Metalation of 2-Chloromethyl-2-oxazolines: Synthesis of 1,2,3-Tris(oxazolinyl)cyclopropanes and Derivatives

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Received July 24, 2001

2-Chloromethyl-2-oxazoline converts cleanly into *trans*-1,2,3-tris(oxazolinyl)cyclopropane upon treatment with strong bases such as LDA or $KN(SiMe_3)_2$. Deprotonation of the above cyclopropane followed by the addition of electrophiles allows the preparation of more functionalized tris-(oxazolinyl)cyclopropanes.

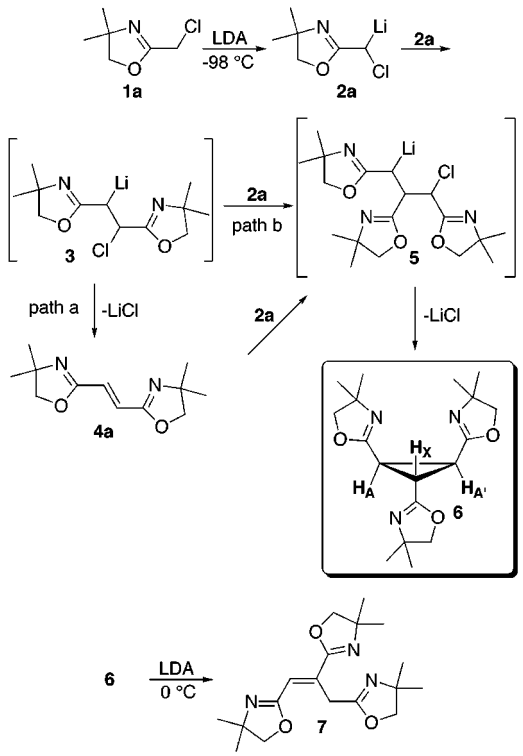
Introduction

Metalated 2-chloroalkyl-2-oxazolines, which are synthetically useful intermediates, have received some attention in recent years:[1] a few papers from our laboratory have proved that lithiated chloroalkyloxazolines behave as Darzens reagents and add to carbonyl compounds and imines to produce functionalized epoxides and aziridines.[2] It was observed that stability and reactivity of such lithiated heterocycles depend markedly on the α substitution so that, while the unsubstituted ones are unstable and very reactive, the substituted ones are quite stable at low temperature and allow a detailed spectroscopic examination.[3]

Results and Discussion

We report herein on the fate of certain metalated chloroalkyloxazolines in the absence of an external electrophile. When treated with 2 equiv of LDA in THF at −98 °C, 2-chloromethyl-2-oxazoline **1a** is quickly (few seconds) and almost quantitatively converted into a compound that has been assigned the structure of *trans*-1,2,3-tris(oxazolinyl)cyclopropane **6** on the basis of elemental analysis, GC−MS, and ^{1}H and ^{13}C NMR data. In particular, the ^{1}H NMR spectrum clearly indicated that the three oxazolinyl groups on the cyclopropane ring are in a trans arrangement. Indeed, the three cyclopropane ring hydrogens constitute two sets of nuclei within an A_2X-type spin system; H_A and $H_{A'}$ (see Scheme 1), which can be interchanged by reflection at a plane of symmetry, are *enantiotopic*, and give a doublet (J = 5.9 Hz) while the third cyclopropane ring hydrogen (H_X) gives a triplet (J = 5.9 Hz), the coupling constant value being also in agreement with a typical trans arrangement.[4] This consideration is also supported by the ^{13}C NMR spectrum, which shows only two ring carbons appearing at 20.5 and 22.6 ppm, confirming the stereochemistry shown. A possible explanation for the formation of **6** is illustrated in Scheme 1.

Scheme 1



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(1) (a) Meyers, A. I.; Knaus, G.; Kendall, P. M. *Tetrahedron Lett.* **1974**, 3495. (b) Kamata, K.; Sato, H.; Takagi, E.; Agata, I.; Meyers, A. I. *Heterocycles*, **1999**, *51*, 373. (c) Liddell, R.; Whiteley, C. G. *J. Chem. Soc., Chem. Commun.* **1983**, 1535. (d) English, R. B.; Liddell, J. R.; Whiteley, C. G. *S.-Afr. J. Chem.* **1987**, *40*, 39. (e) Liddell, J. R.; Whiteley, C. G. *S.-Afr. J. Chem.* **1991**, *44*, 35. (f) Florio, S.; Capriati, V.; Luisi, R.; Abbotto, A. *Tetrahedron Lett.* **1999**, *40*, 7421. (g) Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **2000**, *41*, 5295.

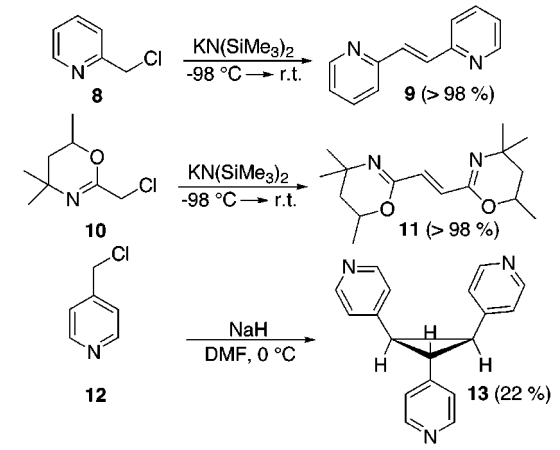
(2) (a) Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **1996**, *37*, 4781. (b) Florio, S.; Troisi, L.; Capriati, V.; Coletta, G. *Tetrahedron* **1999**, *35*, 9859. (c) Florio, S.; Troisi, L.; Capriati, V.; Ingrosso, G. *Tetrahedron Lett.* **1999**, *40*, 6101. (d) Florio, S.; Capriati, V.; Luisi, R.; Abbotto, A.; Pippel, D. J. *Tetrahedron* **2001**, *57*, 6775.

(3) Abbotto, A.; Bradamante, S.; Florio, S.; Capriati, V. *J. Org. Chem.* **1997**, *62*, 8937.

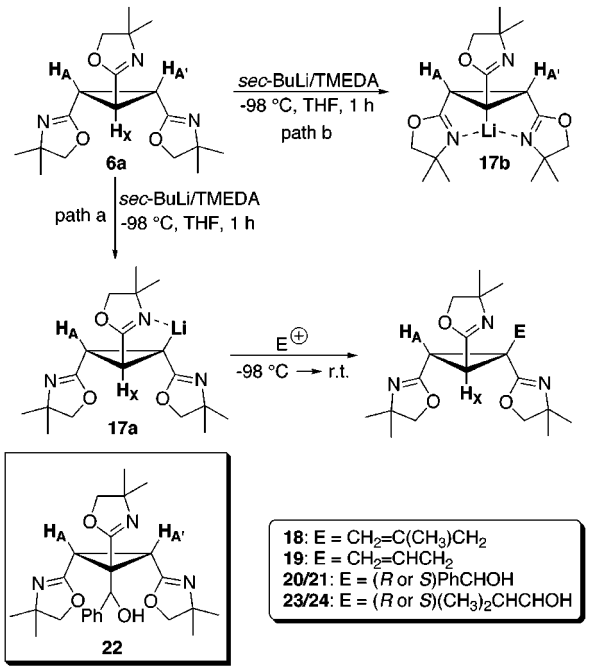
(4) Vicinal coupling constants between protons of cyclopropanes exhibit a strong dependence on the stereochemistry of the two protons and depend also on the electronegativities of the substituents, decreasing as the latter increase. The relationship J_{cis} (8−12 Hz) > J_{trans} (4−7 Hz) is always observed, and there are no known exceptions (see: Gaudemar, A. In *Stereochemistry: fundamentals and methods*; Kagan, H. B., Ed.; Georg Thieme Publishers: Stuttgart, 1977; Vol. 1. Determination of configurations by spectrometric methods, pp 77−83). In our case, *all-trans*-tris(oxazolinyl)cyclopropanes (**6**, **18**−**21**, **23**−**24**) exhibit a $^3J_{H-H}$ in the range of 6.6−7.1, while only in the case of a presumed cis derivative (**22**) the $^3J_{H-H}$ observed has been of 10.1 Hz.

10.1021/jo015962i CCC: $22.00
Published on Web 01/08/2002

Scheme 2



Scheme 3



The acidity of the α hydrogens of **1a** (pK_a likely lower than 20) is such that treatment of **1a** with 2 equiv of LDA should convert it almost quantitatively into **2a**. The homocoupling reaction[5a] of carbenoid **2a** might take place to give compound **3** and then the *E*-bis(oxazolinyl)ethene **4a**[5b] (path a, Scheme 1). Then, a Michael-type addition of **2a** to **4a** would occur leading to the formation of **6**. Such a hypothesis was supported by the experimental evidence that the deprotonation reaction of **1a**, carried out by using only 0.55 equiv of LDA, led to the formation of the ethene **4a** (3.3%), cyclopropane **6** (27%), starting oxazoline **1a** (66%), and compound **7** (3%).[6] Compound **7** is not an intermediate in the **1a** → **6** conversion. Indeed, when in another experiment **7** was subjected to deprotonation with LDA, the resulting stabilized propenyl anion did not cyclize to **6**, and **7** was recovered unchanged after quenching with NH_4Cl. This confirms that cyclopropane **6** arises from the 1,4-addition of **2a** to **4a** followed by the intramolecular cyclization of the resulting organolithium **5**. Instead, compound **7** likely results from the ring opening of **6**. Indeed, treatment of **6** with 2 equiv of LDA at 0 °C afforded an almost quantitative yield of **7**, while the use of only 1 equiv of LDA led to a mixture of **6** (83%) and **7** (17%) (by GC analysis). In another experiment, carried out in order to confirm that alkene **4a** is actually an intermediate, a mixture of 1 equiv of **4a** and 1 equiv of **1a** was treated at −98 °C with 0.5 equiv of LDA: an almost 1:1 mixture of **1a** and **4a** was obtained together with cyclopropane **6** (40% yield, 0.4 equiv).[7] The lack of increase of **4a** in such experiment would support the above mechanism, while there are no evidences that **6** could form via a second nucleophilic substitution of **2a** on **3** to give **5** (path b, Scheme 1). An even cleaner and faster reaction occurred when oxazoline **1a** was treated with $KN(SiMe_3)_2$: cyclopropane **6** formed quantitatively.

The bias of metalated 2-chloromethyl-2-oxazoline **1a** to undergo cyclopropanation seems to be peculiar of this five-membered ring heterocycle. Indeed, we have found that six-membered ring heterocycles such as 2-(chloromethyl)pyridine **8** and 2-(chloromethyl)-4,4,6-trimethyl-5,6-dihydro-4*H*-[1,3]oxazine **10** when treated with $KN(SiMe_3)_2$ under the same conditions used for **1a** gave quantitative yields of (*E*)-1,2-bis(2-pyridyl)ethene **9** and (*E*)-1,2-bis(4,4,6-trimethyl-5,6-dihydro-4*H*-[1,3]oxazin-2-yl)ethene **11**.[5] 4-(Chloromethyl)pyridine **12** has been reported to give *trans*-1,2,3-tris(4-pyridyl)cyclopropane **13** (22% yield) upon treatment with NaH (DMF, 2 days, 0 °C) (Scheme 2).[8]

The different behavior toward $KN(SiMe_3)_2$ shown by chloromethyl derivatives **1a** and **10** could be explained in terms of a different electrophilicity of the corresponding alkenes **4a** and **11**. By using the electrophilicity index proposed by Parr,[9a] we have found that, at the B3LYP/6-31G* level, bis(oxazolinyl)alkene **4a** (ω_{gs} = 1.05 eV) has a larger electrophilic character than the bis(dihydrooxazinyl)alkene **11** (ω_{gs} = 0.91 eV),[9b] and this could explain the fact that **11** does not undergo the Michael-type addition by lithiated 2-chloromethyloxazine **10** to give the corresponding cyclopropane derivative. The diverse electrophilicities could be explained by the dif-

(5) (a) Reaction of carbenoids to give alkenes have been extensively studied; see: Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697. (b) The *E* configuration of **4a** and **11** was established by considering the doublet of doublets arising from ^{13}C satellites for the peaks at δ 6.66 and 6.56 in their ^1H NMR spectra, respectively. The larger splittings due to a $^1J_{13C-H}$ are 168.4 and 166.5 Hz, while the smaller ones due to a $^3J_{H-H}$ splittings are 16.5 and 16.6 Hz. The magnitude of the latter gives evidence for a trans arrangement of the vinylic hydrogens. Spectroscopic data for **4a** and **11** have been reported in: Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049. Malone, G. R.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 618. Compound **9** shows spectroscopic data identical to that of the commercially available one.

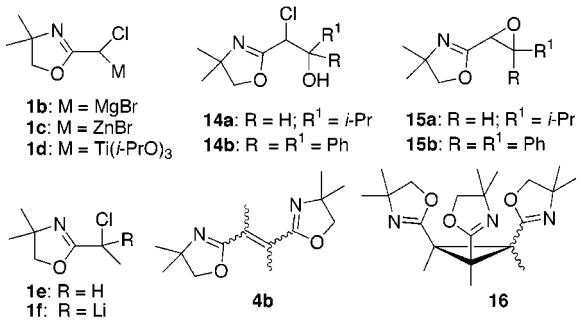
(6) The *E* stereochemistry of the double bond of compound **7** as well as the relative configuration of compounds **20**−**24** have been also supported by their phase-sensitive NOESY spectra.

(7) The minor quantity of **6** found instead of the expected 0.5 equiv could be ascribed to a competitive consumption of base by the cyclopropane **6** formed. **1a**/**4a**/**6** ratio based on the ^1H NMR spectra on the crude reaction mixture.

(8) (a) Breslow, R.; Crispino, G. A. *Tetrahedron Lett.* **1991**, *32*, 601. (b) Breslow, R.; Crispino, G. A. *J. Org. Chem.* **1992**, *57*, 1849.

(9) (a) Parr, R. G.; Szentpály, László, v.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922. (b) Ab initio calculations (Density functional theory (DFT) and B3LYP/6-31G*) have been performed on optimized geometries with a point group symmetry C_{2h} and C_i for alkenes **4a** and **11**, respectively; ω_{gs} has been calculated for both in terms of the ionization potential *I* and electron affinity *A* according to the Parr equation, *I* and *A* being the energy differences between the radical cation and the neutral and between the neutral and the radical anion, respectively. It might be useful pointing out that different values of electrophilicity indexes could be obtained by using different methods of calculation of *I* (HOMO Energy) and *A* (LUMO Energy). (c) One of the referees provided us with the electrophilicity index of **4b** (1.37 eV) calculated (DFT and B3LYP/6-31G*) for the HOMO and LUMO energies for the full optimized molecule at the ground state.

Chart 1



ferent endocyclic nature of the C−N double bond in the oxazolinyl alkene and in the dihydrooxazinyl alkene (five atoms versus six atoms, respectively). The larger strain of the unsaturated five membered ring could polarize more effectively the C−N double bond along the nucleophilic attack of **2a** thus increasing the electrophilicity of the alkene **4a**.

In an effort to tune the reactivity of metalated oxazoline **1a** toward the preferential formation of cyclopropane **6** or ethene **4a**, we addressed our attention to some other metalated derivatives. Addition of LDA to a 1:4.2 mixture of **1a** and $MgBr_2$ at −98 °C produced the putative magnesium derivative **1b** (Chart 1) that rapidly transformed into (*E*)-1,2-bis(oxazolinyl)ethene **4a** (53% isolated yield) and cyclopropane **6** (10% isolated yield). In contrast, zinc derivative **1c**, prepared by addition of LDA to a 1:2 mixture of **1a** and $ZnBr_2$, did not undergo any transformation in the absence of electrophiles, even at room temperature. However, the addition of isobutyraldehyde or benzophenone furnished chlorohydrins **14a**,**b** and epoxides **15a**,**b**[2a,10] upon treatment with NaOH. Titanium derivative **1d**, prepared by addition of LDA to a 1:1.3 mixture of oxazoline **1a** and Ti(*i*-PrO)$_4$, was found to be rather reluctant to undergo the homocoupling reaction at least at low temperature. Indeed, a GC analysis of the reaction mixture after 2 h at low temperature indicated the presence of just small amounts (about 10%) of the alkene **4a**. Warming of the reaction mixture to room temperature afforded a mixture of **4a** and **6** (in a 2:3 ratio; 98% combined yield by ^{1}H NMR).

The homocoupling reaction and consequently the cyclopropanation of metalated chloroalkyloxazolines is markedly sensitive to the α substitution. Indeed, lithiation of 2-(1-chloroethyl)oxazoline **1e**, under the same conditions used for the lithiation of **1a**, generated derivative **1f**, which was found to be much more stable than **2a** and could be kept at low temperature even for days without undergoing any transformation.[3] However, warming of **1f** to room temperature afforded mainly substituted 2-butene **4b** as a mixture of two separable *E*- and *Z*-stereoisomers[11] (17% combined yield, *E*/*Z* = 3/1) and very small amounts of cyclopropane **16 (**detected by GC−MS analysis). The reaction of **1e** with KN(SiMe$_3$)$_2$ (1.3 equiv, −98 °C → r.t., 4 h) furnished mainly 2-butene **4b** (*E* + *Z*) (80% combined yield, *E*/*Z* = 1.6:1). No trace of compound **16** could be detected in this case. The reluctancy of metalated a-chloroethyl oxazoline **1e** could be similarly explained by assuming that alkene **4b** is not sufficiently electrophilic because of the electron-releasing methyl groups on the C−C double bond.[9c]

Lithiation of *trans*-1,2,3-Tris(oxazolinyl)cyclopropane 6. There are two sets of nuclei having chemical shift equivalence (H_A/$H_{A'}$ and H_X) on the cyclopropane ring of **6** which are susceptible of removal by a base to generate metalated species **17a** (path a) and **17b** (path b), both of them being stabilized by intramolecular chelation. In practice, lithiation of **6** with *s*-BuLi/TMEDA occurred in a highly regioselective and stereoselective manner furnishing organolithium **17a** (Scheme 3).

Its trapping with methallylbromide afforded cyclopropane derivative **18** (95% yield, by ^{1}H NMR analysis on the crude reaction mixture), with the oxazolinyl groups in a trans arrangement as suggested by the vicinal coupling between the two cyclopropane ring hydrogens ($^3J_{H-H}$ = 6.8 Hz)[4] and confirmed by a phase-sensitive NOESY experiment showing a cross-peak to be ascribed to the interaction between H_A and the methylene hydrogens belonging to the methallyl chain. Comparable results were obtained when **17a** was treated with allylbromide to give **19** ($^3J_{H-H(trans)}$ = 6.6 Hz)[4] (90% yield, by ^{1}H NMR analysis on the crude reaction mixture) (Scheme 3).

Equally stereoselective was the reaction of **17a** with aldehydes. Indeed, the addition of benzaldehyde to **17a** furnished a very good yield (> 90%, by ^{1}H NMR analysis on the crude reaction mixture) of substituted hydroxybenzylcyclopropanes **20** ($^3J_{H-H(trans)}$ = 7.1 Hz)[4,6] and **21** ($^3J_{H-H(trans)}$ = 6.8 Hz)[4,6] in a 4:1 ratio, traces of **22** ($^3J_{H-H(cis)}$ = 10.1 Hz),[4,6] and about 5% of the starting cyclopropane **6**. The structure of **20** was also unambiguously confirmed by X-ray analysis (Scheme 3).[12]

Moreover, addition of isobutyraldehyde resulted in the stereoselective formation of substituted hydroxyalkyl cyclopropanes **23** and **24** ($^3J_{H-H(trans)}$ = 6.6 Hz for **23**; $^3J_{H-H(trans)}$ = 7.1 Hz for **24**)[4,6] (in a 7/3 ratio; > 80% combined yield by ^{1}H NMR analysis on the crude reaction mixture) (Scheme 3).

Conclusions

In conclusion, in this paper we have shown for the first time that 2-chloroalkyloxazolines, when metalated, behave like chlorocarbenes and tend to "dimerize" to give bis(oxazolinyl)alkenes or to "trimerize" to give tris(oxazolinyl)cyclopropanes depending upon the α substitution and the metal used. Moreover, it is worth pointing out that the above so far undescribed oxazolinylcyclopropanes are potential intermediates for the synthesis of functionalized cyclopropanes, among which oligopeptides, by elaboration of the oxazolinyl groups on the cyclopropane ring.

(10) Capriati, V.; Florio, S.; Luisi, R.; Russo, V.; Salomone, A. *Tetrahedron Lett.* **2000**, *41*, 8835.

(11) The configuration of the two *E*- and *Z*-butenes has been assigned either on the basis of ^{1}H or ^{13}C chemical shifts of the "allylic" proton/carbon atoms. As regards ^{13}C NMR spectra, it has been reported (see: Gaudemar, A. In *Stereochemistry: fundamentals and methods*; Kagan, H. B., Ed.; Georg Thieme Publishers: Stuttgart, 1977; Vol. 1. Determination of configurations by spectrometric methods, pp 55−56) that these carbon atoms resonate at higher field in *Z*-isomers than in *E*-ones (17.51 vs 18.58 δ, in our case). Finally, in ^{1}H NMR spectra, allylic protons in the *E*-isomer should get a double oxazolinyl deshielding effect and so resonate at lower field (2.07 vs 1.94 δ).

(12) Crystallographic data for compound **20** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-163504). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: (int.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. ORTEP view and crystallographic data for compound **20** have been also reported as Supporting Information; all diagrams and calculations were performed using maXus (Nonius, Delft & MacScience, Japan).

Experimental Section

General Methods. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was distilled over finely powdered calcium hydride. 2-Chloromethyl-4,4-dimethyloxazoline (**1a**)[2a] and 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline (**1e**)[3] were prepared as reported. All other chemicals were of commercial grade (Aldrich) and used without further purification. Petroleum ether refers to the 40−60 °C boiling fraction. Commercial solutions of *n*-BuLi (2.5 M solution in hexanes) and *s*-BuLi (1.3 M solution in cyclohexane) were titrated by using *N*-pivaloyl-*o*-toluidine prior to use.[13] For the ^1H and ^{13}C NMR spectra (^1H NMR 300, 500 MHz; ^{13}C NMR 50.3, 125 MHz) $CDCl_3$ was used as solvent. GC−MS spectrometry analyses were performed on a gas chromatograph HP 5890 II (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Melting points were uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished by UV light (254 nm) and by exposing to I_2 vapor. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

Preparation of *trans*-1,2,3-Tris(4,4-dimethyl-2-oxazolin-2-yl)cyclopropane (6). To a stirred solution of 0.5 g (3.38 mmol) of 2-chloromethyl-4,4-dimethyl-2-oxazoline (**1a**) in 20 mL of dry THF was added 9 mL (6.76 mmol) of potassium bis(trimethylsilyl)amide (0.15 M solution in toluene) at − 98 °C, under N_2. After 5 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), the cooling bath removed, and the mixture allowed to warm to room temperature. AcOEt was then added, the organic layer was separated, and the aqueous layer was extracted with AcOEt (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give 370 mg of **6** as a dark-yellow viscose oil (98% yield, by ^1H NMR). Compound **6** could be used straightforwardly in the next chemical transformations. Further purification of the crude oil could be performed either by flash chromatography (silica gel, acetone/CH_2Cl_2 = 9/1, R_f = 0.37) or by high vacuum distillation by means of a kugelrohr apparatus (165 °C, 10^{-2} mmHg). Crystallization of the light yellow oil so obtained by Et_2O gave a white solid: mp 72 °C; ^1H NMR (500 MHz) δ 1.18 (s, 6 H, 2 × C*H*$_3$), 1.19 (s, 6 H, 2 × C*H*$_3$), 1.20 (s, 6 H, 2 × C*H*$_3$), 2.42 (d, J = 5.9 Hz, 2 H, 2 × C*H*), 2.69 (t, J = 5.9 Hz, 1 H, C*H*), 3.78−3.84 (m, 6 H, 3 × C*H*$_2$O); ^{13}C NMR (125 MHz, DEPT) δ 20.5 (*C*H), 22.6 (2 × *C*H), 28.1 (2 × *C*H$_3$), 28.2 (2 × *C*H$_3$), 28.3 (2 × *C*H$_3$), 67.1 [2 × *C*(CH$_3$)$_2$], 67.2 [*C*(CH$_3$)$_2$], 79.1 (2 × *C*H$_2$O), 79.2 (*C*H$_2$O), 160.8 (*C*═N), 162.6 (2 × *C*═N); FT-IR (film, cm^{-1}) 1662 (s, C═N); GC−MS (70 eV) *m*/*z* (%) 333 (M$^+$, 2.8), 319 (25.9), 318 (100.0), 302 (7.6), 246 (47.1), 205 (39.0), 174 (41.4), 55 (9.0). Anal. Calcd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.72; H, 7.93; N, 12.57.

Reaction of 2-Chloromethyl-4,4-dimethyloxazoline (1a) with LDA to Give 4a, 6, and 7. To a precooled (−98 °C, with a methanol liquid nitrogen bath) solution of LDA [prepared from *n*-BuLi (7.05 mmol) and *i*-Pr$_2$NH (7.05 mmol) in dry Et_2O (or dry THF), under N_2 at 0 °C] was added dropwise a solution of **1a** (3.38 mmol) in 20 mL of Et_2O (or THF). The reaction mixture was stirred for 5 min, quenched with saturated aqueous NH_4Cl, extracted with AcOEt (3 × 10 mL), and evaporated under reduced pressure to give a mixture of **6**, **4a**, and **7**, which were separated by column chromatography on silica gel (95% combined yield; **6**/**4a**/**7** = 85:5:10 by ^1H NMR analysis on the crude; AcOEt/petroleum ether 9/1 to elute **4a**[5] (R_f = 0.2), then AcOEt/MeOH 95/5 to elute **7** (R_f = 0.2) and **6** (R_f = 0.1)]. **(*E*)-1,2,3-Tris(4,4-dimethyl-2-oxazolin-2-yl)-propene (7):** waxy solid; ^1H NMR (500 MHz) δ 1.16 (s, 6 H, 2 × C*H*$_3$), 1.23 (s, 12 H, 4 × C*H*$_3$), 3.82−3.92 (m, 8 H, 3 × C*H*$_2$O + C*H*$_2$C═), 6.79 (s, 1 H, C*H*═); ^{13}C NMR (125 MHz, DEPT) δ 28.0 (2 × *C*H$_3$), 28.1 (2 × *C*H$_3$), 28.1 (2 × *C*H$_3$), 66.9 [*C*(CH$_3$)$_2$], 67.0 [2 × *C*(CH$_3$)$_2$], 67.9 (*C*H$_2$C═), 78.6 (*C*H$_2$O), 79.0 (*C*H$_2$O), 79.1 (*C*H$_2$O), 123.4 (*C*H═), 133.2 (*C*═), 160.4 (*C*═N), 161.9 (*C*═N), 163.2 (*C*═N); FT-IR (film, cm^{-1}) 1670 (s, C═N), 1632 (s, C═N); GC−MS (70 eV) *m*/*z* 333 (M$^+$, 72.4), 318 (65.6), 278 (33.8), 277 (30.4), 246 (47.3), 235 (100.0), 219 (40.1), 174 (55.9). Anal. Calcd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.46; H, 7.84; N, 12.57.

Reaction of 2-Chloromethyl-4,4-dimethyl-2-oxazoline (1a) with LDA and $MgBr_2$. To a stirred and precooled (−98 °C) THF (50 mL) solution of compound **1a** (3.38 mmol) and perfectly dry $MgBr_2$ (14.20 mmol) was added dropwise a solution of LDA [from *n*-BuLi (6.08 mmol) and *i*-Pr$_2$NH (6.08 mmol in dry THF (10 mL), under N_2]. The reaction mixture was stirred at −98 °C for 30 min, quenched with saturated aqueous NH_4Cl, extracted with AcOEt (3 × 20 mL), and evaporated in vacuo to give a mixture of **4a** and **6** which was column chromatographed on silica gel using first AcOEt to elute **4a** (200 mg, 53% yield) and then AcOEt /MeOH 95/5 to elute **6** (38 mg, 10% yield).

Reaction of 2-Chloromethyl-4,4-dimethyloxazoline (1a) with LDA and $ZnBr_2$. To a stirred and precooled (−98 °C) Et_2O solution (50 mL) of **1a** (3.38 mmol) and $ZnBr_2$ (6.76 mmol) was added dropwise a solution of LDA [from *n*-BuLi (6.76 mmol) and *i*-Pr$_2$NH (6.76 mmol in dry Et_2O (10 mL), under N_2]. The reaction mixture was slowly allowed to warm to room temperature, and after 2.5 h, isobutyraldehyde (3.71 mmol) was added. The mixture was stirred overnight, quenched with saturated aqueous NH_4Cl, extracted with AcOEt (3 × 20 mL), and evaporated in vacuo to give the crude chlorohydrin **14a** (syn/anti: 1/1), which was quantitatively converted into the epoxide **15a**[10] upon treatment with NaOH 5% w/w (10 mL) in *i*-PrOH (5 mL) and purified by column chromatography (silica gel, petroleum ether/AcOEt 7/3, 65% combined yield, cis/trans 1:1). When 1 equiv of benzophenone was added after 2.5 h to the reaction mixture instead of isobutyraldehyde, chlorohydrin **14b** and then epoxide **15b**[2a] were obtained; the latter being purified by column chromatography (silica gel, AcOEt/petroleum ether 3/7, 53% yield).

Reaction of 2-Chloromethyl-4,4-dimethyl-2-oxazoline (1a) with LDA and Ti(*i*-PrO)$_4$. To a stirred and precooled (−98 °C) solution of LDA [from *n*-BuLi (2.64 mmol) and *i*-Pr$_2$NH (2.64 mmol) in dry Et_2O (10 mL), under N_2] was added dropwise a solution of Ti(*i*-PrO)$_4$ (2.64 mmol) in Et_2O (10 mL); after a few seconds, **1a** (2.03 mmol) was added all at once. After 1.45 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with AcOEt (3 × 20 mL), and evaporated in vacuo to give a mixture of **4a** and **1a** (**4a**/**1a** = 1/9 by ^1H NMR). In another experiment, a solution of LDA (2.64 mmol in 10 mL of Et_2O) was added to a well-stirred and precooled (−98 °C) solution of **1a** (2.03 mmol) and Ti(*i*-PrO)$_4$ (2.64 mmol) in 10 mL of Et_2O. The reaction mixture was monitored by GC analysis with the following results: only compound **1a** was detected after 30 min (at −98 °C); a mixture of **1a**, **4a** and **6** (in a 58/24/18 ratio) after 1.5 h; a mixture of **4a** and **6** (in a 2/3 ratio; 98% combined yield by ^1H NMR) after 4 h. It is possible to isolate **4a** and **6** as reported in the procedure with $MgBr_2$.

Reaction of 2-(1-Chloroethyl)-4,4-dimethyl-2-oxazoline (1b) with Potassium Bis(trimethylsilyl)amide [(Me$_3$Si)$_2$NK]. To a stirred and precooled (−98 °C) solution of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline (**1b**) (0.5 g, 3.1 mmol) in THF (20 mL) was added potassium bis(trimethylsilyl)amide (4.0 mmol, 5.4 mL) under N_2. The reaction mixture was slowly allowed to warm to room temperature and after 4 h was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with AcOEt (3 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give **4b** as a mixture of *E* and *Z* isomers (*Z*/*E* = 1/1.6; 80% combined yield by ^1H NMR on the crude), which were separated and purified by flash chromatography (silica gel, AcOEt, $R_{f(Z)}$ = 0.20, $R_{f(E)}$ = 0.11) and showed the following spectral data:

(2*E*)-Bis(4,4-dimethyl-2-oxazolin-2-yl)-2-butene (4b): light yellow oil; ^1H NMR (500 MHz) δ 1.22 (s, 12 H, 4 × C*H*$_3$ oxazoline), 1.94 (s, 6 H, 2 × C*H*$_3$), 3.86 (s, 4 H, 2 × C*H*$_2$O). ^{13}C NMR (125 MHz, DEPT) δ 17.5 (2 × *C*H$_3$), 27.9 (4 × *C*H$_3$

(13) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509−512.

oxazoline), 67.2 [2 × *C*$(CH_3)_2$], 78.8 (2 × *C*H_2O), 128.6 (2 × *C*═), 163.3 (2 × *C*═N); FT-IR (KBr, cm^{-1}) 1662 (s, C═N), 1642 (s, C═N); GC−MS (70 eV) *m*/*z* 250 (M^+, 0.5), 236 (4.4), 205 (9.2), 194 (96.2), 179 (21.3), 163 (100.0), 149 (4.7), 136 (5.8), 125 (7.2), 108 (10.3), 53 (9.1), 41 (6.3). Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.46; H, 9.12; N, 11.37. **(2*Z*)-Bis(4,4-dimethyl-2-oxazolin-2-yl)-2-butene (4b).** Light yellow oil. ^{1}H NMR (500 MHz) δ 1.28 (s, 12 H, 4 × C*H*$_3$ oxazoline), 2.07 (s, 6 H, 2 × C*H*$_3$), 3.93 (s, 4 H, 2 × C*H*$_2$O). ^{13}C NMR (125 MHz, DEPT) δ 18.5 (2 × *C*H_3), 28.1 (4 × *C*H_3 oxazoline), 67.1 [2 × *C*$(CH_3)_2$], 78.4 (2 × *C*H_2O), 129.2 (2 × *C*═), 163.3 (2 × *C*═N). FT-IR (KBr, cm^{-1}) 1655 (s, C═N). GC-MS (70 eV) *m*/*z* (%) 250 (M^+, 38.0), 235 (11.3), 205 (12.3), 194 (17.6), 178 (27.3), 165 (100.0), 152 (29.2), 138 (57.8), 124 (13.7), 107 (16.2), 80 (13.0), 53 (20.8), 41 (16.1). Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.55; H, 9.19; N, 11.15.

Preparation of Tris(oxazolinyl)cyclopropane Derivatives: General Procedure. To a well-stirred and precooled (−98 °C) solution of **6** (1.35 mmol) and TMEDA (1.48 mmol) in 20 mL of THF, under N_2, was added dropwise *s*-BuLi (1.75 mmol). After 1 h, the electrophile (allyl bromide, methallyl bromide, benzaldehyde or isobutyraldehyde) (1.48 mmol) was added, and the resulting mixture was slowly allowed to warm to room temperature and stirred overnight. After this time, the mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt (3 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product so obtained was purified by flash chromatography on silica gel [AcOEt/MeOH 95/5 in the case of **18** (R_f = 0.15), AcOEt in the case of **19** (R_f = 0.1), **20** (R_f = 0.20), **21** (R_f = 0.21), **22** (R_f = 0.26) and acetone/petroleum ether 3/7 in the case of **23** (R_f = 0.20), **24** (R_f = 0.19)].

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST, Rome) and by the University of Bari and CNR (Rome). We are also indebted to Prof. Marcel Pierrot of the Centre Scientifique Saint-Jérôme, Marseille, France, for performing the X-ray analysis on compound **20** and to Prof. A. Abbotto of the University of Milano-Bicocca for ab initio calculations concerning the electrophilicities of oxazolinyl and oxazinyl ethenes **4a** and **11**. We are also grateful to one of the reviewers of this paper for suggesting that we calculate and use the electrophilicity indexes to explain the different behavior toward cyclopropanation of compounds **4a**, **4b**, and **11**.

Supporting Information Available: Spectroscopic data for compounds **18**−**24**, ORTEP view, and crystallographic data for compound **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015962I