.23 mmol, 1.2 equiv) and TEA (0.52 mL, 3.72 mmol, 2.0 equiv) in DCM (10 mL) at 0 ºC. The resulting solution was allowed to reach room temperature for 16h. 20 mL of a saturated NH_4Cl solution were added, the organic phase was separated and the aqueous phase was extracted with DCM (2x20 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. **2f** was obtained as a thick yellow oil in 89% yield (512 mg) and used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.65 (m, 2H), 7.44–7.30 (m, 2H), 6.67 (br s, 1H), 5.83 (ddt, *J* = 17.2, 10.3, 5.5 Hz, 1H), 5.71–5.53 (m, 1H), 5.29 5.12 (m, 4H), 3.92 (tt, *J* = 5.5, 1.6 Hz, 2H), 3.80 (d, *J* = 6.9 Hz, 2H), 3.66 (s, 2H), 2.45 (s, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 168.3, 144.6, 134.8, 133.7, 131.2, 130.2 (2xCH), 127.6 (2xCH), 121.5, 116.8, 53.4, 51.1, 41.9, 21.7.

Diethyl 2-allyl-2-(2-(allylamino)-2-oxoethyl)malonate **(2g):** Starting from 3,3-bis(ethoxycarbonyl)hex-5-enoic acid[24] and following the procedure described above, **2g** was obtained as a colorless oil in 34% yield (505 mg) after flash column chromatography on silica gel [*n*-hexane-EtOAc (4:1)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93–5.53 (m, 3H), 5.24–5.06 (m,

4H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.85 (tt, *J* = 5.7, 1.5 Hz, 2H), 2.83–2.76 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 170.6 (2xCO), 169.1, 134.2, 132.7, 119.7, 116.6, 61.9 (2xCH_2), 55.8, 42.0, 39.5, 38.0, 14.2 (2xCH_3).

General procedure for the synthesis of "symmetrical" diketo amides 3a-g

To a solution of amide **2a-g** (0.50 mmol) in DCM (5 mL, 0.10 M) under a nitrogen atmosphere, alkyl vinyl ketone (6 equiv) and Hoveyda-Grubbs 2nd generation catalyst (16 mg, 0.05 mmol, 5 mol%) were added. After stirring for 2h at room temperature, a second equal addition of the catalyst followed and the reaction mixture was further stirred at room temperature for 16h. Volatiles were then removed under vacuum and the residue was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (1:1) to pure EtOAc].

(*E*)-6-Oxo-*N*-[(*E*)-4-oxopent-2-en-1-yl]-4-heptenamide (3a): Starting from amide **2a** and methyl vinyl ketone, **3a** was obtained as a dark brown thick oil in 60% yield (67 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.89–6.61 (m, 2H), 6.29 (br s, 1H), 6.18–6.02 (m, 2H), 4.05 (t, *J* = 4.4 Hz, 2H), 2.62-2.52 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 2.22 (s, 3H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 198.8, 198.3, 171.5, 146.3, 143.1, 131.8, 130.9, 40.4, 34.3, 27.9, 27.2, 27.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}NO_3$ 224.1281; found 224.1291.

(*E*)-6-Oxo-*N*-[(*E*)-4-oxohex-2-en-1-yl]-4-octenamide (3b): Starting from amide **2a** and ethyl vinyl ketone, **3b** was obtained as a dark brown thick oil in 56% yield (70 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.89–6.67 (m, 2H), 6.20–6.08 (m, 2H), 5.67 (br s, 1H), 4.07 (td, *J* = 5.8, 1.7 Hz, 2H), 2.65–2.50 (m, 6H), 2.44–2.33 (m, 2H), 1.15–1.01 (m, 6H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 201.0, 200.6, 171.4, 144.5, 141.2, 130.8, 130.1, 40.5, 34.7, 33.7, 33.7, 28.0, 8.2, 8.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{21}NO_3$ 252.1594; found 252.1606.

(*E*)-6-Oxo-*N*-[(*E*)-4-oxohept-2-en-1-yl]-4-nonenamide (3c): Starting from amide **2a** and propyl vinyl ketone, **3c** was obtained as a dark brown thick oil in 36% yield (50 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.93–6.64 (m, 2H), 6.14 (dq, *J* = 15.9, 1.6 Hz, 2H), 5.78 (br s, 1H), 4.06 (td, *J* = 5.7, 1.6 Hz, 2H), 2.67–2.45 (m, 6H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.75–1.52 (m, 6H), 0.92 (t,

J = 7.4 Hz, 6H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 200.7, 200.2, 171.4, 144.7, 141.4, 131.1, 130.4, 42.4 (2xCH_2), 40.5, 34.7, 28.0, 17.7, 17.6, 13.9 (2xCH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{25}NO_3$ 280.1907; found 280.1903.

(*E*)-6-Oxo-*N*-[(*E*)-4-oxonon-2-en-1-yl]-4-undecenamide (3d): Starting from amide **2a** and pentyl vinyl ketone, **3d** was obtained as a dark brown thick oil in 18% yield (30 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.89–6.66 (m, 2H), 6.13–6.10 (m, 2H), 5.62 (br s, 1H), 4.07 (td, *J* = 5.7, 1.7 Hz, 1H), 2.64–2.46 (m, 6H), 2.43–2.31 (m, 2H), 1.39–1.19 (m, 12H), 0.92–0.82 (m, 6H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 200.8, 200.3, 171.4, 144.5, 141.2, 131.1, 130.4, 40.6, 40.5, 40.5, 36.5, 34.7, 31.6, 31.6, 29.2, 28.0, 24.0, 23.8, 22.6, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{33}NO_3$ 336.2533; found 336.2542.

(*E*)-6-Oxo-*N*-[(*E*)-4-oxo-4-phenylbut-2-en-1-yl]-6-phenyl-4-hexenamide (3e): In a variation of the general procedure, the reaction was run at reflux and phenyl vinyl ketone was used. Starting from amide **2a**, **3e** was obtained as a dark brown thick oil in 12% yield (21 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 7.97–7.84 (m, 4H), 7.61–7.51 (m, 2H), 7.51–7.40 (m, 4H), 7.12–6.82 (m, 4H), 5.78 (br s, 1H), 4.18 (dd, *J* = 5.8, 3.6 Hz, 2H), 2.77–2.63 (m, 2H), 2.48 (t, *J* = 7.4 Hz, 1H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 190.7, 190.5, 171.4, 147.1, 143.7, 137.8, 137.5, 133.2, 133.0, 128.8 (2xCH), 128.7 (2xCH), 128.7 (2xCH), 128.7 (2xCH), 127.0, 126.5, 40.9, 34.9, 28.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{21}NO_3$ 348.1594; found 348.1600.

(*E*)-7-Oxo-*N*-[(*E*)-4-oxopent-2-en-1-yl]-5-octenamide (3f): Starting from amide **2b** and methyl vinyl ketone, **3f** was obtained as a dark brown thick oil in 72% yield (85 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.87–6.57 (m, 2H), 6.15-6.06 (m, 2H), 5.71 (br s, 1H), 4.07 (td, *J* = 5.9, 1.7 Hz, 2H), 2.35-2.19 (m, 10H), 1.86 (p, *J* = 7.4 Hz, 2H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 198.7, 198.1, 172.3, 147.0, 142.8, 132.1, 131.1, 40.4, 35.6, 31.9, 27.3, 27.1, 23.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{19}NO_3$ 238.1438; found 238.1447.

(*E*)-7-Oxo-*N*-[(*E*)-4-oxohex-2-en-1-yl]-5-nonenamide (3g): Starting from amide **2b** and ethyl vinyl ketone, **3g** was obtained as a dark brown thick oil in 74% yield (98 mg). ^1H NMR (300

MHz, $CDCl_3$) δ 6.87–6.67 (m, 2H), 6.18-6.09 (m, 2H), 5.67 (br s, 1H), 4.06 (td, *J* = 5.8, 1.7 Hz, 1H), 2.61-2.52 (m, 4H), 2.32–2.18 (m, 4H), 1.90-1.81 (m, 2H), 1.09 (t, *J* = 7.3 Hz, 6H). $^{13}C\{1 H\}$ NMR (75 MHz, $CDCl_3$) δ 201.2, 200.6, 172.3, 145.6, 141.4, 130.8, 130.1, 40.4, 35.6, 33.7, 33.5, 31.9, 23.9, 8.2, 8.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{23}NO_3$ 266.1751; found 266.1751.

(*E*)-7-Oxo-*N*-[(*E*)-4-oxohept-2-en-1-yl]-5-decenamide (3h): Starting from amide **2b** and propyl vinyl ketone, **3h** was obtained as a dark brown thick oil in 51% yield (75 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.87–6.65 (m, 2H), 6.18-6.09 (m, 2H), 5.61 (br s, 1H), 4.06 (td, *J* = 5.8, 1.7 Hz, 2H), 2.55-2.49 (m. 4H), 2.34–2.18 (m, 4H), 1.91-1.81 (m, 2H), 1.70-1.57 (m, 6H), 0.96-0.90 (m, 6H). $^{13}C\{1 H\}$ NMR (75 MHz, $CDCl_3$) δ 200.8, 200.2, 172.3, 145.7, 141.5, 131.2, 130.4, 42.4, 42.3, 40.4, 35.6, 31.9, 23.9, 17.8, 17.6, 14.0, 13.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{27}NO_3$ 294.2064; found 294.2067.

(*E*)-7-Oxo-*N*-[(*E*)-4-oxonon-2-en-1-yl]-5-dodecenamide (3i): Starting from amide **2b** and pentyl vinyl ketone, **3i** was obtained as a dark brown thick oil in 26% yield (45 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.87–6.67 (m, 2H), 6.18-6.09 (m, 2H), 5.59 (br s, 1H), 4.11–4.01 (m, 2H), 2.56-2.50 (m, 4H), 2.33–2.16 (m, 4H), 1.95–1.78 (m, 2H), 1.68–1.60 (m, 2H), 1.40–1.18 (m, 10H), 0.91-0.87 (m, 6H). $^{13}C\{1 H\}$ NMR (75 MHz, $CDCl_3$) δ 200.9, 200.3, 172.3, 145.6, 141.5, 131.1, 130.3, 40.5, 40.4 (2xCH_2), 35.7, 31.9, 31.6, 31.6, 24.1, 23.9, 23.9, 22.6, 22.6, 14.1, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{35}NO_3$ 350.2690; found 350.2682.

***N*-[(*E*)-4-Oxopent-2-en-1-yl]-2-[(*E*)-4-oxopent-2-en-1-yl]oxyacetamide (3j):** Starting from amide **2c** and methyl vinyl ketone, **3j** was obtained as a dark brown thick oil in 39% yield (47 mg). A mixture of mono cross-metathesis products was recovered as well in 31% combined yield. ^1H NMR (300 MHz, $CDCl_3$) δ 6.80-6.70 (m, 3H), 6.30 (dt, *J* = 16.1, 1.9 Hz, 1H), 6.15 (dt, *J* = 16.0, 1.8 Hz, 1H), 4.27 (dd, *J* = 4.6, 1.9 Hz, 2H), 4.17–4.11 (m, 2H), 4.06 (s, 2H), 2.30 (s, 3H), 2.28 (s, 3H). $^{13}C\{1 H\}$ NMR (75 MHz, $CDCl_3$) δ 198.1, 197.9, 169.1, 142.3, 141.0, 131.2,

131.1, 70.2, 70.2, 39.7, 27.5, 27.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}NO_4$ 240.1230; found 240.1242.

***N*-[(*E*)-4-Oxopent-2-en-1-yl]-2-[(*E*)-4-oxopent-2-en-1-yl]thioacetamide (3k):** In a variation of the general procedure, the reaction was run at reflux. Starting from amide **2d** and methyl vinyl ketone, **3k** was obtained as a dark brown thick oil in 12% yield (47 mg). A mixture of mono cross-metathesis products was recovered as well in 19% combined yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (br s, 1H), 6.72-6.58 (m, 2H), 6.19–6.03 (m, 2H), 4.04 (s, 2H), 3.27 (d, *J* = 6.8 Hz, 2H), 3.15 (s, 2H), 2.23-2.20 (m, 6H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 198.1, 197.8, 168.6, 142.4, 140.2, 132.9, 131.2, 40.6, 34.8, 33.9, 27.9, 27.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}NO_3S$ 256.1002; found 256.1005.

***tert*-Butyl {2-oxo-2-[(*E*)-4-oxopent-2-en-1-yl]aminoethyl}[(*E*)-4-oxopent-2-en-1-yl]carbamate (3l):** Starting from amide **2e** and methyl vinyl ketone, **3l** was obtained as a dark brown thick oil in 40% yield (68 mg). A mixture of mono cross-metathesis products was recovered as well in 41% combined yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76–6.62 (m, 2H), 6.15-6.05 (m, 2H), 4.12–4.03 (m, 4H), 3.85 (s, 2H), 2.26 (s, 3H), 2.25 (s, 3H), 1.46 (s, 9H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 198.1 (2xC=O), 169.6, 142.5, 141.5, 131.7, 131.0, 82.1, 51.5, 50.0, 40.3, 28.5 ($3xCH_3$), 27.6, 27.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{26}N_2O_5$ 339.1914; found 339.1921.

2-{4-Methyl-*N*-[(*E*)-4-oxopent-2-en-1-yl]phenylsulfonamido}-*N*-[(*E*)-4-oxopent-2-en-1-yl]acetamide (3m): Starting from amide **2f** and methyl vinyl ketone, **3l** was obtained as a dark brown thick oil in 39% yield (77 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 6.89 (br s, 1H), 6.71 (dt, *J* = 16.0, 5.0 Hz, 1H), 6.50 (dt, *J* = 15.9, 6.3 Hz, 1H), 6.18 (d, *J* = 16.0 Hz, 1H), 6.08 (d, *J* = 15.9 Hz, 1H), 4.13–4.04 (m, 2H), 4.00 (dd, *J* = 6.3, 1.1 Hz, 2H), 2.45 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 198.0, 197.2, 168.2, 145.0, 142.0, 138.7, 134.6, 133.8, 131.7, 130.4 (2xCH), 127.6 (2xCH),

51.7, 51.2, 40.5, 27.7, 27.5, 21.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{24}N_2O_5S$ 393.1479, found 393.1478.

Diethyl 2-{2-oxo-2-[(*E*)-4-oxopent-2-en-1-yl]aminoethyl}-2-[(*E*)-4-oxopent-2-en-1-yl]malonate (3n): Starting from amide **2g** and methyl vinyl ketone, **3n** was obtained as a dark brown thick oil in 59% yield (113 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80–6.61 (m, 2H), 6.22 (br s, 1H), 6.11 (d, *J* = 15.9 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 4H), 4.02 (t, *J* = 4.4 Hz, 2H), 2.95 (d, *J* = 7.6 Hz, 2H), 2.86 (s, 2H), 2.24 (s, 3H), 2.22 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 198.3, 198.2, 170.1, 169.2, 142.8, 141.9, 134.7, 131.1, 62.3 (2xCH_2), 62.0, 55.7, 40.4, 39.6, 36.8, 27.4, 27.4, 14.2 (2xCH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{27}NO_7$ 382.1860, found 382.1863.

General procedure for the synthesis of "unsymmetrical" diketo amides 3o,p

To a solution of 4-pentenoic acid (0.5 mL, 4.90 mmol) and TEA (1.02 mL, 7.35 mmol, 1.5 equiv) in DCM (7mL) at 0 ºC, pivaloyl chloride (0.60 mL, 4.90 mmol, 1.0 equiv) was added dropwise. After stirring at the same temperature for 1h, the solvent was removed under vacuum and the residue was redissolved in a mixture of hexane/EtOAc (5/1) and filtered over Celite. After evaporation of the solvent, 801 mg of the crude mixed anhydride **6** were obtained (89% yield).

300 mg (1.63 mmol) of the mixed anhydride **6** were dissolved in DCM (8 mL). The corresponding alkyl vinyl ketone (3 equiv) was added followed by Hoveyda-Grubbs 2nd generation catalyst (51 mg, 0.08 mmol, 5 mol %). The mixture was stirred for 2h at room temperature after which additional 5 mol % of the catalyst were added. After stirring for 16h, volatiles were removed under vacuum. The residue, containing the intermediate functionalized mixed anhydride **7**, was redissolved in DCM (8 mL) and cooled down to 0 ºC. TEA (0.45 mL, 3.26 mmol, 2 equiv) and allylamine (0.13 mL, 1.79 mmol, 1.1 equiv) were added and the resulting mixture was stirred for 1h at 0 ºC and then for a further 1h at room temperature. At this time, 8 mL of a saturated NH_4Cl solution was added, the organic phase was separated and the

aqueous phase was extracted with DCM (2x10 mL). The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The crude was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (1:1)] to afford the intermediate amide **8**.

(*E*)-*N*-Allyl-6-oxo-4-octenamide (8a): Following the procedure described above and using ethyl vinyl ketone in the cross-metathesis step, **8a** was obtained as a brown oil in 43% yield over 2 steps from the mixed anhydride (137 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.13 (dt, *J* = 15.9, 1.5 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 5.7 Hz, 1H), 5.52 (br s, 1H), 5.22–5.11 (m, 2H), 3.89 (tt, *J* = 5.7, 1.5 Hz, 2H), 2.61–2.52 (m, 4H), 2.35 (t, *J* = 7.4 Hz, 2H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 201.1, 171.2, 144.8, 134.2, 130.8, 116.8, 42.2, 34.8, 33.6, 28.1, 8.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{18}NO_2$ 196.1332, found 196.1332.

(*E*)-*N*-Allyl-6-oxo-4-heptenamide (8b): Following the procedure described above and using methyl vinyl ketone in the cross-metathesis step, **8b** was obtained as a brown oil in 41% yield over 2 steps from the mixed anhydride (121 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (dt, *J* = 16.0, 6.7 Hz, 1H), 6.10 (dt, *J* = 16.0, 1.5 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 5.7 Hz, 1H), 5.51 (br s, 1H), 5.22-5.12 (m, 2H), 3.90 (tt, *J* = 5.7, 1.5 Hz, 2H), 2.67 – 2.52 (m, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.24 (s, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 198.6, 171.1, 146.2, 134.2, 131.9, 116.8, 42.2, 34.7, 28.1, 27.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{16}NO_2$ 182.1176, found 182.1174.

To a solution of amide **8** (0.50 mmol) in DCM (5 mL, 0.10 M) under a nitrogen atmosphere, the corresponding alkyl vinyl ketone (3 equiv) and Hoveyda-Grubbs 2nd generation catalyst (16 mg, 0.05 mmol, 5 mol%) were added. After stirring for 2h at room temperature, a second equal addition of the catalyst followed and the reaction mixture was further stirred at room temperature for 16h. Volatiles were then removed under vacuum and the residue was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (1:1) to pure EtOAc].

(*E*)-6-Oxo-*N*-[(*E*)-4-oxopent-2-en-1-yl]-4-octenamide (3o): Starting from amide **8a** and methyl vinyl ketone, **3o** was obtained as a dark brown thick oil in 54% yield (64 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.71 (dt, *J* = 16.1, 5.2 Hz, 1H), 6.18-6.09 (m, 2H), 5.66 (br s, 1H), 4.08 (td, *J* = 6.0, 1.8 Hz, 2H), 2.66–2.51 (m, 4H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.26 (s, 3H), 1.09 (t, *J* = 7.3 Hz, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 202.9, 201.0, 171.4, 144.4, 142.6, 131.1, 130.9, 40.5, 34.7, 33.7, 28.0, 27.3, 8.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{19}NO_3$ 238.1438; found 238.1443.

(*E*)-6-Oxo-*N*-[(*E*)-4-oxohex-2-en-1-yl]-4-heptenamide (3p): Starting from amide **8b** and ethyl vinyl ketone, **3p** was obtained as a dark brown thick oil in 52% yield (62 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93–5.88 (m, 1H), 5.80 (dd, *J* = 3.3, 1.4 Hz, 1H), 3.41-3.32 (m, 1H), 3.02–2.84 (m, 3H), 2.80–2.55 (m, 3H), 2.21 (s, 3H), 2.13 (ddd, *J* = 13.5, 9.1, 4.6 Hz, 1H), 1.75–1.58 (m, 1H), 1.20 (t, *J* = 7.3 Hz, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 200.6, 198.6, 171.3, 145.9, 141.2, 132.0, 130.1, 40.5, 34.5, 33.7, 27.9, 27.3, 8.1.HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{19}NO_3$ 238.1438; found 238.1443.

General procedure for the tandem cycloaromatization/intramolecular Friedel-Crafts process:

To a solution of amide **3** (0.09 mmol) in CCl_4 (3 mL, 0.03 M) in a pressure vial, 4 Å MS (300 mg) and (*R*)-TRIP-*N*-triflyl phosphoramide (8 mg, 0.009 mmol, 10 mol%) were added. The vial was sealed and the resulting mixture was stirred at 40 ºC in an oil bath for 5 days. Volatiles were then removed under vacuum and the residue was purified by flash chromatography on silica gel. When the starting amide **3** did not show enough solubility in CCl_4, it was sonicated in the solvent until complete dissolution prior to the addition of the catalyst.

For the racemic approach, an analogous protocol was followed using $(PhO)_2P(O)NHTf$ as the achiral organocatalyst and toluene as the solvent at 60 ºC for 16h.

3-Methyl-8-(2-oxopropyl)-7,8-dihydroindolizin-5(6*H*)-one (5a): Starting from **3a**, **5a** was obtained as a light yellow solid (mp = 42-44 ºC) in 84% yield (16 mg) in racemic manner and

76% yield (14 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. When the organocatalytic reaction was repeated starting from 532 mg of **3a** (2.38 mmol), **5a** was obtained in 44% yield (216 mg) and 74:26 er. $[\alpha]_D^{25}$ = -20.0° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.73 (d, *J* = 2.5 Hz, 1H), 3.50-3.43 (m, 1H), 3.02–2.80 (m, 3H), 2.70 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.38 (s, 3H), 2.19 (s, 3H), 1.98-1.86 (m, 1H), 1.46–1.34 (m, 1H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 206.7, 175.1, 135.4, 132.7, 110.6, 107.7, 47.7, 36.7, 31.6, 30.9, 30.6, 20.4, 16.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}NO_2$ 206.1176; found 206.1170. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 14.88 min, t_R(minor) = 17.56 min.

3-Ethyl-8-(2-oxobutyl)-7,8-dihydroindolizin-5(6*H*)-one (5b): Starting from **3b**, **5b** was obtained as a light yellow solid (mp = 64-66 ºC) in 80% yield (17 mg) in racemic manner and 70% yield (15 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -10.3° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dt, *J* = 3.2, 1.2 Hz, 1H), 5.79 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.44-3.35 (m, 1H), 3.01–2.83 (m, 3H), 2.81–2.55 (m, 3H), 2.55–2.40 (m, 2H), 2.12 (dq, *J* = 12.9, 4.8 Hz, 1H), 1.75–1.61 (m, 1H), 1.20 (t, *J* = 7.4 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 209.5, 169.9, 138.0, 135.9, 109.5, 107.0, 46.3, 36.8, 34.2, 30.1, 27.7, 23.0, 13.1, 7.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{19}NO_2$ 234.1489; found 234.1480. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 8.65 min, t_R(minor) = 18.61 min.

8-(2-Oxopentyl)-3-propyl-7,8-dihydroindolizin-5(6H)-one (5c): Starting from **3c**, **5c** was obtained as a yellow oil in 86% yield (20 mg) in racemic manner and 80% yield (19 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -8.7° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 3.3, 1.1 Hz, 1H), 5.77 (dd, *J* = 3.3, 1.6 Hz, 1H), 3.47–3.29 (m, 1H), 2.98–2.53 (m, 6H), 2.47–2.38 (m, 2H), 2.15-2.06 (m, 1H), 1.78–1.52 (m, 5H), 0.99-0.91 (m, 6H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 209.1, 169.9, 136.2, 135.9, 110.5, 106.9, 46.7, 45.5, 34.2, 31.6, 30.1, 27.7, 22.0, 17.4, 14.1, 13.9. HRMS (ESI/Q-

TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{23}NO_2$ 262.1802; found 262.1797. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 7.09 min, t_R(minor) = 11.51 min.

8-(2-Oxoheptyl)-3-pentyl-7,8-dihydroindolizin-5(6*H*)-one (5d): Starting from **3d**, **5d** was obtained as a colorless oil in 83% yield (24 mg) in racemic manner and 63% yield (18 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -4.3° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 3.2, 1.0 Hz, 1H), 5.77 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.50–3.30 (m, 1H), 3.04–2.53 (m, 5H), 2.52–2.37 (m, 2H), 2.22–2.01 (m, 1H), 1.77–1.46 (m, 5H), 1.46–1.16 (m, 9H), 1.00–0.78 (m, 6H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 209., 169.9, 136.5, 135.9), 110.4, 106.9, 46.7, 43.7, 34.2, 31.8, 31.5, 30.1, 29.5, 28.5, 27.7, 23.6, 22.7, 22.6, 14.2, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{31}NO_2$ 318.2428; found 318.2428. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 5.97 min, t_R(minor) = 8.00 min.

8-(2-Oxo-2-phenylethyl)-3-phenyl-7,8-dihydroindolizin-5(6*H*)-one (5e): Starting from **3e**, **5e** was obtained as an orange oil in 60% yield (18 mg) in racemic manner and 44% yield (13 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -82.0° (c 1.0; $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07–7.98 (m, 2H), 7.66–7.58 (m, 1H), 7.58–7.46 (m, 2H), 7.39-7.29 (m, 5H), 6.17 (d, *J* = 3.4 Hz, 1H), 6.02 (dd, *J* = 3.4, 1.5 Hz, 1H), 3.77–3.64 (m, 1H), 3.56 (dd, *J* = 17.2, 5.2 Hz, 1H), 3.25 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.90–2.71 (m, 2H), 2.31-2.22 (m, 1H), 1.98–1.79 (m, 1H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 198.1, 168.9, 138.0, 136.9, 134.7, 134.2, 133.7, 129.1 (2xCH), 129.0 (2xCH), 128.3 (2xCH), 127.7 (2xCH), 127.3, 114.9, 108.1, 42.7, 34.1, 30.7, 28.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}NO_2$ 330.1489; found 330.1492. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 28.57 min, t_R(minor) = 54.63 min.

3-Methyl-9-(2-oxopropyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepin-5-one (5f): Starting from **3f**, **5f** was obtained as a colorless oil in 74% yield (15 mg) in racemic manner and 70% yield (14 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +5.8° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86–5.82 (m, 1H), 5.74 (dd, *J* =

3.3, 1.2 Hz, 1H), 3.45 (td, *J* = 11.5, 5.6 Hz, 1H), 2.96 (dd, *J* = 17.1, 6.0 Hz, 1H), 2.91–2.81 (m, 2H), 2.70 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.40 (s, 3H), 2.20 (s, 3H), 2.01–1.85 (m, 2H), 1.77–1.62 (m, 1H), 1.47–1.33 (m, 1H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 206.8, 175.1, 135.4, 132.7, 110.6, 107.7, 47.7, 36.8, 31.6, 30.9, 30.6, 20.4, 16.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}NO_2$ 220.1332; found 220.1330. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 15.36 min, t_R(minor) = 9.76 min.

3-Ethyl-9-(2-oxobutyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepin-5-one (5g): Starting from **3g**, **5g** was obtained as a yellow oil in 72% yield (16.5 mg) in racemic manner and 71% yield (16 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +4.6° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 3.2, 1.1 Hz, 1H), 5.76 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.58–3.40 (m, 1H), 3.05–2.62 (m, 6H), 2.60–2.37 (m, 2H), 1.98–1.84 (m, 2H), 1.76–1.60 (m, 1H), 1.45–1.30 (m, 1H), 1.17 (t, *J* = 7.4 Hz, 3H), 1.07 (t, *J* = 7.3 Hz, 3H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 209.5, 175.3, 139.2, 135.7, 108.6, 107.6, 46.5, 36.9, 36.7, 31.7, 30.9, 22.6, 20.4, 13.2, 7.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}NO_2$ 248.1645; found 248.1648. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 7.91 min, t_R(minor) = 10.12 min.

9-(2-Oxopentyl)-3-propyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepin-5-one (5h): Starting from **3h**, **5h** was obtained as a yellow oil in 70% yield (18 mg) in racemic manner and 63% yield (16 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +5.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (d, *J* = 3.3 Hz, 1H), 5.75 (dd, *J* = 3.3, 1.1 Hz, 1H), 3.55–3.39 (m, 1H), 3.00–2.61 (m, 6H), 2.43 (td, *J* = 7.2, 2.2 Hz, 2H), 2.01–1.82 (m, 2H), 1.74–1.51 (m, 4H), 1.46–1.20 (m, 2H), 1.04–0.86 (m, 6H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 209.1, 175.3, 137.4, 135.6, 109.6, 107.5, 46.9, 45.4, 36.9, 31.7, 31.2, 30.8, 22.3, 20.5, 17.4, 14.1, 13.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{25}NO_2$ 276.1958; found 276.1960. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 13.04 min, t_R(minor) = 11.60 min.

9-(2-Oxoheptyl)-3-pentyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepin-5-one (5i): Starting from **3i**, **5i** was obtained as a yellow oil in 76% yield (23 mg) in racemic manner and 79% yield (24 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +3.9° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (d, *J* = 3.3 Hz, 1H), 5.75 (dd, *J* = 3.3, 1.1 Hz, 1H), 3.54–3.40 (m, 1H), 2.98–2.61 (m, 6H), 2.43 (td, *J* = 7.3, 2.4 Hz, 2H), 2.01–1.80 (m, 2H), 1.76–1.46 (m, 5H), 1.46–1.17 (m, 9H), 0.91-0.86 (m, 6H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 209.2, 175.3, 137.6, 135.6, 109.4, 107.5, 46.8, 43.5, 36.9, 31.8, 31.7, 31.5, 30.8, 29.1, 28.8, 23.6, 22.7, 22.6, 20.5, 14.2, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{33}NO_2$ 332.2584; found 332.2585. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 17.97 min, t_R(minor) = 11.56 min.

7-Methyl-1-(2-oxopropyl)-1,2-dihydropyrrolo[1,2-d][1,4]oxazepin-5(4*H*)-one (5j): Starting from **3j**, **5j** was obtained as a yellow solid (mp = 105-107 ºC) in 70% yield (14 mg) in racemic manner and 70% yield (14 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (3:2)]. $[\alpha]_D^{25}$ = +10.7° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94–5.88 (m, 1H), 5.80 (dd, *J* = 3.2, 1.1 Hz, 1H), 4.54 (d, *J* = 17.9 Hz, 1H), 4.41 (d, *J* = 17.9 Hz, 1H), 4.00 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.86-3.75 (m, 1H), 3.41 (dd, *J* = 11.3, 10.0 Hz, 1H), 2.99 (dd, *J* = 17.7, 6.1 Hz, 1H), 2.64 (dd, *J* = 17.7, 7.3 Hz, 1H), 2.39 (s, 3H), 2.22 (s, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 205.3, 174.5, 132.9, 132.5, 111.3, 108.3, 72.4, 69.6, 43.3, 32.0, 30.4, 15.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}NO_3$ 222.1125; found 222.1127. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 2 mL/min): t_R(major) = 7.11 min, t_R(minor) = 21.17 min.

7-Methyl-1-(2-oxopropyl)-1,2-dihydropyrrolo[1,2-d][1,4]thiazepin-5(4*H*)-one (5k): Starting from **3k**, **5k** was obtained as a white solid (mp = 78-80 ºC) in 56% yield (12 mg) in racemic manner and 47% yield (10 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +19.0° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dq, *J* = 3.3, 1.1 Hz, 1H), 5.86 (dd, *J* = 3.3, 0.9 Hz, 1H), 3.95 (d, *J* = 17.3 Hz, 1H), 3.71-3.61 (m, 1H), 3.47 (d, *J* = 17.3, 1H), 3.18 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.08 (dd, *J* = 17.6, 5.9 Hz, 1H), 2.85 (dd,

J = 17.6, 7.6 Hz, 1H), 2.46–2.31 (m, 4H), 2.21 (s, 3H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 205.5, 172.3, 133.8, 133.7, 111.2, 109.4, 47.4, 34.7, 34.1, 32.6, 30.6, 16.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}NO_2S$ 238.0896; found 238.0901. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 21.32 min, t_R(minor) = 17.03 min.

tert-Butyl 7-methyl-5-oxo-1-(2-oxopropyl)-1,2,4,5-tetrahydro-3*H*-pyrrolo[1,2-d][1,4]diazepine-3-carboxylate (5l): Starting **3l**, **5l** was obtained as a light yellow oil in 64% yield (18 mg) in racemic manner and 59% yield (17 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (3:2)]. $[\alpha]_D^{25}$ = +11.6° (c 1.0; $CHCl_3$). Due to the presence of two major rotamers, two sets of signals are observable. ^1H NMR (300 MHz, $CDCl_3$) δ 5.81-5.78 (m, 1H), 5.72-5.70 (m, 1H), 4.67 (d, *J* = 18.2 Hz, 0.3H), 4.47 (d, *J* = 18.3 Hz, 0.7H), 3.94-3.81 (m, 1H), 3.68–3.15 (m, 3H), 3.00 (d, *J* = 5.6 Hz, 0.3H), 2.96– 2.92 (m, 0.7H), 2.78–2.59 (m, 1H), 2.32 (s, 2.1H), 2.30 (s, 0.9H), 2.16 (s, 3H), 1.25 (s, 6.3H), 1.23 (s, 2.7H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 205.6, 173.1, 155.2, 132.6, 132.5, 111.2, 108.9, 81.2, 51.7, 49.8, 44.5, 32.3, 30.6, 28.2, 15.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{24}N_2O_4$ 321.1809; found 321.1813. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 2 mL/min): t_R(major) = 9.53 min, t_R(minor) = 7.71 min.

7-Methyl-1-(2-oxopropyl)-3-tosyl-1,2,3,4-tetrahydro-5*H*-pyrrolo[1,2-d][1,4]diazepin-5-one (5m): Starting from **3m**, **5m** was obtained as a yellow oil in 82% yield (27 mg) in racemic manner and 75% yield (25 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (3:2)]. $[\alpha]_D^{25}$ = +6.7° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.41 (m, 2H), 7.19-7.13 (m, 1H), 5.75–5.69 (m, 2H), 4.65 (d, *J* = 18.9 Hz, 1H), 4.04 (d, *J* = 18.9 Hz, 1H), 3.63–3.31 (m, 3H), 3.07–2.97 (m, 1H), 2.80–2.70 (m, 1H), 2.37 (s, 3H), 2.21 (s, 3H), 2.11 (s, 3H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 205.1, 170.8, 143.7, 136.1, 133.0, 132.0, 129.9 (2xCH), 126.6 (2xCH), 111.2, 109.1, 51.5, 50.7, 44.4, 31.9, 30.5, 21.6, 15.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}N_2O_4S$ 375.1373; found 375.1376. HPLC (Chiralcel AD, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 52.12 min, t_R(minor) = 59.32 min.

Diethyl 3-methyl-5-oxo-9-(2-oxopropyl)-5,6,8,9-tetrahydro-7*H*-pyrrolo[1,2-a]azepine-7,7-dicarboxylate (5n): Starting from **3n**, **5n** was obtained as a yellow oil in 72% yield (23 mg) in racemic manner and 62% yield (20 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -16.4° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (dq, *J* = 3.2, 1.0 Hz, 1H), 5.73 (dd, *J* = 3.2, 1.1 Hz, 1H), 4.34–4.13 (m, 2H), 4.11-3.95 (m, 2H), 3.51-3.35 (m, 3H), 3.01 (dd, *J* = 17.5, 5.5 Hz, 1H), 2.76 (dd, *J* = 17.5, 8.2 Hz, 1H), 2.39-2.30 (m, 4H), 2.26-2.17 (m, 4H), 1.28-1.14 (m, 6H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 206.0, 170.4, 170.4, 170.4, 134.2, 132.8, 111.0, 108.2, 62.6, 62.3, 54.1, 47.1, 42.0, 38.0, 30.6, 29.9, 15.7, 14.1, 14.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{25}NO_6$ 364.1755; found 364.1759. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 29.13 min, t_R(minor) = 14.77 min.

3-Methyl-8-(2-oxobutyl)-7,8-dihydroindolizin-5(6*H*)-one (5o): Starting from **3o**, **5o** was obtained as a whit solid (mp = 44-46 ºC) in 80% yield (16 mg) in racemic manner and 70% yield (14 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -9.2° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (dq, *J* = 3.2, 1.2 Hz, 1H), 5.76 (dd, *J* = 3.2, 1.5 Hz, 1H), 3.51–3.34 (m, 1H), 2.93 (dd, *J* = 17.2, 5.4 Hz, 1H), 2.82–2.54 (m, 3H), 2.54–2.40 (m, 5H), 2.13 (dq, *J* = 13.0, 4.8 Hz, 1H), 1.74-1.61 (m, 1H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C{1 H} NMR (75 MHz, $CDCl_3$) δ 209.7, 170.2, 135.8, 131.3, 111.6, 106.9, 46.3, 36.8, 34.0, 30.1, 27.8, 16.2, 7.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}NO_2$ 220.1332; found 220.1338. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 10.44 min, t_R(minor) = 21.24 min.

3-Ethyl-8-(2-oxopropyl)-7,8-dihydroindolizin-5(6*H*)-one (5p): Starting from **3p**, **5p** was obtained as a light brown solid (mp = 55-57 ºC) in 82% yield (16 mg) in racemic manner and 62% yield (12 mg) in enantioenriched manner after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -13.0° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (dq, *J* = 3.2, 1.2 Hz, 1H), 5.76 (dd, *J* = 3.2, 1.5 Hz, 1H), 3.51–3.34 (m, 1H), 2.93 (dd, *J* = 17.2, 5.4 Hz, 1H), 2.82–2.54 (m, 3H), 2.54–2.40 (m, 5H), 2.13 (dq, *J* = 13.0, 4.8 Hz, 1H), 1.74-1.61 (m, 1H), 1.10 (t, *J* =

7.3 Hz, 3H). $^{13}C\{1\ H\}$ NMR (75 MHz, $CDCl_3$) δ 209.7, 170.2, 135.8, 131.3, 111.6, 106.9, 46.3, 36.8, 34.0, 30.1, 27.8, 16.2, 7.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}NO_2$ 220.1332; found 220.1337. HPLC (Phenomenex Cellulose-4, 70:30 hexane/*i*-PrOH, 1 mL/min): t_R(major) = 12.01 min, t_R(minor) = 15.04 min.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxxxxxxxx.

HPLC traces of enantioenriched compounds **5**, vibrational Circular Dichroism (VCD) of **5a** and NMR spectra of compounds **2a** and **2b** and all new compounds (^1H, ^{13}C) (PDF).

AUTHOR INFORMATION

Corresponding Authors

*E-mail: carlos.pozo@uv.es

*E-mail: santos.fustero@uv.es

Notes

The authors declare no competing financial interest.

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