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Unprecedented cooperative DBU-$CuCl_2$ catalysis for the incorporation of carbon dioxide into homopropargylic amines leading to 6-methylene-1,3-oxazin-2-ones

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ABSTRACT

We report the first example of cooperative catalysis by DBU and $CuCl_2$, which allows the carboxylation of homopropargylic amines to high value added 6-methylene-1,3-oxazin-2-ones. This reaction also represents the first efficient method for the catalytic incorporation of CO_2 into an acyclic substrate to give oxazinones. DFT calculations are in agreement with a mechanism involving: a) deprotonation of the substrate by DBU; b) CO_2 capture with formation of a copper carbamate; c) 6-*exo-dig* cyclization through intramolecular triple bond insertion; and d) protonolysis, with regeneration of DBU and $CuCl_2$ catalysts. The structure of a representative product has been confirmed by XDR analysis.

1. Introduction

The catalytic conversion of carbon dioxide into high valueadded products represents one of the major goals of current organic synthesis. The growing interest in using inexpensive and largely available CO_2 for the direct formation of functionalized molecules, heterocyclic derivatives in particular, is testified by the number of reviews dedicated to this topic in recent years [1].

In this work, we have studied the possibility to catalytically incorporate CO_2 into homopropargylic amines **1** under catalytic conditions, in order to achieve a convenient and high value added synthesis of 6-methylene-1,3-oxazin-2-ones **2** (Scheme 1). In fact, a process like this would lead to heterocycles of particular interest [2] starting from very simple building blocks [3]. Previous synthetic approaches to these heterocyclic derivatives include the Au/Ag-catalyzed 6-*endo-dig* cyclization [4] and iodocyclization [5] of homopropargylic carbamates; the Au/Ag-catalyzed cyclization of (buta-2,3-dien-1-yl)carbamates [6]; the basic treatment of 6-(halomethyl)-1,3-oxazin-2-ones [7]; and the acidic treatment of 6-[(trimethylsilyl)methyl)-3,4-dihydro-2*H*-1,3-oxazin-2-ones [8]. However, to the best of our knowledge, the formation of 6-methylene-1,3-oxazin-2-ones by direct carboxylation of acyclic substrates with CO_2 has never been efficiently realized before. The only examples reported in the literature involve the Pd-catalyzed carboxylation of *N*-benzylbut-3-yn-1-amine and *N*-benzylpent-4-yn-2-amine, which led to the corresponding oxazinones in low spectroscopic yields (36 and 37%, respectively; only the first one could be isolated at the pure state in 30% yield from the reaction mixture) [9] and the Ag-promoted carboxylation of buta-2,3-dien-1-amines, which consistently afforded a mixture of products where the oxazinones byproducts were present only in traces (0–6%) [10].

2. Methods

2.1. General experimental methods

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC–MS apparatus at 70 eV ionization voltage. All reactions were analyzed by TLC on silica gel 60 F_{254} or on neutral alumina and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase Column chromatography was performed on silica gel 60 (70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure. Mass spectra were obtained using a GC–MS apparatus at 70 eV ionization voltage (normal resolution) and by electrospray ionization mass spectrometry (ESI-MS) (high resolution) with a UHD accurate-mass Q-TOF spectrometer

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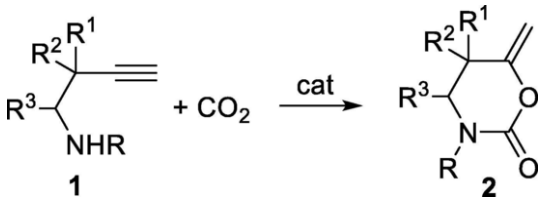


Scheme 1. Work hypothesis: catalytic incorporation of CO_2 into homopropargylic amines for the selective synthesis of 6-methylene-1,3-oxazin-2-ones **2**.

equipped with a Dual AJS ESI source working in positive mode, and were recorded in the 150–1000 *m/z* range. The LC-MS experimental conditions were as follows: N_2 was employed as desolvation gas at 300 °C and a flow rate of 9 L/min. The nebulizer was set to 45 psig. The Sheat gas temperature was set at 350 °C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode. The fragmentor was set to 175 V.

*2.2. Catalytic carboxylation of but-3-yn-1-amines **1** to 1,3-oxazinan-2-ones **2***

A 40 mL stainless steel autoclave was charged with $CuCl_2$ (1.9 mg, 1.41×10^{-2} mmol), DBU (43.0 mg, 2.83×10^{-1} mmol) and a solution of **1** (0.7 mmol; **1a**, 113.1 mg; **1b**, 89.0 mg; **1c**, 121.3 mg; **1d**, 132.1 mg; **1e**, 174.6 mg; **1f**, 122.3 mg; **1g**, 121.9 mg; **1h**, 131.8 mg; **1i**, 131.5 mg; **1j**, 141.3 mg; **1k**, 165.5 mg; **1l**, 185.5 mg; **1m**, 131.5 mg) in CH_3CN (3.5 mL). The autoclave was sealed, purged at room temperature several times with CO_2 with stirring (5 atm), and finally pressurized with CO_2 (40 atm). After being stirred at 100 °C for the required time (8 h for **1a**, **1c** and **1e**; 5 h for **1b** and **1d**; 18 h for **1f**, **1g**, **1h**, **1i** and **1j**; 15 h for **1k** and **1l**; 24 h for **1m**),the autoclave was cooled, degassed and opened. The solvent was evaporated and the products were purified by column chromatography on silica gel using as eluent: 7:3 hexane – AcOEt for **2a**, **2c**, **2f**, **2k** and **2m**; 8:2 hexane – AcOEt for **2b**, **2d**, **2e**, **2g**, **2h**, **2i**, **2j**; pure hexane to 9:1 hexane – AcOEt for **1l**.

*2.2.1. 3-Benzyl-6-methylene-1,3-oxazinan-2-one **2a** (Yield: 117 mg, 82% based on starting **1a**)*

White solid, mp 33–34 °C). IR (KBr): ν = 1718 (s), 1662 (m), 1486 (m), 1444 (m), 1214 (m), 1779 (m), 1115 (m), 715 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.43–7.23 (m, 5H, Ph), 4.66 (s, 1H, =C*H*H), 4.58 (s, 2H, CH_2Ph), 4.24 (s, 1H, =CH*H*), 3.26–3.16 (m, 2H, NCH_2CH_2), 2.54 (t, J = 5.9, 2H, NCH$_2$CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.8, 151.1, 136.2, 128.8, 128.1, 127.9, 92.8, 52.7, 43.2, 26.2; GC–MS (EI, 70 eV): *m/z* = 203 (M^+, 29), 186 (4), 142 (3), 91 (100); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{12}H_{14}NO_2^+$: 204.1019; found, 204.1039. The spectroscopic properies were in good agreement with those reported [6].

*2.2.2. 3-Butyl-6-methylene-1,3-oxazinan-2-one **2b** (Yield: 89 mg, 75% based on starting **1b**)*

Yellow oil. IR (film): ν = 1719 (s), 1664 (s), 1425 (w), 1192 (m), 1090 (w) cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ = 4.62 (s, 1H, =C*H*H), 4.24 (s, 1H, =CH*H*), 3.37 (t, J = 7.5, 2H, NCH_2CH$_2$C=), 3.32 (t, J = 6.3, 2H, CH_2C=), 2.62 (t, J = 6.2, 2H, NCH_2CH$_2$CH$_2$), 1.65–1.51 (m, 2H, NCH$_2$CH_2CH$_2$), 1.34 (hexuplet, J = 7.3, 2H, CH_2CH$_3$), 0.94 (t, J = 7.3, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.9, 150.7, 92.4, 49.5, 44.0, 29.3, 26.3, 19.9, 13.8; GC–MS (EI, 70 eV): *m/z* = 169 (M^+, 14), 140 (16), 126 (100), 112 (21), 84 (36); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_9H_{16}NO_2^+$: 170.1175; found, 170.1161.

*2.2.3. 6-Methylene-3-phenethyl-1,3-oxazinan-2-one **2c** (120 mg, 79% based on starting **1c**)*

White solid, mp 58–59 °C. IR (KBr): ν = 1717 (s), 1452 (m), 1217 (w), 745 (m), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.16 (m, 5H, Ph), 4.62 (s, 1H, =C*H*H), 4.19 (s, 1H, =CH*H*), 3.58 (t, J = 6.8, 2H, NCH$_2$), 3.07 (t, J = 5.4, 2H, NCH$_2$), 2.92 (t, J = 6.8, 2H, NCH$_2$CH_2), 2.51–2.38 (m, 2H, NCH$_2$CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.8, 150.6, 138.6, 128.9, 128.6, 126.7, 92.5, 51.7, 45.0, 33.8, 26.1; GC–MS (EI, 70 eV): *m/z* = 217 (M^+, 34), 126 (65), 104 (100), 91 (87); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{13}H_{16}NO_2^+$: 218.1176; found, 218.1197.

*2.2.4. 6-Methylene-3-(3-phenylpropyl)-1,3-oxazinan-2-one **2d** (Yield: 123 mg, 76% based on starting **1d**)*

Yellow oil. IR (film): ν = 1724 (s), 1663 (m), 1427 (m), 1177 (s), 1111 (m), 752 (m), 702 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.32–7.12 (m, 5H, Ph), 4.61 (s, 1H, =C*H*H), 4.21 (s, 1H, =CH*H*), 3.40 (t, J = 7.4, 2H, NCH$_2$), 3.24 (t, J = 6.1, 2H, NCH$_2$), 2.65 (t, J = 7.7, 2H, CH_2Ph), 2.53 (t, J = 6.1, 2H, CH_2C=), 2.00–1.85 (m, 2H, CH_2CH$_2$Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.8, 150.7, 141.2, 128.4, 128.2, 126.0, 92.5, 49.4, 43.9, 32.9, 28.7, 26.1; GC–MS (EI, 70 eV): *m/z* = 231 (M^+, 11), 188 (55), 127 (51), 118 (29), 117 (39), 91 (100); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{14}H_{18}NO_2^+$: 232.1332; found, 232.1345.

*2.2.5. 3-(2,2-Diphenylethyl)-6-methylene-1,3-oxazinan-2-one **2e** (Yield: 158 mg, 77% based on starting **1e**)*

White solid, mp 143–144 °C. IR (KBr): ν = 1717 (s), 1663 (m), 1481 (w), 1450 (w), 1180 (m), 752 (m), 702 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.16 (m, 10H, aromatic), 4.55 (s, 1H, =C*H*H), 4.48 (t, J = 8.1, 1H, C*H*Ph$_2$), 4.10 (s, 1H, =CH*H*), 3.96 (d, J = 8.1, 2H, NCH$_2$), 2.85 (t, J = 6.1, 2H, NCH_2CH$_2$), 2.20 (t, J = 6.1, 2H, NCH$_2$CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.7, 150.7, 141.7, 128.6, 128.2, 126.9, 92.3, 55.0, 48.8, 45.3, 26.0; GC–MS (EI, 70 eV): *m/z* = 293 (M^+, 17), 223 (5), 180 (100), 167 (71), 126 (61), 103 (15), 82 (31); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{19}H_{20}NO_2^+$: 294.1489; found, 294.1494.

*2.2.6. 6-Methylene-3-(1-phenylethyl)-1,3-oxazinan-2-one **2f** (Yield: 122 mg, 80% based on starting **1f**)*

Colorless oil. IR (film): ν = 1713 (s), 1661 (m), 1422 (m), 1314 (w), 1173 (s), 700 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.41–7.25 (m, 5H, Ph), 5.77 (q, J = 7.1, 1H, C*H*Ph), 4.63 (s, 1H, =C*H*H), 4.20 (s, 1H, =CH*H*), 3.19–3.04 (m, 1H, NC*H*H), 2.90–2.77 (m, 1H, NCH*H*), 2.53–2.33 (m, 2H, NCH$_2$CH_2), 1.56 (d, J = 7.1, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.7, 151.0, 139.3, 128.6, 127.8, 127.3, 92.2, 53.7, 38.0, 26.3, 15.5; GC–MS (EI, 70 eV): *m/z* = 217 (M^+, 5), 188 (1), 151 (1), 105 (100); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{13}H_{16}NO_2^+$: 218.1176; found, 218.1201.

*2.2.7. 3-Benzyl-4-methyl-6-methylene-1,3-oxazinan-2-one **2g** (Yield: 125 mg, 82% based on starting **1g**)*

Colorless oil. IR (film): ν = 1715 (s), 1667 (m), 1445 (w), 1423 (w), 1190 (m), 1128 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.39–7.25 (m, 5H, Ph), 5.07 (dist d, J = 15.2, 1H, PhC*H*H), 4.76 (s, 1H, =C*H*H), 4.26 (s, 1H, =CH*H*), 4.11 (dist d, J = 15.2, 1H, PhCH*H*), 3.52–3.38 (m, 1H, NC*H*Me), 2.59 (dist dd, J = 14.3, 5.5, 1H, C*H*HC=), 2.29 (dist dd, J = 12.3, 2.2, 1H, CH*H*C=), 1.18 (d, J = 6.5, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.11, 151.07, 136.7, 128.8, 127.9, 127.8, 94.3, 50.5, 47.9, 32.9, 18.1; GC–MS (EI, 70 eV): *m/z* = 217 (M^+, 22), 132 (4), 112 (6), 91 (100); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{13}H_{16}NO_2^+$: 218.1176; found, 218.1197.

2.2.8. 4-Methyl-6-methylene-3-phenethyl-1,3-oxazinan-2-one ***2h*** *(Yield: 121 mg, 75% based on starting* ***1h****)*

Yellow solid, mp 52–53 °C. IR (film): ν = 1701 (s), 1663 (s), 1450 (w), 1420 (m), 1217 (w), 1194 (w), 704 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.18 (m, 5H, Ph), 4.71 (s, 1H, =C*H*H), 4.20 (s, 1H, =CH*H*), 3.97–3.84 (m, 1H, NC*H*Me), 3.21–2.83 (m, 4H, C*H*$_2$C*H*$_2$Ph), 2.46 (dist dd, *J* = 14.2, 5.4, 1H, C*H*HC=), 2.16 (dist dd, *J* = 14.2, 1.8, 1H, CH*H*C=), 1.11 (d, *J* = 6.5, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.1, 150.4, 138.8, 128.9, 128.6, 126.6, 94.1, 50.23, 50.19, 34.2, 32.6, 18.6; GC–MS (EI, 70 eV): *m/z* = 231 (M^+, 58), 216 (12), 140 (78), 105 (59), 104 (61), 91 (100); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{14}H_{18}NO_2^+$: 232.1332; found, 232.1359.

2.2.9. 3-Benzyl-4-ethyl-6-methylene-1,3-oxazinan-2-one ***2i*** *(Yield: 131 mg, 81% based on starting* ***1i****)*

Yellow oil. IR (film): ν = 1717 (s), 1663 (m), 1447 (w), 1188 (m), 1128 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.41–7.20 (m, 5H, Ph), 5.15 (dist d, *J* = 15.3, 1H, PhC*H*H), 4.73 (s, 1H, =C*H*H), 4.23 (m, 1H, =CH*H*), 4.06 (dist d, *J* = 15.3, 1H, PhCH*H*), 3.20–3.15 (m, 1H, NC*H*Et), 2.46 (dist d, *J* = 2.9, 2H, CH_2C=), 1.80–1.61 (m, 1H, C*H*HCH$_3$), 1.61–1.40 (m, 1H, CH*H*CH$_3$), 0.87 (t, *J* = 7.4, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.3, 151.2, 136.8, 128.8, 127.9, 127.8, 93.9, 53.7, 51.0, 29.6, 24.7, 10.3; GC–MS (EI, 70 eV): *m/z* = 231 (M^+, 12), 202 (5), 126 (4), 91 (100); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{14}H_{18}NO_2^+$: 232.1332; found, 232.1358.

2.2.10. 4-Ethyl-6-methylene-3-phenethyl-1,3-oxazinan-2-one ***2j*** *(Yield: 131 mg, 76% based on starting* ***1j****)*

Yellow solid, mp 64–65 °C. IR (KBr): ν = 1713 (s), 1661 (m), 1452 (m), 1422 (w), 1219 (m), 1194 (w), 752 (m), 704 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.17 (m, 5H, Ph), 4.67 (s, 1H, =C*H*H), 4.17 (s, 1H, =CH*H*), 4.07–3.95 (m, 1H, NC*H*Et), 3.16–2.75 (m, 4H, C*H*$_2$C*H*$_2$Ph), 2.32 (d, *J* = 3.3, 2H, CH_2C=), 1.69–1.50 (m, 1H, C*H*HCH$_3$), 1.50–1.31 (m, 1H, CH*H*CH$_3$), 0.84 (t, *J* = 7.4, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.3, 150.4, 138.8, 128.9, 128.6, 126.6, 93.7, 56.1, 50.9, 34.1, 29.3, 25.4, 10.3; GC–MS (EI): *m/z* = 245 (M^+, 26), 154 (61), 105 (45), 104 (47), 91 (100); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{15}H_{20}NO_2^+$: 246.1489; found, 246.1517.

2.2.11. 3-Benzyl-6-methylene-4-phenyl-1,3-oxazinan-2-one ***2k*** *(Yield: 153 mg, 78% based on starting* ***1k****)*

White solid, mp 71–72 °C. IR (KBr): ν = 1717 (s), 1663 (m), 1443 (w), 1423 (w), 1196 (m), 1153 (w), 748 (m), 702 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.45–7.10 (m, 10H, aromatic), 5.31 (dist d, *J* = 15.1, 1H, PhC*H*H), 4.70 (s, 1H, =C*H*H), 4.51–4.35 (m, 1H, NC*H*Ph), 4.05 (s, 1H, =CH*H*), 3.67 (dist d, *J* = 15.1, 1H, PhCH*H*), 2.86 (dist dd, *J* = 14.2, 6.2, 1H, C*H*HC=), 2.48 (dist dd, *J* = 14.2, 2.1, 1H, CH*H*C=); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.5, 150.1, 138.7, 136.2, 128.9, 128.8, 128.3, 128.2, 127.9, 126.3, 95.0, 56.0, 50.6, 34.3; GC–MS (EI, 70 eV): *m/z* = 279 (M^+, 15), 146 (13), 104 (100), 91 (48); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{18}H_{18}NO_2^+$: 280.1332; found, 280.1327. The spectroscopic properties were in good agreement with those reported [8].

2.2.12. 3-Benzyl-5,5-dimethyl-6-methylene-4-phenyl-1,3-oxazinan-2-one ***2l*** *(Yield: 144 mg, 67% based on starting* ***1l****)*

White solid, mp 165–166 °C. IR (KBr): ν = 1713 (s), 1659 (m), 1443 (w), 1427 (w), 1211 (m), 1173 (m), 1103 (w), 702 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.42–7.20 (m, 8H, aromatic), 7.20–7.05 (m, 2H, aromatic), 5.28 (dist d, *J* = 14.7, 1H, PhC*H*H), 4.76 (d, *J* = 1.6, 1H, =C*H*H), 4.10 (d, *J* = 1.6, 1H, =CH*H*), 3.73 (s, 1H, NC*H*Ph), 3.48 (dist d, *J* = 14.7, 1H, PhCH*H*), 1.17 (s, 3H, Me), 0.73 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.4, 151.0, 137.1, 136.2, 129.0, 128.7, 128.54, 128.47, 128.0, 127.8, 92.6, 66.9, 50.4, 36.6, 27.3, 22.9; GC–MS (EI, 70 eV): *m/z* = 307 (M^+, 24), 240 (3), 216 (5), 194 (7), 174 (16), 132 (100), 117 (38), 91 (92); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{20}H_{22}NO_2^+$: 308.1645; found, 308.1656.

2.2.13. 4-Methyl-6-methylene-3-(1-phenylethyl)-1,3-oxazinan-2-one ***2m*** *(Mixture of diastereoisomers A + B, A/B ratio ~ 1.3, by ^{1}HNMR; yield: 84 mg, 52% based on starting* ***1m****) Yellow oil*

IR (film): ν = 1711 (s), 1663 (m), 1420 (w), 1184 (m), 1024 (w), 700 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.46–7.25 (m, aromatic, A + B), 5.74 (q, *J* = 7.1, C*H*Ph, B), 5.65 (q, *J* = 7.0, C*H*Ph, A), 4.72 (s, =C*H*H, B), 4.70 (s, =C*H*H, A), 4.18 (s, =CH*H*, A), 4.17 (s, =CH*H*, B), 3.62–3.49 (m, NC*H*Me, A), 3.34–3.20 (m, NC*H*Me, B), 2.63–2.50 (C*H*HC=, A), 2.36–2.20 (CH*H*C=, A, + C*H*HC=, B), 2.13 (dist dd, *J* = 14.4, 2.0, CH*H*C=, B), 1.64 (d, *J* = 7.2, Me, B), 1.59 (d, *J* = 7.1, Me, A), 1.23 (d, *J* = 6.5, Me, B), 0.59 (d, *J* = 6.5, Me, A). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.3 (B), 151.2 (A), 151.1 (B), 150.7 (A), 139.8 (B), 139.5 (A), 128.7 (B), 128.5 (A), 128.1 (A + B), 127.9 (B), 127.3 (A), 93.6 (B), 93.5 (A), 54.7 (A), 54.4 (B), 45.0 (A), 44.4 (B), 34.1 (A), 33.7 (B), 20.6 (B), 19.2 (A), 17.1 (B), 16.1 (A); GC–MS (EI, 70 eV) (A + B): *m/z* = 231 (M^+, 3), 132 (3), 105 (100), 77 (16); HRMS (ESI-TOF) *m/z*: [(M + H)$^+$] cald for $C_{14}H_{18}NO_2^+$: 232.1332; found, 232.1336.

2.3. Catalytic carboxylation of N-benzylbut-3-yn-1-amine ***1a*** *to 3-benzyl-6-methylene-1,3-oxazinan-2-one* ***2a*** *in higher scale*

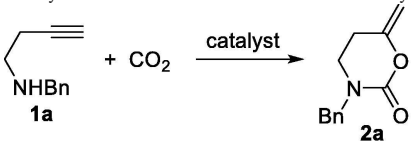
A 300 mL stainless steel autoclave was charged in the presence of air with $CuCl_2$ (8.1 mg, 6.03 × 10^{-2} mmol), DBU (183.2 mg, 1.2 mmol) and a solution of *N*-benzylbut-3-yn-1-amine **1a** (480.5 mg, 3.02 mmol) in CH_3CN (15.1 mL). The autoclave was sealed, purged at room temperature several times with CO_2 with stirring (5 atm), and finally pressurized with CO_2 (40 atm). After being stirred at 100 °C for 8 h, the autoclave was cooled, degassed and opened. The solvent was evaporated, and the product was purified by column chromatography on silica gel using as eluent pure hexane to 7:3 hexane – AcOEt, to give pure 3-benzyl-6-methylene-1,3-oxazinan-2-one **2a** as a colorless solid (Yield: 516 mg, 84% based on starting **1a**).

3. Results and discussion

The first substrate we tested was *N*-benzylbut-3-yn-1-amine **1a**, readily available by amination of commercially available but-3-yn-1ol (see the Supplementary Material for details). This ethynylamine was initially allowed to react with CO_2 (40 atm) at 100 °C in MeCN as the solvent (0.1 mmol of **1a** per mL of MeCN) in the presence of 10 mol% of relatively low expensive 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as strong organobase. After 3 h, no reaction took place (Table 1, entry 1). However, after 24 h the formation of the desired 3-benzyl-6-methylene-1,3-oxazinan-2-one **2a** was observed, albeit in low yield (21%), with a substrate conversion of ca. 30% (Table 1, entry 2). The structure of **2a** was confirmed by XRD analysis (Fig. 1; see the Supplementary Material for details).

This result confirmed the possibility to realize the incorporation of CO_2 into a homopropargylic amine to give a high-value added oxazinone. According to previous studies on superbase-catalyzed CO_2 incorporation into an organic substrate [1], the key intermediate in the formation of **2a** should be the carbamate-DBUH$^+$ species **I** obtained from **1a**, DBU, and CO_2 (Scheme 2). This intermediate could be formed through two different mechanistic routes, shown in Scheme 2. In path *a*, deprotonation of **1a** by DBU would be followed by the attack of anionic nitrogen to CO_2 (possibly activated by the hydrogen bond interaction between oxygen atom and protonated DBU). On the other hand, in path *b*, CO_2 would be attacked by DBU to give the zwitterionic intermediate **II**, followed by the reaction between **II** and **1a** to give **I**. The formation of **II**-type adducts B^+–CO_2^- as key intermediates has

Table 1
Optimization of the reactions conditions for the catalytic carboxylation of *N*-benzyl-but-3-yn-1-amine **1a** into 3-benzyl-6-methylene-1,3-oxazinan-2-one.[a]



entry	DBU (mol%)	$CuCl_2$ (mol%)	Concentration of **1a**[b]	Time (h)	Conversion (%) of **1a**[c]	Yield (%) of **2a**[d]
1	10	0	0.1	3	0	0
2	10	0	0.1	24	30	21
3	10	2	0.1	3	58	48
4	10	2	0.1	5	67	56
5	20	2	0.1	5	85	72
6[e]	20	2	0.1	5	63	29
7	20	2	0.05	5	72	51
8	20	2	0.2	5	89	76
9	20	2	0.2	8	90	77
10[f]	20	2	0.2	15	97	74
11	40	2	0.2	5	90	78
12	40	2	0.2	8	100	84
13	40	0	0.2	5	<1	Traces
14	0	2	0.2	5	0	0
15	0	0	0.2	5	0	0

[a] Unless otherwise noted, all reactions were carried out in MeCN at 100 °C under 40 atm (at 25 °C) of CO_2.
[b] Mmol of **1a** per mL of solvent.
[c] Based on isolated unreacted **1a**.
[d] Isolated yield based on starting **1a**.
[e] The reaction was carried out in dioxane.
[f] The reaction was carried out at 80 °C.

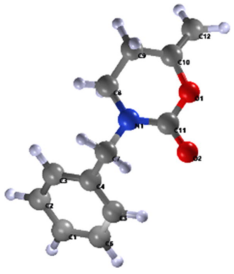


Fig. 1. X-ray structure for 3-benzyl-6-methylene-1,3-oxazinan-2-one **2a** showing the atom labelling scheme for non-H atoms.

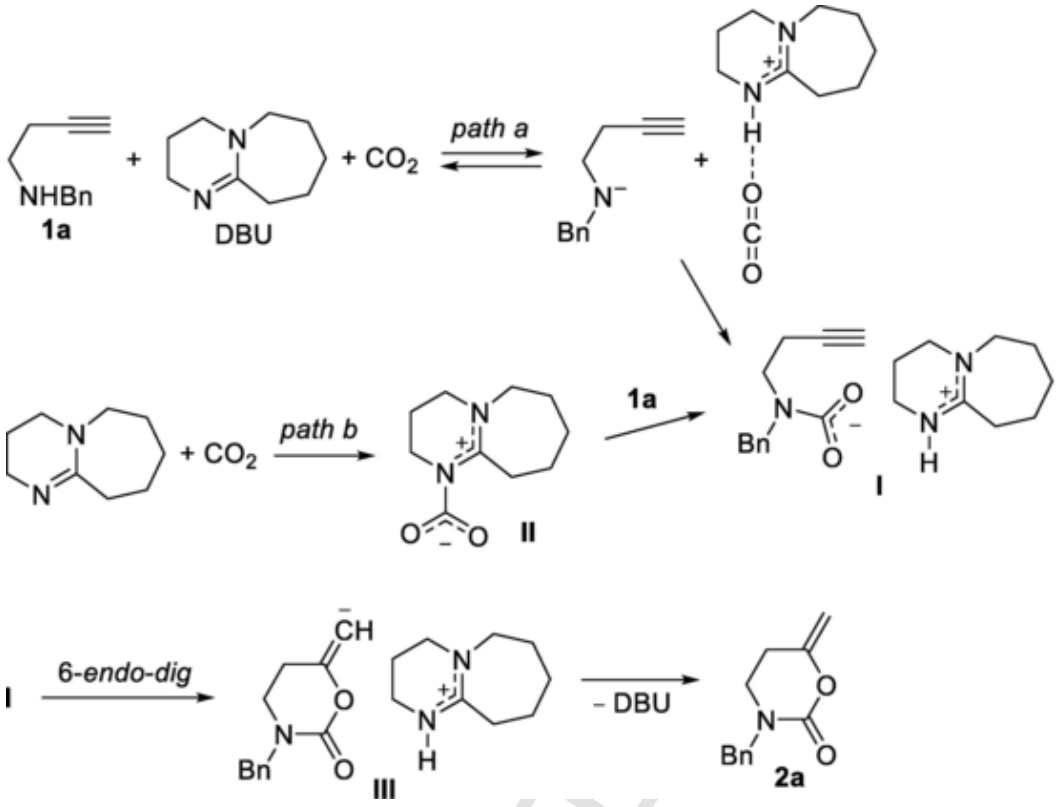
been widely proposed in different CO_2 fixation processes carried out in the presence of an organic superbase B [1]. Allegedly, this has been ascribed to a supposed electrophilic activation of carbon with respect to free CO_2 [1]. However, recent DFT calculations have actually shown that this is not the case [11]. In particular, the net positive charge of carbon in the TBD^+–CO_2^- adduct (TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene) was calculated to be + 0.96, in contrast to the carbon in CO_2 (+1.05), and a thorough theoretical investigation on the TBD-promoted carboxylation of 2-alkynylindoles tended to exclude the involvement of the TBD^+–CO_2^- adduct as intermediate in the process [11a]. In light of these results, path *b* in our reaction seems a less likely pathway with respect to path *a* for the formation of carbamate-$DBUH^+$ **I**. Once formed, this intermediate would then evolve toward the formation of the oxazinone product **2a** through 6-*exo-dig* intramolecular nucleophilic attack to the triple bond to give species **III** followed by protonation of the carbanion by $DBUH^+$, with regeneration of DBU (Scheme 2).

With the aim of achieving a more efficient carboxylation of **1a** into **2a**, we decided to carry out the reaction in the presence of a metal species able to electrophilically activate the triple bond. Our choice fell on $CuCl_2$, based on its expensiveness and on previous successful examples of $CuCl_2$-catalyzed heterocyclization reactions of suitably functionalized acetylenic substrates [12]. Thus, the same reaction as that reported in Table 1, entry 1, was performed in the presence also of 2 mol% $CuCl_2$. Gratifyingly, under these conditions **2a** was obtained in 48% yield at 56% substrate conversion (Table 1, entry 3), while a 56% yield was observed after 5 h reaction time (Table 1, entry 4). From the comparison between the results obtained in entries 3,4 with those observed in entries 1,2 it should be evident the promoting effect exerted by $CuCl_2$ in the carboxylation of **1a**.

To further improve the result obtained in entries 3,4 of Table 1, we screened some reaction parameters, such as the DBU amount, solvent, temperature, and substrate concentration; the results obtained are shown in Table 1, entries 5–12. As can be seen from the Table, the best results were obtained at 100 °C in MeCN using a higher amount of DBU (40 mol%) and a higher substrate concentration (0.2 mmol of **1a** per mL of MeCN): under these optimized conditions, the yield of **2a** was 77% after 5 h (entry 11) and achieved 84% after 8 h reaction time (entry 12). The catalytic effect by $CuCl_2$ was further confirmed by carrying out the same reaction as that of entry 11 in its absence: no reaction occurred after 5 h (Table 1, entry 13). The same took place when the reaction was performed in the absence of DBU (entry 14) or without any catalysts (entry 15). These results further confirmed the necessity of a synergistic cooperative catalysis (by DBU, able to activate the amino group of the substrate to make it more prone to attack CO_2, and $CuCl_2$, able to favor the heterocyclization step) in order for the process to take place in an efficient manner. To the best of our knowledge, our reaction is the first example of cooperative catalysis by DBU and $CuCl_2$ in synthesis.

The optimized process was then generalized to other differently substituted homopropargylic amines **1b-m**, bearing different substituents on nitrogen and on α and β carbons; the results obtained are shown in Table 2, entries 2–13. The reaction was quite sensitive to steric hindrance, so while substrates **1b-e** (Table 2, entries 2–5) behaved similarly to **1a** (Table 2, entry 1), the presence of either a more sterically demanding group on nitrogen (as in **1f**) or substitution α to nitrogen (as in **1g-l**) led to a slower process; however, very good results could be obtained in all cases after 15–18 h reaction time, with yields of the corresponding oxazinones **2f-l** ranging from 67 to 82% (Table 2, entries 6–12). As expected, a substrate such as **1m** bearing both a bulky group on nitrogen and an α-substituent required a longer time (24 h) and a higher copper loading (20 mol%) to achieve complete conversion, with a yield of the corresponding oxazinone **2m** of 52% (Table 2, entry 13). On the other hand, *N*-(*tert*-butyl)but-3-yn-1-amine **2n**, bearing a very bulky *tert*-butyl group on nitrogen, turned out to be unreactive (Table 2, entry 14).

Considering that, as said above, the role of $CuCl_2$ should be to activate the triple bond by electrophilic coordination, we can propose the mechanism shown in Scheme 3 for the formation of **2** from **1** under the cooperative catalysis of both DBU and $CuCl_2$. Thus, the carbamate-$DBUH^+$ species **IV** is first formed through the mechanistic route shown in Scheme 2, path *a*. This is followed by $CuCl_2$ coordination to give π-complex **V**, which then undergoes 6-*exo-dig* intramolecular nucleophilic attack of the carbamate group to the triple bond coordinated to $CuCl_2$ to give the vinylcopper intermediate **VII**. The cyclization step likely occurs through the formation of a cyclic complex **VI** in which copper is simultaneously coordinated by the chlorine atoms, the triple bond and the carbamate oxygen. A final protonolysis step by $DBUH^+$ then leads to the final oxazinone product, with regeneration of both catalysts DBU and $CuCl_2$ (Scheme 3).



Scheme 2. Possible mechanistic pathways for the formation of 3-benzyl-6-methylene-1,3-oxazinan-2-one **2a** by DBU-catalyzed carboxylation of *N*-benzylbut-3-yn-1-amine **1a**.

The key mechanistic steps in the conversion of **1a** to **2a** have been studied at DFT level using the b3lyp functional and a triple-zeta basis set with polarizable and diffuse functions (see the Supplementary Information for computational details). First, an encounter complex (**ec**) between **1a**, DBU and CO_2 has been considered. The optimized **ec** structure presents the N-H bond in **1a** slightly stretched (1.068 Å) and a bent CO_2 (137°), as shown in Fig. 2. Then a geometry scan has been performed forcing the elongation of the N-H bond, in order to study the proton transfer process. A transition state **ts1** and a minimum energy structure **ca**, corresponding to the carbamate species **IV** of Scheme 3, were found. As can be seen from Fig. 2, the transition vector corresponds to a proton transfer process. It presents a small barrier and is energetically favorable. The formation of the N-CO_2 bond is simultaneous. Protonated DBU is coordinated to the newly formed carboxylate group. It is noteworthy that the reaction barrier (7.39 KJ/mol) is smaller, in absolute value, than the difference in zero-point energies between **ec** and **ts1** (−10.24 KJ/mol). Furthermore, in the proton transfer process the possibility of tunneling needs to be considered. Thus, this can be considered a barrierless reaction and **ec** a metastable structure. The triple bond moiety is practically not involved in this step, as it lies far from the carboxylate. Therefore, it is not surprising that when the carbamate structure is coordinated with $CuCl_2$ the resulting structure **ca-$CuCl_2$** (shown in Fig. 3, and corresponding to intermediate **V** of Scheme 3) is very similar to **ca**.

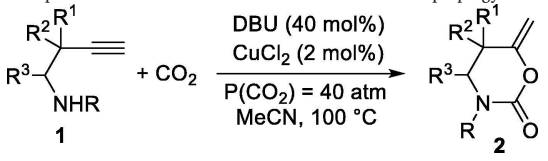
The **ca-$CuCl_2$** structure is the starting point for the second part of the reaction mechanism in which the ring-closure occurs. Two scans, reducing progressively the distance between the carboxylate oxygen atom nearest to the triple bond (labelled O1) and the two carbon atoms involved in the just mentioned functional group, have been performed. For clarity, we label C2 the terminal carbon of the triple bond and C1 the internal one. In the **ca-$CuCl_2$** structure the distances O1-C1 and O1-C2 are 4.16 Å and 5.09 Å, respectively. Both scans lead to a cyclic stable intermediate **ci** (corresponding to intermediate **VI** in Scheme 3) formed from **ca-$CuCl_2$** through the transition state **ts2**. The **ci** structure presents the copper atom coordinated to the two chlorine atoms, to the triple bond and to O1. The two above-mentioned distances are reduced to 3.06 Å (O1-C1) and 3.44 Å (O1-C2), and protonated DBU is hydrogen-bonded to O1. The formation of **ci** is possible only when DBU, CO_2 and $CuCl_2$ interact simultaneously with **1a**. This intermediate presents a large stabilization energy (77.37 KJ/mol) with respect to **ts2**, as its structure is stabilized both by the copper atom coordination and by the hydrogen bond. This explains the simultaneous catalytic promotion by both DBU and $CuCl_2$ (cooperative catalysis).

Intermediate **ci** can be considered as the crossoroad of the reaction mechanism. In fact, from this structure the two scans diverge as the geometric constraints force, respectively, the formation of either the O1-C1 bond (leading to the six-membered intermediate **p6**, corresponding to intermediate **VII** of Scheme 3) or of the O1-C2 bond (leading to a seven-membered intermediate **p7**). These pathways pass through the corresponding transition states **ts3-6** and **ts3-7**, respectively. The six-membered complex **p6**, which eventually leads to the experimentally observed product **2a** upon final protonolysis by $DBUH^+$ (Scheme 3), is clearly favored by a lower barrier and a lower energy, as shown in Fig. 3. It may be noted that, since the benzylic substituent on nitrogen it is not directly involved in any of the studied steps, the results of this computational study can be, at least qualitatively, extended to the other substrates studied in the experimental part of this paper.

4. Conclusions

In conclusion, we have reported the first example of cooperative catalysis by DBU and $CuCl_2$, for the incorporation of carbon dioxide into homopropargylic amines to give oxazinones. While the function of DBU is to deprotonate the substrate and (in its protonated form $DBUH^+$) to electrophilically activate CO_2 (by hydrogen bonding) to yield the key carbamate intermediate, the role of $CuCl_2$ is to favor the intramolecular nucleophilic attack of the carbamate group to the

Table 2
Synthesis of 6-methylene-1,3-oxazin-2-ones **2a-m** by cooperative DBU-$CuCl_2$ catalyzed incorporation of carbon dioxide into homopropargylic amines **1a-m**.[a]



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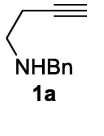
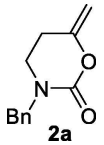
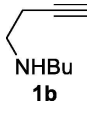
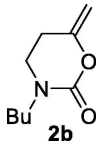
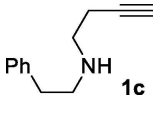
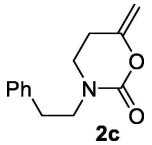
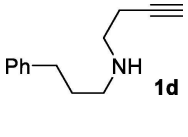
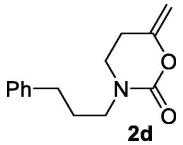
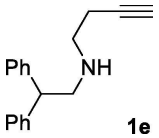
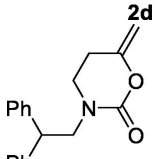
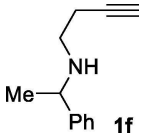
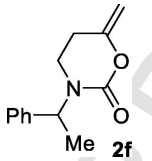
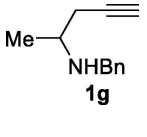
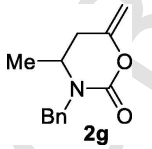
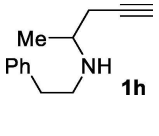
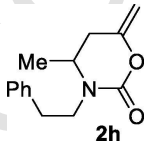
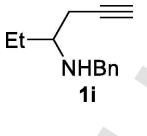
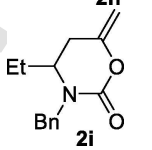
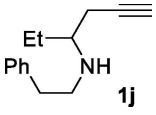
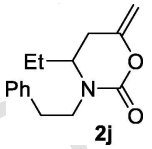
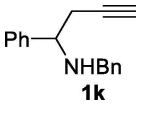
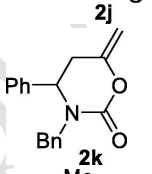
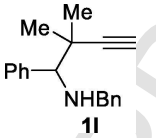
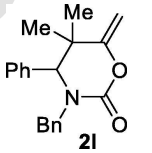
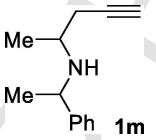
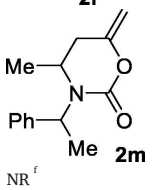
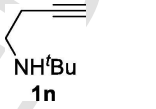
1		8		84
2		5		75
3		8		79
4		5		76
5		8		77
6		18		80
7		18		82
8		18		75
9		18		81

Table 2 (*Continued*)

Entry	1	Time (h)	2	Yield of 2 (%)[b]
10		18		76
11		15		78
12		15		67
13[c,d]		24		52[e]
14		24	NR[f]	

[a] Unless otherwise noted, all reactions were carried out in MeCN (substrate concentration = 0.2 mmol per mL of MeCN) at 100 °C in a stainless steel autoclave under 40 atm of CO_2 (at 25 °C) in the presence of DBU (40 mol%) and $CuCl_2$ (2 mol%).
[b] Isolated yield based on starting **1**. Unless otherwise noted, substrate conversion was quantitative.
[c] The reaction was carried out with 20 mol% of $CuCl_2$.
[d] Substrate **1m** was a mixture of diastereoisomers (ca. 64:36, by ^{1}HNMR).
[e] Product **2m** was a mixture of diastereoisomers (ca. 57:43, by ^{1}HNMR).
[f] NR = no reaction. Substrate conversion was ~0%.

triple bond by coordination. The DFT study confirmed the importance of DBU as basis and as hydrogen-bonded activator and of the copper coordination as activator of the triple bond. The cooperative action of these two catalysts leads to a cyclic intermediate in which copper is simultaneously coordinated by the chlorine atoms, the triple bond and the carbamate oxygen. This complex then evolves to the final product through protonolysis by $DBUH^+$, with regeneration of DBU and $CuCl_2$ catalysts. The geometry and the energetic of the last part of the reaction path show that the six-ring product is strongly favored over the seven-ring one, in agreement with the experimental results.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgement

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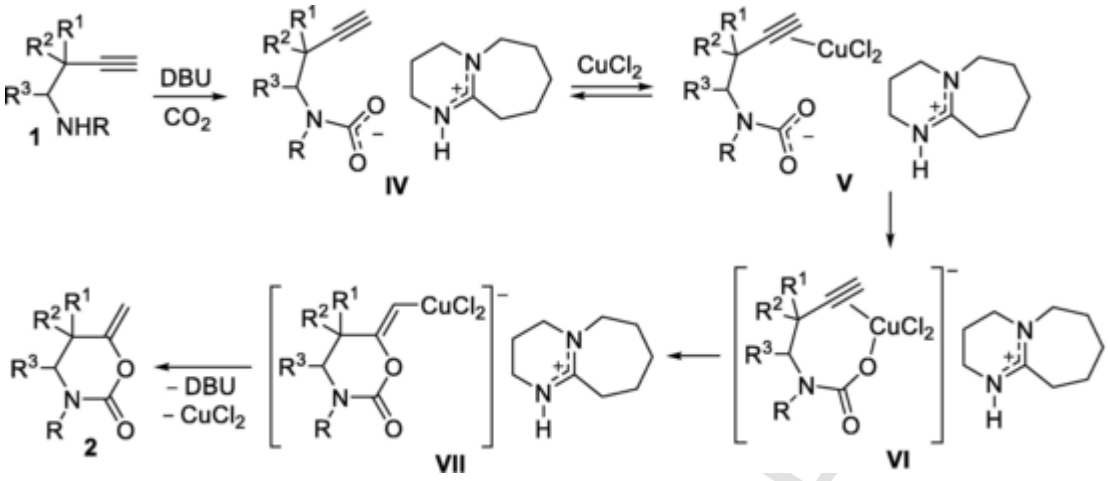
Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2020.03.033.



Scheme 3. Proposed mechanism for the cooperative DBU-$CuCl_2$ catalysis in the carboxylation of **1** to **2**.

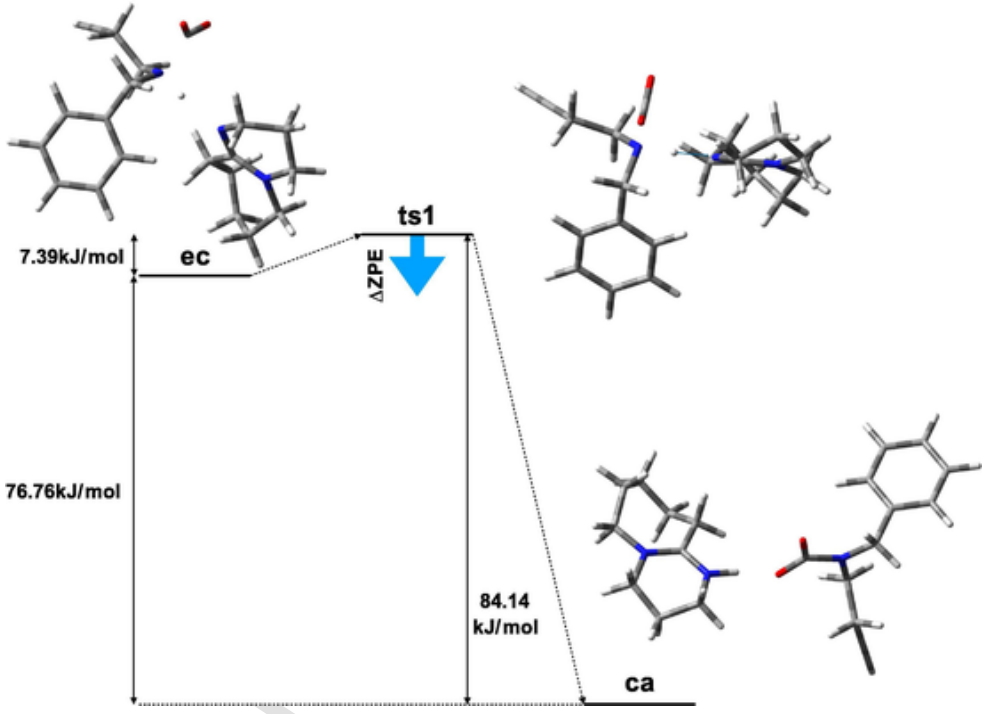


Fig. 2. Structures involved in the proton transfer step of the mechanism. Each structure is nearby its energetic level. The energy differences are in scale. For the **ts1** structure the transition vector is represented by blue arrows (arbitrary scale).

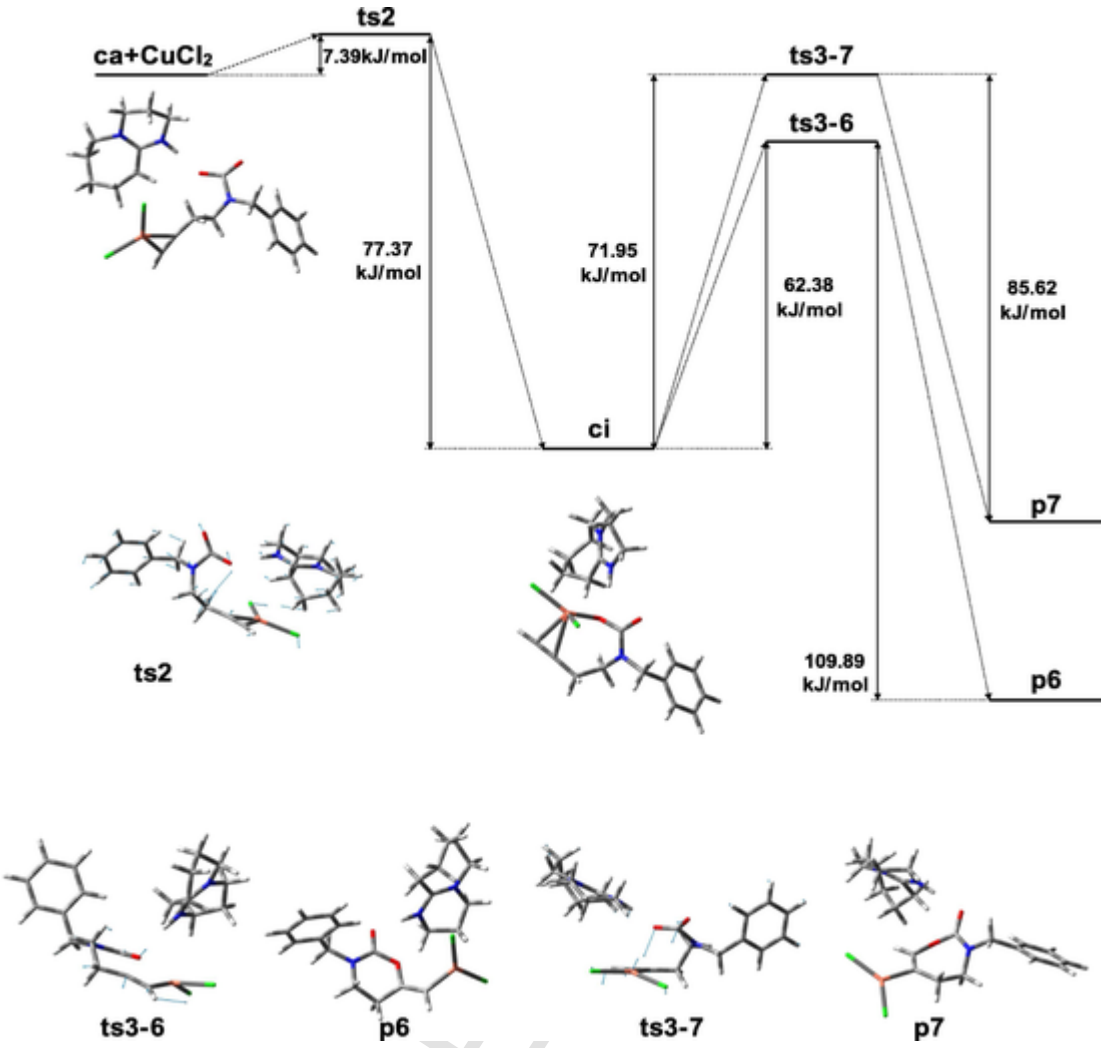


Fig. 3. Structures involved in the ring closure step of the mechanism. When the structures are not nearby their energetic level the label is repeated. The energy differences are in scale. For the transition structures the transition vector is represented by blue arrows (arbitrary scale).

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