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RESEARCH ARTICLE

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Silver-catalysed A^3-coupling reactions in phenylacetic acid/alkylamine *N*-oxide eutectic mixture under dielectric heating: An alternative approach to propargylamines

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Abstract

The development of alternative benign reaction conditions to perform multicomponent reactions is an interesting and desirable strategy to increase the sustainability of organic synthesis. In this paper, we report a new version of A^3-coupling MCR for the preparation of differently substituted propargylamines starting from aldehydes, alkynes and amines in an acidic DES as reaction media, under dielectric heating, and in the presence of a tetraaza-macrocyclic silver complex as catalyst. The reaction scope is broad in terms of aldehyde partners. Electron-rich phenylacetylenes are the more reactive alkynes partners, whereas the nature of the amine is the more serious limitation as only secondary cyclic amines are tolerated.

KEYWORDS

A^3-coupling, DES, microwaves, silver catalysis, sustainable approach

1 | INTRODUCTION

Multicomponent approaches[1] allow increasing the sustainability[2] of synthetic processes. The reduction of operational steps allows to save time and energy, avoid the purification of intermediates and limit the solvents consumption. Catalysis represents another powerful tool in support of sustainability, mainly by the reduction of reaction times and energy consumption and the increase of efficiency in terms of reaction yields. As support, microwave-assisted organic synthesis (MAOS) contribute to accelerate reaction rate under milder reaction conditions with an overall reduction of energy usage and increasing of chemical yields.[3] The common denominator of these strategies is the 'restraint' (of synthetic steps, energy, times, etc.). A different synergic way to approach the problem is the 'replacement' of toxic or dangerous reagents, additives and solvents[4] with more sustainable alternatives. Among eco-friendly solvents, water[5] has a place of honour, but also supercritical carbon dioxide[6] and biomass-derived solvents (e.g. limonene,[7] glycerol,[8] 2-methyloxolane[9]) are suitable candidates. In this context, deep eutectic solvents[10] (DESs) are a modern class of media, useful for different applications, including organic synthesis.[11] The main features of DESs are low melting points, negligible vapour pressures and flammability,

peculiar polarity features, high degree of biodegradability, cheapness, restrained toxicity[12] and favourable reuse and recycling capabilities. A fascinating add value of DESs is that they can act as simple polar solvents ('innocent' DESs), as well as reagents or catalysts ('active' DES).

More used DESs are prepared by blending hydroxylated compounds as hydrogen bonds donors (alcohols, phenols, polyols, carbohydrates, carboxylic[13] and sulfonic[14] acids), with quaternary onium salts (mainly ammonium[15] or phosphonium[16]). The weak intermolecular interactions, mainly H-bonds, occurring between the HBD and the HBA species, as well as between HBD-HBD and HBA-HBA molecules, determine an impossible regular crystal lattice formation, therefore determining liquid formation.[10]

In the last decade, the use of DESs as alternative media for organic transformations has been widely explored.[17] Deep eutectic mixtures proved to be promising sustainable solvents also for metal-catalysed and metal-mediated organic reactions.[18] A recent review demonstrated that these alternative media are also suitable to create the optimal environment for multicomponent reactions.[19] Surprisingly, examples of MCRs involving alkynes in DESs are understated. A representative example was reported in 2014 by Lu and co-workers in the synthesis of imidazo [*1,2-a*]pyridines by $CuFeO_2$@np-catalysed MCR of 2-aminopyridines, aldehydes and terminal alkynes.[20] The authors screened different deep eutectic mixtures and found that the citric acid/DMU (2:3) eutectic mixture at 65°C for 6–14 h gave the best results. The transition metal-catalysed three-component coupling between an aldehyde, an amine and an alkyne[21] (so-called A^3-coupling), is a worthy approach to propargylamines, recurrent moieties in biologically active compounds and useful intermediates for the preparation of a plethora of cyclic and linear nitrogen-containing molecules. Starting from the groundbreaking papers of Dax[22] and Dyatkin,[23] the metal catalysts more frequently used in this MCR are copper(I) salts and complexes.[24] Also, the activity of the other coinage metals, that is, silver[25] and gold,[26] have been successfully explored,[27] and less noble metals such as iron,[28] indium,[29] zinc,[30] nickel,[31] cobalt[32] and mercury[33] proved their ability to promote the A^3-coupling MCR. Recently, a copper-catalysed version of this reaction in the choline chloride/urea eutectic mixture was reported by Tavakol and Abtahi.[34] In this work, the authors tested the reactivity of several different alkyl and (hetero)aryl aldehydes, whereas the assortment of alkynes and amines was very limited. Based on our recent experience in MW-promoted/silver-catalysed multicomponent synthesis of propargylamines[35] and the use of acidic DESs as alternative media for the MW-enhanced synthesis of 3,4-fused 2-pyranones,[36] we were intrigued to explore the scope and limitation of Ag-catalysed/MW-promoted A^3-coupling in our acidic DESs (Figure 1). Based on our experience in the use of complexes of silver with pyridine-containing ligands [PcL] as catalysts for transformations involving alkynes,[37] we planned to test the activity of one of the more active Ag[PcL] complex (Figure 1). In this paper, we describe our findings.

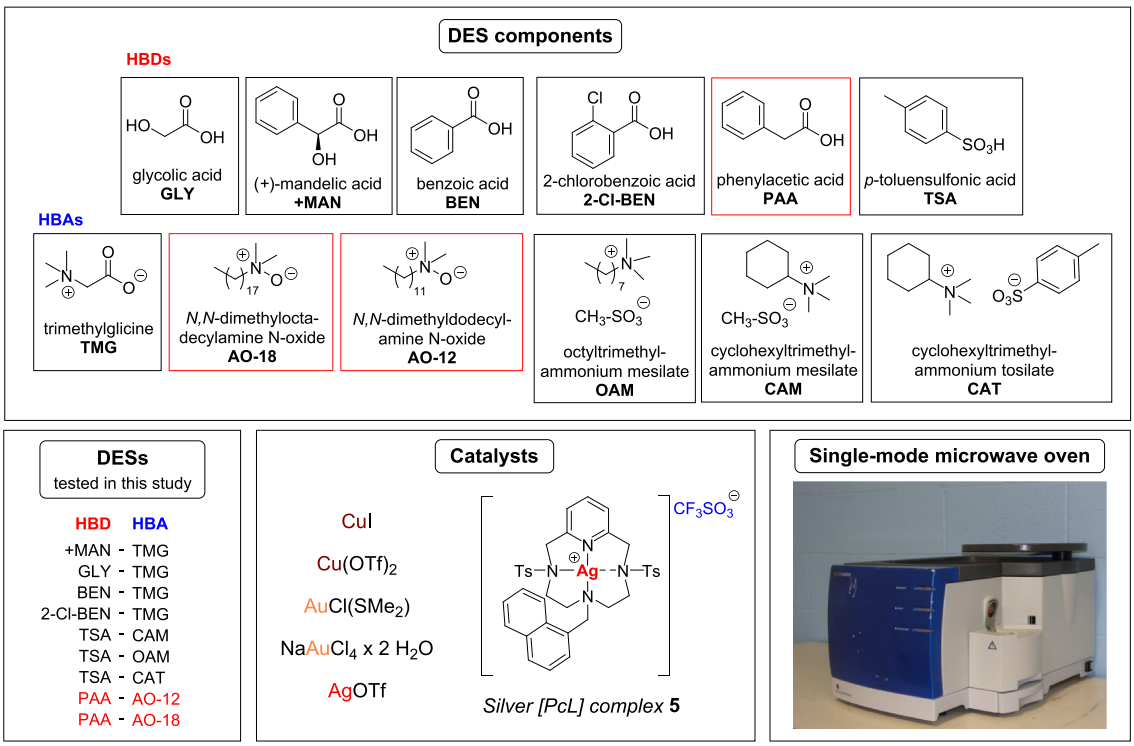


FIGURE 1 Our toolbox

2 | EXPERIMENTAL

All chemicals and conventional solvents are commercially available and were used without further purification. The chromatographic column separations were performed by flash technique using silica gel (pore size 60 Å, particle size 230–400 mesh, Merck Grade 9385). For thin-layer chromatography (TLC), silica on TLC alu foils with a fluorescent indicator (254 nm) was employed, and the detection was performed by irradiation with UV light ($\lambda = 254$ and/or 366 nm). ^{1}H NMR analyses were performed with 300-MHz spectrometers at room temperature. ^{13}C NMR analyses were performed with the same instruments at 75 MHz; the APT sequence was used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. All ^{13}C NMR spectra were recorded with complete proton decoupling. Low-resolution MS spectra were recorded with an electrospray/ion trap instrument using a syringe pump device to directly inject sample solutions. The values are expressed as a mass–charge ratio, and the relative intensities of the most significant peaks are shown in brackets. Microwave-heated reactions were performed in a single-mode microwave synthesizer Personal Chemistry® 'Emrys Creator'. ^{1}H and ^{13}C NMR spectra af all compounds are reported in Supporting Information.

2.1 | Synthesis of DESs

DESs were prepared following the procedures previously reported.[13b,c,14b] In particular, the DES selected as solvent of choice for this study, that is, PAA/AO-12, was prepared as follows: Equimolar amounts of phenylacetic acid and *N,N*-dimethyldodecylamine *N*-oxide were mixed in a screw-capped vial. The solid mixture was magnetically stirred and heated at 30–50°C for 2 h until a clear colourless liquid was obtained. Then, it was used without further purification.

2.2 | Synthesis of the silver [PcL] complex 5

Silver complex **5** was prepared following the procedures reported in the previous paper.[35]

2.3 | General procedure for the A^3-coupling in DES

The suitable aldehyde (0.66 mmol), alkyne (0.99 mmol) and amine (0.99 mmol) were dissolved in the proper DES (0.5 ml). Ag[PcL] complex **5** (5 mol%, 0.033 mmol) was added. The reaction mixture was heated under stirring at 60°C in a single-mode microwave oven for 6 h (unless otherwise stated). The reaction mixture was diluted with NaOH aq. 0.1 M (25 ml) and extracted with EtOAc (3 × 20 ml). The organic layers were washed with brine (2 × 20 ml) and water (2 × 20 ml), dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure. The reaction crude was purified by flash column chromatography over silica gel.

2.4 | 1-(1,3-Diphenylprop-2-yn-1-yl) pyrrolidine (4a)

Eluent: hexane/EtOAc (97:2) + 1% TEA. Orange oil. Yield: 91 mg (53%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.63–7.58$ (m, 2H), 7.52–7.46 (m, 2H), 7.40–7.27 (m, 6H), 4.88 (s, 1H), 2.69 (pt, $J = 6.8$ Hz, 4H), 1.80 (pt, $J = 6.4$ Hz, 4H). Spectral data are in good agreement with literature values.[38]

2.5 | 1-(1-Phenyl-3-(p-tolyl)prop-2-yn-1-yl)pyrrolidine (4b)

Eluent: hexane/EtOAc (97:2) + 1% TEA. Pale yellow solid. Yield: 90 mg (50%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 7.1$ Hz, 2H), 7.41–7.27 (m, 5H), 7.12 (d, $J = 7.8$ Hz, 2H), 4.87 (s, 1H), 2.68 (pt, $J = 6.5$ Hz, 4H), 2.35 (s, 3H), 1.79 (bs, 4H). Spectral data are in good agreement with literature values.[39]

2.6 | 1-(3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-yl)pyrrolidine (4c)

Eluent: hexane/EtOAc (97:2) + 1% TEA. Pale yellow solid. Yield: 153 mg (80%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 7.0$ Hz, 2H), 7.42 (d, $J = 8.8$ Hz, 2H), 7.39–7.27 (m, 3H), 6.84 (d, $J = 8.8$ Hz, 2H), 4.85 (s, 1H), 3.81 (s, 3H), 2.68 (pt, $J = 6.6$ Hz, 4H), 1.80 (pt, $J = 6.0$ Hz, 4H). Spectral data are in good agreement with literature values.[22]

2.7 | *N,N*-Dimethyl-4-(3-phenyl-3-(pyrrolidin-1-yl)prop-1-yn-1-yl)aniline (4d)

Eluent: hexane/EtOAc (95:5) + 1% TEA. Ivory white solid. Yield: 181 mg (90%). Mp: 72.8–75.5°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$ (d, $J = 7.1$ Hz, 2H), 7.40–

7.27 (m, 5H), 6.64 (d, $J = 8.9$ Hz, 2H), 4.87 (s, 1H), 2.97 (s, 6H), 2.69 (pt, $J = 6.5$ Hz, 4H), 1.81 (pt, $J = 5.8$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0 (C arom.), 140.1 (C arom.), 132.8 (2 × CH arom.), 128.3 (2 × CH arom.), 128.1 (2 × CH arom.), 127.3 (CH arom.), 111.9 (2 × CH arom.), 110.4 (C arom.), 87.6 (Csp), 84.1 (Csp), 59.2 (CH), 50.2 (2 × CH_2), 40.2 (2 × CH_3), 23.5 (2 × CH_2). ESI(+)-MS: m/z(%) = 305.09 (35) $[MH]^+$, 234.28 (100) [M-pyrrolidine]$^+$.

2.8 | 1-(3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-yl)pyrrolidine (4e)

Eluent: hexane/EtOAc (97:2) + 1% TEA. White solid. Yield: 61 mg (31%). Mp: 48.4–51.6°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, $J = 7.0$ Hz, 2H), 7.45–7.26 (m, 7H), 4.86 (s, 1H), 2.68 (pt, $J = 6.5$ Hz, 4H), 1.88–1.72 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.4 (C arom.), 134.1 (C arom.), 133.0 (2 × CH arom.), 128.5 (2 × CH arom.), 128.2 (2 × CH arom.), 128.2 (2 × CH arom.), 127.6 (CH arom.), 121.7 (C arom.), 88.0 (Csp), 85.7 (Csp), 59.2 (CH), 50.3 (2 × CH_2), 23.5 (2 × CH_2). ESI(+)-MS: m/z (%) = 298.06 (32) [MH ^{37}Cl]$^+$, 296.07 (100) [MH ^{35}Cl]$^+$.

2.9 | 1-(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-yl) pyrrolidine (4i)

Eluent: hexane/EtOAc (97:2) + 1% TEA. Brown oil. Yield: 95 mg (44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, $J = 8.3$ Hz, 2H), 7.41 (d, $J = 8.9$ Hz, 2H), 7.32 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.9$ Hz, 2H), 4.86 (s, 1H), 3.81 (s, 3H), 2.67 (pt, $J = 7.0$ Hz, 4H), 1.79 (pt, $J = 6.4$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C arom.), 138.3 (C arom.), 133.2 (C arom.), 133.1 (2 × CH arom.), 129.6 (2 × CH arom.), 128.3 (2 × CH arom.), 115.1 (C arom.), 113.9 (2 × CH arom.), 87.1 (Csp), 84.4 (Csp), 58.4 (CH), 55.3 (CH_3), 50.1 (2 × CH_2), 23.5 (2 × CH_2). ESI(+)-MS: m/z(%) = 328.05 (26) [MH ^{37}Cl]$^+$, 326.02 (100) [MH ^{35}Cl]$^+$, 255.26 (65) [M - pyrrolidine]$^+$.

2.10 | 1-(1-(3-Methoxyphenyl)-3-(4-methoxyphenyl)prop-2-yn-1-yl) pyrrolidine (4j)

Eluent: hexane/EtOAc (95:5) + 1% TEA. Orange oil. Yield: 106 mg (50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, $J = 8.9$ Hz, 2H), 7.27 (t, $J = 8.0$ Hz, 1H), 7.19 (m, 2H), 6.88 (m, 3H), 4.81 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.68 (pt, $J = 7.5$ Hz, 4H), 1.79 (pt, $J = 5.1$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C arom.), 159.4 (C arom.), 141.4 (C arom.), 133.1 (2 × CH arom.), 129.1 (CH arom.), 120.7 (CH arom.), 115.4 (C arom.), 113.9 (2 × CH arom.), 113.0 (CH arom.), 86.6 (Csp), 85.2 (Csp), 59.2 (CH), 55.25 (CH_3), 55.24 (CH_3), 50.3 (2 × CH_2), 23.5 (2 × CH_2), one CH arom obscured. ESI(+)-MS: m/z(%) = 321.97 (100) $[MH]^+$.

2.11 | 1-(1-(4-Methoxyphenyl)-4-methylpent-1-yn-3-yl)pyrrolidine (4k)

Eluent: hexane/EtOAc (9:1) + 1% TEA. Yellow oil. Yield: 118 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, $J = 8.8$ Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 3.23 (d, $J = 7.8$ Hz, 1H), 2.77–2.59 (m, 4H), 1.97–1.82 (m, 1H), 1.79 (m, 4H), 1.10 (d, $J = 6.6$, 3H), 1.04 (d, $J = 6.6$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2 (C arom.), 133.0 (2 × CH arom.), 115.8 (C arom.), 113.8 (2 × CH arom.), 86.1 (Csp), 85.3 (Csp), 62.6 (CH), 55.2 (CH), 50.4 (2 × CH_2), 31.9 (CH_3), 23.5 (2 × CH_2), 20.2 (CH_3), 19.4 (CH_3). ESI(+)-MS: m/z(%) = 258.12 (100) $[MH]^+$, 187.16 (68) [M - pyrrolidine]$^+$.

2.12 | 4-(3-(4-Chlorophenyl)-3-(pyrrolidin-1-yl)prop-1-yn-1-yl)-*N*,*N*-dimethylaniline (4l)

Eluent: hexane/EtOAc (9:1) + 1% TEA. Orange solid. Yield: 150 mg (67%). Mp: 67.1–69.3°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 9.0$ Hz, 2H), 7.31 (d, $J = 8.5$ Hz, 2H), 6.64 (d, $J = 9.0$ Hz, 2H), 4.85 (s, 1H), 2.97 (s, 6H), 2.66 (m, 4H), 1.79 (pt, $J = 6.5$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1 (C arom.), 138.7 (C arom.), 133.0 (C arom.), 132.8 (2 × CH arom.), 129.6 (2 × CH arom.), 128.2 (2 × CH arom.), 111.8 (2 × CH arom.), 110.0 (C arom.), 88.1 (Csp), 83.4 (Csp), 58.5 (CH), 50.0 (2 × CH_2), 40.2 (2 × CH_3), 23.5 (2 × CH_2). ESI(+)-MS: m/z(%) = 339.53 (30) $[MH]^+$, 268.39 (100) [M-pyrrolidine]$^+$. Spectral data are in good agreement with literature values.[40]

2.13 | 4-(3-(3-Methoxyphenyl)-3-(pyrrolidin-1-yl)prop-1-yn-1-yl)-*N*,*N*-dimethylaniline (4m)

Eluent: hexane/EtOAc (9:1) + 1% TEA. Orange solid. Yield: 158 mg (72%). Mp: 59.0–60.8°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, $J = 8.9$ Hz, 2H), 7.30–7.16 (m, 3H), 6.85–6.80 (m, 1H), 6.63 (d, $J = 9.0$ Hz, 2H), 4.83 (s, 1H), 3.83 (s, 3H), 2.97 (s, 6H), 2.69 (m, 4H), 1.79

(m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C arom.), 150.0 (C arom.), 141.8 (C arom.), 132.8 (2 × CH arom.), 129.0 (CH arom.), 120.7 (CH arom.), 113.8 (CH arom.), 113.0 (CH arom.), 111.8 (2 × CH arom.), 110.3 (C arom.), 87.5 (Csp), 84.1 (Csp), 59.3 (CH), 55.2 (OCH_3), 50.3 (2 × CH_2), 40.2 (2 × CH_3), 23.5 (2 × CH_2). ESI(+)-MS: m/z(%) = 598.57 (100) [2 × M-pyrrolidine]$^+$, 335.40 (15) [MH]$^+$, 264.41 (35) [M - pyrrolidine]$^+$.

2.14 | *N,N*-Dimethyl-4-(4-methyl-3-(pyrrolidin-1-yl)pent-1-yn-1-yl)aniline (4n)

Eluent: hexane/EtOAc (95:5) + 1% TEA. Yellow solid. Yield: 122 mg (68%). Mp: 48.3–50.5°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 3.23 (d, *J* = 7.8 Hz, 1H), 2.95 (s, 6H), 2.77–2.59 (m, 4H), 1.95–1.81 (m, 1H), 1.81–1.75 (m, 4H), 1.10 (d, J = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.8 (C arom.), 132.6 (2 × CH arom.), 111.9 (2 × CH arom.), 111.0 (C arom.), 86.1 (Csp), 85.1 (Csp), 62.7 (CH), 50.3 (2 × CH_2), 40.3 (2 × CH_3), 32.0 (CH), 23.6 (2 × CH_2), 20.2 (CH_3), 19.4 (CH_3). ESI(+)-MS: m/z(%) = 270.93 (100) [MH]$^+$, 200.15 (57) [M-pyrrolidine]$^+$.

2.15 | *N,N*-Dimethyl-4-(3-(pyrrolidin-1-yl)-3-(thiophen-2-yl)prop-1-yn-1-yl)aniline (4o)

Eluent: hexane/EtOAc (9:1) + 1% TEA. Brown oil. Yield 31 mg (15%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.8 Hz, 2H), 7.29–7.17 (m, 2H), 6.96 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 2H), 5.18 (s, 1H), 2.97 (s, 6H), 2.76 (m, 4H), 1.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1 (C arom.), 144.9 (C arom.), 132.8 (2 × CH arom.), 126.1 (CH arom.), 125.3 (CH arom.), 125.1 (CH arom.), 111.8 (2 × CH arom.), 109.8 (C arom.), 87.2 (Csp), 83.2 (Csp), 54.5 (CH), 49.7 (2 × CH_2), 40.3 (2 × CH_3), 23.6 (2 × CH_2). ESI(+)-MS: m/z(%) = 550.43 (100) [2 × M - pyrrolidine]$^+$, 311.48 (40) [MH]$^+$, 240.30 (77) [M-pyrrolidine]$^+$.

2.16 | 1-(3-(4-Methoxyphenyl)-1-(thiophen-2-yl)prop-2-yn-1-yl)pyrrolidine (4p)

Eluent: hexane/EtOAc (9:1) + 1% TEA. Brown oil. Yield: 20 mg (10%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.8 Hz, 2H), 7.26 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.19 (s, 1H), 3.81 (s, 3H), 2.77 (m, 4H), 1.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C arom.), 144.2 (C arom.), 133.2 (2 × CH arom.), 126.2 (CH arom.), 125.5 (CH arom.), 125.2 (CH arom.), 115.0 (C arom.), 113.9 (2 × CH arom.), 86.3 (Csp), 84.2 (Csp), 55.3 (CH or CH_3), 54.3 (CH or CH_3), 49.8 (2 × CH_2), 23.6 (2 × CH_2). ESI(+)-MS: m/z(%) = 297.98 (70) [MH]$^+$, 227.24 (25) [M-pyrrolidine]$^+$.

2.17 | *N,N*-Dimethyl-4-(3-phenyl-3-(piperidin-1-yl)prop-1-yn-1-yl)aniline (4t)

Eluent: hexane/EtOAc (95:5) + 1% TEA. Orange solid. Yield: 69 mg (33%). Mp: 73.2–74.8°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.3 Hz, 2H), 7.43–7.24 (m, 5H), 6.66 (d, *J* = 8.9 Hz, 2H), 4.78 (s, 1H), 2.98 (s, 6H), 2.56 (t, *J* = 5.3 Hz, 4H), 1.60 (h, *J* = 5.3 Hz, 4H), 1.45 1.45 (q, *J* = 5.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0 (C arom.), 139.2 (C arom.), 132.8 (2 × CH arom.), 128.6 (2 × CH arom.), 127.9 (2 × CH arom.), 127.2 (CH arom.), 112.0 (2 × CH arom.), 110.5 (C arom.), 88.5 (Csp), 83.5 (Csp), 62.5 (CH), 50.7 (2 × CH_2), 40.3 (2 × CH_3), 26.2 (2 × CH_2), 24.5 (CH_2). ESI(+)-MS: m/z(%) = 319.33 (20) [MH]$^+$, 234.33 (100) [M-piperidine]$^+$.

2.18 | 4-(3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-yl)morpholine (4u)

Eluent: hexane/EtOAc (9:1) + 1% TEA. Ivory white solid. Yield: 12 mg (6%). Mp: 78.5–81.4°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.1 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.34 (m, 3H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.77 (s, 1H), 3.82 (s, 3H), 3.77–3.67 (m, 4H), 2.63 (pt, *J* = 4.2 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5 (C arom.), 138.0 (C arom.), 133.2 (2 × CH arom.), 128.6 (2 × CH arom.), 128.2 (2 × CH arom.), 127.7 (CH arom.), 115.1 (C arom.), 113.9 (2 × CH arom.), 88.3 (Csp), 83.5 (Csp), 67.1 (2 × CH_2), 62.1 (CH), 55.3 (CH_3), 49.9 (2 × CH_2). ESI (+)-MS: m/z(%) = 307.99 (73) [MH]$^+$, 221.21 (100) [M-morpholine]$^+$.

2.19 | 4-(3-(Diethylamino)-3-phenylprop-1-yn-1-yl)-*N,N*-dimethylaniline (4v)

Eluent: hexane/EtOAc (97:2) + 1% TEA. Orange oil. Yield: 35 mg (17%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.7 Hz, 2H), 7.43–7.27 (m, 5H), 6.66 (d, *J* = 9.0 Hz, 2H), 5.05 (s, 1H), 2.98 (s, 6H), 2.61 (qd, *J* = 12.7, 7.1 Hz, 4H), 1.09 (t, *J* = 7.1 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0 (C arom.), 140.5

(C arom.), 132.7 (2 × CH arom.), 128.4 (2 × CH arom.), 127.9 (2 × CH arom.), 127.0 (CH arom.), 111.9 (2 × CH arom.), 110.6 (C arom.), 88.1 (Csp), 83.4 (Csp), 57.2 (CH), 44.6 (2 × CH_2), 40.3 (2 × CH_3), 13.6 (2 × CH_3). ESI (+)-MS: m/z(%) = 307.10 (17) $[MH]^+$, 234.19 (100) [M-diethylamine]$^+$.

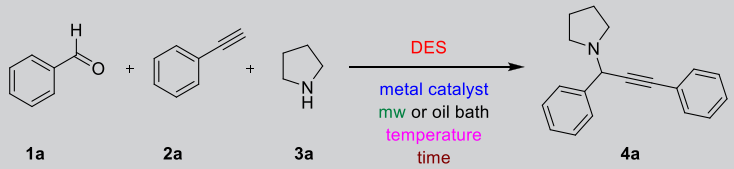
2.20 | 1-(3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-yl)piperidine (4w)

Reaction time: 18 h. Eluent: hexane/EtOAc (95:5) + 1% TEA. Yellow solid. Yield: 65 mg (32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, J = 7.3 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.33 (dt, J = 14.9, 7.0 Hz, 3H), 6.85 (d, J = 8.8 Hz, 2H), 4.77 (s, 1H), 3.81 (s, 3H), 2.55 (t, J = 5.1 Hz, 4H), 1.60 (dt, J = 10.5, 5.4 Hz, 4H), 1.44 (d, J = 5.4 Hz, 2H). Spectral data are in good agreement with literature values.[22]

3 | RESULTS AND DISCUSSION

The screening of the most favourable reaction conditions was done using the coupling among benzaldehyde (**1a**), phenylacetylene (**2a**) and pyrrolidine (**3a**) as a model

TABLE 1 Screening of the optimal reaction conditions (selected entries)



Entry	DES	Catalyst	Cat. loading	Heating	T (°C)	*t* (h)	4a (yield %)[a]
1	+MAN/TMG[13b]	AgOTf	5 mol%	Oil bath	100	3 to 24	-[b]
2	GLY/TMG[13b]	AgOTf	5 mol%	Oil bath	100	3 to 24	-[b]
3	BEN/TMG[13b]	AgOTf	5 mol%	Oil bath	100	3	-[b]
4	2-Cl-BEN/TMG[13b]	AgOTf	5 mol%	Oil bath	100	24	-[b]
5	TSA/CAM[14b]	AgOTf	5 mol%	Oil bath	100	24	-[b]
6	TSA/OAM[14b]	AgOTf	5 mol%	Oil bath	100	24	-[b]
7	TSA/CAT[14b]	AgOTf	5 mol%	Oil bath	100	24	-[b]
8	PAA/AO-12[13c]	AgOTf	5 mol%	Oil bath	100	6	17
9	PAA/AO-18[13c]	AgOTf	5 mol%	Oil bath	100	6	29
10	PAA/AO-18	AgOTf	5 mol%	MW	60	6	31
11	PAA/AO-18	CuI	5 mol%	MW	60	6	33
12	PAA/AO-18	Cu $(OTf)_2$	5 mol%	MW	60	6	28
13	PAA/AO-18	AuCl (SMe_2)	5 mol%	MW	60	6	12
14	PAA/AO-18	$NaAuCl_4 \cdot 2\ H_2O$	5 mol%	MW	60	6	9
15	PAA/AO-18	**5**	5 mol%	MW	60	6	40
16	PAA/AO-18	**5**	3 mol%	MW	60	6	27
17	PAA/AO-18	**5**	1 mol%	MW	60	6	19
18	PAA/AO-18	**5**	5 mol%	MW	70	6	28
19	PAA/AO-18	**5**	5 mol%	MW	80	3	19
20	**PAA/AO-12**	**5**	**5 mol%**	**MW**	**60**	**6**	**53**
21	PAA/AO-12	**5**	3 mol%	MW	60	6	23
22	PAA/AO-12	**5**	5 mol%	MW	70	6	46
23	PAA/AO-12	-	-	MW	60	6	-[b]

[a]Referred to pure isolated product.
[b]TLC analysis display the presence of unreacted starting materials.

reaction. The reactions were conducted in 0.66 mmol scale using the ratio among reagents, more frequently reported in the literature for A^3-couplings (i.e. ratio aldehyde/amine/alkyne = 1: 1.5: 1.5) in 0.5 ml of different acidic DESs and in the presence of a metal salt or complex as a catalyst.

The effects of different reaction times, temperatures, catalyst loading and energy sources were also evaluated. The results of the more representative tests made are reported in Table 1.

We started the study by heating the reaction mixture at 100°C with an oil bath in the presence of 5 mol% of silver triflate. Under these typical reaction conditions, among the different DESs tested (Table 1, Entries 1–9), only PAA/AO-18 and PAA/AO-12 gave the desired product **4a**, although in modest yields (Table 1, Entries 8 and 9). The TLC analysis displayed a dirty reaction crude with some spots, maybe arising from side reactions and partial decomposition of the *N*-oxide component of the DES. To overcome this problem, we reduced the reaction temperature to 60°C and shifted to a more efficient energy source as dielectric heating, achieving a comparable yield (31%) in the same reaction time (Table 1, Entry 10). Taking in mind that also the other coinage metals are suitable catalysts for the A^3-coupling, we tested two copper salts (Table 1, Entries 11 and 12) and two gold salts (Table 1, Entries 13 and 14). Gold salts gave scarce results, whereas copper catalysts gave yields comparable with silver ones, but the reaction crudes were dirtier, and the formation of the by-product arising from the Glaser-type homocoupling[41] of the alkyne was observed. When we tested the silver PcL complex **5** (Figure 1) already successfully used in our previous work on A^3-coupling[35] (Table 1, Entry 15), we were pleased to observe an increase of yield up to 40% in a cleaner reaction crude. A reduction of catalyst loading was detrimental (Table 1, Entries 16 and 17) as well as an increase of reaction temperature (Table 1, Entries 18 and 19). In particular, higher temperatures resulted in dirtier reaction crudes. Moreover, the use of PAA/AO-12 DES allowed a further jump of yield to 53% (Table 1, Entry 20), whereas also in this medium, reduction of the catalyst amount and increase of the reaction temperature gave worse results (Table 1, Entries 21 and 22). Finally, a control experiment in the absence of the silver complex demonstrated the need for the metal catalyst (Table 1, Entry 23).

The scope and limitations of the approach were then explored by changing the nature of the terminal alkyne, the aldehyde and the amine. The propargylamines obtained are depicted in Figures 2–4.

Differently substituted terminal alkyne partners are well tolerated. In particular, the reaction works well and gave the desired products in very good yields in the presence of neutral or electron-rich phenylacetylene derivatives (Figure 2, **4a–4d**). On the contrary, the reaction with electron-poor phenylacetylenes gave modest yields (Figure 2, **4e**) and when the electron-withdrawing group is very strong, the reaction failed (Figure 2, **4f**). Overall, under the standard conditions, the reactivity of phenylacetylene derivatives seems to be strongly correlated to the electronic properties of the substituent. A bit surprisingly, the reactions with electron-rich aliphatic alkynes failed (Figure 2, **4g** and **4h**). As already observed in a recent paper,[42] we cannot exclude that the hydrogen of the terminal alkyne is involved in the H-bond network of the DES. This involvement will be different in function of the acidity of the alkyne, which is determined by the substitution on the other side of the triple bond.

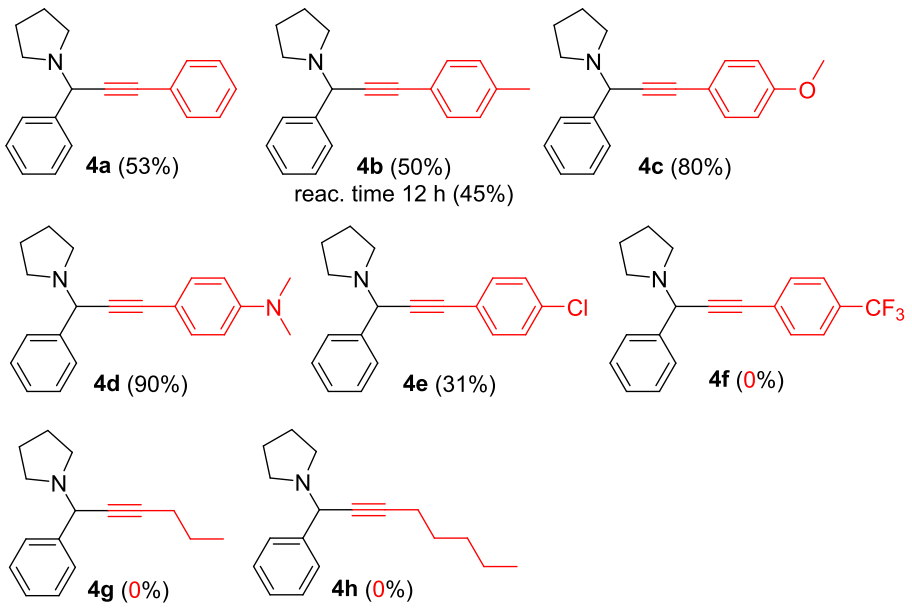


FIGURE 2 Scope and limitation on alkyne partner

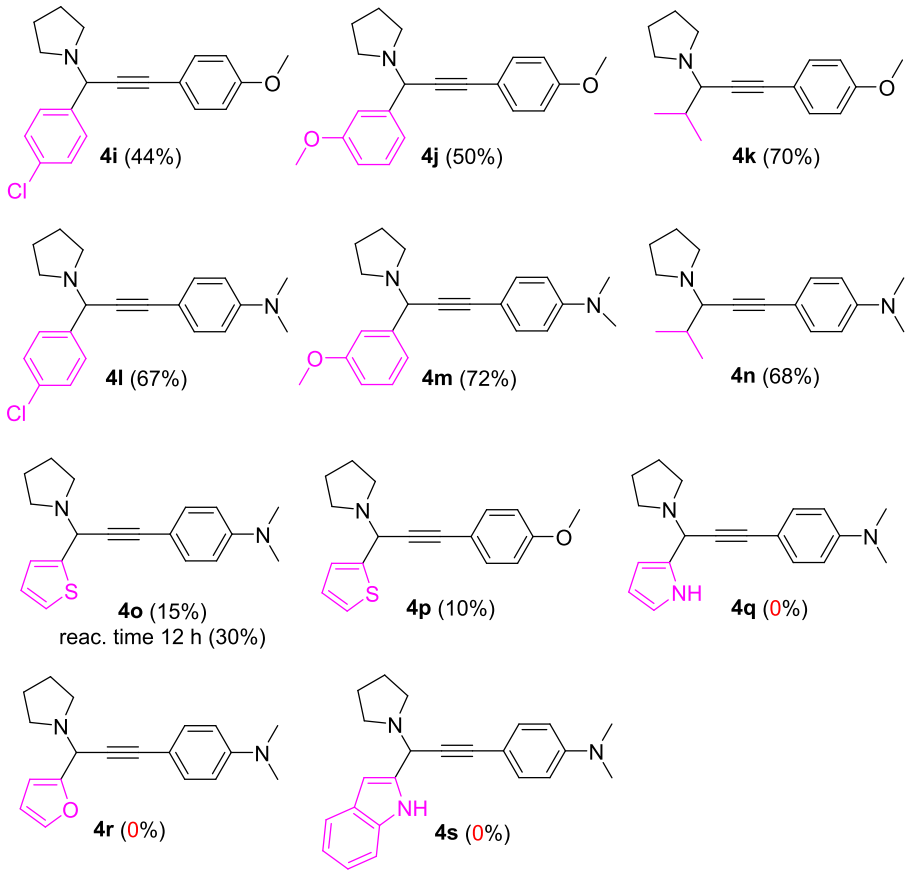


FIGURE 3 Scope and limitation on aldehyde partner

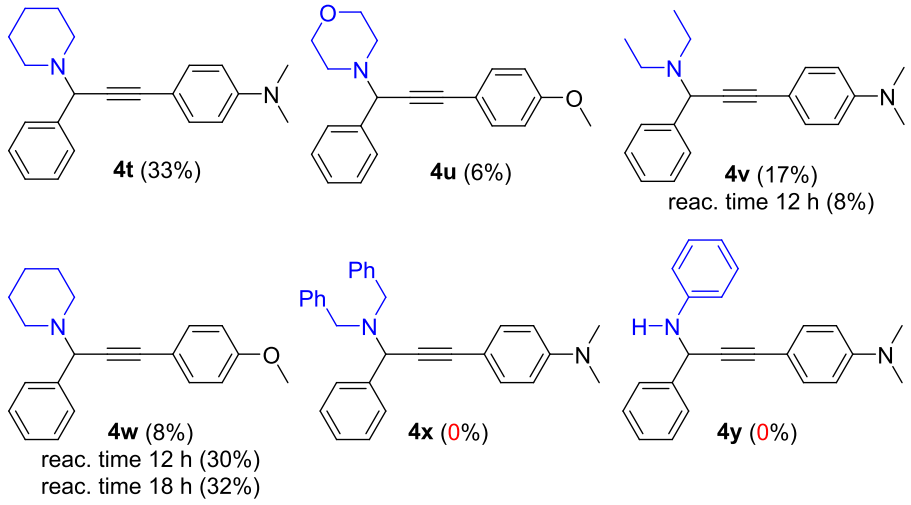


FIGURE 4 Scope and limitation on amine partner

This complex network interaction could impact the coordination of the silver complex to the triple bond.

Despite the presence of electron-withdrawing or electron-donating groups on the phenyl ring and their position, substituted benzaldehyde derivatives are responsive partners for this reaction with yields ranging from 44 to 72% (Figure 3, **4i**, **4j**, **4l** and **4m**). Also aliphatic aldehydes are well-tolerated giving to the desired product in good yields (Figure 3, **4k** and **4n**). On the other hand, heteroaromatic carbaldehydes were demonstrated to be problematic substrates. Only thiophene-2-carbaldehyde gave the corresponding propargylamines in poor yields (see **4o** and **4p**), and a prolonged reaction time is required, whereas the reaction of pyrrole-, furan- and indole-2-carbaldehydes failed (see **4q–4s**). We think that the problem with these heterocyclic aldehydes could be related to the presence of a nitrogen or oxygen heteroatom (H-bond donor/

acceptors) close to the aldehyde group. These atoms are probably involved in the intricate H-bond network of the DES, and this could in somewhat manner hamper the formation of the iminium ion by reaction with the secondary amine.

Finally, we tested the role of the amine. The nature of the amine demonstrated to be the most critical parameter. All replacement of pyrrolidine gave invariably worse results. Piperidine (Figure 4, **4t** and **4w**) gave the corresponding propargylamines in modest yields, and in some cases, a prolonged reaction time was required to improve a bit the yields (Figure 4, **4w**). Diethylamine and morpholine are poorly reactive (Figure 4, **4u** and **4v**), whereas the reactions with dibenzylamine and aniline failed (Figure 4, **4x** and **4y**).

4 | CONCLUSIONS

In conclusion, we have developed a novel version of A^3-coupling MCR in an innovative and environmentally benign acidic DES as reaction media, under microwave heating, and catalysed by an original tetraaza-macrocyclic silver complex. In comparison with the previous recent example of Cu-catalysed A^3-coupling in a choline chloride/urea DES, this study explored more in depth the scope of alkynes and amines reaction partners. Although the yields were not always excellent, the scope was broad in terms of aldehydes partner as both aromatic and aliphatic aldehydes were well tolerated. Regarding alkyne partners, electron-rich phenylacetylenes are well tolerated, whereas the presence of EWG group on the phenyl ring of phenylacetylenes or unsubstituted aliphatic alkynes hampered the reaction. The nature of the amine demonstrated to be critical, and only some secondary cyclic amines gave good results, whereas acyclic secondary amines and anilines gave worse yields or do not react at all. The activity of our original silver(I) [PcL] complex demonstrated to be superior to simple copper, silver and gold salts, and dielectric heating allowed a reduction of the reaction temperature to complete the frame of optimal reaction conditions, also in view to increase the sustainability of the approach. Taking into account the importance of the enantioselective version of this transformation—the so-called AA^3-coupling[43]—and the pivotal example of enantioselective activation catalysed by a chiral Brønsted acid,[44] future efforts will be devoted to testing the activity of the recently developed chiral DESs[45] characterized by the presence of an optically active acidic component as chiral auxiliary able to induce stereoselectivity to this noteworthy MCR.

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AUTHOR CONTRIBUTIONS

Elisa Brambilla: Data curation; investigation. **Alison Bortolla:** Data curation; investigation. **Valentina Pirovano:** Data curation; investigation. **Alessandro Caselli:** Investigation; methodology. **Matteo Tiecco:** Investigation; methodology. **Giorgio Abbiati:** Conceptualization; funding acquisition; methodology; supervision.

CONFLICT OF INTEREST

All authors declared that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available in article supplementary material

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