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# $\beta$ -Lactam and penicillin substituted mesoionic metal carbene complexes

Marta G. Avello, María Moreno-Latorre, María C. de la Torre, Luis Casarrubios, Heinz Gornitzka, Catherine Hemmert and Miguel A. Sierra

1,2,3-Triazolylidene MIC M-complexes (M = Au, Pd, Pt) having 2-azetidinones and penicillin G substituents at the triazole ring were prepared by CuAAC on 2-azetidinones having a terminal alkyne tethered at N1, followed by alkylation of the 1,2,3-triazole ring and transmetalation [Au(I), Pd(II) and Pt(II)]. The Au-MIC complexes efficiently catalyze the regioselective cycloisomerization of enynes, while the Pt-MIC complexes were efficient catalysts in general.

## Introduction

The synthesis and use in different fields of transition metal complexes having  $\beta$ -lactam moieties in their structures has been somewhat neglected.<sup>1</sup> Thus, while coordination complexes containing clinically used  $\beta$ -lactam antibiotics have been profusely reported, their chemical structures and the synergistic effect of metal and antibiotic in their antibacterial activity remain uncertain.<sup>2</sup> Meanwhile bio-organometallic derivatives of cephalosporin and penicillin, as well as those derived from the 2-azetidinone ring, are well characterized compounds, and their antibacterial activities have been reported.<sup>3</sup> Surprisingly, the use of transition metal complexes derived from these easily available and biologically relevant species in catalysis has not been reported.

It is remarkable that while 1,2,3-triazole- $\beta$ -lactam hybrids like, for example, cefatrizine 1 (a potent antibacterial drug),<sup>4</sup> or tazobactam 2 and its analogue 3 (strong inhibitors of  $\beta$ -lactamases) (Fig. 1),<sup>5</sup> have been developed as antibacterial agents;<sup>6</sup> 1,2,3-triazolium mesoionic carbenes (MICs), as well as their transition metal-complexes, substituted by  $\beta$ -lactam or penicillin moieties remain undisclosed.<sup>6</sup>

We have previously described the synthesis of several new metalla- $\beta$ -lactams. Among many others,<sup>7,8</sup> new 6-metallapenicillin derivatives like 4 were obtained by the photocycloaddition of the corresponding ruthenocenecarboxychromium(0) carbene<sup>8a</sup> and 2,2-dimethyl-3-carboxymethyl-2-thiazolidine, and metallatrinems 5 and 6 obtained from the chelated assisted metal N-H bond activation of  $\beta$ -lactams (Fig. 2),<sup>8b</sup> are representative examples.

In parallel, we have reported the preparation of steroidal MIC Ag and Au complexes including giant macrocyclic structures, 7.<sup>9</sup> While structurally impressive, these complexes lack the diversity of coordination points and the lability of the 2-azetidinone ring and its penicillin derivatives. This fact, coupled to the scarcity of MIC-derivatives containing natural products, lead us to investigate the possibility of developing a versatile and general approach to these new classes of products, as well as the preparation of the corresponding MIC complexes.

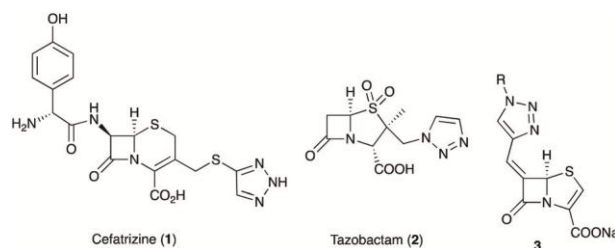


Fig. 1 Some 1,2,3-triazole- $\beta$ -lactam hybrids.

This is a general approach to 2-azetidinone MIC precursors, including penicillin derivatives, the synthesis of Au, Pd and Pt metal complexes having a 1,2,3-triazolylidene- $\beta$ -lactam hybrid ligands in their structures and the initial studies of their potential as catalysts.<sup>10</sup>

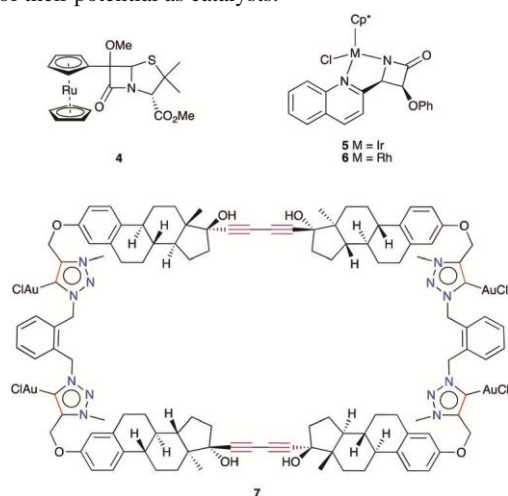
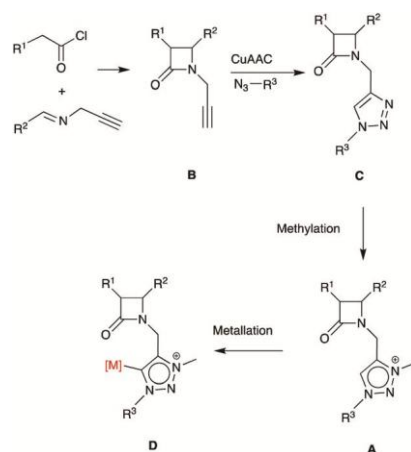


Fig. 2 6-Metallapenicillin 4, metallatrinems 5 and 6 and macrocycles 7.

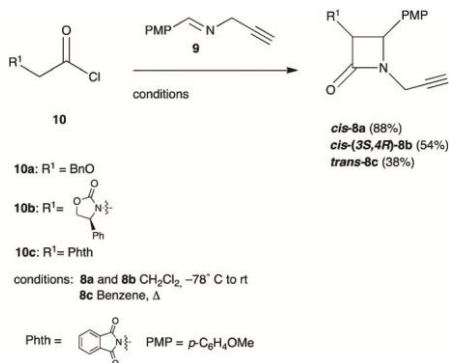
## Results and discussion

The precursors of 1,2,3-triazolium carbenes (MICs), namely the corresponding triazolium salts A were prepared from N-propargyl imines by a Staudinger cycloaddition,<sup>11</sup> yielding intermediates B having a triple bond attached to the four membered ring, a Cu-alkyne azide cycloaddition (CuAAC) with the appropriate azide,<sup>12</sup> to build the 1,2,3-triazole-azetidinone hybrids C, and methylation to form the triazolium salts A. Final metallation allowed the access to complexes D (Scheme 1).

Following this sequence, *cis*-2-azetidinones 8a and 8b were obtained by reaction of imine 9 and the corresponding acid chlorides 10 by treatment with Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 2). Racemic *cis*- $\beta$ -lactam 8a was obtained in 88% yield, while *cis*-2-azetidinone 8b, was obtained in 54% yield as a single (3*S*,4*R*) enantiomer.<sup>13</sup> Reaction of imine 9 with phthalimidylacetyl chloride 10c in the presence of Et<sub>3</sub>N in refluxing benzene yielded pure racemic *trans*-2-azetidinone 8c (38%) (Scheme 2).



Scheme 1 The approach to complexes A having 1,2,3-triazolylidene- $\beta$ -lactam hybrid ligands.

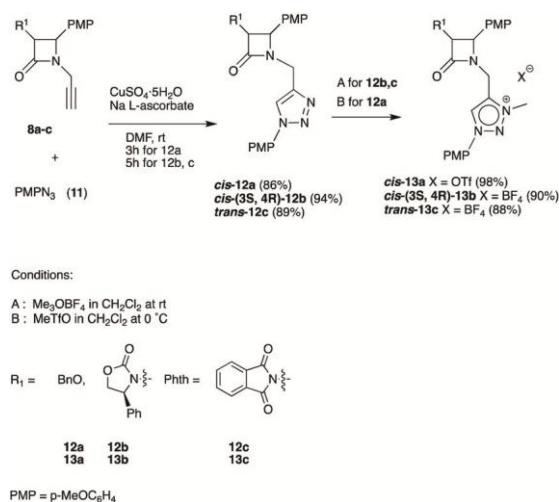


Scheme 2 Synthesis of 2-azetidinones **8**. Compounds *cis*-**8a** and *trans*-**8c** are racemic mixtures.

The relative stereochemistry of the 2-azetidinones **8a–c** was deduced from the H3–H4  $J^3$  values of the 2-azetidinone ring ( $J = 4.4$  Hz and 4.9 Hz for **8a** and **8c**, respectively, attributable to a *cis*-stereochemistry, while  $J = 2.5$  Hz is in accordance with a *trans*-stereochemistry for azetidinone **8c**).<sup>14</sup>

N-Propargyl-2-azetidinones **8a–c** were reacted with azide **11** in the presence of Cu(i) (Scheme 3). In all cases, 1,2,3-triazoles **12a–c** were obtained as single regioisomers in excellent yields. It needs to be pointed that the chiral integrity of the azetidinone **8b** remains unaltered during the CuAAC reaction yielding 1,2,3-triazole **12b** as a single enantiomer. The formation of the 1,2,3-triazole ring agrees with the appearance, in the <sup>1</sup>H-NMR spectra, of a singlet signal between 8.43 and 7.46 ppm (see ESI<sup>+</sup>), attributable to the triazole ring hydrogen, and the disappearance of the signal corresponding to the terminal alkyne proton of the 2-azetidinones **8a–c** (one signal triplet between 2.44 and 2.16 ppm).

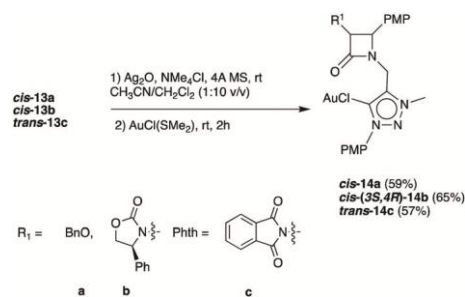
Alkylation of the 1,2,3-triazols **12a–c** was pursued next (Scheme 3). Reaction conditions depended on the substituent



Scheme 3 Synthesis of triazolyl- $\beta$ -lactam hybrids **12a–c** and their triazolium salts **13a–c**. Compounds *cis*-**12a,c** and *trans*-**13a,c** are racemic mixtures.

at C-3 of the  $\beta$ -lactam ring. Thus, 1,2,3-triazoles **12b** and **12c** bearing an oxazolidinone and a phthalimide group, respectively, were methylated by treatment with Me<sub>3</sub>OBf<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> at rt, to obtain triazolium salts **13b** and **13c** in excellent yields (90% and 88% respectively). On the other hand, submission of azetidinone **12a**, having a benzyloxy group at carbon C-3, to these reaction conditions produced a complex mixture of products. Thus, methylation of **12a** was achieved using MeOTf in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C, obtaining 1,2,3-triazolium salt *cis*-**13a** in nearly quantitative yield (98%).

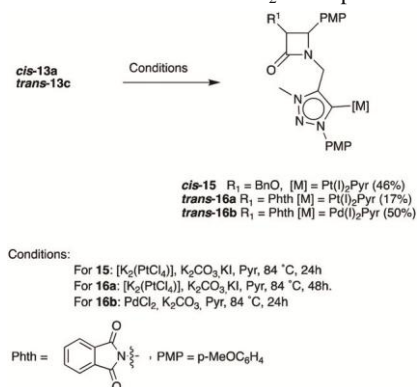
The <sup>1</sup>H-NMR spectra of these salts **13a–c** show a new signal singlet integrating for three protons, attributable to the methyl group at the N3 of the triazole ring. Moreover, the signal corresponding to the triazolium salt hydrogen experiences a 1.0 ppm low field displacement with respect to the non-methylated triazole. With MICs precursors, triazolium salts **13a–c** in hand, the synthesis of the corresponding gold(i) complexes was next pursued. In situ transmetalation from the corresponding Ag(i) carbenes, generated by reaction of the 1,2,3-triazolium salts with Ag<sub>2</sub>O, with AuCl(SMe<sub>2</sub>) provided the mesoionic carbenes **14a–c** in yields ranging from 57% to 65% (Scheme 4). These yields are acceptable considering the high reactivity of the  $\beta$ -lactam ring and its bias to decompose by opening the four membered ring, especially in the presence of organometallic reagents.<sup>15</sup>



Scheme 4 Synthesis of MICs 14a–c. Compounds cis-14a and trans-14c are racemic mixtures.

The proposed structures for carbenes 14a–c agree with their spectroscopic data and with the HRMS analysis. Thus, <sup>1</sup>H-NMR spectra of Au(I) carbenes 14a–c showed the disappearance of the characteristic signal corresponding to the triazole hydrogen present in the precursor salts 13a–c. Especially relevant is the chemical shift for the carbenic carbons, which appear shifted to low field values by around 30 ppm in their <sup>13</sup>C NMR spectra with respect to the free triazolium salt. Thus, for salt 13a the CH triazole carbon appears at 128.0 ppm, while the corresponding carbenic carbon of the complex cis-14a appears at 159.0 ppm.

Preparation of Pd(II) and Pt(II)–MIC complexes was next pursued. Pt(II) complexes 15 and 16a were obtained by direct metalation of the 1,2,3-triazolium salts 13a and 13c with [K<sub>2</sub>(PtCl<sub>4</sub>)] in 46% and 17% yields, respectively. In addition, reaction of triazolium salt 13c with PdCl<sub>2</sub> in the presence of



Scheme 5 Preparation of Pd and Pt–MIC– $\beta$ -lactam complexes.

K<sub>2</sub>CO<sub>3</sub> yielded complex 16b in good yield (50%) (Scheme 5). The lower yields in the preparation of these metallic carbenes compared to their gold analogues can be explained due to the reversion of the triazolium salts 13a and 13c to triazoles 12a and 12c respectively, through a demethylation of the heterocyclic triazolium ring, which competes with the formation of Pd(II) or Pt(II) complexes.<sup>16</sup>

Structures of the new Pd– and Pt–MIC carbenes were established by <sup>1</sup>H–<sup>13</sup>C, 2D correlation NMR spectroscopy and HRMS spectrometry. The carbene carbon of Pd(II) complex 16b resonates at low field with respect to the original 1,2,3-triazolium salt. This shift is smaller ( $\delta_{C-Pd} \cong 137$  ppm) than the observed for Au(I) carbenes ( $\delta_{C-Au} \cong 160$  ppm) and almost negligible for Pt(II) complexes 15 and 16a ( $\delta_{C-Pt} \cong 127$  ppm) (see the Experimental section). Finally, crystals of complex 15 were obtained from EtOAc/hexane solutions and submitted to X-ray analysis.

MIC–platinum complex 15 shows in all independent molecules a nearly perfect classical square planar geometry as expected for Pt(II)–MICs complexes (Fig. 3).

The sequence depicted in the Scheme 1 is, therefore, suitable to prepare MICs precursors having the labile 2-azetidinone ring attached to C4 of the heterocyclic ring. Moreover, the incorporation of these MICs to Au–MIC complexes did not degrade the four membered ring, a usual reaction of these systems in the presence of metals.

To stress this methodology the preparation of MIC complexes bearing the labile penicillin G bicyclic system was next attempted. Potassium salt 17 (Scheme 6) was treated with propargyl bromide in DMF yielding the corresponding alkyne ester in 97% yield, which by reaction with benzyl azide 18 in the presence of Cu(I) afforded the 1,2,3-triazole–penicillin G 19 in excellent yield (93%). Even more, the chiral integrity of the penicillin G is maintained and compound 19 was obtained as a single enantiomer. Selective methylation of triazole ring of 19 was achieved using MeOTf at 0 °C to form triazolium salt 20 (82%). Although gold(I) carbene complex 21 was first obtained by transmetalation of the Ag(I) carbene intermediate with AuCl(SMe<sub>2</sub>), this methodology presents some reproducibility problems. Preparation of the gold(I) carbene by direct

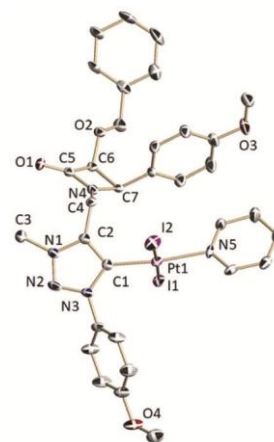
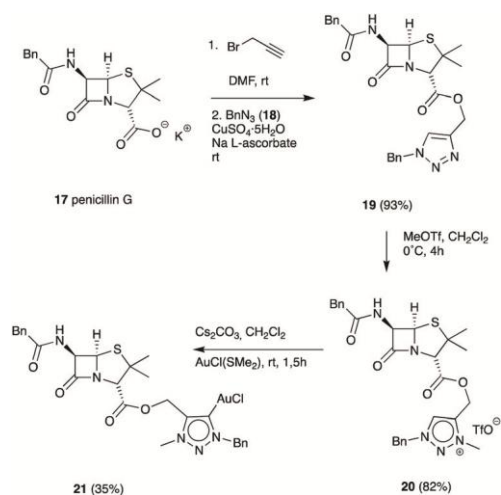


Fig. 3 Solid state structure of complex 15. Only one of three independent molecules present in the asymmetric unit is depicted as thermal ellipsoid plot at the 50% level. Hydrogen atoms and disorders of the pyridine ligand and of the benzyl group connected to O2 are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pt1–C1 1.974(7), Pt1–I1 2.599(1), Pt1–I2 2.596(1), Pt1–N5 2.133(15), I1–Pt1–I2 178.2(1), C1–Pt1–N5 172.4(6), C1–Pt1–I1 87.9(2), C1–Pt1–I2 90.3(2), I1–Pt1–N5 91.2(9), I2–Pt1–N5 90.6(9).

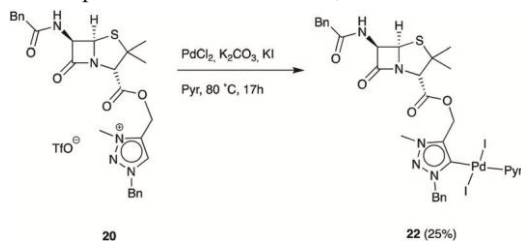


Scheme 6 Synthesis of penicillin-MIC-gold hybrid 21.

metallation in presence of  $\text{Cs}_2\text{CO}_3$  proved to be more effective and reproducible. MIC complex 21 was obtained in 35% yield, which is acceptable due to the lability of the penicillin system.

The Pd(II)-penicillin G MIC complex 22 was obtained in a 25% yield as a single enantiomer (Scheme 7) by reaction of triazolium salt 20 and  $\text{PdCl}_2$  in the presence of  $\text{K}_2\text{CO}_3$ . Attempts to prepare the analogous Pt(II) carbene derived from penicillin were fruitless. Variations of the reaction solvent ( $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ ),  $[\text{PtCl}_2(\text{DMSO})_2]$  as metal source or transmetalation from the corresponding Ag(I) carbene intermediate meet with no success.

As indicated above, penicillin and its derivatives are extremely sensitive to the presence of metals. In fact, the mode of



Scheme 7 Synthesis Pd derivative 22.

action of  $\beta$ -lactamases involves the coordination of a Zn(II) center to the four membered ring promoting the opening of the  $\beta$ -lactam and has precluded the isolation of coordination complexes derived from penicillin and cephalosporin, since, analogously, coordination induces the aperture of the fourmembered ring.<sup>15b</sup>

### Catalytic activity

Mesoionic gold carbenes are efficient catalysts for the cycloisomerization of enynes.<sup>17</sup> We were interested in determining

the suitability as catalysts of the above prepared  $\beta$ -lactam and penicillin substituted MIC-complexes. Based on our previous experience using MIC metal complexes as catalysts<sup>18</sup> we chose the Au(I) cycloisomerization of enynes and the Pt(II) hydrosilylation of alkynes to determine both the catalytic activity of these complexes and the integrity of the labile  $\beta$ -lactam (especially the penicillin bicyclic ring) during the catalytic process. This fact could be tested by determining the influence of the substitution on the four membered ring in the catalytic outcome.

Complexes 14a-c and 21 were thus tested as catalysts in the cycloisomerization of enyne 23. The reaction of 23 with the different MICs-Au complexes was performed in anhydrous  $\text{CH}_2\text{Cl}_2$  in the presence of 3 mol% of catalyst and NaBARF (3 mol%) at rt. In all cases complete conversion was achieved after 2 h. The composition of the reaction mixtures was analyzed by  $^1\text{H-NMR}$  (Table 1).

The relation between the regioselectivity of the cycloisomerization reaction and the presence of coordinating moieties (sulfoxide and sulfinylimines) tethered to the 1,2,3-triazolium carbene ring in determining the selectivity of the cycloisomerization reaction has been reported previously by us.<sup>18a</sup> Now, the presence of 2-azetidinones having coordinating moieties (2-oxazolidinone or the bicyclic ring of the penicillin) tethered to the triazolium MIC succeed in controlling the regioselectivity of the cycloisomerization reactions depicted in Table 1. Therefore, it is probable that the complexation of the 2-azetidinone-oxazolydinyl group or the five membered ring of the penicillin substituents of the MIC to the metal centre determines the selectivity of the reaction.

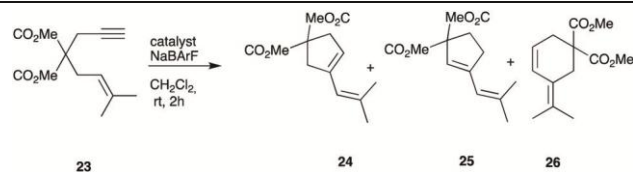
Obviously, the different results obtained with the different substituted MIC establish the integrity of the labile 2-azetidinone ring during the catalytic cycle.

Pt(II) carbenes 15 and 16a were tested as catalysts for the hydrosilylation of phenylacetylene (Scheme 8). The reaction was performed in toluene at 100 °C in the presence of 1.1 eq. of Table 1 Catalyst screening for the cycloisomerization of enyne 23

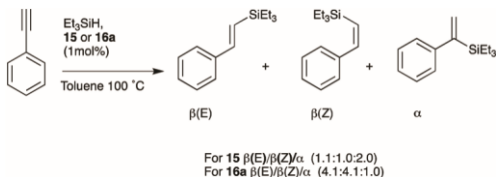
<sup>a</sup> In all cases conversions were 100% after 2 h of reaction. <sup>b</sup> 3% mol of complex and 3% mol of NaBARF were used. All reactions were performed at rt. Ratio of products were measured by  $^1\text{H-NMR}$  of the reaction crudes.

triethylsilane and 1 mol% of catalyst. Both Pt-MICs yielded the three possible reaction products  $\beta(\text{E})/\beta(\text{Z})/\alpha$ . While carbene trans16a produced  $\beta$ - and  $\alpha$ -silylated compounds in a 1.1:1.0 ratio,

Entry <sup>a</sup>	Catalyst <sup>b</sup>	24 : 25 : 26
1	14c	13.1 : 4.7 : 1.0
2	14a	6.6 : 3.6 : 1.0



carbene **15** (Scheme 5) wearing a *cis*-2-azetidinone fragment yielded a mixture  $\beta/\alpha$  (8.2:1.0). No *Z/E* selectivity was observed in either case. The ratio  $\beta/\alpha$  was considerably higher for **16a** than for **15** which points, again, to the participation of the C3-substituent (now a phthalimido vs. a benzyloxy moiety) of the 2-azetidinone ring in determining the selectivity of the process.<sup>18a</sup>



Scheme 8 Hydrosilylation of phenylacetylene.

## Conclusions

In summary, the synthesis of several *cis*- and *trans*-2-azetidinone substituted 1,2,3-triazolylidene MIC metal carbenes, including penicillin G substituted MIC metal carbenes is described for the first time. The synthetic approach to these complexes involves the derivatization of 2-azetidinones with one terminal alkyne at N1 of the four membered ring, followed by a CuAAC reaction to obtain the corresponding 4-substituted-1,2,3-triazoles. Alkylation of the 1,2,3-triazoles using Meerwein salt or MeOTf followed by Au(I)-transmetalation (either direct or through the corresponding Ag(I) intermediates) formed the desired MIC–Au complexes. Yields were good, 57% to 65% for 2-azetidinones, and 35% for the gold carbene derived from penicillin G. It should be highlighted that this is the first time that a  $\beta$ -lactam antibiotic is incorporated to a mesoionic carbene ligand.

The Au(I) complexes are catalysts in the cycloisomerization of enynes, and the presence of a chelating moiety at the C3 of the 2-azetidinone ring or the full penicillin bicyclic system in compound **21** allow for totally regioselective cyclization processes. The integrity of the labile 2-azetidinone moiety during the catalytic cycle is demonstrated by the different results obtained depending on the substitution of the  $\beta$ -lactam ring.

Pd and Pt-direct metalation of 1,2,3-triazolium salts formed the corresponding MICs-complexes. Pt–MICs catalyse the hydrosilylation of phenyl acetylene. In the hydrosilylation reaction, complex **16a** is more selective than MIC–Pt **15** pointing to the ability of phthalimido moiety in the C3 of the 2-azetidinone ring to interact with the metallic catalyst, controlling the selectivity of the reaction.

## Experimental

### General methods

Unless noted otherwise, all manipulations were carried out under argon atmosphere using standard Schlenk techniques. DMF, toluene,

$\text{CH}_2\text{Cl}_2$  and  $\text{CH}_3\text{CN}$  were dried by passage through solvent purification columns containing activated alumina. Other solvents were HPLC grade and were used without purification. All reagents were obtained from commercial sources and used without additional purification, unless noted otherwise. Flash column chromatography was performed using silica gel 60 (Merck, no. 1.09385, 230–400 mesh).

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 400 or 500 MHz (<sup>1</sup>H NMR) and at 100 or 126 MHz (<sup>13</sup>C NMR) using  $\text{CDCl}_3$  or acetonitrile- $d_3$  as solvents with the residual solvent signal as internal reference ( $\text{CHCl}_3$  7.26 and 77.2 ppm), (acetonitrile 1.94, and 118.26 and 1.32, ppm). The following abbreviations are used to describe peak patterns when appropriate: s

(singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and br (broad). The NMR peak assignments were based on the analysis of <sup>1</sup>H–<sup>13</sup>C-HMBC and HSQC recorded spectra along with previously reported data for related compounds. High-resolution mass spectrometry (HRMS) by the ESI technique was performed with an Agilent 6500 accurate mass apparatus with a Q-TOF analyser. IR spectra were recorded on a PerkinElmer 681 spectrophotometer. Melting points were determined on a Koffler block.

Compounds **9**,<sup>7d</sup> **10b**,<sup>13</sup> **10c**,<sup>19</sup> **11**,<sup>20</sup> and **18**<sup>21</sup> were prepared according to previously described procedures. Benzyloxyacetyl chloride **10a** and penicillin G potassium salt were obtained from commercial sources and used without further purification. Selected examples of the synthesis of compounds **8a–8c**, **12b**, **19**, **13b**, **20**, **14b**, **21**, **15** and **22** are presented in the Experimental section. Full details about the synthesis of the compounds reported in this work can be found in the ESI.†

### General procedure for the synthesis of alkynyl- $\beta$ -lactams

**Method A.** A solution of the corresponding acid chloride (1.5 equiv.) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5 mL/1.5 mmol) was purged with argon and cooled to  $-78^\circ\text{C}$ . A solution of  $\text{Et}_3\text{N}$  (3.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (2.5 mL/3.0 mmol of  $\text{Et}_3\text{N}$ ) was added dropwise. The mixture was stirred for 30 min at  $-78^\circ\text{C}$ , and a solution of the imine (1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (2.5 mL/1.0 mmol) was slowly added. Upon completion of the addition, the cooling bath was removed, and the mixture was stirred at rt for 16 h. The reaction was successively quenched with 2 mL of MeOH, diluted with  $\text{CH}_2\text{Cl}_2$  (15 mL/1.0 mmol imine) and washed with  $\text{NaHCO}_3$  and brine. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and solvents were removed under vacuum.  $\text{SiO}_2$  chromatography (Hex/EtOAc mixtures) yielded pure alkynyl- $\beta$ -lactams **8a** and **8b**.

**Method B.** A solution of the acid chloride (1.2 equiv.) in anhydrous benzene (5 mL/1.5 mmol of acid chloride) was added dropwise via syringe to a solution of the corresponding imine (1.0 equiv.) and  $\text{Et}_3\text{N}$  (2.0 equiv.) in refluxing benzene (2.5 mL/1.0 mmol of imine) under argon. The resulting mixture was refluxed for 3 hours. The crude mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (15 mL/1.0 mmol of imine) and washed with saturated  $\text{NaHCO}_3$  and brine. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and solvents were removed

under vacuum. The crude mixture was purified by SiO<sub>2</sub> chromatography (Hex/EtOAc mixtures) to yield pure alkynyl-β-lactam 8c. β-Lactam 8a. Following method A, from a mixture of imine 9 (0.63 g, 3.6 mmol, 1.0 equiv.), Et<sub>3</sub>N (1.11 g, 10.9 mmol, 3.0 equiv.) and benzyloxycarbonyl chloride 10a (1.01 g, 5.5 mmol, 1.5 equiv.), pure 8a (1.03 g, 88%) was obtained as a single cis isomer after purification by SiO<sub>2</sub> chromatography (Hex/EtOAc 3 : 2) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.30 (d, J = 8.7 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 7.25–7.21 (m, 3H, Ph), 7.02–6.98 (m, 2H, Ph), 6.93 (d, J = 8.7 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 4.87 (d, J = 4.4 Hz, 1H, β-lactam cis), 4.83 (d, J = 4.4 Hz, 1H, β-lactam cis), 4.39–4.30 (m, 2H, 1H, N-CH<sub>2</sub>, 1H O-CH<sub>2</sub>), 4.22 (d, J = 11.4 Hz, 1H, O-CH<sub>2</sub>), 3.84 (s, 3H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 3.57 (dd, J = 17.7, 2.5 Hz, 1H, O-CH<sub>2</sub>), 2.18 (t, J = 2.5 Hz, 1H, CuCH). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 166.5 (C, CvO, β-lactam), 160.2 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 136.5 (C, Ph), 130.0 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 128.4 (2CH, Ph), 128.3 (2CH, Ph), 128.1 (CH, Ph), 125.2 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 114.1 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 83.9 (CH, β-lactam), 76.3 (C, CuC), 72.8 (CH, CuCH), 72.4 (CH<sub>2</sub>, O-CH<sub>2</sub>), 61.2 (CH, β-lactam), 55.5 (CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>), 29.4 (CH<sub>2</sub>, N-CH<sub>2</sub>). IR (KBr): ν<sub>max</sub> 1764, 1613, 1514, 1395, 1353, 1250, 1177, 1100, 1030, 839, 699 cm<sup>-1</sup>. MS (ESI) m/z calculated for C<sub>20</sub>H<sub>20</sub>NO<sub>3</sub>: 322.1438 [M + H]<sup>+</sup>; found: 322.1439. Mp: 80–83 °C.

β-Lactam 8b. Following method A, from a mixture of imine 9 (224.0 mg, 1.29 mmol, 1.0 equiv.), Et<sub>3</sub>N (392.0 mg, 3.9 mmol, 3.0 equiv.) and (S)-2-(2-oxo-4-phenyloxazolidin-3-yl) acetyl chloride 10b (465.0 mg, 1.9 mmol, 1.5 equiv.), pure 8b (261.0 mg, 54%) was obtained as a single cis isomer after purification by SiO<sub>2</sub> chromatography (Hex/EtOAc 3 : 7) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.41–7.35 (m, 3H, Ph), 7.27 (d, J = 8.6 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 7.21 (d, J = 3.7 Hz, 1H, Ph), 7.19 (d, J = 2.3 Hz, 1H, Ph), 6.93 (d, J = 8.8 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 4.86 (d, J = 4.9 Hz, 1H, β-lactam cis), 4.47 (dd, J = 17.8, 2.6 Hz, 1H, N-CH<sub>2</sub>), 4.44 (d, J = 4.9 Hz, 1H, β-lactam cis), 4.30–4.19 (m, 2H, 1H oxaz. + 1H CH<sub>2</sub> oxaz.), 3.94 (dd, J = 8.1, 6.9 Hz, 1H, CH<sub>2</sub> oxaz.), 3.84 (s, 3H, CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>), 3.68 (dd, J = 17.8, 2.5 Hz, 1H, N-CH<sub>2</sub>), 2.16 (t, J = 2.6 Hz, 1H, CuC-H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 163.3 (C, CvO, β-lactam), 160.0 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 157.0 (C, CvO, oxaz.), 136.5 (C, Ph), 129.6 (2CH, Ph), 129.5 (CH, Ph), 129.1 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 127.6 (2CH, Ph), 124.8 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 114.4 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 76.2 (CuC-H), 73.2 (CuC-H), 70.3 (CH<sub>2</sub>, O-CH<sub>2</sub> oxaz.), 63.9 (CH, β-lactam), 61.0 (CH, β-lactam), 59.8 (CH, oxaz.), 55.4 (CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>), 30.5 (CH<sub>2</sub>, N-CH<sub>2</sub>). HRMS (ESI) m/z calculated for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: 377.1496 [M + H]<sup>+</sup>; found 377.1502. Mp: 220–228 °C. [α]<sub>D</sub><sup>25</sup> = +59.55 (c 0.41, CHCl<sub>3</sub>).

β-Lactam 8c. Following method B, imine 9 (1.94 g, 11.2 mmol, 1.0 equiv.), Et<sub>3</sub>N (2.46 g, 22.4 mmol, 2.0 equiv.) and phthalimidylacetyl chloride 10c (3.16 g, 13.4 mmol, 1.2 equiv.) yielded pure 8c (1.53 g, 38%) as a single trans isomer after purification by SiO<sub>2</sub> chromatography (Hex/EtOAc 2 : 3) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.90–7.82 (m, 2H,

Phth), 7.77–7.73 (m, 2H, Phth), 7.29 (d, J = 8.7 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 6.93 (d, J = 8.7 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 5.20 (d, J = 2.5 Hz, 1H, β-lactam trans), 5.06 (d, J = 2.5 Hz, 1H, β-lactam trans), 4.41 (dd, J = 17.8, 2.6 Hz, 1H, N-CH<sub>2</sub>), 3.82 (s, 3H, CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>), 3.75 (dd, J = 17.7, 2.6 Hz, 1H, N-CH<sub>2</sub>), 2.30 (t, J = 2.5 Hz, 1H, CuCH). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 166.9 (2C, CvO, Phth), 164.7 (C, CvO, β-lactam), 160.4 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 134.6 (2CH, Phth), 131.8 (2C, Phth), 128.2 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 127.2 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 123.9 (2CH, Phth), 114.7 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 75.9 (C, CuC), 73.2 (CH, CuCH), 62.6 (CH, β-lactam), 60.4 (CH, β-lactam), 55.5 (CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>), 30.6

(CH<sub>2</sub>, N-CH<sub>2</sub>). IR (KBr): ν<sub>max</sub> 1770, 1720, 1613, 1516, 1392, 1250, 1179, 1104, 1031, 927, 837, 717 cm<sup>-1</sup>. HRMS (ESI) m/z calculated for C<sub>21</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>: 361.1183 [M + H]<sup>+</sup>; found 361.1198. Mp: 194–196 °C.

Penicillin-G propargyl derivative. Propargyl bromide (373 μL, 3.4 mmol, 1.3 equiv.) was added to a solution of commercially available penicillin G potassium salt 17 (1.00 g, 2.7 mmol, 1.0 equiv.) in DMF (6 mL). The mixture was stirred under argon at rt overnight. The reaction was quenched with water and the crude was extracted with Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (5 : 1). The organic layer was washed with water (×2) and brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The solvent was removed under vacuum yielding the corresponding propargyl ester as a transparent syrup (964 mg, 97%). The product was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.33–7.13 (m, 5H, Ph), 6.37 (bs, 1H, NH), 5.56 (dd, J = 9.0, 4.2 Hz, 1H, β-lactam cis), 5.43 (d, J = 4.1 Hz, 1H, β-lactam cis), 4.71 (dd, J = 15.5, 2.4 Hz, 1H, O-CH<sub>2</sub>), 4.61 (dd, J = 15.5, 2.5 Hz, 1H, O-CH<sub>2</sub>), 4.32 (s, 1H, β-lactam), 3.54 (s, 2H, Ph-CH<sub>2</sub>), 2.47 (t, J = 2.5 Hz, 1H, CuC-H), 1.40 (s, 6H, 2CH<sub>3</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 173.5 (C, CvO, β-lactam), 170.5 (C, CvO, HN-CvO), 166.9 (C, CvO, O-CvO), 133.9 (C, Ph), 128.3 (2CH, Ph), 127.7 (2CH, Ph), 125.4 (CH, Ph), 76.6 (C, CuC-H), 76.0 (CH, CuC-H), 70.1 (CH, β-lactam), 68.1 (CH, β-lactam), 64.8 (C, C(CH<sub>3</sub>)<sub>2</sub>), 58.9 (CH, β-lactam), 52.9 (CH<sub>2</sub>, O-CH<sub>2</sub>), 43.4 (CH<sub>2</sub>, Ph-CH<sub>2</sub>), 31.8 (CH<sub>3</sub>), 26.8 (CH<sub>3</sub>). IR (KBr): ν<sub>max</sub> 3285, 2970, 1784, 1755, 1662, 1521, 1300, 1202, 1182, 1155, 991, 730, 697 cm<sup>-1</sup>. HRMS (ESI) m/z calculated for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>S: 373.1217 [M + H]<sup>+</sup>; found 373.1202. [α]<sub>D</sub><sup>25</sup> = +48.25 (c 2.07, CHCl<sub>3</sub>).

General procedure for the synthesis of 1,2,3-triazoles

A mixture of organic azide (1.0 equiv.), alkyne (1.2 equiv.), sodium (L)-ascorbate (0.5 equiv.) and CuSO<sub>4</sub>·5H<sub>2</sub>O (0.25 equiv.) in DMF was stirred under argon at rt until completion of the reaction (TLC analysis). The reaction was quenched with water at 0 °C and allowed to reach rt. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (×3). The organic layer was dried over MgSO<sub>4</sub>, filtered, and the solvent removed under vacuum. The crude product was purified by column chromatography (SiO<sub>2</sub>) to afford the pure triazoles 12a, 12b, 12c and 19.

Triazole 12b. Following the general procedure, a mixture of p-anisyl azide 11 (30 mg, 0.2 mmol, 1.0 equiv.), alkyne 8b (90 mg, 0.2 mmol, 1.1 equiv.), sodium (L)-ascorbate (20 mg, 0.1 mmol, 0.5

equiv.) and  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (13 mg, 0.1 mmol, 0.3 equiv.) in DMF (4 mL) was stirred under Ar at rt for 5 h. The crude obtained after workup was purified by  $\text{SiO}_2$  chromatography (Hex/EtOAc 1 : 4) to yield pure 12b as a white solid (98 mg, 94%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.94 (s, 1H,  $\text{N}_3\text{CvCH}$ ), 7.57 (d,  $J = 9.0$  Hz, 2H, p-OMe- $\text{C}_6\text{H}_4$ ), 7.40–7.32 (m, 3H, Ph), 7.28 (d,  $J = 8.7$  Hz, 2H, p-OMe- $\text{C}_6\text{H}_4$ ), 7.22–7.18 (m, 2H, Ph), 6.99 (d,  $J = 9.0$  Hz, 2H, p-OMe- $\text{C}_6\text{H}_4$ ), 6.92 (d,  $J = 8.7$  Hz, 2H, p-OMe- $\text{C}_6\text{H}_4$ ), 4.88–4.83 (m, 2H, 1H  $\beta$ -lactam + 1H N- $\text{CH}_2$ ), 4.39–4.31 (m, 2H, 1H  $\beta$ -lactam + 1H N- $\text{CH}_2$ ), 4.26–4.16 (m, 2H, 1H  $\text{CH}_2$  oxaz. + 1H oxaz.), 3.97–3.90 (m, 1H,  $\text{CH}_2$  oxaz.), 3.86 (s, 3H,  $\text{CH}_3$ , p-OMe- $\text{C}_6\text{H}_4$ ), 3.83 (s, 3H,  $\text{CH}_3$ , p-OMe- $\text{C}_6\text{H}_4$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.7 (C, CvO,  $\beta$ -lactam), 160.0 (C, p-OMe- $\text{C}_6\text{H}_4$ ), 160.0 (C, p-OMe- $\text{C}_6\text{H}_4$ ), 157.0 (C, CvO, oxaz.), 142.9 (C,  $\text{N}_3\text{CvCH}$ ), 136.4 (C, Ph), 130.5 (C, p-OMe- $\text{C}_6\text{H}_4$ ), 129.6 (2CH, Ph), 129.6 (CH, Ph), 129.3 (2CH, p-OMe- $\text{C}_6\text{H}_4$ ), 127.6 (2CH, Ph), 124.9 (C, p-OMe- $\text{C}_6\text{H}_4$ ), 122.3 (2CH, p-OMe- $\text{C}_6\text{H}_4$ ), 121.2 (CH,  $\text{N}_3\text{CvCH}$ ), 114.9 (2CH, p-OMe- $\text{C}_6\text{H}_4$ ), 114.4 (2CH, p-OMe- $\text{C}_6\text{H}_4$ ), 70.3 ( $\text{CH}_2$ , O- $\text{CH}_2$  oxaz.), 63.8 (CH,  $\beta$ -lactam), 61.8 (CH,  $\beta$ -lactam), 60.0 (CH, oxaz.), 55.8 ( $\text{CH}_3$ , p-OMe- $\text{C}_6\text{H}_4$ ), 55.5 ( $\text{CH}_3$ , p-OMe- $\text{C}_6\text{H}_4$ ), 36.8 ( $\text{CH}_2$ , N- $\text{CH}_2$ ). IR (KBr):  $\nu_{\text{max}}$  1757, 1517, 1418, 1253, 1177, 1034, 835, 701  $\text{cm}^{-1}$ . MS (ESI)  $m/z$  calculated for  $\text{C}_{29}\text{H}_{28}\text{N}_5\text{O}_5$ : 526.2085 [ $\text{M} + \text{H}$ ] $^+$ ; found 526.2088. Mp: 104–106 °C.  $[\alpha]_{\text{D}}^{25} = +42.06$  (c 0.23,  $\text{CHCl}_3$ ).

**Triazole 19.** Following the general procedure, a mixture of benzyl azide 18 (126 mg, 0.9 mmol, 1.0 equiv.), penicillin G propargyl ester (400 mg, 1.1 mmol, 1.2 equiv.), sodium (L)ascorbate (88 mg, 0.5 mmol, 0.5 equiv.) and  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (56 mg, 0.2 mmol, 0.3 equiv.) in DMF (6 mL) was stirred under Ar at rt for 3 h. The crude obtained after workup was purified by  $\text{SiO}_2$  chromatography (Hex/EtOAc 3 : 7) to yield pure 19 as a white solid (419 mg, 93%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.46 (s, 1H,  $\text{N}_3\text{CvCH}$ ), 7.33–7.13 (m, 10H, 2Ph), 6.03 (t,  $J = 9.3$  Hz, 1H, NH), 5.55 (dd,  $J = 9.0, 4.2$  Hz, 1H,  $\beta$ -lactam), 5.47 (d,  $J = 14.9$  Hz, 1H, N- $\text{CH}_2$ ), 5.43 (d,  $J = 14.9$  Hz, 1H, N- $\text{CH}_2$ ), 5.37 (d,  $J = 4.2$  Hz, 1H,  $\beta$ -lactam), 5.20 (d,  $J = 12.7$  Hz, 1H, O- $\text{CH}_2$ ), 5.17 (d,  $J = 12.7$  Hz, 1H, O- $\text{CH}_2$ ), 4.26 (s, 1H,  $\beta$ -lactam), 3.55 (s, 2H,

Ph- $\text{CH}_2$ ), 1.32 (s, 3H,  $\text{CH}_3$ ), 1.19 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.5 (C, CvO,  $\beta$ -lactam), 170.3 (C, CvO, HN-CvO), 167.5 (C, CvO, O-CvO), 142.1 (C,  $\text{N}_3\text{CvCH}$ ), 134.3 (C, Ph), 133.8 (C, Ph), 129.5 (2CH, Ph), 129.2 (2CH, Ph), 129.1 (2CH, Ph), 129.0 (CH, Ph), 128.1 (2CH, Ph), 127.7 (CH, Ph), 124.1 (CH,  $\text{N}_3\text{CvCH}$ ), 70.1 (CH,  $\beta$ -lactam), 68.0 (CH,  $\beta$ -lactam), 64.6 (C, C( $\text{CH}_3$ ) $_2$ ), 58.7 (CH,  $\beta$ -lactam), 58.4 ( $\text{CH}_2$ , O- $\text{CH}_2$ ), 54.3 ( $\text{CH}_2$ , N- $\text{CH}_2$ ), 43.4 ( $\text{CH}_2$ , Ph- $\text{CH}_2$ ), 31.7 ( $\text{CH}_3$ ), 26.7 ( $\text{CH}_3$ ). IR (KBr):  $\nu_{\text{max}}$  1784, 1748, 1678, 1521, 1497, 1455, 1300, 1203, 1184, 1156, 1052, 961, 733, 699  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{26}\text{H}_{28}\text{N}_5\text{O}_4\text{S}$ : 506.1857 [ $\text{M} + \text{H}$ ] $^+$ ; found 506.1881.  $[\alpha]_{\text{D}}^{25} = +73.19$  (c 1.33,  $\text{CHCl}_3$ ).

## General procedure for the synthesis of triazolium salts

**Method A.** A mixture of triazole (1.0 equiv.) and Meerwein's salt (1.3 equiv.) in  $\text{CH}_2\text{Cl}_2$  was stirred under argon at rt until reaction completion (TLC analysis). The reaction was quenched with some drops of methanol. The solvent was removed under vacuum and the resulting residue was dissolved in the minimum amount of  $\text{CH}_2\text{Cl}_2$  and precipitated with  $\text{Et}_2\text{O}$ . The solvents were decanted, and the solid was washed with  $\text{Et}_2\text{O}$  ( $\times 3$ ) and vacuum-dried to yield pure triazolium salts 13b and 13c.

**Method B.** MeOTf (0.9 equiv.) was added to a  $\text{CH}_2\text{Cl}_2$  solution of triazole (1.0 equiv.) at 0 °C. The mixture was stirred at 0 °C for 4 h, until no evolution of the reaction was observed. The solvent was removed under vacuum and the resulting residue was dissolved in the minimum amount of  $\text{CH}_2\text{Cl}_2$  and precipitated with  $\text{Et}_2\text{O}$ . The solvents were decanted and the solid was washed with  $\text{Et}_2\text{O}$  ( $\times 3$ ) and vacuum-dried to yield the pure triazolium salts 13a and 20.

**Triazolium salt 13b.** Following Method A, treatment of 12b (85 mg, 0.2 mmol, 1.0 equiv.) with  $\text{Me}_3\text{OBF}_4$  (36 mg, 0.2 mmol, 1.5 equiv.) in  $\text{CH}_2\text{Cl}_2$  (8 mL) afforded pure 13b as a pink solid (91 mg, 90%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.57 (s, 1H,  $\text{N}_3\text{CvCH}$ ), 7.55 (d,  $J = 9.1$  Hz, 2H, p-OMe- $\text{C}_6\text{H}_4$ ), 7.43–7.32 (m, 3H, Ph), 7.24–7.18 (m, 4H, 2H Ph + 2H p-OMe- $\text{C}_6\text{H}_4$ ), 6.98 (d,  $J = 8.7$  Hz, 2H, p-OMe- $\text{C}_6\text{H}_4$ ), 6.78 (d,  $J = 8.2$  Hz, 2H, p-OMe- $\text{C}_6\text{H}_4$ ), 5.03 (d,  $J = 4.6$  Hz, 1H,  $\beta$ -lactam cis), 4.82 (d,  $J = 16.4$  Hz, 1H, N- $\text{CH}_2$ ), 4.70 (d,  $J = 16.6$  Hz, 1H, N- $\text{CH}_2$ ), 4.40 (bs, 4H, 3H N- $\text{CH}_3$  + 1H  $\beta$ -lactam), 4.18–4.05 (m, 2H, 1H  $\text{CH}_2$ -oxaz. + 1H oxaz.), 3.95 (dd,  $J = 8.1, 6.5$  Hz, 1H,  $\text{CH}_2$  oxaz.), 3.85 (s, 3H,  $\text{CH}_3$ , p-OMe- $\text{C}_6\text{H}_4$ ), 3.66 (s, 3H,  $\text{CH}_3$ , p-OMe- $\text{C}_6\text{H}_4$ ).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  164.4 (C, CvO,  $\beta$ -lactam), 162.2 (C, p-OMe- $\text{C}_6\text{H}_4$ ), 160.1 (C, p-OMe- $\text{C}_6\text{H}_4$ ), 157.3 (C, CvO, oxaz.), 139.8 (C,  $\text{N}_3\text{CvCH}$ ), 136.0 (C, Ph), 129.7 (3CH, Ph), 129.6 (2CH, p-OMe- $\text{C}_6\text{H}_4$ ), 128.0 (CH,  $\text{N}_3\text{CvCH}$ ), 127.7 (C, p-OMe- $\text{C}_6\text{H}_4$ ), 127.4 (2CH, Ph), 124.5 (C, p-OMe- $\text{C}_6\text{H}_4$ ), 123.1 (2CH, p-OMe- $\text{C}_6\text{H}_4$ ), 115.4 (2CH, p-OMe- $\text{C}_6\text{H}_4$ ), 114.3 (2CH, p-OMe- $\text{C}_6\text{H}_4$ ), 70.3 ( $\text{CH}_2$ , O- $\text{CH}_2$  oxaz.), 63.9 (CH,  $\beta$ -lactam), 63.1 (CH,  $\beta$ -lactam), 60.0 (CH, oxaz.), 56.0 ( $\text{CH}_3$ , p-OMe- $\text{C}_6\text{H}_4$ ), 55.3 ( $\text{CH}_3$ , p-OMe- $\text{C}_6\text{H}_4$ ), 38.5 ( $\text{CH}_3$ , N- $\text{CH}_3$ ), 34.0 ( $\text{CH}_2$ , N- $\text{CH}_2$ ). IR (KBr):  $\nu_{\text{max}}$  1769, 1611, 1516, 1421, 1258, 1179, 1060, 1027, 837, 702  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{30}\text{H}_{30}\text{N}_5\text{O}_5$ : 540.2242 [ $\text{M}$ ] $^+$ ; found 540.2244. Mp: 115–120 °C.  $[\alpha]_{\text{D}}^{25} = +30.25$  (c 0.81,  $\text{CHCl}_3$ ).

**Triazolium salt 20.** Following Method B, treatment of 19 (231 mg, 0.5 mmol, 1.0 equiv.) with MeOTf (47  $\mu\text{L}$ , 0.4 mmol, 0.9 equiv.) in  $\text{CH}_2\text{Cl}_2$  (15 mL) afforded pure 20 as a white solid (249 mg, 82%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.69 (s, 1H,  $\text{N}_3\text{CvCH}$ ), 7.46–7.21 (m, 10H, 2Ph), 6.30 (m, 1H, NH), 5.67 (s, 2H, N- $\text{CH}_2$ ), 5.59–5.52 (m, 1H,  $\beta$ -lactam), 5.43 (d,  $J = 4.3$  Hz, 1H,  $\beta$ -lactam), 5.39 (dd,  $J = 18.8, 3.0$  Hz, 1H, O- $\text{CH}_2$ ), 5.43–5.23 (m, 2H, O- $\text{CH}_2$ ), 4.39 (s, 1H,  $\beta$ -lactam), 4.28 (s, 3H, N- $\text{CH}_3$ ), 3.64–3.54 (m, 2H, Ph- $\text{CH}_2$ ), 1.38 (s, 3H,  $\text{CH}_3$ ), 1.30 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ): 173.6 (C, CvO,  $\beta$ -lactam), 170.7 (C, CvO, HN-CvO), 167.2 (C, CvO, O-CvO), 138.6 (C,  $\text{N}_3\text{CvCH}$ ),



134.0 (C, Ph), 131.0 (CH, N<sub>3</sub>CvCH), 130.2 (2CH, Ph), 129.7 (4CH, Ph), 129.6 (2CH, Ph), 129.2 (2CH, Ph), 127.7 (C, Ph), 69.9 (CH, β-lactam), 68.0 (CH, β-lactam), 64.6 (C, C(CH<sub>3</sub>)<sub>2</sub>), 59.1 (CH, β-lactam), 57.8 (CH<sub>2</sub>, O-CH<sub>2</sub>), 54.4 (CH<sub>2</sub>, N-CH<sub>2</sub>), 43.3 (CH<sub>2</sub>, Ph-CH<sub>2</sub>), 38.8 (CH<sub>3</sub>, N-CH<sub>3</sub>), 31.9 (CH<sub>3</sub>), 26.6 (CH<sub>3</sub>). IR (KBr): ν<sub>max</sub> 3323, 3063, 2973, 1750, 1668, 1498, 1456, 1267, 1226, 1162, 1031, 735, 639 cm<sup>-1</sup>. HRMS (ESI) m/z calculated for C<sub>27</sub>H<sub>30</sub>N<sub>5</sub>O<sub>4</sub>S: 520.2013 [M]<sup>+</sup>; found 520.2001. Mp: 92–95 °C. [α]<sub>D</sub><sup>25</sup> = +26.24 (c 0.45, CHCl<sub>3</sub>).

#### General procedure for the synthesis of Au–NHCs

In a Schlenk flask charged with 4 Å molecular sieves, a mixture of triazolium salt (1.0 equiv.), NMe<sub>4</sub>Cl (1.5 equiv.) and Ag<sub>2</sub>O (0.8 equiv.) was stirred at rt in the dark in a 1 : 10 CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> mixture until formation of the corresponding silver carbene (<sup>1</sup>H NMR analysis). [AuCl(SMe<sub>2</sub>)] complex (1.0 equiv.) was then added and the mixture was stirred at rt until the reaction was completed (<sup>1</sup>H NMR analysis). The mixture was filtered through a pad of Celite and the volatiles were removed under vacuum to afford the corresponding carbene complexes 14a, 14b and 14c, which were purified through a short pad of SiO<sub>2</sub>.

Au(i) complex 14b. Following the general procedure, a mixture of 13b (100 mg, 0.2 mmol, 1.0 equiv.), NMe<sub>4</sub>Cl (26 mg, 0.2 mmol, 1.5 equiv.) and Ag<sub>2</sub>O (27 mg, 0.1 mmol, 0.8 equiv.) in CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN (11 mL) was stirred under argon at rt overnight. [AuCl(SMe<sub>2</sub>)] (51 mg, 0.2 mmol, 1.1 equiv.) was then added and the mixture was stirred for another 2 h. The residue was purified (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98 : 2) to yield pure 14b as a white solid (80 mg, 65%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.66 (d, J = 9.0 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 7.44–7.37 (m, 3H, Ph), 7.26 (m, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 7.22 (dd, J = 7.6, 1.9 Hz, 2H, Ph), 6.94 (d, J = 9.0 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 6.87 (d, J = 8.7 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 5.07 (d, J = 4.7 Hz, 1H, β-lactam cis), 4.58 (q, J = 15.9 Hz, 2H, N-CH<sub>2</sub>), 4.43 (s, 3H, N-CH<sub>3</sub>), 4.30 (d, J = 4.7 Hz, 1H, β-lactam cis), 4.21 (t, J = 8.1 Hz, 1H, CH<sub>2</sub>-oxaz.), 4.06–3.94 (m, 2H, CH<sub>2</sub>-oxaz. + 1H oxaz.), 3.85 (s, 3H, CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>), 3.77 (s, 3H, CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 163.8 (C, CvO, β-lactam), 161.0 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 160.3 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 158.7 (C, CvO, oxaz.), 157.1 (C, Ph), 141.6 (C, N<sub>3</sub>CvCAu), 135.7 (C, N<sub>3</sub>CvCAu), 131.7 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 130.0 (2CH, Ph), 129.8 (CH, Ph), 129.8 (2CH, Ph), 127.5 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 125.2 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 124.1 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 114.6 (4CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 70.2 (CH<sub>2</sub>, O-CH<sub>2</sub> oxaz.), 64.0 (CH, β-lactam), 63.0 (CH, β-lactam), 60.1 (CH, oxaz.), 55.8 (CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>), 55.4 (CH<sub>3</sub>, p-OMe-C<sub>6</sub>H<sub>4</sub>), 37.7 (CH<sub>3</sub>, N-CH<sub>3</sub>), 35.6 (CH<sub>2</sub>, N-CH<sub>2</sub>). IR (KBr): ν<sub>max</sub> 1767, 1610, 1514, 1254, 1176, 1030, 837 cm<sup>-1</sup>. HRMS (ESI) m/z calculated for C<sub>30</sub>H<sub>29</sub>N<sub>5</sub>O<sub>5</sub>Au: 736.1829 [M - Cl]<sup>+</sup>; found 736.1850. Mp: (dec.). [α]<sub>D</sub><sup>25</sup> = -50.94 (c 0.05, CHCl<sub>3</sub>).

Complex 21. A mixture of 20 (70 mg, 0.1 mmol, 1.0 equiv.),

Cs<sub>2</sub>CO<sub>3</sub> (68 mg, 0.2 mmol, 2.0 equiv.), and AuCl(SMe<sub>2</sub>) (34 mg, 0.1 mmol, 1.1 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (7.0 mL) was stirred under argon at rt for 1.5 h, until complexation of the reaction (<sup>1</sup>H NMR analysis). The solvent was evaporated and the residue was purified by SiO<sub>2</sub> chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98 : 2) to yield pure 21 as a white solid (28 mg, 35%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.54–7.48 (m, 2H, Ph), 7.40–7.27 (m, 6H, Ph),

7.26–7.21 (m, 2H, Ph), 6.04 (d, J = 9.1 Hz, 1H, NH), 5.63 (dd, J = 9.1, 4.3 Hz, 1H, β-lactam), 5.60 (br s, 2H, N-CH<sub>2</sub>), 5.43 (d, J = 4.3 Hz, 1H, β-lactam), 5.24 (d, J = 13.5 Hz, 1H, O-CH<sub>2</sub>), 5.19 (d, J = 13.4 Hz, 1H, O-CH<sub>2</sub>), 4.33 (s, 1H, β-lactam), 4.17 (s, 3H, N-CH<sub>3</sub>), 3.61 (s, 2H, Ph-CH<sub>2</sub>), 1.44 (s, 3H, CH<sub>3</sub>), 1.29 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 173.8 (C, CvO, β-lactam), 170.4 (C, CvO, HN-CvO), 167.6 (C, CvO, O-CvO), 161.4 (C, N<sub>3</sub>CvCAu), 140.9 (C, N<sub>3</sub>CvCAu), 133.8 (C, Ph), 133.2 (C, Ph), 129.6 (2CH, Ph), 129.5 (CH, Ph), 129.3 (2CH, Ph), 129.2 (2CH, Ph), 129.0 (2CH, Ph), 127.8 (CH, Ph), 70.1 (CH, β-lactam), 67.9 (CH, β-lactam), 64.7 (C, C(CH<sub>3</sub>)<sub>2</sub>), 59.2 (CH<sub>2</sub>, N-CH<sub>2</sub>), 58.8 (CH, β-lactam), 56.0 (CH<sub>2</sub>, O-CH<sub>2</sub>), 43.5 (CH<sub>2</sub>, Ph-CH<sub>2</sub>), 37.7 (CH<sub>3</sub>, N-CH<sub>3</sub>), 31.5 (CH<sub>3</sub>), 27.0 (CH<sub>3</sub>). IR (KBr): ν<sub>max</sub> 1783, 1750, 1674, 1496, 1454, 1200, 1180, 1154, 733, 705 cm<sup>-1</sup>. HRMS (ESI) m/z calculated for C<sub>27</sub>H<sub>29</sub>AuN<sub>5</sub>O<sub>4</sub>S: 716.1600 [M - Cl]<sup>+</sup>; found 716.1611. Mp: (dec.). [α]<sub>D</sub><sup>25</sup> = +22.01 (c 0.49, CHCl<sub>3</sub>).

#### General method for the synthesis of Pd/Pt–NHCs

To a mixture of triazolium salt (1.0 equiv.), potassium carbonate (1.1 equiv.), [K<sub>2</sub>(PtCl<sub>4</sub>)] or PdCl<sub>2</sub> (1.1 equiv.) and potassium iodide (5.0 equiv.), 5 mL of pyridine were added. The mixture was stirred under argon at 84 °C for 17–48 h. Pyridine was evaporated under vacuum and the residue was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was removed under vacuum and the crude product was purified by column chromatography (SiO<sub>2</sub>) to afford the pure carbenes 15, 16a, 16b and 23.

Complex 15. Following the general method, a mixture of triazolium salt 13a (150 mg, 0.2 mmol, 1.0 equiv.), K<sub>2</sub>CO<sub>3</sub> (36 mg, 0.3 mmol, 1.1 equiv.), [K<sub>2</sub>(PtCl<sub>4</sub>)] (108 mg, 0.3 mmol, 1.1 equiv.) and KI (191 mg, 1.2 mmol, 5.0 equiv.) was stirred in pyridine (5 mL) at 84 °C for 24 h, yielding, after purification (SiO<sub>2</sub>, Hex/EtOAc 1 : 1), pure 15 (106 mg, 46%) as an orange solid. (A small amount of triazole 12a was also recovered during purification). Suitable crystals for X-ray analysis were obtained after crystallization from an EtOAc/hexane mixture. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.48 (dd, J = 6.5, 1.5 Hz, 2H, Py), 8.20 (d, J = 9.0 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 7.64 (tt, J = 7.7, 1.6 Hz, 1H, Py), 7.50 (d, J = 8.7 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 7.24–7.16 (m, 5H, 3H Ph + 2H Py), 7.06 (d, J = 9.0 Hz, 2H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 7.01–6.91 (m, 4H, 2H Ph + 2H p-OMe-C<sub>6</sub>H<sub>4</sub>), 5.57 (d, J = 4.3 Hz, 1H, β-lactam cis), 4.92 (d, J = 16.0 Hz, 1H, N-CH<sub>2</sub>), 4.88 (d, J = 4.3 Hz, 1H, β-lactam cis), 4.82 (d, J = 15.6 Hz, 1H, N-CH<sub>2</sub>), 4.27 (d, J = 11.5 Hz, 1H, O-CH<sub>2</sub>), 4.23–4.12 (m, 4H, 3H N-CH<sub>3</sub> + 1H O-

CH<sub>2</sub>), 3.89 (s, 3H, p-OMe-C<sub>6</sub>H<sub>4</sub>), 3.89 (overlapped s, 3H, p-OMe-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 167.5 (C, CvO, β-lactam), 160.6 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 159.9 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 153.8 (2CH, Py), 140.3 (C, N<sub>3</sub>CvCpT), 137.3 (CH, Py), 136.5 (C, Ph), 132.7 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 130.7 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 128.3 (2CH, Ph), 128.3 (2CH, Ph), 128.0 (CH, Ph), 127.7 (C, N<sub>3</sub>CvCpT), 126.7 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 125.5 (C, p-OMe-C<sub>6</sub>H<sub>4</sub>), 124.8 (2CH, py), 114.1 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 113.8 (2CH, p-OMe-C<sub>6</sub>H<sub>4</sub>), 84.2 (CH, β-lactam), 72.3 (CH<sub>2</sub>, O-CH<sub>2</sub>), 61.7 (CH, β-lactam), 55.7 (CH<sub>3</sub>, O-CH<sub>3</sub>), 55.5 (CH<sub>3</sub>, O-CH<sub>3</sub>), 37.5 (CH<sub>3</sub>, N-CH<sub>3</sub>), 33.9 (CH<sub>2</sub>, N-CH<sub>2</sub>). IR (KBr): ν<sub>max</sub> 1758, 1513, 1251, 1174, 1029, 835, 735, 694 cm<sup>-1</sup>. HRMS (ESI) m/z calculated for C<sub>33</sub>H<sub>34</sub>I<sub>2</sub>N<sub>5</sub>O<sub>4</sub>Pt: 1013.0345 [M + H]<sup>+</sup>; found 1013.0373. Mp: 141–146 °C.

Complex 22. Following the general method, a mixture of triazolium salt 20 (150 mg, 0.2 mmol, 1.0 equiv.), K<sub>2</sub>CO<sub>3</sub> (62 mg, 0.5 mmol, 2.0 equiv.), PdCl<sub>2</sub> (44 mg, 0.3 mmol, 1.1 equiv.) and KI (185 mg, 1.1 mmol, 5.0 equiv.) was stirred in pyridine (2 mL) at 80 °C for 17 h, yielding, after purification (SiO<sub>2</sub>, Hex/ EtOAc 1 : 1), pure 22 (54 mg, 25%) as an orange solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.96 (dt, J = 5.0, 1.6 Hz, 2H, Py), 7.72 (tt, J = 7.7, 1.7 Hz, 1H, Py), 7.65 (dd, J = 7.5, 2.0 Hz, 2H, Py), 7.45–7.21 (m, 10H, 2Ph), 6.04 (d, J = 9.1 Hz, 1H, NH), 5.95 (s, 2H, N-CH<sub>2</sub>), 5.67–5.60 (m, 2H, 1H β-lactam + 1H, O-CH<sub>2</sub>), 5.57 (d, J = 4.2 Hz, 1H, β-lactam), 5.50 (d, J = 13.5 Hz, 1H, O-CH<sub>2</sub>), 4.49 (s, 1H, β-lactam), 4.05 (s, 3H, N-CH<sub>3</sub>), 3.63 (s, 2H, Ph-CH<sub>2</sub>), 1.56 (s, 3H, CH<sub>3</sub>), 1.47 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 173.5 (C, CvO, β-lactam), 170.4 (C, CvO, HN-CvO), 167.6 (C, CvO, O-CvO), 154.0 (2CH, Py), 139.9 (C, N<sub>3</sub>CvCPd), 137.9 (C, N<sub>3</sub>CvCPd), 137.7 (CH, Py), 133.9 (C, Ph), 133.2 (C, Ph), 130.3 (2CH, Py), 129.7 (2CH, Ph), 129.3 (2CH, Ph), 129.2 (CH, Ph), 129.0 (2CH, Ph), 127.8 (CH, Ph), 124.6 (2CH, Ph), 70.4 (CH, β-lactam), 68.2 (CH, β-lactam), 65.0 (C, C (CH<sub>3</sub>)<sub>2</sub>), 60.1 (CH<sub>2</sub>, N-CH<sub>2</sub>), 58.9 (CH, β-lactam), 57.3 (CH<sub>2</sub>, O-CH<sub>2</sub>), 43.6 (CH<sub>2</sub>, Ph-CH<sub>2</sub>), 37.5 (CH<sub>3</sub>, N-CH<sub>3</sub>), 32.1 (CH<sub>3</sub>), 27.6 (CH<sub>3</sub>). IR (KBr): ν<sub>max</sub> 1782, 1749, 1678, 1447, 1201, 1180, 1153, 695 cm<sup>-1</sup>. HRMS (ESI) m/z calculated for C<sub>27</sub>H<sub>29</sub>I<sub>2</sub>N<sub>5</sub>O<sub>4</sub>PdS: 879.906 [M - Py + H]<sup>+</sup>; found 879.915. Mp: 148–152 °C. [α]<sub>D</sub><sup>25</sup> = +14.01 (c 0.40, CHCl<sub>3</sub>).

#### Catalysis experiments

General procedure for the cycloisomerization of enyne 23. Gold carbene complex (0.006 mmol, 3 mol%) and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (0.006 mmol, 3 mol%) were stirred under Ar in 2 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> for 15 min. A solution of enyne 23 (0.2 mmol, 1.0 equiv.) in 2 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added in one portion to the resulting slurry. The reaction mixture was stirred at rt until completion of the reaction (TLC). The reaction crude was filtered through a short pad of Celite and SiO<sub>2</sub>, the solvent was removed under vacuum and the residue was purified through a short pad of SiO<sub>2</sub>.

General procedure for hydrosilylation of alkynes. To a solution of catalyst (5 mg, 0.005 mmol, 1 mol%) in toluene (3 mL), phenylacetylene (54 μL, 0.49 mmol, 1.0 equiv.) and triethylsilane (86 μL, 0.54 mmol, 1.1 equiv.) were quickly added via syringe. After stirring at 100 °C for 14 h the reaction was stopped and allowed to reach rt. The crude mixture was filtered through a short pad of SiO<sub>2</sub> and the solvent was removed under vacuum. The resulting mixtures were analysed by <sup>1</sup>H NMR spectroscopy.

## Author contributions

M. A. Sierra, M. C. de la Torre, L. Casarrubios designed the Experimental section and wrote the paper. M. G. Avello and Maria Moreno-Latorre executed the Experimental section and participate in the discussion of results. H. Gornitzka and C. Hemmert determined the X-ray structure of complex 15.

M. G. A. and M. M.-L. contributed equally.

## Conflicts of interest

There are no conflicts to declare.

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