Radical Transfer Catalysis *versus* Lewis Acid Catalysis by the Copper(I) Chloride–2,2′-Bipyridine Complex: the Effect of the Structure of the Ligand

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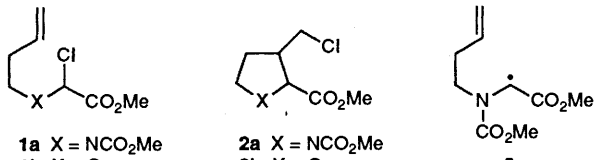
Cyclization of *O*-(but-3-enyl)-α-chloroglycolic acid methyl ester **4** catalysed by copper(I) chloride–2,2′-bipyridine **8** leads primarily to the 5-*exo* product **5**, whereas using copper(I) chloride–6,6′-dimethyl-2,2′-bipyridine as catalyst leads to the 6-*endo* product **6**. This is interpreted in terms of a change from a radical to an ionic mechanism.

Recently, we reported the copper(I) chloride–2,2′-bipyridine-catalysed atom transfer cyclization of α-chloroglycine derivatives **1a** and α-chloroglycolic acid derivatives **1b**.[1] In this way, proline derivatives **2a** and tetrahydrofuran-2-carboxylic acid derivatives **2b** were synthesized. For the glycine derivatives **1a**, we postulated that the copper complex acts as a radical transfer catalyst rather than a Lewis acid catalyst, probably because of the formation of the captodatively stabilized glycine radical **3**.[2] Here, we would like to report the effect of the ligand structure on the regioselectivity of the copper(I) chloride-catalysed cyclization of α-chloroglycolic acid derivative **4**. We will show that it



1a X = NCO_2Me **1b** X = O **2a** X = NCO_2Me **2b** X = O **3**

is possible to control the mechanism of the process by using different ligands, leading to predominant 5-*exo* or, alternatively, 6-*endo* cyclization.

When *O*-(but-3-enyl)-α-chloroglycolic acid methyl ester **4** was heated at reflux in 1,2-dichloroethane in the presence of copper(I) chloride–2,2′-bipyridine for 18 h (Table 1, entry 1), the 5-*exo* cyclization product **5** could be isolated in 73% yield. As a minor product, the 6-*endo* cyclization product **6** is found in 7% yield.† Use of *o*-phenanthroline or 4,4′-dimethyl-2,2′-bipyridine as the ligand (entries 2 and 3) instead of 2,2′-bipyridine gave a similar regioselectivity and stereoselectivity for the cyclization, with the *exo*-cyclization product **5** prevailing. However, the use of 6-methyl-2,2′-bipyridine[3] as the ligand shifted the regioselectivity dramatically in favour of *endo*-cyclization (entry 4): now, tetrahydropyran-2-carboxylic acid derivative **6** was the major product in 54% yield, with only a trace of **5** being isolated (4% yield). When 6,6′-dimethyl-2,2′-bipyridine[3] was used as the ligand for the copper(I) chloride–catalysed reaction, only the *endo*-cyclization product **6** was isolated in 67% yield (entry 5). A similar regio- and stereo-selectivity was found when 2,2′-biquinoline was used as the ligand (entry 6).

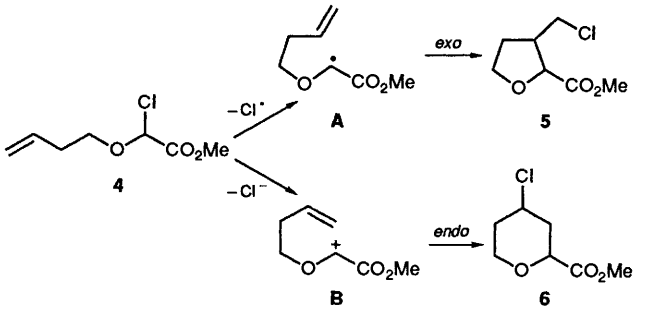
Apparently, two different mechanisms are operating depending on the ligand used. In the case of the unsubstituted 2,2′-bipyridine the radical transfer reaction prevails,‡ leading to

Table 1 Cyclization of *O*-(but-3-enyl)-α-chloroglycolic acid methyl ester[a]

Entry	Ligand	% Yield (*cis*/*trans* ratio)[b] 5	6
1	2,2′-Bipyridine	73 (2:1)	7 (1:2)
2	*o*-Phenanthroline	61 (2:1)	7 (1:2)
3	4,4′-Dimethyl-2,2′-bipyridine	61 (2:1)	7 (1:2)
4	6-Methyl-2,2′-bipyridine	4 (2:1)	54 (1:4)
5	6,6′-Dimethyl-2,2′-bipyridine	—	67 (1:4)
6	2,2′-Biquinoline	—	52 (1:13)

[a] *Reaction conditions:* CuCl (0.3 equiv.), ligand (0.3 equiv.), 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.

the formation of the 5-*exo* cyclization product **5** *via* the captodatively stabilized radical **A** (Scheme 1). This can be



Scheme 1

inferred from the tin hydride cyclization of the corresponding α-thiophenyl precursor, which is known to give only 5-*exo* cyclization.[4] When 6,6′-dimethyl-2,2′-bipyridine is used as the ligand, radical transfer cyclization of chloride **4** does not occur. Instead, the 6-*endo* cyclization product **6** is formed, probably *via* oxonium ion **B** (Scheme 1), which is known to give only *endo*-cyclization.[5] Now, the copper complex acts exclusively as a Lewis acid catalyst.

To determine whether a radical transfer reaction is possible at all when 6,6′-disbustituted bipyridines are used as ligand, we investigated the intermolecular radical transfer reaction of methyl dichloroacetate with styrene in the presence of the copper(I) chloride catalyst[6] under similar conditions. In this case, copper will only catalyse a radical reaction. When 2,2′-bipyridine was used as the ligand (Table 2, entry 1), the coupling

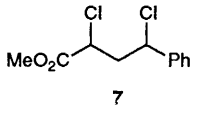
† Unfortunately, the presence of the minor isomer **6** in the cyclization mixture of chloride **4** with copper(I) chloride–2,2′-bipyridine was not mentioned in ref. 1.

‡ Formation of **6** without participation of the copper complex does not occur, because chloride **4** appeared to be sable in a blank experiment (1,2-dichloroethane, 0.3 mol dm^{-3}, reflux, 18 h).

Table 2 Coupling of methyl dichloroacetate and styrene to give **7**[a]

Entry	Ligand	% Yield **7**[b]
1	2,2′-Bipyridine	77 (1.2:1)
2	6-Methyl-2,2′-bipyridine	46 (1.2:1)
3	6,6′-Dimethyl-2,2′-bipyridine	—
4	2,2′-Biquinoline	—

[a] *Reaction conditions:* CuCl (0.3 equiv.), ligand (0.3 equiv.), 1,2-dichloroethane (1 mol dm^{-3}), reflux, 3 h. [b] Isolated yields. Product **7** was appropriately characterized by its IR, NMR and mass spectra.



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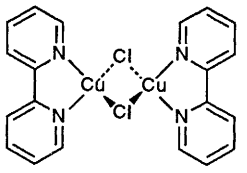

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reaction proceeded smoothly to give adduct **7** in 77% yield. Under the same conditions, use of 6-methyl-2,2′-bipyridine as the ligand (entry 2) provided only 46% of adduct **7**. When 6,6′-dimethyl-2,2′-bipyridine or -2,2′-biquinoline were employed as ligands (entries 3 and 4), the coupling product **7** was not formed.

These results strongly indicate that the copper(I) chloride–6,6′-dimethyl-2,2′-bipyridine complex is indeed not able to catalyse a radical transfer reaction. Thus, chloride **4** cyclizes *via* an ionic pathway when 6,6′-dimethyl-2,2′-bipyridine is used as a ligand in the copper(I) chloride-catalysed reaction, leading to the exclusive formation of the tetrahydropyran derivative **6** *via* cation **B**. When 2,2′-bipyridine is used as a ligand, chloride **4** predominantly cyclizes *via* a radical pathway *via* **A**, giving rise to the formation the tetrahydrofuran derivative **5**.

Apparently, the copper(I) chloride–6,6′-dimethyl-2-2′,bipyridine complex does not abstract a chlorine radical as effectively as the corresponding 2,2′-bipyridine complex. This can be understood if the differences in the coordination spheres of copper(I) and copper(II) are considered. Copper(I) chloride–2,2′-bipyridine is present in aprotic, organic solvents as a binuclear complex **8** with two bridging chlorine atoms.[7] Four-coordinate copper(I) tends to favour a regular tetrahedral arrangement,[8] while copper(II) prefers a square-planar structure.[9] In the catalysis of the radical reaction of **4**, the metal changes its oxidation state from copper(I) to copper(II). The presence of 6,6′-methyl substituents in the ligand may have important implications for the steric feasibility of both types of coordination. In the present case, the eventual close proximity of these methyl groups and chlorine ligands probably disfavours the change from a tetrahedral into a square planar coordination of copper. This steric problem is probably also reflected in the redox potential of $[Cu(6,6'\text{-dimethyl-2,2'-bipyridine})_2]^+$, which is considerably higher[10] than that of the corresponding complex without methyl groups.[8]

In conclusion, we have shown that copper(I) complexes are able to catalyse the cyclization of α-chloroglycolic acid derivative **1**, and that the mechanism, determining the regiochemical outcome of this cyclization, depends on the structure of the ligand used. Our present investigations concentrate on further determining the scope and applications of this type of copper catalysis.

Acknowledgements

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