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# Stable and Persistent Acyclic Diaminocarbenes with Cycloalkyl Substituents and Their Transformation to β-Lactams by Uncatalysed Carbonylation with CO

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*Dedicated to Prof. Dietmar Stalke on the occasion of his 60th birthday*

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**Abstract:** Four new acyclic diaminocarbenes (ADACs), viz. [(*cyclo*-$C_nH_{2n-1}$)$_2$N]$_2$C (*n* = 5 – 7) and *i*Pr$_2$N–C–N(*cyclo*-$C_6H_{11}$)$_2$, were synthesised by reacting the corresponding formamidinium hexafluorophosphates with NaN(SiMe$_3$)$_2$. Their nucleophilicities and electrophilicities were respectively judged from the $^1J_{CH}$ values determined for the N$_2$CH unit of the corresponding formamidinium cations and from the $^{77}$Se NMR chemical shifts of the selenourea derivatives obtained from the reaction of elemental selenium with the corresponding ADACs. An ambiphilic profile essentially identical to that of the "Alder carbene" (*i*Pr$_2$N)$_2$C was found in each case. Similar to the latter carbene, the new ADACs undergo a well-defined thermal decomposition by β-fragmentation, affording an alkene and a formamidine. The stabilities of [(*cyclo*-$C_nH_{2n-1}$)$_2$N]$_2$C depend strongly on the value of *n*, following the order 6 > 5 > 7, with the latter congener being too unstable for isolation. [(*cyclo*-C$_6$H$_{11}$)$_2$N]$_2$C shows no thermal decomposition at room temperature in solution and is thus significantly more stable than (*i*Pr$_2$N)$_2$C. The stability of *i*Pr$_2$N–C–N(*cyclo*-C$_6$H$_{11}$)$_2$ is intermediate between that of (*i*Pr$_2$N)$_2$C and [(*cyclo*-C$_6$H$_{11}$)$_2$N]$_2$C, its β-fragmentation selectively affording propene and *i*PrN=CH–N(*cyclo*-C$_6$H$_{11}$)$_2$. [(*cyclo*-$C_nH_{2n-1}$)$_2$N]$_2$C (*n* = 5 – 7) react readily with CO under mild conditions, selectively affording trisubstituted spirocyclic β-lactam derivatives with an antimicrobial activity spectrum similar to that of penicillin G.

## Introduction

Acyclic diaminocarbenes (ADACs) are currently attracting increased attention.[1, 2] This may be surprising at first glance, because the number of ADACs which are sufficiently stable for isolation is very limited and only four crystallographically characterised examples are known to date.[3] However, even $(Me_2N)_2C$, which is the sterically least encumbered ADAC that can be generated as a free carbene in solution, is sufficiently persistent for follow-up chemistry.[2k, 4] The attractiveness of ADACs lies in their special steric and electronic properties,[1] which are substantially different from those of the more familiar N-heterocyclic carbenes (NHCs).[5] ADACs exhibit comparatively wide N–C–N angles (ca. 121°[3] vs. ca. 100 – 106° for standard five-membered ring NHCs[6]). Consequently, their substituents are positioned closer to the divalent carbon atom, which may be advantageous for catalytic applications.[1c,f] In terms of electronics, ADACs exhibit a much higher electrophilicity and nucleophilicity than NHCs. ADACs are superior even to cyclic (alkyl)(amino)carbenes (CAACs)[7] in this respect.[4a] Owing to their ambiphilic profile, CAACs are suitable for the activation of fundamentally important small molecules like ammonia and carbon monoxide at room temperature or below.[8] We recently found that ADACs, too, react with CO under very mild conditions.[4b, 9] This behaviour is perfectly plausible in view of the similar electronic profiles of CAACs and ADACs.[4a, 10] The primary carbonylation product of an ADAC is the corresponding diaminoketene $(R_2N)_2C{=}C{=}O$, which is a transient species too unstable for isolation.[10, 11] It is usually trapped through nucleophilic addition of unreacted ADAC, affording a betainic oxyallyl compound of the type $[(R_2N)_2C]_2CO$.[4b] This process is unfavourable in sterically encumbered cases such as, for example, the iconic "Alder carbene" $(i\mathrm{Pr}_2N)_2C$,[3c] where instead a *retro*-Wolff rearrangement of the diaminoketene takes place.[4b, 9b] The resulting transient (amido)(amino)carbene $R_2N{-}C{-}C(O)NR_2$[12] subsequently undergoes an intramolecular C–H insertion, affording a β-lactam derivative. In addition to the

previously unrecognised high reactivity of the "Alder carbene" towards carbon monoxide, we also uncovered that this long-known ADAC is not stable at room temperature in solution, but undergoes a β-fragmentation, cleanly affording propene and *N*,*N*,*N*'-triisopropylformamidine.[13] In the same vein, the unsymmetrical ADAC (*i*Pr$_2$N)C(PipMe$_2$) (PipMe$_2$ = *cis*-2,6-dimethylpiperidino) reported by Herrmann and co-workers[14] was found to show a carbonylation and β-fragmentation behaviour strictly analogous to that of the "Alder carbene".[9a] This similarity in chemical behaviour is not at all surprising because the cyclic amino group (PipMe$_2$) can be viewed as a conformationally constrained version of the *i*Pr$_2$N group. In contrast to these two isolable, but still highly reactive, dialkylamino-substituted acyclic carbenes, alkyl(aryl)amino-substituted congeners (ArMeN)$_2$C (Ar = mesityl,[3b] 2,6-diisopropylphenyl[15]) reported by Bielawski and co-workers are significantly less reactive. They show perfect thermal stability at room temperature. Similar to the widely used and highly popular NHCs, they are inert towards carbon monoxide.[16] This may be ascribed to their comparatively low electrophilicity, as indicated by the $^{77}$Se NMR signal of the corresponding selenium adducts[17] located at ca. 400 ppm.[3a] This value is already at the low-field end of the region typical of selenium adducts of NHCs.[18] Selenium adducts of other acyclic diaminocarbenes exclusively exhibit signals at significantly lower field (≥ ca. 450 ppm).[3a] According to the "selenium scale", diamidocarbenes are considerably more electrophilic than ADACs, since their selenium adducts show signals at extremely low field (ca. 850 ppm).[17a] However, this enhanced electrophilicity coincides with attenuated nucleophilicity lower than that of prototypical NHCs.[19] Note that these carbenes do not tend to form stable carbonylation products and thus apparently lack the ambiphilic profile necessary for this reaction.[10, 20, 21] We herein describe the synthesis and chemical properties of three ADACs of the type [(*cyclo*-C$_n$H$_{2n-1}$)$_2$N]$_2$C (**1a** – **c**; *n* = 5, 6, 7). These compounds are the first cycloalkyl-substituted ADACs. They are akin to the "Alder carbene", since a cycloalkyl substituent can be viewed as a conformationally constrained version of an

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isopropyl substituent (Figure 1). While the steric parameter of a cyclohexyl group is identical to that of an isopropyl group on Beckhaus' $S_f$ scale (2.29), the steric impact of a cyclopentyl ($S_f$ = 1.81) and a cycloheptyl group ($S_f$ = 2.94) is respectively lower and higher than that.[22]

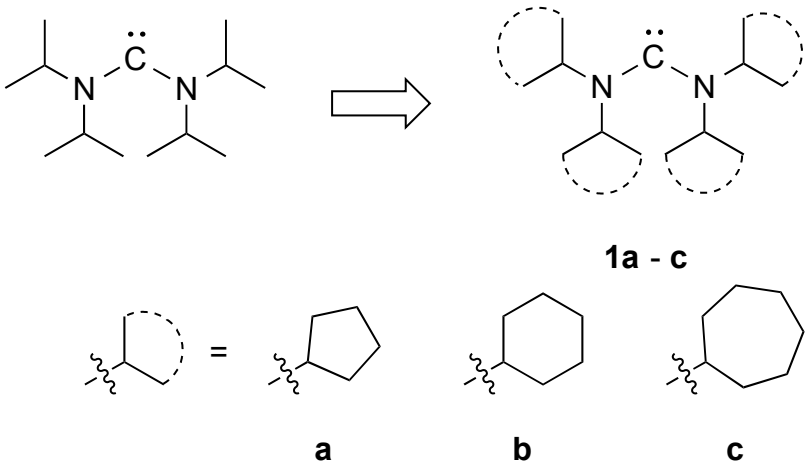


**Figure 1.** Analogy between the "Alder carbene" ($i$Pr$_2$N)$_2$C and the ADACs of type **1** studied in this work.

## Results and Discussion

### Synthesis

Free ADACs are usually generated by deprotonation of the corresponding formamidinium salts,[23] which is also the most widely used method for the synthesis of NHCs.[24] The use of hexafluorophosphate as counter anion is known to facilitate the purification of these most popular diaminocarbene precursors.[25] The ADAC precursors of the type **1**H[PF$_6$] were synthesised according to the protocol developed by Alder and co-workers (Scheme 1).[25]

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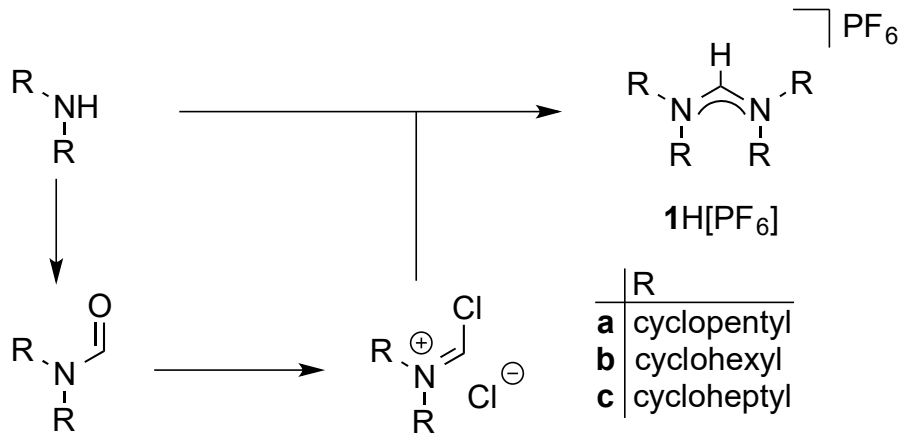


**Scheme 1.** Synthesis of the ADAC precursors of the type **1**H[$PF_6$].

The sequence starts from the secondary amines (*cyclo*-$C_nH_{2n-1})_2NH$ ($n$ = 5, 6, 7). The respective amine was transformed to the formamide (*cyclo*-$C_nH_{2n-1})_2N–CHO$ with formic acid. Subsequent activation of the formamide with oxalyl chloride afforded the Vilsmeyer complex [(*cyclo*-$C_nH_{2n-1})_2N{=}CHCl]Cl$, which was then reacted with (*cyclo*-$C_nH_{2n-1})_2NH$ to afford the formamidinium chloride **1**HCl. One equivalent of triethylamine was used to mop up the hydrogen chloride produced in the latter step. Finally, an anion exchange was performed with ammonium hexafluorophosphate. **1b**H[$PF_6$] and **1c**H[$PF_6$] were structurally characterised by single-crystal X-ray diffraction (vide infra).

The target ADACs were generated by treatment of the respective formamidinium hexafluorophosphate with sodium bis(trimethylsilyl)amide. The three carbenes show markedly different thermal stabilities. Only **1b** could be isolated in crystalline form and was structurally characterised by single-crystal X-ray diffraction (vide infra). In view of the β-fragmentation observed for the "Alder carbene" already at room temperature (vide supra), we were surprised to find that the cyclohexyl congener **1b** is perfectly stable in $C_6D_6$ solution even at elevated temperatures up to ca. 40 °C. In contrast, **1a** decomposes faster than the "Alder carbene". When the work-up was performed rapidly, only traces of the fragmentation products *N*,*N*,*N*'-tricyclopentylformamidine and cyclopentene were apparent in the $^1$H NMR spectrum; after several days at room temperature in $C_6D_6$, the $^{13}$C NMR signal at 266.0 ppm

due to the divalent carbon atom was not observed any more, indicating quantitative decomposition of **1a** on this timescale (see Figures S16 – S21 in the Supporting Information). The decomposition of **1c** to cycloheptene and *N*,*N*,*N*'-tricycloheptylformamidine was considerably faster and happened on a timescale of hours (see Figures S24 – S27 in the Supporting Information). The diagnostic $C_{carbene}$ signal at 254.7 ppm could be observed only when the carbene was subjected to $^{13}C$ NMR spectroscopic analysis immediately after its generation in $C_6D_6$. The corresponding signal of the stable ADAC **1b** is located at 259.0 ppm, which is approximately half-way in between the chemical shifts found for **1a** and **1c**. For comparison, the ADACs $(i\mathrm{Pr}_2\mathrm{N})_2\mathrm{C}$ and $(i\mathrm{Pr}_2\mathrm{N})\mathrm{C}(\mathrm{PipMe}_2)$ exhibit $C_{carbene}$ NMR signals at 255.5 and 258.9 ppm, respectively, in $C_6D_6$ solution.[3c, 14] In the case of **1c** the chemical shift was probably influenced by the presence of equimolar amounts of sodium hexafluorophosphate. It is well documented that the interaction of diaminocarbenes with alkali metal cations leads to noticeable high-field shifts of the $C_{carbene}$ NMR signal.[26, 27] For example, in the case of $(\mathrm{Me}_2\mathrm{N})_2\mathrm{C}$ this signal is shifted from 259.7 ppm in THF-$d_8$[27a] to 253.1 ppm by the presence of 1.25 equivalents of lithium ions.[4b]

The thermal stabilities of the three new ADACs in solution follow the order **1b** > **1a** > **1c**. The decomposition of these carbenes leads to the formation of the corresponding cycloalkene *cyclo*-$C_nH_{2n-2}$ ($n$ = 5, 6, 7) and *N*,*N*,*N*'-tricycloalkylformamidine (*cyclo*-$C_nH_{2n-1})_2$N–CH=N(*cyclo*-$C_nH_{2n-1}$). In each case this process involves the breaking of a methylene C–H bond. In the analogous reaction of the "Alder carbene", it is a methyl C–H bond which is cleaved. As a rule, primary C–H bonds are stronger than secondary ones by ca. 4 kcal/mol.[28] Consequently, it seems reasonable to expect that the thermal stability of the "Alder carbene" is higher than that of the ADACs of type **1**. This is indeed true for **1a** and **1c**. In addition, there is a significant influence of the ring size on the C–H bond strengths in cycloalkanes. The C–H bond dissociation enthalpy of cyclohexane (99.5 kcal/mol) is higher

than that of cyclopentane (95.6 kcal/mol) and cycloheptane (94.0 kcal/mol).[29] These values are fully in line with the order of the thermal stabilities of **1a** – **c**.

In view of the higher stability of $(Cy_2N)_2C$ (**1b**, Cy = cyclohexyl) in comparison to $(i Pr_2N)_2C$, we surmised that the stability of the corresponding "hybrid carbene" $i Pr_2N–C–NCy_2$ (**2**, synthesised according to the route outlined in Scheme 1 starting from $Cy_2NH$ and $i Pr_2N–CHO$) will be intermediate between that of the "Alder carbene" and **1b**. This indeed turned out to be the case. According to NMR-spectroscopic analysis, the decomposition of **2** by β-fragmentation is more sluggish at room temperature than that of $(i Pr_2N)_2C$ and exclusively involves the $i Pr_2N$ unit.

We now come to the electronic properties of the new carbenes of this study.[30] The nucleophilicity of ADACs **1a** – **c** and **2** was judged from the $^1J_{CH}$ value determined for the $N_2CH$ unit of the respective formamidinium cation. Ganter and Kunz have pointed out that these $^1J_{CH}$ coupling constants correlate inversely with the σ-donor strength, and hence nucleophilicity, of the corresponding carbenes, since the σ-donor strength decreases with increasing s-character of the σ-orbital at the divalent carbon atom and large $^1J_{CH}$ coupling constants reflect high s-character of the carbon valence orbital involved in the C–H bond.[17a, 31] $^1J_{CH}$ coupling constants determined for the protonated standard NHCs IMes and SIMes are 225 and 206 Hz, respectively.[17a] The protonated six-membered ring analogue of SIMes exhibits a $^1J_{CH}$ coupling constant of only 200 Hz, in line with the enhanced donor capacity of ring-expanded NHCs.[32] The $^1J_{CH}$ coupling constants determined for the three formamidinium compounds of the type **1**H[$PF_6$] are much lower, viz. 183 Hz. The same value was obtained for the "Alder carbene" precursor $(i Pr_2N)_2CH[PF_6]$ and for **2**H[$PF_6$]. These $^1J_{CH}$ coupling constants can be obtained from proton-coupled $^{13}C$ NMR spectra or, more conveniently and accurately, from the $^{13}C$ satellite signals present in the $^1H$ NMR spectra, because the formamidinium $N_2CH$ signals generally show not overlap with other signals.

The electrophilicity of ADACs **1a** – **c** and **2** was probed by a $^{77}$Se NMR spectroscopic investigation of the corresponding easily available (see Experimental Section) selenourea derivatives of the type **1**Se. This well-established method[33] was recently applied by us for a broad range of ADAC-derived selenoureas.[3a] The chemical shifts of the $^{77}$Se NMR signals of these compounds in $CDCl_3$ lie in the range from 381 – 758 ppm. The signal of $(i\mathrm{Pr_2N})_2\mathrm{CSe}$ is located in the middle of this range, at 563 ppm. The signals of **1a**Se, **1b**Se and **1c**Se were observed at only marginally higher field (546, 539 and 550 ppm, respectively), which points to an almost identical electrophilicity of the "Alder carbene" and its analogues of type **1**. The $^{77}$Se NMR signal of **2**Se at $\delta$ = 559 ppm lies even closer to that of the "Alder carbene". In the case of selenoureas derived from standard five-membered ring NHCs the chemical shifts lie between ca. –20 and 200 ppm,[17] in line with the comparatively low electrophilicity of these widely used carbenes. In addition to their spectroscopic characterisation, the crystal structures of **1a**Se and **1b**Se were determined by single-crystal X-ray diffraction (vide infra). **1c**Se was obtained as an oil that showed no tendency to crystallise, which is reminiscent of the behaviour of $(i\mathrm{Pr_2N})_2\mathrm{CSe}$.[17e]

In view of the very similar steric and electronic properties of the "Alder carbene" and its analogues of type **1**, we expected the latter carbenes also to react readily with CO, cleanly affording racemic β-lactam derivatives. This indeed turned out to be the case (Scheme 2). The spirocyclic products **3a** – **c** were isolated as viscous oils, which slowly solidified upon standing. However, crystals suitable for X-ray diffraction were obtained only in the case of **3a** and **3c**. **3b** was therefore treated with HCl in diethyl ether, which furnished single crystals of the hydrochloride **3b**HCl.

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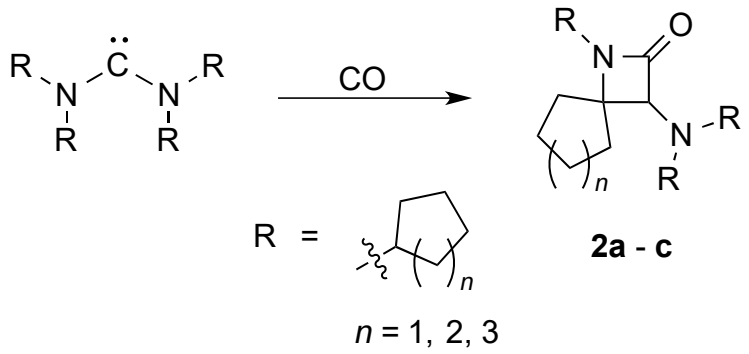


**Scheme 2.** Reaction of **1a** – **c** with carbon monoxide.

Metal-catalysed methods for the synthesis of β-lactams using carbon monoxide as building block have been known for almost four decades.[34, 35] Together with our previously reported carbonylations of ($i$Pr$_2$N)$_2$C and ($i$Pr$_2$N)C(PipMe$_2$), the reactions shown in Scheme 2 represent the first metal-free method in this context. In view of the fact that secondary aliphatic amines serve as our starting point (Scheme 1), our method is related to that reported recently by Gaunt and co-workers, which affords β-lactams by $Pd^{II}$-catalysed C–H carbonylation reactions using secondary aliphatic amines.[36] We note that Gaunt's metal-catalysed approach is based on the activation of methyl or methylene C–H bonds and gives access to mono- and disubstituted β-lactams. Our metal-free method achieves the activation of tertiary C–H bonds and therefore opens the door to trisubstituted β-lactams not available by Gaunt's method.

## Crystal structures

The molecular structures of the cation of **1b**H[PF$_6$], the stable ADAC **1b** and the corresponding selenourea derivative **1b**Se in the solid state are shown in Figures 2, 3 and 4 (see Figures S1, S2 and S3 in the Supporting Information for the molecular structures of **1c**H[PF$_6$], **2**H[PF$_6$]·CHCl$_3$ and **1a**Se). Pertinent structural parameters are collected in Table 1.

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Structural data for the "Alder carbene" ($i$Pr$_2$N)$_2$C and its precursor [($i$Pr$_2$N)$_2$CH](OTf) are included in the Table for comparison.

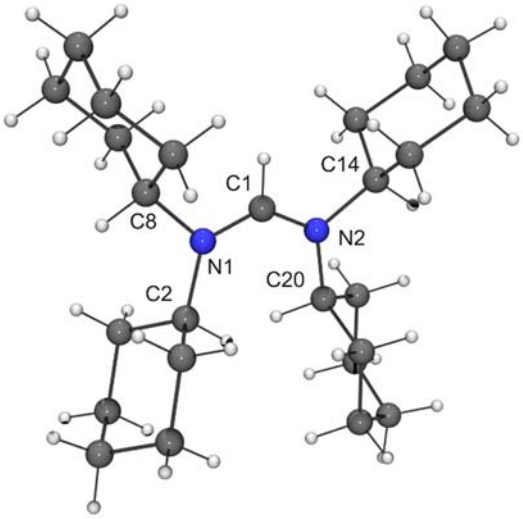


**Figure 2.** Molecular structure of the cation of **1b**H[$PF_6$] in the crystal.

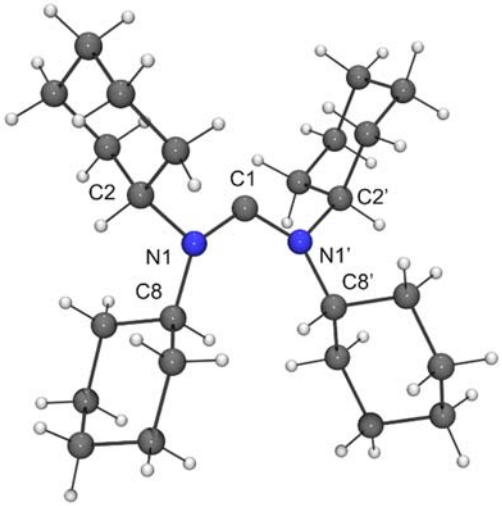


**Figure 3.** Molecular structure of **1b** in the crystal.

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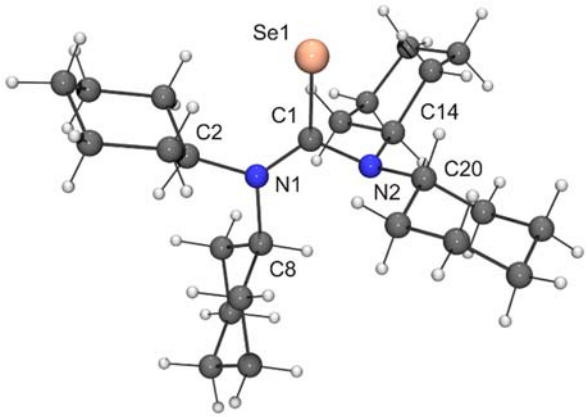


**Figure 4.** Molecular structure of **1b**Se in the crystal.

**Table 1.** Selected bond lengths and angles for acyclic formamidinium salts, ADACs and ADAC-based selenourea compounds.

| | N–CN [Å] | N–C–N [°] | Sum of angles at N [°] | Dihedral angle [°][a] |
|---|---|---|---|---|
| **1b**H[$PF_6$] | 1.317(5) | 133.4(4) | 359.9(3) | 5.6 |
| | 1.324(5) | | 359.9(3) | 10.0 |
| **1c**H[$PF_6$] | 1.294(10) | 131.2(8) | 360.0(7) | 0.0 |
| | 1.307(10) | | 359.9(7) | 0.0 |
| **2**H[$PF_6$]·$CHCl_3$ | 1.319(3)[b] | 131.3(3) | 359.5(2)[b] | 18.3[b] |
| | 1.317(3)[c] | | 359.9(2)[c] | 18.6[c] |
| [(*i*Pr$_2$N)$_2$CH](OTf)[d] | 1.316(4) | 133.2(2) | 359.8(2) | 9.7 |
| | 1.317(4) | | 360.1(2) | 5.0 |
| (*i*Pr$_2$N)$_2$C[e] | 1.362(9) | 121.0(5) | 359.7(5) | 9.8 |
| | 1.381(8) | | 359.8(5) | 7.7 |
| **1b**[f] | 1.353(2) | 120.7(2) | 357.93(15) | 20.5 |
| **1a**Se | 1.327(6) | 115.1(4) | 359.8(4) | 4.5 |
| | 1.431(6) | | 343.2(4) | 78.9 |
| **1b**Se | 1.332(4) | 115.2(2) | 359.9(2) | 5.7 |

| | | |
|---|---|---|
| 1.435(3) | 341.7(2) | 85.4 |

[a] Angle of the $N_2C$ plane with the $NC_2$ plane of each amino group. [b] Refers to the $Cy_2N$ unit. [c] Refers to the *i*$Pr_2N$ unit. [d] Ref.[24] [e] Ref.[3c] [f] Crystallographically imposed molecular $C_2$ symmetry.

We first turn our attention to the formamidinium salts and the ADACs listed in Table 1, since these compounds exhibit rather similar structural features. Their nitrogen atoms are in a trigonal planar bonding environment (sum of angles ca. 360°), compatible with $sp^2$ hybridisation. The dihedral angles formed by the $N_2C$ plane and the $NC_2$ planes of the amino units are fairly small, which can be ascribed to the π-delocalisation in the central $N_2C$ unit. These angles are largest for the cation of **2**H[$PF_6$]·$CHCl_3$ (18.3° and 18.6°). It is not clear whether this is mainly due to the presence of the solvent molecule. Closer inspection of the structural parameters reveals that the degree of π-delocalisation is higher for the formamidinium cations than for the free diaminocarbenes, which is a long known phenomenon already noted by Arduengo and co-workers in their seminal paper describing the first stable diaminocarbene.[37] The C−N bond lengths of the central $N_2C$ unit of the formamidinium cations listed in Table 1 are ca. 1.31 Å on average, which is significantly shorter than the average value of 1.36 Å exhibited by the ADACs, both being in between the values typical for C($sp^2$)−N($sp^2$) single (1.41 Å) and double bonds (1.28 Å).[38] A lesser degree of π-delocalisation in the ADACs is also indicated by their larger dihedral angles between the $N_2C$ plane and the $NC_2$ plane of each amino group in comparison to those of the corresponding formamidinium cation. This effect is particularly pronounced for the pair **1b**H[$PF_6$]/**1b**, since **1b** shows with a substantial margin the largest dihedral angles (20.5°) of all structurally characterised ADACs,[39] indicative of significant strain due to steric repulsion between its two bis(cyclohexyl)amino groups. Closer inspection reveals that this twisting is caused by the cyclohexyl substituents which are pointing away from the $C_{carbene}$ atom. The

distance between their tertiary carbon atoms is 3.14 Å, which is substantially below the sum of the van der Waals radii of two $sp^3$ hybridised carbon atoms (3.54 Å).[40] For comparison, the corresponding interatomic distance for the "Alder carbene" is 3.19 Å.[3c]

The structures of **1a**Se and **1b**Se are similar to those of other selenourea derivatives of ADACs containing very bulky amino groups such as, for example, (*i*Pr$_2$N)C(PipMe$_2$).[3a] The most notable feature is the fact that one of the two amino group is in an almost perpendicular orientation to the N$_2$C plane (dihedral angle: 78.9 and 85.4° for **1a**Se and **1b**Se, respectively; see Table 1). This conformation prevents an efficient participation of the lone pair of electrons of this particular amino group in π-delocalisation. Consequently, the N atom is pyramidalised (sum of anglec ca. 342°) and exhibits an N–CSe bond length significantly larger than that of the second amino group (ca. 1.43 vs. 1.33 Å) and compatible with a single bond. The C–Se bond lengths of **1a**Se and **1b**Se are ca. 1.85 Å, which compares well with values determined for closely related selenourea derivatives.[3a] The distances are in between the values typical of carbon−selenium single and double bonds, which has been rationalised in terms of a significant contribution of zwitterionic structures that feature single $N_2C^+-Se^-$ dative bonds.[41]

We finally come to the structures of the β-lactam derivatives **3a** (Figure 5) and **3c** (see Figure S4 in the Supporting Information) and to the structure of the hydrochloride **3b**HCl (Figure 6). For comparison, the structure of the hydrochloride of the β-lactam derivative obtained by carbonylation of the "Alder carbene" (**A**HCl) is shown in Figure S5 in the Supporting Information.[16] Pertinent bond lengths and angles are collected in Table 2.

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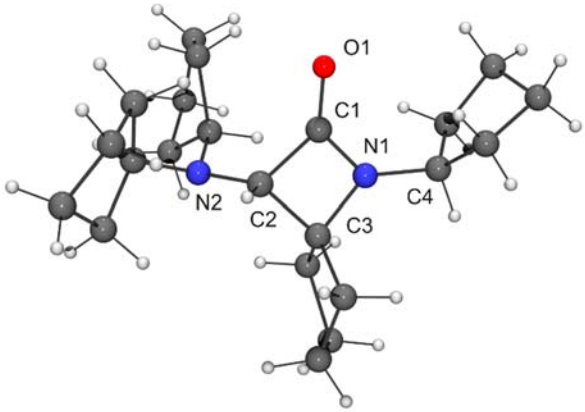


**Figure 5.** Molecular structure of **3a** in the crystal.

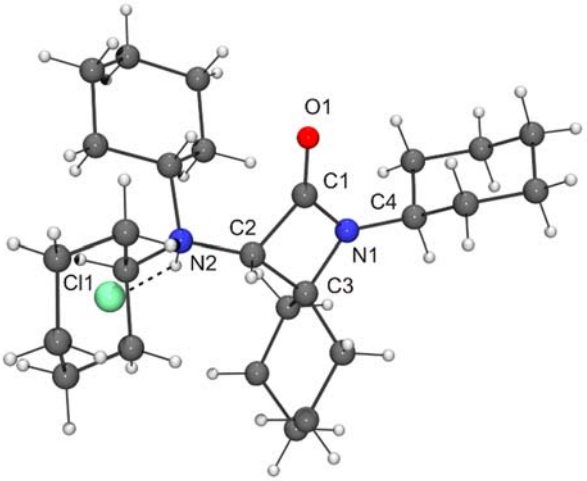


**Figure 6.** Molecular structure of **3b**HCl in the crystal. The broken line indicates a hydrogen bond between the chloride anion and the cationic (*cyclo*-$C_6H_{11}$)$_2$HN substituent.

**Table 2.** Selected bond lengths an angles for β-lactam derivatives.

| | C1–O1 [Å] | C1–N1 [Å] | C3–N1 [Å] | C1–C2 [Å] | C2–C3 [Å] | C2–N2 [Å] |
|---|---|---|---|---|---|---|
| **3a** | 1.220(5) | 1.340(5) | 1.474(6) | 1.524(6) | 1.587(5) | 1.440(5) |
| **3c** | 1.222(2) | 1.351(3) | 1.485(3) | 1.544(3) | 1.603(3) | 1.434(3) |
| **3b**HCl | 1.213(6) | 1.355(6) | 1.495(6) | 1.545(6) | 1.582(6) | 1.509(6) |
| **A**HCl[a] | 1.236(6) | 1.332(6) | 1.508(6) | 1.540(7) | 1.570(7) | 1.531(6) |
| | 1.211(6) | 1.357(6) | 1.510(6) | 1.546(7) | 1.580(7) | 1.533(6) |

[a] Two independent molecules.

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The structural parameters of the compounds listed in Table 2 compare well with those of related amino-substituted β-lactam derivatives.[42] Not surprisingly, the C2–N2 bond is significantly longer in the hydrochloride compounds, where the former amino nitrogen atom N2 is protonated and hence four-coordinate. Note that ordinary trialkylammonium cations such as, for example, $Me_3NH^+$ exhibit C–N bond lengths ≤ 1.50 Å, whereas values of ca. 1.53 Å, similar to those determined for **A**HCl, have been reported for sterically congested cases.[43] Steric strain in the cation of **A**HCl is also indicated by the C–N2–C angles, which range from 110.2(4) to 114.0(4)° (average value 112.6°). For comparison, $Me_3NH^+$ exhibits an average C–N–C angle of only 111.4°.[43] In the same vein, the amino nitrogen atom N2 of the β-lactam derivatives **3a** and **3c** shows a tendency towards planarization in each case, the sum of angles at nitrogen being 346.5(4) and 351.7(2)°, respectively. The difference between these two values of ca. 5° indicates that the steric congestion due to the cycloheptyl substituents is significantly more pronounced than that due to the cyclopentyl substituents, which is in line with their substantially different steric parameters (see above). For comparison, in the case of the bulky trialkylamine *i*Pr$_3$N the sum of angles at nitrogen is 348.6(1)° at 84 K.[44]

**Antimicrobial activity of 3a – c**

We have investigated the antimicrobial activity of the new β-lactam derivatives **3a** – **c** against Gram-positive and Gram-negative bacteria by determining their minimal inhibitory concentrations (MICs). The results are summarised in Table 3.

**Table 3.** Minimal inhibitory concentrations.

| Gram-negative | Gram-positive |
|---|---|

| | *Escherichia coli* | *Acinetobacter baumannii* | *Pseudomonas aeruginosa* | *Bacterium subtilis* 168 | *Staphylococcus aureus* (type strain) | *Staphylococcus aureus* (MRSA) |
|---|---|---|---|---|---|---|
| **3a** | no activity | no activity | no activity | 256 μg $mL^{-1}$ | 512 μg $mL^{-1}$ | no activity |
| **3b** | no activity | no activity | no activity | 64 μg $mL^{-1}$ | 64 μg $mL^{-1}$ | 64 μg $mL^{-1}$ |
| **3c** | no activity | no activity | no activity | 256 μg $mL^{-1}$ | 256 μg $mL^{-1}$ | 256 μg $mL^{-1}$ |
| Penicillin G | 64 μg $mL^{-1}$ | no activity | no activity | 8 μg $mL^{-1}$ | 0.5 μg $mL^{-1}$ | 16 μg $mL^{-1}$ |
| Amoxicillin | 64 μg $mL^{-1}$ | no activity | no activity | 2 – 4 μg $mL^{-1}$ | 2 μg $mL^{-1}$ | 48 μg $mL^{-1}$ |

All three compounds exhibit significant activities against the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*. **3b** has the most pronounced activity, with an MIC value of 64 μg $mL^{-1}$ for *B. subtilis* 168 as well as for the *S. aureus* type strain (DSM 20231) and a methicillin-resistant *S. aureus* (MRSA) strain. Its antibiotic activity is four times higher than that determined previously by us for the β-lactam derivative **A** obtained by carbonylation of the "Alder carbene" (MIC = 256 μg $mL^{-1}$),[9a] the activity of which equals that of **3c**. **3a** exhibits the same activity against *B. subtilis* 168 as **3c**, but its activity against the *S. aureus* type strain is lower by a factor of two and it is inactive against the *S. aureus* MRSA strain. All these β-lactam derivatives are inactive against Gram-negative bacteria. Their spectrum of activity resembles that of penicillin G or amoxicillin, whose activities, however, are higher than that of **3b** by approximately two orders of magnitude.

## Conclusion

The new ADACs $[(cyclo\text{-}C_nH_{2n-1})_2N]_2C$ ($n$ = 5 – 7) and $i$Pr$_2$N–C–NCy$_2$ exhibit the same ambiphilic profile as the iconic "Alder carbene" ($i$Pr$_2$N)$_2$C, which explains their ability to activate fundamentally important small molecules like CO. Their carbonylation affords β-

lactam derivatives with a spirocyclic scaffold. Compounds of this type have emerged as important candidates for biological evaluations.[45] The carbonylation of sterically encumbered ADACs is the first metal-free method for the synthesis of β-lactams using CO as a building block. This method complements the metal-catalysed one recently published by Gaunt,[36] which also uses secondary amines as starting point, but only allows the synthesis of mono- and disubstituted β-lactams, while our method provides facile access to trisubstituted derivatives. The surprising thermal stability of $(Cy_2N)_2C$, which is significantly higher than that of $(i Pr_2N)_2C$, is currently under investigation by DFT methods. We surmise that the pathway identified for the β-fragmentation of $(i Pr_2N)_2C$[13] is also operative in the case of $(Cy_2N)_2C$, but is impeded by conformational restraints leading to higher barriers.

## Experimental Section

All reactions involving air-sensitive compounds were performed in an inert atmosphere (argon or dinitrogen) by using standard Schlenk techniques or a conventional glovebox. Starting materials were procured from standard commercial sources and used as received. The secondary amines $(cyclo\text{-}C_nH_{2n-1})_2NH$ ($n$ = 5, 7)[46] were synthesised by following adapted versions of the published procedures. The formamides $(cyclo\text{-}C_nH_{2n-1})_2N{-}CHO$ ($n$ = 5, 6) were synthesised from formic acid and the respective secondary amine by using an established method.[47] Their spectroscopic data were identical to those reported in the literature.[48] $^1H$ and $^{13}C$ NMR spectra were recorded at ambient temperature with Varian NMRS-500 and MR-400 spectrometers operating at 500 and 400 MHZ, respectively, for $^1H$. $^{77}Se$ NMR spectra were recorded with a Varian NRMS-500 spectrometer with neat dimethylselenide as external standard ($\delta$ = 4 ppm).[49] High-resolution (HR) ESI and APCI

mass spectra were obtained with a micrOTOF time-of-flight mass spectrometer (Bruker Daltonics, Bremen, Germany) using an Apollo$^{TM}$ "ion funnel" ESI source. Mass calibration was performed immediately prior to the measurement with ESI Tune Mix Standard (Agilent, Waldbronn, Germany). IR spectra were obtained with a Bruker ALPHA FT-IR spectrometer (ATR mode). A Mettler-Toledo ReactIR 15 instrument was used for monitoring carbonylation reactions in situ and in real time. Elemental analyses were carried out with a HEKAtech Euro EA-CHNS elemental analyser at the Institute of Chemistry, University of Kassel, Germany.

**Synthesis of (*cyclo*-$C_7H_{13}$)$_2$N–CHO:** Formic acid (1.10 g, 23.9 mmol) was added to a solution of dicycloheptylamine (2.00 g, 9.6 mmol) in toluene (150 mL). The mixture was refluxed for 4 d with continuous removal of water by means of a Dean-Stark apparatus. The solution was allowed to cool down to ambient temperature. Volatile components were removed under vacuum, leaving the product as a pale yellow crystalline solid. Yield 2.13 g (93%). $^1$H NMR ($CDCl_3$): $\delta$ = 8.09 (s, 1H, CHO), 3.88, 3.22 (2 × br. m, 2 × 1H, NC*H*$CH_2$), 2.1 – 1.3 ppm (m, 24H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 166.7 (CHO), 56.4, 55.3 (2 × N*C*H$CH_2$), 33.0, 31.0, 27.6, 27.3, 25.4, 24.2 ppm (6 × $CH_2$); HRMS/APCI(+): *m*/*z* = 238.21654 $[M + H]^+$, 238.21709 calcd for $[C_{15}H_{28}NO]^+$.

**General procedure for the synthesis of the formamidinium salts of the type 1H[$PF_6$]:** In a typical experiment, freshly distilled oxalyl chloride (1.27 g, 10.0 mmol) was added dropwise to a stirred solution of the formamide (*cyclo*-$C_nH_{2n-1}$)$_2$N–CHO (9.0 mmol) in dichloromethane (50 mL) cooled to –20 °C. The cooling bath was removed and stirring was continued for 2 h. Volatile components were removed under vacuum, leaving the Vilsmeyer complex [(*cyclo*-$C_nH_{2n-1}$)$_2$N=CHCl]Cl as a colourless solid. Dichloromethane (40 mL) was added and the suspension cooled to –20 °C with stirring. A solution of the secondary amine

(*cyclo*-$C_nH_{2n-1}$)$_2$NH (9.0 mmol) and triethylamine (9.0 mmol) in dichloromethane (50 mL) was cooled to −20 °C and slowly added via cannula. The cooling bath was removed and stirring was continued for 3 h. Volatile components were removed under vacuum. Acetone (100 mL) was added and insoluble material removed by filtration. The filtrate was reduced to dryness under vacuum. The residue was taken up in ice cold ethanol (50 mL). The product was precipitated by addition of an ice cold saturated aqueous solution of ammonium hexafluorophosphate (1.96 g, 12.0 mmol). The precipitate was filtered off, washed with ice cold water (2 × 10 mL), followed by ice cold diethyl ether (2 × 10 mL) and subsequently dried under vacuum. While this procedure afforded analytically pure **1a**H[$PF_6$] (3.16 g) and **1b**H[$PF_6$] (3.69 g) as ochre crystalline solids in 76% and 79% yield, respectively, further purification was necessary in the case of **1c**H[$PF_6$]. This was achieved by placing the crude product in a Soxhlet thimble containing silica gel (50 g) and subjecting it for 1 d each to extraction with hexane, followed by extraction with toluene and finally with diethyl ether. The hydrocarbon extracts were discarded. The ether extract was reduced to dryness under vacuum, leaving **1c**H[$PF_6$] (2.86 g) as a pale yellow crystalline solid in 55% yield.

**1a**H[$PF_6$]: $^1$H NMR ($CDCl_3$): $\delta$ = 7.43 (s, 1H, $N_2CH$), 4.02 (br., 4H, NC*H*$CH_2$), 2.15, 1.82 (2 × br., 2 × 8H, $CH_2$), 1.68 ppm (br., 16H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 153.3 ($N_2CH$), 61.8 (br., N*C*H$CH_2$), 33.3 (br., $CH_2$), 24.6 ppm ($CH_2$); HRMS/ESI(+): *m*/*z* = 317.29515 [M – $PF_6$]$^+$, 317.29567 calcd for [$C_{21}H_{37}N_2$]$^+$; elemental analysis calcd (%) for $C_{21}H_{37}N_2F_6P$ (462.50): C 54.54, H 8.06, N 6.06; found: C 54.85, H 8.05, N 6.06. **1b**H[$PF_6$]: $^1$H NMR ($CDCl_3$): $\delta$ = 7.33 (s, 1H, $N_2CH$), 3.57, 3.40 (2 × br., 2 × 2H, NC*H*$CH_2$), 1.94 (br., 16H, $CH_2$), 1.72, 1.47 1.31 ppm (3 × br., 24H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 151.6 ($N_2CH$), 62.5, 59.0 (2 × br., N*C*H$CH_2$), 34.5, 31.0 (2 × br., $CH_2$), 25.7, 24.5 ppm (2 × $CH_2$); HRMS/ESI(+): *m*/*z* = 373.35526 [M – $PF_6$]$^+$, 373.35827 calcd for [$C_{25}H_{45}N_2$]$^+$; elemental analysis calcd (%) for $C_{25}H_{45}N_2F_6P$ (518.60): C 57.90, H 8.75, N 5.40; found: C 58.02, H 8.73, N 5.47. **1c**H[$PF_6$]:

$^{1}$H NMR (acetone-$d_6$): $\delta$ = 7.27 (s, 1H, $N_2CH$), 3.76, 3.53 (2 × br., 2 × 1H, N*C*HCH$_2$) 3.42 (br., 2H, N*C*HCH$_2$), 2.1 – 1.2 ppm (br., 48H, $CH_2$); $^{13}$C NMR (acetone-$d_6$): $\delta$ = 151.0 ($N_2CH$), 63.8, 61.9 (2 × br., N*C*HCH$_2$), 57.3 (N*C*HCH$_2$), 36.7, 32.6 (2 × br., $CH_2$), 30.9, 27.4, 26.5 (3 × $CH_2$), 24.7 (br., $CH_2$), 23.5 ppm ($CH_2$); HRMS/ESI(+): *m*/*z* = 429.41712 $[M - PF_6]^+$, 429.42087 calcd for $[C_{29}H_{53}N_2]^+$; elemental analysis calcd (%) for $C_{29}H_{53}N_2F_6P$ (574.71): C 60.61, H 9.30, N 4.87; found: C 59.74, H 9.24, N 4.72.

**Synthesis of 2H[PF$_6$]:** Freshly distilled oxalyl chloride (2.16 g, 17.0 mmol) was added dropwise to a stirred solution of diisopropylformamide (2.00 g, 15.5 mmol) in dichloromethane (50 mL) cooled to –20 °C. The cooling bath was removed and stirring was continued for 2 h. Volatile components were removed under vacuum. Dichloromethane (50 mL) was added to the remaining solid and the suspension cooled to 0 °C with stirring. A solution of dicyclohexylamine (2.81 g, 15.5 mmol) and triethylamine (1.57 g, 15.5 mmol) in dichloromethane (50 mL) was slowly added via cannula. The cooling bath was removed and stirring was continued for 3 h. Volatile components were removed under vacuum. Acetone (100 mL) was added and insoluble material removed by filtration. The filtrate was reduced to dryness under vacuum. The residue was taken up in ice cold ethanol (70 mL). The product was precipitated by addition of an ice cold saturated aqueous solution of ammonium hexafluorophosphate (3.00 g, 18.4 mmol). The precipitate was filtered off, washed with ice cold water (2 × 20 mL), followed by ice cold diethyl ether (2 × 20 mL) and subsequently dried under vacuum. Yield 5.57 g (82%). $^{1}$H NMR (acetone-$d_6$): $\delta$ = 7.74 (s, 1H, $N_2CH$), 4.26, 3.82 (2 × br., 2 × 2H, NC*H*C), 1.97 (br., 4H, $CH_2$), 1.84 (br., 8H, $CH_2$), 1.63 (br., 2H, $CH_2$), 1.48 (d, $^{3}J_{HH}$ = 6.7 Hz, 12H, Me), 1.43 (br., 4H, $CH_2$), 1.25 (br., 2H, $CH_2$); $^{13}$C NMR (acetone-$d_6$): $\delta$ = 153.1 ($N_2CH$), 26.3 (Me), 25.3 ($CH_2$), signals due to the isopropyl and cyclohexyl CH units could not be detected even with prolonged acquisition times;

HRMS/ESI(+): $m/z$ = 293.29404 $[M - PF_6]^+$, 293.29567 calcd for $[C_{19}H_{37}N_2]^+$; elemental analysis calcd (%) for $C_{19}H_{37}N_2F_6P$ (438.48): C 52.05, H 8.51, N 6.39; found: C 52.38, H 8.50, N 6.22.

**1a:** THF (3 mL) was cooled to –20 °C and added to a mixture of sodium bis(trimethylsilyl)amide (37 mg, 0.20 mmol) and **1a**H[$PF_6$] (94 mg, 0.20 mmol). The mixture was stirred for 10 min. Volatile components were removed under vacuum. The residue was extracted with hexane (3 × 3 mL). The combined extracts were passed through a glass filter to remove traces of insoluble material. Volatile components were removed from the filtrate under vacuum, leaving the crude product as a reddish brown oil. Due to the thermal decomposition of the carbene and its extreme sensitivity towards air and moisture, further purification was not possible. Yield: 25 mg (39%). $^1$H NMR ($C_6D_6$): $\delta$ = 3.93 (quint, $^3J_{HH}$ = 7.9 Hz, 4H, CH), 2.09 (br., 8H, $CH_2$), 1.86 (br., 16H, $CH_2$), 1.7 – 1.5 ppm (br., 8H, $CH_2$); $^{13}$C NMR ($C_6D_6$): $\delta$ = 266.0 ($C_{carbene}$), 61.1 (CH), 34.1, 25.3 ppm (2 × $CH_2$).

**1b:** THF (5 mL) was cooled to –20 °C and added to a mixture of sodium bis(trimethylsilyl)amide (367 mg, 2.00 mmol) and **1a**H[$PF_6$] (1.037 g, 2.00 mmol). The mixture was stirred for 10 min. Volatile components were removed under vacuum. The residue was extracted with toluene (3 × 10 mL). The combined extracts were passed through a glass filter to remove traces of insoluble material. The volume of the solution was reduced under vacuum until crystallisation started. Subsequent storage at –80 °C afforded the product as colourless crystals. The mother liquor was decanted off and the crystals were dried under vacuum. Yield 430 mg (58%). $^1$H NMR ($C_6D_6$): $\delta$ = 3.25 (br., 4H, CH), 1.89 (br., 8H, $CH_2$), 1.77 (br., 16H, $CH_2$), 1.56 (br., 4H, $CH_2$), 1.26 (br., 8H, $CH_2$), 1.10 ppm (br., 4H, $CH_2$); $^{13}$C NMR ($C_6D_6$): $\delta$ = 259.0 ($C_{carbene}$), 59.8 (br., CH), 34.8 (br., $CH_2$), 26.8, 25.7 ppm (2 × $CH_2$).

**1c:** Sodium bis(trimethylsilyl)amide (35 mg, 0.19 mmol) was added to a suspension of **1c**H[$PF_6$] (103 mg, 0.18 mmol) in $C_6D_6$ (0.5 mL). The mixture was stirred for 5 min. Insoluble material was removed by filtration. The filtrate was placed in an NMR tube and immediately subjected to NMR spectroscopic analysis. $^1$H NMR ($C_6D_6$): $\delta$ = 3.8 – 3.2 (br., 4H, CH), 2.9 – 1.1 (br., 48H, $CH_2$); $^{13}$C NMR ($C_6D_6$): $\delta$ = 254.7 ($C_{carbene}$), 55.9 (CH), 36.5, 29.6, 27.0, 25.2 ppm (4 × $CH_2$).

**2:** THF (10 mL) was cooled to –20 °C and added to a mixture of sodium bis(trimethylsilyl)amide (421 mg, 2.30 mmol) and **2**H[$PF_6$] (1.021 g, 2.33 mmol). The mixture was stirred for 10 min. Insoluble material was removed by filtration. The filtrate was reduced to dryness under vacuum, leaving the crude product as a grey solid. Yield: 552 mg (84%). $^1$H NMR ($C_6D_6$): $\delta$ = 3.66, 3.28 (2 × br., 2 × 2H, CH), 1.76 (br., 10H, $CH_2$), 1.53 (br., 3H, $CH_2$), 1.28 (d, $^3J_{HH}$ = 6.4 Hz, 12H, Me), 1.10 (br., 7H, $CH_2$); $^{13}$C NMR ($C_6D_6$): $\delta$ = 258.6 ($C_{carbene}$), 60.0, 49.8 (2 × br., 2 × CH), 34.9 (br., $CH_2$), 27.0 (Me), 24.4 (br., $CH_2$).

**1aSe:** THF (5 mL) was cooled to –20 °C and added to a mixture of **1b**H[$PF_6$] (93 mg, 0.20 mmol), sodium bis(trimethylsilyl)amide (37 mg, 0.20 mmol) and grey selenium powder (16 mg, 0.20 mmol). The mixture was stirred at ambient temperature for 2 h. Volatile components were removed under vacuum. Pentane (10 mL) was added to the residue, followed by water (5 drops). The mixture was stirred for 10 min. Insoluble material was removed by filtration through a Celite pad and washed with pentane (3 × 5 mL). The filtrate and extracts were combined and volatile components removed under vacuum. The crude product was obtained as a dark yellow oil, which was subjected to purification by column chromatography (silica gel, pentane/ethyl acetate 9:1). The yellow oil was dissolved in a mixture of diethyl ether (20

mL) and acetonitrile (20 drops). Slow evaporation of the diethyl ether afforded the product as yellow crystals, which were dried under vacuum after removal of the mother liquor via cannula. Yield 51 mg (64%). $^{1}$H NMR ($CDCl_3$): $\delta$ = 4.31 (quint, $^{3}J_{HH}$ = 8.6 Hz, 4H, CH), 1.91 (m, 16H, $CH_2$), 1.75, 1.53 ppm (2 m, 2 × 8H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 201.9 (CSe), 63.8 (CH), 29.9, 24.3 ppm (2 × $CH_2$); $^{77}$Se NMR ($CDCl_3$): $\delta$ = 546 ppm; HRMS/ESI(+): *m*/*z* = 419.19248 $[M + Na]^+$, 419.19414 calcd for $[C_{21}H_{36}N_2NaSe]^+$; elemental analysis calcd (%) for $C_{21}H_{36}N_2Se$ (395.48): C 63.78, H 9.18, N 7.08; found: C 63.64, H 9.18, N 7.08.

**1bSe:** Grey selenium powder (79 mg, 1.00 mmol) was added to a solution of **1b** (373 mg, 1.00 mmol) in hexane (20 mL). The mixture was stirred for 1 h. Trace amounts of insoluble material were removed by filtration through a glass filter. The filtrate was reduced to dryness under vacuum, which afforded the product as a yellow crystalline solid. Yield 379 mg (84%). $^{1}$H NMR ($CDCl_3$): $\delta$ = 4.06 (quint, $^{3}J_{HH}$ = 8.3 Hz, 4H, CH), 2.0 – 1.0 ppm (m, 40H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 203.0 (CSe), 64.0 (CH), 32.3, 26.9, 26.0 ppm (3 × $CH_2$); $^{77}$Se NMR ($CDCl_3$): $\delta$ = 539 ppm; HRMS/ESI(+): *m*/*z* = 967.46409 $[2 M + Cu]^+$, 967.46354 calcd for $[C_{50}H_{88}N_4CuSe_2]^+$; elemental analysis calcd (%) for $C_{25}H_{44}N_2Se$ (451.59): C 66.49, H 9.82, N 6.20; found: C 67.70, H 9.72, N 6.15.

**1cSe:** A solution of sodium bis(trimethylsilyl)amide (50 mg, 0.27 mmol) in THF (1 mL) was added dropwise to a stirred suspension grey selenium powder (24 mg, 0.30 mmol) and **1c**H[$PF_6$] (150 mg, 0.26 mmol) in THF (15 mL) cooled to –80 °C. The cooling bath was removed after 10 min. Stirring was continued for 1.5 h. Volatile components were removed under vacuum. Hexane (20 mL) was added to the residue. Small amounts of insoluble material were removed by filtration through a Celite pad. Volatile components were removed from the filtrate under vacuum. The crude product was obtained as a yellow oil which showed

no tendency to crystallise. Attempts to obtain an analytically pure sample by column chromatography failed. Yield 83 mg (63%). $^{1}$H NMR ($CDCl_3$): $\delta$ = 3.85, (m, 4H, CH), 1.8 – 1.1 ppm (m, 48H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 198.2 (CSe), 65.0 (CH), 34.2, 28.2, 26.7, 25.0 (4 × $CH_2$); $^{77}$Se NMR ($CDCl_3$): $\delta$ = 550 ppm; HRMS/ESI(+): *m*/*z* = 1079.45851 [2 M + Cu]$^{+}$, 1079.58874 calcd for $[C_{58}H_{104}N_4CuSe_2]^{+}$.

**2Se:** The synthesis was performed in strict analogy to that described for **1c**Se using **2**H[$PF_6$] (100 mg, 0.23 mmol), grey selenium powder (20 mg, 0.25 mmol) and sodium bis(trimethylsilyl)amide (44 mg, 0.24 mmol). The product was obtained as a red oil. Yield 56 mg (68%). $^{1}$H NMR ($CDCl_3$): $\delta$ = 4.34 (sept, $^{3}J_{HH}$ = 6.8 Hz, 2H, C*H*Me$_2$), 3.93 (m, 2H, NCH), 1.92 – 1.58 (m, 14H, $CH_2$), 1.37 (d, $^{3}J_{HH}$ = 6.8 Hz, 12H, Me), 1.28 – 1.05 (m, 6H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 161.7 (CSe), 63.0, 53.3 (2 × CH), 31.8, 26.6, 25.8, 21.4. $^{77}$Se NMR ($CDCl_3$): $\delta$ = 550 ppm; HRMS/ESI(+): *m*/*z* = 395.19367 [M + Na]$^{+}$, 395.19414 cald for $[C_{19}H_{36}N_2NaSe]^{+}$.

**3a:** THF (20 mL) was cooled to –20 °C and added to a mixture of **1a**H[$PF_6$] (2.31 g, 4.99 mmol) and sodium bis(trimethylsilyl)amide (920 mg, 5.02 mmol). The mixture was stirred for 10 min. The inert gas atmosphere was replaced by carbon monoxide. Stirring was continued at ambient temperature for 2 h. Volatile components were removed under vacuum. The residue was subjected to purification by column chromatography (silica gel, hexane/ethyl acetate 1:9, which afforded the product as a yellow oil, which crystallised over the course of several days. Crystals suitable for a single-crystal X-ray diffraction study were obtained by sublimation (80 °C, $10^{-2}$ mbar). Yield 1.22 g (71%). $^{1}$H NMR ($CDCl_3$): $\delta$ = 3.71 (s, 1H, CHCO), 3.29 (quint, $^{3}J_{HH}$ = 7.8 Hz, 1H, C(O)NCH), 3.04 (br., 2H, CHNC*H*CH$_2$), 1.9 – 1.0 ppm (m, 32H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 168.8 (CO), 73.6 ($C_{quat}$), 71.5 (C(O)N*C*H), 60.8,

56.1, 52.7 (3 × CH), 34.4, 31.7, 30.7, 30.1 (4 × $CH_2$), 29.9 (br., $CH_2$), 28.9, 24.9, 24.3 (3 × $CH_2$), 24.0 (br., $CH_2$), 23.3, 23.3 (2 × $CH_2$), 22.7 ppm (br., $CH_2$); HRMS/ESI(+): *m*/*z* = 367.30452 $[M + Na]^+$, 367.27253 calcd for $[C_{22}H_{36}N_2NaO]^+$; IR (ATR): $\nu_{CO}$ = 1722 $cm^{-1}$; elemental analysis calcd (%) for $C_{22}H_{36}N_2O$ (344.53): C 76.69, H 10.53, N 8.13; found: C 76.13, H 10.47, N 7.85.

**3b: 1b** (373 mg, 1.00 mmol) was dissolved in hexane (20 mL). The inert gas atmosphere was replaced by carbon monoxide and the solution stirred at ambient temperature for 2 h. Volatile components were removed under vacuum, leaving the crude product as a reddish brown semi-solid. Yield 365 mg (91%). $^1$H NMR ($CDCl_3$): $\delta$ = 3.77 (s, 1H, CHCO), 2.97 (quint, $^3J_{HH}$ = 7.6 Hz, 1H, C(O)NCH), 2.55 (quint, $^3J_{HH}$ = 7.8 Hz, 2H, CHNC*H*$CH_2$), 2.0 – 0.9 (m, 40H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 169.8 (CO), 74.0 ($C_{quat}$), 66.1, 52.1, 37.2 (3 × CH), 33.2 (br., $CH_2$), 33.0, 32.5, 31.8, 31.2, 27.0 (5 × $CH_2$), 26.5 (br., $CH_2$), 25.9, 25.2, 24.1, 23.5 (4 × $CH_2$); IR (ATR): $\nu_{CO}$ = 1720 $cm^{-1}$. The product was converted to its hydrochloride, which was easier to purify and analyse.

**3bHCl:** The crude product (300 mg, 0.75 mmol) obtained from the reaction of **1b** with carbon monoxide was dissolved in diethyl ether (5 mL). A solution of HCl in diethyl ether (2.0 M, 0.4 mL, 0.80 mmol) was added dropwise with stirring. The colourless precipitate was isolated by filtration, washed with diethyl ether (2 × 1 mL) and dried under vacuum. Yield 306 mg (93%). $^1$H NMR ($CDCl_3$): $\delta$ = 10.71 (br. s, 1H, $NH^+$), 3.84 (br., 2H, CH), 3.64, 3.29 (2 m, × 1H, NCH), 2.7 – 1.0 (m, 40H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 160.1 (CO), 70.7, 64.9 (2 × CH), 64.1 ($C_{quat}$), 63.7, 56.5 (2 × CH), 37.4, 32.5, 31.3, 31.1, 28.3, 26.0, 25.5, 25.0, 24.7, 24.3, 23.1, 23.0 (12 × $CH_2$); HRMS/ESI(+): *m*/*z* = 401.35144 $[M – Cl]^+$, 401.35319 calcd for

$[C_{26}H_{45}N_2O]^+$; elemental analysis calcd (%) for $C_{26}H_{45}N_2ClO$ (437.10): C 71.44, H 10.38, N 6.41; found: C 71.47, H 10.42, N 6.41.

**3c:** The synthesis was carried out in analogy to that described for **2a**, using **1c**H[$PF_6$] (2.86 g, 4.99 mmol) and sodium bis(trimethylsilyl)amide (920 mg, 5.02 mmol). The product was obtained as a beige oil, which slowly crystallised upon storage at –40 °C. Yield 1.48 g (65%). $^1$H NMR ($CDCl_3$): $\delta$ = 3.89 (m, 1H, CH), 3.71 (s, 1H, CHCO), 3.24, 3.16 (2 × br. m, 2 × 1H, CH), 2.7 – 1.1 (m, 48H, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 169.1 (CO), 77.0 ($C_{quat}$), 69.4, 55.4, 39.2 (3 × CH), 34.8, 34.2, 33.8, 31.7, 31.4, 31.5, 27.8, 27.7, 25.2, 24.9, 24.0, 23.8 (12 × $CH_2$); HRMS/ESI(+): *m*/*z* = 457.41002 $[M + H]^+$, 457.41579 calcd for $[C_{30}H_{53}N_2O]^+$; IR (ATR): $\nu_{CO}$ = 1715 $cm^{-1}$.

**MIC tests:** Compounds were tested against *Escherichia coli* DSM 30083, *Acinetobacter baumannii* DSM 30007, *Pseudomonas aeruginosa* DSM 50071, *Bacillus subtilis* DSM 402, *Staphylococcus aureus* DSM 20231, and *Staphylococcus aureus* ATCC 43300 (MRSA) in a microtiter plate assay according to CLSI guidelines, as described in ref.[50] *E. coli*, *A. baumannii*, *S. aureus*, and *B. subtilis* were grown in Mueller Hinton broth, *P. aeruginosa* in cation-adjusted Mueller Hinton II. Compounds were dissolved in DMSO 1.25, 2.5, 5, or 10 mg/mL stock solution. Serial dilution in culture media were prepared with the Tecan Freedom Evo 75 liquid handling workstation (Tecan, Männedorf, Switzerland). Dilutions, starting from a 10 mg/mL stock solution, typically covered a range from 512 to 0.5 µg/mL. Compound dilutions were inoculated with $5\times10^5$ bacteria/mL from late exponential cultures grown in the same media. Assay volumes were 200 µL per well. Cells were incubated for 16 – 18 h at 37 °C. The lowest compound concentration inhibiting visible bacterial growth was recorded as MIC.

**X-ray crystallography:** For each data collection a single crystal was mounted on a micro-mount and all geometric and intensity data were taken from this sample. Data collections were carried out using Mo$K_\alpha$ radiation ($\lambda$ = 0.71073 Å ) either on a Stoe IPDS2 diffractometer equipped with a 2-circle goniometer and an area detector or on a Stoe StadiVari diffractometer equipped with a 4-circle goniometer and a DECTRIS Pilatus 200K detector. **1b** and **1aSe** were measured on a Stoe StadiVari Diffractometer using Cu$K_\alpha$ radiation ($\lambda$ = 1.54186 Å ). The data sets were corrected for absorption (by integration), Lorentz and polarisation effects. The structures were solved by direct methods (SIR 2008)[51] and refined using alternating cycles of least-squares refinements against $F^2$ (SHELXL2014/7).[52] H atoms were included to the models in calculated positions with the 1.2 fold isotropic displacement parameter of their bonding partner. Experimental details for each diffraction experiment are given in Table S1 in the Supporting Information. CCDC 1874081 – 1874090 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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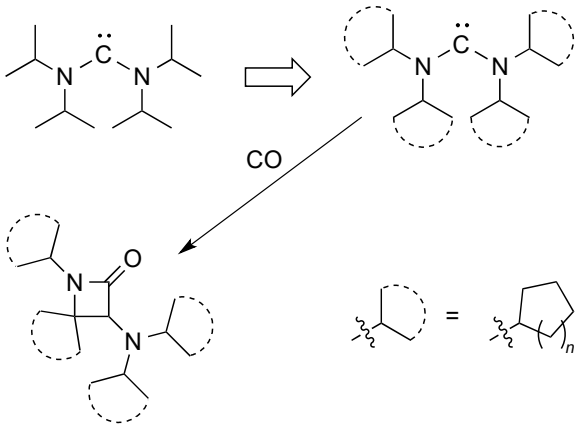
## Graphical abstract




**Acyclic diaminocarbenes** of the type [(*cyclo*-$C_nH_{2n-1}$)$_2$N]$_2$C ($n$ = 5 – 7) are akin to the iconic "Alder carbene" ($i$Pr$_2$N)$_2$C, since the cycloalkyl groups can be viewed as conformationally constrained versions of the isopropyl group. In the cyclohexyl case, this leads to a bis(dialkylamino)carbene of unprecedented thermal stability in solution. Independent of $n$, these carbenes react readily with CO, selectively affording spirocyclic β-lactams with useful antibiotic properties.

**Keywords**

amines; carbenes; carbonylation; lactams; selenourea derivatives