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$AlCl_3$ as an efficient Lewis acid catalyst in water

Francesco Fringuelli,* Ferdinando Pizzo and Luigi Vaccaro

Dipartimento di Chimica, Università Perugia, Via Elce di Sotto, 8 06123-Perugia, Italy

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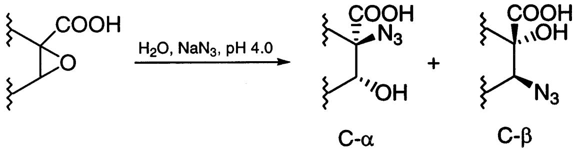
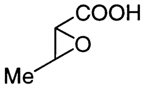
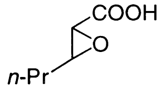
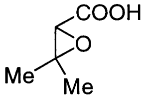
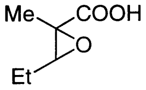
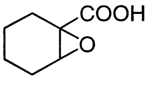
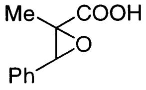
Abstract—For the first time $AlCl_3$ has been conveniently employed as a Lewis acid in water and efficiently catalysed regio- and stereoselective azidolysis of α,β-epoxycarboxylic acids in water. © 2001 Elsevier Science Ltd. All rights reserved.

Lewis acid catalysed organic reactions in water are currently of great research interest.[1] Lanthanide triflates are the most popular *water-tolerant* Lewis acids.[2] They catalyse many reactions[1,3] and are reported to be stable

Table 1. Azidolysis in water at pH 4.0 of α,β-epoxycarboxylic acids catalysed by 1 mol% of $AlCl_3$



Entry	Epoxyacid	Catalyst (1 mol%)	T (°C)	t (h)	C[a] (%)	C-α (%)	C-β (%)	Diol
1		none	30	16	25	50	50	0
2		$AlCl_3$	30	3.5	> 99	< 1	> 99	0
3		none	65	24	82	44	56	0
4		$AlCl_3$	65	1.5	> 99	< 1	> 99	0
5		none	30	3	13	< 1	> 99	0
6		$AlCl_3$	30	0.6	> 99	< 1	> 99	0
7		none	30	8	20	1	99	0
8		$AlCl_3$	30	0.75	> 99	< 1	> 99	0
9		none	30	0.25	2	1	99	0
10		$AlCl_3$	30	0.25	> 99	< 1	> 99	0
11		none	65	20	> 99	1	99	0
12		$AlCl_3$	65	0.25	> 99	0	97	3

[a] Reaction conversion, C-α and C-β percentages were determined by GC analyses; C-β products were isolated in 93-95% yield and the structures agree with those reported in the literature.[4b, 6]

Keywords: aluminum chloride; Lewis acid catalysts; water; azidolysis; green chemistry.

* Corresponding author.

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in water,[3] different from common metal salts (e.g. $AlCl_3$) that decompose readily in water and therefore are thought to be unusable in aqueous medium.[3]

$AlCl_3$ is a hard Lewis acid that coordinates hard basic centres like the oxygen atom of a carbonyl group and that of an epoxide, activating the reagent for a nucleophilic attack. Water is a hard base and therefore nucleophilic reactions catalysed by $AlCl_3$ are recommended to be carried out in organic solvents under anhydrous conditions.

Continuing our investigations[4] on the use of water as reaction medium for organic reactions, we discovered that 1 mol% of $AlCl_3$ effectively catalysed the azidolysis of α,β-epoxycarboxylic acids in water at pH 4.0.

The results for a variety of α,β-epoxycarboxylic acids in the presence and in the absence of $AlCl_3$ are illustrated in Table 1. All the experiments were carried out at pH 4.0, held constant for the whole reaction time.

The reactions carried out in the presence of $AlCl_3$ are fast and completely regio- and diastereoselective. The β-azido-α-hydroxycarboxylic acid coming from the *anti* attack of the azido ion was the sole reaction product, which was isolated in excellent yields. For *trans*-α,β-epoxy-α-methylcinnamic acid only, 3% diol was also detected (Table 1, entry 12).

The comparisons between the uncatalysed (without $AlCl_3$) and catalysed (with $AlCl_3$) reactions, all carried out under the same acidic conditions (see Table 1), show that in the absence of $AlCl_3$ the reactions are much slower, which indicates that under the pH conditions used, Brønsted catalysis is not significant. For example in the absence of $AlCl_3$ the azidolysis α,β-epoxycyclohexanecarboxylic acid at pH 4.0 after 0.25 h gave only a 2% conversion (Table 1, entry 9) whereas, in the presence of $AlCl_3$, after the same reaction time the conversion was complete (Table 1, entry 10); and for α-methyl-*trans*-α,β-epoxy-β-phenylpropanoic acid the complete conversion was reached after 20 h in the absence of Lewis acid catalyst (Table 1, entry 11) and in only 15 min in the presence of $AlCl_3$ (Table 1, entry 12). Furthermore for *trans*-α,β-epoxypropanoic acid and *trans*-α,β-epoxyhexanoic acid the uncatalysed azidolysis is not regioselective (Table 1, entries 1 and 3), while by using 1 mol% of $AlCl_3$ only *anti*-β-azido-α-hydroxycarboxylic acids were obtained.

$AlCl_3$ is not the active catalytic species. $AlCl_3$ dissociates in water very quickly and hydration occurs immediately with the formation of the corresponding aqua ion ($Al(H_2O)_6^{3+}$; $pK_{1,1} = 4.97–5.5^{5a–c}$). At pH 4.0 it was estimated that about 5% hydrolysis of the aqua ion occurs and only monomeric species were present.[5] Therefore we believe that the catalytic species is the aluminium aqua ion that coordinates the epoxycarboxylic acid and azide ion forming a reacting complex; the nucleophile is then regio- and stereoselectively transferred to the substrate β-carbon.

In a typical procedure, the α,β-epoxycarboxylic acid (1.0 mmol) and NaN_3 (5.0 mmol) were dissolved in water (2 mL) with stirring at a suitable temperature (see Table 1) in a thermostated flask equipped with a pH-stat apparatus. An 0.5 M $AlCl_3$ aqueous solution (20 μL) was added and the pH adjusted to 4.0 value by adding 50% H_2SO_4 solution (150 μL). The mixture was stirred for a suitable time (see Table 1) keeping the pH constant at 4.0 by a pH-stat (100 μL of 50% H_2SO_4 aqueous solution). At the end, the mixture was cooled at 0°C, acidified to pH 2.0, extracted with diethyl ether and worked-up as usual to give the β-carbon adduct obtained in pure form in a 93–95% yield.

The mother liquor that remained after the work-up of the reaction can be re-used.[7] We have found that the aqueous solutions from the azidolysis of *trans*-α,β-epoxyhexanoic acid and α,β-epoxycyclohexancarboxylic acid can be re-used three times without loss of reactivity and selectivity.[7]

The azidolysis of α,β-epoxycarboxylic acids and their ester derivatives has been widely investigated and many catalysts have been tested,[4c,6] but a 1 mol% amount of catalyst has never been used. To our knowledge this is also the first report on the use of $AlCl_3$ in water to catalyse an organic reaction.

The possibility of using $AlCl_3$ in water opens new research strategies in organic synthesis, which are being studied in our laboratory.

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References

1. (a) Li, C. J.; Chang, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; (b) Various authors *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998.
2. (a) Kobayashi, S. *Synlett* **1994**, 689; (b) Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.
3. Xie, W.; Jin, Y.; Wang, P. G. *Chemtech* **1999**, 23.
4. (a) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **1999**, *64*, 6094; (b) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synlett* **2000**, 311; (c) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, 646.
5. (a) Richens, D. T. *The Chemistry of Aqua Ions*; Wiley: New York, 1997; (b) Baes Jr., C. F.; Mesmer, R. E. *The Hydrolysis of Cations*; Wiley: New York, 1976; (c) Various authors, *Coordination Chemistry of Aluminum*; Robinson, G. H., Ed.; VCH: New York, 1993; (d) Brown, P. L.; Sylva, R. N.; Batley, G. E.; Ellis, J. *J. Chem. Soc., Dalton Trans.* **1985**, 1967.

6. (a) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560; (b) Saito, S.; Takahashi, N.; Ishikawa, T.; Moriwake, T. *Tetrahedron Lett.* **1991**, *32*, 667; (c) Azzena, F.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron* **1995**, *48*, 13409; (d) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 1; (e) Thijs, L.; Porskamp, J. J. M.; van Loon, A. A. W. M.; Derks, M. P. W.; Feenstra, R. W.; Legters, J.; Zwanenburg, B. *Tetrahedron* **1990**, *46*, 2611.
7. Powdered NaN_3 (5 mmol) was added to the remaining mother liquor (ca. 2 mL) after extraction of β-azido-α-hydroxycarboxylic acid. Then α,β-epoxycarboxylic acid (1 mmol) was added and the pH of the reaction medium was adjusted to pH 4.0 by 50% H_2SO_4 aqueous solution (ca. 100 μL). The mixture was stirred at the temperature and for the time indicated in Table 1 and the pH was kept at the 4.0 value by using a pH-stat. The mixture was then worked-up as indicated in the typical procedure. The mother liquor was reused three times without loss of reactivity and selectivity.