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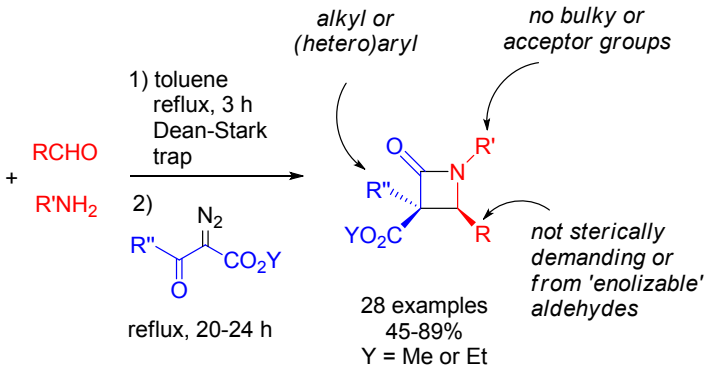


ABSTRACT: Thermally promoted reaction of α-acyl-α-diazoacetates with imines has been investigated. The transformation, earlier reported predominantly under transition metal catalyzed conditions, delivers α-alkoxycarbonyl-substituted β–lactams with outstanding diastereoselectivity. DFT calculations performed in order to evaluate energetically feasible reaction pathways revealed the intermediacy of 1,3-oxazin-4-one intermediates hitherto never implicated in the Staudinger synthesis of β-lactams.

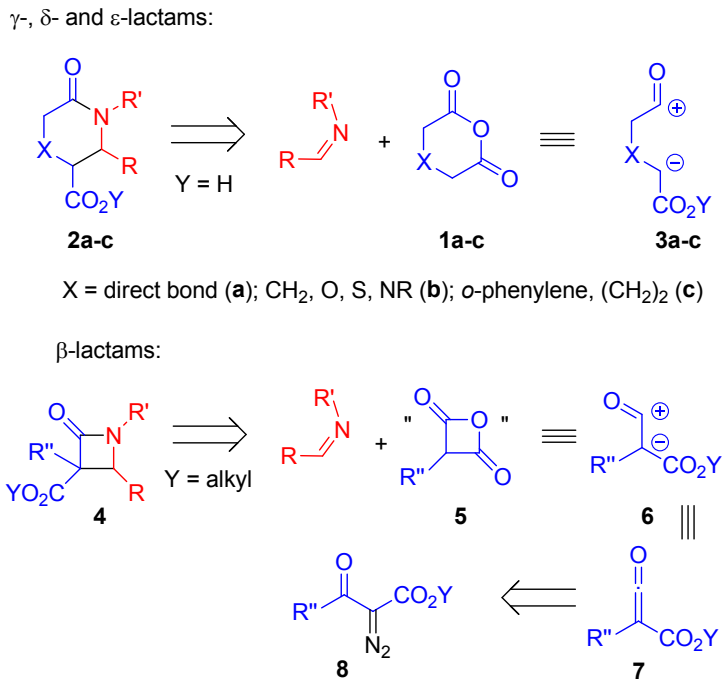
INTRODUCTION

Thermally promoted cyclocondensation of imines with various dicarboxylic acid anhydrides **1a-c** (exemplifying only a portion of the feasible reagent scope[1]) has been a prolific source of polysubstituted lactam carboxylic acids **2a-c** and their derivatives dubbed the Castagnoli-Cushman reaction.[2] In these practically convenient transformations, carried out at ambient or, more frequently, elevated temperatures, anhydrides **1a-c** essentially manifest themselves as 1,3-, 1,4- and 1,5-dipolar synthons **3a-c**, delivering δ- and γ-lactams[3] (including heteroatom-containing variants of the latter[4]) as well as recently reported ε-lactams,[5] respectively. Retrosynthetic analysis of similarly substituted β-

lactams **4**, however, breaks them down to imines and difficult-to-obtain and unstable[6] malonic anhydrides **5**. The latter, being essentially synthetic equivalents of 1,2-dipolar synthons **6**, can be visualized as ketenes **7** obtainable, in principle, *via* the Wolff rearrangement of respective α-acyl-α-diazoacetates **8** (Figure 1).

The literature analysis revealed that the overwhelming majority of reported β-lactam syntheses which exploit the disconnection in question, involve generating ketenes such as **7** *via* Rh(II) carbenes[7] which, in our view, somewhat tarnishes this approach compared to the convenience and practical simplicity of the catalyst-free Castagnoli-Cushman chemistry. Considering that there are also examples involving thermally[8] and photochemically[9] generated ketenes **7** in the literature, we set off to investigate the feasibility of thermally promoted cyclocondensation of α-acyl-α-diazoacetates **8** with imines as an entry into β-lactam scaffold. In light of the prominence of β-lactams in antibacterial drug design[10] (as well as other target areas[11]) and the recently described approach to various diazo compounds in array fashion,[12] a practically simple, catalyst-free method toward this classical cores would be highly beneficial both from early discovery and process chemistry prospective.[13] Herein, we present the results of these studies.

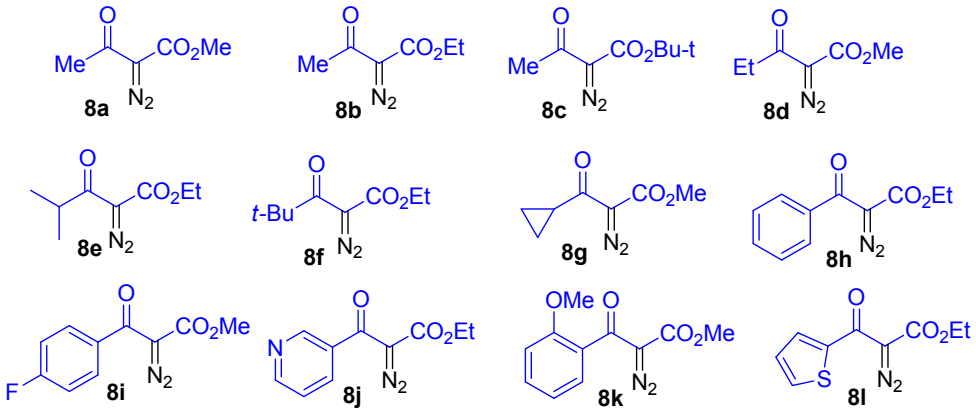
Figure 1. Polysubstituted lactam carboxylic acid derivatives of various sizes accessed via condensation reactions of imines.



RESULTS AND DISCUSSION

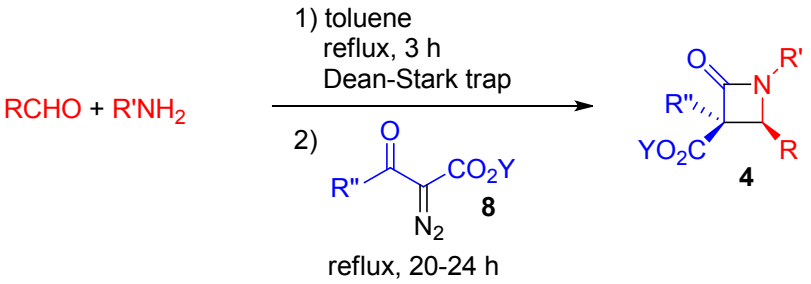
The initial attempt to realize the thermal cyclocondensation of methyl α-acetyl-α-diazoacetate (**8a**) with an imine generated *in situ* turned out to be successful and was performed as follows. Benzylamine and *p*-tolualdehyde were reacted in refluxing toluene for 3 h (with a Dean-Stark trap to allow separation of water to drive the imine formation forward) at which point diazo compound **8a** was added and after additional 24 h, anticipated β-lactam compound **4a** was isolated as a single *cis*-diastereomer as was confirmed by single-crystal X-ray analysis. Such a remarkable diastereoselectivity drew our attention and needed to be understood from the mechanistic perspective (*vide infra*). A somewhat lower yield of **4a** (66%) was obtained in a microwave-promoted reaction of **8a** with the same preformed imine, however, over a substantially shorter period of time (1 h). Considering the clear yield advantage offered by conventional heating, such a procedure was employed throughout the subsequent study aimed at evaluating the scope of various amine/aldehyde combinations in thermally promoted cyclocondensation with diazo compounds **8a-l** involving the Wolff rearrangement of the latter (Figure 2).

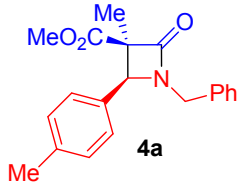
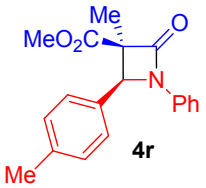
Figure 2. α-Acyl-α-diazoacetates **8** employed in this study.

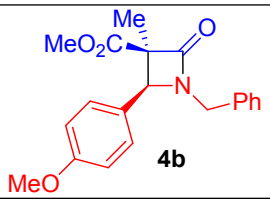
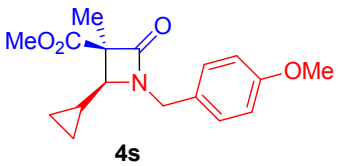
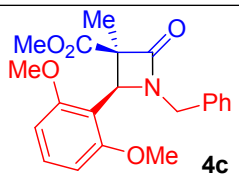
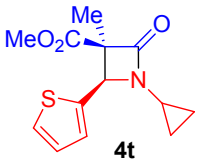
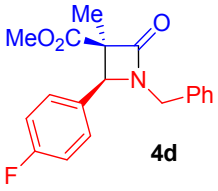
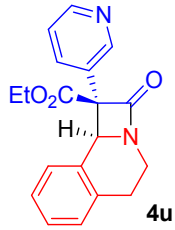
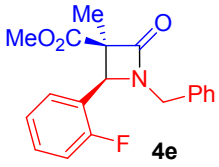
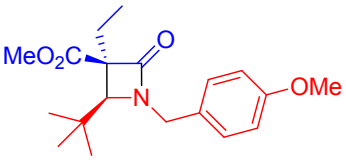
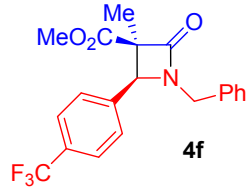
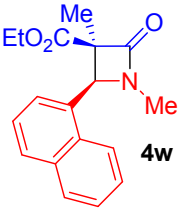
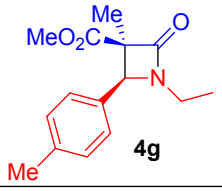
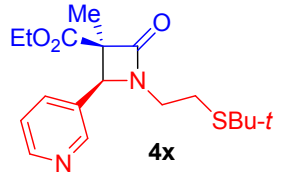
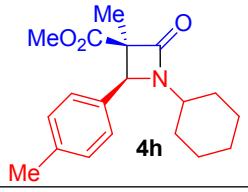
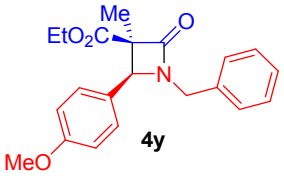
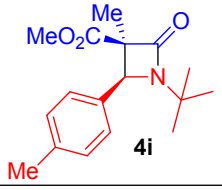
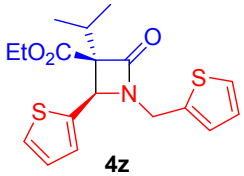
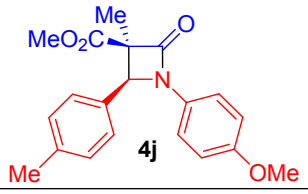
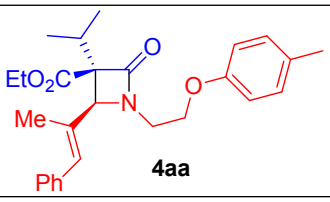


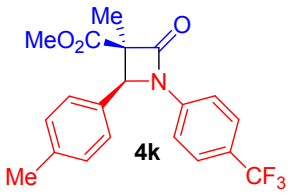
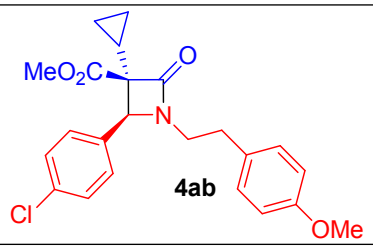
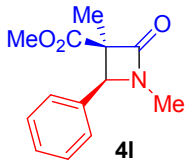
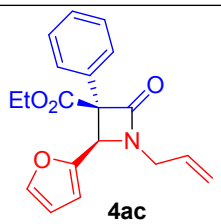
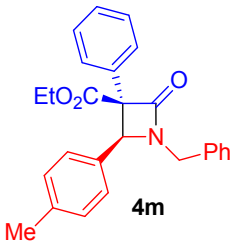
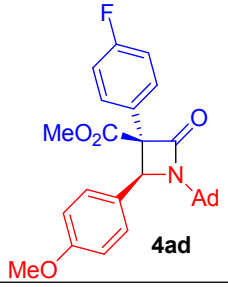
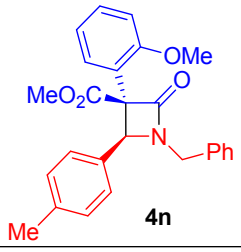
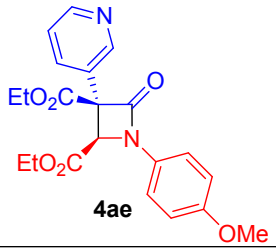
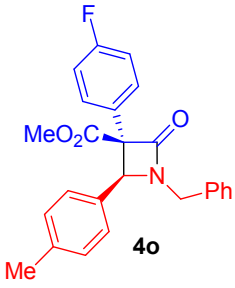
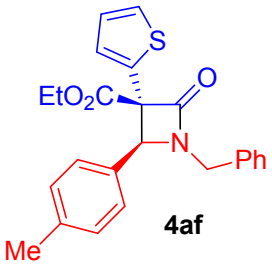
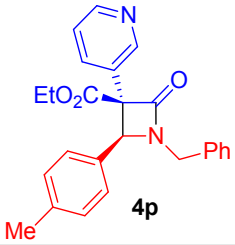
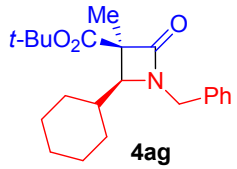
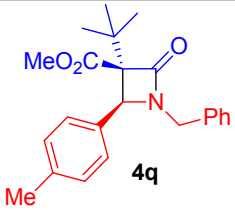
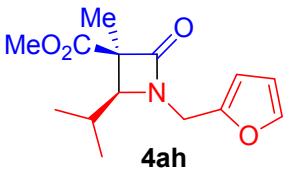
To our delight, the β-lactams **4** successfully synthesized in this study, were obtained almost exclusively (except for compounds **4e-f**) as a single diastereomer which was confirmed by single X-ray crystallography to have the carboxylic ester (CO_2Y) and the aldehyde-derived R group on the same face of the β-lactam ring (Table 1). The imine procedure had to be modified slightly when either the aldehyde or the amine were volatile and did not permit the imine formation in refluxing toluene. In these cases, the imine was pre-formed by reacting the aldehyde and the amine at room temperature in the presence of 4Å molecular sieves and filtering the latter off.

Table 1. β-Lactams **4** investigated in this study.



Entry	**8**	Product	Yield, %	Entry	**8**	Product	Yield, %
1	**8a**	 **4a**	86[a]	18	**8a**	 **4r**	81

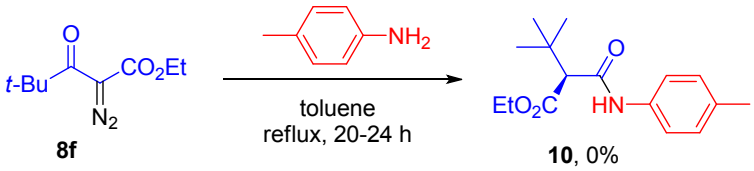
2	**8a**	 **4b**	86	19	**8a**	 **4s**	65
3	**8a**	 **4c**	**0**	20	**8a**	 **4t**	53[d]
4	**8a**	 **4d**	71	21	**8j**	 **4u**	50[a,d]
5	**8a**	 **4e**	57[b]	22	**8d**	 **4v**	**0**[d]
6	**8a**	 **4f**	57[c]	23	**8b**	 **4w**	51[d,e]
7	**8a**	 **4g**	70[d]	24	**8b**	 **4x**	71
8	**8a**	 **4h**	60[d]	25	**8b**	 **4y**	89
9	**8a**	 **4i**	**0**[d]	26	**8e**	 **4z**	82
10	**8a**	 **4j**	61[a]	27	**8e**	 **4aa**	63[d]

11	**8a**	 **4k**	**0**	28	**8g**	 **4ab**	45[f]
12	**8a**	 **4l**	57[d]	29	**8h**	 **4ac**	76
13	**8h**	 **4m**	87	30	**8i**	 **4ad**	68[d,g]
14	**8k**	 **4n**	71	31	**8j**	 **4ae**	77[e]
15	**8i**	 **4o**	85	32	**8l**	 **4af**	65%
16	**8j**	 **4p**	73	33	**8c**	 **4ag**	**0**[h]
17	**8f**	 **4q**	**0**	34	**8a**	 **4ah**	**0**[i]

[a]Structure confirmed by single-crystal X-ray analysis. [b]Contains traces of the other diastereomer. [c]*dr* 8.2:1.0. [d] Imine prepared in a separate step. [e]Additional 1.0 equiv. of **8c** was added after 9 h. [f]Additional 0.5 equiv. of **8g** was added after 18 h. [g]Ad = 1-adamantyl. [h]Enamide by-product **12** isolated in 22% yield and characterized. [i]Enamide and malonic monoamide were the observed by-products (not isolated).

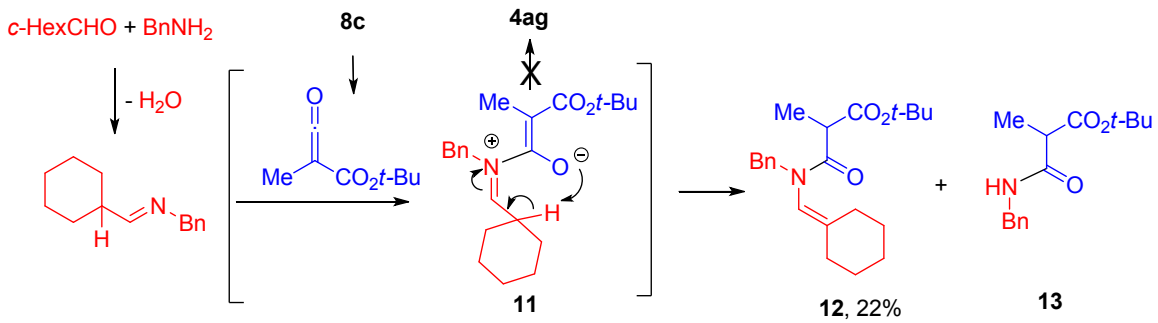
The successful Wolff rearrangement (with subsequent 'trapping' of the ketene intermediate with imine) apparently involved not only migration of primary and secondary alkyl (e. g., Me, Et, *i*-Pr) but also cyclopropyl as well as various (hetero)aryl groups. The reaction was remarkably sensitive to the steric effects in the aldehyde and the amine portion (*cf.* **4c**, **4v**, **4ag -** and **4i**, respectively, which failed to form) as well as electronic effects in the amine portion - *cf.* attempted preparation of **4k** where introducing electron-withdrawing group at the aniline made the formation of β-lactam ring ineffective. The failure of compound **4q** to form is likely attributable to the reluctance of **8f** to enter the Wolff rearrangement, as could be preliminarily concluded based on the absence of a typical ketene-derived anilide **10** when **8f** was reacted under the same conditions with *p*-toluidine (Scheme 1).

Scheme 1. Evidence for ineffective Wolff rearrangement of **8f**.



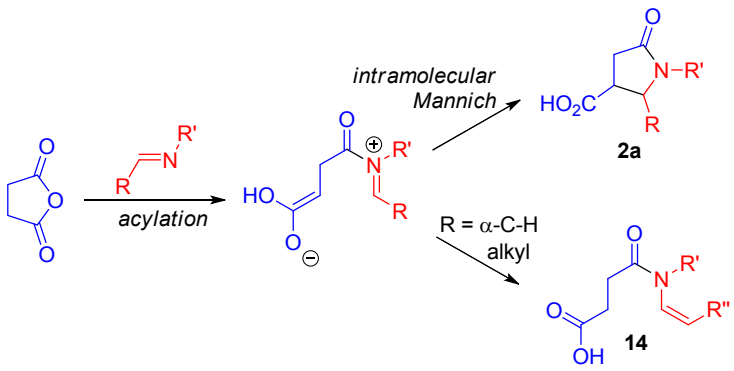
A substantial limitation of the reaction scope discovered in the course of these studies was the inability of enolizable α-C-H imines to give the expected β-lactam products (*cf.* **4ag**). In this case, the principal products (derived, presumably, from betaine **11**) are enamide **12** and malonic monoamide **13** (not isolated) thought to be the product of hydrolysis of **12** by adventitious water (Scheme 2). Similar outcome was observed in the attempt to prepare compound **4ah**.

Scheme 2. Reaction of an enolizable α-C-H imine with compound **8c** under thermal conditions.



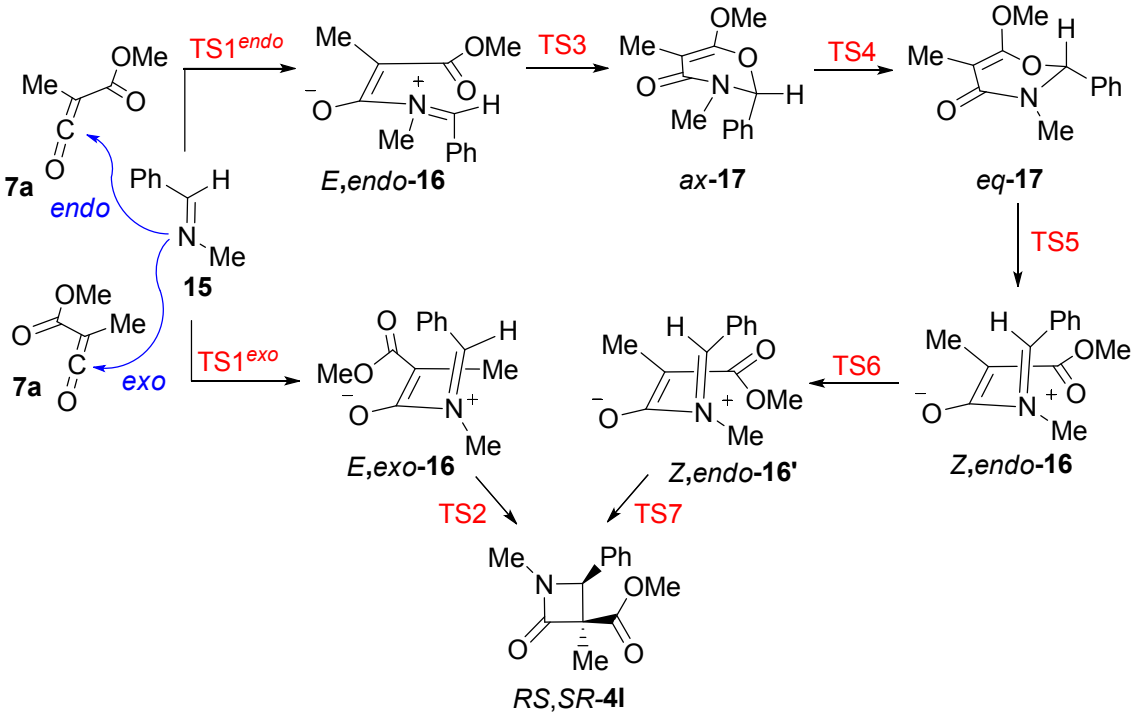
The apparent sensitivity of the β-lactam formation to the availability of the imine nitrogen atom for acylation (in steric as well as electronic sense) and the failure to obtain β-lactams from α-C-H imines argues for the importance of the stepwise formation of the β-lactam ring involving acylation (rather than concerted [2+2]-cycloaddition). Moreover, it allows drawing an almost exact analogy between the β-lactam syntheses described herein and the Castagnoli-Cushman reaction of succinic anhydride (an exemplary dicarboxylic acid anhydride) which proceeds with 'non-enolizable' imines under nearly the same conditions as described herein, to give γ-lactams **2a** *via N*-acylation/intramolecular Mannich sequence[14] and fails to give **2a** with α-C-H imines, delivering enamides **14**[4,15] (similar to **12**) instead (Scheme 3).

Scheme 3. Mechanistically relevant formation of γ-lactams **2a** and enamides **14**.



In order to verify the validity of this mechanistic interpretation, preliminarily devised from the experimental facts, as well as to understand the origin of the high diastereoselectivity observed in the formation of β-lactams **4**, we performed DFT calculations of the possible reaction pathways (Scheme 4) and the associated energy profiles (Figure 3) for the interaction of imine **15** and ketene **7a** (derived from diazo compound **8a**) *en route* to β-lactam *RS*,*SR*-**4l**.

Scheme 4. Plausible mechanistic interpretation for the formation of compound *RS*,*SR*-**4l**



Imine **15** can approach ketene **7a** from *endo* or *exo* directions leading, *via* TS1^{endo} and TS1^{exo} transition states, to two alternative betaine adducts – *E,endo*-**16** and *E,exo*-**16**, respectively. The free energy levels of TS1^{endo} and TS1^{exo} are very close. However, *E,endo*-**16** betaine adduct is substantially lower in energy compared to *E,exo*-**16**. Rotation around the C=N bond in betaine *E,exo*-**16** results in the direct formation of lactam *RS,SR*-**4l** proceeding *via* transition state TS2. However, the energy of TS2 is overly high for this pathway to be realized under the reaction conditions. Alternatively, the more stable *E,endo*-**16** betaine adduct can be converted into *RS,SR*-**4l**. Such a reaction pathway turns out to be energetically more favorable, despite its multistep character. Indeed, this transformation includes the successive formation of oxazinones *ax*-**17** and *eq*-**17** which are nearly equal in energy and differ only by the axial and equatorial position of the phenyl group. Subsequent evolution of oxazinone *eq*-**17** proceeds with ring opening to give betaine *Z,endo*-**16** (*Z* arrangement of the Ph and Me groups) which undergoes a sigma-bond rotation of the methoxycarbonyl group (passing through a surprisingly high energy barrier TS6) and finally cyclizes, *via* TS7, to give the sole observed diastereomer *RS,SR*-**4l**, with the highest negative free energy change of all the above elementary steps.

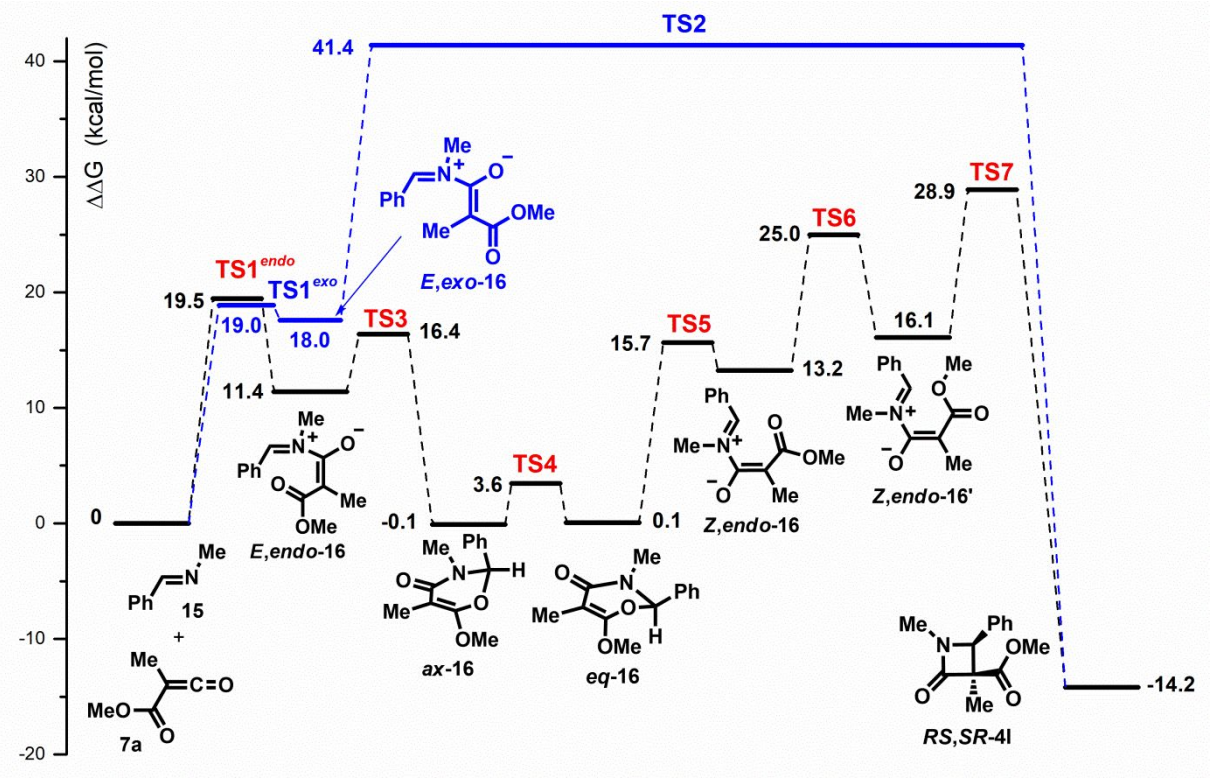
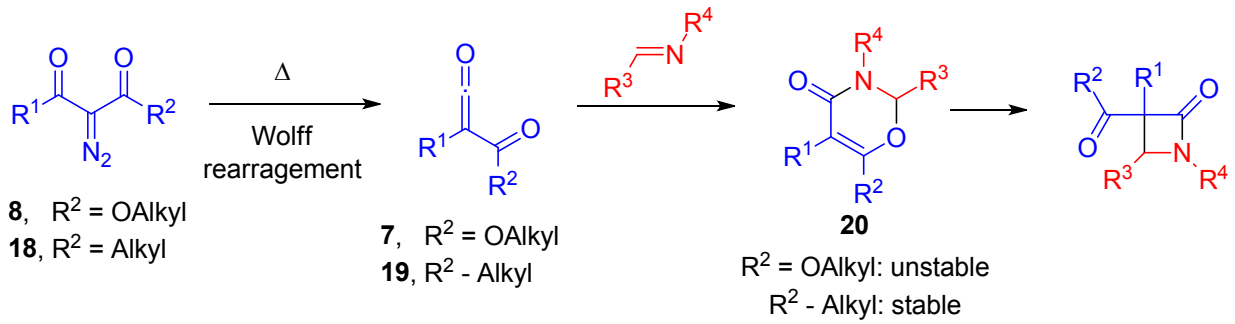


Figure 3. Energy profile (Gibbs free energies) obtained by DFT wb97xd/cc-pvtz calculations (PCM, toluene, 383 K) for cycloaddition of imine **15** to ketene **7a**.

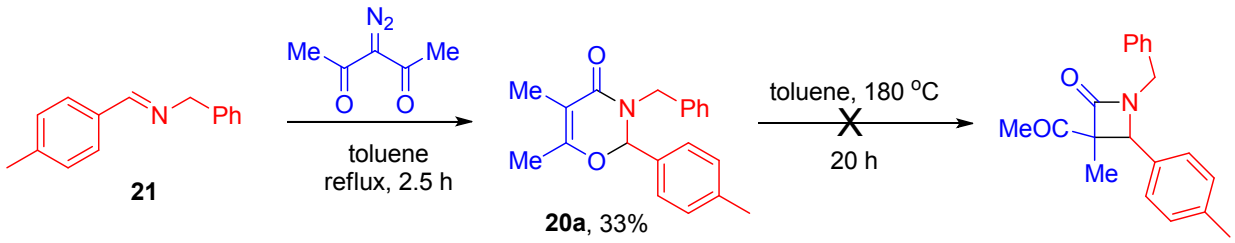
Besides rationalizing the formation of the sole observed diastereomer of **4l**, these DFT calculations reveal the following significant mechanistic clue. Oxazinones analogous to **17** are commonly isolable products in the reactions of imines with acyl ketenes derived from α-diazo-β-diketones.[7a,16] However, their formation has never been implicated in the observed Staudinger-type reactions of imines. The mechanistic picture involving the formation of the oxazinone intermediate can potentially unify the two types of reactions – those of ketenes **7** derived from α-acyl-α-diazoacetates **8** - and of ketenes **19** formed *via* the Wolff rearrangement of α-diazo-β-diketones **18**. If oxazinones **20** are indeed the true intermediates in both cases, their propensity to give β-lactams via ring opening and 1,4-recyclization can be attributed to the destabilization by the R^2 alkoxy substituent while alkyl-substituted oxazinones **20** are stable, isolable adducts (Figure 4).

Figure 4. Plausible unified mechanistic interpretation for the reactions of imines with ketenes.



The proposed mechanistic interpretation requires further investigation. Preliminarily, we synthesized oxazinone **20a** and attempted to observe its transformation under forcing conditions. However, the only observed product was the starting imine **21** and not the β-lactam in question (Scheme 5).

Scheme 5. Preparation and attempted thermal transformation of oxazinone **20a**.



In summary, we have investigated thermally-promoted reaction of α-acyl-α-diazoacetates with imines which proceeds *via* the Wolff rearrangement and formation of the respective ketenes. The reaction is conveniently conducted with imines prepared *in situ* or in a separate step in refluxing toluene and delivers densely substituted β-lactams with remarkable diastereoselectivity. Compared to the majority of the literature reports involving such transformations, the approach does not involve generating a transition metal (Rh(II)) carbene and is, therefore, more amenable to pharmaceutical production. The reaction can be viewed as a mechanistic congener of the Castagnoli-Cushman reaction of imines and cyclic anhydrides and suffers from similar side-reactions and limitations. Mechanistic analysis of energetically feasible reaction pathways using DFT calculations revealed the intriguing intermediacy of oxazinone species which are known as stable and isolable products in reactions on imines with ketenes derived from α-diazo-β-diketones. The transformation of oxazinone intermediates into β-

lactams *via* ring opening/ring closure requires further experimental investigation which is currently underway in our laboratories.

EXPERIMENTAL SECTION

General information. NMR spectra were acquired with a 400 MHz Bruker Avance III spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in $CDCl_3$ and were referenced to residual solvent proton signals (δH = 7.26) and solvent carbon signals (δC = 77.16). Melting points were determined with a melting point apparatus Stuart SMP 50 in open capillary tubes. Mass spectra were acquired with a Bruker maXis HRMS-ESI-qTOF spectrometer (electrospray ionization mode, positive ions detection). X-ray single crystal analyses were performed on Agilent Technologies «Xcalibur» and «Supernova» diffractometers with monochromated Mo Kα or Cu Kα radiation, respectively. The temperature was kept at 129 (**4a**) or 100 K (**4j, 4u**) during data collection. Using Olex2, the structure was solved with the olex2.solve structure solution program using Charge Flipping and refined with the olex2.refine refinement package using Gauss-Newton minimization[17]. Column chromatography was carried out on silica gel grade 60 (0.040−0.063 mm) 230−400 mesh. Diazocompounds **8** were prepared according to SAFE-protocol[18]. Aldehydes, amines and solvents were obtained from commercial sources and were used without further purification.

General procedure for preparation of lactams 4

In a 25 mL round-bottom flask, an amine (0.8 mmol, 1 eq.) and an aldehyde (0.9 mmol, 1.1 eq.) were dissolved in 10 mL toluene and refluxed with azeotropic removal of water. After one hour, half of the solvent was distilled off and an α-acyl-α-diazoacetate (**8a-l**, 1.0 mmol, 1.2 eq.) was added. The mixture was then refluxed overnight and the reaction progress was followed via TLC. When no more diazo compound was detectable (20-24h), the solvent was evaporated in vacuo and the resulting mixture was purified by column chromatography on silica gel with a linear gradient (0-20%) of acetone in hexane (total volume of eluent - 450 mL) to provide pure compounds **4**.

*(±) (3R,4S)-Methyl 1-benzyl-3-methyl-2-oxo-4-(p-tolyl)azetidine-3-carboxylate (**4a**)*: yield 222 mg, 86%; white powder; mp 112,5-114,0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 3H), 7.21 – 7.16 (m, 4H), 7.15 – 7.07 (m, 2H), 5.01 (d, *J* = 14.9 Hz, 1H), 4.21 (s, 1H), 3.92 (d, *J* = 14.9 Hz, 1H), 3.35 (s, 3H), 2.37 (s, 3H), 1.63 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.1, 167.2, 138.6, 135.1, 130.8, 129.2, 128.9, 128.5, 127.9, 126.8, 66.7, 65.5, 51.7, 44.6, 21.2, 17.2 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{21}NO_3Na$ 346.1414; Found 346.1419.

*(±) (2S,3R)-Methyl 1-benzyl-2-(4-methoxyphenyl)-3-methyl-4-oxoazetidine-3-carboxylate (**4b**)*: yield 234 mg, 86%; light yellow powder; mp 134 – 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 3H), 7.19 – 7.14 (m, 4H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.99 (d, *J* = 14.9 Hz, 1H), 4.20 (s, 1H), 3.92 (d, *J* = 14.9 Hz, 1H), 3.83 (s, 3H), 3.37 (s, 3H), 1.63 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.1, 167.1, 160.0, 135.1, 128.9, 128.5, 128.2, 127.9, 125.6, 113.9, 66.7, 65.3, 55.3, 51.8, 44.5, 17.1 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{21}NNaO_4$ 362.1363; Found 362.1367.

*(±) (2S,3R)-Methyl 1-benzyl-2-(4-fluorophenyl)-3-methyl-4-oxoazetidine-3-carboxylate (**4d**)*: yield 187 mg, 71%; white powder; mp 84 − 86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 3H), 7.26 – 7.11 (m, 4H), 7.06 (t, *J* = 8.6 Hz, 2H), 4.99 (d, *J* = 14.9 Hz, 1H), 4.22 (s, 1H), 3.93 (d, *J* = 14.9 Hz, 1H), 3.36 (s, 3H), 1.63 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.8, 166.9, 162.9 (d, *J* = 248.1 Hz), 134.9, 129.7 (d, *J* = 3.2 Hz), 129.0, 128.6 (d, *J* = 8.3 Hz), 128.5, 128.0, 115.6 (d, *J* = 21.7 Hz), 66.8, 64.9, 51.8, 44.7, 17.1 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{18}FNNaO_3$ 350.1163; Found 350.1175.

*(±) (2R,3R)-Methyl 1-benzyl-2-(2-fluorophenyl)-3-methyl-4-oxoazetidine-3-carboxylate (**4e**)*: yield 154 mg, 57%; yellow powder; mp 71 − 72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 5H), 7.17 – 7.04 (m, 3H), 7.03 – 6.91 (m, 1H), 4.94 (d, *J* = 14.8 Hz, 1H), 4.51 (s, 1H), 3.92 (d, *J* = 14.9 Hz, 1H), 3.24 (s, 3H), 1.59 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.9, 167.3, 161.1 (d, *J* = 248.2 Hz), 135.0, 130.3 (d, *J* = 8.3 Hz), 129.1, 128.6, 128.2, 127.4 (d, *J* = 3.5 Hz), 124.0 (d, *J* = 3.8 Hz), 121.9 (d, *J* = 13.1 Hz), 115.7 (d, *J* = 20.9 Hz), 66.7, 59.0 (d, *J* = 5.0 Hz), 51.9, 45.3, 16.9 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}FNO_3$ 328.1343; Found 328.1353.

*(±) (3R,4S)-Methyl 1-benzyl-3-methyl-2-oxo-4-(4-(trifluoromethyl)phenyl)azetidine-3-carboxylate (**4f**)*: yield 172 mg, 57%; light yellow powder; mp 79 − 81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.44 – 7.29 (m, 5H), 7.17 (dd, *J* = 7.1, 2.2 Hz, 2H), 5.02 (d, *J* = 14.9 Hz, 1H), 4.28 (s, 1H), 3.95 (d, *J* = 14.8 Hz, 1H), 3.32 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.5, 166.8, 138.3, 134.6, 131.0 (q, *J* = 32.6 Hz), 129.0, 128.5, 128.2, 127.3, 125.5 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.3 Hz), 67.0, 64.9, 51.9, 45.0, 17.2 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{18}F_3NNaO_3$ 400.1131; Found 400.1144.

*(±) (3R,4S)-Methyl 1-ethyl-3-methyl-2-oxo-4-(p-tolyl)azetidine-3-carboxylate (**4g**)*: yield 146 mg, 70%; light yellow powder; mp 43 − 45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 4H), 4.45 (s, 1H), 3.66 (dq, *J* = 14.7, 7.4 Hz, 1H), 3.33 (s, 1H), 3.06 (dq, *J* = 14.3, 7.2 Hz, 1H), 2.36 (s, 3H), 1.70 (s, 3H), 1.16 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.2, 167.1, 138.7, 131.3, 129.2, 126.7, 66.3, 65.9, 51.7, 35.5, 21.2, 17.5, 12.6 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}NNaO_3$ 284.1257; Found 284.1261.

*(±) (3R,4S)-Methyl 1-cyclohexyl-3-methyl-2-oxo-4-(p-tolyl)azetidine-3-carboxylate (**4h**)*: yield 150 mg, 60%; beige powder; mp 68 - 70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.41 (s, 1H), 3.44 (ddd, *J* = 15.3, 7.7, 3.8 Hz, 1H), 3.34 (s, 3H), 2.35 (s, 3H), 2.09 – 2.03 (m, 1H), 1.92 – 1.84 (m, 1H), 1.83 – 1.76 (m, 1H), 1.72 – 1.64 (m, 2H), 1.66 (s, 3H), 1.62 – 1.56 (m, 1H), 1.34 – 1.02 (m, 4H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.3, 167.4, 138.6, 132.5, 129.0, 126.8, 65.7, 65.5, 53.1, 51.7, 31.2, 30.5, 25.19, 25.17, 25.0, 21.2, 17.7 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{26}NO_3$ 316.1907; Found 316.1904.

*(±) (3R,4S)-Methyl 1-(4-methoxyphenyl)-3-methyl-2-oxo-4-(p-tolyl)azetidine-3-carboxylate (**4j**)*: yield 164 mg, 61%; beige powder; mp 173 − 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.23 (m, 2H), 7.20 – 7.05 (m, 4H), 6.92 – 6.70 (m, 2H), 4.85 (s, 1H), 3.78 (s, 3H), 3.32 (s, 3H), 2.35 (s, 3H), 1.81 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.9, 163.8, 156.3, 138.7, 131.0, 130.5, 129.2, 126.7, 118.6, 114.3, 66.3, 65.9, 55.5, 51.8, 21.2, 17.6 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{21}NNaO_4$ 362.1363; Found 362.1380.

*(±) (3R,4S)-methyl 1,3-dimethyl-2-oxo-4-phenylazetidine-3-carboxylate (**4l**)*: yield 133 mg, 57%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 3H), 7.25 (dd, *J* = 7.9, 1.7 Hz, 2H), 4.42 (s, 1H), 3.28 (s, 3H), 2.92 (s, 3H), 1.72 (s, 3H).ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169, 167.3, 134.0, 128.8, 128.6, 126.7, 68.3, 67.2, 51.7, 27.6, 17.4 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_3$ 234.1125; Found 234.1126.

*(±) (3R,4S)-Ethyl 1-benzyl-2-oxo-3-phenyl-4-(p-tolyl)azetidine-3-carboxylate (**4m**)*: yield 279 mg, 87%; light yellow powder; mp 89,5 – 91,5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.55 (m, 2H), 7.41 – 7.30 (m, 3H), 7.24 – 7.18 (m, 7H), 7.10 – 7.01 (m, 2H), 4.98 (d, *J* = 15.0 Hz, 1H), 4.75 (s, 1H), 3.96 (d, *J* = 15.0 Hz, 1H), 3.86 – 3.68 (m, 2H), 2.37 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.2, 165.2, 139.0, 135.1, 135.0, 131.1, 129.6, 128.9, 128.7, 128.4, 128.2, 127.9, 127.6, 127.3, 74.1, 66.0, 61.6, 44.6, 21.3, 13.7 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{25}NNaO_3$ 422.1727; Found 422.1730.

*(±) (3R,4S)-Methyl 1-benzyl-3-(2-methoxyphenyl)-2-oxo-4-(p-tolyl)azetidine-3-carboxylate (**4n**)*: yield 233 mg, 71%; beige powder; mp 124 − 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.26 – 7.19 (m, 5H), 7.10 – 7.06 (m, 2H), 7.03 – 6.94 (m, 2H), 4.99 (d, *J* = 15.1 Hz, 1H), 4.90 (s, 1H), 3.97 (d, *J* = 15.1 Hz, 1H), 3.82 (s, 3H), 3.41 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.4, 165.3, 157.5, 138.4, 135.0, 130.9, 129.6, 128.8, 128.7, 128.38, 128.35, 128.0, 127.6, 123.9, 120.7, 111.9, 72.9, 64.4, 55.3, 52.0, 44.3, 21.3 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{25}NNaO_4$ 438.1676; Found 438.1692.

*(±) (3R,4S)-Methyl 1-benzyl-3-(4-fluorophenyl)-2-oxo-4-(p-tolyl)azetidine-3-carboxylate (**4o**)*: yield 286 mg, 86%; white powder; mp 77,5 – 79,5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.48 (m, 2H), 7.29 – 7.19 (m, 7H), 7.14 – 7.03 (m, 4H), 5.04 (d, *J* = 15.0 Hz, 1H), 4.70 (s, 1H), 3.99 (d, *J* = 15.0 Hz, 1H), 3.39 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.7, 164.9, 162.7 (d, *J* = 247.7 Hz), 139.3, 134.8, 130.7, 130.7, 129.7, 129.4 (d, *J* = 8.1 Hz), 128.9, 128.4, 128.0, 127.1, 115.7 (d, *J* = 21.6 Hz), 73.4, 66.3, 52.4, 44.7, 21.4 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}FNNaO_3$ 426.1476; Found 426.1478.

*(±) (3R,4S)-Ethyl 1-benzyl-2-oxo-3-(pyridin-3-yl)-4-(p-tolyl)azetidine-3-carboxylate (**4p**)*: yield 233 mg, 73%; light orange powder; mp 90,5 − 92°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 – 8.85 (m, 1H), 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.04 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1H), 7.32 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.28 – 7.22 (m, 7H), 7.10 – 7.05 (m, 2H), 5.01 (d, *J* = 15.0 Hz, 1H), 4.73 (s, 1H), 3.99 (d, *J* = 15.0 Hz, 1H), 3.88 – 3.69 (m, 2H), 2.40 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5, 164.0, 149.4, 148.9, 139.3, 135.0, 134.6, 131.0, 130.3, 129.6, 128.9, 128.3, 128.0, 127.2, 123.3, 72.0, 65.6, 61.9, 44.7, 21.2, 13.6 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{24}N_2NaO_3$ 423.1679; Found 423.1682.

*(±) (3R,4S)-Methyl 3-methyl-2-oxo-1-phenyl-4-(p-tolyl)azetidine-3-carboxylate (**4r**)*: yield 250 mg, 81%; white powder; mp 162 − 164°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.25 (m, 4H), 7.25 – 6.88 (m, 5H), 4.89 (s, 1H), 3.33 (s, 3H), 2.35 (s, 3H), 1.82 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.7, 164.3, 138.7, 137.4, 130.4, 129.2, 129.1, 126.6, 124.2, 117.3, 66.2, 65.9, 51.9, 21.2, 17.6 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{19}NNaO_3$ 332.1257; Found 332.1262.

*(±) (2S,3R)-Methyl 2-cyclopropyl-1-(4-methoxybenzyl)-3-methyl-4-oxoazetidine-3-carboxylate (**4s**)*: yield 150 mg, 65%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.64 (d, J = 15.0 Hz, 1H), 4.09 (d, J = 15.0 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.33 (d, J = 9.8 Hz, 1H), 1.45 (s, 3H), 0.85 – 0.66 (m, 1H), 0.55 – 0.46 (m, 1H), 0.46 – 0.37 (m, 1H), 0.09 – 0.01 (m, 1H), -0.00 – -0.08 (m, 1H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.2, 166.5, 159.2, 129.5, 127.7, 114.1, 68.3, 62.9, 55.2, 52.2, 43.8, 16.8, 8.5, 3.9, 1.0 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{22}NO_4$ 304.1543; Found 304.1540.

*(±) (3R,4R)-Methyl 1-cyclopropyl-3-methyl-2-oxo-4-(thiophen-2-yl)azetidine-3-carboxylate (**4t**)*: yield 114 mg, 53%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 5.0, 1.1 Hz, 1H), 7.07 (d, J = 3.4 Hz, 1H), 7.02 (dd, J = 5.0, 3.6 Hz, 1H), 4.58 (s, 1H), 3.46 (s, 3H), 2.67 – 2.60 (m, 1H), 1.64 (s, 3H), 1.12 – 1.03 (m, 1H), 0.84 – 0.62 (m, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.0, 167.3, 137.9, 127.1, 126.7, 126.0, 66.3, 63.4, 52.0, 23.8, 17.2, 5.5, 5.1 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_3S$ 266.0845; Found 266.0846.

*(±) (1S,9bS)-Ethyl 2-oxo-1-(pyridin-2-yl)-2,4,5,9b-tetrahydro-1H-azeto[2,1-a]isoquinoline-1-carboxylate (**4u**)*: yield 122 mg, 50%; light yellow crystalline powder; mp 151 − 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, J = 2.4 Hz, 1H), 8.76 – 8.49 (m, 1H), 8.07 (dt, J = 8.0, 2.0 Hz, 1H), 7.39 (dd, J = 8.0, 4.8 Hz, 1H), 7.30 (dq, J = 7.2, 3.9, 3.1 Hz, 3H), 7.25 – 7.18 (m, 1H), 4.95 (s, 1H), 4.24 (ddd, J = 13.6, 6.6, 1.3 Hz, 1H), 3.76 (dq, J = 10.8, 7.1 Hz, 1H), 3.64 (dq, J = 10.8, 7.1 Hz, 1H), 3.27 (ddd, J = 15.9, 11.9, 6.4 Hz, 1H), 3.07 (ddd, J = 13.6, 11.8, 4.1 Hz, 1H), 2.81 (dd, J = 15.8, 4.0 Hz, 1H), 0.77 (t, J = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.7, 164.8, 149.4, 149.2, 135.3, 135.3, 130.6, 130.2, 129.7, 128.2, 127.0, 127.0, 123.3, 71.5, 61.9, 59.9, 37.6, 28.7, 13.2 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{18}N_2NaO_3$ 345.1210; Found 345.1207.

*(±) (2S,3R)-ethyl 1,3-dimethyl-2-(naphthalen-1-yl)-4-oxoazetidine-3-carboxylate (**4w**)*: yield 120 mg, 51%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.86 (m, 2H), 7.83 (dd, J = 7.4, 2.0 Hz, 1H), 7.61 – 7.45 (m, 4H), 5.24 (s, 1H), 3.62 – 3.41 (m, 2H), 3.05 (s, 3H), 1.93 (s, 3H), 0.52 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.2, 167.8, 133.7, 131.3, 130.1, 128.9, 128.9, 126.7, 126.1, 124.9, 123.8, 122.6, 66.9, 65.1, 60.8, 28.2, 17.5, 13.3 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{19}NNaO_3$ 320.1257; Found 320.1260.

*(±) (3R,4S)-ethyl 1-(2-(tert-butylthio)ethyl)-3-methyl-2-oxo-4-(pyridin-3-yl)azetidine-3-carboxylate (**4x**)*: yield 198 mg, 71%; orange powder; mp 65,5 − 67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, J = 4.8, 1.7 Hz, 1H), 8.56 (d, J = 2.3 Hz, 1H), 7.61 (dt, J = 7.9, 2.0 Hz, 1H), 7.32 – 7.28 (m, 1H), 4.67 (s, 1H), 3.90 (dt, J = 14.3, 6.7 Hz, 1H), 3.85 – 3.67 (m, 2H), 3.09 (dt, J = 14.4, 6.6 Hz, 1H), 2.83 (dt, J = 13.2, 6.7 Hz, 1H), 2.69 (dt, J = 12.9, 6.6 Hz, 1H), 1.76 (s, 3H), 1.30 (s, 9H), 0.91 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.1, 166.9, 150.1, 148.8, 134.5, 130.3, 123.3, 66.8, 64.9, 61.3, 42.7, 40.9, 30.9, 26.8, 17.6, 13.7 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{26}N_2NaO_3S$ 373.1556; Found 373.1559.

*(±) (2S,3R)-Ethyl 1-benzyl-2-(4-methoxyphenyl)-3-methyl-4-oxoazetidine-3-carboxylate (**4y**)*: yield 314 mg, 89%; light yellow powder; mp 69 − 71°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (td, *J* = 5.3, 2.4 Hz, 3H), 7.23 – 7.12 (m, 4H), 6.92 – 6.81 (m, 2H), 4.99 (d, *J* = 14.8 Hz, 1H), 4.20 (s, 1H), 3.93 (d, *J* = 14.9 Hz, 1H), 3.89 – 3.69 (m, 5H), 1.62 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 167.3, 160.0, 135.2, 128.9, 128.5, 128.3, 127.9, 125.8, 113.9, 66.6, 65.3, 61.1, 55.3, 44.5, 17.2, 13.8 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{23}NNaO_4$ 376.1519; Found 376.1531.

*(±) (3R,4R)-ethyl 3-isopropyl-2-oxo-1,4-di(thiophen-2-yl)azetidine-3-carboxylate (**4z**)*: yield 238 mg, 82%; light orange powder; mp 69 − 71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.26 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.87 (d, *J* = 3.4 Hz, 1H), 5.10 (d, *J* = 15.5 Hz, 1H), 4.72 (s, 1H), 4.20 (d, *J* = 15.5 Hz, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 2.36 (hept, *J* = 6.7 Hz, 1H), 1.16 – 1.04 (m, 9H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.8, 165.1, 138.1, 136.8, 127.7, 127.3, 127.1, 126.4, 126.0, 125.9, 75.8, 61.0, 56.9, 38.2, 30.9, 19.2, 17.4, 13.8 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{21}NNaO_3S_2$ 386.0855; Found 386.0855.

*(±) ((3R,4S)-ethyl 3-isopropyl-2-oxo-4-((E)-1-phenylprop-1-en-2-yl)-1-(2-(p-tolyloxy)ethyl)azetidine-3-carboxylate (**4aa**)*: yield 219 mg, 63%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.6, 6.7 Hz, 2H), 7.28 – 7.22 (m, 3H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.53 (s, 1H), 4.26 (s, 1H), 4.20 – 3.98 (m, 5H), 3.37 (ddd, *J* = 14.6, 7.8, 3.3 Hz, 1H), 2.39 (hept, *J* = 6.6 Hz, 1H), 2.31 (s, 3H), 1.90 (d, *J* = 1.3 Hz, 3H), 1.25 – 1.12 (m, 9H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.7, 166.4, 156.0, 136.9, 132.4, 130.5, 130.0, 128.9, 128.2, 127.2, 126.8, 114.2, 74.9, 65.6, 65.2, 61.0, 39.9, 31.1, 20.5, 19.3, 17.6, 16.7, 14.2 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{33}NNaO_4$ 458.2302; Found 458.2304.

*(±) (2S,3R)-methyl 2-(4-chlorophenyl)-3-cyclopropyl-1-(4-methoxyphenethyl)-4-oxoazetidine-3-carboxylate (**4ab**)*: yield 149 mg, 45%; yellow oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 2.3 Hz, 2H), 7.08 (d, *J* = 2.4 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.38 (s, 1H), 3.88 (dt, *J* = 14.4, 7.4 Hz, 1H), 3.81 (s, 3H), 3.36 (s, 3H), 3.12 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.82 (t, *J* = 7.2 Hz, 2H), 1.54 (tt, *J* = 8.3, 5.3 Hz, 1H), 0.91 – 0.80 (m, 1H), 0.65 – 0.48 (m, 2H), 0.42 – 0.27 (m, 1H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.7, 164.1, 158.5, 134.7, 132.8, 129.8, 129.5, 128.8, 128.3, 114.1, 71.7, 64.6, 55.3, 51.8, 41.5, 33.0, 12.8, 2.4, 1.4 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{24}ClNNaO_4$ 436.1286; Found 436.1283.

*(±) (2R,3R)-ethyl 1-allyl-2-(furan-2-yl)-4-oxo-3-phenylazetidine-3-carboxylate (**4ac**)*: yield 167 mg, 76%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.66 (m, 2H), 7.50 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.47 – 7.34 (m, 3H), 6.58 – 6.42 (m, 2H), 5.70 (dddd, *J* = 17.1, 10.2, 7.1, 5.3 Hz, 1H), 5.20 – 5.04 (m, 2H), 4.99 (s, 1H), 4.22 (ddt, *J* = 15.6, 5.3, 1.6 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.60 (ddt, *J* = 15.7, 7.2, 1.3 Hz, 1H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 164.4, 148.5, 143.4, 134.7, 130.8, 128.7, 128.3, 127.3, 119.1, 110.8, 109.9, 72.9, 61.8, 59.9, 43.3, 13.8 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}NO_4$ 326.1387; Found 326.1380.

*(±) (2S,3R)-methyl 1-(adamantan-1-yl)-3-(4-fluorophenyl)-2-(4-methoxyphenyl)-4-oxoazetidine-3-carboxylate (**4ad**)*: yield 254 mg, 68%; white crystalline powder; mp 133 − 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 6.97 (m, 3H), 6.86 – 6.74 (m, 3H), 6.73 – 6.58 (m, 2H), 5.39 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.07 – 2.02 (m, 3H), 2.00 (d, *J* = 2.8 Hz, 6H), 1.64 (d, *J* = 3.0 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.9, 163.8, 161.9 (d, *J* = 246.8 Hz), 159.5, 130.3 (d, *J* = 8.1 Hz), 129.3,

128.8 (d, J = 3.3 Hz), 128.6, 114.9 (d, J = 21.5 Hz), 113.4, 71.0, 61.6, 56.22, 55.2, 53.2, 40.8, 36.0, 29.1 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{30}FNNaO_4$ 486.2051; Found 486.2051.

*(±) (2R,3R)-Diethyl 1-(4-methoxyphenyl)-4-oxo-3-(pyridin-3-yl)azetidine-2,3-dicarboxylate (**4ae**)*: yield 246 mg, 77%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 2.4 Hz, 1H), 8.63 – 8.56 (m, 1H), 7.93 – 7.71 (m, 1H), 7.37 – 7.29 (m, 3H), 6.92 (d, J = 9.0 Hz, 2H), 5.36 (s, 1H), 4.38 – 4.28 (m, 2H), 3.94 – 3.71 (m, 5H), 1.28 (t, J = 7.1 Hz, 3H), 0.92 (td, J = 7.2, 0.9 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.8, 166.8, 158.4, 157.1, 149.9, 149.2, 135.7, 130.1, 127.8, 123.3, 118.6, 114.5, 69.8, 63.3, 62.0, 60.8, 55.5, 14.0, 13.7 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}N_2O_6$ 399.1551; Found 399.1550.

*(±) (3S,4S)-Ethyl-1-benzyl-2-oxo-3-(thiophen-2-yl)-4-(p-tolyl)azetidine-3-carboxylate (**4af**)*

Yield 210 mg, 65 %, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 5.2, 1.3 Hz, 1H), 7.30 – 7.25 (m, 4H), 7.21 (s, 4H), 7.16 (dd, J = 7.1, 2.4 Hz, 2H), 7.02 (dd, J = 5.1, 3.6 Hz, 1H), 5.06 (d, J = 15.0 Hz, 1H), 4.62 (s, 1H), 4.02 (d, J = 15.0 Hz, 1H), 3.87 – 3.78 (m, 2H), 2.39 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4, 164.2, 139.1, 136.0, 134.8, 130.3, 129.4, 128.8, 128.5, 127.9, 127.1, 126.7, 126.3, 126.1, 71.5, 68.0, 61.8, 44.8, 21.2, 13.6.ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{23}NO_3SNa$ 428.1291; Found 428.1293.

*tert-Butyl 3-(benzyl(cyclohexylidenemethyl)amino)-2-methyl-3-oxopropanoate (**12**)*

Column chromatography was carried out using neutral alumina. Yield 69 mg, 22%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.05 (m, 5H), 5.75 (s, 1H), 4.83 (d, J = 14.0 Hz, 1H), 4.44 (d, J = 14.1 Hz, 1H), 3.63 (q, J = 7.1 Hz, 1H), 2.08 (t, J = 5.6 Hz, 2H), 2.05 – 1.91 (m, 2H), 1.63 – 1.48 (m, 6H), 1.43 (s, 9H), 1.34 (d, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 170.1, 144.6, 137.2, 128.9, 128.3, 127.2, 120.1, 81.1, 51.3, 44.5, 33.0, 28.0, 27.9, 27.8, 26.6, 26.2, 13.7 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{31}NO_3Na$ 380.2196; Found 380.2199.

*3-Benzyl-5,6-dimethyl-2-(p-tolyl)-2H-1,3-oxazin-4(3H)-one (**20a**)*: A solution of 3-diazopentane-2,4-dione (151 mg, 1.2 mmol) and imine **21** (209 mg, 1.0 mmol) in dry toluene (2 mL) was refluxed for 2.5 h. After evaporation of volatiles the residue was subjected to flash column chromatography on silica gel (eluent – acetone in *n*-hexane from 5% to 40%). Yield 103 mg, 33%; white solid; mp 92 − 94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 3H), 7.21 – 7.15 (m, 6H), 5.99 (s, 1H), 5.32 (d, J = 15.4 Hz, 1H), 3.86 (d, J = 15.4 Hz, 1H), 2.39 (s, 3H), 1.88 (s, 3H), 1.84 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.5, 158.7, 139.4, 137.3, 133.1, 129.1, 128.5, 127.8, 127.32, 127.27, 105.6, 86.7, 46.7, 21.2, 17.3, 10.5 ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; Found 308.1651.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, crystallographic data, computational details. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 1938173 (**4a**), 1938204 (**4j**) and 1939763 (**4u**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk.

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Notes

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REFERENCES

1. Krasavin, M.; Dar'in, D. Current diversity of cyclic anhydrides for the Castagnoli-Cushman-type formal cycloaddition reactions: prospects and challenges. *Tetrahedron Lett.* **2016**, *57*, 1635-1640.

2. Cushman, M.; Castagnoli, N. Novel approach to the synthesis of nitrogen analogs of the tetrahydrocannabinols. *J. Org. Chem.* **1973**, *38*, 440.

3. Lepikhina, A.; Bakulina, O.; Dar'in, D.; Krasavin, M. The first solvent-free synthesis of privileged gamma- and delta-lactams via the Castagnoli-Cushman reaction. *RSC Advances*, **2016**, *6*, 83808.

4. Dar'in, D.; Bakulina, O.; Chizhova, M.; Krasavin, M. New Heterocyclic Product Space for the Castagnoli-Cushman Three-Component Reaction. *Org. Lett*. **2015**, *17*, 3930.

5. (a) Adamovskyi, M. I.; Ryabukhin, S. V.; Sibgatulin, D. A.; Rusanov, E.; Grygorenko, O. O. Beyond the Five and Six: Evaluation of Seven-Membered Cyclic Anhydrides in the Castagnoli-Cushman Reaction. *Org. Lett.* **2017**, *19*, 130; (b) Bakulina, O.; Dar'in, D.; Krasavin, M. *o*-Phenylenediacetic acid anhydride in the Castagnoli-Cushman reaction: extending the product space to epsilon-lactams. *Synlett* **2017**, *28*, 1165; (c) Bakulina, O.; Chizhova, M.; Dar'in, D.; Krasavin, M. A General Way to Construct Arene-Fused Seven-Membered Nitrogen Heterocycles. *Eur. J. Org. Chem.* **2018**, 362.

6. (a) Perrin, C. L.; Arrhenius, T. Malonic anhydride. *J. Am. Chem. Soc.* **1978**, *100*, 5249; (b) O'Murchu, C. Process for the preparation of malonic anhydride (2,4-oxetanedione) by ozonization of diketene and process for the preparation of malonic acid derivatives (e.g. Meldrum's acid) therefrom. Eur. Pat. EP496362; *Chem. Abstr.* **1993**, *118*, 101968; (c) O'Murchu, C. Cycloaddition reaction of ketones with malonic anhydride in the preparation of 2,2-substituted-4,6-dioxo-1,3-dioxanes. Eur. Pat. 637581; *Chem. Abstr.* **1995**, *122*, 239714.

7. (a) Subba Reddy, B. V.; Karthik, G.; Rajasekaran, T.; Antony, A.; Sridhar, B. $Rh_2(OAc)_4$ catalyzed substrate selective [4+2]/[2+2] cycloaddition of acylketenes: a highly chemo- and regioselective synthesis of spiro(oxindolyl)oxazinones and β-lactams. *Tetrahedron Lett.* **2012**, *53*, 2396; (b) Mandler, M. D.; Truong, P. M.; Zavalij, P. Y.; Doyle, M. P. Catalytic Conversion of Diazocarbonyl Compounds to Imines: Applications to the Synthesis of Tetrahydropyrimidines and β-Lactams. *Org. Lett.* **2014**, *16*, 740; (c) Long, C.; Wang, K.; Shao, Y.; Sun, J. Stereoselective Synthesis of Fully Substituted β-Lactams via Metal–Organo Relay Catalysis. *Org. Lett.* **2019**, *21*, 3804; (d) Chen, L.; Zhang, L. Shao, Y.; Xu, G.; Zhang, X.; Tang, S.; Sun, J. Rhodium-Catalyzed C═N Bond

Formation through a Rebound Hydrolysis Mechanism and Application in β-Lactam Synthesis. *Org. Lett.* **2019**, *21*, 4124.

8. Ohno, M.; Itoh, M.; Ohashi, T.; Eguchi, S. Ethyl 3-(1-Adamantyl)-2-diazo-3-oxopropanoate: Synthetic Use for the Preparation of Some Adamantane Derivatives. *Synthesis* **1993**, 793.

9. Tsuno, T.; Kondo, K.; Sugiyama, K. Cycloaddition Reaction of Schiff Bases with Ketenes Generated by Pyrolysis of 2-Aryl-substituted 1,5,7-Trioxaspiro[2.5]octane-4,8-diones. *J. Heterocyclic Chem.* **2006**, *43*, 21.

10. (a) Fernandes, R.; Amador, P.; Prudencio, C. β-Lactams: chemical structure, mode of action and mechanisms of resistance. *Rev. Med. Microbiol.*, **2013**, *24*, 7; (b) McGeary, R. P.; Tan, D. T. C.; Schenk, G. Progress toward inhibitors of metallo-β-lactamases. *Future Med. Chem.*, **2017**, *9*, 673.

11. Veinberg, G.; Potorocina, I.; Vorona, M. Recent Trends in the Design, Synthesis and Biological Exploration of β-Lactams. *Curr. Med. Chem.*, **2014**, *21*, 393.

12. Dar'in, D.; Kantin, G.; Krasavin, M. A 'Sulfonyl-Azide-Free' (SAFE) Aqueous-Phase Diazo Transfer Reaction for Parallel and Diversity-Oriented Synthesis. *Chem. Commun.* **2019**, *55*, 5239.

13. (a) Egorova, K. S.; Ananikov, V. P. Toxicity of Metal Compounds: Knowledge and Myths. *Organometallics* **2017**, *36*, 4071; (b) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. Transition Metal Catalysis in the Pharmaceutcial Industry. Ch. 1 in Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industry Perspective, Crawley, M. L. and Trost, B. M., Eds.; John Wiley & Sons, **2012**.

14. Dar'in, D.; Bakulina, O.; Nikolskaya, S.; Gluzdikov, I.; Krasavin, M. The rare cis-configures trisubstitututed lactam products obtained by the Castagnoli-Cushman reaction in N,N-dimethylformamide. *RSC Advances* **2016**, *6*, 49411.

15. Kulyashova, A.; Krasavin, M. Convenient modular construction of medicinally important 5-acylamino-4,5-dihydroisoxazoles featuring four elements of diversity. *Tetrahedron Lett.* **2016**, *57*, 4395.

16. (a) Xu, J.; Zhang, Q.; Chen, L.; Chen, H. Chemoselectivity in reactions of an α-diazo-β-diketone with some conjugative double-bond systems. *J. Chem. Soc., Perkin Trans.* 1 **2001**, 2266; (b) Xu, J.; Chen, L. Reactions of unsymmetrical α-diazo-β-diketones with imines: Syntheses of 4*H*-1,3-oxazin-4-ones. *Heteroatom Chem.* **2002**, *13*, 165; (c) Khlebnikov, A. F.; Novikov, M. S.; Pakalnis, V. V.; Yufit, D. S. Nonconcerted Cycloaddition of 2*H*-Azirines to Acylketenes: A Route to *N*-Bridgehead Heterocycles. *J. Org. Chem.* **2011**, *76*, 9344; (d) Jiao, L.; Liang, Y.; Xu, J. Origin of the Relative Stereoselectivity of the β-Lactam Formation in the Staudinger Reaction. *J. Am. Chem. Soc*. **2006**, *128*, 6060.

17. (a) Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J, Howard, J.A.K.; Puschmann, H. OLEX2: A Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Cryst.* **2009**, *42*, 339; (b) Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. The anatomy of a comprehensive constrained, restrained refinement program for the modern computing environment – Olex2 dissected. *Acta Cryst.* **2015**, *A71*, 59;

18. Dar'in, D.; Kantin G.; Krasavin M. A 'sulfonyl-azide-free' (SAFE) aqueous-phase diazo transfer reaction for parallel and diversity-oriented synthesis. *Chem. Commun.*, **2019**, *55*, 5239.