Copper(II)-Catalyzed Aminohalogenation of Alkynyl Carbamates

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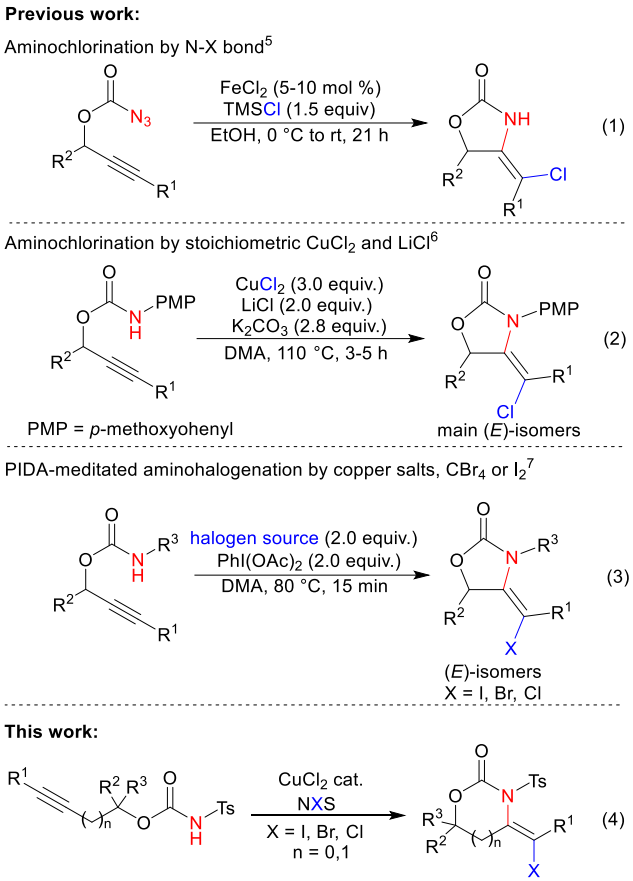
Abstract: A useful aminohalogenation reaction for the cyclization of *O*-alkynyl carbamates under copper catalysis has been developed. *N*-Halosuccinimides have been used as the halogen source. The intramolecular C-N bond formation occurs selectively affording haloalkylidene substituted heterocycles. Just in the case of α,α-cyclohexyl-substituted propargyl carbamate the alkoxyhalogenation pathway was operative. The mechanism for the two alternative reaction pathways was investigated by modelling the corresponding transition states at the DFT level.

Dedication (To prof. Franco Cozzi to celebrate his 70th birthday)

Introduction

The difunctionalization reactions of carbon-carbon multiple bonds are particularly attractive in organic synthesis because they represent an effective tool to increase the efficiency of synthetic procedures.[1] Moreover, they fulfil the concept of environmentally and economically favourable process reducing the number of laboratory operations and the amount of chemicals and solvents needed. The attractiveness for this type of reactions is also remarkable in intramolecular processes as it allows access to cyclic scaffolds starting from easily available substrates. In particular, (poly)functionalized heterocyclic compounds as well as bicyclic ring systems can be achieved with rapid increase in the structural complexity by direct difunctionalization procedures.[2] Among the different achievable combination of new bonds, it is worth noting the importance of the halocyclizations as they provide compounds that are susceptible of further and easy functionalization due to the presence of the halogen in the structure.[3]

Following our interest toward transition metal-catalyzed reactions for the synthesis of functionalized heterocyclic structures,[4] herein we describe a copper-catalyzed procedure for the aminohalogenation of *O*-alkynyl carbamates providing haloalkylidene substituted heterocycles. Some procedures for aminohalogenation processes starting from *O*-propargyl carbamates bearing different nucleophilic pendant are reported in literature. The chloroamination of propargyloxycarbonyl azides was realized with TMSCl under $FeCl_2$ catalysis (Scheme 1, equation 1).[5] Stoichiometric copper chloride was used either to promote the intramolecular amination or as a chlorine source for the chlorocyclization of *O*-propargyl *N*-PMP (Scheme 1, equation 2).[6] Alkynyl carbamates undergo aminohalogenation by treatment with various halogen sources and $PhI(OAc)_2$ as oxidant (Scheme 1, equation 3).[7]

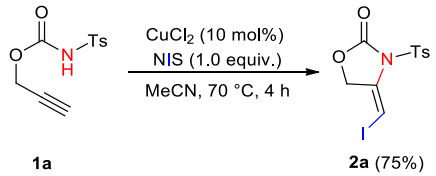


Scheme 1. Synthetic procedures for aminohalogenation of *O*-alkynyl carbamates

Taking as a starting point the reaction conditions that allowed to carry out the cyclization of alkynyl ureas and alkynyl amides through totally selective *exo-dig* alkoxyhalogenation reactions,[8] we investigated the possibility to define general conditions for the halocyclization of alkynyl carbamates based on the use of a catalytic copper salt in the presence of halosuccinimides as the halogen source (Scheme 1, equation 4).

Results and Discussion

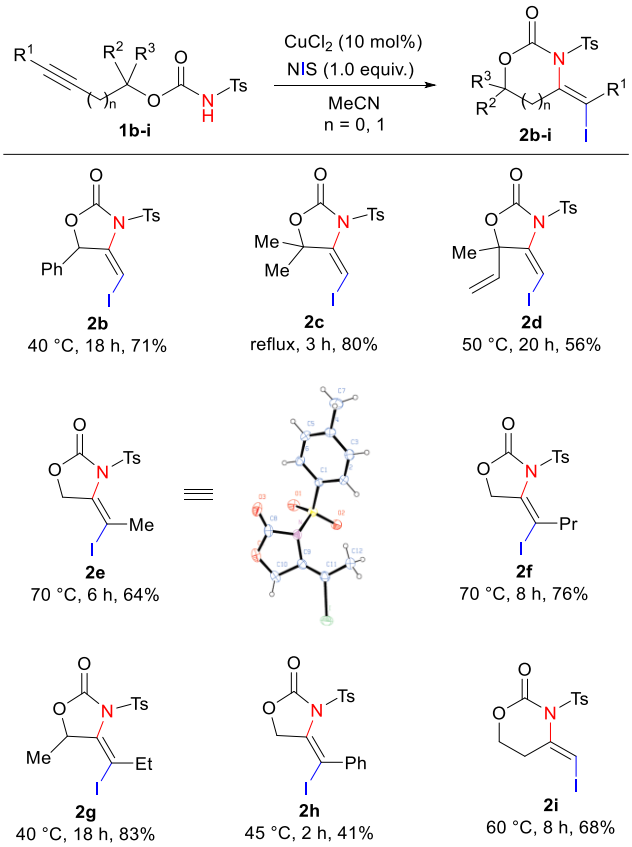
Having in mind a priority for iodo-substituted heterocycles, at first we treated the *O*-propargyl *N*-tosyl carbamate **1a** with catalytic $CuCl_2$ and stoichiometric NIS in acetonitrile. After heating at 70 ° C for 4 h, the 4-iodomethylidene oxazolidinone **2** was obtained in 75% yield, with totally selective *E*-configuration which was determined by NOESY experiments (Scheme 2). The presence of the tosyl protecting group on nitrogen atom was essential. In fact, other differently substituted aryl groups (*p*-nitrophenyl, *p*-methoxyphenyl) didn't give positive results. Changing the solvent with THF, DMF or DCE didn't furnish the product in higher yields.



Scheme 2. Synthetic procedures for the aminoiodination of *O*-alkynyl carbamates

The behavior of some differently substituted carbamates was investigated to determine the scope of the reaction. The iodomethylidene derivatives obtained as well as reaction temperatures and times are collected in Scheme 3. The presence of a phenyl group in the propargyl position does not preclude the aminoiodination process, as evidenced by the formation of compound **2b**, isolated in 71% yield after heating at 40° C for 18 h. Similarly, the α,α-disubstituted propargyl carbamate provided the oxazolidinone **2c** in 80% yield after 3 h at reflux. An alkenyl group does not interfere in the aminoiodination process, as highlighted with the formation of **2d**, isolated in 56% yield. Terminal substituted propargyl substrates also undergo 5-*exo-dig* cyclization/iodination whose efficiency depends on the size of the substituent. Thus oxazolidinones **2e-g** were isolated in 64-83% yield, whereas the phenyl substituted **2h** was obtained in 41% yield. The formation of the 1,3-oxazine derivative **2i**, isolated in

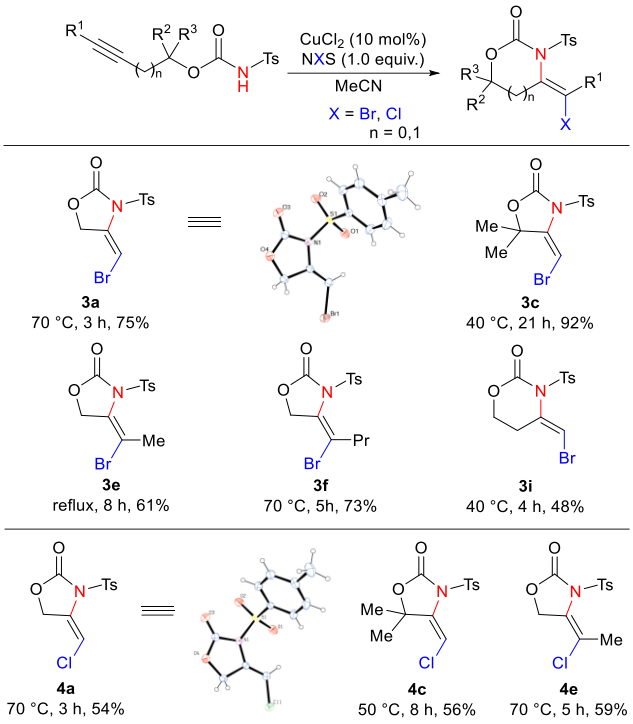
68% yield, confirmed the effectiveness of these conditions also for 6-*exo-dig* aminoiodination processes. NOESY experiments are in agreement with the *E* configuration of the alkenyl double bond and a confirmation of the structure was achieved by single crystal X-ray analysis performed on compound **2e**.[9]



[a]Reaction conditions: **1b–i** (0.5 mmol), NIS (0.5 mmol), $CuCl_2$ (0.05 mmol) in MeCN (10 mL).

Scheme 3. Scope of aminoiodination reactions[a]

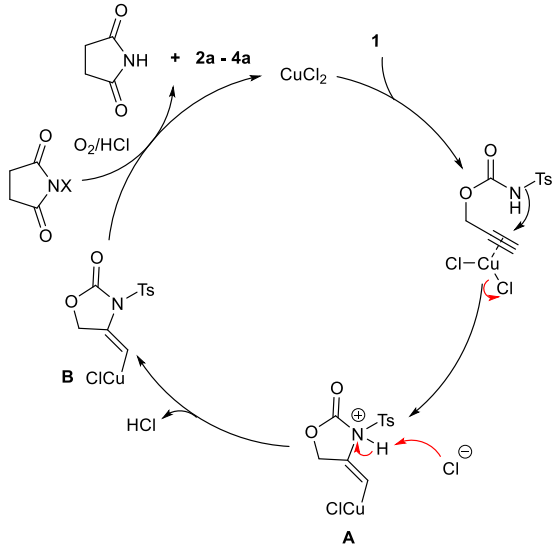
Based on the positive outcome of the aminoiodination reactions, we directed our attention to the treatment of the alkynyl carbamates in the same catalytic conditions with other halosuccinimides. A selection of substrates including different nature of alkynyl moieties was treated with a catalytic amount of $CuCl_2$, bromine and chlorine sources. All the alkynyl carbamates chosen were converted into the corresponding halomethylidene substituted products in times and temperature shown in Scheme 4. Vinyl bromides **3a**, **3c**, **3e** and **3f** were isolated in moderate to high yields, whereas the aminochlorination reaction afforded the oxazolidinones **4a**, **4c** and **4e** only in moderate yields. The attempt to improve the formation of the chloro-substituted products working with stoichiometric amount of $CuCl_2$ as the promoter of the cyclization and chlorine source failed. Unambiguous evidences of the *E* configuration of the exocyclic carbon-carbon double bond for bromo and chloro derivatives arose from single crystal X-ray diffraction undertaken on compounds **3a** and **4a**.[9]



[b]Reaction conditions: **1a,c,e,f,i** (0.5 mmol), NBS or NCS (0.5 mmol), $CuCl_2$ (0.05 mmol) in MeCN (10 mL).

Scheme 4. Scope of bromoamination and chloroamination reactions.[b]

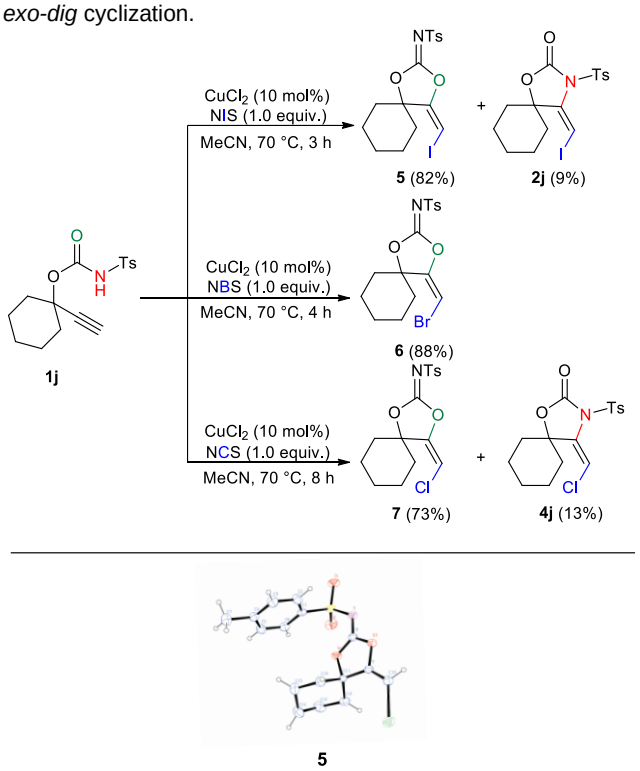
On the basis of the results reported above and on the fact that the reaction performed with NCS in the absence of the catalyst didn't give the product, we proposed a mechanism to justify the role of the copper in the aminohalogenation process (Scheme 5). The first step showed the activation of the triple bond by the catalyst, followed by the nucleophilic attack of the nitrogen atom resulting in the metal-substituted intermediate **A**. The subsequent deprotonation afforded the intermediate **B**, able to interact with NXS to provide the final product and to regenerate the copper catalyst through the intervention of the oxygen.



Scheme 5. Proposed mechanism for the Cu-catalyzed aminohalogenation.

Continuing our investigation to achieve further evidence on the effect of bulky substituents in the cyclohalogenation of alkynyl carbamates, we applied the standard reaction conditions to the α,α-cyclohexyl-substituted propargyl carbamate **1j** (Scheme 6). Its treatment with $CuCl_2$ (10 mol%) and NIS (1 equiv.) in acetonitrile at reflux allowed the formation of two cycloiodination compounds, one of which in greatly amount compared to the other (82% *vs* 9% yields). The NMR analysis carried out on the major product were surprisingly consistent for the spiro-dioxolyl structure **5**, arising from an alkoxyiodination process. The X-ray analysis of a single crystal of **5** confirmed the structure with the *E* configuration of the exocyclic iodo-vinyl moiety.[9] The aminoiodination path was only in part operative, providing the oxazolidinone **2j** in 9% yield. The structure of product **2j** was

established by the n.O.e. interaction between the vinylic hydrogen and the aromatic ring of the tosyl group, which was possible only for the amination product. The preference for the formation of the intramolecular carbon-oxygen bond on the substrate **1j** was proven to be effective with the reactions performed with bromo- and chloro- succinimide, which took place by selective 5-*exo-dig* cyclization.



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[c]Reaction conditions: **1j** (0.5 mmol), NXS (0.5 mmol), $CuCl_2$ (0.05 mmol) in MeCN (10 mL).

Scheme 6. Cyclization/halogenation reaction of the substrate **1j**[c]

Thus, the alkoxybromination and the alkoxychlorination compounds (*E*)-**6** and (*E*)-**7** were isolated in 88% and 73% yields, respectively. If the oxazolidinone (*E*)-**4j** was isolated in the pure state in 13% yield in the case of the chlorocyclization, it was not possible to recover the corresponding bromo vinyl derivative as product of the aminobromination path. Whereas the *O*-functionalization of ureas and amides has several precedents in the literature,[10] the alkoxylation processes of the carbamate group are quite rare.[11]

Thus, a theoretical investigation was performed with the aim to rationalize the behavior observed starting from the α,α-cyclohexyl-substituted propargyl carbamate **1j**. We assumed that the cyclization reaction is under kinetic control, as a thermodynamic equilibrium between the oxazolidinone and dioxolyl products is not observed. Consequently, the selectivity can be driven by the relative stability of the two transition states (TSs) following the "*N*-attack" or the "*O*-attack". We thus modelled the two alternative TSs deriving from **1a** and **1j** reactants using the density functional theory (DFT). First, we found that the keto form of the carbamate moiety was the most stable for the *O*-attack TS. Conversely, the enol tautomer was found as the most stable in the *N*-attack TS. Several attempts to optimize alternative tautomers at the TS level were done, all leading to higher energy structures or convergence failure. Additionally, several conformations were explored for each TS by rotating the N-SO_2 and the SO_2-Ar bonds, followed by full optimization. The most stable TS geometries for the *O*- and *N*-attack of **1a** (TS-1a-O and TS-1a-N, respectively) and **1j** (TS-1j-O and TS-1j-N, respectively) are depicted in Figure 1, together with displacement vectors of the corresponding imaginary frequency, representative distances, and relative enthalpies computed by including the solvation effects for MeCN.

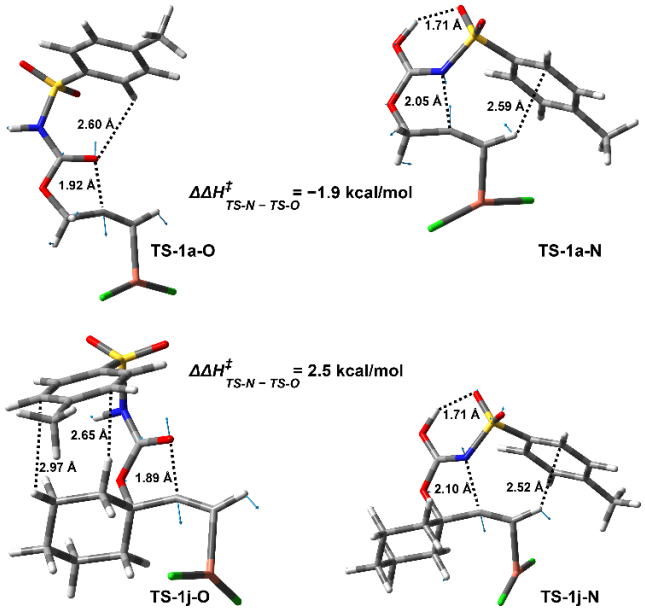

Figure 1. Transition state structures for the *O*- and *N*-attack of model systems **1a** and **1j**. Reported enthalpy differences include solvation effects for MeCN. Displacement vectors for the unique imaginary frequency are shown as blue arrows.

The computed relative enthalpies show that the *N*-attack is favored by 1.9 kcal/mol for **1a**. The *O*-attack is instead favored by 2.5 kcal/mol for **1j**, accordingly to the experimental outcome. It can be observed that both *N*-attack TSs share similar geometries. Indeed, TS-1a-N and TS-1j-N are both stabilized by a CH/π interactions involving the propargyl hydrogen and the *p*-tolyl group (H···C_{Ar} distance = 2.59 and 2.52 Å, respectively), and by a H-bond between the enolic carbamate and SO_2 (OH···O=S distance = 1.71 Å). The computed length of the forming N-C bond is of 2.05 and 2.10 Å for TS-1a-N and TS-1j-N, respectively. Conversely, the two *O*-attack TSs are notably different. Indeed, the *p*-tolyl group, that is not allowed to interact with the propargyl hydrogen by geometrical constraints, is only stabilized by a weak H-bond with the reacting carbamate carbonyl in TS-1a-O (C_{Ar}H···O=C distance = 2.60 Å). On the other hands, when reactant **1j** is considered, the *p*-tolyl group can be involved in stabilizing dispersive interactions with the spirocyclohexyl group, as shown for TS-1j-O in Figure 1. These interactions are not allowed for the *N*-attack, and are presumably weaker for **1a-i** reactants, lacking the cyclohexyl group, where the oxazolidinone is the only product observed. To verify this hypothesis, we performed Quantum Theory of Atoms in Molecules (QTAIM)[12] calculations. Indeed, QTAIM analyses were found useful to describe the role of weak interactions among competing reaction paths[13] or in stabilization of molecular geometries.[14] Starting from the wavefunction obtained from the optimized geometry, we computed the network of bond critical points (BCPs) and bond paths (BPs) of TS-1j-O (Figure 2).

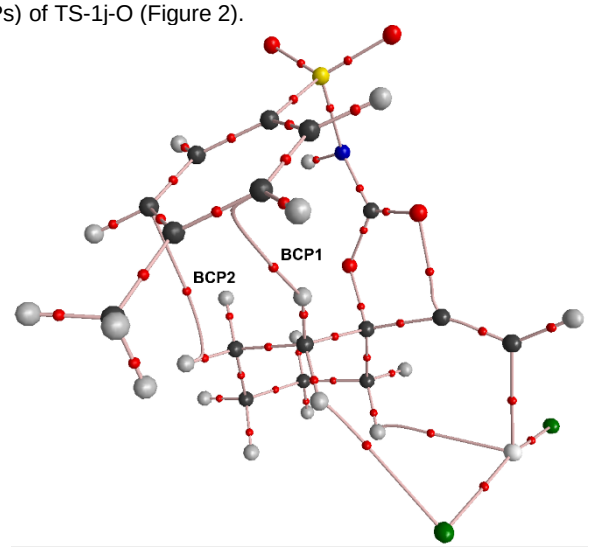

Figure 2. Molecular graph showing BCPs and BPs obtained by the QTAIM analysis of the optimized geometry of TS-1j-O. The BPs describing the stabilizing weak interactions between the spirocyclohexyl and the tosyl group are characterized by BCP1 ($\rho(r_c)$ = 0.0090 a.u.) and BCP2 ($\rho(r_c)$ = 0.0056 a.u.)

We found two BPs connecting the spirocyclohexane equatorial C2 and C3 hydrogens with the tosyl *meta* carbons. The values of $\rho(r_c)$, that are proportional to the strength of the interaction,[12a] at BCP1 ($\rho(r_c)$ = 0.0090 a.u.) and BCP2 ($\rho(r_c)$ = 0.0056 a.u.) are in line with those reported for similar weak interactions[12a] and confirm a clear stabilization effect in TS-1j-O. Thus, we can safely argue that the dispersive interactions between the *p*-tolyl group and the spirocyclohexyl ring, by lowering the TS energy, are the

main responsible of the observed outcome. Indeed, only for the **1j** reaction, the dioxolyl product is the most abundant in all the adopted conditions.

Conclusions

In conclusion, we have developed a useful procedure for the synthesis of oxazol-2-ones and 1,3-oxazin-2-ones bearing an exocyclic halomethylidene moiety starting from *O*-alkynyl carbamates. The reactions proceed under mild conditions using catalytic $CuCl_2$ and a halosuccinimides as the halide source. The cyclization involves selectively an *exo-dig* aminohalogenation which is tolerated by alkyl and aryl substituents on the alkynyl chain. The increase in steric hindrance by the α,α-disubstitution with a cyclohexyl ring on the carbon atom in position α at the carbamate oxygen fosters the alkoxyhalogenation process, precluding the formation of nitrogen-containing heterocycles. In this case, the preference for the intramolecular formation of a carbon-oxygen bond found a justification by the theoretical studies carried out to get light on this behavior.

Experimental Section

General information. Melting points were determined by the capillary method with a Büchi B-540 apparatus and are uncorrected. IR spectra were measured with a Jasco FT/IR 5300 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with: AVANCE 400 Bruker spectrometer at 400 and 100 MHz, Varian Gemini 200 MHz spectrometer at 200 MHz and 50 MHz and Varian Oxford 300 MHz spectrometer at 300 and 75 MHz, respectively. Chemical shifts are given as δ values in ppm relative to residual solvent peaks ($CHCl_3$) as the internal reference. ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. Two-dimensional experiments NOESY were performed with 2048-4096 points in the F2 direction and 256 points in F1. The spectra were acquired with 16-32 scans and with mixing time values range of 500 ms – 3 s depending on the spectra acquired. Mass spectra were determined with a LCQ Advantage Thermo Finningan. Elemental analyses were executed on Perkin-Elmer CHN Analyzer Series II 2400. Thin-layer chromatographic separations were performed on Merck silica-gel 60-F_{254} precoated. Preparative separations were performed by flash chromatography by using Merck silica gel 0.035-0.070 mm.

General procedure for the preparation of *O*-alkynyl carbamates 1a-j: to a stirred solution of the appropriate propargyl alcohol (7.13 mmol) in DCE (10 mL) the appropriate isocyanate (7.13 mmol) was slowly added. After 24 hours the solvent was removed under reduced pressure. The characterization of products **1a, b, e, h, j**[15] **and 1c, i**[16] are consistent with those reported in the literature.

***N*-Tosyl-*O*-(3-methylpenten-4-yn-3-yl)carbamate (1d):** 3-Methyl-1-penten-4-yn-3-ol (7.13 mmol, 0.685 g). Yellow oil, (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 5.88 (dd, *J* = 17.1, 10.3 Hz, 1H), 5.55 (d, *J* = 17.0 Hz, 1H), 5.24 (dd, *J* = 10.3, 0.5 Hz, 1H), 2.66 (s, 1H), 2.45 (s, 3H), 1.67 (s, 3H). MS (ESI): m/z 294.10 $[M+H]^+$. Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.78; found: C, 57.41; H, 5.18; N, 4.72.

***N*-Tosyl-*O*-(2-hexynyl)carbamate (1f):** 2-Hexyn-1-ol (7.13 mmol, 0.699 g). White solid, (92% yield); m.p.: 84-85° C. IR: 3221, 1763, 1458, 865 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93(d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.64 (t, *J* = 2,2 Hz, 2H), 2.41 (s, 3H), 2.12 (m, 2H), 1.44 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.08, 145.04, 135.40, 129.54, 128.44, 88.88, 72.94, 55.10, 21.65, 21.58, 20.60, 13.31. MS (ESI): m/z 295.97 $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; found: C, 57.00; H, 5.84; N, 4.69.

***N*-Tosyl-*O*-(1-methyl-2-pentynyl)carbamate (1g):** 3-Hexyn-2-ol (7.13 mmol, 0.699 g). Yellow oil, (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 5.20-5.17 (m, 1H), 2.27 (s, 3H), 1,99 (qd, *J* = 7.5, 1.8 Hz, 2H), 1.26 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H). MS (ESI): m/z 318.25 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; found: C, 56.96; H, 5.78; N, 4.78.

General procedure for the preparation of 4-halomethylidene-3-tosyloxazolidin-2one 2a-j, 3a, c, e, f, i, 4a, c, e, j, 5, 6, 7. To a stirred solution of the appropriate *O*-alkynyl carbamate (0.561 mmol) in MeCN (10 mL), halosuccinimide (0.561 mmol) and $CuCl_2$ (0.056 mmol, 0.008 g) were added and the reaction was heated for 2-21 h. The resulting mixture was filtered through a silica pad and the solvent was removed under reduced pressure. The characterization of products **2a**[17] and **2e, 3a, 3e, 4a, 4e**[18] are consistent with that reported in the literature.

(4*E*)-4-(Iodomethylidene)-5-phenyl-3-tosyloxazolidin-2-one (2b): Substrate **1b** (0.561 mmol, 0.185 g), NIS (0.561 mmol, 0.126 g).18 hours at 40° C. Light-yellow solid (71% yield); m.p.: 127-129° C. IR: 1794, 1385, 1136, 702, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.39–7.22 (m, 5H), 6.94 (d, *J* = 2.1 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 146.8, 136.5, 134.0, 133.6, 130.1, 130.0, 129.0, 128.4, 128.2, 83.0, 59.1, 21.8. MS (ESI): m/z 478.04 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{14}INO_4S$: C, 44.85; H, 3.10; N, 3.08; found: C, 44.90; H, 3.13; N, 3.04

(4*E*)-4-(Iodomethylidene)-5,5-dimethy-3-tosyloxazolidin-2-one (2c): Substrate **1c** (0.561 mmol, 0.158 g), NIS (0.561 mmol, 0.126 g). 3 hours at reflux. Light-yellow solid (80% yield). m.p.: 117-119° C. IR: 1781, 1386, 1263, 1110, 865 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 1H), 2.46 (s, 3H), 1.69 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 146.4, 141.1, 134.2, 130.0, 128.2, 84.9, 52.3, 25.0, 21.8. MS (ESI): m/z 429.93 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{14}INO_4S$: C, 38.34; H, 3.47; N, 3.44; found: C, 38.38; H, 3.42; N, 3.47.

(4*E*)-4-(Iodomethylidene)-5-methyl-3-tosyl-5-vinyloxazolidin-2-one (2d): Substrate **1d** (0.561 mmol, 0.165 g), NIS (0.561 mmol, 0.126 g). 20 hours at 50° C. The crude material was purified on silica gel (1/1 Hex/Et_2
O) to afford **2d** as a yellow solid (56% yield); m.p.: 77-80° C. IR: 1780, 1347, 1123, 815 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, **J** = 8.4 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.91 (s, 1H), 6.05 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.33 (t, *J* = 13.5 Hz, 2H), 2.46 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 146.5, 139.3, 134.1, 133.5, 130.0, 128.2, 118.5, 85.2, 54.4, 23.0, 21.8. MS (ESI): m/z 442.07 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{14}INO_4S$: C, 40.11; H, 3.37; N, 3.34; found: C, 40.15; H, 3.34; N, 3.39.

(4*E*)-4-(1-Iodobutylidene)-3-tosyloxazolidin-2-one (2f): Substrate **1f** (0.561 mmol, 0.166 g), NIS (0.561 mmol, 0.126 g). 8 hours at 70° C. The crude material was purified on silica gel (7/3 Hex/EtOAc) to afford **2f** as a yellow solid (76% yield); m.p.: 82-85° C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.63 (t, *J* = 1.4 Hz, 2H), 2.67-2.57 (m, 2H), 2.46 (s, 3H), 1.69 – 1.56 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 146.2, 134.7, 130.0, 128.4, 128.2, 99.3, 74.5, 41.8, 23.6, 21.8, 13.1. MS (ESI): m/z 422.23 $[M+H]^+$. Anal. Calcd for $C_{14}H_{16}INO_4S$: C, 39.92; H, 3.83; N, 3.33; found: C, 39.88; H, 3.87; N, 3.30.

(4*E*)-4-(1-Iodopropylidene)-5-methyl-3-tosyloxazolidin-2-one (2g): Substrate **1g** (0.561 mmol, 0.166 g), NIS (0.561 mmol, 0.126 g).18 hours at 40° C. Pale brown wax (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.37 (q, *J* = 6.1 Hz, 1H), 2.60-2.50 (m, 2H), 2.43 (s, 3H), 1.68 (d, *J* = 6.5Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 146.1, 134.4, 132.0, 129.8,

128.9, 100.9, 82.6, 34.1, 21.7, 17.9, 14.8. MS (ESI): m/z 443.97 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{16}INO_4S$: C, 39.92; H, 3.83; N, 3.33; found: C, 39.90; H, 3.87; N, 3.29.

(4*E*)-4-(Iodo(phenyl)methylidene)-3-tosyloxazolidin-2-one (2h): Substrate **1h** (0.561 mmol, 0.185 g), NIS (0.561 mmol, 0.126 g). 2 hours at 45° C under N_2. The crude material was purified on silica gel (7/3 Hex/EtOAc) to afford **2h** as a yellow solid (41% yield); m.p.: 110-114° C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.11 (m, 9H), 4.88 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 141.2, 133.9, 130.2, 129.6, 129.4, 129.2, 128.9, 128.6, 85.9, 74.7, 21.7. MS (ESI): m/z 456.11 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}INO_4S$: C, 44.85; H, 3.10; N, 3.08; found: C, 44.88; H, 3.14; N, 3.04;

(4*E*)-4-(Iodomethylidene)-3-tosyl-1,3-oxazin-2-one (2i): Substrate **1i** (0.561 mmol, 0.149 g), NIS (0.561 mmol, 0.126 g). 8 hours at 60° C. The crude material was purified on silica gel (1/1 Hex/EtOAc and then 6/4 Hex/EtOAc) to afford **2i** as a light-yellow solid (68% yield); m.p.: 112-115° C. IR: 1712, 1370, 1163, 816 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.65 (s, 1H), 4.28 (t, *J* = 6.2 Hz, 2H), 2.88 (t, *J* = 6.2 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 145.7, 135.3, 134.5, 129.7, 128.9, 73.5, 66.3, 32.6, 21.7. MS (ESI): m/z 416.74 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{12}INO_4S$: C, 36.66; H, 3.08; N, 3.56; found: C, 36.61; H, 3.06; N, 3.59.

4*E*)-4-(Iodomethylidene)-3-tosyl-1,3-oxo[4,5]spirodecan-2-one (2j): Substrate **1j** (0.561 mmol, 0.180 g), NIS (0.561 mmol, 0.126 g). 3 hours at 70° C. Yellow wax (9% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 1H), 2.60-2.52 (m, 2H), 2.46 (s, 3H), 1.68-1.54 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 152.6, 137.0, 133.6, 130.0, 128.2, 75.9, 52.1, 32.2, 24.1, 21.8, 21.3.
MS (ESI): m/z 448.07 $[M+H]^+$. Anal. Calcd for $C_{16}H_{18}INO_4S$: C, 42.96; H, 4.06; N, 3.13; found: C, 42.94; H, 4.04; N, 3.13.

(4*E*)-4-(Iodomethylidene)-2-tosylimine-1,3-dioxo[4,5]spirodecane (5): Substrate **1j** (0.561 mmol, 0.180 g), NIS (0.561 mmol, 0.126 g). 3 hours at 70° C. Yellow solid (82% yield); m.p.: 90-93° C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.03 (s, 1H), 2.41 (s, 3H), 2.34-2.38 (m, 2H), 1.90-1.87 (m, 2H), 1.78-1.75 (m, 3H), 1.66-1.60 (m, 2H), 1.33-1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 152.6, 143.6, 138.2, 129.3, 127.2, 50.3, 32.6, 24.0, 21.6, 21.2. MS (ESI): m/z 448.03 $[M+H]^+$. Anal. Calcd for $C_{16}H_{18}INO_4S$: C, 42.96; H, 4.06; N, 3.13; found: C, 42.92; H, 4.05; N, 3.16.

(4*E*)-4-(Bromomethylidene)-5,5-dimethyl-3-tosyloxazolidin-2-one (3c): Substrate **1c** (0.561 mmol, 0.158 g), NBS (0.561 mmol, 0.0998 g). 21 hours at 40° C. The crude material was purified on silica gel (1/1 Hex/CH_2Cl_2) to afford **3c** as a white solid (92% yield); m.p.: 116-119 ° C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.13 (s, 1H), 2.41 (s, 3H), 1.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 152.0, 143.8, 138.0, 129.4, 127.2, 84.8, 24.4, 21.6. MS (ESI): m/z 381.46 $[M+Na]^+$, 383.25 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{14}BrNO_4S$: C, 43.35; H, 3.92; N, 3.89; found: C, 43.39; H, 3.90; N, 3.86.

(4*E*)-4-(Bromobutylidene)-3-tosyloxazolidin-2-one (3f): Substrate **1f** (0.561 mmol, 0.166 g), NBS (0.561 mmol, 0.0998 g). 5 hours at 70° C. Yellow solid (73% yield); m.p.: 89-93 ° C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 4.70 (s, 2H), 2.68 (m, 2H), 2.46 (s, 3H), 1.76 – 1.62 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 146.2, 134.6, 130.0, 128.4, 125.8, 120.6, 70.5, 39.2, 21.7, 21.5, 13.3. MS (ESI): m/z 373.67 $[M+H]^+$, 375.38 $[M+H]^+$. Anal. Calcd for $C_{14}H_{16}BrNO_4S$: C, 44.93; H, 4.31; N, 3.74; found: C, 44.90; H, 4.35; N, 3.77.

(4*E*)-4-(Bromomethylidene)-3-tosyl-1,3-oxazin-2-one (3i): Substrate **1i** (0.561 mmol, 0.149 g), NBS (0.561 mmol, 0.0998 g). 4 hours at 40° C. The crude material was purified on silica gel (1/1 Hex/EtOAc and then 9.9/0.1 CH_2Cl_2/MeOH) to afford **3i** as a light yellow solid (48% yield); m.p.: 85-88° C. IR: 1721, 1362, 1163, 816 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.61 (s, 1H), 4.29 (t, *J* = 6.2 Hz, 2H), 2.88 (dd, *J* = 6.1, 5.5 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 145.8, 135.2, 131.9, 129.8, 128.9, 102.2, 66.3, 28.7, 21.7. MS (ESI): m/z 368.11 $[M+Na]^+$, 347.08 $[M+H]^+$ Anal. Calcd for $C_{12}H_{12}BrNO_4S$: C, 41.63; H, 3.49; Br, 23.08; N, 4.05; found: C, 41.66; H, 3.45; N, 4.10.

(4*E*)-4-(Bromomethylidene)-2-tosylimine-1,3-dioxo[4,5]spirodecane (6): Substrate **1j** (0.561 mmol, 0.180 g), NBS (0.561 mmol, 0.0998 g). 4 hours at 70° C. The crude material was purified on silica gel (6/4 Hex/EtOAc) to afford **6** as a yellow wax (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.12 (s, 1H), 2.40 (s, 3H), 2.31-2.26 (m, 2H), 1.91-1.86 (m, 2H), 1.77-1.70 (m, 3H), 1.53-1.63 (m, 2H), 1.32-1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 151.9, 143.7, 138.1, 129.4, 127.2, 84.9, 32.3, 24.0, 21.5, 21.2.
MS (ESI): m/z 400.05 $[M+H]^+$, 401.98 $[M+H]^+$. Anal. Calcd for $C_{16}H_{18}BrNO_4S$: C, 48.01; H, 4.53; N, 3.50; found: C, 48.06; H, 4.56; N, 3.45.

(4*E*)-4-(Chloromethylidene)-5,5-dimethy-3-tosyloxazolidin-2-one (4c): Substrate **1c** (0.561 mmol, 0.158 g), NCS (0.561 mmol, 0.0749 g). 8 hours at 50° C. The crude material was purified on silica gel (7/3 Hex/EtOAc) to afford **4c** as a white solid (56% yield); m.p.: 86-88 ° C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.78 (s, 1H), 2.46 (s, 3H), 1.63 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 146.6, 138.8, 134.0, 130.0, 128.2, 96.0, 84.0, 24.7, 21.8. MS (ESI): m/z 316.26 $[M+H]^+$. Anal. Calcd for $C_{13}H_{14}ClNO_4S$: C, 49.45; H, 4.47; N, 4.44; found: C, 49.49; H, 4.44; N, 4.49.

(4*E*)-4-(Chloromethylidene)-3-tosyl-1,3-oxo[4,5]spirodecan-2-one (4j): Substrate **1j** (0.561 mmol, 0.180 g), NCS (0.561 mmol, 0.0749 g). 8 hours at 70 ° C. The crude product was purified by chromatographed on a flash silica gel column (7/3 Hex/EtOAc) to afford **4j** as a white solid (13% yield); m.p.: 115-118 ° C. IR: 1796, 1372, 1110, 769 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.09 (s, 1H), 2.35 (s, 3H), 2.20-2.12 (m, 2H), 1.86-1.50 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 142.6, 137.1, 133.5, 128.4, 126.2, 98.1, 86.1, 31.2, 23.0, 20.5, 20.2. MS (ESI): m/z 378.32 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{18}ClNO_4S$: C, 54.01; H, 5.10; N, 3.94; found: C, 54.06; H, 5.15; N, 3.90.

(4*E*)-4-(Chloromethylidene)-2-tosylimine-1,3-dioxo[4,5]spirodecane (7): Substrate **1j** (0.561 mmol, 0.180 g), NCS (0.561 mmol, 0.0749 g). 8 hours at 70 ° C. The crude product was purified by chromatographed on a flash silica gel column (7/3 Hex/EtOAc) to afford **7** as a yellow wax (73% yield).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.74 (s, 1H), 2.39 (s, 3H), 2.34-2.26 (m, 2H), 1.65-1.48 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 146.4, 138.5, 134.1, 130.0, 128.2, 99.6, 86.0, 32.1, 24.2, 21.8, 21.2. MS (ESI): m/z 378.15 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{18}ClNO_4S$: C, 54.01; H, 5.10; N, 3.94; found: C, 54.05; H, 5.15; N, 3.91.

Computational Methods. The TS structures TS-1a-O, TS-1a-N, TS-1j-O and TS-1j-N were initially constructed starting from the crystal structures of compounds **2e** and **5**, opportunely modified with the GaussView6 software.[19] Quantum mechanical calculations were then performed with the Gaussian16 package.[20] Each geometry was optimized in the gas phase by DFT level using the MPWBK1 functional[21] with the GD3 empirical correction for dispersion.[22] The choice of this functional was supported by recent literature, were it was described as outstanding for describing metal-catalyzed reactions.[23] Solvent was not considered at this stage since its effect is often negligible on geometry.[24] The 6-31G(d) basis set was applied to all atoms except S, Cl and Cu. The 6-31G(3df) basis set was used for the S atom, as recommended for a correct treatment of its electronic structure.[25] The Cu and Cl atoms were instead described by the LANL2DZ basis set and the Hay and Wadt effective core potential (ECP).[26] Additional polarization functions were also added to Cu (ζf = 3.525) and Cl (ζd = 0.640) atoms,[27] as already used for similar calculations.[28] A vibrational analysis was performed at the same level of theory to calculate the zero-point and thermochemical corrections to the electronic energy at standard conditions (1 atm, 298.15 K). Only one imaginary frequency, corresponding to the stretching of the forming bond, was observed. Single point energies were computed at the MPWB1K-GD3 level and the 6-311+G(d,p) basis set for all atoms except S (6-311+G(3df)) Cu and Cl (LANL2DZ with polarization and ECP). Solvation effects were considered by the CPCM model for MeCN.[29] Absolute energies of optimized TSs are

reported in Table S1, Supporting Information (SI). Value of imaginary frequencies, Cartesian coordinates are also provided in the SI for each geometry as Gaussian input files. QTAIM analyses were performed with the AIM2000 software[30] using the default options. The wavefunction for TS-1j-O was generated by a single point calculation at the MPWBK1-GD3/6-311+G(d,p) level on the previously optimized geometry.

Keywords: aminohalogenation • alkoxyhalogenation • copper catalysis • carbamates • intramolecular reaction • DFT calculation • QTAIM

Supporting Information: Absolute energies, and imaginary frequency of TS structures discussed here. Complete Gaussian input files with optimized Cartesian coordinates.

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[9] CCDC-2046636 (**2e**), CCDC-2046639 (**3a**), CCDC-2046638 (**4a**), CCDC-2046637 (**5**) numbers contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* ww.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: ++44 1223 336 033; or deposit@ccdc.cam.ac.uk).

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