Radical-transfer Catalysis *versus* Lewis Acid Catalysis by the Copper(I) Chloride/2,2′-Bipyridine Complex: an Illustration of the Synthetic Significance of Captodative Radical Stabilization

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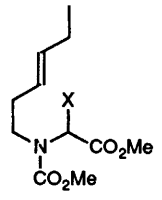
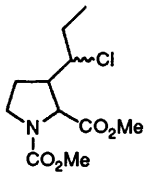
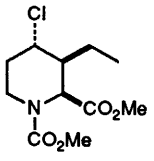
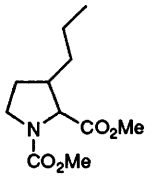
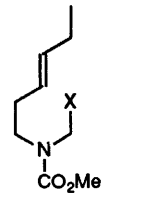
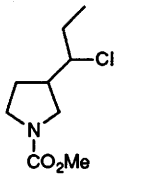
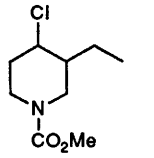
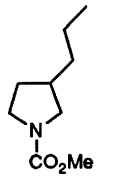
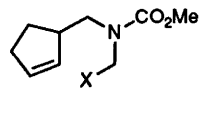
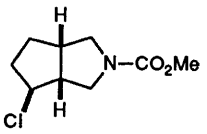
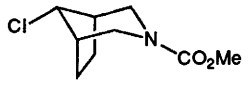
The mechanism of the copper(I) chloride/2,2′-biyridine catalysed π-cyclization of *N*-(chloromethyl)alk-3-enylcarbamates changes from a cationic process (leading to piperidines) into a radical-transfer process (leading to pyrrolidines) upon introduction of an ester substituent at the reactive carbon atom, owing to the captodative effect.

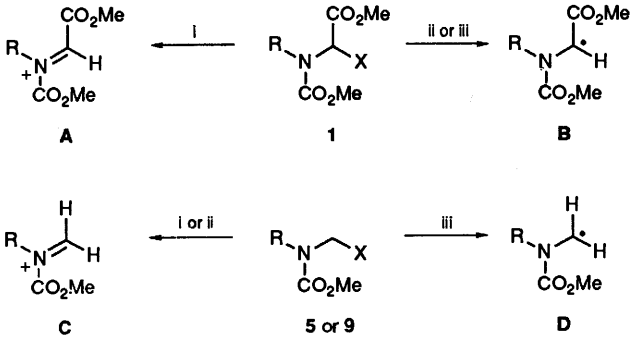
Recently, we published a novel copper(I) chloride/2,2′-bipyridine catalysed radical-transfer cyclization process of α-chloroglycine derivatives [*e.g.* **1** (Table 1, entry 1)] to substituted pyrrolidine-2-carboxylic esters (proline analogues, *e.g.* **2**).[1,2] In this communication we wish to report that upon replacing the ester substituent at the reactive carbon atom by hydrogen, the mechanism of this ring closure becomes a cationic process, leading to piperidines as the main products. We argue that this dual catalytic behaviour of the copper complex is a consequence of the presence or absence of captodative radical stabilization.[3]

The experimental results are collected in Table 1. Treatment of the *N*-hex-3-enylcarbamate **1** (entry 1)[1] with 0.3 equiv. of the *in-situ* formed 1:1 complex of copper(I) chloride and 2,2′-bipyridine in 1,2-dichloroethane at reflux for 18 h gave the 5-*exo* cyclization product **2** in 78% yield, along with a trace amount of the 6-*endo* product **3** (2%). Ring closure also took place without catalyst (entry 4), but then produced the same 6-*endo* product **3** as the sole cyclization product in 33% yield. The piperidine **3** must be the result of a cationic ring closure *via* iminium ion **A** (Scheme 1) as the intermediate. This conclusion is based on previous work on the $SnCl_4$-mediated cyclization of **1** (entry 3), which gives **3** as the sole product in 80% yield.[4] On the other hand, a genuine radical cyclization of **1** (X = Cl) should only lead to the 5-*exo* product, as can be inferred from the Bu_3SnH-mediated cyclization of **1** (entry 2), which produces only the proline derivative **4** in 93% yield.[5] Thus, in the presence of the

Table 1 Cyclization of *N*-(α-chloroalkyl)carbamates to pyrrolidines and piperidines

Entry	Cyclization precursor: Structure	X	Reaction conditions[a]	Products, % yield[b] (*cis*/*trans*[c] ratio)			
1	 **1**	Cl	Cu(bpy)Cl	 **2**	78 (20:80)[d]	 **3**	2	 **4**	—
2[e]		SPh	Bu_3SnH		—		—		93 (35:65)
3[f]		OAc	$SnCl_4$		—		80		—
4		Cl	blank		—		33		—
5	 **5**	Cl	Cu(bpy)Cl	 **6**	—	 **7**	82 (46:54)	 **8**	—
6		SPh	Bu_3SnH		—		—		30
7′		OMe	$SnCl_4$		—		95 (5:95)		—
8		Cl	blank		—		66 (87:13)		—
9	 **9**	Cl	Cu(bpy)Cl	 **10**	30	 **11**			32
10		Cl	$SnCl_4$		37				32
11		Cl	blank		—				—

[a] *Reaction conditions:* Cu(bpy)Cl = CuCl (0.3 equiv.), 2,2′-bipyridine (0.3 equiv.), 1,2-dichloroethane (0.3 mol dm^{-3}), reflux, 18 h; Bu_3SnH = Bu_3SnH (1.4 equiv.), AIBN (cat.), toluene (0.04 mol dm^{-3}), 80–90 °C, see ref. 5; $SnCl_4$ = $SnCl_4$ (2 equiv.), CH_2Cl_2, −78 °C ⟶ room temp., see ref. 4; blank = 1,2-dichloroethane (0.3 mol dm^{-3}), reflux, 18 h. [b] Isolated yields. All new products were appropriately characterized by their IR, NMR and mass spectra. [c] *cis*/*trans* ratio pertaining to ring substitution pattern. [d] Both the *cis* and *trans* isomer consist of a *ca.* 1:1 mixture of chlorine epimers. [e] See ref. 5. [f] See ref. 4.



Scheme 1 *Reagents:* i, $SnCl_4$; ii, Cu(bpy)Cl; iii, Bu_3SnH

copper catalyst, **1** (X = Cl) cyclizes almost exclusively *via* a radical mechanism. We presume that the radical route is preferred in the presence of copper(I), owing to the formation of the relatively stable captodative glycine radical **B** (Scheme 1).[6]

To test this hypothesis, we studied the ring closure of carbamate **5**, which lacks the ester function to stabilize the radical. Chloride **5** was readily prepared from the corresponding hydroxymethyl analogue[7] *via* reaction with PCl_5 in CCl_4. Treatment of **5** with the copper catalyst (entry 5) under the same conditions as for **1** yielded the 6-*endo* cyclization product **7** in 82% yield as the sole product with **6** being undetectable in the reaction mixture. Without catalyst, cyclization also took place (entry 8) to give the same product **7** in 66% yield. Again, the six-membered ring **7** must have been formed in a cationic process *via* **C**, because the $SnCl_4$-mediated cyclization of **5** (X = OMe) is known to give **7** in quantitative yield.[4] The radical reaction of **5** (X = SPh) with Bu_3SnH gave only the product of 5-*exo* cyclization **8** (30%, and 46% of starting material). Thus, in the presence of the copper catalyst, chloride **5** cyclizes in a cationic mechanism *via* **C**. The remarkably different stereoselectivities in the formation of the six-membered ring **7** *via* the three different methods are not readily explained, but do indicate that the copper catalyst functions as a Lewis acid. It is furthermore noteworthy that the radical cyclization of **5** (X = Cl or SPh), which lacks the ester function, is a very slow process. A similar result has been reported for the corresponding α-thiosulfonamides by Padwa *et al.*[8] On the other hand, Bachi *et al.*[9] did not observe salient differences between similar tin hydride mediated radical cyclizations, with or without an ester substituent.

The Lewis acidic activity of the copper catalyst was confirmed in the next series of reactions. Chloride **9** containing a cyclopentenyl function was prepared in the same way as **5** from methyl cyclopent-2-enylmethylcarbamate. The latter compound arose from the BF_3·Et_2O-mediated coupling of cyclopent-2-enyltrimethylsilane[10] with methyl acetoxymethylcarbamate.[4,5] When chloride **9** was treated with the copper catalyst, compounds **10** (30%) and **11** (32%) were isolated. The bridged bicyclic system **11** is the product of 6-*endo* cyclization, which is indicative of an ionic mechanism. Without catalyst, **9**, surprisingly, did not give any trace of cyclization products (entry 11). When treated with $SnCl_4$, chloride **9** cyclized to a mixture of **10** (37%) and **11** (32%). As the regioselectivities of the copper-catalysed cyclization and the $SnCl_4$-mediated cyclization are virtually the same, we presume that the cuprous chloride/2.2′-bipyridine complex now functions as a Lewis acid catalyst. Without copper, the ionic cyclization does not take place, probably because of the difficulty in forming the somewhat strained bicyclic system.

In conclusion, the cuprous chloride/2,2′-bipyridine complex may catalyse two different reaction types, namely radical and cationic processes. Depending on the relative ease of radical and cation generation, respectively, the copper complex may act as a radical transfer catalyst or as a Lewis acid catalyst. The α-chloroglycine derivative **1** leads to a relatively stable captodative radical **B**,[3] whereas the cation is destabilized by the ester function. Therefore, radical reactions prevail with the copper complex. On the other hand, *N*-chloromethylcarbamates **5** or **9** would lead to radicals **D**, lacking special stabilization, so that the copper catalyst in this case functions as a Lewis acid catalyst, producing cations **C**. The copper catalyst thus uniquely illustrates the synthetic relevance of the captodative effect.[11] Our present investigations concentrate on further determining the scope and applications of the copper catalysis as well as the influence of ligand structure.

Acknowledgements

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