

The Catalytic Regio- and Stereoselective Synthesis of 1,6-Diazabicyclo[4.3.0]nonane-2,7-diones

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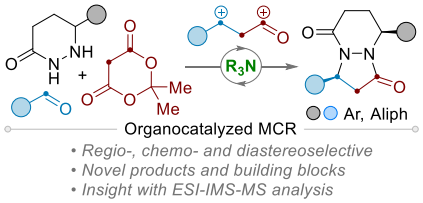
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The catalytic regio- and stereoselective synthesis of 1,6-diazabicyclo[4.3.0]nonane-2,7-diones

Arthur Lebrêne,[a] Thomas Martzel,[a] Laura Gouriou,[a†] Morgane Sanselme,[b] Vincent Levacher,[a] Sylvain Oudeyer,[a] Carlos Afonso,[a†] Corinne Loutelier-Bourhis[a†*] and Jean-François Brière[a*]

Supporting Information Placeholder

ABSTRACT: A straightforward synthesis of original 1,6-diazabicyclo[4.3.0]nonane-2,7-diones was achieved through a DBU-organocatalyzed multicomponent Knoevenagel-aza-Michael-Cyclocondensation (KMC) reaction which takes advantage of an unprecedented highly regio- and diastereoselective conjugate addition of pyridazinones to alkylidene Meldrum's acid intermediates. The key reactive intermediates of this complex process were analyzed by means of electrospray ionization mass spectrometry coupled to ion mobility spectrometry (ESI-IMS-MS) allowing to valid the proposed mechanism.



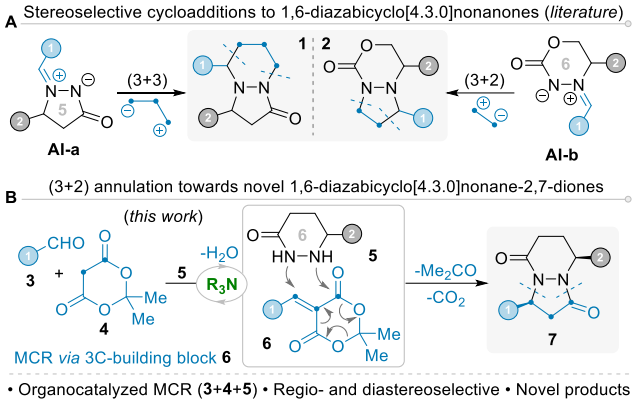
INTRODUCTION

The development of new routes to synthesize small chiral azaarenes has become an important exercise in drug development.[1] These Csp^3- rich heterocycles proved to be versatile platforms e.g., for the elaboration of novel drug candidates or to populate compound libraries useful for the increasingly popular fragment-based drug discovery (FBDD).[2] By exploring the 3D-chemical space, it has been shown that sp^3-rich compounds could lead to better selectivity towards the bio-targets while decreasing the toxicity issues.[3] In that context, the substituted diazabicyclo[4.3.0]nonanone derivatives **1** and **2** are versatile fused bicyclic structures (Scheme 1), also encountered within bioactive molecules.[4,5,6] Amongst the most straightforward stereoselective syntheses of these types of molecules, the transformation of chiral azomethine imines (AI), accessible from the corresponding aldehydes (R^1CHO) and cyclic hydrazines (R^2NH-NHR), stands out (Scheme 1A).[4] The diastereoselective (3+3) cycloadditions of readily available chiral Dorn-Otto type five-membered ring azomethine imines **AI-a** have recently emerged to give 1,6-diazabicyclo[4.3.0]nonan-7-ones **1**.[5,6] On the other hand, Husson, Micouin and colleagues reported on an original (3+2) cycloaddition allowing the construction of the five-membered

ring moiety of the obtained isomeric 1,6-diaza-3-oxobicyclo[4.3.0]nonan-2-one product **2**, from the corresponding and much less explored six-membered ring derived dipoles **AI-b**.[7]

In quest of opening the topology space of these valuable diazabicyclo[4.3.0]nonanone derivatives, we tackled an alternative disconnection based on the regioselective addition of pyridazinones **5** to a three-carbon unit like **6** to form 1,6-diazabicyclo[4.3.0]nonane-2,7-diones **7** (Scheme 1B). During preliminary investigations, we discovered that chiral hydroxylamines and pyrazolidinones, as aza-bisnucleophiles,[8] led to a novel domino aza-Michael-cyclocondensation sequence to the highly reactive and in-situ formed alkylidene Meldrum's acids **6** upon catalytic conditions.[9] However, the application of this process to 6-membered ring pyridazinones **5** is not obvious and raised several questions concerning (1) the reactivity issue as long as the regioselective aza-Michael of these valuable cyclic hydrazines **5** remains largely unexplored. Next (2), the preliminary investigation with the 5-phenyl-pyrazolidinone (5-membered ring) showed that the diastereoselectivity outcome strongly depends on the nature of the aldehyde.[8a] Nonetheless, through the anticipated formal (3+2) annulation between pyridazinones **5** and **6**, contrarywise to the azomethine imine-based sequence (Scheme 1A *versus* 1B), the R^1 and R^2 functional groups of the thus obtained bicyclic structure **7** will be apart to each other, and the two carbonyls lying at opposite position, which has been rarely described in the literature.[10] Then, this sequence would eventually provide original products **7** with potentially unique properties and functionalization opportunities.

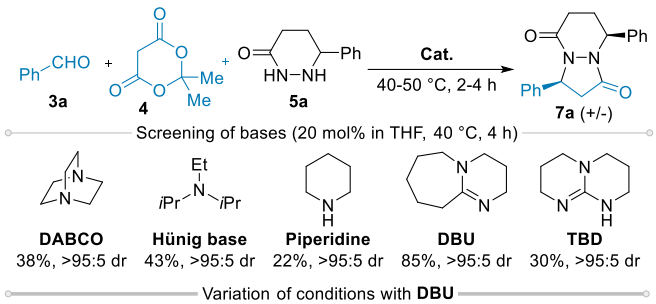
Scheme 1. Known synthesis of 1,6-diazabicyclo[4.3.0]nonanones (A) and new development (B)



Nevertheless, the orchestration of a versatile process, in an efficient multicomponent fashion,[11] requires the selective formation and reaction of the alkylidene Meldrum's acid intermediate **6** (from aldehyde **3** + **4**) in the presence of pyridazinone **5**, which might be in competition with the azomethine imine species, akin to **AI-b**, resulting from the condensation of **5** and **3**. Notwithstanding these challenges, we are pleased to report that the chemoselective multicomponent Knoevenagel-aza-Michael-Cyclocondensation (KMC) reaction takes place under organocatalytic conditions and leads to the highly stereoselective synthesis of novel 1,6-diazabicyclo[4.3.0]nonane-2,7-diones **7**. Importantly, an ESI-IMS-MS study allowed to get insight into the formation of key intermediates of this otherwise complex sequence.

RESULTS AND DISCUSSION

Table 1. Proof of concept and optimization



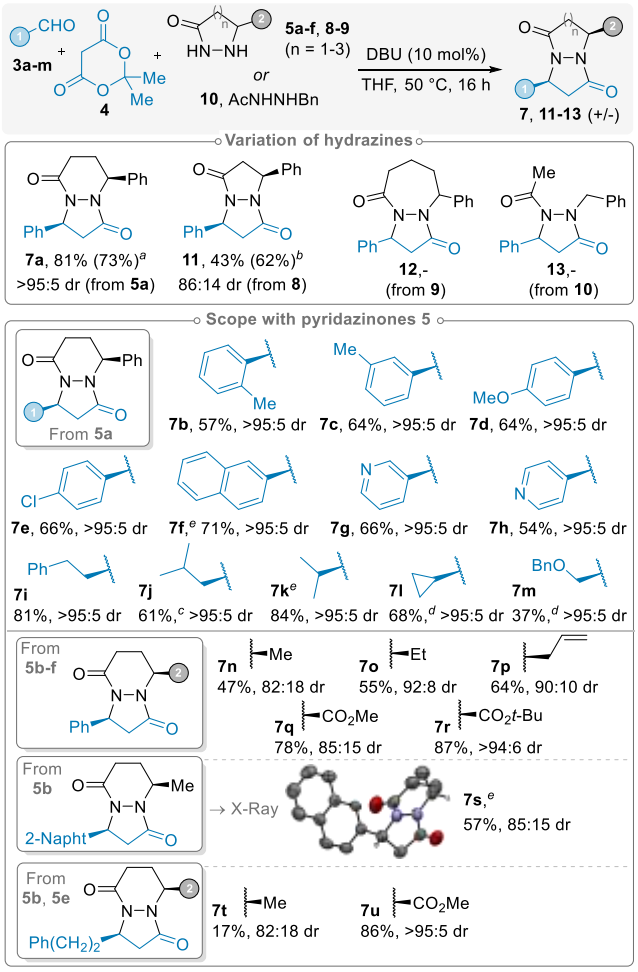
Entry	DBU (mol%)	Solvent	time/temp	Yield (%)[a]	dr[b]
1	20	PhMe	2 h/40 °C	7	-
2	20	CH_2Cl_2	2 h/40 °C	8	-
3	20	AcOEt	2 h/40 °C	33	>95:5
4	20	MeCN	2 h/40 °C	14	>95:5
5	20	THF	2 h/40 °C	40	>95:5
6	20	THF	4 h/40 °C	85	>95:5
7	10	THF	4 h/40 °C	45	>95:5
8	10	THF	4 h/50 °C	88(83)[c]	>95:5
9	-	THF	4 h/50 °C	0(27)[c]	-

Reaction performed at 0.1 M on 0.2 mmol scale with 1 equivalent of each component. [a]NMR yield determined by an internal standard. [b]Diastereoisomeric ratio determined by ^{1}H NMR on the crude. [c]The reaction was performed from pre-formed alkylidene Meldrum's acid **6a**.

The tetrahydropyridazinones **5** are usually constructed by a linear condensation/reduction sequence from the keto-esters. We found that the addition of Grignard or organolithium reagents to the readily available 4,5-dihydropyridazin-3(2*H*)-one gave rise to a straightforward formation of various tetrahydropyridazinones **5** albeit in moderate yields (see experimental section).[12] With this type of precursor in hands, the multicomponent reaction (MCR) was investigated by mixing pyridazinone **5a**, benzaldehyde **3a** and Meldrum's acid **4** (1 equivalent of each). We found that 20 mol% of DABCO in THF for 4 hours at 40 °C gave the corresponding diazabicyclononanedione **7a** in 38% NMR yield (Table 1-Screening of bases, see SI for further details). To our delight, essentially one diastereoisomer was obtained (>95:5 dr) and, with regard to a series of X-Ray analyses (*vide infra*), the two phenyl moieties are likely lying *cis* to each other. The nature of the Brønsted base strongly influenced the efficiency of the reaction (Table 1), and the higher the pK_{aH} (from DABCO, Hünig, piperidine bases and see SI other examples) the better the conversion with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) giving the best yield of 85% in only 4 hours. However, a plateau was reach as long as stronger guanidine bases, such as TBD, led to a lower yield of 30%. As seen in entries 1-5, a faster MCR took place in THF as solvent and the organocatalyst loading could be decreased to 10 mol% (entries 6-7), although a reaction temperature of 50 °C was required to reach a complete conversion into **7a** in an excellent 88% yield (entry 8). Despite no product formation was observed without DBU, 27% of diazabicyclononanedione **7a** was obtained by starting directly from alkylidene Meldrum's acid **6a** (entry 9), showing the likely formation of this intermediate **6a** during the MCR (see also entry 8) and the role of the base on several stages of the catalytic cycle. During this optimization, the accumulation of an intermediate (*vide infra*) was observed at 40 °C, which indeed completely disappeared at 50 °C; no trace of the regioisomer (from the azomethine imine intermediate) was detected on the crude product by ^{1}H NMR.

To our delight, this MCR could be carried out with phenyl-pyridazinone **5a** to furnish the corresponding product **7a** as a single diastereoisomer in 81% isolated yield after column chromatography and 73% yield on 1 mmol scale (Scheme 2 – variation of hydrazines). Furthermore, preliminary investigations showed that diazabicyclononanedione **7a** could be obtained with >99% enantiomeric excess from an enantiopure sample of pyridazinone **5a** (see ES and SI).

Scheme 2. Scope and limitation



Reaction performed with pyridazinone **5** or analogues **8-10**, aldehydes **3** (0.3 mmol, 1 equiv of each) and Meldrum's acid **4** (1.3 equiv.) in THF (0.1 M) at 50 °C for 16 h; isolated yields (%) of the major diastereoisomer after column chromatography and dr determined by ^{1}H NMR on the crude product. [a]Performed on 1 mmol scale. [b]Yield of both diastereoisomers. [c]30 hours of reaction. [d]24 hours of reaction. [e]Structures determined by X-Ray diffraction analyses.

For a sake of comparison with a previous observation,[8a] these conditions could be applied to pyrazolidinone **8** to yield **11** in 62% but in a mixture of hardly separable diastereoisomers (86:14 dr). Furthermore, neither the seven-membered ring hydrazine **9** nor the non-cyclic hydrazine **10** led to any pyrazolidinone derivatives **12-13** formation. These results show the specific reactivity and selectivity of pyridazinone nucleophiles in the multicomponent KMC reaction. Then, we explored the scope of this catalyzed MCR giving rise to the formation of novel 1,6-diazabicyclo[4.3.0]nonane-2,7-diones **7** (Scheme 2-Scope). Starting from pyridazinone **5a**, a series of bicyclic heterocycles **7b-7h** could be easily elaborated with various aromatic aldehydes **3b-3f** and heteroaromatic aldehydes **3g-3h** with isolated yields ranging from 54% to 71%. Aliphatic linear (**3i-3j**), branched (**3k**) and cyclopropyl (**3l**) aldehydes were smoothly transformed into the corresponding products **7i-7l** in 61% to 84% yields, albeit an ether derived but enolisable aldehyde **3m** led to a less efficient reaction providing the product **7m** with moderate 37% yield. Importantly, in every case only one diastereoisomer was obtained and isolated in this series. Then, we turned our attention to the use of various pyridazinones **5b-f** in order to probe the diastereoselectivity issue of this MCR. Even with a small methyl group on pyridazinone **5b**, the corresponding major diastereoisomers of diazabicyclononanediones **7n** and **7s** were isolated in 47% and 57% yields (easily separated by column chromatography) from the crude mixture displaying

promising dr ranging from 82:18 to 85:15. The diastereoisomeric excesses were markedly improved by means of cyclic hydrazines **5** flanked by more hindered substituents to afford ethyl (**7o**, 55%, 92:8 dr), allyl (**7p**, 64%, 90:10 dr) and esters (**7q**, 64%, 85:15 dr and **7r**, 87%, >94:6 dr). Excellent results were also obtained with an aliphatic aldehyde to give the ester-derived diazabicyclononanedione **7u** with 86% yield and high >95:5 dr although a limitation was encountered with pyridazinone **5b** with a small methyl-group yielding product **7t** in 17% (82:18 dr).

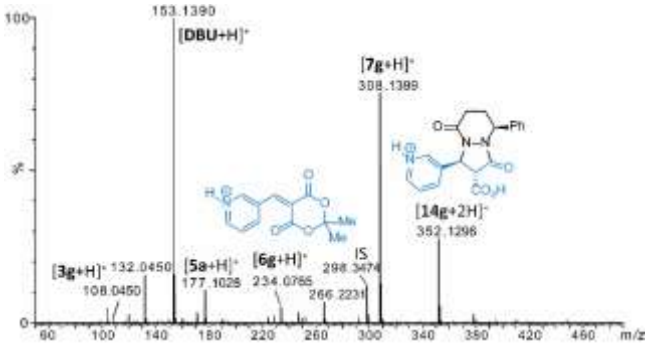


Figure 1. ESI-IMS-MS insight into reaction intermediates (see also Table 2) after 60 minutes. The reaction was carried out at 30 °C to prevent a too fast process. IS: internal standard.

Getting experimental evidence of intermediates involved into a complex organocatalyzed MCR is not a trivial task, especially with labile Meldrum's acid derivatives.[13] By means of soft electrospray ionization mass spectrometry (ESI-MS),[13] key intermediates were sought at various time intervals. We reasoned that the pyridyl moiety onto aldehyde **3g** would afford an ideal probe to detect ions (protonated intermediates) in positive mode. To our delight, the ESI-MS and MS/MS data as well as accurate mass measurements were consistent with the pyridazinone **5a** and 3-pyridyl-carboxaldehyde **3g** reactants, the DBU catalyst and the product **7g** (Figure 1, see also SI). Importantly, the ions [**6g+H**]$^+$ and [**14g+2H**]$^+$ of putative intermediates **6g** and **14g**, the precursor undergoing the decarboxylative-protonation event, were clearly identified as well. Next, the coupling of ion mobility spectrometry (IMS) with MS, allowed the determination of the experimental collision cross section (CCS) values,[14] known to be chemical descriptors that give information about the shape of ionic compounds in the gas phase, increasing the identification confidence. Accordingly, the experimental $^{TW}CCS_{He}$ values match with the calculated $^{TM}CCS_{He}$ (using trajectory method) obtained from the DFT studies, which confirm the expected structures (Table 2).[15] Then, the key intermediate of the KMC sequence was highlighted and the carboxylate ion **14g** (detected as [**14g**+2H]$^+$) is, likely, the species (before the resting state) which was detected by ^{1}H NMR when reactions were performed at temperature lower than 50 °C, due to an energy demanding decarboxylation reaction (see SI).

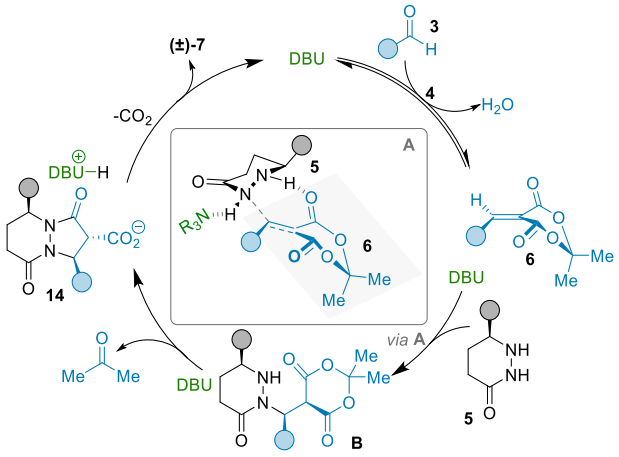
Table 2. Accurate mass measurements and CCS estimation

Ion [M+H]$^+$	Measured (*m/z*)	Mass error (ppm)	$^{TW}CCS_{He}$[a] (Å^2)	$^{TM}CCS_{He}$[b] (Å^2)
DBU	153.1389	2.6	72.8±0.4	71 ±1
3g	108.0448	3.7	63.2±0.7	56±1
5a	177.1027	2.8	79.2±0.3	77±1
7g	308.1398	1.3	108.3±0.4	109 ± 1
6g	234.0766	2.1	93.0±0.8	91±1
14g	352.1297	1.4	122.3±0.9	120±1

[a]Experimental CCS. [b]Calculated CCS.

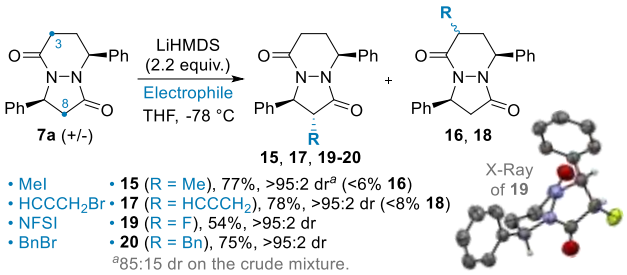
Based on the results of the ESI-MS and IMS-MS studies, we proposed the catalytic cycle depicted in Scheme 3. The first step would be a reversible DBU-promoted Knoevenagel condensation between an aldehyde **3** and Meldrum's acid **4**, yielding the alkylidene Meldrum's acid **6**. Next, a base promoted aza-Michael driven by a hydrogen-bonding takes place between **5** and **6** (via transition state **A**),[16] whose substituents of each partner are away to each other to minimize the steric repulsion to give rise to the stereoselective formation of adduct **B**. Then, a facile cyclocondensation (-acetone) would take place on the more nucleophilic secondary amine of the hydrazine function securing the first chemoselective conjugate addition and affording the ammonium carboxylate **14**. Eventually, a likely energy demanding decarboxylation of **14** can take place, followed by a protonation of the transient enolate, leading to the desired product **7**.

Scheme 3. Proposed catalytic cycle and model of induction



Then, we undertook a preliminary functionalization investigation of these novel heterocylic platforms (Scheme 4).

Scheme 4. Chemical transformations



Interestingly, by means of an excess of LiHMDS, the initially formed or more reactive five membered-ring lithium-enolate species of precursor **7a** underwent a selective methylation reaction at 8-position with 85:15 dr (**15**). The major diastereosiomer **15** was isolated with 77% yield but with a small amount of the inseparable and likely other regioisomer **16**. By means of a more sterically hindered electrophile, the propargylation reaction took place with a high >95:5 dr to give the isolated product **17** and traces of **18**. However, fluorination and benzylation reactions occurred with an excellent regio- and diastereoselectivity (>95:5 dr) to furnish the corresponding products **19** and **20** in 54% and 75% yields respectively.

CONCLUSION

In summary, a DBU-based organocatalyzed multicomponent KMC reaction highlights a key chemo-selective aza-Michael reaction of pyridazinones to alkylidene Meldrum's acid intermediates to provide a highly diastereoselective synthesis of original 1,6-diazabicyclo[4.3.0]nonane-2,7-dione derivatives. In line with preliminary promising results, the regio- and stereoselective transformation of these novel small-heterocyclic platforms is currently under investigation to move towards more complex architectures.

EXPERIMENTAL SECTION

General Information. Reactions were performed using oven dried glassware under inert atmosphere of dry argon

or nitrogen with freshly distilled or purified aldehydes. Internal NMR standards were distilled prior to use. Grignard reagents and organolithium were titrated using reported procedure prior to use. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers and were used as received. THF, PhMe, MeCN and CH_2Cl_2 were dried over MBRAUN MB SPS-800 Apparatus. Reactions were monitored by thin-layer chromatography with silica gel 60 F_{254} pre-coated aluminium plates (0.25 mm). Visualization was performed under UV light, phosphomolybdic acid or $KMnO_4$ oxidation. Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm). Melting points were measured on a WME Köfler hot-stage (Stuart SMP3) and are uncorrected. Infrared spectra (IR) were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. Liquids and solids were applied onto the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Data are reported in cm^{-1}. ^1H NMR spectra (300 MHz), $^{13}C\{^1H\}$ NMR spectra (75 MHz) and ^{19}F NMR spectra (282 Hz) were recorded on a Bruker Avance300. Data appear in the following order: chemical shifts in ppm which were referenced to the internal solvent signal, multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quadruplet; *hept*, heptuplet; *m*, multiplet, *AB*, AB system; *br*, broad), coupling constant *J* in Hertz and number of protons. Accurate Mass measurements (HRMS) were performed by the Mass Spectrometry Laboratory of the University of Rouen using a Waters LCT Premier XE mass spectrometer or a JEOL AccuTOF 4G mass spectrometer. HPLC analyses were performed with Daicel Chiralpak® columns (250 mm x 4.6 mm). A Thermo Scientific™ UltiMate™ DAD-3000 UV detector was used. X-Ray structures are depicted as thermal ellipsoids at a 50% probability level using the following colour code: C, grey; H, white; F, light green; N, light purple; O, red. The supplementary crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures/.

General procedure for the synthesis of tetrahydropyridazinone 5 by hydrazone reduction of dihydropyridazinone. 6-Substituted-4,5-dihydropyridazin-3(2*H*)-one (1 equiv) was dissolved in MeOH (0.2 M) at RT and the mixture was cooled to 0 °C. $NaBH_3CN$ (2 equiv) was added. The pH of the reaction mixture was maintained between 4 and 5 by dropwise addition of HCl (37% v/v in H_2O) and the reaction mixture was allowed to reach RT. During the required time, the pH of the reaction mixture was maintained between 4 and 5 by dropwise addition of HCl (37% v/v in H_2O). The pH of the reaction mixture was then adjusted between 8 and 9 by dropwise addition of NaOH 4 M at RT. The solution was stirred for 1 h at RT and concentrated under reduced pressure. The paste was partially dissolved in MeOH, adsorbed on silica and purified by flash column chromatography on silica gel.

*6-Phenyltetrahydropyridazin-3(2H)-one (**5a**).* The title compound was prepared according to the above general procedure from 6-phenyl-4,5-dihydropyridazin-3(2*H*)-one[17] (6.1 g, 34.8 mmol, 1 equiv) and $NaBH_3CN$ (4.4 g, 69.7 mmol, 2 equiv) in MeOH (162.0 mL, 0.2 M) at a pH between 3 and 4 in 7 h. Flash column chromatography over silica gel (CH_2Cl_2/MeOH 95:5 v/v to 90:10 v/v) afforded the title compound as a white powder (2.3 g, 38%). R_f = 0.29 (CH_2Cl_2/MeOH 95:5 v/v). ^1H NMR (300 MHz, $CDCl_3$) δ_H

7.40–7.28 (m, 5H), 7.13 (br s, 1H), 4.18 (br s, 1H), 3.99 (br s, 1H), 2.74–2.56 (m, 2H), 2.48–2.38 (m, 1H), 2.27–2.14 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 171.8 (C), 139.6 (C), 128.8 (CH), 128.0 (CH), 126.8 (CH), 57.8 (CH), 29.2 (CH_2), 29.0 (CH_2). HRMS (API/TOF): *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{13}N_2O$ 177.1023; Found 177.1030. The spectroscopic data are in agreement with literature.[17] The enantiomers were separated by semi-preparative HPLC (OJ-H, *i*PrOH/*n*-heptane 30/70, flow rate = 15.0 mL/min, *l* = 213 nm) t_R = 11.8 min (first),14.0 min (second). Both enantiomers were recovered in 99% *ee*. *Remark*: It was observed sometimes that **5a** was partially oxidize into 6-phenyl-4,5-dihydro-pyridazin-3(2*H*)-one during storage at RT.

*6-Methyltetrahydropyridazin-3(2H)-one (**5b**).* The title compound was prepared according to the above general procedure from 6-methyl-4,5-dihydropyridazin-3(2*H*)-one[18] (474.8 mg, 4.2 mmol, 1 equiv) and $NaBH_3CN$ (532.0 mg, 8.5 mmol, 2 equiv) in MeOH (19.7 mL, 0.2 M) in 6 h. Flash column chromatography over silica gel (CH_2Cl_2/MeOH 94:6 v/v) afforded the title compound as a white powder (299.4 mg, 82%). R_f = 0.17 (CH_2Cl_2/MeOH 94:6 v/v). ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.10 (br s, 1 H), 3.55 (br s, 1H), 3.14 (dtd, *J* = 9.4, 6.6, 4.2 Hz, 1H), 2.58–2.40 (m, 2H), 2.08 (dddd, *J* = 13.8, 7.1, 4.9, 4.2 Hz, 1H), 1.59 (dtd, *J* = 13.8, 9.4, 8.2 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 3H). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_5H_{11}N_2O$ 115.0866; Found 115.0863. The spectroscopic data are in agreement with literature.[19]

*Methyl 6-oxohexahydropyridazine-3-carboxylate (**5e**).* The title compound was prepared according to the above general procedure from methyl 6-oxo-4,5-dihydropyridazine-3-carboxylate[20] (760 mg, 4.87 mmol, 1 equiv) and $NaBH_3CN$ (612.1 mg, 9.7 mmol, 2 equiv) in MeOH (24.4 mL, 0.2 M) in 3 h. Flash column chromatography over silica gel (CH_2Cl_2/MeOH 94:6 v/v) afforded the title compound as a white powder (399 mg, 52%). m.p. 96–97 °C. IR (neat) ν_{max} 3261, 2963, 1675, 1401, 1222 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.81 (br s, 1 H), 4.42 (br s, 1H), 3.80 (dd, *J* = 8.5, 6.2 Hz, 1H), 3.74 (s, 3H), 2.57–2.40 (m, 2H), 2.33–2.22 (m, 1H), 2.12–2.00 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 172.6, 171.9, 56.0, 52.5, 28.5, 26.4. HRMS (API/TOF) *m/z*: $[M+MeCN+H]^+$ Calcd for $C_8H_{14}N_3O_3$ 200.1029; Found 200.1031.

tert-*Butyl 6-oxohexahydropyridazine-3-carboxylate (**5f**).* The title compound was prepared according to the above general procedure from *tert*-butyl 6-oxo-4,5-dihydro-pyridazine-3-carboxylate[21] (650 mg, 3.28 mmol, 1 equiv) and $NaBH_3CN$ (412.2 mg, 6.6 mmol, 2 equiv) in MeOH (16.4 mL, 0.2 M) in 4 h. Flash column chromatography over silica gel (CH_2Cl_2/MeOH 97:3 v/v) afforded the title compound as a white powder (353 mg, 54%). m.p. 109–110 °C. IR (neat) ν_{max} 3247, 2977, 2927, 1723, 1645, 1364, 1235, 1155, 915, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.32 (br s, 1 H), 4.13 (br s, 1H), 3.68 (dd, *J* = 8.7, 6.0 Hz, 1H), 2.58–2.41 (m, 2H), 2.32–2.21 (m, 1H), 2.09–1.97 (m, 1H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 172.4, 170.7, 82.4, 56.6, 28.6, 28.0 (3C), 26.8. HRMS (API/TOF) *m/z*: $[M+H]^+$ Calcd for $C_9H_{17}N_2O_3$ 201.1234; Found 201.1237.

General procedure for the synthesis of tetrahydropyridazinones 5 via nucleophilic addition on dihydropyridazinone. 4,5-Dihydropyridazin-3(2*H*)-one[12] (1 equiv) was introduced in dried glassware under Ar atmosphere. Three *purge-and-refill* procedures were carried out (subjected to

vacuum and then refilled with argon), then anhydrous toluene (0.1 M) was added. The mixture was stirred at 0 °C, then appropriate Grignard reagent (4 equiv) or organolithium (2.2 equiv) was added dropwise. The ice bath was removed after 10 min. After 3.5 h, the reaction was quenched at 0 °C by aqueous saturated NH_4Cl for 30 min. The reaction mixture was extracted with EtOAc (3 times). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by flash column chromatography over silica gel.

*6-Phenyltetrahydropyridazin-3(2H)-one (**5a**).* The title compound was prepared according to the above general procedure from 4,5-dihydropyridazin-3(2*H*)-one (4.9 g, 50.0 mmol, 1 equiv) and PhLi (53.7 mL, 110.0 mmol, 2.2 equiv, 2.05 M in nBu$_2$O) in anhydrous toluene (500 mL, 0.1 M). Flash column chromatography over silica gel (CH_2Cl_2/MeOH 95:5 v/v to 90:10 v/v) afforded the title compound as a white powder (3.4 g, 39%). R_f = 0.29 (CH_2Cl_2/MeOH 95:5 v/v). The spectroscopic data are in agreement with literature.[17]

*6-Ethyltetrahydropyridazin-3(2H)-one (**5c**).* The title compound was prepared according to the above general procedure from 4,5-dihydropyridazin-3(2*H*)-one (14.7 mg, 0.15 mmol, 1 equiv) and EtMgBr (140.8 µL, 0.6 mmol, 4 equiv, 4.3 M in Et_2O) in anhydrous toluene (1.5 mL, 0.1 M).. Flash column chromatography over silica gel (CH_2Cl_2/MeOH 97:3 v/v to 96:4 v/v) afforded the title compound as a yellow oil (6.5 mg, 34%). R_f = 0.16 (CH_2Cl_2/MeOH 97:3 v/v). IR (neat) ν_{max} 3227, 2964, 2934, 1639, 1400 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.08 (br s, 1H), 3.61 (br s, 1H), 2.93–2.84 (m, 1H), 2.57–2.39 (m, 2H), 2.15–2.05 (m, 1H), 1.64–1.34 (m, 3H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 172.8 (C), 56.5 (CH), 29.0 (CH_2), 28.9 (CH_2), 26.6 (CH_2), 10.9 (CH_3). HRMS (ESI/TOF) *m/z*: [M+H]$^+$ Calcd for $C_6H_{13}N_2O$ 129.1023; Found 129.1027.

*6-Allyltetrahydropyridazin-3(2H)-one (**5d**).* The title compound was prepared according to the above general procedure from 4,5-dihydropyridazin-3(2*H*)-one (147.2 mg, 1.5 mmol) and allylMgBr (6.0 mL, 6 mmol, 4 equiv, 1.0 M in Et_2O) in anhydrous toluene (15.0 mL, 0.1 M).. Flash column chromatography over silica gel (CH_2Cl_2/MeOH 95:5 v/v) afforded the title compound as a yellow oil (51.7 mg, 25%). R_f = 0.15 (CH_2Cl_2/MeOH 95:5 v/v). IR (neat) ν_{max} 3221, 2930, 1638, 911, 440 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.99 (br s, 1H), 5.88–5.74 (m, 1H), 5.16–5.12 (m, 1H), 5.09 (t, J = 1.3 Hz, 1H), 3.70 (brs, 1H), 3.14–3.05 (m, 1H), 2.58–2.40 (m, 2H), 2.33–2.19 (m, 2H), 2.17–2.05 (m, 1H), 1.73–1.59 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 172.5 (C), 134.2 (CH), 117.9 (CH_2), 54.4 (CH), 37.8 (CH_2), 28.8 (CH_2), 28.5 (CH_2). HRMS (ESI/TOF) *m/z*: [M+H]$^+$ Calcd for $C_7H_{13}N_2O$ 141.1023; Found 141.1022.

General procedure for the diastereoselective preparation of 1,6-diazabicyclo[4.3.0]nonane-2,7-diones 7. To a mixture of tetrahydropyridazin-3(2*H*)-one **5** (0.3 mmol, 1 equiv) and Meldrum's acid **4** (56.2 mg, 0.4 mmol, 1.3 equiv) under Ar, THF (3 mL, 0.1 M) and DBU (4.5 µL, 0.03 mmol, 0.01 equiv) were added. Aldehyde **3** (0.3 mmol, 1 equiv) was then introduced at room temperature. The tube was sealed, and the mixture was stirred at 50 °C (oil bath temperature) during the required time. Then the reaction mixture was allowed to reach room temperature, diluted by CH_2Cl_2 and washed with a solution of Na_2CO_3 (10% w/w in H_2O, 10 mL).

The aqueous layer was then extracted twice by CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by flash column chromatography over silica gel. Unless otherwise noted, the crude reaction mixture showed a diastereoisomeric ratio > 95:5 by means of ^1H NMR.

*5,9-Diphenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7a**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and benzaldehyde **3a** (30.5 µL, 0.3 mmol, 1 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a whitish oil (74.6 mg, 81%, >95:5 *dr*). On 1 mmol scale the product was obtained from **5a** (176.2 mg, 1.0 mmol, 1.0 equiv), Meldrum's acid **4** (187.4 mg, 1.3 mmol, 1.3 equiv) and benzaldehyde **3a** (101.7 µL, 1.0 mmol, 1.0 equiv) with DBU (15.0 µL, 0.1 mmol, 0.01 equiv) and THF (10 mL, 0.1 M) in 73% yield (222.8 mg, 73%, >95:5 *dr*). *Remark*: a small-scale reaction with enantiopure **5a** (17.0 mg, 0.1 mmol, 1 equiv, 99% *ee*) afforded the enantiopure compound **7a** as a whitish oil (11.8 mg, 40%, >95:5 *dr*, 99% *ee*). HPLC (IE, *i*PrOH/*n*-heptane = 50/50, flow rate = 1.0 mL/min, *l* = 204 nm) t_R = 13.8 (major), 15.6 (minor). R_f = 0.22 (EtOAc). IR (neat) ν_{max} 3037, 2931, 1699, 1647, 1348, 1331, 1254, 909, 696, 504 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.41–7.33 (m, 5H), 7.31–7.26 (m, 3H), 7.18–7.13 (m, 2H), 5.86 (dd, *J* = 10.5, 2.7 Hz, 1H), 5.59 (t, *J* = 5.0 Hz, 1H), 3.31 (dd, *J* = 17.4, 10.5 Hz, 1H), 2.91 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.53–2.47 (m, 2H), 2.36–2.29 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.7 (C), 165.1 (C), 139.0 (C), 137.9 (C), 129.0 (CH), 128.9 (CH), 128.5 (CH), 128.1 (CH), 126.5 (CH), 126.0 (CH), 55.1 (CH), 52.3 (CH), 37.3 (CH_2), 28.0 (CH_2), 26.1 (CH_2). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O_2$ 307.1441; Found 307.1444.

*9-(2-Methylphenyl)-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7b**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and 2-methylbenzaldehyde **3b** (34.9 µL, 0.3 mmol, 1 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a colourless oil (54.7 mg, 57%, >95:5 *dr*). R_f = 0.30 (EtOAc/MeOH 98:2 v/v). IR (neat) ν_{max} 2924, 1694, 1649, 1348, 1328, 1252, 911, 725, 699, 495, 462 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.40–7.30 (m, 5H), 7.21–7.19 (m, 2H), 7.13–7.07 (m, 2H), 5.91 (dd, *J* = 10.7, 3.5 Hz, 1H), 5.62 (t, *J* = 5.2 Hz, 1H), 3.36 (dd, *J* = 17.3, 10.7 Hz, 1H), 2.68 (dd, *J* = 17.3, 3.5 Hz, 1H), 2.71–2.29 (m, 4H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.73 (C), 165.67 (C), 137.9 (C), 137.8 (C), 134.9 (C), 131.2 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 126.5 (CH), 126.3 (CH), 124.4 (CH), 52.8 (CH), 52.7 (CH), 38.1 (CH_2), 28.4 (CH_2), 25.6 (CH_2), 19.5 (CH_3). HRMS (CI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{21}N_2O_2$ 321.1598; Found 321.1589.

*9-(3-Methylphenyl)-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7c**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and 3-methylbenzaldehyde **3c** (35.3 µL, 0.3 mmol, 1 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a yellow solid (61.5 mg, 64%, >95:5 *dr*). R_f = 0.27 (EtOAc/MeOH 98:2 v/v).

m.p. 87-89 °C. IR (neat) ν_{max} 2937, 1672, 1326, 1238, 904, 759, 700, 623, 533, 488 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.29–7.13 (m, 9H), 5.81 (dd, *J* = 10.5, 2.7 Hz, 1H), 5.60 (t, *J* = 5.0 Hz, 1H), 3.30 (dd, *J* = 17.4, 10.5 Hz, 1H), 2.88 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.54–2.49 (m, 2H), 2.36–2.28 (m, 2H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.7 (C), 165.0 (C), 139.0 (C), 138.8 (C), 137.9 (C), 129.2 (CH), 128.88 (CH), 128.85 (CH), 128.1 (CH), 127.0 (CH), 126.1 (CH), 123.6 (CH), 55.1 (CH), 52.2 (CH), 37.5 (CH_2), 28.0 (CH_2), 25.9 (CH_2), 21.5 (CH_3). HRMS (CI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{21}N_2O_2$ 321.1598; Found 321.1604.

*9-(4-Methoxyphenyl)-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7d**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and *p*-anisaldehyde **3d** (36.5 µL, 0.3 mmol, 1 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as an orange solid (64.4 mg, 64%, >95:5 *dr*). R_f = 0.19 (EtOAc). m.p. 75-76 °C. IR (neat) ν_{max} 2928, 1670, 1513, 1329, 1251, 1174, 829, 701, 523 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.34–7.23 (m, 5H), 7.16–7.11 (m, 2H), 6.92–6.87 (m, 2H), 5.82 (dd, *J* = 10.4, 2.6 Hz, 1H), 5.58 (t, *J* = 4.8 Hz, 1H), 3.82 (s, 3H), 3.28 (dd, *J* = 17.4, 10.4 Hz, 1H), 2.89 (dd, *J* = 17.4, 2.6 Hz, 1H), 2.54–2.43 (m, 2H), 2.39–2.26 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.7 (C), 164.6 (C), 159.7 (C), 138.0 (C), 131.1 (C), 128.9 (CH), 128.02 (CH), 128.00 (CH), 125.9 (CH), 114.3 (CH), 55.4 (CH), 54.6 (CH), 52.2 (CH_3), 37.1 (CH_2), 27.9 (CH_2), 26.1 (CH_2). HRMS (CI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{21}N_2O_3$ 337.1547; Found 337.1564.

*9-(4-Chlorophenyl)-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7e**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and 4-chlorobenzaldehyde **3e** (42.2 mg, 0.3 mmol, 1 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a white solid (67.5 mg, 66%, >95:5 *dr*). R_f = 0.21 (EtOAc/MeOH 98:2 v/v). m.p. 137-138 °C. IR (neat) ν_{max} 2935, 1694, 1652, 1330, 1242, 1174, 816, 704, 525, 434 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.35–7.28 (m, 7H), 7.17–7.14 (m, 2H), 5.81 (dd, *J* = 10.5, 2.8 Hz, 1H), 5.59 (t, *J* = 5.0 Hz, 1H), 3.31 (dd, *J* = 17.4, 10.5 Hz, 1H), 2.85 (dd, *J* = 17.4, 2.8 Hz, 1H), 2.54–2.49 (m, 2H), 2.37–2.29 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.3 (C), 165.1 (C), 137.7 (C), 137.5 (C), 134.3 (C), 129.1 (CH), 128.9 (CH), 128.2 (CH), 127.9 (CH), 125.9 (CH), 54.4 (CH), 52.3 (CH), 37.1 (CH_2), 28.0 (CH_2), 25.8 (CH_2). HRMS (CI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{18}ClN_2O_2$ 341.1052; Found 341,1059.

*9-(Naphthalen-2-yl)-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7f**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and 2-naphthaldehyde **3f** (46.9 mg, 0.3 mmol, 1 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a white powder (76.3 mg, 71%, >95:5 *dr*). R_f = 0.31 (EtOAc). m.p. 134-135 °C. IR (neat) ν_{max} 2968, 1690, 1641, 1344, 1241, 818, 755, 744, 704, 531, 479 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.88–7.83 (m, 2H), 7.76–7.71 (m, 2H), 7.53–7.40 (m, 3H), 7.29–7.19 (m, 5H), 6.02 (dd, *J* = 10.6, 2.7 Hz, 1H), 5.63 (br t, *J* = 5.0 Hz,

1H), 3.39 (dd, *J* = 17.4, 10.6 Hz, 1H), 2.99 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.57–2.53 (m, 2H), 2.39–2.33 (m, 2H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.7 (C), 165.3 (C), 137.9 (C), 136.3 (C), 133.2 (C), 129.2 (CH), 129.0 (CH), 128.22 (CH), 128.20 (CH), 127.8 (CH), 126.7 (CH), 126.6 (CH), 126.1 (CH), 125.4 (CH), 124.4 (CH), 55.3 (CH), 52.4 (CH), 37.5 (CH_2), 28.2 (CH_2), 26.0 (CH_2). *Remark*: one signal of a quaternary carbon is missing due to overlapping issue. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{21}N_2O_2$ 357.1598; Found 357.1594. Crystals suited for X-Ray diffraction structure determination were obtained by slow evaporation of CH_2Cl_2 in *n*-heptane. CCDC 2049517 contains the crystallographic data for this compound.

*5-Phenyl-9-(pyridin-3-yl)-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7g**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmo, 1 equiv l) and nicotinaldehyde **3g** (28.2 µL, 0.3 mmol, 1 equiv) in 16 hours. Two flash column chromatographies over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 95:5 v/v; then CH_2Cl_2/MeOH 95:5 v/v) were mandatory to afford the pure title compound as a yellow solid (60.6 mg, 66%, >95:5 *dr*). R_f = 0.17 (CH_2Cl_2/MeOH 95:5 v/v). m.p. 101-102 °C. IR (neat) ν_{max} 2929, 1695, 1643, 1349, 1332, 1298, 1254, 697, 455 cm^{-1}. ^{1}H NMR (300 MHz, CDCl3) δ_H 8.64 (d, *J* = 17.1 Hz, 2H), 7.64 (dt, *J* = 7.8, 1.6 Hz, 2H), 7.33–7.28 (m, 3H), 7.19–7.15 (m, 2H), 5.86 (dd, *J* = 10.7, 3.1 Hz, 1H), 5.61 (t, *J* = 5.0 Hz, 1H), 3.38 (dd, *J* = 17.5, 10.7 Hz, 1H), 2.89 (dd, *J* = 17.5, 3.1 Hz, 1H), 2.56–2.52 (m, 2H), 2.39–2.32 (m, 2H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.4 (C), 165.0 (C), 149.7 (CH), 148.1 (CH), 137.5 (CH), 134.7 (C), 134.0 (CH), 129.0 (CH), 128.2 (CH), 125.7 (CH), 123.6 (C), 53.1 (CH), 52.4 (CH), 36.9 (CH_2), 28.0 (CH_2), 25.7 (CH_2). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{18}N_3O_2$ 308.1394; Found 308.1402.

*5-Phenyl-9-(pyridin-4-yl)-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7h**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and isonicotinaldehyde **3h** (28.3 µL, 0.3 mmol, 1 equiv) in 16 hours. Two flash column chromatographies over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 93:7 v/v; then CH_2Cl_2/MeOH 95:5 v/v) were mandatory to afford the title compound as a yellow solid (50.0 mg, 54%, >95:5 *dr*). R_f = 0.36 (CH_2Cl_2/MeOH 95:5 v/v). m.p. 148-149 °C. IR (neat) ν_{max} 2929, 1701, 1651, 1333, 1248, 759, 704, 526, 494 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.63 (br s, 2H), 7.34–7.28 (m, 5H), 7.21–7.18 (m, 2H), 5.82 (dd, *J* = 10.9, 3.2 Hz, 1H), 5.63 (t, *J* = 5.0 Hz, 1H), 3.39 (dd, *J* = 17.5, 10.9 Hz, 1H), 2.85 (dd, *J* = 17.5, 3.2 Hz, 1H), 2.62–2.57 (m, 2H), 2.50–2.30 (m, 2H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.8 (C), 164.9 (C), 150.6 (CH), 147.7 (C), 137.4 (C), 129.1 (CH), 128.4 (CH), 125.9 (CH), 121.2 (CH), 54.1 (CH), 52.5 (CH), 36.8 (CH_2), 28.2 (CH_2), 25.7 (CH_2). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{18}N_3O_2$ 308.1394; Found 308.1404.

*9-Phenethyl-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7i**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and hydrocinnamaldehyde **3i** (39.5 µL, 0.3 mmol, 1 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a colourless oil (81.4 mg, 81%, >95:5 *dr*). R_f = 0.35 (EtOAc/MeOH 98:2 v/v). IR (neat) ν_{max} 2933, 1698, 1645, 1453, 1332, 1255, 750, 698, 559, 496 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.40–7.19 (m, 10H), 5.55 (t, *J*

= 5.1 Hz, 1H), 4.84 (dtd, *J* = 9.6, 7.2, 2.2 Hz, 1H), 2.97 (dd, *J* = 17.2, 9.6 Hz, 1H), 2.82–2.65 (m, 2H), 2.50–2.19 (m, 6H), 1.95–1.82 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.9 (C), 165.6 (C), 140.7 (C), 138.1 (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 126.3 (CH), 125.6 (CH), 52.7 (CH), 51.9 (CH), 36.2 (CH_2), 35.9 (CH_2), 32.0 (CH_2), 28.0 (CH_2), 26.2 (CH_2). HRMS (CI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{23}N_2O_2$ 335.1754; Found 335.1758.

*9-Isobutyl-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7j**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and isovaleraldehyde **3j** (32.2 µL, 0.3 mmol, 1 equiv) in 30 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a yellowish solid (52.1 mg, 61%, >95:5 *dr*). R_f = 0.57 (EtOAc/MeOH 98:2 v/v). m.p. 85-86 °C. IR (neat) ν_{max} 2950, 1685, 1325, 1226, 1167, 702, 606, 536 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.40–7.24 (m, 5H), 5.52 (t, *J* = 5.2 Hz, 1H), 4.91–4.82 (m, 1H), 2.95 (dd, *J* = 17.1, 9.4 Hz, 1H), 2.46–2.25 (m, 4H), 2.36 (dd, *J* = 17.1, 2.0 Hz, 1H), 1.83 (ddd, *J* = 13.2, 7.5, 6.5 Hz, 1H), 1.69 (hept, *J* = 6.7 Hz, 1H), 1.38 (dt, *J* = 13.2, 7.5 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 166.3 (C), 165.7 (C), 138.3 (C), 129.0 (CH), 128.0 (CH), 125.7 (CH), 52.0 (CH), 51.5 (CH), 43.3 (CH_2), 36.3 (CH_2), 28.1 (CH_2), 26.5 (CH_2), 25.0 (CH), 22.6 (CH_3), 22.5 (CH_3). HRMS (CI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{23}N_2O_2$ 287.1754; Found 287.1750.

*5-Phenyl-9-isopropyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7k**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and isobutyraldehyde **3k** (27.4 µL, 0.3 mmol, 1 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a yellowish solid (68.4 mg, 84%, >95:5 *dr*). R_f = 0.32 (EtOAc/MeOH 98:2 v/v). m.p. 94 °C. IR (neat) ν_{max} 2957, 2917, 2864, 1700, 1674, 1333, 1250, 1181, 768, 700, 527 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.40–7.27 (m, 5H), 5.49 (t, *J* = 5.6 Hz, 1H), 4.51 (ddd, *J* = 10.2, 8.3, 2.7 Hz, 1H), 2.84 (dd, *J* = 17.4, 10.2 Hz, 1H), 2.62–2.42 (m, 3H), 2.37–2.24 (m, 2H), 2.12–2.00 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 167.3 (C), 166.4 (C), 138.2 (C), 128.9 (CH), 128.1 (CH), 126.0 (CH), 58.5 (CH), 52.6 (CH), 33.4 (CH_2), 31.6 (CH), 28.7 (CH_2), 26.3 (CH_2), 19.0 (CH_3), 17.7 (CH_3). HRMS (CI/TOF): $[M+H]^+$ Calcd for $C_{16}H_{21}N_2O_2$ 273.1598; Found 273.1594. Crystals suited for X-Ray diffraction structure determination were obtained by slow evaporation of CH_2Cl_2 in *n*-heptane. CCDC 2049519 contains the crystallographic data for this compound.

*9-Cyclopropyl-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7l**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and cyclopropanecarbaldehyde **3l** (22.4 µL, 0.3 mmol, 1 equiv) in 24 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 98:2 v/v) afforded the title compound as a colourless oil (55.3 mg, 68%, >95:5 *dr*). R_f = 0.17 (EtOAc). IR (neat) ν_{max} 3004, 1698, 1643, 1348, 1333, 1244, 1020, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.40–7.28 (m, 5H), 5.55 (t, *J* = 4.9 Hz, 1H), 4.35–4.28 (m, 1H), 2.94 (dd, *J* = 17.2, 9.8 Hz, 1H), 2.52–2.42 (m, 3H), 2.31–2.24 (m, 2H), 1.33–1.21 (m, 1H), 0.73–0.58

(m, 3H), 0.40–0.34 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.9 (C), 164.8 (C), 138.3 (C), 129.0 (CH), 128.0 (CH), 125.7 (CH), 56.7 (CH), 51.9 (CH), 35.3 (CH_2), 27.8 (CH_2), 26.4 (CH_2), 15.4 (CH), 3.8 (CH_2), 2.4 (CH_2). HRMS (CI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1441; Found 271.1454.

*9-((Benzyloxy)methyl)-5-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7m**).* The title compound was prepared according to the above general procedure from **5a** (52.9 mg, 0.3 mmol, 1 equiv) and (benzyloxy)acetaldehyde **3m** (42.2 µL, 0.3 mmol, 1 equiv) in 24 hours. Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 95:5 v/v) afforded the title compound as a colourless oil (38.4 mg, 37%, >95:5 *dr*). R_f = 0.23 (EtOAc/MeOH 95:5 v/v). IR (neat) ν_{max} 3030, 2924, 2858, 1699, 1642, 1354, 1261, 1115, 1067, 751, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.43–7.29 (m, 7H), 7.23–7.09 (m, 3H), 5.60 (t, *J* = 4.3 Hz, 1H), 4.92–4.85 (m, 1H), 4.66 (d, *J* = 11.9 Hz, 1H, AB), 4.57 (d, *J* = 11.9 Hz, 1H, AB), 3.96 (dd, *J* = 9.7, 3.5 Hz, 1H), 3.60 (dd, *J* = 9.7, 3.5 Hz, 1H), 2.95 (dd, *J* = 17.3, 10.2 Hz, 1H), 2.85 (dd, *J* = 17.3, 4.2 Hz, 1H), 2.48–2.17 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.3 (C), 164.1 (C), 137.6 (C), 137.5 (C), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.82 (CH), 127.76 (CH), 125.7 (CH), 73.6 (CH_2), 69.9 (CH_2), 52.5 (CH), 52.2 (CH), 32.4 (CH_2), 27.5 (CH_2), 25.8 (CH_2). HRMS (CI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{23}N_2O_3$ 351.1703; Found 351.1704.

*5-Methyl-9-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7n**).* The title compound was prepared according to the above general procedure from 6-methyltetrahydropyridazin-3(2*H*)-one **5b** (34.2 mg, 0.3 mmol, 1 equiv) and benzaldehyde **3a** (30.5 µL, 0.3 mmol, 1 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (89% NMR yield, 82:18 *dr*). Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 97:3 v/v) afforded the title compound as a diastereo-enriched mixture as a white solid (34.7 mg, 47%, 93:7 *dr*). R_f = 0.27 for the minor diastereoisomer, 0.20 for the major diastereoisomer (EtOAc/MeOH 97:3 v/v). IR (neat) ν_{max} 1678, 1641, 1357, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.39–7.27 (m, 5H), 5.71 (dd, *J* = 10.8, 2.7 Hz, 0.89H, major diastereoisomer), 5.57 (dd, *J* = 10.8, 3.5 Hz, 0.05H, minor diastereoisomer), 4.63 (h, *J* = 6.5 Hz, 1H), 3.26 (dd, *J* = 17.2, 10.6 Hz, 1H), 2.69 (dd, *J* = 17.2, 2.7 Hz, 1H), 2.72–2.46 (m, 2H), 2.17–2.05 (m, 1H), 1.91–1.81 (m, 1H), 1.38 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 164.8 (C), 164.6 (C), 139.9 (C), 129.1 (CH), 128.3 (CH), 125.7 (CH), 55.0 (CH), 45.3 (CH), 38.4 (CH_2), 27.8 (CH_2), 26.0 (CH_2), 17.1 (CH_3). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{17}N_2O_2$ 245.1285; Found 245.1285.

*5-Ethyl-9-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7o**).* The title compound was prepared according to the above general procedure from 6-ethyltetrahydropyridazin-3(2*H*)-one **5c** (38.5 mg, 0.3 mmol, 1 equiv) and benzaldehyde **3a** (30.5 µL, 0.3 mmol, 1 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (71% NMR yield, 92:8 *dr*). Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 97:3 v/v) afforded the major diastereoisomer as a yellow oil (42.6 mg, 55%, >95:5 *dr*). R_f = 0.39 for the minor diastereoisomer, 0.24 for the major diastereoisomer (EtOAc/MeOH 97:3 v/v). IR (neat) ν_{max} 1688, 1639, 1358, 726 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.39–7.27 (m, 5H), 5.75 (dd, *J* = 10.5, 2.6 Hz, 1H),

4.45–4.37 (m, 1H), 3.26 (dd, *J* = 17.2, 10.5 Hz, 1H), 2.74 (dd, *J* = 17.2, 2.6 Hz, 1H), 2.67–2.46 (m, 2H), 2.12–1.91 (m, 2H), 1.90–1.77 (m, 1H), 1.68–1.56 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.1 (C), 164.7 (C), 139.7 (C), 129.1 (CH), 128.3 (CH), 125.8 (CH), 54.9 (CH), 50.8 (CH), 38.2 (CH_2), 27.7 (CH_2), 24.0 (CH_2), 23.6 (CH_2), 10.5 (CH_3). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{19}N_2O_2$ 259.1441; Found 259.1442.

*5-Allyl-9-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7p**).* The title compound was prepared according to the above general procedure from 6-allyltetrahydropyridazin-3(2*H*)-one **5d** (42.1 mg, 0.3 mmol, 1 equiv) and benzaldehyde **3a** (30.5 µL, 0.3 mmol, 1 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (88% NMR yield, 90:10 *dr*). Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 97:3 v/v) afforded the major diastereoisomer as a yellow oil (51.9 mg, 64%, >95:5 *dr*). R_f = 0.49 for the minor diastereoisomer, 0.25 for the major diastereoisomer (EtOAc/MeOH 98:2 v/v). IR (neat) ν_{max} 1693, 1644, 1353, 1333, 1256, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.38–7.28 (m, 5H), 5.84–5.70 (m, 1H), 5.72 (dd, *J* = 10.6, 2.9 Hz, 1H), 5.15–5.07 (m, 2H), 4.61–4.53 (m, 1H), 3.25 (dd, *J* = 17.3, 10.6 Hz, 1H), 2.73 (dd, *J* = 17.3, 2.9 Hz, 1H), 2.67–2.46 (m, 3H), 2.41–2.31 (m, 1H), 2.09–1.93 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 164.9 (C), 164.8 (C), 139.6 (C), 132.8 (CH), 129.1 (CH), 128.4 (CH), 126.1 (CH), 119.2 (CH_2), 55.0 (CH), 48.7 (CH), 38.0 (CH_2), 35.4 (CH_2), 27.6 (CH_2), 23.4 (CH_2). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}N_2O_2$ 271.1441; Found 271.1443.

*5-Methylcarboxy-9-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7q**).* The title compound was prepared according to the above general procedure from tetrahydropyridazinone **5e** (47.4 mg, 0.3 mmol, 1 equiv) and benzaldehyde **3a** (30.5 µL, 0.3 mmol, 1 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (81% NMR yield, 85:15 *dr*). Flash column chromatography over silica gel (EtOAc/MeOH 98:2 v/v) afforded the major diastereoisomer **7q** as a yellow oil (67.3 mg, 78%, >95:5 *dr*). IR (neat) ν_{max} 3488, 2954, 1743, 1702, 1647, 1351, 1258, 1213, 954, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.47–7.44 (m, 2H), 7.41–7.29 (m, 3H), 5.67 (dd, *J* = 10.8, 3.4 Hz, 1H), 5.10 (dd, *J* = 5.7, 4.1 Hz, 1H), 3.79 (s, 3H), 3.31 (dd, *J* = 17.6, 10.8 Hz, 1H), 2.77 (dd, *J* = 17.6, 3.4 Hz, 1H), 2.55–2.41 (m, 3H), 2.25–2.13 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 168.8, 165.4, 163.4, 139.9, 129.0 (2C), 128.3, 126.2 (2C), 55.6, 53.1, 51.3, 38.2, 28.5, 22.1. HRMS (API/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_4$ 289.1183; Found 289.1186.

*5-*tert*-Butylcarboxy-9-phenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7r**).* The title compound was prepared according to the above general procedure from tetrahydropyridazinone **5f** (60.1 mg, 0.3 mmol, 1 equiv) and benzaldehyde **3a** (30.5 µL, 0.3 mmol, 1 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (90% NMR yield, 94:6 *dr*). Flash column chromatography over silica gel (EtOAc/MeOH 99:1 v/v) afforded the major diastereoisomer **7r** as a yellow oil (86.5 mg, 87%, >95:5 *dr*). IR (neat) ν_{max} 2978, 1733, 1705, 1651, 1455, 1352, 1255, 1150, 842, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.50–7.47 (m, 2H), 7.41–7.28 (m, 3H), 5.65 (dd, *J* = 10.9, 3.8 Hz, 1H), 4.98 (dd, *J* = 5.7, 4.3 Hz, 1H), 3.30 (dd, *J* = 17.6, 10.9 Hz, 1H), 2.76 (dd, *J* = 17.6, 3.8 Hz, 1H), 2.58–2.51 (m, 2H), 2.47–2.38 (m, 1H), 2.21–2.08 (m, 1H), 1.49 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz,

$CDCl_3$) δ_C 167.2, 165.3, 163.5, 140.1, 128.9 (2C), 128.1, 126.1 (2C), 83.5, 55.5, 52.1, 38.3, 28.5, 28.0 (3C), 22.1. HRMS (API/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{23}N_2O_4$ 331.1652; Found 331.1649.

*5-Methyl-9-(naphthalen-2-yl)-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7s**).* The title compound was prepared according to the above general procedure from 6-methyltetrahydropyridazin-3(2*H*)-one **5b** (34.2 mg, 0.3 mmol, 1 equiv) and 2-naphthaldehyde **3f** (46.9 mg, 0.3 mmol, 1 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (100% NMR yield, 85:15 *dr*). Flash column chromatography over silica gel (EtOAc to EtOAc/MeOH 97:3 v/v) afforded the title compound as a diastereo-enriched mixture as a yellow solid (44.2 mg, 57%, 96:4 *dr*). R_f = 0.43 for the minor diastereoisomer, 0.37 for the major diastereoisomer (EtOAc/MeOH 95:5 v/v). IR (neat) ν_{max} 1673, 1329, 1179, 822, 756, 474, 408 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.87–7.75 (m, 4H), 7.52–7.46 (m, 2H), 7.38 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.87 (dd, *J* = 10.5, 2.7 Hz, 1H), 4.68 (dq, *J* = 12.1, 6.5 Hz, 1H), 3.33 (dd, *J* = 17.3, 10.5 Hz, 1H), 2.79 (dd, *J* = 17.3, 2.7 Hz, 1H), 2.72–2.48 (m, 2H), 2.14 (ddt, *J* = 13.9, 11.0, 5.8 Hz, 1H), 1.88 (ddt, *J* = 13.9, 5.8, 4.6 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 164.9 (C), 164.6 (C), 137.0 (C), 133.2 (C), 133.1 (C), 129.4 (CH), 128.1 (CH), 127.8 (CH), 126.6 (CH), 126.5 (CH), 124.9 (CH), 123.4 (CH), 55.2 (CH), 45.4 (CH), 38.2 (CH_2), 27.8 (CH_2), 26.0 (CH_2), 17.1 (CH_3). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}N_2O_2$ 295.1441; Found 295.1453. Crystals suited for X-Ray diffraction structure determination were obtained by slow evaporation of CH_2Cl_2 in *n*-heptane. CCDC 2049520 contains the crystallographic data for this compound.

*5-Methyl-9-phenethyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7t**).* The title compound was prepared according to the above general procedure from 6-methyltetrahydropyridazin-3(2*H*)-one **5b** (34.2 mg, 0.3 mmol, 1 equiv) and hydrocinnamaldehyde **3i** (39.5 µL, 0.3 mmol, 1 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (40% NMR yield, 82:18 *dr*). Flash column chromatography over silica gel (PE/EtOAc 10:90 v/v to EtOAc/MeOH 97:3 v/v) afforded the major diastereoisomer as a colourless oil (14.0 mg, 17%, >95:5 *dr*). R_f = 0.32 for the minor diastereoisomer, 0.24 for the major diastereoisomer (EtOAc/MeOH 97:3 v/v). IR (neat) ν_{max} 1693, 1639, 1361, 1338, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.31–7.28 (m, 2H), 7.21–7.17 (m, 3H), 4.75 (dtd, *J* = 9.1, 6.7, 2.2 Hz, 1H), 4.58–4.48 (m, 1H), 2.90 (dd, *J* = 17.1, 9.6 Hz, 1H), 2.68 (dd, *J* = 8.8, 7.2 Hz, 2H), 2.63–2.54 (m, 1H), 2.50-2.40 (m, 1H), 2.34 (dd, *J* = 17.1, 2.2 Hz, 1H), 2.14–2.02 (m, 2H), 1.88–1.71 (m, 2H), 1.29 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 165.5 (C), 165.1 (C), 140.8 (C), 128.7 (CH), 128.4 (CH), 126.3 (CH), 52.6 (CH), 45.1 (CH), 36.0 (CH_2), 35.7 (CH_2), 31.5 (CH_2), 28.0 (CH_2), 26.2 (CH_2), 17.1 (CH_3). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{21}N_2O_2$ 273.1598; Found 273.1603.

*5-Methylcarboxy-9-phenethyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**7u**).* The title compound was prepared according to the above general procedure from tetrahydropyridazinone **5e** (47.4 mg, 0.3 mmol, 1 equiv) and hydrocinnamaldehyde **3i** (39.5 µL, 0.3 mmol, 1 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (96% NMR yield, >95:5 *dr*). Flash column chromatography over silica gel (EtOAc/MeOH 98:2 v/v) afforded the major

diastereoisomer **7u** as a white solid (82 mg, 86%, >95:5 *dr*). m.p. 97–98 °C. IR (neat) ν_{max} 2915, 1742, 1693, 1631, 1432, 1370, 1240, 979, 757, 707 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.32–7.17 (m, 5H), 5.00 (dd, *J* = 6.0, 4.9 Hz, 1H), 4.80–4.72 (m, 1H), 3.79 (s, 3H), 2.94 (dd, *J* = 17.2, 9.6 Hz, 1H), 2.78–2.64 (m, 2H), 2.52–2.13 (m, 6H), 1.97–1.85 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 168.8, 166.0, 164.1, 140.8, 128.5 (2C), 128.4 (2C), 126.1, 53.1, 50.8, 35.42, 35.38, 31.4, 28.6, 22.5. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{21}N_2O_4$ 317.1496; Found 317.1492.

General procedure for the synthesis of 15, 17, 19 and 20. 1,6-Diazabicyclo[4.3.0]nonane-2,7-dione **(±)-7a** (61.2 mg, 0.2 mmol, 1 equiv) was dissolved in THF (2 mL, 0.067 M) under nitrogen atmosphere. The solution was cooled down to -78 °C (acetone/dry ice bath) and LiHMDS (273 µL, 2.2 equiv, 1.6 M in THF) was added dropwise. After stirring at -78 °C for 1 hour, a solution of electrophile E (0.3 mmol, 1.5 equiv) in THF (1 mL, 0.3 M) was added dropwise. The mixture was stirred at -78 °C for 1 hour, then slow return to 10 °C was initiated by removing dry ice of the bath and the mixture was stirred for an additional 16 hours. The reaction was eventually quenched with a saturated aqueous NH_4Cl solution at 0 °C and extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by flash column chromatography over silica gel to afford the product of electrophilic addition in 8 position (major product) which was in some cases obtained in an inseparable mixture with the product of addition in 3 position.

*8-Methyl-5,9-diphenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**15**).* The title compound was prepared according to the above general procedure from 1,6-diazabicyclo[4.3.0]nonane-2,7-dione **7a** and methyl iodide (18.7 µL, 0.3 mmol, 1.5 equiv) in 16 hours to give the crude product as a mixture of stereoisomers (84% NMR yield, 85:15 *dr*). Flash column chromatography over silica gel (PE/EtOAc 30:70 v/v) afforded the major diastereoisomer **15** (mixture with **16** in a 94:6 ratio) as a colourless oil (49.2 mg, 77%, >95:5 *dr*). IR (neat) ν_{max} 1695, 1650, 1329, 1249, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.33–7.18 (m, 8H), 7.17–7.10 (m, 2H), 5.54–5.51 (m, 1H), 5.23 (d, *J* = 3.7 Hz, 1H), 2.91 (ddd, *J* = 14.8, 7.4, 3.8 Hz, 1H), 2.46–2.40 (m, 2H), 2.32–2.19 (m, 2H), 1.40 (d, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 168.7, 165.5, 139.0, 137.8, 129.0 (2C), 128.9 (2C), 128.4, 128.1, 126.4 (2C), 126.0 (2C), 63.5, 52.3, 44.4, 28.0, 26.0, 16.5. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{21}N_2O_2$ 321.1598; Found 321.1602.

*5,9-Diphenyl-8-propargyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**17**).* The title compound was prepared according to the above general procedure from 1,6-diazabicyclo[4.3.0]nonane-2,7-dione **7a** and propargyl bromide (33.4 µL, 0.3 mmol, 1.5 equiv, sol. 80% w/w in PhMe) in 16 hours. Flash column chromatography over silica gel (CH_2Cl_2/Et_2O 96:4 v/v) afforded **17** (mixture with **18** in a 92:8 ratio) as a white solid (53.5 mg, 78%, >95:5 *dr*). m.p. 115–116 °C. IR (neat) ν_{max} 3240, 1700, 1651, 1493, 1454, 1349, 1325, 1257, 750, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.41–7.25 (m, 10H), 5.71 (d, *J* = 3.1 Hz, 1H), 5.66–5.63 (m, 1H), 3.11–3.06 (m, 1H), 2.89–2.73 (m, 2H), 2.56–2.51 (m, 2H), 2.40–2.33 (m, 2H), 2.10 (t, *J* = 2.6 Hz, 1H). $^{13}C\{^1H\}$ NMR

(75 MHz, $CDCl_3$) δ_C 166.3, 165.8, 139.1, 137.7, 129.1 (2C), 129.0 (2C), 128.4, 128.2, 126.3 (2C), 126.1 (2C), 79.3, 71.3, 60.4, 52.7, 48.2, 28.3, 26.2, 20.9. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{21}N_2O_2$ 345.1598; Found 345.1595.

*8-Fluoro-5,9-diphenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**19**).* The title compound was prepared according to the above general procedure from 1,6-diazabicyclo[4.3.0]nonane-2,7-dione **7a** (30.6 mg, 0.1 mmol, 1 equiv) and NFSI (63.1 mg, 2 equiv, 0.2 mmol) in 4 hours. Flash column chromatography over silica gel (PE/EtOAc 70:30 v/v to 60:40 v/v) afforded **19** as a white solid (17.5 mg, 54%, >95:5 *dr*). m.p. 104–105 °C. IR (neat) ν_{max} 1727, 1686, 1322, 1173, 758, 725, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.38–7.31 (m, 6H), 7.27–7.22 (m, 4H), 5.81 (d, J_{HF} = 27.6 Hz, 1H), 5.62 (t, J = 5.4 Hz, 1H), 5.19 (dd, J_{HF} = 51.7, J_{HH} = 1.3 Hz, 1H), 2.72–2.58 (m, 2H), 2.55–2.41 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 166.6 (C), 160.2 (C) (d, J_{CF} = 21.5 Hz), 137.0 (C), 134.5 (C) (d, J = 10.7 Hz), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.6 (CH), 126.4 (CH), 126.2 (CH), 92.2 (CH) (d, J_{CF} = 191.5 Hz), 62.0 (CH) (d, J_{CF} = 23.8 Hz), 53.4 (CH), 28.5 (CH_2), 26.2 (CH_2). HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{18}FN_2O_2$ 325.1347; Found 325.1353. Crystals suited for X-Ray diffraction structure determination were obtained by slow evaporation of CH_2Cl_2 in *n*-heptane. CCDC 2049518 contains the crystallographic data for this compound.

*8-Benzyl-5,9-diphenyl-1,6-diazabicyclo[4.3.0]nonane-2,7-dione (**20**).* The title compound was prepared according to the above general procedure from 1,6-diazabicyclo[4.3.0]nonane-2,7-dione **7a** and benzyl bromide (35.7 µL, 0.3 mmol, 1.5 equiv) in 16 hours. Flash column chromatography over silica gel (PE/EtOAc 60:40 v/v) afforded the major diastereoisomer **20** as a white solid (59.3 mg, 75%, >95:5 *dr*). m.p. 133–134 °C. IR (neat) ν_{max} 1692, 1651, 1454, 1364, 1260, 886, 751, 731, 700, 669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.40–7.24 (m, 11H), 7.20–7.12 (m, 4H), 5.62 (d, J = 2.0 Hz, 1H), 5.46–5.43 (m, 1H), 3.28–3.23 (m, 1H), 3.22–3.18 (m, 2H), 2.35–2.23 (m, 1H), 2.19–2.03 (m, 2H), 1.82–1.70 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C 167.3, 164.7, 138.9, 137.7, 136.3, 129.7 (2C), 128.9 (2C), 128.84 (2C), 128.80 (2C), 128.2, 128.0, 127.4, 126.2 (2C), 126.0 (2C), 59.6, 52.1, 50.7, 36.8, 27.5, 25.5. HRMS (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{25}N_2O_2$ 397.1911; Found 397.1920.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

Full experimental details, spectral characterization and crystallographic data.

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The authors declare no competing financial interest.

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