Palladium Catalysis in the Intramolecular Carbene C–H Insertion of α-Diazo-α-(methoxycarbonyl)acetamides to Form β-Lactams

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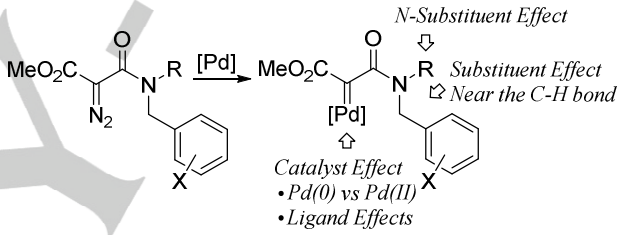
Abstract: The intramolecular carbene C–H insertion of α-diazo-α-(methoxycarbonyl)acetamides leading to β-lactams is effectively catalyzed by palladium complexes. It is found that whereas Pd(0)-catalysts typically produce mixtures of β-lactams together with Buchner-type reaction products, the use of Pd(II)-catalysts results in highly chemoselective transformations. According to DFT calculations, this insertion reaction occurs stepwise and involves an unprecedented Pd(II)-promoted Mannich-type reaction through a metallacarbene-induced zwitterionic intermediate.

Introduction

The transition metal-catalyzed intramolecular carbene C–H insertion by decomposition of diazo compounds is a well-established powerful carbon-carbon bond-forming methodology for the construction of carbocyclic and heterocyclic frameworks.[1] Many transition metal complexes have been used as effective catalysts to generate reactive metallacarbenes starting from diazo derivatives.[2] Among them, rhodium(II),[3] copper(I),[4] and more recently ruthenium(II) catalyst[5] have proven especially useful for the development of highly selective carbene C–H insertion methodologies via a variety of reaction modes.

Surprisingly, palladium, though one of the most commonly employed metals in homogeneous catalysis, has been scarcely applied to promote carbene C–H insertion processes.[6] In this context, we recently reported that palladium catalysts are able to promote Csp^3–H insertion of carbenes derived from α-diazoesters to form pyrrolidines through intramolecular Csp^3–Csp^3 bond formation.[7] We also explored the palladium-catalyzed carbene C–H insertion of α-diazo-α-(methoxycarbonyl)acetanilides. We found that when using palladium catalysts the C–H insertion of such amides occurs selectively into the arylic Csp^2–H to give the oxindole.[8]

The aim of the current work was to explore the palladium-catalyzed intramolecular carbene insertion of α-diazo-α-(methoxycarbonyl)acetamides for β-lactam elaboration. The β-lactam system has attracted considerable attention due to its ubiquitous presence in the molecular structure of natural products and biologically active compounds.[9] We studied how the selectivity of the process[10] is affected by the type of catalyst, using two oxidation states of palladium, and the substituents on the α-diazoacetamide (Scheme 1).



Scheme 1. Substituent and catalyst effects on Pd-catalyzed reactions of α-diazoacetamides

Results and Discussion

We commenced our investigation by studying the palladium-catalyzed reactions of *N*,*N*-dibenzyl-α-diazoacetamide **1** (Table 1).[11]

Treatment of **1** with $Pd_2(dba)_3$ in 1,2-dichloroethane at reflux for 24 h resulted in 76% conversion to give a 1:1 mixture of cycloheptapyrrolone **2** and β-lactam ***trans*-3**, together with some β-lactam ***cis*-3** and the recovery of significant amounts of unreacted starting material (Table 1, entry 1). When the reaction was performed in the absence of the palladium catalyst, ca. 40% of conversion was observed, giving a 1:0.1:1 mixture of **2**, ***cis*-3** and ***trans*-3**, together with the unreacted material (Table 1, entry 2). The complete consumption of the starting material was achieved when reactions were run in refluxing toluene (Table 1, entries 3-4).

On the other hand, the $[(IMes)Pd(NQ)]_2$-catalyzed decomposition of **1** in DCE at reflux gave cycloheptapyrrolone **2** as the major product (55%), together with small amounts of β-lactams ***cis*-3** and ***trans*-3** (Table 1, entry 5). The complete consumption of the starting material and the notably different selectivity of the latter reaction compared to the thermal process in DCE (Table 1, entry 2) clearly supports the role of $[(IMes)Pd(NQ)]_2$ as a catalyst in the decomposition of α-diazoacetamide **1**.

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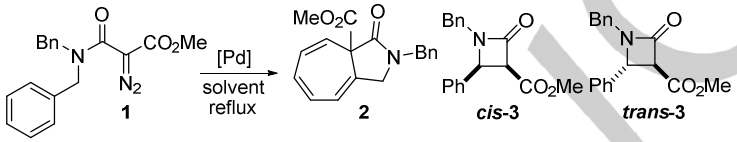
Pd(II)-catalysts were also able to promote the carbene reactions of **1**, which resulted in the major formation of β-lactams ***cis*-3** and ***trans*-3** at the expense of the Buchner product **2**. Thus, the $[Pd(allyl)Cl]_2$-catalyzed decomposition of **1** afforded a 1:1.4:0.5 mixture of cycloheptapyrrolone **2** and β-lactams ***cis*-3** and ***trans*-3** (Table 1, entry 7). However, after flash chromatography, only **2** (20%) and ***trans*-3** (23%) were isolated because β-lactam ***cis*-3** underwent isomerization to the more stable *trans* isomer during the purification process. When using (SIPr)Pd(allyl)Cl as the catalyst, products **2** and ***trans*-3** were isolated in comparable yields (Table 1, entry 8). Finally, $Pd(TFA)_2$ also led to the formation of the β-lactams as the main products, although a longer reaction time was required and ***trans*-3** was still isolated in poor yield (Table 1, entry 10).

Table 1. Pd-catalyzed cyclisation reactions of α-diazoamide **1**[a]



entry	catalyst (mol%)	solvent	^{1}H NMR ratio[b]	yield [%][c]
1	$Pd_2(dba)_3$ (10)	DCE	**1**/**2**/***cis*-3**/***trans*-3** (1:1.5:0.15:1.5)	---
2	---	DCE	**1**/**2**/***cis*-3**/***trans*-3** (1:0.3:0.04:0.3)	---
3	$Pd_2(dba)_3$ (10)	toluene	**2**/***cis*-3**/***trans*-3** (1:0.1:1)	**2** (42), ***trans*-3** (42)
4	---	toluene	**2**/***cis*-3**/***trans*-3** (1:0.25:1)	**2** (43), ***trans*-3** (45)
5	$[(IMes)Pd(NQ)]_2$ (2.5)	DCE	**2**/***cis*-3**/***trans*-3** (1:0.1:0.2)	**2** (55), ***trans*-3** (5)
6	$[(IMes)Pd(NQ)]_2$ (2.5)	CH_2Cl_2	**1**	---
7	$[Pd(allyl)Cl]_2$ (5)	DCE	**2**/***cis*-3**/***trans*-3** (1:1.4:0.5)	**2** (20), ***trans*-3** (23)[d]
8	(SIPr)Pd(allyl)Cl (15)	DCE[e]	**2**/***cis*-3**/***trans*-3** (1:0.25:1.1)	**2** (22), ***trans*-3** (20)[d]
9	(SIPr)Pd(allyl)Cl (10)	DCE[e]	**1**/**2**/***cis*-3**/***trans*-3** (1:1.1:0.3:1.4)	---
10	$Pd(TFA)_2$ (10)	$CHCl_3$[e]	**2**/***cis*-3**/***trans*-3** (1:1.2:1)	**2** (15), ***trans*-3** (24)[d]

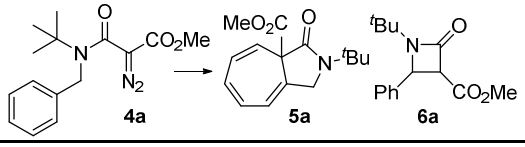
[a] Reaction conditions: Catalyst (see table) in the indicated solvent at reflux for 24 h. [b] Ratio determined by ^{1}H NMR (400 MHz) from the reaction mixture. [c] Yields refer to products isolated by chromatography. [d] Small amounts (≤10%) of *N,N*-dibenzyl-α-chloro-α-(methoxycarbonyl)acetamide were also obtained. [e] Reaction time: 48 h. $Pd_2(dba)_3$ = Tris(dibenzylideneacetone)dipalladium(0). $[(IMes)Pd(NQ)]_2$ = 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer. (SIPr)Pd(allyl)Cl = Allyl-chloro-[1,3-bis-(2,6-diisopropylphenyl)-2-imidazolidinylidene]palladium(II).

The competition between Csp^3–H insertion leading to β-lactams and intramolecular aromatic cycloaddition to give the corresponding cycloheptapyrrolone is also common in reactions of α-diazoacetamides catalyzed by Rh(II)[11a] and Ru(II)-catalysts.[11b,12] According to previous mechanistic studies on related Rh(II)-catalyzed transformations, the competitive formation of β-lactams and aromatic ring reaction products is probably due to the stereoelectronic competition between the two conformational isomers of the metallacarbene undergoing the intramolecular reactions.[13] A strategy to improve site-selectivity in the transition metal-catalyzed carbene reactions of α-diazoacetamides involves replacing one of the *N*-substituents at the amide moiety with a bulky group,[14] which sterically biases the conformational preference around the amide N–C(O) bond and makes the metallacarbene reaction at the remaining substituent more feasible.

In search of higher site-selectivity in the palladium-catalyzed insertion leading to β-lactams, we decided to replace one of the benzyl groups in **1** with a *tert*-butyl substituent. Table 2 shows the results of the palladium-catalyzed reactions with *N*-benzyl-*N*-*t*butyl-α-diazoacetamide **4a**.[15]

When α-diazoamide **4a** was decomposed in the presence of $Pd_2(dba)_3$ (Table 2, entry 1), cycloheptapyrrolone **5a** (20%) was isolated together with β-lactams ***cis*-6a** (9%) and ***trans*-6a** (42%)[16] On changing the catalyst to $[(IMes)Pd(NQ)]_2$, a slight increase in the formation of the Buchner product was observed (Table 2, entry 2). To our delight, the more electrophilic $[Pd(allyl)Cl]_2$ or (SIPr)Pd(allyl)Cl catalysts exclusively promoted the Csp^3–H insertion to give the β-lactams, which were isolated in good overall yields (Table 2, entries 3-4).

Table 2. Pd-catalyzed cyclisation reactions of α-diazoamide **4a**[a]



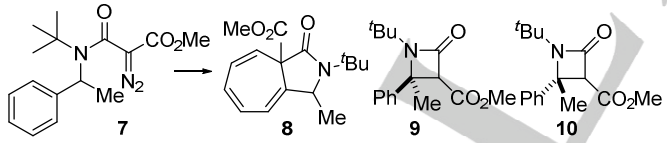
4a **5a** **6a**

entry	catalyst (mol%)	**5a**/***cis*-6a**/***trans*-6a**[b],[c]	products (%)[d]
1	$Pd_2(dba)_3$ (10)	26/46/28	**5a** (20) ***cis*-6a** (9) ***trans*-6a** (42)
2	$[(IMes)Pd(NQ)]_2$ (2.5)	35/40/25	**5a** (28) ***cis*-6a** (35) ***trans*-6a** (23)
3	$[Pd(allyl)Cl]_2$ (5)	0/47/53	***cis*-6a** (25) ***trans*-6a** (65)
4	(SIPr)Pd(allyl)Cl (15)	0/29/71	***cis*-6a** (17) ***trans*-6a** (59)

[a] Reaction conditions: Catalyst in DCE at reflux for 24 h. [b] ^{1}H NMR ratio. [c] All reactions were performed twice. While the **5a**/**6a** ratio was essentially the same in the two runs, the *cis*/*trans* ratio was quite different due to the partial isomerization of *cis* β-lactam to the more stable *trans* isomer during the work-up. [d] Isolated yields.

The palladium-catalyzed carbene insertion was also explored from α-diazoamide **7**, which bears the α-methylbenzyl substituent at the nitrogen (Table 3). Similarly to the reactions of *N*-benzylamide **4a**, when Pd(0)-catalysts were used to promote the decomposition of **7** a significant amount of the Buchner product **8** was obtained (Table 3, entries 1 and 2).

Table 3. Pd-catalyzed cyclisation reactions of α-diazoamide **7**[a]



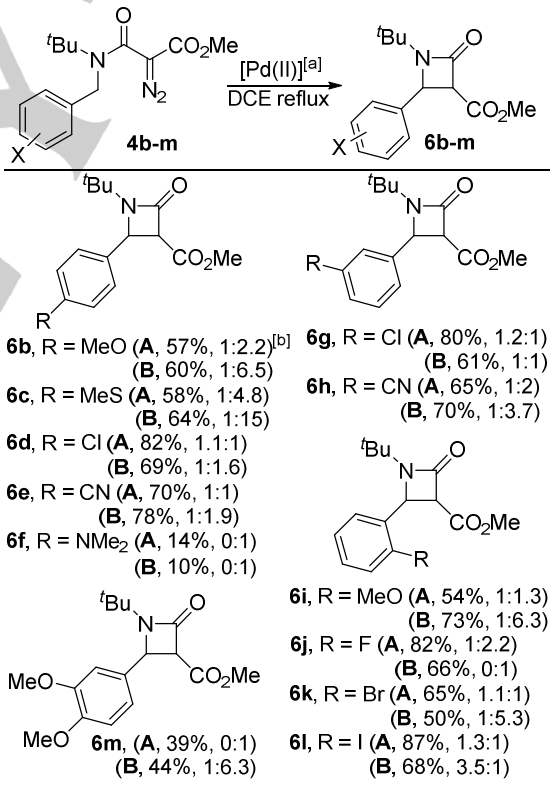
7 **8** **9** **10**

entry	catalyst (mol%)	**8**/**9**/**10**[b]	products (%)[c]
1	$Pd_2(dba)_3$ (10)	26/37/37	**8**[d] (15) **9** (18), **10** (24)
2	$[(IMes)Pd(NQ)]_2$ (2.5)	65/20/15	**8**[e] (42) **9** (7), **10** (13)
3	$[Pd(allyl)Cl]_2$ (5)	0/36/64	**9** (23), **10** (47)
4	(SIPr)Pd(allyl)Cl (15)	0/57/43	**9** (24), **10** (18)

[a] Reaction conditions: Catalyst in DCE at reflux for 24 h. [b] ^{1}H NMR ratio. [c] Isolated yields. [d] 1:1.2 mixture of stereoisomers. [e] 1:2.2 mixture of stereoisomers.

Interestingly, when the reaction was catalyzed by $Pd_2(dba)_3$, both **4a** and **7** gave a ca. 1:3 Buchner/β-lactam ratio. On the contrary, when the reaction of **7** was promoted by the sterically encumbered $[(IMes)Pd(NQ)]_2$ catalyst, cycloheptapyrrolone **8** was obtained as the major product, suggesting that the Pd(0)-catalyzed reaction is highly sensitive to the steric hindrance on the reactive Csp^3–H bond. At variance, similar to the reactions of **4a**, the use of Pd(II)-catalysts with **7** resulted in the chemoselective insertion into the Csp^3–H bond (Table 3, entries 3 and 4), $[Pd(allyl)Cl]_2$ once again affording the best result.

The studies with α-diazoacetamides **4a** and **7** gave us two experimental procedures for the insertion reaction based on the use of either $[Pd(allyl)Cl]_2$ (Method A) or (SIPr)Pd(allyl)Cl (Method B) as the catalyst. To explore how the introduction of substituents at the benzylic group might influence the insertion process leading to β-lactams, these catalytic systems were studied with α-diazoacetamides **4b-m** (Scheme 2, see Table S1 in the SI for additional details).



Scheme 2. Synthesis of β-lactams by Pd(II)-catalyzed cyclisation of α-diazoamides. [a] Method **A**: $[Pd(allyl)Cl]_2$ or Method **B**: (SIPr)Pd(allyl)Cl. [b] (Method, Isolated yield (%), *cis*/*trans* ratio after chromatography).

The effect of the substituent varied according to its electronic nature as well as its position on the aromatic ring. The introduction of electron-releasing groups at the benzyl

substituent led to an increased formation of the cycloheptapyrrolone product, especially when using (SIPr)Pd(allyl)Cl as the catalyst. The increase was lower when the substituent was located at the *ortho*-position, probably due to steric interactions. In contrast, electron-withdrawing groups generally diverted the palladacarbene away from the Buchner reaction in favor of the Csp^3–H insertion. Similar electronic effects have been observed in related Rh(II)-catalyzed transformations.[11a]

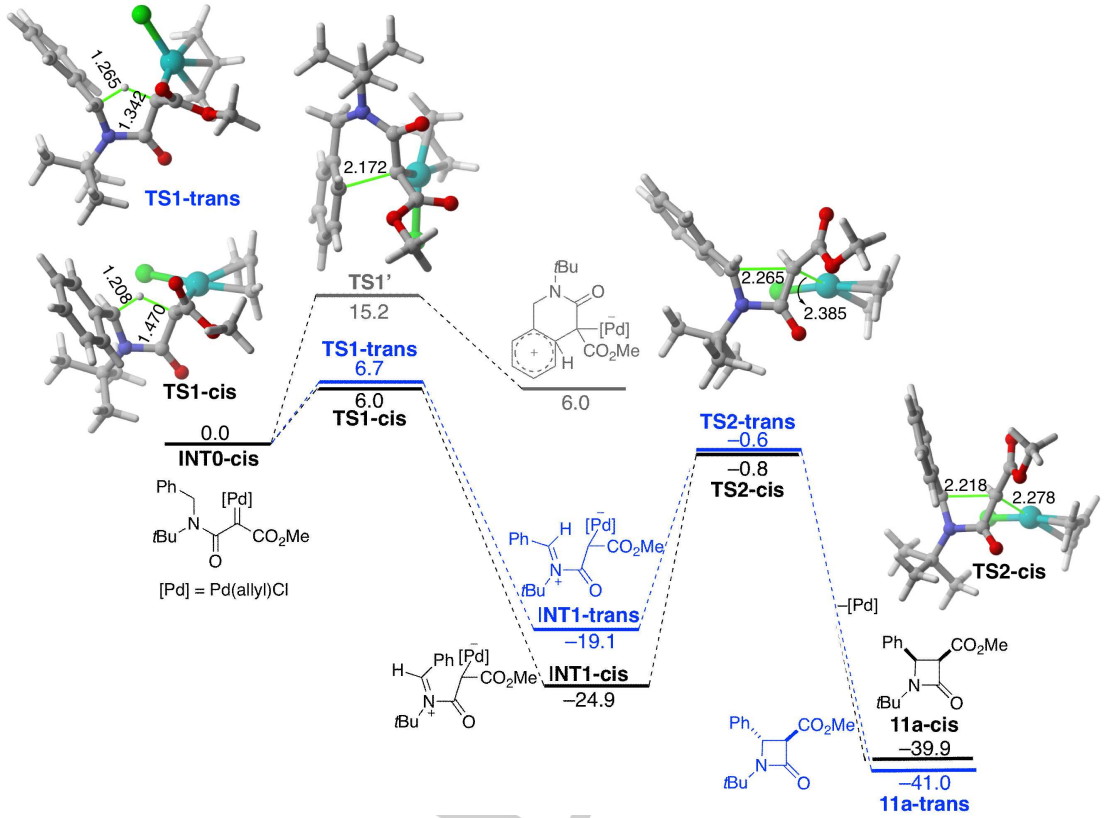


Figure 1. Computed reaction profiles for the formation of β-lactams **6a**. Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and angstroms (Å), respectively

The examples in Tables 2 and 3, and Scheme 2 confirm the generality and functional group tolerance of this novel Pd(II)-catalyzed insertion. The resulting β-lactams were obtained in moderate to good overall yields (44-90%), usually as mixtures of *cis* and *trans* isomers, in transformations proceeding with high site-selectivity. As an exception, the Pd(II)-catalyzed decomposition of **4f** gave ***trans*-6f** in poor yield together with major amounts of 4-(dimethylamino)benzaldehyde. It is worth noting that no product from the potentially competitive Pd-catalyzed cross-coupling of the aryl halide with the α-diazoamide moiety was observed in the reactions of **4k** and **4l**, which bear an *ortho*-bromo and *ortho*-iodo substituent, respectively.

The above results also confirm the significant impact of the electronic nature of the palladium catalyst and ensuing electrophilicity of the carbene intermediate in the reaction pathway. Thus, whereas benzylic Csp^3–H insertion is strongly favored over the Buchner reaction when using Pd(II)-catalysts, an increased cycloheptapyrrolone product formation is usually observed with the more electron-rich Pd(0)-catalysts. Interestingly, Rh(II)-catalyzed transformations show opposite reactivity trends, in which highly electrophilic Rh(II)-complexes favor Buchner reactions over benzylic Csp^3–H insertion.[10]

Our previous work has shown that the mechanism involved in palladium-catalyzed insertion reactions[7,8] differs considerably from that accepted for Rh(II)-catalyzed transformations. Whereas Rh(II)-catalysts typically proceed in a concerted process that directly releases the insertion product and metal catalyst in a single step,[17] palladium catalysts involve stepwise reaction mechanisms initiated by a metal-mediated hydrogen migration. To shed light on the reaction mechanism and the influence of the Pd(II)-catalyst on the selectivity of the C–H insertion described herein, density functional theory (DFT) calculations were carried out.[18] To this end, the process involving **4a** in the presence of the $[Pd(allyl)Cl]_2$ catalyst (see Table 2, entry 3) was explored.

The data in Figure 1, which gathers the computed reaction profile starting from the initial Pd(II)-carbene intermediate **INT0**, indicate that the formation of the corresponding β-lactams **6a** occurs stepwise. Thus, **INT0** is first transformed into the zwitterionic intermediate **INT1**[19] in a highly exergonic process via the transition state **TS1**. This step can be viewed as a 1,4-hydrogen migration that is not directly assisted by the metal, therefore resembling the mechanism involved in related Ru(II)-C–H activation processes previously studied by us.[7b] The transformation ends with the formation of the new C–C bond via the transition state **TS2**, again in a strongly exergonic transformation that releases the β-lactam with concomitant regeneration of the active Pd(II)-catalyst. According to the rather similar relative energies computed for the *cis*/*trans* transition states **TS1** and **TS2**, a ca. 50:50 mixture of ***cis*-6a** and ***trans*-6a** can be expected, which is fully consistent with the experimental findings (Table 2, entry 3).

Finally, we also investigated the reasons for the non-formation of cycloheptapyrrolone **5a** when using these reaction conditions (i.e. **4a** in the presence of $[Pd(allyl)Cl]_2$). Our calculations suggest that the first step of the alternative Buchner reaction, which involves a palladium-promoted C–C bond formation, is not competitive in view of the much higher activation barrier required to reach the corresponding transition state **TS1'** as compared to **TS1-trans** ($\Delta\Delta G^{\neq}$ = 8.5 kcal/mol) as well as the endergonicity ($\Delta\Delta G$ = +6.0 kcal/mol) associated with this step. Therefore, no Buchner reaction product should be expected, which agrees nicely with the complete selectivity observed experimentally (Table 2, entry 3).

Conclusions

In summary, we have shown that palladium can be used to promote the carbene Csp^3–H insertion of α-diazoacetamides to form β-lactams, Pd(II)-catalysts giving the best chemoselectivities. DFT calculations suggest that this transformation involves an unprecedented Pd(II)-promoted Mannich-type reaction through a metallacarbene-induced zwitterionic intermediate.

Experimental Section

General Methods. All commercially available reagents were used without further purification. ^{1}H- and ^{13}C NMR spectra were recorded using Me_4Si as the internal standard, with a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si for ^{1}H and ^{13}C NMR. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light or 1% aqueous $KMnO_4$. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator.

Representative Procedure for the Preparation of Diazoacetamides 1, 4a-m and 7.

To a solution of dibenzylamine (0.6 mL, 3.04 mmol) and Et_3N (0.86 mL, 6.1 mmol) in CH_2Cl_2 (18 mL), cooled at 0 °C, was added slowly methyl malonyl chloride (0.67 mL, 6.1 mmol). The mixture was stirred at room temperature for 24 h. After the reaction was completed, the mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$ aqueous solution, dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from hexanes to hexanes/EtOAc 3:2) to give *N,N*-dibenzyl-α-(methoxycarbonyl)acetamide (0.88 g, 97%).

To a solution of *N,N*-dibenzyl-α-(methoxycarbonyl)acetamide (678 mg, 2.28 mmol) and DBU (0.52 mL, 3.43 mmol) in dry acetonitrile (16 mL) was added dropwise a solution of *p*-ABSA (602 mg, 2.5 mmol) in dry acetonitrile (6 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 and 10% NaOH aqueous solution. The organic extracts were dried, filtered and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) to give *N,N*-dibenzyl-α-(methoxycarbonyl)-α-diazoacetamide (**1**, 554 mg; 75%).

***N,N*-Dibenzyl-α-(methoxycarbonyl)-α-diazoacetamide (1).** Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 4.51 (s, 4H), 7.15-7.19 (m, 4H), 7.25-7.36 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 50.5 (broad signal, 2 CH_2), 52.5 (CH_3), 67.0 (C), 127.8 (CH), 127.9 (2 CH), 128.8 (2 CH), 136.4 (C), 162.4 (C), 163.0 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}N_3O_3$: 324.1343 $[M+H]^+$; found: 324.1347.

***N*-Benzyl-*N*-*tert*-butyl-α-(methoxycarbonyl)-α-diazoacetamide (4a).** **4a** was obtained as a yellow oil that solidified on refrigeration (433 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1 equiv.), Et_3N (1 equiv.); (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 75% two steps]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 9H), 3.77 (s, 3H), 4.62 (s, 2H), 7.18-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.7 (CH_2), 52.3 (CH_3), 59.1 (C), 68.2 (C), 126.9 (2 CH), 127.5 (CH), 128.8 (2 CH), 139.7 (C), 163.1 (C), 163.2 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}N_3$ NaO_3: 312.1319 $[M+H]^+$; found: 312.1327.

***N*-*tert*-Butyl-*N*-(4-methoxybenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4b). 4b** was obtained as a yellow oil that solidified on refrigeration (600 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.2 equiv.), Et_3N (1.2 equiv.), 61%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 98%]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 9H), 3.76 (s, 3H), 3.78 (s, 3H), 4.54 (s, 2H), 6.84 (d, *J* = 8.4 Hz, 2H) 7.09 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.2 (CH_2), 52.3 (CH_3), 55.4 (CH_3), 59.0 (C), 68.2 (C), 114.1 (2 CH), 128.1 (2 CH), 131.5 (C), 159.0 (C), 163.1 (C), 163.2 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{21}N_3$ NaO_4: 342.1424 $[M+H]^+$; found: 342.1423.

***N*-*tert*-Butyl-*N*-[4-(methylthio)benzyl]-α-(methoxycarbonyl)-α-diazoacetamide (4c). 4c** was obtained as a yellow oil that solidified on refrigeration (555 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.2 equiv.), Et_3N (1.2 equiv.), 68%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 94%]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (s, 9H), 2.47 (s, 3H), 3.76 (s, 3H), 4.56 (s, 2H), 7.10 (d, *J* = 8.0 Hz, 2H) 7.20 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.0 (CH_3), 28.9 (3 CH_3), 51.3 (CH_2), 52.3 (CH_3), 59.1 (C), 68.2 (C), 126.9 (2 CH), 127.4 (2 CH), 136.5 (C), 137.6 (C), 163.0 (C), 163.2 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}N_3O_3S$: 336.1376 $[M+H]^+$; found: 336.1378.

***N*-*tert*-Butyl-*N*-[4-chlorobenzyl]-α-(methoxycarbonyl)-α-diazoacetamide (4d). 4d** was obtained as a yellow oil that solidified on refrigeration (514 mg) following the procedures described above [(a)

$ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 54%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 83%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 3.77 (s, 3H), 4.58 (s, 2H), 7.14 (d, *J* = 8.4 Hz, 2H) 7.30 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.1 (CH_2), 52.4 (CH_3), 59.2 (C), 68.4 (C), 128.3 (2 CH), 129.0 (2 CH), 133.2 (C), 138.3 (C), 163.0 (C), 163.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}ClN_3NaO_3$: 346.0929 $[M+H]^+$; found: 346.0937.

***N-tert*-Butyl-*N*-(4-cyanobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4e). 4e** was obtained as a red oil that solidified on refrigeration (155 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 52%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 33%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 3.77 (s, 3H), 4.67 (s, 2H), 7.33 (d, *J* = 8.0 Hz, 2H) 7.63 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 51.2 (CH_2), 52.4 (CH_3), 59.5 (C), 68.8 (C), 111.5 (C), 118.7 (C), 127.6 (2 CH), 132.6 (2 CH), 145.7 (C), 162.8 (C), 163.6 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{18}N_4NaO_3$: 337.1271 $[M+H]^+$; found: 337.1279.

***N-tert*-Butyl-*N*-[4-(dimethylamino)benzyl]-α-(methoxycarbonyl)-α-diazoacetamide (4f). 4f** was obtained as a yellow oil that solidified on refrigeration (190 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 58%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 85%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 2.93 (s, 6H), 3.77 (s, 3H), 4.52 (s, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 40.8 (2 CH_3), 51.3 (CH_2), 52.3 (CH_3), 58.9 (C), 68.0 (C), 112.7 (2 CH), 126.9 (C), 127.9 (2 CH), 150.0 (C), 163.0 (C), 163.3 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{25}N_4O_3$: 333.1921 $[M+H]^+$; found: 333.1925.

***N-tert*-Butyl-*N*-(3-chlorobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4g). 4g** was obtained as a yellow oil that solidified on refrigeration (505 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.2 equiv.), Et_3N (1.2 equiv.), 82%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 85%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 9H), 3.77 (s, 3H), 4.59 (s, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.18 (broad s, 1H), 7.22-7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 51.2 (CH_2), 52.4 (CH_3), 59.3 (C), 68.4 (C), 125.0 (CH), 127.1 (CH), 127.7 (CH), 130.1 (CH), 134.8 (C), 142.0 (C), 163.0 (C), 163.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}ClN_3NaO_3$: 346.0929 $[M+H]^+$; found: 346.0933.

***N-tert*-Butyl-*N*-(3-cyanobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4h). 4h** was obtained as a yellow oil that solidified on refrigeration (330 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.); (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 63% two steps]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 3.78 (s, 3H), 4.65 (s, 2H), 7.45-7.51 (m, 3H), 7.55-7.59 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 51.0 (CH_2), 52.4 (CH_3), 59.4 (C), 68.8 (C), 113.0 (C), 118.6 (C), 129.7 (CH), 130.4 (CH), 131.3 (CH), 131.4 (CH), 141.7 (C), 162.8 (C), 163.6 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{18}N_4NaO_3$: 337.1271 $[M+H]^+$; found: 337.1278.

***N-tert*-Butyl-*N*-(2-methoxybenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4i). 4i** was obtained as a yellow oil that solidified on refrigeration (384 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1 equiv.), Et_3N (1 equiv.); (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 70% two steps]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 9H), 3.77 (s, 3H), 3.80 (s, 3H), 4.60 (s, 2H), 6.85 (dd, *J* = 8.0, and 1.2 Hz, 1H), 6.92 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.18 (dd, *J* = 7.6 and 1.2 Hz, 1H), 7.25 (ddd, *J* = 8.0, 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.6 (3 CH_3), 48.5 (CH_2), 52.2 (CH_3), 55.6 (CH_3), 58.6 (C), 68.0 (C), 110.7 (CH), 120.5 (CH), 127.1 (C), 128.8 (CH), 129.3 (CH), 157.9 (C), 163.5 (C), 163.7 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}N_3O_4$: 320.1605 $[M+H]^+$; found: 320.1601.

***N-tert*-Butyl-*N*-(2-fluorobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4j). 4j** was obtained as a yellow oil that solidified on refrigeration (563 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1 equiv.), Et_3N (1 equiv.), 84%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 56%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (s, 9H), 3.78 (s, 3H), 4.67 (s, 2H), 7.00-7.14 (m, 2H) 7.22-7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.8 (3 CH_3), 46.2 (d, *J* = 3.4 Hz, CH_2), 52.3 (CH_3), 58.9 (C), 68.2 (C), 116.0 (d, *J* = 21.7 Hz, CH), 124.3 (d, *J* = 3.7 Hz, CH), 126.4 (d, *J* = 13.4 Hz, C), 129.3 (d, *J* = 8.2 Hz, CH), 129.5 (d, *J* = 4.3 Hz, CH), 160.8 (d, *J* = 246.5 Hz, C), 163.1 (C), 163.6 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}FN_3NaO_3$: 330.1224 $[M+H]^+$; found: 330.1225.

***N*-(2-Bromobenzyl)-*N-tert*-butyl-α-(methoxycarbonyl)-α-diazoacetamide (4k). 4k** was obtained as a yellow oil that solidified on refrigeration (417 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1 equiv.), Et_3N (1 equiv.); (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 83% two steps]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.76 (s, 3H), 4.72 (s, 2H), 7.13 (ddd, *J* = 8.0, 7.6 and 2.4 Hz, 1H), 7.26-7.34 (m, 2H), 7.54 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.6 (CH_2), 52.4 (CH_3), 59.4 (C), 67.6 (C), 122.1 (C), 127.5 (CH), 128.6 (CH), 128.9 (CH), 133.4 (CH), 138.5 (C), 163.2 (C), 163.6 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}BrN_3NaO_3$: 390.0424 $[M+H]^+$; found: 390.0432.

***N-tert*-Butyl-*N*-(2-iodobenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4l). 4l** was obtained as a yellow oil that solidified on refrigeration (260 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 64%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 89%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.76 (s, 3H), 4.63 (s, 2H), 6.97 (ddd, *J* = 8.0, 7.6 and 1.6 Hz, 1H), 7.24 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.35 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.83 (dd, *J* = 8.0 and 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.0 (3 CH_3), 52.4 (CH_3), 56.7 (CH_2), 59.6 (C), 67.6 (C), 97.1 (C), 127.9 (CH), 128.4 (CH), 129.1 (CH), 140.0 (CH), 141.2 (C), 163.2 (C), 163.5 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}IN_3NaO_3$: 438.0258 $[M+H]^+$; found: 438.0283.

***N-tert*-Butyl-*N*-(3,4-dimethoxybenzyl)-α-(methoxycarbonyl)-α-diazoacetamide (4m). 4m** was obtained as a yellow oil that solidified on refrigeration (570 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.2 equiv.), Et_3N (1.2 equiv.), 68%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 80%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 3.78 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.56 (s, 2H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.74 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.9 (3 CH_3), 51.3 (CH_2), 52.3 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 59.1 (C), 67.9 (C), 110.0 (CH), 111.4 (CH), 119.0 (CH), 132.1 (C), 148.4 (C), 149.2 (C), 163.2 (2 C). HRMS (ESI-TOF) calcd. for $C_{17}H_{24}N_3O_5$: 350.1710 $[M+H]^+$; found: 350.1713.

***N-tert*-Butyl-*N*-(1-phenylethyl)-α-(methoxycarbonyl)-α-diazoacetamide (7). 7** was obtained as a yellow oil (210 mg) following the procedures described above [(a) $ClCOCH_2CO_2Me$ (1.3 equiv.), Et_3N (1.3 equiv.), 35%; (b) *p*-ABSA (1.1 equiv.), DBU (1.5 equiv.), 63%]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 1.80 (d, *J* = 7.2 Hz, 3H), 3.70 (s, 3H), 5.19 (q, *J* = 7.2 Hz, 1H), 7.22-7.28 (m, 1H), 7.32-7.37 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.2 (CH_3), 29.5 (3 CH_3), 52.3 (CH_3), 56.3 (CH), 60.1 (C), 66.8 (C), 126.9 (2 CH), 127.2 (CH), 128.6 (2 CH), 142.3 (C), 163.2 (C), 164.2 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{21}N_3NaO_3$: 326.1475 $[M+H]^+$; found: 326.1471.

Representative Procedure for the Pd-Catalyzed Cyclisation Reactions (Table 2, Entry 3). A mixture of diazoamide **4a** (50 mg, 0.17 mmol), $[Pd(allyl)Cl]_2$ (3 mg, 0.008 mmol) in dichloroethane (10 mL) was stirred at reflux under Argon atmosphere for 24 h. The solvent was

removed in vacuo, and the residue was purified by chromatography (SiO_2, from hexanes to hexanes-EtOAc 2:3) to give β-lactam ***trans*-6a** (29.5 mg, 65%) and β-lactam ***cis*-6a** (11 mg, 25%).

Methyl 2-benzyl-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (2). 25 mg (55%, Table 1, Entry 5). Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.61 (s, 3H), 4.01 (dd, *J* = 14.8 and 1.6 Hz, 1H), 4.27 (dd, *J* = 14.8 and 2.4 Hz, 1H), 4.53 (d, *J* = 14.8 Hz, 1H), 4.69 (d, *J* = 14.8 Hz, 1H), 5.65 (d, *J* = 9.6 Hz, 1H), 6.24 (m, 1H), 6.42-6.54 (m, 3H), 7.23-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 47.0 (CH_2), 50.3 (CH_2), 53.0 (CH_3), 60.0 (C), 120.9 (CH), 122.4 (CH), 128.0 (CH), 128.1 (2 CH), 128.3 (CH), 128.7 (CH), 129.0 (2 CH), 130.0 (CH), 130.4 (C), 135.6 (C), 168.6 (C), 171.1 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}NO_3$: 296.1281 $[M+H]^+$; found: 296.1281.

Methyl *cis*-1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate (*cis*-3). This compound could not be isolated and characterized. ^{1}H NMR ($CDCl_3$, 400 MHz, significant signals from the crude reaction mixture) δ 3.33 (s, 3H), 3.93 (d, *J* = 14.8 Hz, 1H), 4.34 (d, *J* = 6.0 Hz, 1H), 4.71 (dd, *J* = 6.0 and 1.2 Hz, 1H), 4.94 (d, *J* = 14.8 Hz, 1H).

Methyl *trans*-1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate (*trans*-3). 10.5 mg (23%, Table 1, Entry 7). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 3.84 (d, *J* = 15.2 Hz, 1H), 3.93 (dd, *J* = 2.0 and 0.8 Hz, 1H), 4.71 (d, *J* = 2.0 Hz, 1H), 4.85 (d, *J* = 15.2 Hz, 1H), 7.14-7.17 (m, 2H), 7.23-7.40 (m, 8H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 45.1 (CH_2), 52.9 (CH_3), 57.2 (CH), 63.4 (CH), 126.9 (2 CH), 128.0 (CH), 128.5 (2 CH), 129.0 (2 CH), 129.2 (CH), 129.3 (2 CH), 134.8 (C), 136.0 (C), 162.4 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{18}NO_3$: 296.1281 $[M+H]^+$; found: 296.1275.

***N,N*-Dibenzyl-α-chloro-α-(methoxycarbonyl)acetamide.** Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 3H), 4.34 (d, *J* = 14.8 Hz, 1H), 4.45 (d, *J* = 17.2 Hz, 1H), 4.62 (d, *J* = 17.2 Hz, 1H), 4.88 (d, *J* = 14.8 Hz, 1H), 5.13 (s, 1H), 7.18-7.23 (m, 4H), 7.28-7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 48.9 (CH_2), 50.6 (CH_2), 54.0 (CH), 54.5 (CH_3), 126.7 (2 CH), 128.0 (CH), 128.3 (CH), 128.4 (2 CH), 129.0 (2 CH), 129.3 (2 CH), 132.3 (C), 136.2 (C), 165.5 (C), 165.6 (C). HRMS (ESI-TOF) calcd. for $C_{18}H_{19}ClNO_3$: 332.1048 $[M+H]^+$; found: 332.1049.

Methyl 2-*tert*-butyl-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5a). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 8:1 mixture of **5a** and ***trans*-6a**) δ 1.46 (s, 9H), 3.59 (s, 3H), 4.24 (dd, *J* = 15.2 and 1.6 Hz, 1H), 4.47 (dd, *J* = 15.2 and 2.0 Hz, 1H), 5.59 (dd, *J* = 9.2 and 0.8 Hz, 1H), 6.28 (m, 1H), 6.38-6.46 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 8:1 mixture of **5a** and ***trans*-6a**) δ 27.6 (3 CH_3), 49.6 (CH_2), 52.8 (CH_3), 55.0 (C), 61.3 (C), 120.5 (CH), 123.2 (CH), 127.8 (CH), 128.9 (CH), 129.9 (CH), 131.3 (C), 169.0 (C), 170.8 (C).

Methyl *cis*-1-*tert*-butyl-2-oxo-4-phenylazetidine-3-carboxylate (*cis*-6a). 11 mg (25%, Table 2, Entry 3). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.32 (s, 3H), 4.23 (d, *J* = 6.4 Hz, 1H), 4.91 (d, *J* = 6.4 Hz, 1H), 7.28-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.0 (CH_3), 55.2 (C), 56.8 (CH), 59.3 (CH), 127.2 (CH), 128.6 (2 CH), 128.9 (2 CH), 136.7 (C), 163.0 (C), 166.6 (C).). HRMS (ESI-TOF) calcd. for $C_{15}H_{20}NO_3$: 262.1438 $[M+H]^+$; found: 262.1439.

Methyl *trans*-1-*tert*-butyl-2-oxo-4-phenylazetidine-3-carboxylate (*trans*-6a). 29 mg (65%, Table 2, Entry 3). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 3.72 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 4.86 (d, *J* = 2.0 Hz, 1H), 7.31-7.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.8 (CH_3), 55.4 (C), 56.6 (CH), 62.5 (CH), 126.8 (2 CH), 128.9 (CH), 129.2 (2 CH), 139.2 (C), 162.1 (C), 167.7 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{20}NO_3$: 262.1438 $[M+H]^+$; found: 262.1439.

Methyl 2-*tert*-butyl-6-methoxy-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5b). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 10:1 mixture of **5b** and ***trans*-6b**) δ 1.45 (s, 9H), 3.60 (s, 3H), 3.61 (s, 3H), 4.18 (ddd, *J* = 14.4, 2.0 and 0.8 Hz, 1H), 4.42 (ddd, *J* = 14.4, 2.4 and 1.2 Hz, 1H), 5.63 (dd, *J* = 7.2 and 1.6 Hz, 1H), 5.73 (d, *J* = 10.8 Hz, 1H), 6.15 (dt, *J* = 7.2 and 2.0 Hz, 1H), 6.26 (dd, *J* = 10.8 and 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 10:1 mixture of **5b** and ***trans*-6b**) δ 27.6 (3 CH_3), 49.5 (CH_2), 52.9 (CH_3), 54.9 (C), 55.0 (CH_3), 60.8 (C), 101.8 (CH), 118.8 (CH), 124.9 (CH), 125.1 (C), 126.2 (CH), 159.0 (C), 169.3 (C), 170.7 (C).

Methyl *cis*-1-*tert*-butyl-4-(4-methoxyphenyl)-2-oxoazetidine-3-carboxylate (*cis*-6b). 8 mg (18%, Table S1, Entry 1). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 3.38 (s, 3H), 3.80 (s, 3H), 4.20 (d, *J* = 6.4 Hz, 1H), 4.87 (d, *J* = 6.4 Hz, 1H), 6.86 (d, *J*= 8.4 Hz, 2H), 7.29 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.0 (CH_3), 55.1 (C), 55.4 (CH_3), 56.4 (CH), 59.3 (CH), 113.9 (2 CH), 128.4 (2 CH), 128.5 (C), 160.0 (C), 163.1 (C), 166.8 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_4$: 292.1543 $[M+H]^+$; found: 292.1549.

Methyl *trans*-1-*tert*-butyl-4-(4-methoxyphenyl)-2-oxoazetidine-3-carboxylate (*trans*-6b). 18 mg (39%, Table S1, Entry 1). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 3.69 (d, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 4.81 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J*= 8.4 Hz, 2H), 7.30 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.8 (CH_3), 55.3 (C), 55.5 (CH_3), 56.3 (CH), 62.5 (CH), 114.5 (2 CH), 128.1 (2 CH), 131.0 (C), 160.1 (C), 162.2 (C), 167.9 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_4$: 292.1543 $[M+H]^+$; found: 292.1547.

Methyl 2-*tert*-butyl-6-(methylthio)-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5c). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 3.3:1 mixture of ***trans*-6c** and **5c**) δ 1.45 (s, 9H), 2.32 (s, 3H), 3.61 (s, 3H), 4.21 (d, *J* = 14.8 Hz, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 5.64 (d, *J* = 10.4 Hz, 1H), 6.14 (d, *J* = 6.8 Hz, 1H), 6.38 (d, *J* = 10.8 Hz, 1H), 6.39 (d, *J* = 6.8 Hz, 1H).

Methyl *cis*-1-*tert*-butyl-4-[4-(methylthio)phenyl]-2-oxoazetidine-3-carboxylate (*cis*-6c). 4.5 mg (10%, Table S1, Entry 3). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 2.48 (s, 3H), 3.37 (s, 3H), 4.22 (d, *J* = 6.4 Hz, 1H), 4.87 (d, *J* = 6.4 Hz, 1H), 7.20 (d, *J*= 8.4 Hz, 2H), 7.29 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.6 (CH_3), 28.3 (3 CH_3), 52.1 (CH_3), 55.2 (C), 56.4 (CH), 59.2 (CH), 126.1 (2 CH), 127.7 (2 CH), 133.2 (C), 139.6 (C), 163.0 (C), 166.6 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_3S$: 308.1315 $[M+H]^+$; found: 308.1319.

Methyl *trans*-1-*tert*-butyl-4-[4-(methylthio)phenyl]-2-oxoazetidine-3-carboxylate (*trans*-6c). 22 mg (48%, Table S1, Entry 3). Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 2.49 (s, 3H), 3.68 (d, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 4.82 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J*= 8.0 Hz, 2H), 7.30 (d, *J*= 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.7 (CH_3), 28.3 (3 CH_3), 52.8 (CH_3), 55.4 (C), 56.3 (CH), 62.4 (CH), 126.8 (2 CH), 127.3 (2 CH), 135.8 (C), 139.7 (C), 162.1 (C), 167.7 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_3S$: 308.1315 $[M+H]^+$; found: 308.1318.

Methyl *cis*-1-*tert*-butyl-4-(4-chlorophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6d). 19 mg (42%, Table S1, Entry 5). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 3.38 (s, 3H), 4.23 (d, *J* = 6.4 Hz, 1H), 4.89 (d, *J* = 6.4 Hz, 1H), 7.33 (s, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.2 (CH_3), 55.3 (C), 56.1 (CH), 59.2 (CH), 128.6 (2 CH), 128.8 (2 CH), 134.8 (C), 135.4 (C), 162.8 (C), 166.4 (C).

HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1050.

Methyl *trans*-1-*tert*-butyl-4-(4-chlorophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6d). 18 mg (40%, Table S1, Entry 5). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 3.67 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 4.84 (d, *J* = 2.0 Hz, 1H), 7.32-7-38 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.9 (CH_3), 55.5 (C), 55.9 (CH), 62.5 (CH), 128.1 (2 CH), 129.4 (2 CH), 134.8 (C), 137.9 (C), 162.0 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1051.

Methyl *cis*-1-*tert*-butyl-4-(4-cyanophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6e). 12 mg (27%, Table S1, Entry 8). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 3.34 (s, 3H), 4.28 (d, *J* = 6.4 Hz, 1H), 4.94 (d, *J* = 6.4 Hz, 1H), 7.52 (d, *J*= 8.4 Hz, 2H), 7.65 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.2 (CH_3), 55.5 (C), 56.0 (CH), 59.2 (CH), 112.9 (C), 118.4 (C), 128.0 (2 CH), 132.4 (2 CH), 142.5 (C), 162.5 (C), 166.0 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}N_2O_3$: 287.1390 $[M+H]^+$; found: 287.1389.

Methyl *trans*-1-*tert*-butyl-4-(4-cyanophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6e). 23 mg (51%, Table S1, Entry 8). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 3.67 (d, *J* = 2.4 Hz, 1H), 3.79 (s, 3H), 4.92 (d, *J* = 2.4 Hz, 1H), 7.53 (d, *J*= 8.4 Hz, 2H), 7.69 (d, *J*= 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 53.1 (CH_3), 55.7 (C), 55.8 (CH), 62.5 (CH), 113.0 (C), 118.3 (C), 127.5 (2 CH), 133.1 (2 CH), 144.9 (C), 161.7 (C), 167.0 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}N_2O_3$: 287.1390 $[M+H]^+$; found: 287.1393.

Methyl *trans*-1-*tert*-butyl-4-[4-(dimethylamino)phenyl]-2-oxoazetidine-3-carboxylate (*trans*-6f). 6 mg (14%, Table S1, Entry 9). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 2.96 (s, 6H), 3.70 (d, *J* = 2.0 Hz, 1H), 3.76 (s, 3H), 4.77 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J*= 8.8 Hz, 2H), 7.23 (d, *J*= 8.8 Hz, 2H). HRMS (ESI-TOF) calcd. for $C_{17}H_{25}N_2O_3$: 305.1860 $[M+H]^+$; found: 305.1860.

Methyl *cis*-1-*tert*-butyl-4-(3-chlorophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6g). 20 mg (44%, Table S1, Entry 11). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.40 (s, 3H), 4.24 (d, *J* = 6.4 Hz, 1H), 4.87 (d, *J* = 6.4 Hz, 1H), 7.26-7.32 (m, 3H), 7.39 (d, *J*= 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.1 (CH_3), 55.4 (C), 56.1 (CH), 59.3 (CH), 125.4 (broad CH), 127.4 (broad CH), 129.1 (CH), 129.9 (CH), 134.6 (C), 139.0 (C), 162.8 (C), 166.3 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1057.

Methyl *trans*-1-*tert*-butyl-4-(3-chlorophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6g). 16.5 mg (36%, Table S1, Entry 11). Brown gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 3.68 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 4.83 (d, *J* = 2.0 Hz, 1H), 7.27-7.34 (m, 3H), 7.39 (broad singlet, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.9 (CH_3), 55.6 (C), 55.9 (CH), 62.5 (CH), 124.8 (CH), 127.0 (CH), 129.2 (CH), 130.5 (CH), 135.2 (C), 141.5 (C), 161.9 (C), 167.3 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}ClNO_3$: 296.1048 $[M+H]^+$; found: 296.1050.

Methyl *cis*-1-*tert*-butyl-4-(3-cyanophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6h). 10 mg (22%, Table S1, Entry 13). Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.38 (s, 3H), 4.28 (d, *J* = 6.4 Hz, 1H), 4.93 (d, *J* = 6.4 Hz, 1H), 7.50 (dd, *J*= 8.4 and 7.6 Hz, 1H), 7.64 (dt, *J*= 7.6 and 1.6 Hz, 1H), 7.65-7.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.3 (CH_3), 55.5 (C), 55.7 (CH), 59.3 (CH), 112.9 (C), 118.4 (C), 129.5 (CH), 130.9 (broad, CH), 131.5 (broad, CH), 132.6 (CH), 138.8 (C), 162.5 (C), 166.1 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}N_2O_3$: 287.1390 $[M+H]^+$; found: 287.1399.

Methyl *trans*-1-*tert*-butyl-4-(3-cyanophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6h). 19.5 mg (43%, Table S1, Entry 13). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 3.68 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 4.91 (d, *J* = 2.4 Hz, 1H), 7.54 (td, *J*= 7.6 and 0.4 Hz, 1H), 7.64-7.71 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 53.0 (CH_3), 55.5 (CH), 55.7 (C), 62.5 (CH), 113.5 (C), 118.3 (C), 130.2 (CH), 130.4 (CH), 130.8 (CH), 132.6 (CH), 141.2 (C), 161.7 (C), 167.0 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{19}N_2O_3$: 287.1390 $[M+H]^+$; found: 287.1387.

Methyl *cis*-1-*tert*-butyl-4-(2-methoxyphenyl)-2-oxoazetidine-3-carboxylate (*cis*-6i). 5 mg (10%, Table S1, Entry 16). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 9H), 3.29 (s, 3H), 3.85 (s, 3H), 4.22 (d, *J* = 6.4 Hz, 1H), 5.43 (d, *J* = 6.4 Hz, 1H), 6.85 (d, *J*= 8.0 Hz, 1H), 6.94 (ddd, *J*= 8.0, 7.6 and 0.8 Hz, 1H), 7.26 (dd, *J* = 8.0 and 7.6 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 1:8 mixture of **5i** and ***cis*-6i**) δ 28.1 (3 CH_3), 50.0 (CH), 51.8 (CH_3), 54.9 (C), 55.8 (CH_3), 58.7 (CH), 110.6 (CH), 120.2 (CH), 124.8 (C), 127.5 (CH), 129.6 (CH), 157.3 (C), 163.8 (C), 166.8 (C).

Methyl *trans*-1-*tert*-butyl-4-(2-methoxyphenyl)-2-oxoazetidine-3-carboxylate (*trans*-6i). 29 mg (63%, Table S1, Entry 16). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 3.78 (s, 3H), 3.84 (s, 3H), 3.86 (broad, 1H), 5.17 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J*= 8.0 and 1.2 Hz, 1H), 6.96 (td, *J*= 7.6 and 1.2 Hz, 1H), 7.30 (ddd, *J*= 8.0, 7.6 and 2.0 Hz, 1H), 7.35 (dd, *J*= 7.6 and 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.0 (3 CH_3), 52.2 (broad, CH), 52.7 (CH_3), 55.0 (C), 55.5 (CH_3), 60.4 (CH), 111.0 (CH), 120.9 (CH), 126.5 (C), 128.5 (broad, CH), 129.9 (CH), 157.7 (C), 162.5 (C), 168.4 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_4$: 292.1543 $[M+H]^+$; found: 292.1539.

Methyl *cis*-1-*tert*-butyl-4-(2-fluorophenyl)-2-oxoazetidine-3-carboxylate (*cis*-6j). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 8:1 mixture of ***cis*-6j** and ***trans*-6j**) δ 1.32 (s, 9H), 3.36 (broad s, 3H), 4.28 (d, *J* = 6.4 Hz, 1H), 5.30 (broad, 1H), 7.05 (ddd, *J*= 10.4, 8.0 and 1.2 Hz, 1H), 7.15 (td, *J*= 7.6 and 1.2 Hz, 1H), 7.27-7.33 (m, 1H), 7.49 (ddd, *J*= 8.0, 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 8:1 mixture of ***cis*-6j** and ***trans*-6j**) δ 28.1 (3 CH_3), 52.1 (CH_3), 55.2 (C), 58.5 (broad, CH), 61.1 (broad, CH), 115.7 (d, *J* = 21.5 Hz, CH), 124.0 (d, *J* = 12.0 Hz, CH), 124.0 (d, *J*= 3.6 Hz, CH), 128.0 (broad, C), 130.4 (d, *J* = 8.3 Hz, CH), 163.0 (C), 166.4 (C). One C was not observed.

Methyl *trans*-1-*tert*-butyl-4-(2-fluorophenyl)-2-oxoazetidine-3-carboxylate (*trans*-6j). 30 mg (66%, Table S1, Entry 18). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 3.79 (s, 3H), 3.84 (d, *J* = 2.4 Hz, 1H), 5.16 (d, *J* = 2.4 Hz, 1H), 7.08 (ddd, *J*= 10.4, 8.0 and 1.2 Hz, 1H), 7.18 (td, *J*= 7.6 and 1.2 Hz, 1H), 7.30-7.36 (m, 1H), 7.43 (td, *J*= 7.6 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.0 (3 CH_3), 50.3 (d, *J* = 3.8 Hz, CH), 52.9 (CH_3), 55.3 (C), 61.1 (d, *J* = 1.8 Hz, CH), 116.3 (d, *J* = 21.5 Hz, CH), 124.8 (d, *J* = 3.6 Hz, CH), 126.0 (d, *J* = 11.9 Hz, C), 128.5 (d, *J*= 3.6 Hz, CH), 130.6 (d, *J* = 8.4 Hz, CH), 160.9 (d, *J* = 248.7 Hz, C), 161.9 (C), 167.6 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}FNO_3$: 280.1343 $[M+H]^+$; found: 280.1345.

Methyl 2-*tert*-butyl-8-bromo-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5k). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1:2 mixture of **5k** and ***trans*-6k**) δ 1.48 (s, 9H), 3.61 (s, 3H), 4.15 (d, *J* = 16.0 Hz, 1H), 4.28 (d, *J* = 16.0 Hz, 1H), 5.65-5.69 (m, 1H), 6.36-6.43 (m, 2H), 6.50-6.57 (m, 1H).

Methyl *cis*-4-(2-bromophenyl)-1-*tert*-butyl-2-oxoazetidine-3-carboxylate (*cis*-6k). 16 mg (34%, Table S1, Entry 19). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 9H), 3.31 (s, 3H), 4.31 (d, *J* = 6.4 Hz, 1H), 5.39 (d, *J* = 6.4 Hz, 1H), 7.18 (ddd, *J*= 8.0, 7.2 and 1.6 Hz, 1H), 7.33 (ddd, *J*= 7.6, 7.2 and 1.2 Hz, 1H), 7.53-7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.1 (3 CH_3), 52.0 (CH_3), 55.2 (C), 55.5 (CH), 58.4 (CH), 123.4 (C), 127.2 (CH), 128.5 (CH), 130.0 (CH), 133.0 (CH), 135.7 (C), 163.3 (C), 166.2 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}BrNO_3$: 340.0543 $[M+H]^+$; found: 340.0542.

Methyl *trans*-4-(2-bromophenyl)-1-*tert*-butyl-2-oxoazetidine-3-carboxylate (*trans*-6k). 14 mg (31%, Table S1, Entry 19). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.59 (broad, 1H), 3.80 (s, 3H), 5.38 (broad, 1H), 7.19 (ddd, *J*= 8.0, 7.6 and 1.2 Hz, 1H), 7.37 (ddd, *J*= 8.0, 7.6 and 1.2 Hz, 1H), 7.50 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.57 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.1 (3 CH_3), 52.9 (CH_3), 55.2 (broad, CH), 55.4 (C), 62.1 (broad, CH), 127.2 (broad, CH), 128.1 (CH), 128.5 (C), 130.1 (CH), 133.0 (C), 133.4 (broad, CH), 162.5 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}BrNO_3$: 340.0543 $[M+H]^+$; found: 340.0552.

Methyl 2-*tert*-butyl-8-iodo-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5l). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1:3.3 mixture of **5l** and ***trans*-6l**) δ 1.49 (s, 9H), 3.60 (s, 3H), 4.04 (d, *J* = 16.4 Hz, 1H), 4.22 (d, *J* = 16.4 Hz, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 6.23 (dd, *J* = 11.6 and 6.0 Hz, 1H), 6.43 (dd, *J* = 10.0 and 6.0 Hz, 1H), 6.72 (d, *J* = 11.6 Hz, 1H).

Methyl *cis*-4-(2-iodophenyl)-1-*tert*-butyl-2-oxoazetidine-3-carboxylate (*cis*-6l). 23 mg (49%, Table S1, Entry 21). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 9H), 3.30 (s, 3H), 4.31 (d, *J* = 6.4 Hz, 1H), 5.22 (d, *J* = 6.4 Hz, 1H), 7.02 (ddd, *J*= 8.0, 7.2 and 1.6 Hz, 1H), 7.36 (ddd, *J*= 8.0, 7.2 and 1.6 Hz, 1H), 7.52 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.83 (dd, *J* = 8.0 and 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.2 (3 CH_3), 52.0 (CH_3), 55.3 (C), 58.4 (CH), 60.6 (CH), 98.7 (C), 128.0 (CH), 128.2 (CH), 130.4 (CH), 138.5 (C), 139.7 (CH), 163.2 (C), 166.1 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}INO_3$: 388.0404 $[M+H]^+$; found: 388.0405.

Methyl *trans*-4-(2-iodophenyl)-1-*tert*-butyl-2-oxoazetidine-3-carboxylate (*trans*-6l). 18 mg (38%, Table S1, Entry 21). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.55 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 3H), 5.24 (d, *J* = 2.0 Hz, 1H), 7.03 (ddd, *J*= 8.0, 7.2 and 2.0 Hz, 1H), 7.40 (ddd, *J*= 8.0, 7.2 and 1.2 Hz, 1H), 7.46 (dd, *J* = 8.0 and 2.0 Hz, 1H), 7.85 (dd, *J* = 8.0 and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.2 (3 CH_3), 52.9 (CH_3), 55.5 (C), 60.3 (CH), 62.4 (CH), 98.4 (C), 126.9 (broad, CH), 128.9 (CH), 130.4 (CH), 140.0 (broad, CH), 141.4 (C), 162.5 (C), 167.4 (C). HRMS (ESI-TOF) calcd. for $C_{15}H_{19}INO_3$: 388.0404 $[M+H]^+$; found: 388.0404.

Methyl 2-*tert*-butyl-5,6-dimethoxy-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (5m). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1.5:1 mixture of **5m** and ***trans*-6m**) δ 1.46 (s, 9H), 3.61 (s, 3H), 3.67 (s, 3H), 3.73 (s, 3H), 4.21 (ddd, *J* = 14.4, 1.6 and 0.8 Hz, 1H), 4.40 (ddd, *J* = 14.4, 2.4 and 1.2 Hz, 1H), 5.01 (s, 1H), 5.67 (d, *J* = 7.2 Hz, 1H), 6.00 (ddd, *J* = 7.2, 2.4 and 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 1.5:1 mixture of **5m** and ***trans*-6m**) δ 27.6 (3 CH_3), 49.2 (CH_2), 52.9 (CH_3), 55.0 (C), 55.9 (CH_3), 56.2 (CH_3), 57.9 (C), 99.8 (CH), 103.5 (CH), 117.3 (CH), 131.1 (C), 152.3 (C), 154.9 (C), 169.9 (C), 171.1 (C).

Methyl *cis*-1-*tert*-butyl-4-(3,4-dimethoxyphenyl)-2-oxoazetidine-3-carboxylate (*cis*-6m). 3 mg (6%, Table S1, Entry 24). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.40 (s, 3H), 3.88 (s, 6H), 4.21 (d, *J* = 6.4 Hz, 1H), 4.86 (d, *J* = 6.4 Hz, 1H), 6.82 (d, *J*= 8.4 Hz, 1H), 6.91-6.93 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (3 CH_3), 52.2 (CH_3), 55.1 (C), 56.0 (CH_3), 56.1 (CH_3), 56.8 (CH), 59.3 (CH), 109.8 (broad, CH), 110.9 (CH), 120.1 (broad, CH), 129.0 (C), 149.0 (C), 149.4 (C), 163.0 (C), 166.8 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{24}NO_5$: 322.1654 $[M+H]^+$; found: 322.1656.

Methyl *trans*-1-*tert*-butyl-4-(3,4-dimethoxyphenyl)-2-oxoazetidine-3-carboxylate (*trans*-6m). 17.5 mg (38%, Table S1, Entry 24). Amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 3.71 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 3.89 (s, 6H), 4.82 (d, *J* = 2.4 Hz, 1H), 6.85 (d, *J*= 8.0 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.0 and 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.2 (3 CH_3), 52.8 (CH_3), 55.3 (C), 56.1 (CH_3), 56.2 (CH_3), 56.6 (CH), 62.5 (CH), 109.1 (CH), 111.4 (CH), 119.6 (CH), 131.4 (C), 149.5 (C), 149.6 (C), 162.2 (C), 167.8 (C). HRMS (ESI-TOF) calcd. for $C_{17}H_{24}NO_5$: 322.1654 $[M+H]^+$; found: 322.1655.

Methyl 2-*tert*-butyl-1-methyl-3-oxo-1H-2,3-dihydrocyclohepta[*c*]pyrrole-3a-carboxylate (8). 7 mg (15%, Table 3, Entry 1). ^{1}H NMR ($CDCl_3$, 400 MHz, signals from a 1:1.2 mixture of stereoisomers) δ 1.37 (d, *J* = 6.0 Hz, 3H minor isomer), 1.50 (s, 9H major isomer), 1.51 (s, 9H minor isomer), 1.72 (d, *J* = 6.0 Hz, 3H major isomer), 3.55 (s, 3H minor isomer), 3.60 (s, 3H major isomer), 4.53 (qd, *J* = 6.0 and 1.6 Hz, 1H major isomer), 4.75 (qd, *J* = 6.0 and 1.6 Hz, 1H minor isomer), 5.57 (d, *J* = 9.6 Hz, 1H major isomer), 5.65 (d, *J* = 9.6 Hz, 1H minor isomer), 6.23-6.28 (m, 1H major and 1H minor isomer), 6.35-6.53 (m, 3H major and 3H minor isomer). ^{13}C NMR ($CDCl_3$, 100.6 MHz, signals from a 1:1.2 mixture of stereoisomers) δ 25.7 (CH_3), 28.3 (CH_3), 28.4 (3 CH_3), 29.4 (3 CH_3), 52.8 (CH_3), 52.9 (CH_3), 55.3 (C), 55.4 (C), 57.5 (CH), 57.6 (CH), 60.7 (C), 61.0 (C), 118.8 (CH), 119.8 (CH), 122.8 (CH), 124.0 (CH), 127.7 (2 CH), 128.6 (CH), 128.9 (CH), 129.4 (CH), 130.0 (CH), 138.4 (C), 138.6 (C), 168.9 (C), 169.0 (C), 170.1 (C), 170.7 (C).

Methyl (2RS,3RS)-1-(*tert*-butyl)-2-methyl-4-oxo-2-phenylazetidine-3-carboxylate (9). 10.5 mg (23%, Table 3, Entry 3). Yellow gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 2.11 (s, 3H), 3.23 (s, 3H), 3.84 (s, 1H), 7.29-7.38 (m, 3H), 7.46-7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.2 (CH_3), 28.6 (3 CH_3), 51.8 (CH_3), 55.8 (C), 64.9 (C), 66.8 (CH), 126.6 (2 CH), 128.3 (2 CH), 139.9 (C), 162.8 (C), 166.7 (C). One CH was not observed. HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_3$: 276.1594 $[M+H]^+$; found: 276.1595.

Methyl (2RS,3SR)-1-(*tert*-butyl)-2-methyl-4-oxo-2-phenylazetidine-3-carboxylate (10). 21 mg (47%, Table 3, Entry 3). Amorphous orange solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 1.96 (s, 3H), 3.75 (s, 3H), 3.86 (s, 1H), 7.32 (ddd, *J* = 7.2, 6.0 and 1.2 Hz, 1H), 7.37-7.42 (m, 2H), 7.47-7.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7 (CH_3), 28.6 (3 CH_3), 52.4 (CH_3), 56.0 (C), 62.6 (C), 67.0 (CH), 125.5 (2 CH), 128.3 (CH), 128.9 (2 CH), 143.3 (C), 162.9 (C), 167.3 (C). HRMS (ESI-TOF) calcd. for $C_{16}H_{22}NO_3$: 276.1594 $[M+H]^+$; found: 276.1596.

Computational Details. All the calculations reported in this paper were performed with the Gaussian 09 suite of programs.[20] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[21] in conjunction with the D3 dispersion correction suggested by Grimme et al.[22] using the double-ζ quality plus polarization def2-SVP[23] basis set for all atoms. Reactants and products were characterized by frequency calculations,[24] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic

Reaction Coordinate (IRC) method.[25] Solvents effects were also taken into account using the Polarizable Continuum Model (PCM)[26] during the geometry optimizations. This level is denoted PCM-(dichloroethane)-B3LYP-D3/def2-SVP. Single-point energy refinements were carried out at the M06L[27]/def2-TZVPP[24] level of theory employing the PCM model to account for solvation. This level is denoted PCM(dichloroethane)-M06L/def2-TZVP//PCM-(dichloroethane)-B3LYP-D3/def2-SVP.

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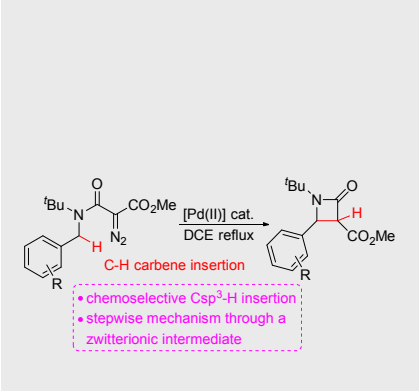
Layout 1:

FULL PAPER

The intramolecular carbene C–H insertion of α-diazo-α-(methoxycarbonyl)acetamides leading to β-lactams is effectively catalyzed by Pd(II)-complexes. According to DFT calculations, this insertion reaction occurs stepwise through a metallacarbene-induced zwitterionic intermediate.



C-H activation*

Daniel Solé, Ferran Pérez-Janer, M.-Lluïsa Bennasar, and Israel Fernández**

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Palladium Catalysis in the Intramolecular Carbene C–H Insertion of α-Diazo-α-(methoxycarbonyl)acetamides to Form β-Lactams

*one or two words that highlight the emphasis of the paper or the field of the study