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The synthesis of group 10 and 11 metal complexes of 3,6,9-trithia-1-(2,6)-pyridinacyclodecaphane and their use in A³-coupling reactions

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Dedicated to Professor A. G. M. Barrett, F.R.S on the occasion of his 65th birthday.

Abstract: The reaction between 3,6,9-trithia-1-(2,6)-pyridinacyclodecaphane and representative group 10 and 11 metal salts [Cu(NO₃)₂, NiCl₂ or Ag(CF₃CO₂)] afforded 1:1 complexes which in the case of Cu(II) and Ag(I) were characterized by single crystal X-ray crystallography. The catalytic activity of these complexes in A³-coupling reactions between aldehydes, terminal alkynes and amines was assessed in both protic (water) and aprotic (toluene) media. These A³-reactions prove to be more efficient, proceed with lower catalyst loadings and with faster reaction rates, when conducted in a focused microwave reactor as compared to the same reactions promoted by standard, thermal, modes of activation.

Introduction

Multicomponent reactions (MCRs) have proven to be powerful synthetic tools in the development of more efficient synthesis of complex structures from readily available feedstocks.¹ In general, these reactions are important because of their synthetic efficiency, intrinsic atom economy, potential for high selectivity and procedural simplicity. MCRs have the potential for reduced environmental impact as a number of reactions can be kaleidoscoped into a single operation. This mode of operation may reduce energy consumption and facilitate more effective waste management.² In this context, transition-metal catalyzed A³-coupling reactions³ (Mannich-type coupling reactions) offer a most appealing approach to the synthesis of propargylamines, intermediates which are of interest because of their biological properties, and because of their potential for further elaboration.⁴ In the A³-reaction a mixture of an Aldehyde, Alkyne, secondary Amine and suitable catalyst are reacted together in a single pot in a process which leads directly to substituted propargylamines (Scheme 1).

The A³-reaction has been the subject of intense scrutiny in recent years especially in connection with the development of more active catalysts^{3b,c} or in the development of enantioselective variants.^{3h} Metal salts and their complexes including iron, indium, iridium, zinc, nickel, cobalt, rhodium, gold, silver, copper and bimetallic systems such as RuCl₃/CuBr have been found to catalyze A³-coupling reactions⁵⁻⁹ although it may

be argued that the development of catalysts based upon the more abundant coinage metals would be preferable. In addition, concerns arising from the use of heavy metals in chemical processes and the drive to recycle expensive catalysts has resulted in the development of heterogeneous protocols for such reactions.¹⁰ The seminal contributions by Li and co-workers concerning the efficacy of silver iodide^{11a} as a catalyst for the promotion of chemoselective A³-reactions^{11b} even in aqueous media^{11c} highlighted the potential of this reaction in organic synthesis, even though relatively little is currently known as to precise mechanistic details of these reactions.³ⁱ More recently Abbiati and Caselli^{11d} prepared and fully characterized silver(I) complexes (**A**, Figure 1) of substituted 3,6,9-trithia-1-(2,6)-pyridinacyclodecaphanes and found them to be highly effective in catalyzing a number of organic transformations including A³-^{11e} and Henry reactions.^{11f}

Scheme 1: The A³-coupling reaction.

Following on from these reports our own interest^{12a-c} in the synthesis and co-ordination chemistry of macrocycles possessing mixed-donor sites encouraged us to investigate the utility of the transition metal complexes derived from these ligands as catalysts for the promotion of A³-coupling reactions.¹³

Figure 1: Complexes used in this study

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Results and Discussion

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In an exploratory investigation we decided to prepare a series of transition metal complexes (**B**, Figure 1) using the 3,6,9-trithia-1(2,6)-pyridinacyclodecaphane^{14a,b} motif as the ligating group. This particular class of pyridinacyclodecaphanes have proven binding affinity for late transition metal ions^{14c} and are readily accessible by an adaption of Vögtle's original synthetic procedure.^{14a} Hence, reaction of either 4-bromo-2,6-bis(bromomethyl)pyridine,^{15a} **1** or 2,6-bis(bromomethyl)pyridine,^{15b} **2** with commercially available 2,2'-thiodiethanethiol in the presence of KOH using a ternary ethanol-water-toluene solvent system cleanly afforded the macrocycles **3** and **4** in 66% and 75% isolated yield respectively (Scheme 2). Complex formation with macrocycles **3** or **4** proved uneventful and was accomplished by the dissolution of the ligand in either methanol or dichloromethane followed by the addition of silver trifluoroacetate, nickel chloride or copper sulphate in a 1:1 molar ratio. Slow evaporation of the solvent resulted in the isolation of the desired complexes **3a**, **3b**, **4a-4c** in good overall yields (ca. 90%).

Scheme 2: Synthesis of ligands **3** and **4**. Scheme 3: Metal complexes prepared (**3a**, **3b**, **4a**, **4b**, and **4c**) or discussed (**4d** prepared previously, see ref. 14a, but not used in this study)

In the case of **3a** and **4a** the ¹H NMR and ¹³C NMR data are in consonance with the presumption that association of the ligand with the metal centre persists in solution. In particular, the resonances associated with both the benzylic and methylene protons and carbons experience downfield shifts in the complexes when compared to the free ligands (see ESI). In addition to these chemical shift differences is the observation that the resonances associated with the -SCH₂CH₂S- linkage, which appear as relatively sharp singlets at ca. δ 2.5 ppm in the

free ligands, are split into two broadened, four hydrogen, multiplets centred at ca. δ 2.4 and 2.7 ppm in complexes **3a** and **4a**, observations are in keeping with those reported earlier by Vögtle.^{14a} Fortunately, in the case of **3a**, **4a** and **4b**, slow recrystallization from methanol-dichloromethane afforded crystals of suitable quality to enable single crystal X-ray structures to be determined. The crystal structures of both **3a** and **4a** are similar to that previously reported by Chacko and co-workers^{14b} for complex **4d**, which had been previously obtained from the reaction between silver nitrate with ligand **4**. In the case of **3a** the Ag⁺ ion adopts a distorted square pyramidal co-ordination geometry, being ligated in an *endo*-fashion to two sulphur atoms (S1 and S3) and the pyridine nitrogen atom (N1)

Complex **3a**. Selected bond lengths (Å): Ag1-N1=2.400(4); Ag1-S1=2.652(1); Ag1-S2(intramolecular)=3.116; Ag1-S3=2.650(1); S2-Ag1(inter-molecular)=2.541(1). Complex **4a**. Selected bond lengths (Å): Ag1-N1=2.353(8); Ag1-S1(intramolecular)=2.878(3); Ag1-S2=2.701(3); Ag1-S3=2.676(2); S1-Ag1(inter-molecular)=2.488(2).Figure 2: X-ray structures of **3a** and **4a** (H-atoms omitted for clarity; ellipsoids at 50% probability).

of the macrocycle which defines the base of the pyramid. A fourth co-ordination site, notionally occupied by S2, is effectively

Figure 3: Comparison of the X-ray crystal structures of **4a** (top) and **3a** (bottom); ellipsoids at 50% probability.

vacant as the S2-Ag distance is longer (3.116 Å) than that normally associated with a Ag-S covalent bond.^{14b} The Ag⁺ ion is displaced out of the mean plane described by N1, S1, S2 and S3 by 1.04 Å. The vertex of the square pyramid is occupied by the sulphur atom, S1', of a neighboring molecule. This *endo*-, *exo*-binding mode^{14d} results in the generation of a one-dimensional polymeric structure in which the macrocycle is incorporated into an infinite zigzag motif. The structure of **4a** is similar to that observed for **3a** with the exception that all four heteroatoms (N, S1, S2 and S3) of the macrocycle now appear to be bound to the central Ag⁺ ion, which once again adopts a distorted square pyramidal co-ordination geometry. On this occasion the Ag⁺ ion is displaced by 1.314 Å from the base of the pyramid. Notably, the intermolecular S-Ag bond lengths which we observe in the case of **3a** and **4a** (2.541(1) Å for **3a**; 2.490(2) Å for **4a**) are considerably shorter than the intra-nuclear distances between the silver and sulphur atoms that are *trans*- to the pyridine nitrogen (3.118 Å for **3a**; 2.884(2) Å for **4a**), an

observation which has also been noted elsewhere.^{14b} In addition there is essentially no contact between the Ag⁺ ion and the trifluoroacetate counter ion in these complexes (**3a** = 5.800 Å; **4a** = 7.756 Å), Figure 2. The structural variation between **3a** and **4a** is most likely due to packing forces where the conformational requirements of the macrocyclic ring are outweighed by intermolecular forces. Here we suspect that the pyridine ring

Figure 5 X-ray structures of **3b**^{12c} (top) and **4b** (bottom); H-atoms omitted for clarity; ellipsoids at 50% probability.

acts as a lever on the macrocycle, disrupting some of the already weakened, intramolecular, Ag-S bonds within the ring, Figure 3. In contrast, when dissolved in DMSO-*d*₆ at least, ¹H DOSY, ¹⁹F DOSY and ¹⁹F HOESY NMR experiments,^{14e} conducted at ambient temperatures, indicate that the polymeric structure of **4a** is disrupted and that the complex is essentially monomeric in nature (Figure 4).^{14f} In particular the ¹⁹F HOESY NMR experiment indicates that the trifluoroacetate anion is associated with the pyridine fragment of the complex while the ¹H DOSY spectra suggests that DMSO is co-ordinated to the silver centre. The difference in diffusion constants derived from the ¹H and ¹⁹F DOSY experiments (2 × 10⁻¹⁰ m² s⁻¹ and 4.5 × 10⁻¹⁰ m² s⁻¹ respectively) also suggests that the trifluoroacetate anion and ligated silver cation exist as a loose ion pair when dissolved in DMSO.^{14g}

Figure 4: (a) ^1H DOSY NMR spectrum of complex **4a** in DMSO at 298 K (a diffusion coefficient of $2 \times 10^{-10} \text{ m}^2 \text{s}^{-1}$ correlates^{14f} with a MW of 604 g mol^{-1}); (b) ^{19}F DOSY spectrum of complex **4a** in DMSO at 298 K; (c) ^{19}F - ^1H HOESY NMR spectrum of complex **4a** in DMSO at 298 K.

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In a previous study^{12c} we reported the crystal structure of **3b**, which was isolated from the reaction between **3** with copper nitrate pentahydrate followed by recrystallization from methanol-dichloromethane. In the case of **3b** the X-ray analysis reveals that the copper adopts a distorted octahedral co-ordination geometry which incorporates the three sulphur atoms and the pyridyl nitrogen atom of the ligand together with an axially-bound η^1 -nitrate ligand and an equatorially disposed, ligated, water molecule. In the case of **4b**, which was prepared similarly to **3b**, a single crystal X-ray structure determination revealed that the Cu^{2+} ion once again adopts a distorted octahedral co-ordination geometry and on this occasion two η^1 -nitrate ligands are bound to copper. As to be expected the Cu1-N1 bond length of 2.014(2) Å is considerably shorter than those for Cu-S (Cu-S1Cu1-S2, Cu-S3 bond lengths of 2.4176(6), 2.5709(8) and 2.25509(7) Å respectively) or Cu-O (Cu1-O3 and Cu1-O4 of 1.943(2) and 2.243(2) Å respectively) and are similar to those reported for the related $[\text{Cu}(\text{dthp})(\text{NO}_3)_2]$ and Cu(II) pyridine-thioether complexes described by the groups of Yamauchi^{12d} and Lee.^{12e} Complex **4b** also shows a Jahn-Teller distortion such that the axially disposed ligands Cu1-S2 and Cu1-O4 are lengthened compared to Cu1-S1/Cu1-S3 and Cu1-O2 which are contained within the equatorial plane, Figure 5.

Finally, reaction of ligand **4** with NiCl_2 in methanol at reflux afforded the nickel complex **4c**, a blue-coloured solid, which resisted all attempts at recrystallization. Characterization of this material was therefore limited to IR, UV-visible, mass spectrometry and combustion microanalysis. In passing, and not unexpectedly, it is noted that both the λ_{max} of the free ligands (**3**: $\lambda_{\text{max}} = 275 \text{ nm}$ ($\epsilon = 3.2 \times 10^4$); **4**: $\lambda_{\text{max}} = 276 \text{ nm}$ ($\epsilon = 3.6 \times 10^4$)) and the complexes **3a**, **3b** and **4a-c** are relatively insensitive to introduction of a bromine substituent onto the pyridine ring of the ligand or to the nature of the metal ion itself (λ_{max} between 274–282 nm).

Having prepared a number of metal-S₃N complexes we now wished to evaluate their efficacy in the promotion of A³-coupling reactions. Spurred on by Casselli's and Abbiati's recent results on the use silver-N4 complexes as catalysts in A³-reactions^{11e,16a-c} we elected to investigate a standard A³-reaction between benzaldehyde, phenyl acetylene and piperidine in the presence of metal complex **4a** as catalyst in toluene (Table 1). These initial experiments provided a baseline for the catalytic activity of complex **4a**: reactions were very slow at ambient temperature (Table 1, run no. 1) but 30% conversion to the desired propargylic amine did result after a reaction time of 24 hours at 40 °C (run 2). Further optimisation of the reaction conditions (catalyst loading of 5 mol%, in toluene, at 90 °C for 16 hours) resulted in improved conversions and led to the isolation of the desired product in 70% yield (run 4). The use of catalyst loadings of < 5% resulted in lower isolated yields of product, as did conducting the reactions at higher temperature (Table 1: runs 6 and 7). In an effort to develop more environmentally friendly experimental protocols the same A³-coupling reaction was briefly investigated using water as solvent,^{11c} a reaction which afforded the desired product in 69% isolated yield under optimised conditions (Table 1; run 9). In this case it is interesting to note that the low solubility of the pre-formed catalyst **4a** in water does not affect the yields of these reactions

even though the deposition of a silver mirror occurs during the course of this particular set of reactions. This observation may also suggest that, under these reaction conditions, the A³-coupling reaction is promoted by silver nano-particles.^{11g} This conjecture is the subject of continuing investigations.[†]

Upon completion of the initial screening exercise the A³-coupling reaction of a series of aromatic aldehydes with secondary amines was undertaken. As is evident from Table 2 all of the catalysts screened are effective in promoting A³-reactions in either toluene or water as the reaction medium. The use of inexpensive nickel catalysts^{8b-d} **4c** in aqueous media is particularly noteworthy in the green chemistry context. Unfortunately none of these catalyst systems promoted the A³-reaction between primary amines and aromatic aldehydes,^{4c} a reaction which has also proven to be problematic with other catalyst systems.^{4e}

Given the beneficial effects that we^{7a} and others^{11e,g} have noted in the promotion of A³-reactions when using focused microwave radiation as a heating source we turned our attention to this mode of activation in the present study. After some experimentation we noted that much reduced reaction times (30 minutes instead of 16 hours) and catalyst loadings (typically 2 mol%) can be utilized to good effect when irradiating these reactions (to an internal temperature of 150 °C) in a focused microwave reactor. The use of either toluene or water as reaction medium is tolerated in these reactions without any appreciable diminution in the yields of the desired, purified, A³-products, which are typically in the range of 60% (Table 3).

Conclusions

In conclusion we report that complexation of Ag(I), Cu(II) and Ni(II) with the readily available S₃N ligands **3** and **4** affords a family of complexes which exhibit catalytic activity in A³-coupling reactions. The complexes **3a**, **4a** and **4b** have been characterized by single crystal X-ray crystallography where it has been shown that, in the case of **3a** and **4a**, the ligand binds to Ag⁺ in both *endo*- and *exo*-modes generating one-dimensional co-ordination polymers.^{16,18} A³-reactions proceed efficiently in either toluene or aqueous media when conducted in the presence of these complexes; A³-coupling reactions conducted in a focused microwave^{11e,11g,7b,19} reactor have a beneficial effect both on reaction rate and catalyst loading. Further optimization of these A³-reactions is currently under investigation.

Experimental Section

General Experimental Details.

All reactants and reagents were purchased from either Sigma-Aldrich or Alfa Aesar and were used without further purification. Solvents used were purified by standard methods. Synthetic procedures were carried out under an atmosphere of dry nitrogen in dry solvents unless otherwise noted. Chromatographic purifications were performed using silica gel SDS (particle size 0.04–0.06 mm). Melting points were determined on a Sanyo Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were measured by Bruker Alpha FT-IR machine and absorption peaks ($\tilde{\nu}_{\text{max}}$) are quoted in wave numbers (cm^{-1}). Deuterated chloroform (CDCl_3) was used as solvent unless otherwise stated to record the Nuclear magnetic resonance (NMR) spectra. ¹H NMR spectra were recorded on B400 Bruker Avance III 400 MHz or B500 Bruker Avance II+ 500 MHz spectrometers, using TMS as an internal standard (0.00 ppm). Signal splitting patterns are described as singlet (s), doublet (d), triplet (t),

* Blank reactions indicate that complex **4a** is stable in toluene at reflux: see ESI for details. The lower yields at elevated temperatures may point towards instability of the iminium ions formed during the course of these reactions.

[†] We presume that the silver mirror is produced as a by-product from the oxidation of the aldehyde by Ag⁺. See ref. 16d for recent studies

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multiplet (m). Low resolution mass spectra were measured on Micromass Trio 200 spectrometer. High resolution mass spectra were measured on Kratos Concept IS spectrometer. A Carlo Erba EA 1108 Elemental Analyzer was used for determination of % levels of carbon, hydrogen and nitrogen. A Metrohm 686 Titrprocessor +665 Dosimat Autotitrator was used to measure chlorine.

4-Bromo-2,6-bis(bromomethyl)pyridine^{15a} was prepared from chelidamic acid^{17a}. Chelidamic acid was first converted into dimethyl 4-hydroxypyridine-2,6-dicarboxylate^{17b} as described previously. Reaction of this ester with PBr₅ at 90 °C for 3 hours afforded dimethyl 4-bromopyridine-2,6-dicarboxylate which on reduction with NaBH₄ afforded 4-bromo-2,6-pyridinedimethanol.^{17d}

Synthesis of 4-bromo-2,6-bis(bromomethyl)pyridine: A mixture of 4-bromo-2,6-pyridinedimethanol^{17d} (2.8 g, 13.1 mmol) and 33% HBr in acetic acid (50 mL) was heated at 125 °C for 5 hours. The reaction mixture was then poured onto crushed ice and neutralised with 1 M NaOH to pH 4–5. The precipitated *title compound* was collected at the pump as a colourless powder (3.9 g, 89 %). M.p. 127–129 °C (lit^{15a} 125–126 °C). ¹H NMR: δ (400 MHz, DMSO-*d*₆) 4.66 (4H, s) 7.81 (2H, s) ppm. ¹³C NMR: δ (125 MHz, DMSO-*d*₆) 33.5, 125, 133.4, 158.6 ppm. MS (ES⁺) *m/z* [M+H]⁺ 341.8. Accurate Mass: [C₇H₇N⁷⁹Br₃]⁺, [M+H]⁺ requires 341.8128; found 341.8129. $\tilde{\nu}_{\max}$ (ATR): 2971, 1563, 1452, 1355, 1283 cm⁻¹.

Synthesis of 2,6-bis(bromomethyl)pyridine^{15b}: Pyridine-2,6-diylmethanol (1.82 g, 13.1 mmol) was added to 33% HBr in acetic acid (26 mL) and the reaction mixture heated to 100 °C for 90 minutes. The reaction mixture was poured onto crushed ice and neutralised with 1 M NaOH to pH 9. The precipitated *title compound* was collected at the pump as an off-white solid (3.00 g, 88%). M.p. 79–80 °C (lit^{15b} 80–82 °C). ¹H NMR: δ (300 MHz, CDCl₃) 4.55 (4H, s, CH₂), 7.38 (2H, d, *J* = 7 Hz), 7.72 (1H, t, *J* = 7 Hz) ppm. ¹³C NMR: δ (75 MHz, CDCl₃) 33.8, 123.1, 138.4, 157.1 ppm. $\tilde{\nu}_{\max}$ (ATR): 1168, 1205, 1451, 1581, 2981, 3029 cm⁻¹. Accurate Mass: (ES⁺) [C₇H₈NO₄⁷⁹Br₂]⁺, [M+H]⁺ requires 263.9007; found 263.9011.

Synthesis of Ligands:

Synthesis of 1⁴-bromo-3,6,9-trithia-1(2,6)-pyridinacyclodecaphane (3): 2,2-Thiodiethanethiol (0.28 mL, 2.11 mmol) was added to 4-bromo-2,6-bis(bromomethyl)pyridine (0.791 g, 2.11 mmol) and KOH (0.24 g, 4.22 mmol) in toluene (25 mL) - ethanol/H₂O (50:1 v/v; 25 mL) at room temperature. The reaction mixture was stirred vigorously for 24 hours, under an atmosphere of nitrogen, and the solvent was then removed *in vacuo*. The residue was triturated with DCM (50 mL) and the organic extracts washed with water (6 x 20 mL). The organic phase was dried (MgSO₄) and solvent removed *in vacuo*. Recrystallisation of the residue (DCM:Pet) afforded the *title compound* as a colourless, crystalline, solid (0.462 g, 66%). M.p. 122–123 °C. ¹H NMR: δ (CDCl₃, 400 MHz) 2.52 (8H, s), 3.79 (4H, s), 7.49 (2H, s) ppm. ¹³C NMR: δ (CDCl₃, 100 MHz) 30.1, 31.0, 35.4, 125.7, 134.6, 158.7 ppm. $\tilde{\nu}_{\max}$ (ATR): 1187, 1348, 1478, 1558, 1724, 3106, 3307 cm⁻¹. MS: (ES⁺) *m/z* [M+H]⁺ 336. Accurate Mass: (ES⁺) [C₁₁H₁₄⁷⁹BrNS₃]⁺, [M]⁺ requires 335.9547; found 335.9545. Microanalysis: C₁₁H₁₄BrNS₃ requires C, 39.28; H, 4.2; N, 4.16 %; found: C, 39.16; H, 4.17; N, 3.82 %. $\lambda_{\max}$ = 275 nm (ϵ = 3.2 x 10⁴).

Synthesis of 3,6,9-trithia-1(2,6)-pyridinacyclodecaphane (4)^{14a}: 2,2-Thiodiethanethiol (0.28 mL, 2.11 mmol) was added to 2,6-bis(bromomethyl)pyridine (0.56 g, 2.11 mmol) and KOH (0.24 g, 4.22 mmol) in toluene (25 mL)-ethanol/H₂O (50:1 v/v; 25 mL) at room temperature. The reaction mixture was stirred vigorously for 24 hours, under an atmosphere of nitrogen, and the solvent was then removed *in vacuo*. The residue was triturated with DCM (50 mL) and the organic extracts washed with water (6 x 20 mL). The organic phase was dried (MgSO₄) and solvent removed *in vacuo*. Purification of the crude product by recrystallization (DCM:petrol) afforded the *title compound* as a colourless, crystalline, solid (0.406 g, 75%). M.p. 164–165 °C (lit^{14a} 162–163 °C). ¹H NMR: δ (400 MHz, DMSO-*d*₆) 2.50 (s, 8H), 3.85 (s, 4H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.84 (t, *J* = 7.5 Hz, 1H) ppm. ¹³C NMR: δ (125 MHz, DMSO-*d*₆) 29.6, 30.5, 35.3, 122.5, 138.8, 157.5 ppm. MS: (ES⁺) *m/z* [M+H]⁺ 258.2. Accurate Mass: (ES⁺) [C₁₁H₁₅NS₃]⁺, [M]⁺ requires 257.0361; found 257.0362. $\tilde{\nu}_{\max}$ (ATR): 2921, 1588, 1569, 1451, 1428, 1280, 1208, 1154 cm⁻¹. $\lambda_{\max}$ = 276 nm (ϵ = 3.6 x 10⁴).

Synthesis of metal complexes:

Synthesis of silver(I) complex (4a): A modified version of Vögtle's^{14a} original procedure was adopted for these preparations. To a solution of 3,6,9-trithia-1(2,6)-pyridinacyclodecaphane (0.260 g, 1.0 mmol) in DCM (40 mL) was slowly added, over 20–25 minutes at room temperature, a solution of silver trifluoroacetate (0.120 g, 1.0 mmol) in methanol (40 mL). Slow concentration of the reaction mixture at ambient temperature, overnight, afforded the *title compound* as a colourless powder (0.421 g, 88%). M.p. 211–212 °C. ¹H NMR: δ (400 MHz, DMSO-*d*₆) 2.28–2.45 (4H,

m), 2.65–2.81 (4H, m), 4.14 (4H, s), 7.42 (2H, d, *J* = 8 Hz), 7.87 (1H, t, *J* = 8 Hz). ¹³C NMR: δ (125 MHz, DMSO-*d*₆) 30.1, 31.3, 37.2, 124.4, 138.7, 156.1 ppm. ¹⁹F NMR: (470.5 MHz, DMSO-*d*₆) δ ppm -73.5 ppm. MS: (ES⁺) *m/z* [M+H]⁺ 479.3. $\tilde{\nu}_{\max}$ (ATR): 2923, 1681, 1583, 1570, 1452, 1401, 1193, 1151, 1114 cm⁻¹. Microanalysis: C₁₃H₁₅AgF₃NS₃O₂·H₂O requires C, 31.5; H, 3.5; N, 2.8; S, 19.4 %; found: C, 31.5; H, 3.3; N, 2.8; S, 18.9 %. $\lambda_{\max}$ = 274 nm (ϵ = 3.4 x 10⁴). A sample suitable for X-ray diffraction was obtained by slow recrystallisation from CH₂Cl₂-MeOH.

Synthesis of silver(I) complex (3a):

To a solution of 1⁴-bromo-3,6,9-trithia-1(2,6)-pyridinacyclodecaphane (0.052 g, 0.15 mmol) in DCM (10 mL) was slowly added a solution of silver trifluoroacetate (0.034g, 0.15 mmol) in methanol (10 mL) over a period of 20–25 minutes at room temperature. Slow concentration of the reaction mixture at ambient temperature afforded the *title compound* as a colourless powder (0.074 g, 90%). M.p. 195–196 °C. ¹H NMR: (400 MHz, DMSO-*d*₆) δ ppm 2.40–2.49 (4H, m) 2.75–2.77 (4H, m) 4.16 (4H, s) 7.74 (2H, s). ¹³C NMR: (125 MHz, DMSO-*d*₆) δ ppm 29.9, 31.0, 36.3, 126.7, 127.7, 157.5. ¹⁹F NMR: (376.4 MHz, DMSO-*d*₆) δ ppm -73.3 ppm. $\tilde{\nu}_{\max}$ (ATR): 3043, 2960, 1560, 1481, 1356, 1319, 1303 cm⁻¹. MS: (ES⁺) *m/z* [M+H]⁺ 555.3. $\lambda_{\max}$ = 278 nm (ϵ = 3.2 x 10⁴). A sample suitable for X-ray diffraction was obtained by slow recrystallisation from CH₂Cl₂-MeOH.

Synthesis of Ni(II) complex (4c): To a solution of 3,6,9-trithia-1(2,6)-pyridinacyclodecaphane (0.252g, 1.0 mmol) in methanol (25 mL) was added anhydrous nickel(II) chloride (0.130g, 1.0mmol). The reaction mixture was then brought to a gentle reflux, under an atmosphere of nitrogen, for 1.5 hours, under an atmosphere of nitrogen, and then allowed to cool to ambient temperature. On doing so the *title compound* precipitated from solution as a blue-coloured powder which was collected at the pump (0.200 g, 52%). $\tilde{\nu}_{\max}$ (ATR): 2943, 2919, 2890, 1645, 1620, 1457, 1413, 1389, 1165, 1013 cm⁻¹. Microanalysis: C₁₁H₁₅Cl₂NNiS₃ requires C, 34.1; H, 3.9; N, 3.6 Cl, 18.3, S 24.8 %; found: C, 33.8; H, 3.9; N, 3.5, Cl, 18.2, S 24.6 %. $\lambda_{\max}$ = 274 nm (ϵ = 2.9 x 10⁴).

Synthesis of Cu(II) complex (4b): To a solution of 3,6,9-trithia-1(2,6)-pyridinacyclodecaphane (0.013 g, 0.05 mmol) in DCM (4 mL) was added, dropwise, a solution of copper nitrate pentahydrate (0.012 g, 0.05 mmol) in methanol (4 mL) over a period of 20–25 minutes at room temperature. Slow concentration of the reaction mixture at ambient temperature, overnight, afforded the *title compound* as a dark green-coloured crystalline solid (0.021 g, 91%). M.p. 225–226 °C. $\tilde{\nu}_{\max}$ (ATR): 3028, 2995, 1434, 1418, 1353, 1262 cm⁻¹. Microanalysis: C₁₁H₁₅CuN₃O₆S₃ requires C 29.6; H, 3.4; N, 9.4, S 21.6; found: C, 29.5; H, 3.4; N, 9.3, S 21.5%. $\lambda_{\max}$ 280 nm (ϵ = 3.3 x 10⁴). A sample suitable for X-ray diffraction was obtained by slow recrystallisation from CH₂Cl₂-MeOH.

Synthesis of Cu(II) complex (3b): To a solution of 1⁴-bromo-3,6,9-trithia-1(2,6)-pyridinacyclodecaphane, **3** (0.017 g, 0.05 mmol) in DCM (4 mL) was slowly added a solution of copper nitrate pentahydrate (0.012 g, 0.05 mmol) in methanol (4 mL) over a period of 20–25 minutes at room temperature. Slow concentration of the reaction mixture at ambient temperature afforded the *title compound* as a dark green-coloured crystalline solid. Yield 0.025 g (92%); m.p. 252–254 °C. $\tilde{\nu}_{\max}$ (ATR): 2977, 2951, 2932, 2163, 1585, 1286, 1228 cm⁻¹. MS: (ES⁺) *m/z* [M+H]⁺ 540.86. Microanalysis: C₁₁H₁₄BrCuN₃O₆S₃·2H₂O requires C, 23.6; H, 3.2; Br 14.3; N, 7.5%; found: C, 23.7; H, 3.4; Br 13.1; N, 7.3, Br 13.1. $\lambda_{\max}$ = 282 nm (ϵ = 3.5 x 10⁴).

General procedure for the catalysis of the A³-coupling reaction of aldehyde, amine and alkyne under conventional heating:

A mixture of the complex **3a,3b,4a,4b** or **4c** (for precise ratios of reagents see Table 1 and Table 2) in toluene (3 mL) or water (3 mL) in a sealed microwave reaction vial equipped with a stirring bar was heated to 90 °C for 10 min under an atmosphere of nitrogen. Phenylacetylene (for quantities see Table 1 and Table 2) was then introduced into the reaction mixture via a syringe and the reaction mixture was heated (see Table 1 and Table 2 for conditions). The reaction mixture was cooled to room temperature, poured into water and extracted with DCM. The organic extracts were dried over MgSO₄ and concentrated *in vacuo* to afford the crude product. Purification of the residue by column chromatography (SiO₂; hexane:DCM = 9:1 v/v) afforded the *title compound*.

General procedure for the catalysis of the A³-coupling reaction of aldehyde, amine and alkyne in a microwave reactor:

A mixture of the complex **3a,3b,4a,4b** or **4c**, aldehyde, amine and phenylacetylene (for precise ratios of reagents see Table 3) in toluene (1 mL) or water (1 mL) in a sealed microwave reaction vial equipped with a stirring bar was heated, under nitrogen, at 150 °C, in a focused microwave reactor for 30 minutes.[‡] The reaction mixture was cooled to ambient temperature, poured into water and extracted with DCM. The organic extracts were dried over MgSO₄ and concentrated *in vacuo* to

[‡] A Biotage InitiatorTM microwave reactor (maximum power output of 300 W; operating frequency 2450 MHz) was used in these experiments.

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afford the crude product. Purification of the residue by column chromatography (SiO₂; hexane:DCM = 9:1 v/v) afforded the *title compound*.

Synthesis of 4-(1-(2,5-dimethoxyphenyl)-3-phenylprop-2-yn-1-yl)morpholine: ¹H NMR δ (400 MHz, CDCl₃) 2.60 - 2.69 (2 H, m), 2.71 - 2.79 (2 H, m), 3.71 - 3.76 (4 H, m), 3.80 (3 H, s), 3.84 (3 H, s), 5.16 (1 H, s), 6.84 (d, J = 2.9 Hz, 1 H), 6.87 (1 H) 7.25 (d, J = 3.2 Hz, 1 H) 7.28 - 7.33 (3 H, m) 7.45 - 7.50 (2 H, m) ppm. ¹³C NMR δ (125 MHz, CDCl₃) 50.1, 55.1, 55.7, 56.7, 67.1, 86.5, 86.6, 112.8, 113.4, 116.3, 123.1, 127.4, 128.1, 128.2, 131.7, 151.6, 153.3 ppm. MS: (ES⁺) m/z [M+H]⁺ 338.2. Accurate Mass: (ES⁺) [C₂₁H₂₄NO₃]⁺, [M+H]⁺ requires 338.1751; found 338.1750. $\bar{\nu}_{\max}$ (ATR): 1201, 1243, 1438, 1500, 2985, 3041 cm⁻¹.

Synthesis of 1-(1-(2,5-dimethoxyphenyl)-3-phenylprop-2-yn-1-yl)piperidine: ¹H NMR: δ (400 MHz, CDCl₃) 1.27 - 1.58 (6 H, m), 2.42 - 2.65 (4 H, m), 3.72 (s, 3 H), 3.75 (s, 3 H), 5.08 (1 H, s), 6.71 - 6.75 (1 H, m), 6.77 (1 H, s), 7.16 (1H, d, J = 2.9 Hz) 7.20 - 7.24 (3 H, m), 7.37 - 7.42 (2 H, m) ppm. ¹³C NMR: δ (125 MHz, CDCl₃) 24.4, 26.1, 50.8, 55.4, 55.7, 57.0, 86.1, 87.6, 112.9, 113.2, 116.4, 123.4, 127.9, 128.1, 131.7, 151.7, 153.3 ppm. MS: (ES⁺) m/z [M+H]⁺ 336.3. Accurate Mass: (ES⁺) [C₂₂H₂₆NO₂]⁺, [M+H]⁺ requires 336.1958; found 336.1955. $\bar{\nu}_{\max}$ (ATR): 1198, 1250, 1418, 1560, 1600, 2975, 3053 cm⁻¹.

Synthesis of 1-(1-(2,5-dimethoxyphenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine: ¹H NMR δ (400 MHz, CDCl₃) 1.80 (4 H, t, J = 5 Hz), 2.75 (4 H, t, J = 5 Hz), 3.80 (3 H, s), 3.83 (3 H, s), 5.30 (1 H, s), 6.79 - 6.86 (2 H, m), 7.28 - 7.32 (4 H, m), 7.43 - 7.49 (2 H, m) ppm. ¹³C NMR: δ (125 MHz, CDCl₃) 23.4, 50.5, 51.8, 55.7, 58.5, 85.3, 87.8, 112.2, 113.3, 115.7, 123.4, 127.9, 128.2, 128.9, 131.7, 150.9, 153.4 ppm. MS: (ES⁺) m/z

[M+H]⁺ 322.2. Accurate Mass: (ES⁺) [C₂₁H₂₄NO₂]⁺, [M+H]⁺ requires 322.1802; found 322.1800. $\bar{\nu}_{\max}$ (ATR): 1185, 1290, 1420, 1545, 1610, 2965, 3075 cm⁻¹.

Synthesis of 1-(1-(4-chlorophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine: ¹H NMR δ (400 MHz, CDCl₃) 1.68 - 1.74, (4 H), 2.54 - 2.63 (4 H, m), 4.78 (1 H, s), 7.22 - 7.26 (5 H, m), 7.38 - 7.42 (3 H, m), 7.47 (2 H, d, J = 8.9 Hz) ppm. ¹³C NMR: (125 MHz, CDCl₃) δ ppm 26.2, 50.7, 61.7, 85.4, 88.2, 123.1, 128.2, 128.3, 129.0, 129.8, 131.8, 133.2, 137.4 ppm. MS: (ES⁺) m/z [M+H]⁺ 296.1. Accurate Mass: (ES⁺) [C₁₉H₁₉N³⁵Cl]⁺, [M+1]⁺ requires 296.1201; found 296.1197. $\bar{\nu}_{\max}$ (ATR): 1155, 1350, 1425, 1551, 1630, 2985, 3025 cm⁻¹.

Synthesis of 4-(1-(4-chlorophenyl)-3-phenylprop-2-yn-1-yl)morpholine: ¹H NMR: (400 MHz, CDCl₃) δ ppm 2.63 (t, J = 4.52 Hz, 4 H) 3.69 - 3.80 (m, 4 H) 4.78 (s, 1 H) 7.33 - 7.38 (m, 5 H) 7.51 - 7.55 (m, 2 H) 7.59 (d, J = 8.30 Hz, 2 H). ¹³C NMR: (125 MHz, CDCl₃) δ ppm 49.8, 61.4, 67.1, 84.4, 88.9, 122.7, 128.3, 128.4, 128.5, 129.9, 131.8, 133.6, 136.5. MS: (ES⁺) [M+H]⁺ 312.1. Accurate Mass: (ES⁺) [C₁₉H₁₉N³⁵ClO]⁺, [M+H]⁺ requires 312.1150 found 312.1148. $\bar{\nu}_{\max}$ (ATR): 1073, 1174, 1330 1415, 1521, 1600, 2965, 3045 cm⁻¹.

Synthesis of 1-(1-(4-chlorophenyl)-3-phenylprop-2-yn-1-yl)piperidine: ¹H NMR: δ (400 MHz, CDCl₃) 1.40 - 1.51 (2 H, m), 1.54 - 1.66 (4 H, m), 2.55 (3 H, t, J = 5.00 Hz), 4.77 (1 H, s) 7.32 - 7.37 (5 H, m) 7.50 - 7.55 (2 H, m), 7.60 (2 H, d, J = 8.30 Hz) ppm. ¹³C NMR: δ (125 MHz, CDCl₃) 23.4, 50.1, 58.3, 85.9, 122.9, 128.1, 128.2, 128.3, 128.9, 129.5, 129.8, 131.7, 133.2, 138.1, 145.3 ppm. MS: (ES⁺) [M+H]⁺ 310. Accurate Mass: (ES⁺) [C₂₀H₂₁N³⁵Cl]⁺, [M+H]⁺ requires 310.1357 found

Table 1. Optimisation of the A³-coupling reaction catalyzed by complex **4a**

Run no.	Catalyst (C mmol%)	Aldehyde ^a	Amine (X mmol)	Phenylacetylene (Y mmol)	Solvent (S)	Thermal T °C / H hr	Conversion ^b or Yield ^c (%)
1	4a (6 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.2 mmol)	Phenylacetylene (1.2 mmol)	Toluene (5 mL)	20 °C / 24 h	- ^b
2	4a (6 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.2 mmol)	Phenylacetylene (1.2 mmol)	Toluene (5 mL)	40 °C / 24 h	30 ^b
3	4a (6 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.2 mmol)	Phenylacetylene (1.2 mmol)	Toluene (3 mL)	80 °C / 24 h	55 ^c
4	4a (5 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.5 mmol)	Phenylacetylene (1.5 mmol)	Toluene (3 mL)	90 °C / 16 h	73 ^c
5	4a (5 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.5 mmol)	Phenylacetylene (1.5 mmol)	Toluene (3 mL)	110 °C / 16 h	60 ^c
6	4a (3 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.5 mmol)	Phenylacetylene (1.5 mmol)	Toluene (3 mL)	90 °C / 16 h	70 ^c
7	4a (3 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.5 mmol)	Phenylacetylene (1.5 mmol)	Toluene (3 mL)	110 °C / 16 h	55 ^c
8	4a (5 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.5 mmol)	Phenylacetylene (1.5 mmol)	Water (3 mL)	40 °C / 16 h	35 ^b
9	4a (5 mol%)	Benzaldehyde (1.0 mmol)	Piperidine (1.5 mmol)	Phenylacetylene (1.5 mmol)	Water (3 mL)	90 °C / 16 h	69 ^c

Reaction conditions: Reaction conditions: ^a1 mmol aldehyde, C mmol% catalyst, X mmol amine, Y mmol phenylacetylene, S mL solvent heated to T °C for H hours under an atmosphere of N₂. ^bDegree of conversion determined from the ¹H NMR spectrum of the crude reaction mixture. ^cIsolated yield refers to yield of product after column chromatography.

Table 2: A³-coupling reaction promoted by complexes **3a**, **3b**, **4a**, **4b** or **4c** under conventional heating.

Substrate			Product (% yield)									
Aldehyde	Amine	Alkyne	3a ^{a,c}	3a ^{b,c}	4a ^{a,c}	4a ^{b,c}	3b ^{a,c}	3b ^{b,c}	4b ^{a,c}	4b ^{b,c}	4c ^{a,c}	4c ^{b,c}
Benzaldehyde	Piperidine	Phenyl acetylene	73	69	73	74	69	65	66	62	62	60
4-Chloro benzaldehyde	Piperidine	Phenyl acetylene	68	70	64	70	64	63	63	61	61	59
2,5-Dimethoxy benzaldehyde	Piperidine	Phenyl acetylene	61	58	59	55	61	59	57	60	60	58
Benzaldehyde	Pyrrolidine	Phenyl acetylene	71	68	74	69	68	64	66	66	62	60
4-Chloro benzaldehyde	Pyrrolidine	Phenyl acetylene	64	66	68	59	62	59	64	61	63	61
2,5-Dimethoxy benzaldehyde	Pyrrolidine	Phenyl acetylene	60	55	58	59	63	62	62	60	66	63
Benzaldehyde	Morpholine	Phenyl acetylene	75	77	71	70	67	64	66	62	61	58
4-Chloro benzaldehyde	Morpholine	Phenyl acetylene	68	65	66	63	65	61	61	60	62	59
2,5-Dimethoxy benzaldehyde	Morpholine	Phenyl acetylene	65	68	62	64	59	65	61	62	57	59

Reaction conditions: ^a1.0 mmol aldehyde, 1.5 mmol amine, 1.5 mmol phenylacetylene, 3 mL toluene, metal catalyst **3a**, **3b**, **4a**, **4b** or **4c** (5.0 mol%), 16 hours, 90 °C. ^b1.0 mmol aldehyde, 1.5 mmol amine, 1.5 mmol phenylacetylene, 3 mL water, metal catalyst **3a**, **3b**, **4a**, **4b** or **4c** (5.0 mol%); ^cisolated yield after column chromatography.

Table 3: A³-coupling reaction catalysed with metal complexes **3a**, **3b**, **4a**, **4b**, **4c** under microwave heating

Substrate			Product (% yield)									
Aldehyde	Amine	Alkyne	3a ^{a,d}	3a ^{b,c}	4a ^{a,d}	4a ^{b,c}	3b ^{a,d}	3b ^{b,c}	4b ^{a,d}	4b ^{b,c}	4c ^{a,c}	4c ^{b,c}
Benzaldehyde	Piperidine	Phenyl acetylene	78	75	78	73	75	75	75	70	65	60
4-Chloro benzaldehyde	Piperidine	Phenyl acetylene	71	68	67	65	70	65	65	65	60	55
2,5-Dimethoxy benzaldehyde	Piperidine	Phenyl acetylene	66	59	65	65	60	60	65	60	55	50
Benzaldehyde	Pyrrolidine	Phenyl acetylene	73	68	74	70	70	65	75	70	60	60
4-Chloro benzaldehyde	Pyrrolidine	Phenyl acetylene	65	63	65	60	70	65	65	60	60	55
2,5-Dimethoxy benzaldehyde	Pyrrolidine	Phenyl acetylene	66	61	62	60	65	60	60	55	65	65
Benzaldehyde	Morpholine	Phenyl acetylene	63	60	65	70	60	60	65	70	60	55
4-Chloro benzaldehyde	Morpholine	Phenyl acetylene	64	61	61	65	60	60	63	65	65	60
2,5-Dimethoxy benzaldehyde	Morpholine	Phenyl acetylene	65	65	62	60	65	60	61	55	60	55

Reaction conditions: ^a1.0 mmol aldehyde, 1.5 mmol amine, 1.5 mmol phenylacetylene, 1 mL toluene, metal catalyst **3a**, **3b**, **4a**, **4b**, **4c** (2.0 mol%), 0.5 hours, 150 °C. ^b1.0 mmol aldehyde, 1.5 mmol amine, 1.5 mmol phenylacetylene, 1 mL water, metal catalyst **3a**, **3b**, **4a**, **4b** or **4c** (2.0 mol%), 0.5 hours, 150 °C. ^c Conversion calculated from the ¹H NMR spectrum of the crude product. ^d Isolated yield after column chromatography.

310.1353. $\tilde{\nu}_{\max}$ (ATR): 1048, 1165, 1320, 1459, 1550, 2244, 2778, 2822, 2941, 3051 cm⁻¹.

Synthesis of 4-(1,3-diphenylprop-2-yn-1-yl)morpholine²⁰: ¹H NMR: δ (400 MHz, CDCl₃) 2.58 - 2.72 (4 H, m), 3.68 - 3.83 (4 H, m), 4.81 (1 H, s) 7.32 - 7.43 (6 H, m), 7.51 - 7.56 (2 H, m), 7.66 (2 H, d, J = 7.3 Hz) ppm. ¹³C NMR: δ (125 MHz, CDCl₃) 49.8, 53.4, 61.9, 87.1, 85.0, 88.4, 122.9, 127.7, 128.1, 128.2, 128.3, 128.8, 131.7, 137.8 ppm. MS: (ES+) [M+H]⁺ 278.2. Accurate Mass: (ES+) [C₁₉H₂₀NO]⁺, [M+H]⁺ requires 278.1539; found 278.1532. $\tilde{\nu}_{\max}$ (ATR): 1159, 1330, 1485, 1581, 2300, 2975, 3045 cm⁻¹.

Synthesis of 1-(1,3-diphenylprop-2-yn-1-yl)piperidine²⁰: ¹H NMR: δ (400 MHz, CDCl₃) 1.41 - 1.50 (2 H, m), 1.55 - 1.66 (4 H, m), 2.58 (4 H, t, J = 5.1 Hz), 4.81 (1 H, s), 7.29 - 7.40 (6 H, m), 7.52 - 7.56 (2 H, m), 7.65 (2 H, d, J = 7.3 Hz) ppm. ¹³C NMR: (125 MHz, CDCl₃) δ ppm 26.2, 50.6, 61.7, 85.4, 88.2, 123.1, 128.2, 128.3, 128.9, 129.8, 131.8, 133.2, 137.4 ppm. MS: (ES+) [M+H]⁺ 276.2. Accurate Mass: (ES+) [C₂₀H₂₂N]⁺, [M+H]⁺ requires 276.1741; found 276.1745. $\tilde{\nu}_{\max}$ (ATR): 1169, 1335, 1429, 1530, 1600, 2254, 2954, 3034 cm⁻¹.

Synthesis of 1-(1,3-diphenylprop-2-yn-1-yl)pyrrolidine²⁰: ¹H NMR: δ (400 MHz, CDCl₃) 1.75 - 1.86 (4 H, m), 2.71 (4 H, t, J = 6.71 Hz), 4.90 (1 H, s), 7.30 - 7.41 (6 H, m), 7.49 - 7.53 (2 H, m), 7.63 (2 H, d, J = 7.8 Hz) ppm. ¹³C NMR: δ (125 MHz, CDCl₃) 23.1, 49.9, 58.8, 86.3, 86.5, 122.9, 127.2, 127.7, 127.9, 128.0, 131.4, 139.2 ppm. MS: (ES+) m/z [M+H]⁺ 262.2. Accurate Mass: (ES+) [C₁₉H₂₀N]⁺, [M+H]⁺ requires 262.1590 found 262.1585. $\tilde{\nu}_{\max}$ (ATR): 1165, 1330, 1415, 1525, 1625, 2274, 2685, 2800, 2960, 3044 cm⁻¹.

Cif files for **3a** (CCDC 1542954), **4a** (CCDC 1542952) and **4b** (CCDC 1542953) have also been deposited with the CCDC and be obtained, free of charge, via www.ccdc.cam.ac.uk/data_request/cif

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Keywords: A³-reaction • Alkyne • Aldehyde • Propargylamine • S3N ligand • Microwave

- [1] (a) A. C. Boukis, B. Monney, M. A. R. Meier, *Beilstein J. Org. Chem.* **2017**, *13*, 54-62; (b) O. Prakash, H. Joshi, U. Kumar, A. Sharma, A. K. Singh, *Dalton Trans.* **2015**, *44*, 1962-1968; (c) J. Zhu, H. Bienayme, *Multicomponent reactions*, Eds., Wiley-WCH, Weinheim, **2006**; (d) J. Paul, M. Presset, E. Le Gall, *Eur. J. Org. Chem.* **2017**, DOI:10.1002/ejoc.201700038; (e) S. S. Bhojgude, A. Bhunia, A. T. Biju, *Acc. Chem. Res.* **2016**, *49*, 1658-1670; (f) H. Pellissier, *Adv. Synth. Catal.* **2016**, *358*, 2194-2259; (g) T. Kaur, P. Wadhwa, S. Bagchi, A. Sharma, *Chem. Commun.* **2016**, *52*, 6958-6976; (h) D. Urabe, *Chem.*

Pharm. Bull. **2015**, *63*, 565-572; (i) M. H. Elnagdi, M. S. Moustafa, S. M. Al-Mousawi, R. A. Mekheimer, K. U. Sadek, *Mol. Divers.* **2015**, *19*, 625-651; P. Bai, Y.-Q. Li, Z.-Z. Huang, *Org. Lett.* **2017**, *19*, 1374-1377; R. Lei Y. Wu, S. Dong, K. Jia, S. Liu, W. Hu, J. *Org. Chem.* **2017**, *82*, 2862-2869; L. A. Wessjohann, O. Kreye, D. G. Rivera, *Angew. Chem. Int. Ed.* **2017**, *56*, 3501-3505; M. Leonardi, M. Villacampa, J. C. Menéndez, *J. Org. Chem.* **2017**, *82*, 2570-2578; H. M. Seifert, K. R. Trejo, E. V. Anslyn, *J. Am. Chem. Soc.* **2016**, *138*, 10916-10924.

- [2] (a) J. B. Bariwal, D. S. Ermolat'ev, E. V. Van der Eycken, *Chem. Eur. J.* **2010**, *16*, 3281-3284; (b) H.-B. Chen, Y. Zhao, Y. Liao, *RSC Adv.* **2015**, *5*, 37737-37741; (c) G. S. Kauffman, G. D. Harris, R. L. Dorow, B. R. P. Stone, R. L. Parsons Jr., J. A. Pesti, N. A. Mangus, J. M. Fortunak, P. N. Confalone, W. A. Nugent, *Org. Lett.* **2000**, *2*, 3119-3121; (d) B. Jiang, M. Xu, *Angew. Chem. Int. Ed.* **2004**, *43*, 2543-2546; (e) G. Abbiata, E. Rossi, *Beilstein J. Org. Chem.* **2014**, *10*, 481-513.

- [3] (a) V. A. Peshov O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790-3807; (b) X. Liu, B. Lin, Z. Zhang, H. Lei, Y. Li, *RSC Adv.* **2016**, *6*, 94399-94407; (c) Y. Cai, X. Tang, S. Ma, *Chem. Eur. J.* **2016**, *22*, 2266-2269; (d) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, *9*, 1472-1483; (e) C.-J. Li, *Acc. Chem. Res.* **2010**, *43*, 581-587; (f) C. Zhao, D. Seidal, *J. Am. Chem. Soc.*, **2015**, *137*, 4650-4653; (g) J. Cao, G. Xu, P. Li, M. Tao, W. Zhang, *ACS Sustainable Chem. Eng.* **2017**, DOI: 10.1021/acssuschemeng.7b00103; (h) B. V. Rokade, P. J. Guiry, *ACS Catal.* **2017**, *7*, 2334-2338 and references therein; (i) see A. Grirrane, E. Álvarez, H. García, A. Corma, *Chem. Eur. J.* **2017**, *23*, 2792-2801 and references cited therein.

- [4] (a) R. C. Carmona, E. P. Wendler, G. H. Sakae, J. V. Comassetto, A. A. D. Santos, *J. Braz. Chem. Soc.*, **2015**, *26*, 117-123. (b) M. J. Albaladejo, F. Alonso, Y. Moglie, M. Yus., *Eur. J. Org. Chem.*, **2012**, 3093-3104. (c) W.-J. Yoo, L. Zhao, C.-J. Li, *J. Aldrichimica Acta*, **2011**, *44*, 43-51; (c) A. A. Nechaev, A. A. Peshkov, K. Van Hecke, V. A. Peshkov, E. V. Van der Eycken, *Eur. J. Org. Chem.* **2017**, 1063-1069; (e) X. Li, B. Lin, Z. Zhang, H. Lei, Y. Li, *RSC Adv.* **2016**, *6*, 94339-94407.

- [5] (a) H.-B. Chen, Y. Zhao, Y. Liao, *RSC Adv.*, **2015**, *5*, 37737-37741. (b) R. P. Herrera, W. M. Lopez, *Multicomponent reactions: Concept and applications for design and synthesis*, Wiley-WCH, **2015**, 187-192. (c) P. Li, Y. Zhang, L. Wang, *Chem. Eur. J.*, **2009**, 2045-2049. (d) M.-T. Chen, B. Landers, O. Navarro, *Org. Biomol. Chem.* **2012**, *10*, 2206-2208. (e) D.-C. N. Gommerrmann, K. Christopher, P. Kurt, K. Paul, *Angew. Chem. Int.* **2003**, *42*, 5763-5766. (f) Y. Zhang, P. Li, M. Wang, L. Wang, *J. Org. Chem.* **2009**, *74*, 4346-4367.

- [6] (a) W. Fan, W. Yuan, S. Ma, *Nature Commun.* **2014**, *5*, 1-9. (b) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638-5639. (c) S. Sakaguchi, T. Mizuta, M. Furuwan, T. Kubo, Y. Ishii, *Chem. Commun.* **2004**, 1638-1644.

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- [7] (a) G. A. Price, A. K. Brisdon, S. Randall, E. Lewis, D. M. Whittaker, R. G. Pritchard, C. A. Muryn, K. R. Flower, P. Quayle, *J. Organomet. Chem.* **2017**, *846*, 251-262; (b) G. A. Price, A. K. Brisdon, K. R. Flower, R. G. Pritchard, P. Quayle, *Tetrahedron Lett.* **2014**, *55*, 151-154. (c) G. A. Price, A. K. Brisdon, K. R. Flower, R. G. Pritchard, P. Quayle, *Dalton Trans.* **2011**, *40*, 11696-11697.
- [8] (a) Y.-J. Choi, H.-Y. Jang, *Eur. J. Org. Chem.* **2016**, 3047-3050; (b) S. Samai, G. C. Nandi, M. S. Singh, *Tetrahedron Lett.*, **2010**, *51*, 5555-5558; (c) K. Namitharan, K. Pitchumani, *Eur. J. Org. Chem.* **2010**, 411-415; (d) A. L. Gajengi, T. Sasaki, B. M. Bhanage, *Catal. Commun.* **2015**, *72*, 174-179.
- [9] (a) S. Frindy, A. E. Kadib, M. Lahcini, A. Primo, H. Garcia, *Catal. Sci. Technol.* **2016**, *6*, 4306-4317; (b) M.-T. Chen, O. Navarro, *Synlett* **2013**, *24*, 1190-1192. (c) S. Wang, X. He, L. Song, Z. Wang, *Synlett* **2009**, *3*, 447-450; (d) Cu nanoparticles: S. Cheng, N. Shang, C. Feng, S. Gao, C. Wang, Z. Wang, *Catal. Commun.* **2017**, *89*, 91-95.
- [10] For recent approaches see: (a) A. GhavamiNejad, A. Kalantarifard, G. S. Yang, C. S. Kim, *Microporous Mesoporous Mater.* **2016**, *225*, 296-302; (b) A. M. Munshi, M. Shi, S. P. Thomas, M. Saunders, M. A. Spackman, K. S. Iyer, N. M. Smith, *Dalton Trans.* **2017**, DOI:10.1039/CDT00058H; (c) A. Elhampour, M. Malmir, E. Kowsari, F. B. Ajdari, F. Memati, *RSC Adv.* **2016**, *6*, 96623-96634; (d) G. Bosica, R. Abdilla, *J. Mol. Catal. A: Chem.* **2017**, *426*, 542-549; (e) P. Li, L. Wang, Y. Zhang, M. Wang, *Tetrahedron Lett.* **2008**, *49*, 6650-6655.
- [11] (a) C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *43*, 4473-4475; (b) P. Zhao, H. Feng, H. Pan, Z. Sun, M. Tong, *Org. Chem. Front.* **2017**, *4*, 37-41; (c) H. Feng, P. Zhao, L. Huang, Z. Sun, M. Tong, *Asian J. Org. Chem.* **2017**, *6*, 161-164 and references therein; (d) T. Pedrazzini, P. Pirovano, M. Dell'Acqua, F. Ragaini, P. Illiano, P. Macchi, G. Abbiati, A. Caselli, *Eur. J. Inorg. Chem.* **2015**, 5089-5098; (e) M. Trose, M. Dell'Acqua, T. Pedrazzini, V. Pirovano, E. Gallo, E. Rossi, A. Caselli, G. Abbiati, *J. Org. Chem.* **2014**, *79*, 7311-7320; (f) G. Tseberlidis, M. Dell'Acqua, D. Valcarengi, E. Gallo, E. Rossi, G. Abbiati, A. Caselli, *RSC Adv.* **2016**, *6*, 97404-97419; (g) D. Li, X. Dai, X. Zhang, H. Zhuo, Y. Jiang, Y.-B. Yu, P. Zhang, X. Huang, H. Wang, *J. Catal.* **2017**, *348*, 276-281.
- [12] (a) O. K. Rasheed, P. D. Bailey, A. Lawernce, P. Quayle, J. Raftery, *Eur. J. Org. Chem.* **2015**, 6988-6993; (b) O. K. Rasheed, A. Lawrence, P. Quayle, P. D. Bailey, *Synlett* **2016**, *27*, 905-911; (c) O. K. Rasheed, J. J. W. McDouall, C. Muryn, J. Raftery, I. J. Vitorica-Yrezabal and P. Quayle, *Dalton Trans.* **2017**, *46*, 5229-5239; (d) H. Masuda, T. Sugimori, T. Kohzuma, A. Odani, O. Yamauchi, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 786-793; (e) E. Lee, S. S. Lee, *Inorg. Chem.* **2011**, *50*, 5803-5807.
- [13] For the use of silver complexes containing sulphur and selenium ligands in the promotion of A³-reactions see: K. N. Sharma, A. K. Sharma, H. Joshi, A. K. Singh, *ChemistrySelect*, **2016**, *1*, 3573-3579.
- [14] (a) E. Weber, F. Vögtle, *Liebigs Ann. Chem.* **1976**, 891-915; (b) P. J. Reddy, V. Ravichandran, K. K. Chacko, E. Weber, W. Saenger, *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1989**, *C45*, 1871-1874; (c) see O. Heitzsch, K. Gloe, H. Stephan, E. Weber, *Solv. Extr. Ion Exch.* **1994**, *12*, 475-496; (d) H. J. Kim, I.-H. Park, J.-E. Lee, K.-M. Park, S. S. Lee, *Cryst. Growth Des.*, **2014**, *14*, 6269-6281; (e) for a recent example see: M. Huang, J. R. Corbin, N. C. Dolan, C. G. Fry, A. I. Vinokur, I. A. Guzei, J. M. Schomaker, *Inorg. Chem.*, **2017**, *56*, 6725-6733; (f) estimation of molecular weights follows from the treatment developed by Morris *et al.*: R. Evans, Z. Deng, A. K. Rogerson, A. S. McLachlan, J. J. Richards, M. Nilsson, G. A. Morris, *Angew. Chem. Int. Ed.* **2013**, *52*, 3199-3202; (g) for an overview see P. S. Pregosin, *Magn. Res. Chem.* **2017**, *55*, 405-413.
- [15] (a) A. Jouaiti and M. W. Hosseini, *Helvetica Chimica Acta*, **2009**, *92*, 2497-2506; P. Demay-Drouhard, L.-M. Chamoiseau, R. Guillot, C. Policar, H. C. Bertrand, *Eur. J. Org. Chem.* **2017**, 131-137; (b) X.-M. Shi, R. R. Tang, G. L. Gu and K. L. Huang, *Spectrochim. Acta, Part A*, **2009**, *72*, 198-203.
- [16] (a) M. Vetrichelvan, Y.-H. Lai, K. F. Mok, *Dalton Trans.*, **2003**, 295-303; (b) R.-H. wang, M.-C. Hong, W.-P. Su, Y.-C. Liang, R. Cao, Y.-J. Zhao, J.-B. Weng, *Inorganica Chimica Acta*, **2001**, *323*, 139-146; (c) E. Lee, S. S. Lee, *CrystEngComm*, **2013**, *15*, 1814-1818; (d) J. Liu, J. Cui, F. Vilela, J. He, M. Zeller, A. D. Hunter, Z. Xu, *Chem. Commun.*, **2015**, *51*, 12197-1220.
- [17] (a) G. Horvath, C. Rusa, Z. Kontos, J. Gerencser and P. Huszthy, *Syn. Commun.*, **1999**, *29*, 3719-3725. (b) L. Pellegatti, J. Zhang, B. Drahos, S. Villette, F. Suzenet, G. Guillaumet, S. Petoud, E. Tóth, *Chem. Commun.*, **2008**, 6591-6594. (c) B. Karimi, A. Maleki, D. Elhamifar, J. H. Clark, A. J. Hunt, *Chem. Comm.*, **2010**, *46*, 6947-6949. (d) J. Kupai, P. Huszthy, K. Székely, T. Tóth, L. Párkányi, *ARKIVOC*, **2011**, *9*, 77-93.
- [18] For the use of a Cu(I) co-ordination polymer as catalyst in A³-reactions see: N.-X. Zhu, C.-W. Zhao, J. Yang, X.-R. Wang, J.-P. Ma, Y.-B. Dong, *RSC Adv.* **2016**, *6*, 108645-108633.
- [19] For a discussion of the "microwave effect" see: G. B. Dudley, R. Richert, A. E. Stiegman, *Chem. Sci.* **2015**, *6*, 2144-2152.
- [20] N. Gharibpour, M. Abdollahi-Alibeik, A. Moaddeli, *ChemistrySelect* **2017**, *2*, 3137-3146.

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The synthesis of group 10 and 11 metal complexes of 3,6,9-trithia-1-(2,6)-pyridinacyclodecaphane and their use in A^3 -coupling reactions is described.