3-Oxa- and 3-Azabicyclo[3.1.0]hexan-2-ones *via* Tandem Radical Cyclization−Intramolecular S_N2 Reactions

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In connection with our studies of radical cyclizations leading to bicyclic lactones and lactams,[1] we have investigated the behavior of δ-ethylenic α,α-dichloromalonates and malonamides on treatment with CuCl. The reducing metal-catalyzed inter- and intramolecular additions of perchlorocarbonyl compounds to double bonds are well known.[2] The performance of lactone and lactam ring closures using this atom transfer methodology has been the subject of a renewed interest over the last few years.[3,4] To our knowledge most of these works employed dichloro- and trichloroacetic acid derivatives, none of which dealt with β-dicarbonylated substrates, with the exception of the work of Weinreb[5] who studied the cyclization of α,α-dichloro-β-keto esters initiated with Cu(I) or Ru(II).

We report in this paper the stoichiometric reaction of α,α-dichlormalonamides and malonates with Cu(I) which leads to 3-aza- and 3-oxa-2-oxobicyclo[3.1.0]hexanes respectively, in good yields. The fused five−three ring skeleton is generally built *via* α-diazo esters or amides,[6] although it has recently been reported that the tandem Michael−S_N2 reaction is a safe alternative pathway for the preparation of bicyclic amides in 50−60% yield.[7a] An alternative methodology, developed by Moriarty,[7b] involves hypervalent iodine. Mn(III)-mediated oxidative cyclization of malonic esters was also shown to lead to 3-oxa-2-oxobicyclo[3.1.0]hexanes,[1a,8] but this procedure is restricted to ethylenic esters bearing a monosubstituted double bond.

Results and Discussion

Ethyl 3-oxa- and 3-aza-2-oxobicyclo[3.1.0]hexane-1-carboxylates are key intermediates in the synthesis of strained amino acids.[9] We first investigated the CuCl-catalyzed cyclizations of amide **1** with the goal of a two-step synthesis (from **1**) of the above-mentioned strategic bicyclic structure. When **1** was allowed to react, under catalytic conditions in the presence of 0.1 equiv of Cu(bpy)Cl in isobutyronitrile, at reflux for 16 h (Scheme 1), the two diastereomeric lactams **2a,b** were isolated in 58% yield (77% with respect to converted starting material) in a 6:4 ratio. However, 25% of the starting material was recovered unchanged. Similar reactions reported in the literature are often conducted in the presence of 0.3 equiv of catalyst. We have observed that both the yield and of course the rate of the reaction were sensitive to the stoichiometry of Cu(I). Furthermore, a third product appeared as the ratio of catalyst to substrate increased. Not only was the relative proportion of the isomeric lactams time dependent, but it was also sensitive to the amount of catalyst. As an example, as reported in Scheme 1, when **1** was treated with 1 equiv of Cu(bpy)Cl complex, the ratio of **2a:2b** was reversed (4:6) and the isomeric lactams accounted for only 70% of the products (the bicyclic lactam **3** accounted for the remaining 30%).

The Cu(I)-catalyzed cyclizations are generally rationalized according to Scheme 2. The three-step process involves the reduction of the substrate **A** into radical **B** followed by a 5-exo cyclization leading to **C** and **C′**. The last step is a ligand transfer oxidation leading to the isomeric chlorides **D** and **D′** and regenerating the catalyst.

Our experimental observations suggested that with greater than 10−20% of the reducing mediator the mechanism should be complemented, as presented in Scheme 3, by the cleavage of **D** and **D′** by CuCl (possibly reversible) and the reduction of the intermediate radical **E** into the Cu(II) enolate **F**, responsible for the cyclopropanation. If this mechanistic proposal is correct, then the reaction should lead to 3-azabicyclo[3.1.0]hexanes, provided that 2 equiv of the Cu(I) complex was used instead of a catalytic amount.

In order to confirm this last proposal, the two isomeric lactams **2a** and **2b** were submitted separately to heating in the presence of a catalytic amount (0.1 equiv) of Cu(bpy)Cl. No isomerization occurred, which clearly demonstrated that Cu(I) is not able to reversibly cleave the C−Cl bond.[10] Therefore, the observed dependence of their ratio on the Cu(I) stoichiometry must result from

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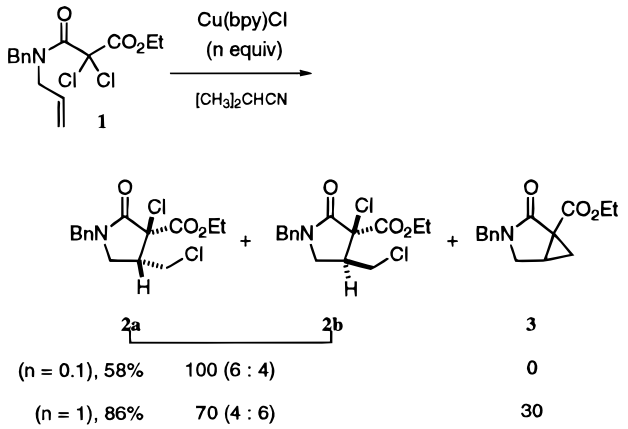
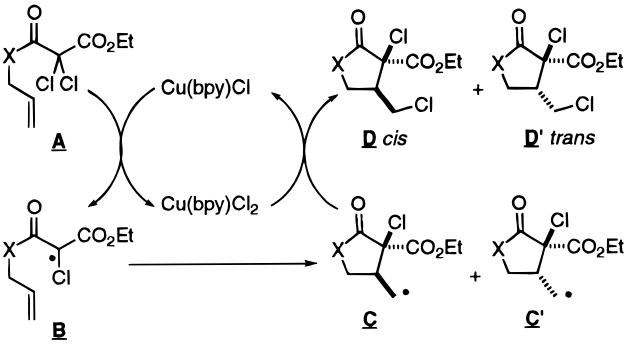
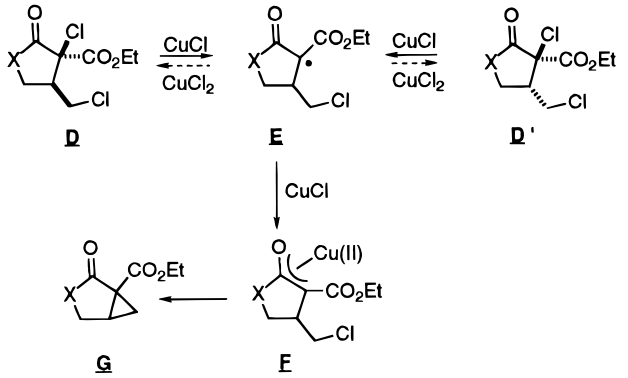
Scheme 1



Scheme 2



Scheme 3

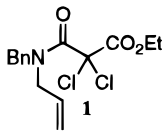
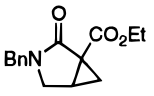
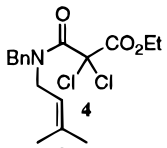
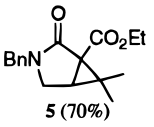
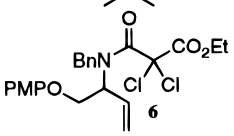
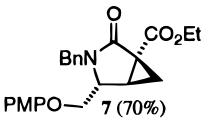
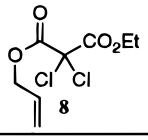
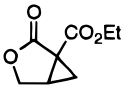


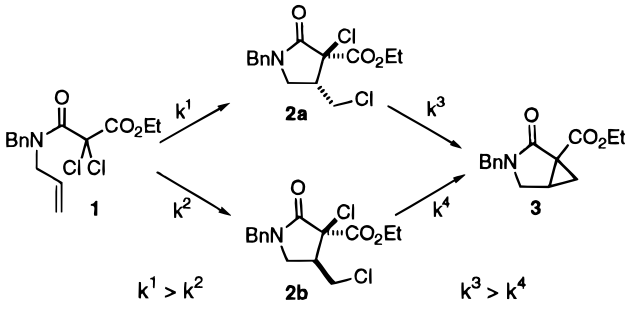
the fact that their reductions by Cu(I) proceeded at different rates. When **1** was allowed to react with 2 equiv of Cu(I) complex, as reported in Table 1, lactam **3** was the only product (isolated in 77% yield). Monitoring the reaction conducted at rt, by HPLC, confirmed the validity of the above hypotheses. The chlorinated lactams were formed very rapidly, and though **2a** was the major product in the presence of a catalytic amount of reducing agent, it was transformed into **3** faster than **2b**. Thus, as the reaction proceeded, the ratio of **2a** to **2b** decreased and was progressively reversed (**2b** became the major stereoisomer, Figure 1). At rt, due to the slow rate of the formation of the cyclopropane ring, Cu(I) was partially destroyed before the reaction was ended, and thus, the monocyclic lactams were not totally transformed into **3**.

The reaction also proceeds when the substrate carries a substituted ethylenic linkage. As shown in Table 1, it can be applied to amide **4** which bears an isoprenyl chain.

(10) A similar conclusion was established by Weinreb for the Cu(I)-based cyclization of α,α-dichloro-β-keto esters (cf. ref 5a).

Table 1. Cyclizations in the Presence of 2 equiv of Cu(bpy)Cl

Substrate	Product (isolated yield)
 **1**	 **3** (77%)
 **4**	 **5** (70%)
 **6**	 **7** (70%)
 **8**	 **9** (76%)



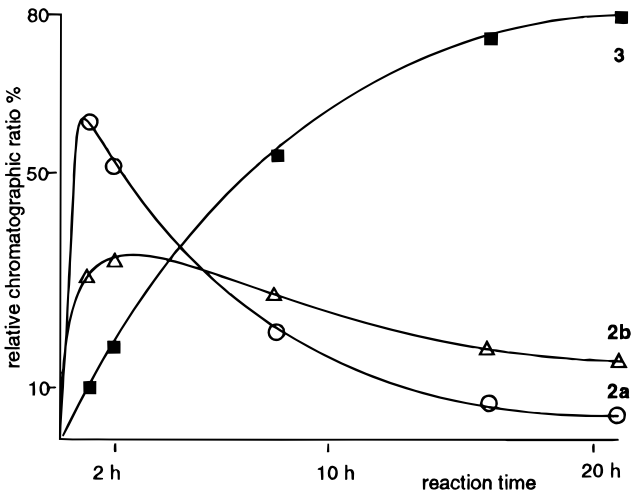
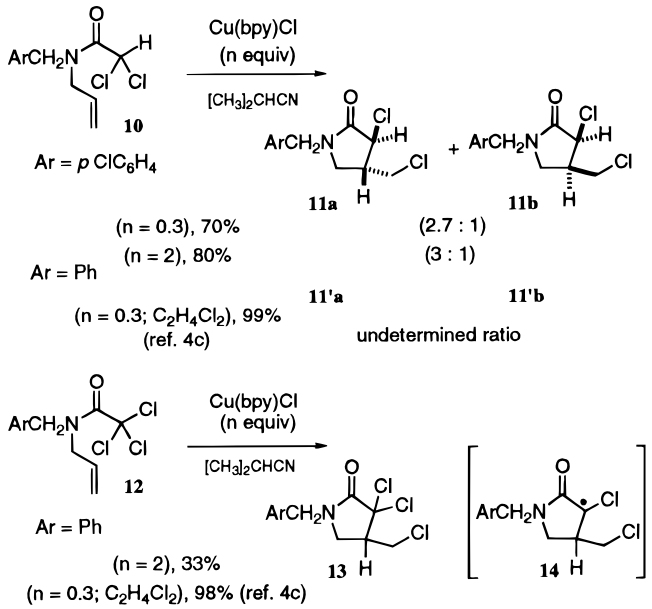


Figure 1. Stoichiometric reduction of **1** (2 equiv of Cu(bpy)-Cl) at rt.

The high degree of stereocontrol in the cyclization of amide **6** allowed the stereoselective synthesis of **7** (the other diastereomer was detected in trace amounts by NMR).[11] The same strategy can be applied to the synthesis of bicyclic lactones. When allyl ethyl dichloromalonate (**8**) was treated with 2 equiv of Cu(I) bipyridine complex the reaction led to **9** in 76% yield. It should be noted that Speckamp[12] has achieved the closely related cyclopropanation of polychloro medium-sized-lactones through a reaction with a dialkyl cuprate.

Scheme 4



In addition, we investigated if the presence of two carbonyl functions was absolutely necessary for obtaining bicyclo[3.1.0]hexanes. Neither **10** nor **12** (Scheme 4) gave bicyclic products when submitted to 2 equiv of reducing complex.

The dichloroacetamide **10** led to the diastereomeric lactams **11ab**, in a similar ratio, not depending on the amount of reducing metallic complex (as **2a** and **2b**, neither **11a** nor **11b** were isomerized on further treatment with 0.1 equiv of Cu(bpy)Cl). These results support the conclusion that the C−Cl bond cannot be cleaved again by Cu(I). **12** was reported to give **13** in 98% yield in the presence of 0.3 equiv of Cu(bpy)Cl.[4c] Therefore, the low yield of lactam **13** from **12** in the presence of 2 equiv of Cu(I) suggested that **13** can further be degraded *via* radical **14**. But the absence of the cyclopropane ring closure seemed to indicate that no further reduction of **14** had occurred.

In summary, the treatment of dichloromalonic derivatives with 2 equiv of Cu(I) provides an easy access to fused five-three ring skeletons. Further studies in the field of Cu(I)-mediated cyclopropanations are currently under investigation.

Experimental Section

NMR spectra were recorded in $CDCl_3$ solutions on a Bruker AC 200 or AC 100 spectrometer. *J* values are given in Hz. Column chromatography was performed on silica gel 60 (Merck 7734). HPLC analyses were conducted on a Waters Nova-Pack Silica (4 μm) column (3.9 i.d. × 15 cm) coupled to a refractometer. The amides and the ester, precursors of the substrates, were prepared by classical procedures involving the substitution of ethyl chlorocarbonyl ethanoate with the corresponding amines or alcohol.

General Procedure for the Preparation of Dichlorinated Substrates. In a typical experiment, in a 50 mL flask, cooled at 0 °C with an ice bath, were introduced sodium hypochlorite (1.8 M, 2.2 mL, 4.0 mmol, 4 equiv) and Na_2CO_3, 10 H_2O (2.3 g, 8 mmol, 8 equiv). A CCl_4 solution (3 mL) of the corresponding starting material (400 mg, 1.0 mmol, 1 equiv) was slowly added dropwise, and the reaction mixture was stirred at 0 °C for 5 h and then at rt for 1 h more. After filtration, the aqueous layer was extracted three times with cooled (0 °C) CH_2Cl_2. The combined organic layers were washed at 0 °C with brine and then dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (2,2,4-trimethylpentane/EtOAc 7/3) to isolate **6** (350 mg, 75%).

***N*-Allyl-*N*-benzyl-2,2-dichloromalonamic Acid Ethyl Ester (1).** **1** (2.3 g) was isolated in 60% yield from the corresponding malonamide (3.0 g, 11.5 mmol) after chromatography on silica gel (pentane/Et_2O 8/2). ^1H NMR (200 MHz): (7/3 mixture of rotamers): 1.30 (t, *J* = 7.2, 3H); 3.89 (d, *J* = 5.1, 0.6H); 4.00 (d, *J* = 5.6, 1.4H); 4.32 (2 superimposed q, *J* = 6.9, 2H); 4.62 (s, 1.4 H); 4.78 (s, 0.6H); 5.05−5.40 (m, 2H); 5.65−5.90 (m, 1H); 7.15−7.45 (m, 5H). ^{13}C NMR (50 MHz): 13.67 (CH_3); 48.50 (NCH_2); 49.85 (NCH_2); 64.64 (OCH_2); 119.76 (=CH_2); 127.59 (CH=); 127.91 (CH=); 128.63 (CH=); 131.57 (CH=); 135.70 (C=);162.09 (C=O); 163.42 (C=O). The other quaternary carbon did not appear under the registration conditions. Anal. Calcd for $C_{15}H_{17}NO_3Cl_2$: C, 54.70; H, 5.21; N, 4.26. Found: C, 54.69; H, 5.10; N, 4.22.

***N*-Benzyl-*N*-(3-methylbut-2-enyl)-2,2-dichloromalonamic Acid Ethyl Ester (4).** **4** (1.8 g) was prepared in 73% yield from the corresponding amide (2.0 g, 6.9 mmol) after purification by chromatography on silica gel (pentane/Et_2O 8/2). ^1H NMR (200 MHz): (7/3 mixture of rotamers): 1.33 (t, *J* = 7.1, 3H); 1.41 (s, 0.9H); 1.50 (s, 2.1H); 1.70 (s, 0.9H); 1.75 (s, 2.1H); 3.85−4.02 (m, 2H); 4.33 (q, *J* = 7.1, 2H); 4.60 (s, 1.4H); 4.72 (s, 0.6H); 5.08−5.22 (m, 1H); 7.15−7.40 (m, 5H). ^{13}C NMR (50 MHz): 13.71 (CH_3); 17.96 (CH_3); 25.72 (CH_3); 44.12 (NCH_2); 45.45 (NCH_2); 48.56 (NCH_2); 50.90 (NCH_2); 64.62 (CH_2O); 80.15 (CCl_2); 90.70 (CCl_2); 117.58 (CH=); 118.33 (CH=); 127.19 (CH=); 127.51 (CH=); 127.89 (CH=); 128.58 (CH=); 136.09 (C=); 137.88 (C=); 162.08 (C=O); 163.63 (C=O). Anal. Calcd for $C_{17}H_{21}NO_3Cl_2$: C, 57.13; H, 5.93; N, 3.92. Found: C, 57.13; H, 5.91; N, 3.93.

***N*-Benzyl-*N*-[1-[(4-methoxyphenoxy)methyl]prop-2-enyl]-2,2-dichloromalonamic Acid Ethyl Ester (6).** ^1H NMR (200 MHz): (mixture of rotamers): 1.20−1.40 (m, 3H); 3.75 (s, 3H); 3.80−4.60 (m, 5H); 4.60−5.50 (m, 4H); 5.80−6.20 (m, 1H); 6.65−6.90 (m, 4H); 7.15−7.40 (m, 5H). ^{13}C NMR (25 MHz): 13.75 (CH_3); 40.10 (CH_2); 55.75 (CH_3); 63.08 (CH); 64.80 (CH_2); 68.66 (CH_2); 114.68 (CH=); 115.80 (CH=); 119.19 (CH_2=); 126.89 (CH=); 128.11 (CH=); 128.59 (CH=); 132.55 (CH=); 135.14 (C=); 152.43 (C=); 154.29 (C=); 163.52 (C=O). The other quaternary carbons did not appear under the registration conditions. Correct elemental analysis could not be obtained due to thermal decomposition.

Allyl Ethyl Dichloromalonate (8). **8** (3.13 g) was prepared in 65% yield from allyl ethyl malonate (3.44 g, 20 mmol) after purification by chromatography on silicagel (pentane/Et_2O 9/1). ^1H NMR (200 MHz): 1.34 (t, *J* = 7.1, 3H); 4.38 (q, *J* = 7.1, 2H); 4.79 (d, *J* = 5.8, 2H); 5.30−5.46 (m, 2H); 5.93 (ddt, *J* = 17.2, 10.4, 5.8, 1H). ^{13}C NMR (50 MHz): 13.81 (CH_3); 64.79 (OCH_2); 68.70 (OCH_2);120.06 (CH_2=); 130.22 (CH=); 162.59 (C=O); 162.74 (C=O). The signal of the quaternary carbon bearing the chlorine atoms is not visible, under the conditions of registration. Anal. Calcd for $C_8H_{10}Cl_2O_4$: C, 39.86; H, 4.18; Cl, 29.41. Found: C, 39.82; H, 4.16; Cl, 29.30.

***N*-Allyl-*N*-(*p*-chlorobenzyl)-α,α-dichloroacetamide (10).** A solution containing *p*-chlorobenzylamine (1.46 g, 8.1 mmol, 1 equiv) and triethylamine (1.01 g, 10 mmol, 1.2 equiv) in dichloromethane (15 mL) was added at 0 °C to a solution of dichloroacetyl chloride (1.30 g, 10 mmol, 1 equiv) in dichloromethane (30 mL). After the addition was ended the reaction mixture was allowed to warm to rt and was stirred for 4 h more. The solution was washed with water and then with brine and dried over anhydrous sodium sulfate. After concentration, the oily residue was chromatographed on silica gel (Et_2O/pentane 5/95), leading to **10** (1.56 g, 66%) as a mixture of rotamers. ^1H NMR (200 MHz): 3.92−4.04 (m, 2H); 4.58 (s, 1.4H); 4.69 (s, 0.6H); 5.06−5.38 (m, 2H); 5.60−5.91 (m, 1H); 6.20 (s, 0.3H); 6.24 (s, 0.7 H); 7.10−7.41 (m, 4H). ^{13}C NMR (50 MHz): 48.73 (CH_2); 49.45 (CH_2); 49.82 (CH_2); 64.87 (CH); 65.10 (CH); 118.37 (CH_2=); 118.55 (CH_2=); 128.02 (CH=); 128.89 (CH=); 129.17 (CH=); 129.41 (CH=); 130.96 (CH=); 131.74 (CH=); 133.62 (C=); 133.68 (C=); 133.91 (C=); 134.49 (C=); 164.23 (C=O). Anal. Calcd for

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(12) Speckamp, W. N. Private communication.

$C_{12}H_{12}NOCl_3$: C, 49.26; H, 4.13; N, 4.79, Cl, 36.35. Found: C, 49.20; H, 4.15, N, 4.76, Cl, 36.3.

***N*-Allyl-*N*-benzyltrichloroacetamide (12).**[4c] According to the same protocol, *N*-benzylallylamine was allowed to react with trichloroacetyl chloride; **12** was obtained in 60% yield. ^{1}H NMR (200 MHz): 3.67 (broad s, 0.6H); 4.00 (broad s, 1.4H); 4.37 (broad s, 1.4H); 4.67 (broad s, 0.6H); 4.83−5.15 (m, 2H); 5.37−5.70 (m, 1H); 6.88−7.15 (m, 5H). ^{13}C NMR (50 MHz): 49.86 (CH_2); 51.08 (CH_2); 52.26.(CH_2); 93.03 (C); 118.27 (CH═); 119.60 (CH═); 127.05 (CH═); 127.66 (CH═); 128.35 (CH═); 128.67 (CH═); 130.66 (CH═); 131.78 (CH═); 135.68 (C═); 160.67 (C═O). Anal. Calcd for $C_{12}H_{12}NOCl_3$: C, 49.26; H, 4.13; N, 4.49. Found: C, 49.20; H, 4.12; N, 4.77.

General Procedure for Radical Cyclization. CuCl was prepared according to a known procedure,[13] dried under vacuum, and stored under nitrogen in the dark. In a typical experiment, into a three-necked flask fitted with a lateral bent glass tube filled with freshly prepared CuCl (18 mg, 0.18 mmol, 0.1 equiv) were introduced **1** (0.6 g, 1.8 mmol, 1 equiv), 2,2′-bipyridine (27 mg, 0.18. mmol, 0.1 equiv), and isobutyronitrile (10 mL). The solution was degassed several times under vacuum and then brought back to atmospheric pressure under argon. The reaction mixture was stirred at reflux, and CuCl was added all at once. After the reaction was ended, metallic salts were filtered on a short pad of silica and the solvent was evaporated under reduced pressure. Purification of the residue by preparative HPLC (2,2,4-pentane/EtOAc 8/2) afforded by order of elution **1** (150 mg, 25%), **2a** (140 mg, 23%), and **2b** (210 mg, 35%).

Ethyl 1-Benzyl-3-chloro-4-(chloromethyl)-2-oxopyrrolidine-3-carboxylate (2a). ^{1}H NMR (200 MHz): 1.23 (t, J = 7.2, 3H); 3.03−3.15 (m, 1H); 3.20 (pseudo t, J = 8.9, 1H); 3.38 (pseudo t, J = 10.5, 1H); 3.50 (dd, J = 8.9, 7.1, 1H); 3.80 (dd, J = 10.8, 4.4, 1H); 4.26 (q, J = 7.2, 2H); 4.55 (AB quartet, J_{AB} = 14.6, $\Delta\nu$ = 79.2 Hz, 2H); 7.23−7.43 (m, 5H). ^{13}C NMR (50 MHz): 13.98 (CH_3); 41.00 (CH_2); 47.90 (CH_2); 48.31 (CH_2); 49.75 (CH); 63.64 (CH_2); 71.84 (C); 128.12 (CH═); 128.38 (CH═); 128.84 (CH═); 134.79 (C═); 165.00 (C═0); 166.96 (C═0). **2b.** ^{1}H NMR (200 MHz): 1.35 (t, J = 7.1, 3H); 3.05 (m, 1H); 3.40−3.49 (m, 2H); 3.50−3.63 (m, 1H); 3.65−3.78 (m, 1H); 4.37 (q, J = 7.1, 2H); 4.50 (AB quartet, J_{AB} = 14.9 Hz, $\Delta\nu$ = 39.5 Hz, 2H); 7.20−7.40 (m, 5H). ^{13}C NMR (50 MHz): 13.98 (CH_3); 41.3 (CH_2); 44.87 (CH); 47.24 (CH_2); 47.39 (CH_2); 63.73 (CH_2); 71.90 (C); 128.04 (CH═); 128.12 (CH═); 128.96 (CH═); 134.91 (C═); 166.12 (C═O); 167.33 (C═O). Anal. Calcd for $C_{15}H_{17}NO_3Cl_2$ (**2a** + **2b**): C, 54.70; H, 5.21; N, 4.26; Cl, 21.25. Found: C, 54.62; H, 5.17; N, 4.21; Cl, 21.20.

Treating **1** (0.5 g, 1.5 mmol) with 2 equiv of Cu(bpy)Cl afforded **3** (300 mg, 77%) after 2 h of reflux and a purification by chromatography on silica gel (Et_2O).

Ethyl 3-Benzyl-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (3). ^{1}H NMR (200 MHz): 0.93 (pseudo t, J = 4.9, 1H); 1.20 (t, J = 7.2, 3H); 1.80 (dd, J = 8.1, 4.6, 1H); 2.20 (pseudo dt, J = 8.4, 5.6, 1H); 2.99 (d, J = 10.5, 1H); 3.32 (dd, J = 10.5, 5.6, 1H); 4.13 (q, J = 7.2, 2H); 4.26 (AB quartet, J_{AB} = 14.9, $\Delta\nu$ = 47.7 Hz, 2H); 7.00−7.27 (m, 5H). ^{13}C NMR (50 MHz): 14.09 (CH_3); 20.59 (CH_2); 22.61 (CH); 31.50 (C); 46.26 (CH_2); 46.35 (CH_2); 61.33 (CH_2); 127.57 (CH═); 128.06 (CH═); 128.61 (CH═); 136.21 (C═); 168.58 (C═O); 169.13 (C═O). Anal. Calcd for: $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.44; H, 6.59; N, 5.39.

Cyclization of 4. According to the above protocol, **4** (0.5 g, 1.4 mmol) was treated for 16 h by Cu(bpy)Cl (2 equiv). After treatment, a purification by semipreparative HPLC (2,2,4-trimethylpentane/EtOAc: 65/35) afforded **5** (280 mg, 70%).

Ethyl 3-Benzyl-6,6-dimethyl-2-oxo-3-azabicyclo[3.1.0]-hexane-1-carboxylate (5). ^{1}H NMR (200 MHz): 0.99 (s, 3H); 1.21 (s, 3H); 1.33(t, J = 7.1, 3H); 2.10 (d, J = 6.6, 1H); 2.95 (d, J = 11.0, 1H); 3.44 (dd, J = 11.0, 6.6, 1H); 4.27 (q, J = 7.1, 2H); 4.35 (AB quartet, J_{AB} = 14.4 Hz, $\Delta\nu$ = 36.9 Hz, 2H); 7.15−7.36 (m, 5H). ^{13}C NMR (50 MHz): 14.29 (CH_3); 14.90 (CH_3); 21.74 (CH_3); 29.37 (CH); 43.50 (C); 43.86 (CH_2); 46.63 (CH_2); 61.42 (CH_2); 127.72 (CH═); 128.58 (CH═); 128.70 (CH═); 135.83 (C═); 167.60 (C═O); 168.00 (C═O). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.05; H, 7.32; N, 4.83.

Cyclization of 6. According to the above protocol, **6** (300 mg, 0.64 mmol) was treated at reflux of isobutyronitrile, for 6 h, by Cu(bpy)Cl (2 equiv). After treatment, a purification by semipreparative HPLC (2,2,4-trimethylpentane/EtOAc 65/35) afforded **7** (180 mg, 70%).

Ethyl 3-Benzyl-4-[(4-methoxyphenoxy)methyl]-2-oxo-3-azabicyclo [3.1.0]hexane-1-carboxylate (7). ^{1}H NMR (200 MHz): 0.98 (pseudo t, J = 5.0, 1H); 1.33 (t, J = 7.1, 3H); 1.90 (dd, J = 8.0, 4.7, 1H); 2.29 (dd, J = 8.0, 5.2, 1H); 3.60 (t, J = 4.9, 1H); 3.75 (s, 3H); 3.95 (ABX pattern, J_{AB} = 9.7, 2H); 4.02 (d, J = 14.8, 1H); 4.28 (q, J = 7.1, 2H); 4.93 (d, J = 14.8, 1H); 6.80 (AA′BB′ pattern, 4H); 7.15−7.25 (m, 2H); 7.25−7.40 (m, 3H). ^{13}C NMR (50 MHz): 14.25 (CH_3); 19.26 (CH_2); 25.52 (CH); 31.12 (C); 45.04 (CH_2); 55.76 (CH_3); 56.19 (CH); 61.56 (CH_2); 69.33 (CH_2); 114.79 (CH═); 115.46 (CH═); 127.80 (CH═); 128.32 (CH═); 128.84 (CH═); 136.76 (C═); 152.38 (C═); 154.40 (C═); 168.51 (C═O) 169.74 (C═O). Correct elemental analysis could not be obtained due to thermal instability. HRMS: calcd for $C_{23}H_{25}NO_5$ 395.1733, found 395.1737.

Cyclization of 8. After **8** (0.51 g, 2.1 mmol, 1 equiv) was treated with Cu(bpy)Cl (2 equiv) at reflux of butyronitrile (16 mL) during 22 h, chromatography on silica gel of the residue (pentane/Et_2O 10/0−5/5) afforded lactone **9** (270 mg, 76%).

Ethyl 3-Oxa-2-oxobicyclo[3.1.0]hexane-1-carboxylate (9). ^{1}H NMR (200 MHz): 1.32 (t, J = 7.1, 3H); 1.35 (t, J = 4.7, 1H); 2.08 (dd, J = 8.1, 4.7, 1H); 2.73 (dtd, J = 8.1, 4.7, 1.3, 1H); 4.12 (broad d, J = 9.6, 1H); 4.27 (q, J = 7.1, 2H); 4.37 (dd, J = 9.6, 4.7, 1H). ^{13}C NMR (50 MHz): 14.14 (CH_3); 20.80 (CH_2); 28.02 (CH); 29.40 (C); 62.04 (OCH_2); 67.12 (CH_2) (C_5); 166.77 (C═O); 170.73 (C═O). Anal. Calcd for $C_8H_{10}O_4$: C, 56.47, H, 5.92. Found: C, 56.41; H, 6.01.

Cyclization of 10.[4c] After **10** (0.25 g, 0.8 mmol, 1 equiv) was treated with CuCl (0.17 g, 1.7 mmol, 2 equiv) at reflux of isobutyronitrile (16 mL) during 24 h, filtration on a short pad of silica, and concentration, 250 mg of an oily residue was isolated. Preparative HPLC on silica gel (pentane/Et_2O 10/0−5/5) afforded lactone **11a** (149 mg, 60%) and **11b** (49 mg, 20%).

3-(*p*-Chlorobenzyl)-5-chloro-2-(chloromethyl)-3-azacyclopentan-2-one (11a). ^{1}H NMR (200 MHz): 2.84 (m, 1H); 3.19 (dd, J =10.0, 7.1, 1H); 3.40 (dd, J = 10.0, 8.1, 1H); 3.62−3.78 (AB part of an ABX spectrum, J_{AB} = 11.7, 2H); 4.40 (d, J = 7.8, 1H); 4.48 (AB quartet, J_{AB} = 14.9, $\Delta\nu$ = 28.2 Hz, 2H); 7.21−7.65 (AA′XX′ pattern, 4H). ^{13}C NMR (50 MHz): 43.43 (CH_2); 44.75 (CH); 46.72 (CH_2); 46.95 (CH_2); 56.56 (CH); 129.04 (CH═); 129.13 (CH═); 129.62 (CH═); 133.72 (C═); 134.01 (C═); 168.66 (C═O).

3-(*p*-Chlorobenzyl*)*-5-chloro-2-(chloromethyl)-3-azacyclopentan-2-one (11b). ^{1}H NMR (200 MHz): 2.90 (pseudo-quint, J = 7.3, 1H); 3.15 (dd, J = 10.0, 8.0, 1H); 3.35 (dd, J = 10.0, 7.3, 1H); 3.57 (dd, J = 11.2, 7.8, 1H); 3.78 (dd, J = 11.0, 6.8, 1H); 4.45 (AB quartet, J_{AB} = 14.6, $\Delta\nu$ = 38.1 Hz, 2H); 4.50 (d, J = 6.3, 1H); 7.10−7.35 (AA′XX′ pattern, 4H). ^{13}C NMR (50 MHz): 40.49 (CH); 41.73 (CH_2); 46.09 (CH_2); 47.74 (CH_2); 57.32 (CH); 128.91 (CH═); 129.25 (CH═); 133.61 (C═); 133.73 (C═); 169.13 (C═O). Anal. Calcd for $C_{12}H_{12}NOCl_3$ (**11a** + **11b**): C, 49.26; H, 4.13; N, 4.79; Cl, 36.35. Found: C, 49.30; H, 4.26; N, 4.79; Cl, 36.2.

Cyclization of 12. **12** (0.3 g, 1.0 mmol) was treated with 2 equiv of Cu(bpy)Cl in isobutyronitrile (10 mL) over 36 h, at reflux. After purification by preparative HPLC (2,2,4-trimethylpentane/EtOAc 8/2) **13** was isolated (100 mg, 33%).

3-Benzyl-2-(chloromethyl)-5,5-dichloro-3-azacyclopentan-2-one (13).[4c] ^{1}H NMR (200 MHz): 3.00−3.15 (m, 2H); 3.35−3.53 (m, 1H); 3.57−3.73 (m, 1H); 3.95 (dd, J = 11.5, 4.1, 1H); 4.53 (AB quartet, J_{AB} = 14.9Hz, $\Delta\nu$ = 37.3 Hz, 2H); 7.17−7.40 (m, 5H).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **6** and **7** and COSY HH and COSY CH of compound **7** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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