Article:
Holmes, J, Kearsey, RJ, Paske, KA et al. (5 more authors) (2019) Tethered N-Heterocyclic Carbene-Carboranyl Silver Complexes for Cancer Therapy. Organometallics, 38 (12). pp. 2530-2538. ISSN 0276-7333

https://doi.org/10.1021/acs.organomet.9b00228

Tethered N-Heterocyclic Carbene-Carboranyl Silver Complexes for Cancer Therapy

Jordan Holmes,[a] Rachel J. Kearsey,[a] Katie A. Paske,[a] Frances N. Singer,[a] Suliman Atallah,[b] Christopher M. Pask,[a] Roger M. Phillips[b] and Charlotte E. Willans[a]*

[a]School of Chemistry, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK. Email: c.e.willans@leeds.ac.uk.

[b]School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield, HD1 3DH, UK.

ABSTRACT. Silver complexes of tethered *N*-heterocyclic carbene-carboranyl ligands have been prepared and fully characterized. The first example of silver bonded directly to the cage of *ortho*-carborane has been identified in the solid state. The presence of a carboranyl *N*-substituent on the *N*-heterocyclic carbene significantly enhances the *in vitro* cytotoxicity of the silver complex against HCT116 $p53^{+/+}$ and HCT116 $p53^{-/-}$ colon cancer cells compared to a phenyl derivative. Conversely, the presence of a carboranyl on the backbone of a xanthine derived *N*-heterocyclic carbene decreases the *in vitro* cytotoxicity of the silver complex compared to its phenyl derivative. Stability studies on the xanthine-derived ligands and complexes show that decomposition *via* deboronation occurs in hydrous dimethyl sulfoxide, which may attribute to the contrasting *in vitro* behavior of the carborane-containing complexes.

INTRODUCTION. Both *N*-heterocyclic carbenes (NHCs)[1-2] and carboranes[3-6] are distinct classes of ligand, which have shown interaction with elements across the whole periodic table through varying coordination modes. Complexes of NHCs and carboranes have displayed broad ranging applications, including in the areas of catalysis, materials and biomedicine.[1, 7-10] Silver is renowned for its antimicrobial properties,[11] with the anticancer effects of silver being recognized relatively recently.[12-13] One of the first silver compounds reported to exhibit cytotoxic properties against cancer cells was a silver fluorobenzoate dimer.[14] Five years later the first Ag^{I}-NHC complexes to display *in vitro* cytotoxicity were reported by Youngs and co-workers (**1**, Figure 1),[15] and were screened against OVCAR-3 (ovarian), MB157 (breast) and HeLa (cervical) cancer cell lines. The complexes exhibited greatest cytotoxicity towards the MB157 cell line and had little effect on the HeLa cell line, highlighting the selectivity towards specific cancers for this type of complex. Work from our group has extended the natural xanthine-derived NHC ligand class,[16] and

shown that increased steric bulk on the ligand and increased hydrophilicity of the silver complex delivers greater cytotoxic effects against the cancer cells screened (**2**, Figure 1).[17]

Recently, work from our group and from Lavallo and co-workers has demonstrated that NHCs and carboranes may be combined into the same ligand architecture. Lavallo has reported NHC ligands in which carborane clusters are linked directly to the nitrogen atom of the *N*-heterocycle.[18-21] We have reported ligands with flexible $(CH_2)_n$ spacers between the NHC and *ortho*- or *nido*-carboranes, which offer versatile coordination to a range of metals (**3**, Figure 1).[22-23] Preparation of Rh, Ir and Ru complexes of these ligands involves *in situ* deprotonation by silver oxide prior to transmetallation on to the transition metals. We envisaged that isolation of the Ag intermediates of these reactions would provide further insight into their reactivity, in addition to novel Ag complexes with enhanced tuneability which may be applied in cancer therapeutics. Though Ag-NHCs have shown significant promise in recent years as potent inhibitors of cancer cells,[24] *in vivo* stability presents a serious challenge that needs addressing. Carboranes have also attracted attention for medicinal applications owing to their high catabolic stability.[6, 25] Incorporating carboranes into NHC ligands has the potential to modify the stability, solubility and activity of these complexes, allowing for further tuning for cancer therapy. Furthermore, the approach offers the possibility of combined chemotherapy/BNCT and the ability to modify the carborane derivative for targeted therapy.[26]

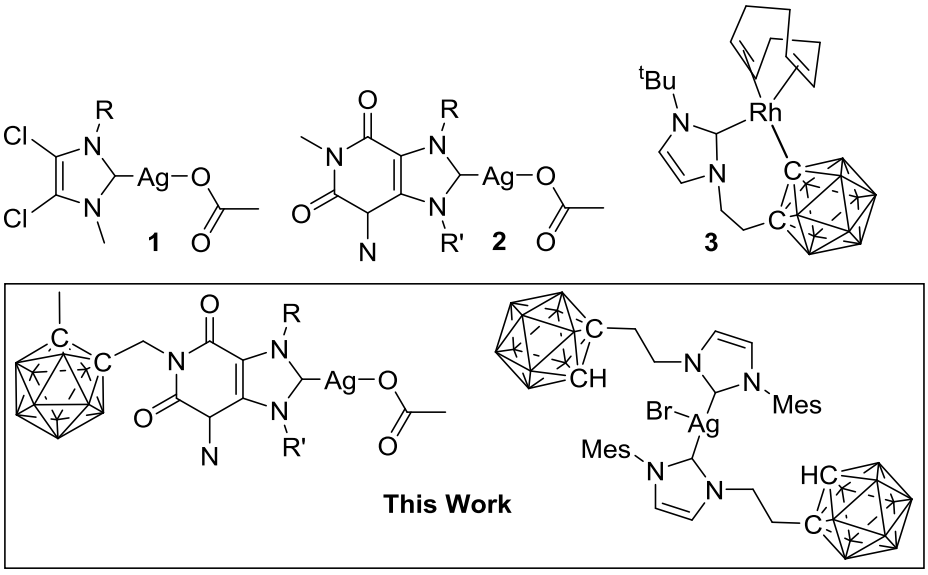
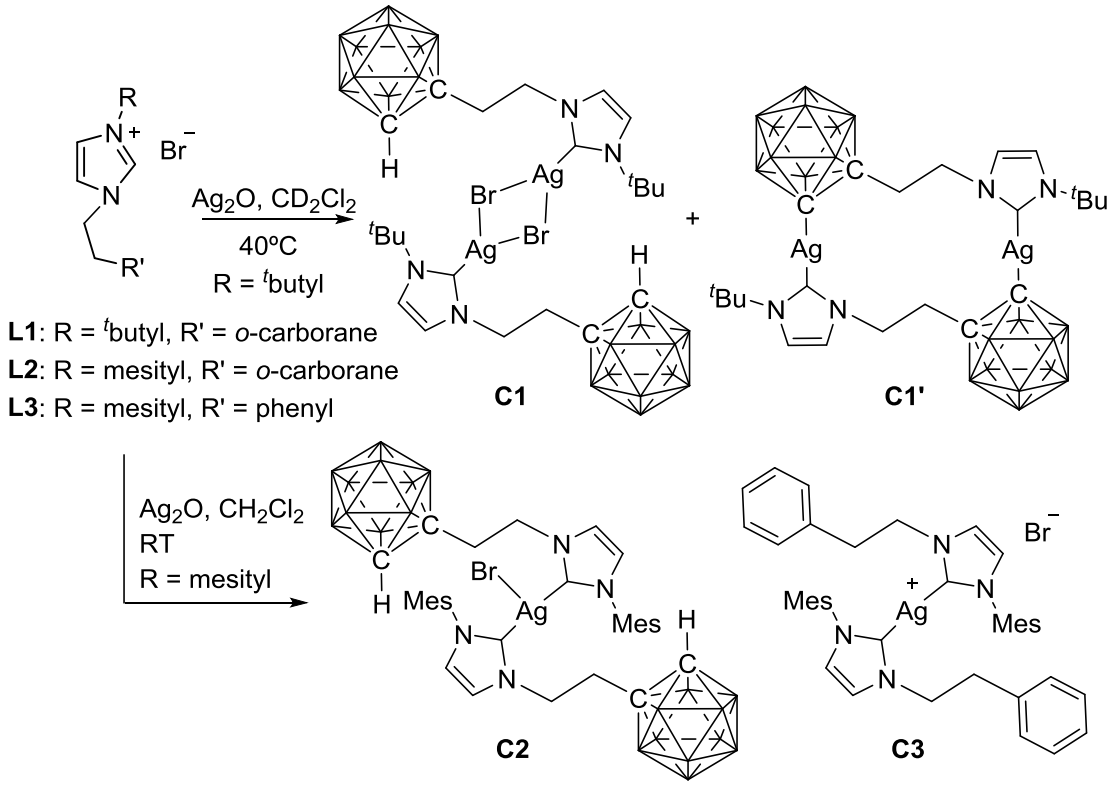


Figure 1. Structures of the first cytotoxic Ag^{I}-NHCs (**1**), xanthine-derived Ag^{I}-NHCs (**2**), a tethered NHC-carboranyl ligand coordinated to Rh^{I} (**3**) and Ag^{I} NHC-carboranyl complexes developed in this work.

RESULTS AND DISCUSSION. Previously we reported that Rh^{I}- and Ir^{III}-NHC complexes could be prepared from ligand precursor **L1**. Activation of the carborane substituent resulted in a *closo*-dicarbadodecaborane anion, which chelated the Rh center through a carbon atom (**3**, Figure 1) and to the Ir center through a boron atom of the cage. Activation of both the imidazolium NCHN proton and the carborane CH or BH proton was promoted using silver oxide in CH_3CN solvent. **L1** was reacted with Ag_2O in anhydrous CD_2Cl_2 and the reaction monitored using ^{1}H NMR spectroscopy (Scheme 1). The imidazolium NCHN proton resonance disappeared completely after 9 hours at 40°C, indicating that a Ag-NHC (**C1**) had formed (Figure 2). The carboranyl CH resonance is masked by the CH_2 resonance at 4.31ppm. A 2D $^{1}H^{13}C$ HMQC experiment revealed that the carboranyl resonance is still present after 9 hours reaction time, with strong coupling observed between this and the carboranyl cage carbon atom at 63.3ppm (Figure 2).



Scheme 1. Synthesis of $[Ag(NHC)Br]_2$ **C1** with formation of $[Ag_2(NHC\text{-carboranyl})_2]$ macrocycle **C1'**, and synthesis of $Ag(NHC)_2Br$ **C2** and $Ag(NHC)_2Br$ **C3**.

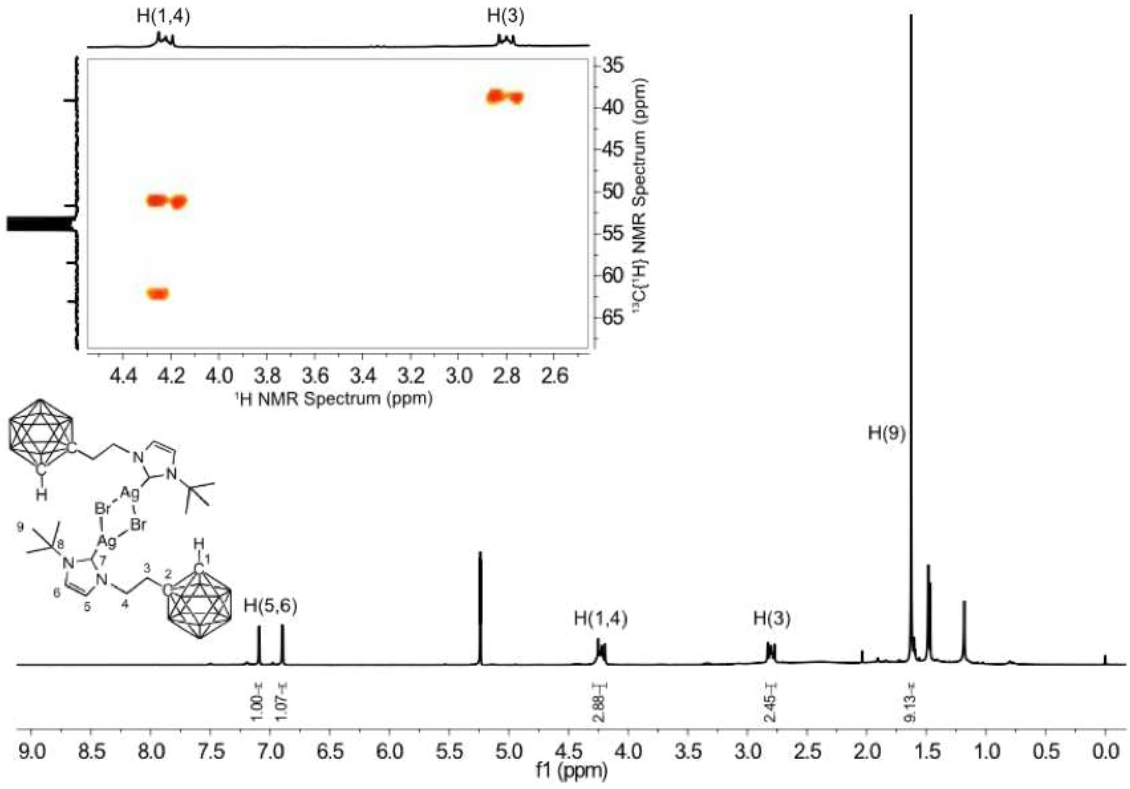


Figure 2. ^{1}H NMR and $^{1}H^{13}C$ HMQC spectra (300MHz, CD_2Cl_2) of $[Ag(NHC)Br]_2$ **C1**. Inset highlights the coupling between the masked carboranyl CH proton resonance and the carboranyl cage carbon resonance at 63.3ppm.

Complex **C1** appeared very unstable hence it was not possible to obtain further data on this complex. However, crystals of a second complex, **C1'**, were found in the product mixture. Single crystal X-ray diffraction analysis revealed a remarkable structure, in which the Ag is bound to the NHC of one ligand and the carborane carbon atom of a second ligand, to give a macrocycle (Figure 3). The geometry about each silver atom is slightly distorted linear, with the solid state structure exhibiting relatively long Ag-$C_{carbene}$ bond lengths (2.112(3) Å and 2.128(3) Å). As complex **C1** appears unstable, with the solution darkening over time, presumably **C1'** is a decomposition product. As a second product was not observed in the NMR data, it is likely that **C1'** is a

crystallization effect with concomitant HBr formation, and was found to be too unstable to re-dissolve and analyze in solution. This is, however, the first structurally elucidated example of silver bound directly to the cage of *ortho*-carborane.

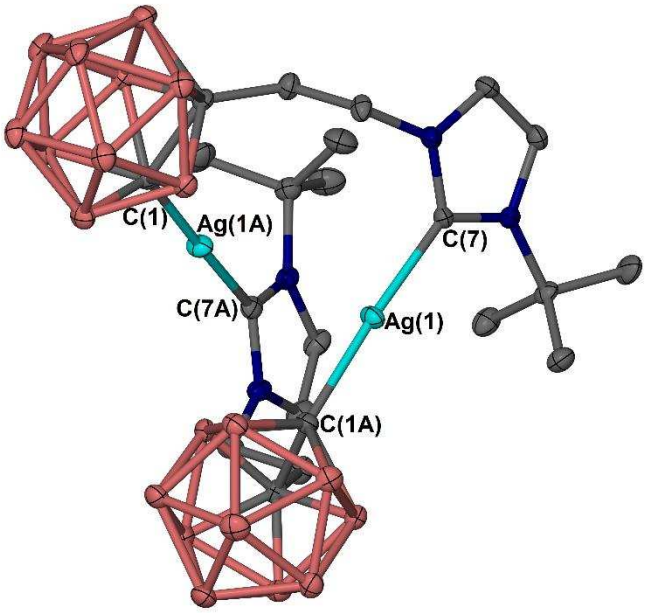
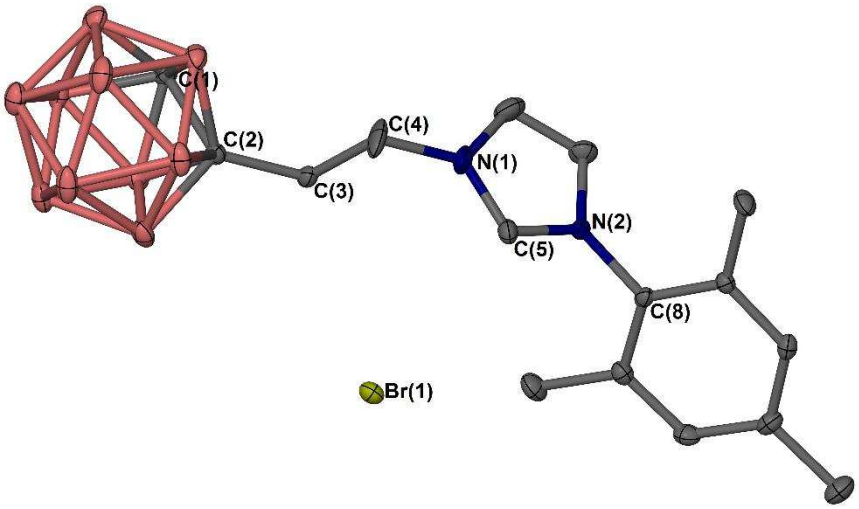


Figure 3. Molecular structure of **C1'**. Ellipsoids are drawn at 50 % probability, and H atoms have been omitted for clarity. Ag(1)-C(7): 2.112(3)Å; Ag(1)-C(1A): 2.128(3)Å; Ag(1A)-C(7A): 2.097(2)Å; Ag(1A)-C(1): 2.118(2)Å; C(1)-Ag(1A)-C(7A): 177.15(10)°; C(7)-Ag(1)-C(1A): 176.29(10)°.

In an attempt to increase the stability of the Ag-NHC complex, ligand precursor **L2** was prepared in which the steric encumbrance of the *N*-substituent was decreased from a ^{t}butyl to a mesityl group (Scheme 1). Reaction of mesityl imidazole with 1-bromoethyl-ortho-carborane resulted in imidazolium bromide **L2**, which was fully characterized including through X-ray diffraction analysis (Figure 4). Reaction of **L2** with Ag_2O in CH_2Cl_2 results in $Ag(NHC)_2Br$ complex **C2**, which was fully characterized using multinuclear NMR spectroscopy, mass spectrometry, elemental analysis and X-ray diffraction analysis. The structure reveals a T-shape geometry around

the Ag center, bound by two NHCs linear to each other, and a Br ion (Figure 4). The Ag-$C_{carbene}$ bond lengths are relatively long (2.117(6) Å and 2.087(5) Å;), though within the normal range for complexes with T-shaped geometry.[27] It is unusual for a Ag-bis(NHC) complex to result from an imidazolium salt with a coordinating anion, with $2Ag(NHC)X \rightleftharpoons [Ag(NHC)_2][AgX_2]$ (X = coordinating anion) being more common.[28] Elemental analysis confirms the $Ag(NHC)_2Br$ stoichiometry in the bulk of **C2**, which was isolated in 68% yield. AgBr formed in the process (*i.e.* to the right of the mono-NHC/bis-NHC equilibrium) would be removed during work-up which involved filtration of the solution through Celite®.



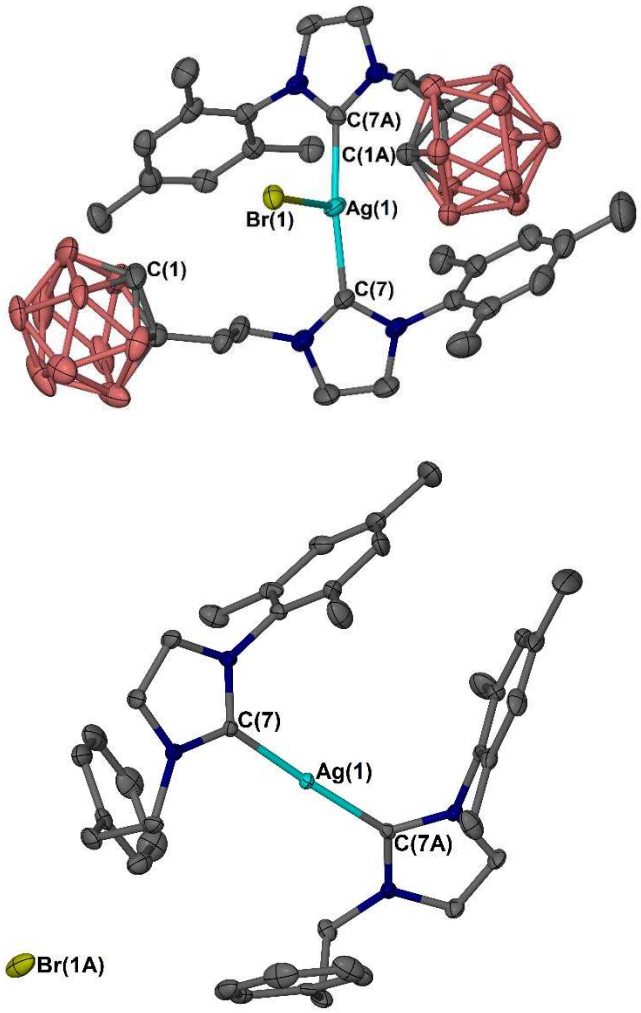


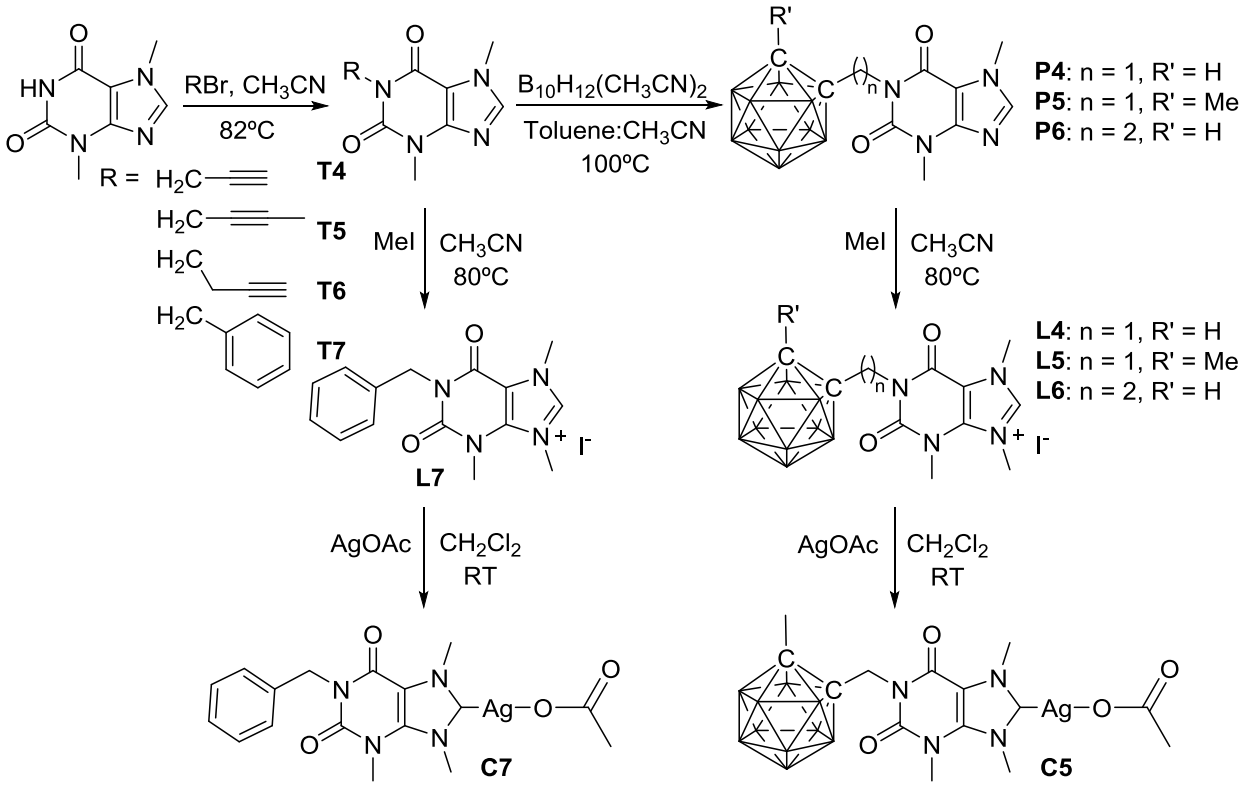
Figure 4. Molecular structures of **L2** (top) **C2** (middle) and **C3** (bottom). Ellipsoids are drawn at 50 % probability, and H atoms have been omitted for clarity. **C2** Ag(1)-C(7): 2.117(6)Å; Ag(1)-C(7A): 2.087(5)Å; Ag(1)-Br(1): 3.0021(8)Å; C(7)-Ag(1)-C(7A): 158.2(2)°; C(7)-Ag(1)-Br(1): 105.39(18)°. **C3** Ag(1)-C(7): 2.061(6)Å; Ag(1)-C(7A): 2.070(6)Å; C(7)-Ag(1)-C(7A): 176.4(2)°.

Exchanging the solvent from CH_2Cl_2 to CH_3CN has previously resulted in CH activation/deprotonation of the carborane cage in addition to imidazolium NCHN deprotonation.[23] Ag_2O was added to **L2** in CD_3CN and heated at 40°C, with the mixture being analyzed over time using ^{1}H NMR spectroscopy. The imidazolium NCHN proton resonance had disappeared after 22

hours reaction time, though the carboranyl CH resonance remains present, even after a further 21 hours reaction time and addition of more Ag_2O with further heating. This indicates that deprotonation of the carboranyl CH proton is metal assisted upon formation of a transition metal complex, whereby a M-NHC (M = Rh, Ir) is formed initially, with subsequent deprotonation of the carboranyl CH.

C3, which is a non-carborane phenyl derivative of **C2**, was prepared from **L3** in an analogous manner to **C2** for comparison in biological studies. Single crystals of complex **C3** were grown *via* slow evaporation of Et_2O into a concentrated CH_2Cl_2 solution. In this case the molecular structure exhibits the more common cationic structure, in which the NHC ligands coordinate in a planar arrangement with no contact between the silver center and the bromide anion (Figure 4), though the overall stoichiometry of complexes **C2** and **C3** is the same.

Silver complexes of NHC ligands derived from natural xanthine precursors have shown *in vitro* cytotoxicity against cancer cells in the micromolar range.[17] In addition to the low toxicity of xanthine-derivatives, these compounds have themselves shown medicinal properties against cancer and other disease.[29] We therefore extended our library of NHC-carboranyl silver complexes to include xanthine-derived ligands. Theobromine was reacted with a range of alkenyl halides to incorporate alkenyl groups on to the xanthine backbone (**T4**-**T7**), with subsequent reactions with $B_{10}H_{12}(CH_3CN)_2$ under anhydrous conditions producing carboranyl imidazole precursors **P4**-**P6** (Scheme 2). Each precursor was methylated using MeI to produce imidazolium salts **L4**-**L6**. In addition, a phenyl derivative, **L7**, was prepared directly from **T7**.



Scheme 2. Synthesis of xanthine-derived imidazolium salts **L4**-**L7**, and Ag^{I}-NHCs **C5** and **C7**.

Attempts were made to prepare Ag^{I} complexes of the xanthine-derived ligands through reaction with Ag_2O in a range of solvents, though surprisingly deprotonation of the imidazolium salts did not occur. Reaction of **L5** and **L7** with AgOAc at room temperature allowed the corresponding Ag-NHC complexes **C5** and **C7** to be isolated (Scheme 2), which were fully characterized using multinuclear NMR spectroscopy and mass spectrometry. Although the mass spectra exhibited major molecular ion peaks corresponding to $[Ag(NHC)_2]^+$, elemental analysis confirmed the Ag(NHC)OAc stoichiometry, with ligand scrambling in the mass spectrometer being well documented.[30] The molecular structures of complexes **C5** and **C7** were elucidated by X-ray diffraction analysis (Figure 5). Crystals suitable for both complexes were obtained *via* the slow diffusion of Et_2O into concentrated CH_2Cl_2 solutions. The Ag-$C_{carbene}$ bond lengths of 2.067(10) Å (**C5**) and 2.060(3) Å (**C7**) are within the expected range for Ag(NHC)OAc type complexes,[17,

[31] and the geometry about the silver atoms deviate slightly from linearity. Analogous reactions using ligand precursors **L4** and **L6** resulted in the formation of a black precipitate rather than the corresponding Ag-NHCs.

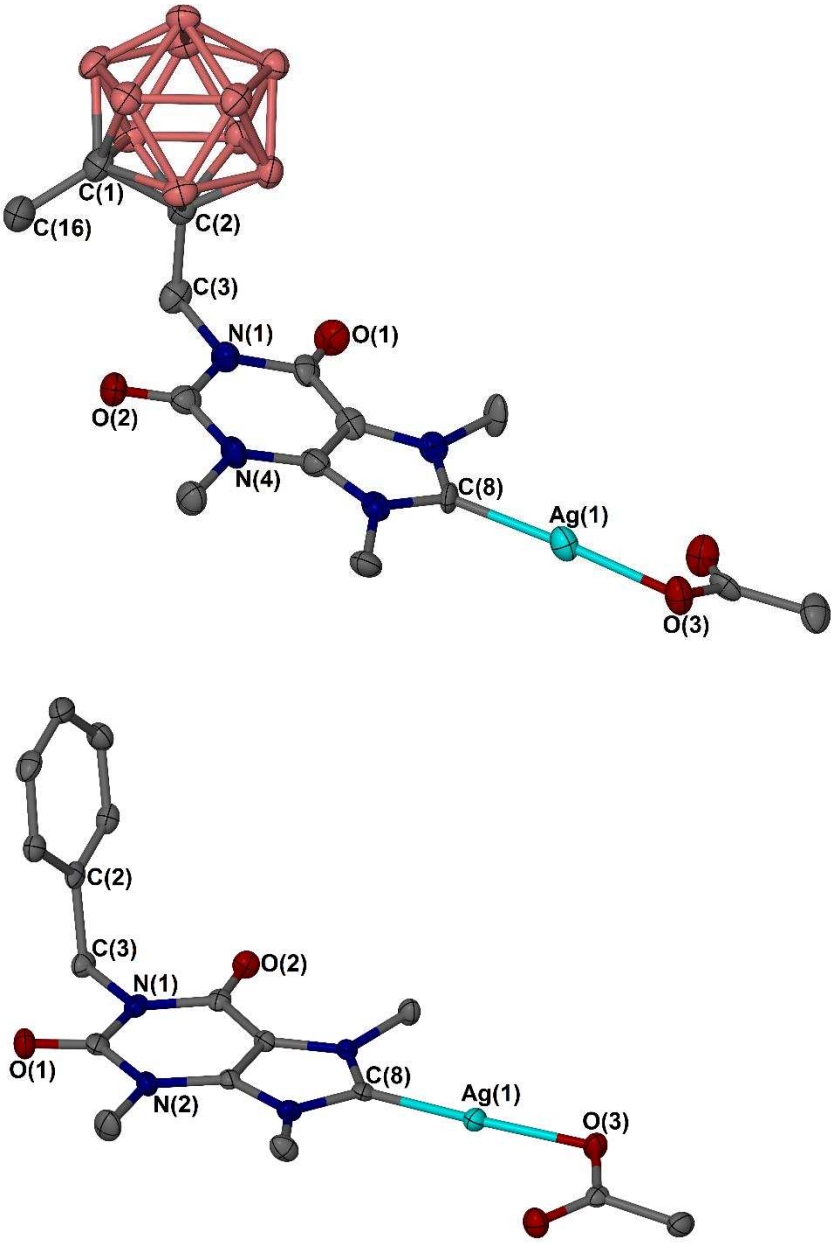


Figure 5. Molecular structures of **C5** (top) and **C7** (bottom). Ellipsoids are drawn at 50 % probability, and H atoms have been omitted for clarity. **C5** Ag(1)-C(8): 2.067(10)Å; Ag(1)-O(3):

2.131(9)Å: C(8)-Ag(1)-O(3): 175.7(4)°; C(2)-C(3)-N(1): 113.2(10)°. **C7** Ag(1)-C(8): 2.060(3)Å; Ag(1)-O(3): 2.104(2)Å: C(8)-Ag(1)-O(3): 171.80(12)°; C(2)-C(3)-N(1): 112.5(3)°.

The *in vitro* cytotoxicity of silver complexes **C2**, **C3**, **C5** and **C7** against the colon cancer cell lines HCT116 $p53^{+/+}$ and HCT116 $p53^{-/-}$ was determined using MTT-based assays involving a 96 hour drug-exposure period (Table 1). The IC_{50} values for each complex are the same irrespective of the cell line they are screened against. HCT116 $p53^{-/-}$ does not possess the p53 gene, a key tumor suppressor protein that is a most commonly mutated gene in cancer patients. Apoptosis induced by the silver complexes appears to be independent of the p53 gene, which is a desired feature in the search for new chemotherapeutic compounds.

Entry	Complex	HCT116 $p53^{+/+}$ IC_{50} (μM)	HCT116 $p53^{-/-}$ IC_{50} (μM)
1	**C2**	1.3 ± 0.2	1.5 ± 0.4
2	**C3**	10.5 ± 4.8	9.8 ± 3.7
3	**C5**	17.6 ± 2.1	20.2 ± 5.0
4	**C7**	11.6 ± 4.6	11.3 ± 4.6

Table 1. IC_{50} (μM) for Ag-NHC complexes screened against HCT116 $p53^{+/+}$ and HCT116 $p53^{-/-}$ cell lines. Each value represents the mean ± standard deviation for three independent experiments.

Carborane-containing complex **C2** displayed greater cytotoxicity than its phenyl derivative **C3** by an order of magnitude (Table 1, entries 1-2). The $C_2B_{10}H_x$ cage occupies approximately the same volume as a rotating phenyl ring, with both the carborane and the phenyl being hydrophobic entities. We have previously shown that increased sterics around the Ag^I center enhances the cytotoxicity of Ag-NHCs, with the three-dimensional structure of the carborane in **C2** likely providing greater steric protection than the phenyl group in **C3** and a slower release of Ag^I over the drug exposure period. **C5**, in which the carborane moiety is remote from the Ag^I center, has comparable cytotoxicity to its phenyl derivative **C7** within error (Table 1, entries 3-4). The steric

encumbrance around the Ag^I centers in **C5** and **C7** is the same, hence this further corroborates that steric factors play a pivotal role in the activity of these complexes. In an attempt to understand the relative stabilities of these complexes which may link to pharmacokinetic differences, a series of stability studies were carried out.

Complexes **C5** and **C7** were dissolved in hydrous DMSO-d_6 (the same solvent that complexes are dissolved in prior to cell line studies) and observed over time both visually and using NMR spectroscopy. The phenyl complex **C7** remains stable in hydrous DMSO-d_6, with no sign of decomposition by ^{1}H NMR spectroscopy, even after several weeks. In contrast, complex **C5** starts to decompose within hours, with the formation of black precipitate and a downfield resonance at 9.25ppm in the ^{1}H NMR spectrum indicative of imidazolium formation. In addition, a broad resonance appears at -3ppm which is characteristic of a bridging proton of the open face of *nido*-carborane. After 9 days in hydrous DMSO, complex **C5** fully converts to imidazolium-*nido*-carborane **D5** and black precipitate, presumably Ag^0 (Figure 6). Deboronation under such mild conditions is unusual, though there is precedent. Kahl *et al*. reported the degradation of a *closo*-carboranyl porphyrin to the *nido*-species in hydrous DMSO.[32] Following a series of studies, it was concluded that deboronation was i) dependent on the ability of the solvent to stabilize nucleophilic attack by water, and ii) facilitated by electron withdrawing α-substituents. Release of silver during decomposition upon dissolution in DMSO will lead to the relatively low cytotoxicity of complex **C5** observed in MTT assays.

To expand this understanding to our theobromine-derived carboranyl compounds, imidazoles **P4-P6** and imidazolium salts **L4-L6** were dissolved in anhydrous DMSO-d_6 (<0.02% H_2O) and monitored by ^{1}H and ^{11}B{^{1}H} NMR spectroscopy. In accordance with Kahl's findings, no deboronation occurred in the absence of water after 4 days in solution. To each sample was added

40μL D_2O, with deboronation being observed in **P4** and **L4** within a few hours (Figure 6). The disubstituted carboranyl compounds **P5** and **L5** were found to be resistant towards deboronation after 4 days, due to the electron donating nature of the methyl substituent reducing the electropositive nature of the boron atoms and thus their susceptibility towards nucleophilic attack. Compounds containing a longer tether between the electron withdrawing theobromine unit and the cage, **P6** and **L6**, also resist deboronation, again, due to the decreased electropositive nature of the cage. These results indicate that complex **C5**, which has a disubstituted cage, might also resist deboronation, hence it is somewhat surprising that the complex was found to decompose in this manner in the presence of H_2O. The presence of silver may render the theobromine-derived NHC more electron withdrawing than its imidazole/imidazolium counterparts and result in a more electropositive carborane cage. The weakly basic acetate present in the complex may also be involved in the deboronation step, though we are not aware of any literature precedent for this.

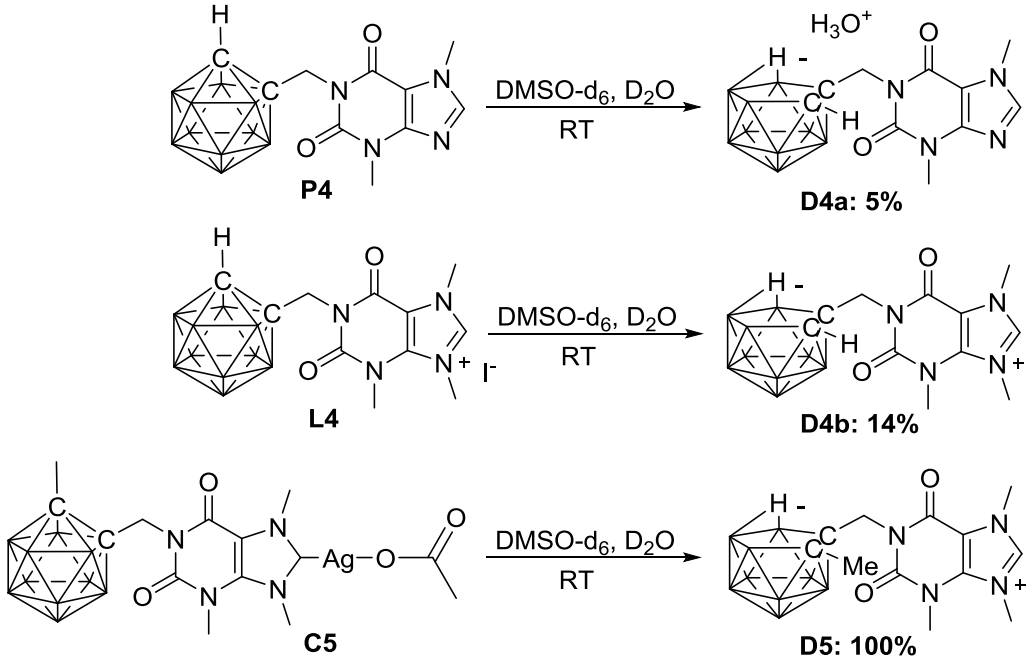


Figure 6. Reactions of theobromine derived imidazole, imidazolium and NHC with D_2O in DMSO for 48 hours. 100% conversion to **D5** after 9 days.

CONCLUSION. In summary, reactions of imidazolium salts bearing carboranyl *N*-substituents, either on the *N*-heterocycle or on the backbone of a xanthine derivative, with basic silver precursors have been investigated. When the carboranyl substituent is tethered to the heterocycle, the steric properties of the second *N*-substituent affect the stability of the resulting silver-NHC complex. Decomposition of a silver-NHC bearing a sterically encumbering ligand led to isolation of the first complex in which silver is bonded directly to the cage of *ortho*-carborane (**C1'**). Reducing the steric bulk of the second *N*-substituent allowed a stable Ag^I-NHC-carborane complex to be prepared (**C2**). A series of xanthine-derived imidazoles and imidazolium salts, in which the carboranyl substituent was tethered to the backbone, were also prepared. Reactions with AgOAc found that when the carborane carbon atom possesses an acidic CH proton, a stable silver complex could not be isolated. However, when this was substituted for a methyl group, the corresponding Ag^I-NHC (**C5**) was prepared in good yield. The *in vitro* cytotoxicity of the silver complexes were examined against the colon cancer cells HCT116 $p53^{+/+}$ and HCT116 $p53^{-/-}$ and compared to the phenyl derivatives. Complex **C2** was found to be more cytotoxic than its phenyl derivative by an order of magnitude, whereas complex **C5** was found to have significantly higher IC_{50} values than its phenyl derivative. This was attributed to the instability of complex **C5** in hydrous DMSO, which was found to decompose *via* deboronation and imidazolium formation.

EXPERIMENTAL SECTION

Anhydrous solvents were prepared by passing over activated alumina to remove water, copper catalyst to remove oxygen and molecular sieves to remove any remaining water, *via* the Dow-Grubbs solvent system, and then freeze-pump-thaw degassed prior to use. Decaborane was

purchased from KatChem and all other chemicals used in this work were bought from either Sigma Aldrich or Alfa and used without further purification. **L1** was prepared according to the published procedure.[23] NMR spectra were recorded on a Bruker AV500 or a Bruker DPX300 spectrometer. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR chemical shifts were referenced against residual solvent peaks. Assignment of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra was aided by the use of 2D $^{1}H^{1}H$ COSY, $^{1}H^{13}C$ HMQC, $^{1}H^{13}C$ HMBC and $^{13}C\{^{1}H\}$ DEPT 135. Mass spectra were collected on a Bruker Daltonics (micro TOF) instrument operating in the electrospray mode. Elemental analyses were performed by Mr Stephen Boyer at London Metropolitan University.

X-ray diffraction data were collected on an Agilent SuperNova diffractometer fitted with an Atlas CCD detector with Mo- Kα radiation (λ = 0.71073 Å) or Cu- Kα (λ = 1.54184 Å). Crystals were mounted under oil on nylon fibers and data collected at 110, 120 or 293 K. Data sets were corrected for absorption using a Gaussian integration method, the structures were solved by direct methods using SHELXS-97[33] or intrinsic phasing using SHELXT[34] and refined by full-matrix least squares on F^2 using ShelXL2014,[35] interfaced through the program Olex2.[36] Molecular graphics for all structures were generated using POV-RAY in the X-Seed program.[37]

C1/C1'. **L1** (15 mg, 0.04 mmol), Ag_2O (9 mg, 0.04 mmol) and anhydrous CD_2Cl_2 (0.5 mL) were added to a Youngs NMR tube in the Glovebox. The tube was wrapped in foil and kept at room temperature for 9 hours, with regular agitation (see SI Figure S34 for NMR spectrum). The reaction mixture was filtered through Celite® and slow diffusion of Et_2O into the filtrate produced crystals of **C1** and **C1'**.

L2. To an ampoule was added mesityl imidazole (100 mg, 0.531 mmol) and 1-bromoethyl-ortho-carborane (149 mg, 0.591 mmol) and degassed. Anhydrous toluene (5 mL) was added and the solution was heated at 90°C for 18 hours. The resulting white solid was filtered, washed with

toluene, hexane and Et_2O. The product was collected as a white solid. Yield: 159 mg, 0.363 mmol (68 %). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.53 (s, 1H, NCHN), 8.18 (s, 1H, NCH), 7.95 (s, 1H, NCH), 7.15 (s, 2H, Ar), 5.38 (s, 1H, carboranyl CH), 4.46 (t, 2H, J = 10 Hz, CH_2) 3.12 (t, 2H, J = 10 Hz, CH_2) 2.33 (s, 3H, CH_3) 2.03 (s, 6H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 140.3 (C), 137.9 (CH), 134.2 (CH), 131.0 (C), 129.3 (C), 123.9 (NCH), 123.1 (NCH), 72.7 (carboranyl-C), 63.4 (carboranyl-CH), 47.7 (CH_2), 34.8 (CH_2), 20.6 (CH_3), 16.9 (CH_3). ^{11}B{^{1}H} NMR (161 MHz, DMSO-d_6): δ (ppm) -3.0, -5.5, -9.7, -12.1. HRMS (ESI$^+$): *m/z* $[C_{16}H_{29}B_{10}N_2]^+$ 357.3346, calcd for $[M - Br]^+$ 357.3328.

C2. An ampoule was charged with imidazolium precursor **L2** (200 mg, 0.46 mmol) and Ag_2O (53 mg, 0.23 mmol) and degassed. Anhydrous CH_2Cl_2 (5 mL) was added and the mixture was stirred at room temperature for 24 hours. The solution was filtered through Celite® and the solvent removed *in vacuo*. The residue was dissolved in Et_2O (5 mL) and the product was precipitated with hexane (15 mL), filtered and dried *in vacuo* to give a beige powder. Yield: 141 mg, 0.16 mmol (68 %). ^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) 7.07 (d, J = 1.8 Hz, 1H, NCH), 6.97 (s, 2H, Ar), 6.87 (d, J = 1.8 Hz, 1H, NCH), 5.33 (br. s, 1H, carboranyl CH), 4.07 (m, 2H, CH_2), 3.05 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 1.89 (s, 6H, CH_3). ^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) 139.6 (C), 136.7 (C), 135.7 (C), 129.7 (CH), 122.7 (NCH), 121.2 (NCH), 73.1 (carboranyl-C), 64.4 (carboranyl-CH), 50.7 (CH_2), 37.8 (CH_2), 21.4 (CH_3), 18.2 (CH_3). ^{11}B{^{1}H} NMR (161 MHz, DMSO-d_6): δ (ppm) −2.9, −5.3, −9.4, −12.9. HRMS (ESI$^+$): *m/z* $[C_{32}H_{56}B_{20}AgN_4]^+$ 819.5598, calcd for $[M - Br]^+$ 819.5562. Anal. Calcd for $C_{32}H_{56}B_{20}AgBrN_4$: C, 42.67; H, 6.27; N, 6.22. Found: C, 42.49; H6.16; N, 6.17.

L3. To an ampoule was added CH_3CN (2 mL), mesityl imidazole (576 mg, 3.09 mmol) and 2-bromoethyl-benzene (0.42 mL, 3.09 mmol) and the solution was heated at reflux for 18 hours. The

reaction was cooled to room temperature and the product precipitated with Et_2O (30 mL), filtered and dried *in vacuo* to give a white microcrystalline solid. Yield: 886 mg, 2.39 mmol (77 %). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.35 (t, J = 1.5 Hz, 1H, NCHN), 8.12 (t, J = 1.7 Hz, 1H, NCH), 7.87 (t, J = 1.8 Hz, 1H, NCH), 7.28 (m, 2H, CH), 7.24 (s, 2H, CH), 7.22 (m, 1H, CH), 7.10 (s, 2H, CH), 4.62 (t, J = 6.8 Hz, 2H, CH_2), 3.26 (t, J = 6.8 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.86 (s, 6H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 140.2 (C), 137.2 (NCHN), 136.6 (C), 134.1 (C), 130.9 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 126.8 (CH), 123.8 (NCH), 123.1 (NCH), 50.2 (CH_2), 34.9 (CH_2), 20.5 (CH_3), 16.7 (CH_3). HRMS (ESI$^+$): *m/z* $[C_{20}H_{23}N_2]^+$ 291.1870, calcd for $[M - Br]^+$ 291.1856.

C3. An ampoule was charged with **L3** (200 mg, 0.54 mmol) and Ag_2O (69 mg, 0.30 mmol) and degassed. Anhydrous CH_2Cl_2 (5 mL) was added and the mixture stirred at room temperature for 24 hours. The solution was filtered through Celite® and the solvent removed *in vacuo*. CH_3OH (5 mL) was added, the insoluble particulate filtered and the product was precipitated from the filtrate with Et_2O (30 mL). The product was collected *via* filtration and dried *in vacuo* to give a white powder. Yield: 145 mg, 0.19 mmol (70 %). ^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) 7.20 (s, 1H, NCH), 7.18 (m, 3H, CH), 6.90 (m, 4H, CH), 6.84 (s, 1H, NCH), 4.26 (t, J = 6.5 Hz, 2H, CH_2), 3.00 (t, J = 6.5 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.74 (s, 6H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 182.9 (carbenic-C), 139.9 (C), 137.7 (C), 136.1 (C), 135.4 (C), 129.6 (CH), 129.4 (CH), 129.1 (CH), 127.4 (CH), 123.0 (NCH), 122.4 (NCH), 53.4 (CH_2), 38.0 (CH_2), 21.4 (CH_3), 17.9 (CH_3). HRMS (ESI$^+$): *m/z* $[C_{40}H_{44}AgN_4]^+$ 689.2621, calcd for $[M - Br]^+$ 689.2615. Anal. Calcd for C, 62.51; H, 5.77; N, 7.29. Found: C, 62.38; H, 5.89; N, 7.17.

T4. To a round-bottom flask was added CH_3CN (30 mL), theobromine (3.00 g, 16.70 mmol), Cs_2CO_3 (10.80 g, 33.30 mmol) and propargyl bromide (2.27 mL, 25.00 mmol, 80 wt % toluene)

and the mixture heated at 80 °C for 18 hours. The reaction was cooled to room temperature and the solvent removed *in vacuo*. CH_2Cl_2 (50 mL) was added, the mixture filtered and H_2O (30 mL) was added to the filtrate, with the organic phase being collected. This was further washed with H_2O (2 × 30 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The off-white residue was recrystallized from CH_2Cl_2 (20 mL) with pentane (50 mL) to give a white powder. Yield: 2.99 g, 13.70 mmol (82 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.52 (m, 1H, NCHN), 4.79 (d, J = 2.5 Hz, 2H, CH_2), 3.99 (m, 3H, CH_3), 3.59 (s, 3H, CH_3), 2.17 (t, J = 2.5 Hz, 1H, CH). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 154.5 (CO), 151.0 (CO), 149.3 (C), 141.9 (NCHN), 107.7 (C), 78.8 (C≡CH), 70.6 (C≡CH), 33.8 (CH_3), 30.6 (CH_2), 29.9 (CH_3). HRMS (ESI$^+$): *m/z* $[C_{10}H_{10}N_4O_2Na]^+$ 241.0700, calcd for $[M + Na]^+$ 241.0696.

P4. To a Schlenk flask was added **T4** (1.00 g, 4.58 mmol) and $B_{10}H_{12}(CH_3CN)_2$ (927 mg, 4.58 mmol) and degassed. Anhydrous toluene (10 mL) and anhydrous CH_3CN (3 mL) were added and the mixture was slowly heated to 100 °C and kept at this temperature for 18 hours. The reaction was cooled to room temperature and the solvent removed *in vacuo*. Et_2O (2 × 15 mL) was added to the product and filtered to remove insoluble material. The filtrate was washed with 1 M NaOH solution (2 × 10 mL), H_2O (2 × 10 mL), dried over $MgSO_4$, filtered and the solvent removed from the filtrate *in vacuo*. The residue was recrystallized from Et_2O (10 mL) with hexane (30 mL), filtered and the white solid dried *in vacuo*. Yield: 807 mg, 2.40 mmol (52 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 (s, 1H, NCHN), 4.88 (d, J = 14.9 Hz, 1H, CH_2), 4.60 (d, J = 14.9 Hz, 1H, CH_2), 4.20 (br. s, 1H, carboranyl-CH), 3.98 (s, 3H, CH_3), 3.58 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 154.5 (CO), 151.6 (CO), 149.4 (C), 142.6 (NCHN), 107.3 (C), 74.0 (carboranyl-C), 61.3 (carboranyl-CH), 45.3 (CH_2), 33.9 (CH_3), 30.2 (CH_3). ^{11}B{^{1}H} NMR (161 MHz, $CDCl_3$):

δ (ppm) −1.4, −4.8, −10.0, −10.8, −12.9. HRMS (ESI^+): *m/z* $[C_{10}H_{21}B_{10}N_4O_2]^+$ 337.2670, calcd for $[M + H]^+$ 337.2667.

T5. Prepared as described for **T4** from theobromine (3.00 g, 16.70 mmol), Cs_2CO_3 (10.80 g, 33.30 mmol) and 1-bromo-2-butyne (1.60 mL, 18.40 mmol) in CH_3CN (30 mL). After work up the product was obtained as a white powder. Yield: 2.95 g, 12.70 mmol (76 %). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.50 (m, 1H, NCHN), 4.72 (q, J = 2 Hz, 2.5 Hz, 2H, CH_2), 3.98 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 1.76 (t, *J* = 2Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 154.7 (CO), 151.1 (CO), 149.1 (C), 141.7 (NCHN), 107.7 (C), 78.3 (C≡C), 73.9 (C≡C), 33.7 (CH_3), 31.1 (CH_2), 29.9 (CH_3), 3.8 (CH_3). HRMS (ESI^+): *m/z* $[C_{11}H_{12}N_4O_2Na]^+$ 255.0857, calcd for $[M + Na]^+$ 255.0852.

P5. To a Schlenk flask was added **T5** (1.00 g, 4.31 mmol) and $B_{10}H_{12}(CH_3CN)_2$ (871 mg, 4.31 mmol) and degassed. Anhydrous toluene (10 mL) and anhydrous CH_3CN (3 mL) were added and the reaction slowly heated to 100 °C and kept at this temperature for 18 hours. The reaction was cooled to room temperature and the solvent removed *in vacuo*. The residue was dissolved in a minimum amount of CH_2Cl_2 and purified by silica chromatography, which was eluted with ethyl acetate/hexane 1:2. The product fractions were combined and the solvent removed *in vacuo*. The residue was dissolved in Et_2O (5 mL) and the product was precipitated as a white powder with hexane (30 mL), which was filtered and dried *in vacuo*. Yield: 573 mg, 1.63 mmol (38 %). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 (d, *J* = 0.6 Hz, 1H, NCHN), 4.86 (d, *J* = 14.8 Hz, 1H, CH_2), 4.64 (d, *J* = 14.8 Hz, 1H, CH_2), 3.99 (d, *J* = 0.6 Hz, 3H, CH_3), 3.59 (s, 3H, CH_3), 2.34 (s, 3H, carboranyl-CCH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 154.7 (CO), 151.5 (CO), 149.5 (C), 142.4 (NCHN), 107.4 (C), 77.4 (carboranyl-C), 75.9 (carboranyl-$\underline{C}CH_3$), 42.5 (CH_2), 33.9 (CH_3),

30.2 (CH_3), 23.5 (carboranyl-C<u>C</u>H_3). $^{11}B\{^1H\}$ NMR (161 MHz, $CDCl_3$): δ (ppm) −3.2, −6.0, −9.9. HRMS (ESI^+): *m/z* $[C_{11}H_{23}B_{10}N_4O_2]^+$ 351.2824, calcd for $[M + H]^+$ 351.2824.

T6. Prepared as described for **T4** from theobromine (3.00 g, 16.70 mmol), Cs_2CO_3 (10.80 g, 33.30 mmol) and 4-bromo-1-butyne (1.88 mL, 20.00 mmol) in CH_3CN (30 mL). After work up the product was obtained as a white powder. Yield: 1.55 g, 6.68 mmol (40 %). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.50 (s, 1H, NCHN), 4.23-4.20 (m, 2H, CH_2), 3.98 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 2.58 (td, *J* = 7.3, 2.7 Hz, 2H, CH_2), 1.96 (t, *J* = 2.7 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 155.1 (CO), 151.4 (CO), 149.0 (C), 141.7 (NCHN), 107.7 (C), 81.0 (<u>C</u>≡CH), 69.9 (CH_2), 39.7 (CH_2), 33.7 (CH_3), 29.8 (CH_3), 17.8 (C≡<u>C</u>H). HRMS (ESI^+): *m/z* 255.0860 $[C_{11}H_{12}N_4O_2Na]^+$, calcd for $[M + Na]^+$ 255.0858.

P6. To a Schlenk flask was added **T6** (1.00 g, 4.31 mmol) and $B_{10}H_{12}(CH_3CN)_2$ (871 mg, 4.31 mmol) and degassed. Anhydrous toluene (10 mL) and anhydrous CH_3CN (3 mL) were added and the reaction slowly heated to 100 °C and kept at this temperature for 18 hours. The reaction was cooled to room temperature and the solvent removed *in vacuo*. The residue was dissolved in a minimum amount of CH_2Cl_2 and purified by silica chromatography, which was eluted with ethyl acetate/hexane 1:2, and then the product was eluted with CH_2Cl_2/CH_3OH (10 %). The product fractions were combined and the solvent removed *in vacuo*. The residue was dissolved in Et_2O (5 mL) and the product precipitated as a white powder with hexane (30 mL), filtered and dried *in vacuo*. Yield: 680 mg, 1.93 mmol (45 %). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.52 (s, 1H, NCHN), 4.12 (m, 2H, CH_2), 3.96 (s, 3H, CH_3), 3.73 (br. s, 1H, carboranyl-CH), 3.55 (s, 3H, CH_3), 2.52 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 154.8 (CO), 151.2 (CO), 149.2 (C), 142.0 (NCHN), 107.6 (C), 72.4 (carboranyl-CH), 61.6 (carboranyl-C), 40.0 (CH_2), 35.12 (CH_2), 33.8 (CH_3), 29.89 (CH_3). $^{11}B\{^1H\}$ NMR (96 MHz, DMSO-d_6): δ (ppm) −2.1, −5.3, −9.1, −11.6. HRMS

(ESI$^+$): *m/z* $[C_{13}H_{23}B_{10}N_5O_2Na]^+$ 413.2600, calcd for $[M + CH_3CN + Na - 2H]^+$ 413.2716. (Note: only one of the CH_2 resonance is observed).

T7. Prepared as described for **T4** from theobromine (3.00 g, 16.70 mmol), Cs_2CO_3 (10.80 g, 33.30 mmol) and benzyl bromide (1.99 mL, 16.70 mmol) in CH_3CN (30 mL). After work up the product was obtained as a white powder. Yield: 3.62 g, 13.40 mmol (80 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.49 (m, 3H, 1H, NCHN), 7.30 (m, 2H, Ar-CH), 7.24 (m, 1H, Ar-CH), 5.19 (s, 2H, CH_2), 3.98 (m, 3H, CH_3), 3.57 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 155.4 (CO), 151.8 CO), 149.0 (C), 141.7 (NCHN), 137.5 (Ar-C), 129.0 (Ar-CH), 128.5 (Ar-CH), 127.7 (Ar-CH), 107.8 (C), 44.6 (CH_2), 33.7 (CH_3), 29.9 (CH_3). HRMS (ESI$^+$): *m/z* $[C_{14}H_{14}N_4O_2Na]^+$ 293.1025, calcd for $[M + Na]^+$ 293.1009.

L4. An ampoule was charged with CH_3CN (5 mL), **P4** (1.17 g, 3.48 mmol) and MeI (6.49 mL, 104.3 mmol) and heated at 80 °C for 7 days. The reaction was cooled to room temperature and the solvent removed *in vacuo*. To the residue was added Et_2O (30 mL) which was then sonicated, the solid filtered, washed with Et_2O (20 mL) and dried *in vacuo* to give a white powder. Yield: 631 mg, 1.46 mmol (42 %). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.35 (s, 1H, NCHN), 5.11 (br. s, 1H, carboranyl-CH), 4.81 (d, J = 15.1 Hz, 1H, CH_2), 4.58 (d, J = 15.1 Hz, 1H, CH_2), 4.16 (s, 3H, CH_3), 4.06 (s, 3H, CH_3), 3.76 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 152.7 (CO), 150.1 (CO), 140.5 (NCHN), 139.9 (C), 107.5 (C), 73.2 (carboranyl-C), 62.4 (carboranyl-CH), 45.1 (CH_2), 37.0 (CH_3), 35.8 (CH_3), 31.8 (CH_3). ^{11}B{^{1}H} NMR (161 MHz, DMSO-d_6): δ (ppm) −2.9, −5.2, −10.0, −11.6, −13.0. HRMS (ESI$^+$): *m/z* $[C_{11}H_{23}B_{10}N_4O_2]^+$ 352.2800, calcd for $[M - I]^+$ 352.2800.

L5. Prepared as described for **L4** from **P5** (500 mg, 1.43 mmol) and MeI (2.67 mL, 42.6 mmol) in CH_3CN (5 mL). After purification the product was obtained as a white powder. Yield: 287 mg,

0.64 mmol (45 %). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.34 (s, 1H, NCHN), 4.86 (d, *J* = 15.4 Hz, 1H, CH_2), 4.64 (d, *J* = 15.4 Hz, 1H, CH_2), 4.16 (s, 3H, CH_3), 4.07 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 2.35 (s, 3H, carboranyl-CCH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 152.9 (CO), 150.1 (CO), 140.5 (NCHN), 140.0 (C), 107.4 (C), 77.9 (carboranyl-C), 75.7 (carboranyl-$\underline{C}CH_3$), 43.0 (CH_2), 37.0 (CH_3), 35.8 (CH_3), 31.8 (CH_3), 22.6 (carboranyl-$C\underline{C}H_3$). ^{11}B{^{1}H} NMR (161 MHz, DMSO-d_6): δ (ppm) −2.9, −5.2, −10.0, −11.6, −12.9. HRMS (ESI$^+$): *m/z* $[C_{11}H_{23}B_{10}N_4O_2]^+$ 366.2963, calcd for $[M - I]^+$ 366.2944.

L6. Prepared as described for **L4** from **P6** (450 mg, 1.28 mmol) and MeI (2.40 mL, 38.5 mmol) in CH_3CN (5 mL). After purification the product was obtained as a yellow powder. Yield: 189 mg, 0.86 mmol (67 %). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.29 (s, 1H, NCHN), 5.38 (br. s, 1H, carboranyl-CH), 4.14 (s, 1H, CH_3), 4.04 (s, 3H, CH_3), 3.98 (m, 2H, CH_2), 3.72 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 152.8 (CO), 149.7 (CO), 140.0 (NCHN), 139.5 (C), 107.8 (C), 73.0 (carboranyl-CH), 63.6 (carboranyl-C), 36.9 (CH_3), 35.6 (CH_3), 33.0 (CH_2), 31.4 (CH_3). ^{11}B NMR (96 MHz, CD_3CN): δ (ppm) −2.89, −5.25, −9.97, −11.40, −12.97. HRMS (ESI$^+$): *m/z* $[C_{11}H_{23}B_{10}N_4O_2]^+$ 366.2960, calcd for $[M - I]^+$ 366.2944. (Note: only one of the CH_2 resonances is observed).

L7. An ampoule was charged with CH_3CN (5 mL), **P7** (1.00 g, 3.70 mmol) and MeI (6.91 mL, 111 mmol) and heated at 80 °C for 100 hours. The reaction was cooled to room temperature and the solvent removed *in vacuo*. To the residue was added CH_2Cl_2 (5 mL) and the product recrystallized with hexane (30 mL) which was filtered yielding a sticky orange solid. This was dissolved in CH_2Cl_2 (5 mL) and hexane (5 mL), and the solvent removed *in vacuo* to give a fluffy golden solid, which was highly hygroscopic. Yield: 1.30 g, 3.15 mmol (85 %). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.32 (s, 1H, NCHN), 7.33 (m, 4H, Ar-CH), 7.28 (m, 1H, Ar-CH), 5.09

(s, 2H, CH_2), 4.15 (s, 3H, CH_3), 4.07 (s, 3H, CH_3), 3.74 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 153.2 (CO), 150.0 (CO), 139.8 (NCHN), 139.6 (C), 136.2 (Ar-C), 128.3 (Ar-CH), 127.7 (Ar-CH), 127.4 (Ar-CH), 107.8 (C), 44.5 (CH_2), 36.9 (CH_3), 35.7 (CH_3), 31.5 (CH_3). HRMS (ESI^+): *m/z* $[C_{15}H_{17}N_4O_2]^+$ 285.1343, calcd for $[M - I]^+$ 285.1346.

C5. An ampoule was charged with **L5** (150 mg, 0.31 mmol) and AgOAc (102 mg, 0.61 mmol) and degassed. Anhydrous CH_2Cl_2 (5 mL) was added and the reaction and stirred at room temperature for 48 hours. The reaction mixture was filtered through Celite®, washed with CH_2Cl_2 (5 mL) and the solvent volume from the filtrate reduced to 5 mL *in vacuo*. The product was precipitated with Et_2O (30 mL), filtered and dried *in vacuo* to give a white powder. Yield: 90 mg, 0.17 mmol (55 %). ^1H NMR (500 MHz, CD_2Cl_2): δ (ppm) 4.88 (d, J = 14.9 Hz, 1H, CH_2), 4.61 (d, J = 14.9 Hz, 1H, CH_2), 4.21 (s, 3H, CH_3), 4.11 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 2.32 (s, 3H, carboranyl-CCH_3), 1.95 (s, 3H, OAc-CH_3). ^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) 188.4 (NCN), 178.8 (OAc-C), 153.3 (CO), 151.2 (CO), 141.2 (C), 110.1 (C), 78.2 (carboranyl-$\underline{C}CH_3$), 75.8 (carboranyl-C), 43.6 (CH_2), 40.5 (CH_3), 39.2 (CH_3), 32.9 (CH_3), 23.7 (carboranyl-$C\underline{C}H_3$), 22.9 (OAc-CH_3). $^{11}B\{^1H\}$ NMR (161 MHz, CD_2Cl_2): δ (ppm) −3.3, −6.2, −10.0. Anal. Calcd for $C_{14}H_{27}AgB_{10}N_4O_4$: C, 31.65; H, 5.12; N, 10.54. Found: C, 31.58; H, 4.97; N, 10.37. Complex could not be characterized by HRMS due to ligand scrambling.

C7. Prepared as described for **C5** from **L7** (300 mg, 0.73 mmol) and AgOAc (255 mg, 1.53 mmol) in anhydrous CH_2Cl_2 (5 mL) with stirring at room temperature for 48 hours. After purification the product was obtained as a white powder. Yield: 191 mg, 0.42 mmol (58 %). ^1H NMR (500 MHz, CD_2Cl_2): δ (ppm) 7.42-7.39 (m, 2H, Ar-CH), 7.33-7.24 (m, 3H, Ar-CH), 5.15 (s, 2H, CH_2), 4.16 (s, 3H, CH_3), 4.11 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 1.94 (s, 3H, OAc-CH_3). ^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) 187.2 (NCN), 178.7 (OAc-C), 153.9 (CO), 151.2 (CO), 140.8

(C), 137.2 (Ar-C), 129.1 (Ar-CH), 128.9 (Ar-CH), 128.3 (Ar-CH), 110.4 (C), 45.6 (CH_2), 40.3 (CH_3), 39.1 (CH_3), 32.4 (CH_3), 22.9 (OAc-CH_3). Anal. Calcd for $C_{17}H_{20}AgN_4O_4$: C, 45.15; H, 4.46; N, 12.39. Found: C, 45.17; H, 34.10; N, 12.48. Complex could not be characterized by HRMS due to ligand scrambling. The major molecular ion peak observed corresponds to *m/z* $[C_{30}H_{32}AgN_8O_4]^+$ 675.1602, calcd for $[Ag(NHC)_2]^+$ 675.1592.

MTT Assays. *In vitro* cell tests were performed in the School of Applied Sciences at the University of Huddersfield. Cells were incubated in 96-well plates, at 2×10^3 cells per well in 200 μL of growth media (RPMI 1640 supplemented with 10 % fetal calf serum, sodium pyruvate (1 mM) and L-glutamine (2 mM)). Cells were incubated for 24 hours at 37 °C under an atmosphere of 5 % CO_2 prior to drug exposure. Silver compounds were dissolved in DMSO at a concentration of 25 mM and diluted with medium to obtain drug solutions ranging from 25 μM to 0.049 μM. The final DMSO concentration was 0.1 % (v/v) which is non-toxic to cells. Drug solutions were applied to cells and incubated for 96 hours at 37 °C under an atmosphere of 5 % CO_2. The solutions were removed from the wells and fresh medium added to each well along with 20 μL MTT (5 mg mL^{-1}), and incubated for 4 hours at 37 °C under an atmosphere of 5 % CO_2. The solutions were removed and DMSO (150 μL) was added to each well to dissolve the purple formazan crystals. A plate reader was used to measure the absorbance at 540 nm. Lanes containing medium only (no cells), and cells in medium only (no drug), were used as blanks for the spectrophotometer and 100 % cell survival respectively. Cell survival was determined as the true absorbance of treated cells divided by the true absorbance of controls and expressed as a percentage. The concentration required to kill 50 % of cells (IC_{50}) was determined from plots of % survival against drug concentration. The values presented are an average of three separate runs.

ASSOCIATED CONTENT

Supporting Information. NMR spectra and X-ray crystallographic information.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

The work was funded through the EPSRC (DTA awards to JH and FNS) and the Universities of Leeds and Huddersfield.

REFERENCES

1. Peris, E., Smart N-Heterocyclic Carbene Ligands in Catalysis. *Chem. Rev.* **2018,** *118* (19), 9988-10031.
2. Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F., An overview of N-heterocyclic carbenes. *Nature* **2014,** *510* (7506), 485-496.
3. Weller, A., Ligand design: The two faces of carboranes. *Nat Chem* **2011,** *3* (8), 577-578.
4. Grimes, R. N., Chapter 13 - Metallacarboranes of the transition and lanthanide elements. In *Carboranes (Second Edition)*, Grimes, R. N., Ed. Academic Press: Oxford, 2011; pp 773-1014.
5. Grimes, R. N., Chapter 15 - Carboranes in catalysis. In *Carboranes (Second Edition)*, Grimes, R. N., Ed. Academic Press: Oxford, 2011; pp 1037-1052.
6. Grimes, R. N., Chapter 16 - Carboranes in medicine. In *Carboranes (Second Edition)*, Grimes, R. N., Ed. Academic Press: Oxford, 2011; pp 1053-1082.
7. Liu, W.; Gust, R., Metal N-heterocyclic carbene complexes as potential antitumor metallodrugs. *Chem. Soc. Rev.* **2013,** *42* (2), 755-73.
8. Grimes, R. N., Carboranes in the chemist's toolbox. *Dalton Trans.* **2015,** *44* (13), 5939-5956.
9. Mata, J. A.; Hahn, F. E.; Peris, E., Heterometallic complexes, tandem catalysis and catalytic cooperativity. *Chemical Science* **2014,** *5* (5), 1723-1732.
10. Mercs, L.; Albrecht, M., Beyond catalysis: N-heterocyclic carbene complexes as components for medicinal, luminescent, and functional materials applications. *Chem. Soc. Rev.* **2010,** *39* (6), 1903-1912.
11. Klasen, H. J., A historical review of the use of silver in the treatment of burns. II. Renewed interest for silver. *Burns* **2000,** *26* (2), 131-138.
12. Monteiro, D. C. F.; Phillips, R. M.; Crossley, B. D.; Fielden, J.; Willans, C. E., Enhanced cytotoxicity of silver complexes bearing bidentate N-heterocyclic carbene ligands. *Dalton Trans.* **2012,** *41* (13), 3720-3725.
13. Allison, S. J.; Sadiq, M.; Baronou, E.; Cooper, P. A.; Dunnill, C.; Georgopoulos, N. T.; Latif, A.; Shepherd, S.; Shnyder, S. D.; Stratford, I. J.; Wheelhouse, R. T.; Willans, C. E.;

Phillips, R. M., Preclinical anti-cancer activity and multiple mechanisms of action of a cationic silver complex bearing N-heterocyclic carbene ligands. *Cancer Letters* **2017,** *403*, 98-107.
14. Zhu, H. L.; Zhang, X. M.; Liu, X. Y.; Wang, X. J.; Liu, G. F.; Usman, A.; Fun, H. K., Clear Ag-Ag bonds in three silver(I) carboxylate complexes with high cytotoxicity properties. *Inorg. Chem. Commun.* **2003,** *6* (8), 1113-1116.
15. Medvetz, D. A.; Hindi, K. M.; Panzner, M. J.; Ditto, A. J.; Yun, Y. H.; Youngs, W. J., Anticancer Activity of Ag(I) N-Heterocyclic Carbene Complexes Derived from 4,5-Dichloro-1H-Imidazole. *Met Based Drugs* **2008,** *2008*, 384010.
16. Kascatan-Nebioglu, A.; Melaiye, A.; Hindi, K.; Durmus, S.; Panzner, M. J.; Hogue, L. A.; Mallett, R. J.; Hovis, C. E.; Coughenour, M.; Crosby, S. D.; Milsted, A.; Ely, D. L.; Tessier, C. A.; Cannon, C. L.; Youngs, W. J., Synthesis from caffeine of a mixed N-heterocyclic carbene-silver acetate complex active against resistant respiratory pathogens. *J. Med. Chem.* **2006,** *49* (23), 6811-6818.
17. Mohamed, H. A.; Lake, B. R. M.; Laing, T.; Phillips, R. M.; Willans, C. E., Synthesis and anticancer activity of silver(i)-N-heterocyclic carbene complexes derived from the natural xanthine products caffeine, theophylline and theobromine. *Dalton Trans.* **2015,** *44* (16), 7563-7569.
18. Estrada, J.; Lavallo, V., Fusing Dicarbollide Ions with N-Heterocyclic Carbenes. *Angewandte Chemie International Edition* **2017,** *56*, 9906-9909.
19. El-Hellani, A.; Lavallo, V., Fusing N-Heterocyclic Carbenes with Carborane Anions. *Angewandte Chemie International Edition* **2014,** *53* (17), 4489-4493.
20. Fisher, S. P.; El-Hellani, A.; Tham, F. S.; Lavallo, V., Anionic and zwitterionic carboranyl N-heterocyclic carbene Au(i) complexes. *Dalton Trans.* **2016**, *45*, 9762-9765.
21. Asay, M. J.; Fisher, S. P.; Lee, S. E.; Tham, F. S.; Borchardt, D.; Lavallo, V., Synthesis of unsymmetrical N-carboranyl NHCs: directing effect of the carborane anion. *Chem. Commun.* **2015,** *51* (25), 5359-5362.
22. Holmes, J.; Pask, C. M.; Fox, M. A.; Willans, C. E., Tethered N-heterocyclic carbene-carboranes: unique ligands that exhibit unprecedented and versatile coordination modes at rhodium. *Chem. Commun.* **2016,** *52* (38), 6443-6446.
23. Holmes, J.; Pask, C. M.; Willans, C. E., Chelating N-heterocyclic carbene-carboranes offer flexible ligand coordination to IrIII, RhIII and RuII: effect of ligand cyclometallation in catalytic transfer hydrogenation. *Dalton Trans.* **2016,** *45* (40), 15818-15827.
24. Mohamed, H. A.; Willans, C. E., Silver-N-heterocyclic carbene complexes as promising anticancer compounds. In *Organometallic Chemistry: Volume 39*, The Royal Society of Chemistry: 2014; Vol. 39, pp 26-50.
25. Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A., The medicinal chemistry of carboranes. *Coord. Chem. Rev.* **2002,** *232* (1–2), 173-230.
26. Lai, C. H.; Lin, Y. C.; Chou, F. I.; Liang, C. F.; Lin, E. W.; Chuang, Y. J.; Lin, C. C., Design of multivalent galactosyl carborane as a targeting specific agent for potential application to boron neutron capture therapy. *Chem. Commun.* **2012,** *48* (4), 612-614.
27. Wan, K. Y.; Lough, A. J.; Morris, R. H., Transition Metal Complexes of an (S,S)-1,2-Diphenylethylamine-Functionalized N-Heterocyclic Carbene: A New Member of the Asymmetric NHC Ligand Family. *Organometallics* **2016,** *35* (11), 1604-1612.

28. Hintermair, U.; Englert, U.; Leitner, W., Distinct Reactivity of Mono- and Bis-NHC Silver Complexes: Carbene Donors versus Carbene–Halide Exchange Reagents. *Organometallics* **2011,** *30* (14), 3726-3731.
29. Daly, J. W., Caffeine analogs: biomedical impact. *Cellular and Molecular Life Sciences* **2007,** *64* (16), 2153-2169.
30. Garrison, J. C.; Youngs, W. J., Ag(I) N-heterocyclic carbene complexes: Synthesis, structure, and application. *Chem. Rev.* **2005,** *105* (11), 3978-4008.
31. Panzner, M. J.; Hindi, K. M.; Wright, B. D.; Taylor, J. B.; Han, D. S.; Youngs, W. J.; Cannon, C. L., A theobromine derived silver N-heterocyclic carbene: synthesis, characterization, and antimicrobial efficacy studies on cystic fibrosis relevant pathogens. *Dalton Trans.* **2009,** (35), 7308-7313.
32. Schaeck, J. J.; Kahl, S. B., Rapid Cage Degradation of 1-Formyl- and 1-Alkyloxycarbonyl-Substituted 1,2-Dicarba-closo-dodecaboranes by Water or Methanol in Polar Organic Solvents. *Inorg. Chem.* **1999,** *38* (1), 204-206.
33. Sheldrick, G., A short history of SHELX. *Acta Crystallographica Section A* **2008,** *64* (1), 112-122.
34. Sheldrick, G., SHELXT - Integrated space-group and crystal-structure determination. *Acta Crystallographica Section A* **2015,** *71* (1), 3-8.
35. Sheldrick, G., Crystal structure refinement with SHELXL. *Acta Crystallographica Section C* **2015,** *71* (1), 3-8.
36. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H., OLEX2: a complete structure solution, refinement and analysis program. *Journal of Applied Crystallography* **2009,** *42* (2), 339-341.
37. Barbour, L. J., X-Seed — A Software Tool for Supramolecular Crystallography. *Journal of Supramolecular Chemistry* **2001,** *1* (4), 189-191.

For TOC Only