Lithiation of 2-(1-Chloroethyl)-2-oxazolines: Synthesis of Substituted Oxazolinyloxiranes and Oxazolinylaziridines

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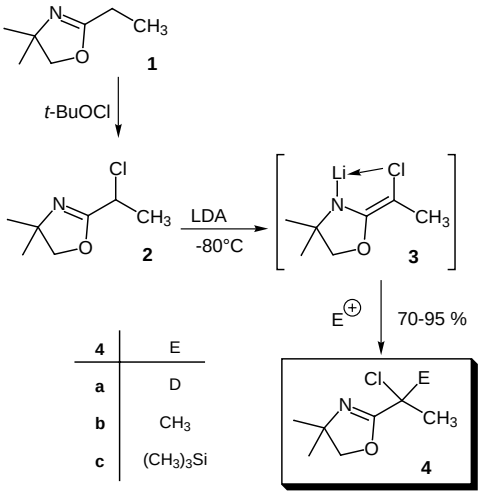
Abstract: Lithiation of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline **2** leads to lithiated derivative **3**, which is quite stable and can be deuterated, methylated and silylated to give oxazolines **4a**–**c**. The reaction of **3** with carbonyl compounds and imines furnishes good to excellent yields of oxazolinylepoxides **6a**–**m** and aziridines **17a**–**f**, respectively. Methylation and $NaBH_4$ reduction of epoxides **6** afford oxazolidines **7** highly stereoselectively. Acylepoxides can be obtained by hydrolysis of the oxazolidine moiety.

Key words: oxazolinyloxiranes, oxazolinylaziridines, carbanion, nucleophilic addition

Lithiated 2-halomethyl-2-oxazolines are useful but extremely reactive intermediates for undergoing smooth homocoupling reaction to give *trans*-bis(oxazolinyl)ethenes and *trans*-tris(oxazolinyl)cyclopropanes.[1] The capture of such lithiated oxazolines by electrophiles is made possible by adding the electrophile soon after their generation or by generating them in the presence of the electrophile (Barbier's conditions).[2] Lithiated α–haloethyloxazolines are quite stable at low temperature even for long times so that for some of them a spectroscopic investigation performed to elucidate the structural features has been reported.[3] In the present paper we report on the generation of some lithiated 2-(1-chloroethyl)-2-oxazolines and their reactions with electrophiles.

2-(1-Chloroethyl)-4,4-dimethyl-2-oxazoline (**2**) has been prepared by chlorination of 2-ethyl-4,4-dimethyl-2-oxazoline **1** with *t*-butylhypochlorite.[4] Treatment of **2** with lithium diisopropylamide (LDA) afforded lithiated derivative **3**. The formation of **3** was confirmed by its trapping with electrophiles (deuteration, methylation and trimethylsilylation) to give compounds **4a**–**c** (Scheme 1, Table 1).

The reaction of **3** with acetone (Scheme 2) afforded a very good yield of chlorohydrin **5a** that was quantitatively transformed into oxazolinylepoxide **6a** upon treatment



Scheme 1

Table 1 Oxazolines **4** Prepared from Lithiated 2-(1-chloroethyl)-2-oxazoline (**3**)

Product [a]	Yield (%)	IR (film, cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
4a	95 [b]	1663	1.24 (s, 3 H), 1.25 (s, 3 H), 1.67 (s, 3 H), 3.97 (s, 2 H)	22.1, 28.2, 67.6, 80.0, 164.3
4b	95 [b]	1655	1.24 (s, 6 H), 1.76 (s, 6 H), 3.98 (s, 2 H)	28.1, 30.7, 61.6, 67.6, 80.0, 166.8
4c	70 [c]	1660	0.14 (s, 9 H), 1.23 (s, 3 H), 1.26 (s, 3 H), 1.71 (s, 3 H), 3.94 (s, 2 H)	2.4, 24.4, 28.1, 53.8, 67.3, 79.7, 167.0

[a] Satisfactory microanalyses.
[b] Yield determined by ^1H NMR analysis of the crude reaction mixture.
[c] Yield of isolated material.

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with NaOH in *i*–PrOH. Similarly, the reaction of **3** with cyclohexanone provided chlorohydrin **5b** and then epoxide **6b** (Tables 2, 3). In the case of benzophenone, the epoxide **6c** was obtained straightforwardly.

Methylation of **6c** with $CF_3SO_3CH_3$ followed by the addition of MeMgBr/2·HMPT furnished an excellent yield of oxazolidine **7a** (Scheme 3) with a satisfactory diastereoselection (dr = 80:20). HMPT plays an important role in the oxazoline-oxazolidine transformation. Due to its strong solvating effect it prevents the Grignard reagent from the double addition to the C–N double bond that would provoke ring opening of the formed oxazolidine moiety.[5] Comparable results were obtained with other Grignard reagents (Scheme 3). In particular, highly diastereoselective were the reactions of **6c** with vinyl, allyl and ethynyl magnesium halides (Table 5). A highly stereoselective reduction took place with cyclohexylmagnesium chloride to give **7b**. In comparison, the reaction with $NaBH_4$ was much less stereoselective (dr = 75:25).

The coupling reaction of **3** with aldehydes was also studied. Thus, the reaction of **3** with benzaldehyde produced an almost 1:1 mixture of diastereomeric (*syn*+*anti*) chlorohydrins **5d–e** (Table 3) in good yields. Chlorohydrins **5d** and **5e** were then separated by column chromatography and stereospecifically cyclized to the corresponding epoxides **6d** and **6e** (Table 4) upon treatment with NaOH/*i*-PrOH. Comparable results were obtained with other aldehydes (Scheme 2). In particular, diastereomeric oxazoli-

Table 2 Chlorohydrins **5** Prepared from Lithiated 2-(1-chloroethyl)-2-oxazoline (**3**)

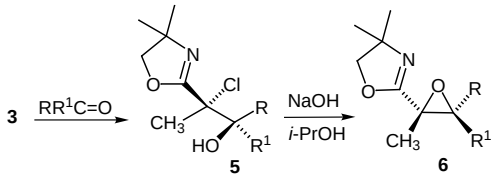
Product[a,b]	Yield (%)[c]	Mp (°C)	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
5a	83	–	1648[d]	1.25 (s, 3 H), 1.27 (s, 3 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.76 (s, 3 H), 4.01–3.94 (2 × d, AB system, 2 H, *J* = 8.2 Hz), 4.87 (s, 1 H, exchanges with D_2O)	24.8, 25.0, 27.8, 27.9, 67.7, 71.1, 74.9, 79.1, 165.8
5b	76	61–63	1651	1.25 (s, 3 H), 1.26 (s, 3 H), 1.77 (s, 3 H), 1.98−1.00 (m, 10 H), 4.00–3.98 (2 × d, AB system, 2 H, *J* = 8.2 Hz), 4.30 (s, 1 H, exchanges with D_2O)	21.5, 21.7, 24.6, 25.7, 27.9, 28.0, 31.3, 31.6, 67.7, 72.3, 75.5, 79.1, 165.7
5d	61[e]	89–91	1650	1.17 (s, 3 H), 1.25 (s, 3 H), 1.57 (s, 3 H), 4.00 (s, 2 H), 4.65–4.64 (s broad, 1 H, exchanges with D_2O), 5.09 (s, 1 H), 7.25−7.50 (m, 5 H)	23.5, 28.0, 28.2, 67.6, 68.9, 78.0, 79.6, 127.9, 128.1, 128.5, 137.6, 165.8
5e		104–106	1650	1.24 (s, 3 H), 1.30 (s, 3 H), 1.60 (s, 3 H), 4.05 (s, 2 H), 4.66 (s, 1 H, exchanges with D_2O), 5.12 (s, 1 H), 7.25−7.47 (m, 5 H)	23.5, 27.8, 28.0, 67.5, 68.5, 77.8, 79.4, 127.7, 128.4, 137.1, 165.6
5h	47[e]	130–132	1650	1.29 (s, 3 H), 1.33 (s, 3 H),1.57 (s, 3 H), 4.03 (s, 2 H), 5.30–5.10 (s broad, 1 H, exchanges with D_2O), 6.24 (s, 1 H), 7.42−7.90 (m, 4 H)	21.4, 27.7, 28.0, 65.1, 67.6, 70.6, 79.7, 124.1, 128.9, 130.2, 131.3, 131.8, 166.4
5i		88–90	1655	1.24 (s, 3 H), 1.27 (s, 3 H), 1.61 (s, 3 H), 4.06 (s, 2 H), 5.60–5.70 (s broad, 1 H, exchanges with D_2O), 6.29 (s, 1 H), 7.56−7.64 (m, 1 H), 7.70−7.80 (m, 1 H) 7.88−7.82 (m, 1 H), 8.20−7.94 (m, 1 H)	21.4, 27.4, 27.43, 66.3, 67.6, 69.5, 79.6, 124.0, 129.3, 130.8, 132.0, 132.9, 164.9
5j	69[e]	129–131	1650	1.33 (s, 3 H), 1.35 (s, 3 H), 1.74 (s, 3 H), 4.04 (s, 2 H), 5.20−5.17 (s, 1 H), 5.73−5.75 (s, 1 H), 7.22−7.65 (m, 4 H)	22.9, 27.8, 28.1, 66.2, 67.6, 74.2, 79.3, 126.3, 129.3, 129.6, 129.7, 134.5, 136.0, 165.5
5k		81–83	1655	1.33 (s, 3 H), 1.34 (s, 3 H), 1.60 (s, 3 H), 4.06 (s, 2 H), 5.50−5.65 (s broad, 1 H, exchanges with D_2O), 5.65 (s, 1 H), 7.24−7.92 (m, 4 H)	14.1, 22.6, 31.6, 60.4, 67.5, 72.6, 79.5, 126.5, 128.4, 128.9, 129.5, 131.3, 135.1, 165.5
5l	67[e]	87–89	1645	1.33 (s, 6 H), 1.70 (s, 3 H), 3.83 (s, 3 H), 4.02 (s, 2 H), 4.90−5.30 (s broad, 1 H, exchanges with D_2O), 5.56 (s, 1 H), 6.85−7.53 (m, 4 H)	14.1, 23.3, 27.9, 28.0, 55.4, 67.3, 73.9, 79.3, 110.8, 120.2, 126.4, 129.3, 129.5, 157.3, 165.5
5m		87–89	1650	1.30 (s, 3 H), 1.33 (s, 3 H), 1.55 (s, 3 H), 3.82 (s, 3 H), 4.03 (s, 2 H), 5.27 (s 1 H, exchanges with D_2O), 5.58 (s, 1 H), 6.83−7.80 (m, 4 H)	15.3, 24.1, 27.9, 28.1, 55.3, 65.9, 70. 6, 79.4, 110.0, 120.4, 125.8, 129.2, 130.3, 156.7, 166.6

[a] Satisfactory microanalyses.
[b] Spectroscopic data of chlorohydrins **5f** and **5g** have been reported in ref. [6a]
[c] Yield of isolated material.
[d] Film in this case.
[e] Overall yields of isolated diastereomeric chlorohydrins (*syn* + *anti*) separable by flash chromatography (see experimental). Diastereomeric ratio determined by weighing the isolated *syn* and *anti* diastereomers: dr **5d/5e** = 56/44; **5f/5g** = 57/43; **5h/5i** = 55/45; **5j/5k** = 49/51; **5l/5m** = 42/58.

Table 3 Oxazolinylepoxides **6** Prepared from Lithiated 2-(1-chloroethyl)-2-oxazoline (**3**)

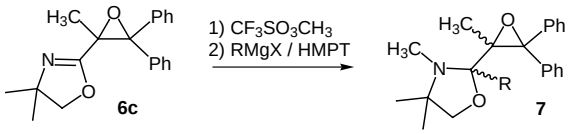
Product[a]	Yield (%)[b]	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
6a	83	1670[c]	1.08 (s, 3 H), 1.09 (s, 3 H), 1.14 (s, 3 H), 1.17 (s, 3 H), 1.34 (s, 3 H), 3.74–3.82 (m, 2 H)	17.3, 20.1, 20.6, 28.3, 60.3, 62.7, 67.5, 79.3, 164.4
6b	76	1657	1.16 (s, 6 H), 1.43 (s, 3 H), 1.21–1.64 (m, 10 H), 3.84 (s, 2 H)	16.8, 24.7, 24.9, 25.5, 28.2, 28.3, 30.2, 31.0, 60.7, 66.9, 67.6, 79.2, 164.4
6c	66	1666	0.87 (s, 3 H), 1.07 (s, 3 H), 1.43 (s, 3 H), 3.54 (d, 1 H, *J* = 8.0 Hz), 3.69 (d, 1 H, *J* = 8.0 Hz), 7.18–7.34 (m, 6 H), 7.47–7.51 (m, 4 H)	17.6, 27.7, 27.9, 62.9, 67.3, 70.4, 79.2, 127.1, 125.5, 127.7, 127.8, 128.3, 137.9, 138.5, 163.0

[a] Satisfactory microanalyses.
[b] Yield of isolated material.
[c] Film in this case



5,6	R	R1
a	CH_3	CH_3
b	- $(CH_2)_5$ -	
c	Ph	Ph
d	H	Ph
e	Ph	H
f	H	*p*-$CH_3C_6H_4$
g	*p*-$CH_3C_6H_4$	H
h	H	*o*-$NO_2C_6H_4$
i	*o*-$NO_2C_6H_4$	H
j	H	*o*-ClC_6H_4
k	*o*-ClC_6H_4	H
l	H	*o*-$CH_3OC_6H_4$
m	*o*-$CH_3OC_6H_4$	H

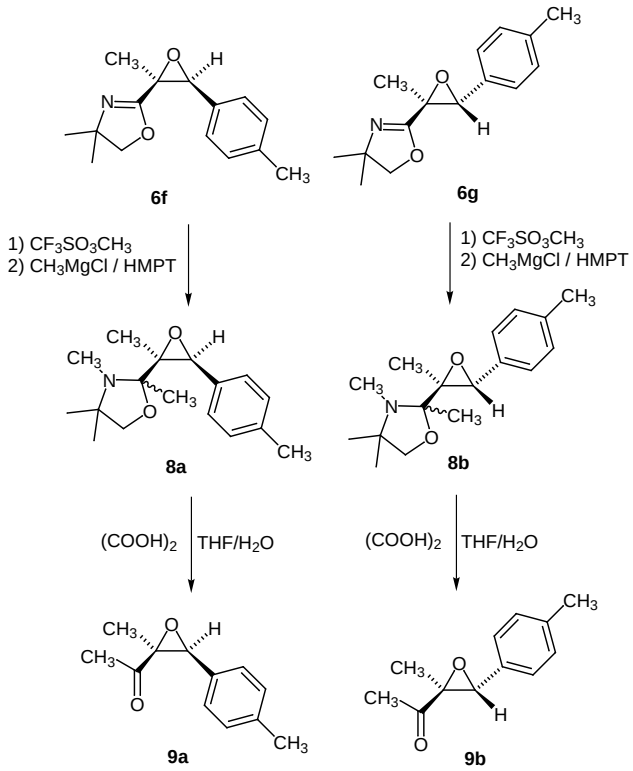
Scheme 2



7	R	dr	RMgX
a	CH_3	80/20	CH_3MgCl
b	H	95/5	CyMgBr
c	CH_2=CH-CH_2	90/10	CH_2=$CHCH_2MgBr$
d	C_4H_9	8020	C_4H_9MgCl
e	CH_2=CH	95/5	CH_2=CHMgBr
f	CH C	95/5	CH CMgBr
g	$PhCH_2$	75/25	$PhCH_2MgCl$
h	Ph	60/40	PhMgBr

Scheme 3

nyloxiranes **6f** and **6g** were converted into the oxazolidines **8a**[6a] and **8b**[6a] upon N-methylation with $CF_3SO_3CH_3$ followed by the addition of MeMgBr/2·HMPT with good to excellent diastereoselection (Scheme 4).



Scheme 4

The hydrolysis of (*Z*)-oxazolidinyloxirane **8a** carried out with oxalic acid (8 equiv) in THF/H_2O afforded a low yield (40%) of the expected acetyltolyloxirane **9a**[6a] after 7 days. The (*E*)-acetyltolyloxirane **9b**[6a] was obtained starting from the (*E*)-oxazolidinyloxirane **8b** (11 equiv of oxalic acid, THF/H_2O; 3 days). The acetyloxirane **10** does form when the oxazolidinyloxirane **7a** is treated with oxalic acid, but it was not possible to isolate it due to its isomerization to 3,3-diphenyl-2,4-pentanedione **12**. Moreover, the reaction of **7a** with MeI in acetone furnished 1,1-diphenyl-2-propanone **13** (Scheme 5). In contrast, oxazolidine **7b** could be easily hydrolyzed to the corresponding formyloxirane **11** upon treatment with oxalic acid in THF/H_2O.[6a]

Table 4 Oxazolinylepoxides **6** prepared from lithiated 2-(1-chloroethyl)-2-oxazoline (**3**)

Product[a,b]	Yield (%)[c]	IR (film, cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
6d	61	1665	1.30 (s, 6 H), 1.32 (s, 3 H), 4.00 (s, 2 H), 4.40 (s, 1 H), 7.24−7.35 (m, 5 H)	13.7 (*C*H_3C–O), 28.2 (2 × *C*H_3C–N), 57.4, 63.6 (*C*H–O), 67.7, 79.5 (*C*H_2–O), 126.6, 126.8, 128.0, 128.1, 128.4, 134.2, 164.2
6e		1665	0.96 (s, 3 H), 1.03 (s, 3 H), 1.72 (s, 3 H), 3.66 (s, 2 H), 4.02 (s, 1 H), 7.25−7.39 (m, 5 H),	20.5 (qd, *C*H_3C–O ^1J_q = 128.9 Hz, ^3J_d = 2.0 Hz), 27.6 (2 × *C*H_3C–N), 59.6, 63.9 (d with fine structure, ^1J_d = 175.7 Hz, *C*H-O), 67.3, 79.2 (t with fine structure, ^1J_t = 144.7 Hz, *C*H_2–O), 126.6, 127.7, 127.9, 134.1, 161.6
6h	47	1655[d]	1.30 (s, 3 H), 1.40 (s, 6 H), 4.10 (s, 2 H), 4.87 (s, 1 H), 7.30−8.30 (m, 4 H)	14.3 (q, ^1J_q = 129.0 Hz, *C*H_3C–O), 28.0 (*C*H_3C–N), 28.3 (*C*H_3C–N), 58.0, 61.8 (d with fine structure ^1J_d = 186.5 Hz, *C*H–O), 68.0, 79.7 (t with fine structure, ^1J_t = 149.2 Hz, *C*H_2–O), 124.9, 129.1, 129.4, 131.7, 134.1, 147.0, 163.5
6i		1650[d]	0.65 (s, 3 H), 1.01 (s, 3 H), 1.80 (s, 3 H), 3.55–3.57 (2 × d, AB system, 2 H, *J* = 8.2 Hz), 4.51 (s, 1 H), 7.44−8.14 (m, 4 H)	19.9 (qd, ^1J_q = 129.2 Hz, ^3J_d = 1.8 Hz, *C*H_3C–O), 27.7 (2 × *C*H_3C–N), 59.1, 62.8 (d with fine structure, ^1J_d = 186.8 Hz, *C*H-O), 67.1, 79.4 (t with fine structure, ^1J_t = 149.6 Hz, *C*H_2-O), 124.0, 128.7, 130.2, 131.4, 133.6, 147.1, 161.4
6j	69	1655	1.27 (s, 3 H), 1.30 (s, 3 H), 1.31 (s, 3 H), 4.05–3.98 (2 × d, AB system, 2 H, *J* = 8.1 Hz), 4.47 (s, 1 H), 7.21−7.37 (m, 4 H)	14.0 (q, ^1J_q = 129.1 Hz, *C*H_3C-O), 28.2 (2 × *C*H_3C-N), 57.3, 61.1 (d with fine structure, ^1J_d = 181.9 Hz, *C*H-O), 67.9, 79.6 (t with fine structure, ^1J_t = 149.3 Hz, *C*H_2-O), 128.1, 128.9, 129.0, 129.1, 132.8, 132.9, 163.8
6k		1670	0.76 (s, 3 H), 0.98 (s, 3 H), 1.71 (s, 3 H), 3.58−3.52 (2 × d, AB system, 2 H, *J* = 7.9 Hz), 4.07 (s, 1 H), 7.10−7.40 (m, 4 H)	19.9 (qd, ^1J_q = 129.0 Hz, ^3J_d = 1.8 Hz, *C*H_3C-O), 27.8 (*C*H_3C-N), 27.9 (*C*H_3C-N), 59.1, 62.5 (d with fine structure, ^1J_d = 180.6 Hz, *C*H–O), 67.2, 79.3 (t with fine structure, ^1J_t = 149.3 Hz, *C*H_2–O), 126.0, 128.3, 128.8, 129.0, 132.4, 132.9, 161.6
6l	67	1650	1.30 (s, 3 H), 1.31 (s, 6 H), 3.80 (s, 3 H), 4.01 (s, 2 H), 4.47 (s, 1 H), 6.83−7.27 (m, 4 H)	13.9 (q, ^1J_q = 128.8 Hz, *C*H_3C–O), 28.2 (*C*H_3C-N), 26.3 (*C*H_3C-N), 55.4 (q, ^1J_q = 144.1 Hz, *C*H_3O–Ar), 57.2, 59.7 (d with fine structure, ^1J_d = 180.3 Hz, *C*H–O), 67.8, 79.4 (t with fine structure, ^1J_t = 149.3 Hz, *C*H_2–O), 109.9, 120.1, 123.0, 127.5, 129.0, 157.8, 164.5
6m		1665	0.89 (s, 3 H), 1.00 (s, 3 H), 1.71 (s, 3 H), 3.60 (s, 2 H), 3.80 (s, 3 H), 4.14 (s, 1 H), 6.76−7.31 (m, 4 H)	20.3 (qd, ^1J_q = 128.8 Hz, ^3J_d = 1.9 Hz, *C*H_3C–O), 27.9 (*C*H_3C–N), 28.0 (*C*H_3C–N), 55.5 (q, ^1J_q = 144.1 Hz, *C*H_3O–Ar), 59.1, 61.0 (d with fine structure, ^1J_d = 183.1 Hz, *C*H–O), 67.2, 79.1 (t with fine structure, ^1J_t = 149.2 Hz, *C*H_2–O), 109.6, 119.7, 122.7, 127.6, 128.8, 157.9, 162.1

[a] Satisfactory microanalyses.
[b] The *E* and *Z* configuration of epoxides **6d**–**m** was established on the basis of the $^3J_{CH}$ coupling constant value between the oxirane ring hydrogen and the CH_3 on the adjacent ring carbon as discussed in ref. [6b] Spectroscopic data of oxazolinylepoxides **6f** and **6g** have been reported in ref. [6a]
[c] Overall yields of isolated diastereomeric epoxides *(E + Z)* separable by flash chromatography (see experimental). Diastereomeric ratio determined by weighing the isolated *E* and *Z* diastereomers: dr **6d/6e** = 56/44; **6f/6g** = 57/43; **6h/6i** = 55/45; **6j/6k** = 49/51; **6l/6m** = 42/58.
[d] KBr in this case.

On the basis of previous results, the Darzens reaction of chiral 2-(1-chloroethyl)-2-oxazolines with carbonyl compounds has also been examined.[7,8] Lithiation (LDA, THF, –78 °C) of a 1:1 diastereomeric mixture of (1*R*,4'*S*,5'*S*) and (1*S*,4'*S*,5'*S*)-*2*-(1-chloroethyl)-4-methoxymethyl-5-phenyl-2-oxazoline **15a**, (Scheme 6) prepared by chlorination of the corresponding 2-ethyl derivative **14** with *t*-butylhypochlorite (see experimental section), afforded the expected lithiated species **15b** that was stable at low temperature and could be captured with ketones (3-pentanone, cyclohexanone, cyclododecanone) to give a high yield of the corresponding tetrasubstituted epoxides **16a**–**c** as a diastereomeric mixture (Table 6) that could not be separated by chromatography. The diastereomeric ratios were measured by ^1H NMR and no diastereoselectivity was observed (Scheme 6).

Table 5 Oxazolidine Derivatives **7** Prepared from Oxazolinylepoxide (**6c**) with RMgX

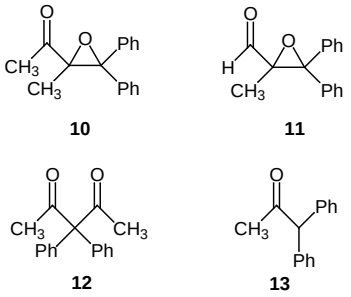
Product[a]	Yield (%)[b]	IR (film cm^{-1})	dr[c]	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
7a	95	1444 1096	80:20[d]	minor: 0.88 (s, 3 H), 1.02 (s, 3 H), 1.13 (s, 3 H), 1.18 (s, 3 H), 1.91 (s, 3 H), 3.62 (d, 1 H, *J* = 7.7 Hz), 3.69 (d, 1 H, *J* = 7.7 Hz), 7.10–7.60 (3 m, 10 H); major: 0.97 (s, 3 H), 1.04 (s, 3 H), 1.20 (s, 3 H), 1.37 (s, 3 H), 2.33 (s, 3 H), 3.28 (d, *J* = 7.5 Hz, 1 H), 3.76 (d, 1 H, *J* = 7.5 Hz), 7.22−7.53 (3 m, 10 H)	minor: 18.6, 20.4, 21.7, 24.9, 27.2, 75.8, 77.3 78.0, 79.0, 98.6, 126.9, 127.0, 127.3, 127.9, 128.2, 128.7, 142.0; major: 18.2, 21.1, 21.4, 24.2, 60.2, 68.3, 72.4 74.6, 77.3, 96.0, 126.4, 126.9, 127.1, 127.2, 127.9, 128.7, 142.5, 143.9
7b	51	1447[e] 1069	≥ 95:5	0.81 (s, 3 H), 1.10 (s, 3 H), 1.16 (s, 3 H), 2.21 (s, 3 H), 3.49 (s, 1 H), 3.62 (s, 2 H), 7.16−7.35 (m, 6 H), 7.57−7.44 (m, 4 H)	12.9, 16.5, 23.3, 57.8, 60.0, 68.1, 69.3, 79.4, 95.6, 127.4, 127.7, 127.8, 128.0, 128.6, 128.7, 140.4, 141.3
7c	95	1638 1488 1055	90:10	0.98 (s, 3 H major + 3 H minor), 1.14 (s, 3 H major + 3 H minor), 1.17 (s, 3 H major + 3 H minor), 2.46 (s, 3 H major + 3 H minor), 2.48−2.59 (m, 1 H major, 2 H minor), 2.68 (dd, 1 H major, ^2J = 14.4 Hz, ^3J = 7.9 Hz), 3.18−3.20 (d, 1 H major, *J* = 7.4 Hz), 3.49−3.65 (2 × d, AB system, 2 H minor), 3.80−3.82 (d, 1 H major, *J* = 7.4 Hz), 5.04−5.24 (m, 2 H major + 2 H minor), 5.87−6.01 (m, 1 H major + 1 H minor), 7.10−7.30 (m, 5 H major + 5 H minor), 7.40−7.55 (m, 5 H major + 5 H minor)	major + minor: 96.6, 117.5, 126.0, 126.1, 126.4, 126.5, 126.9, 127.0, 127.6, 127.9, 128.5, 134.6, 134.9, 141.4, 143.0
7d	87	1446 1060	80:20	0.88–1.00 (m, 3 H major + 3 H minor), 0.98 (s, 3 H major), 1.14 (s, 3 H major), 1.15 (s, 3 H major), 1.16 (s, 3 H minor), 1.19 (s, 3 H minor), 1.23−1.37 (m, 4 H major + 4 H minor), 1.58−1.90 (m, 2 H major + 2 H minor), 2.44 (s, 3 H major + 3 H minor), 3.15 (d, 1 H major, *J* = 7.2 Hz), 3.42−3.59 (2 × d, AB system, 2 H minor, *J* = 7.7 Hz), 3.81 (d, 1 H major, *J* = 7.2 Hz), 7.05−7.55 (m, 10 H major + 10 H minor)	major + minor: 18.7, 19.7, 22.4, 23.4, 23.6, 23.7, 23.8, 25.1, 26.4, 26.9, 27.3, 33.8, 35.2, 59.5, 61.0, 72.9, 74.2, 75.3, 76.9, 77.9, 97.5, 99.4, 126.4, 126.7, 127.0, 127.2, 127.3, 127.7, 127.9, 128.3, 128.7
7e	93	1444[e] 1066	≥ 95:5	0.80 (s, 3 H), 0.90 (s, 3 H), 1.21 (s, 3 H), 2.25 (s, 3 H), 3.41−3.77 (2 × d, AB system, 2 H *J* = 7.2 Hz), 5.28 (dd, 1 H, ^3J = 10.8 Hz, ^2J = 1.9 Hz), 5.39 (dd, 1 H, ^3J = 17.3 Hz, ^2J = 1.9 Hz), 5.95 (dd, 1 H, ^3J = 17.30 Hz, ^3J = 10.9 Hz), 7.01−7.46 (m, 10 H)	18.5, 20.6, 23.7, 30.1, 57.8, 60.5, 72.0, 72.9, 96.4, 116.6, 126.4, 127.1, 127.2, 127.3, 127.6, 128.7, 137.4, 142.2, 143.9
7f	83	3303[e] 1445 1079	≥ 95:5	0.60 (s, 3 H), 1.00 (s, 3 H), 1.31 (s, 3 H), 2.26 (s, 3 H), 2.66 (s, 1 H), 3.47−3.56 (2 × d, AB system, 2 H, *J* = 7.14 Hz), 7.06−7.54 (m, 10 H)	18.2, 19.6, 23.1, 60.9, 72.2, 72.6, 78.0, 78.4, 81.6, 93.5, 126.5, 126.9, 127.4, 128.0, 128.8, 124.0, 137.3, 143.57
7g	85	1447 1075	75:25	0.49 (s, 3 H minor), 0.65 (s, 3 H major), 1.17 (s, 3 H minor), 1.19 (s, 3 H minor), 1.20 (s, 3 H major), 1.38 (s, 3 H major), 1.96 (s, 3 H minor), 2.69 (s, 3 H major), 2.85 (s, 2 H minor), 3.08−3.32 (2 x d, AB system, 2 H major, *J* = 13.8 Hz), 3.12 (d, 1 H major, *J* = 7.2 Hz), 3.36−3.51 (2 × d, AB system, 2 H minor, *J* = 7.7 Hz), 3.80 (d, 1 H major, *J* = 7.2 Hz), 7.05−7.75 (m, 10 H major + 10 H minor)	major + minor: 18.9, 20.1, 21.7, 23.5, 24.3, 24.73, 27.7, 30.2, 40.1, 41.2, 59.4, 59.9, 68.8, 73.4, 73.8, 74.8, 77.6, 77.7, 97.8, 100.6, 126.3, 126.6, 126.7, 127.0, 127.1, 127.2, 127.3, 127.7, 128.1, 128.3, 128.5, 128.7, 128.8, 132.0, 132.5, 137.9, 138.6, 141.7, 142.5, 143.9, 144.0
7h	77	1600 1444 1066	60:40	0.46 (s, 3 H major), 0.79 (s, 3 H major), 0.87 (s, 3 H minor), 1.13 (s, 3 H major), 1.17 (s, 3 H minor), 1.18 (s, 3 H minor), 1.20 (s, 3 H minor), 2.05 (s, 3 H major), 3.78 (d, 1 H major, *J* = 7.3 Hz), 3.87 (d, 1 H major, *J* = 7.3 Hz), 3.92 (d, 1 H minor, *J* = 7.5 Hz), 4.23 (d, 1 H minor, *J* = 7.5 Hz), 7.03−7.24 (m, 4 H major + 4 H minor), 7.30−7.41 (m, 6 H major + 6 H minor), 7.47−7.68 (m, 5 H major + 5 H minor)	20.0, 20.6, 21.2, 22.4, 23.0, 24.1, 60.7, 62.2, 68.6, 71.0, 73.9, 74.3, 77.8, 78.2, 97.8, 100.7, 126.1, 126.6, 126.8, 127.1, 127.3, 127.4, 127.4, 127.8, 128.0, 128.1, 128.1, 128.5, 128.7, 128.8, 140.2, 140.5, 142.1, 142.2, 144.0, 144.4.

[a] Satisfactory microanalyses.
[b] Yield of isolated material.
[c] Diastereomeric ratio, determined by ^1H NMR on the crude reaction mixture; ± 5 % error of the stated value.
[d] Separated by column chromatography on silica gel (petroleum ether–AcOEt, 9:1).
[e] KBr in this case.

Table 6 Oxazolinylepoxides **16** Prepared from Lithiated 2-(1-chloroethyl)-2-oxazoline (**15b**)

Product[a]	Yield (%)[b]	IR (film, cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
16a	86	1673	0.94−1.40 (2 × t, 6 H major + 6 H minor), 1.50–1.84 (m, 4 H major + 4 H minor), 1.63 (s, 3 H major + 3 H minor), 3.37 (s, 3 H minor), 3.38 (s, 3 H major), 3.42–3.52 (m, 1 H major + 1 H minor), 3.60–3.67 (m, 1 H major + 1 H minor), 4.16–4.22 (m, 1 H major + 1 H minor), 5.37 (d, 1 H major + 1 H minor, *J* = 6.9 Hz), 7.27–7.38 (m, 5 H major + 5 H minor)	9.5, 17.2, 17.6, 22.7, 23.4, 23.8, 59.3, 59.5, 61.6, 61.8, 69.6, 69.7, 74.0, 74.2, 74.5, 74.7, 84.2, 125.8, 125.9, 128.5, 129.0, 140.5, 140.9, 167.0
16b	75	1672	1.40–1.80 (m, 10 H major + 10 H minor), 1.61 (s, 3 H minor),1.62 (s, 3 H major), 3.35 (s, 3 H major), 3.37 (s, 3 H minor), 3.40–3.52 (m, 1 H major + 1 H minor), 3.55–3.64 (m, 1 H major + 1 H minor), 4.14–4.25 (m, 1 H major + 1 H minor), 5.35 (d, 1 H major + 1 H minor, *J* = 6.9 Hz), 7.27–7.38 (m, 5 H major + 5 H minor)	16.8, 17.1, 25.1, 25.14, 25.2, 25.7, 30.4, 30.5, 31.2, 31.4, 59.3, 59.5, 61.2, 61.4, 67.3, 67.5, 74.0, 74.2, 74.5, 74.7, 84.2, 84.3, 125.8, 126.0, 126.1, 128.5, 128.53, 129.0, 140.5, 140.8, 166.8, 167.0
16c	75	1670	1.20–1.80 (m, 22 H major + 22 H minor), 1.63 (s, 3 H major + 3 H minor), 3.37 (s, 3 H major), 3.38 (s, 3 H minor), 3.40–3.52 (m, 1 H major + 1 H minor), 3.55–3.64 (m, 1 H major + 1 H minor), 4.17–4.21 (m, 1 H major + 1 H minor), 5.37 (d, 1 H major, *J* = 6.9 Hz), 5.38 (d, 1 H minor, *J* = 6.6 Hz), 7.27–7.38 (m, 5 H major + 5 H minor)	17.4, 17.8, 20.3, 20.4, 20.5, 22.4, 22.5, 26.3, 26.6, 26.61, 27.2, 28.0, 59.4, 61.1, 61.3, 68.8, 74.0, 74.2, 74.5, 74.7, 84.0, 125.8, 126.0, 126.1, 128.5, 128.9, 129.0, 140.5, 140.9, 167.0, 167.2

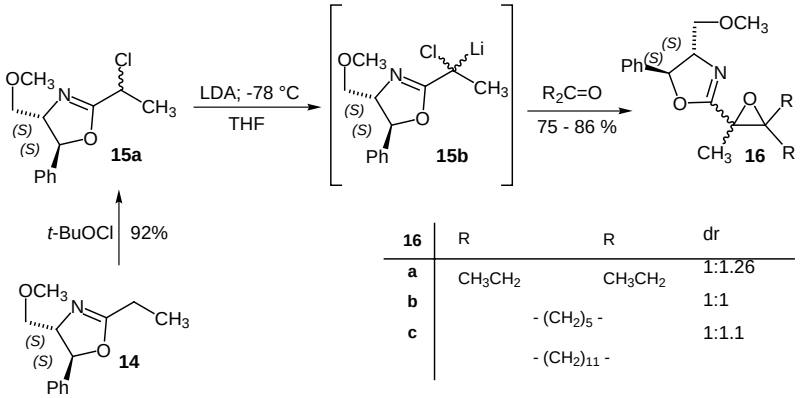
[a] Satisfactory microanalyses.
[b] Isolated yields.



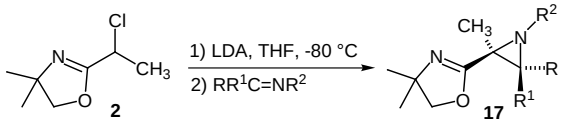
Scheme 5

We found that 2-lithio-(1-chloroethyl)-2-oxazoline **3** reacts efficiently with imines (Scheme 7). Indeed, satisfactory to very good yields of oxazolinylaziridines **17a–f** could be obtained when **3** was treated with the appropriate Schiff's bases.[9] It is worth noting that in some cases the coupling reaction proceeded with complete *E* diastereoselection affording oxazolinylaziridines **17d–f**, while **17c** was found to be a mixture of *E* and *Z* diastereoisomers (Table 7).

In conclusion, this paper describes a simple preparation of oxazolinyl- and oxazolidinylepoxides and oxazolinylaziridines, which look like useful synthetic intermediates.



Scheme 6



17	R	R^1	R^2
a	CH_3	CH_3	Ph
b	- $(CH_2)_5$ -		Ph
c	CH_3	C_2H_5	Ph
d	Ph	H	$PhCh_2$
e	Ph	H	$PhSo_2$
f	Ph	CH_3	Ph

Scheme 7

Tetrahydrofuran (THF) was freshly distilled under N_2 from sodium benzophenone ketyl. Petroleum ether refers to the 40–60 °C boiling fraction. Commercial hexanes solutions of *n*-BuLi and Grignard reagents (Et_2O solutions) were purchased from Aldrich and were titrated by using *N*-pivaloyl-*o*-toluidine prior to use.[10] All other chemicals were of commercial grade (Aldrich) and distilled just prior to use. 2-(1-Chloroethyl)-4,4-dimethyl-2-oxazoline was prepared as reported.[3,9] NMR Varian EM 390, Varian XL 200 (200 MHz and 50.3 MHz for ^1H and ^{13}C, respectively), Bruker (300 MHz for ^1H) were used for NMR spectroscopic determination. For ^1H NMR, $CDCl_3$ was used as solvent, (δ_H = 7.24) and TMS as internal standard; for ^{13}C NMR, $CDCl_3$ (δ_C = 77.0) and [D_6] acetone (δ_C = 20.83). IR spectra were recorded on Perkin Elmer 283 and FTIR spectra on Perkin Elmer 1600. GC-MS spectrometry analyses were performed with a HP 5995C gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Microanalyses were performed with a Carlo Erba Mod. 1106 C, H, N analyzer. Melting points are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished with UV light (254 nm). Column chromatography was performed by using silica gel (70–230 mesh) with petroleum ether–Et_2O (or AcOEt) mixtures as the eluent. A –80 °C bath refers to a mixture of liquid nitrogen and EtOH; the temperature was controlled with a spirit filled low-temperature thermometer (Aldrich) and kept at a fixed value by adding liquid nitrogen from time to time. All reactions involving air sensitive reagents were performed under N_2 in oven–dried glassware using syringe septum cap techniques.

Reaction of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline Lithium Derivative (3) with Electrophiles; General Procedure for the Synthesis of 4a–c.

Procedure for a 2 mmol scale: A solution of 2.4 mmol of lithium diisopropylamide (LDA) (from diisopropylamine (347 μL) and 2.5 M *n*-BuLi (960 μL) in anhyd THF (10 mL) was prepared under N_2 and stirred at 0 °C for 15 min. To this solution, pre-cooled to –80 °C with an EtOH-liquid N_2 bath, 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline (**2**) (323 mg, 2.0 mmol) in anhyd THF (5 mL) was added dropwise and the resulting yellow solution stirred at this temperature for 20 min. The electrophile (CD_3OD, CH_3I or $(CH_3)_3SiCl$) (5 mmol) was then added and the resulting solution warmed to r.t. The reaction mixture was then quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 × 30 mL). Combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. In the case of compound **4c**, the crude mixture was flash-chromatographed (silica gel; petroleum ether–AcOEt ,9:1) and the product isolated. The crude mixture of **4a** and **4b** was instead analyzed without further purification.

Reaction of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline Lithium Derivative (3) with Carbonyl compounds; General Procedure for the Synthesis of the Chlorohydrins (5a–b, 5d–m).

Procedure for a 2 mmol scale: A solution of 2.4 mmol of LDA (from diisopropylamine (347 μL) and 2.5 M *n*-BuLi (960 μL) in anhyd

Table 7 Oxazolinylaziridines **17** Prepared from Lithiated 2-(1-chloroethyl)-2-oxazoline (**3**)

Product[a,b]	Yield (%)[c]	IR (film, cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
17a	60	1660, 1500	1.21 (s, 3 H), 1.32 (s, 6 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 4.0 (s, 2 H), 6.74−7.25 (m, 5 H)	13.6, 16.3, 23.2, 28.1, 28.2, 44.5, 45.3, 67.2, 79.0, 120.2, 120.8, 128.3, 145.5, 165.6
17b	55	1670, 1500	1.29 (s, 3 H), 1.31 (s, 3 H), 1.45 (s, 3 H), 1.10−1.80 (m, 10 H), 3.98 (s, 2 H), 6.75−7.26 (m, 5 H)	14.2, 25.5, 25.9, 26.5, 28.9, 29.0, 34.6, 45.4, 51.5, 68.0, 79.7, 121.0, 121.5, 129.0, 146.3, 166.5
17c[d]	85	1650, 1500	1.0–1.8 (m, 17 H), 3.9−4.0 (m, 2 H), 6.7−7.3 (m, 5 H)	10.3, 12.8, 13.6, 14.0, 19.8, 24.6, 28.3, 28.40, 28.42, 29.5, 29.6, 49.2, 67.4, 79.0, 120.0, 121.0, 128.5, 145.7, 165.5
17d[e]	80	1650, 1500	1.20 (s, 3 H), 1.26 (s, 3 H), 1.28 (s, 3 H), 3.65 (s, 1 H), 3.85 (d, 1 H, *J* = 14.0 Hz), 3.90 (d, 1 H, *J* = 14.0 Hz), 3.92 (s, 2 H), 7.25−7.46 (m, 10 H)	16.7, 28.3, 28.6, 43.1, 50.8, 56.4, 67.4, 78.8, 126.7, 126.9, 127.8, 127.9, 128.0, 136.5, 139.5, 163.5
17e[e]	55	1670, 1450	1.29 (s, 3 H), 1.40 (s, 6 H), 4.09−4.19 (2 × d, AB system, 2 H, *J* = 7.9 Hz), 4.87 (s, 1 H), 7.16−7.48 (m, 5 H), 7.50−7.62 (m, 3 H), 8.00−8.05 (m, 2 H)	16.6, 27.5, 27.8, 50.2, 50.6, 67.6, 79.7, 126.0, 127.0, 128.0, 128.2, 128.9, 132.3, 133.0, 140.0, 161.0

[a] Satisfactory microanalyses.
[b] Spectroscopic data and the *E* configuration of aziridine **17f** have been reported in ref. [9]
[c] Isolated yields.
[d] *E* + *Z* diastereomeric mixture.
[e] The *E* configuration of aziridine **17d** has been discussed in ref. [9]. The *E* configuration of aziridine **17e** was established on the basis of the vanishing $^3J_{CH}$ ~ 0 Hz between the aziridine ring hydrogen and the CH_3 on the adjacent carbon according to ref. [6b]

THF (10 mL)) was prepared under N_2 and stirred at 0 °C for 15 min. To this solution, cooled to –80 °C, 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline (**2**) (323 mg, 2.0 mmol) in anhyd THF (5 mL) was added dropwise and the resulting yellow solution stirred at this temperature for 20 min. The carbonyl compound (2.4 mmol in 5 mL of anhyd THF) was then added dropwise at –80 °C and the resulting solution stirred for further 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 × 30 mL). Combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was flash-chromatographed (silica gel; petroleum ether–AcOEt, 6:4) to give pure chlorohydrins **5a–b, 5d–m**.

Preparation of Oxazolinylepoxides 6a–m

The chlorohydrins **5a–m** were cyclized quantitatively to epoxides **6a–m**, respectively, in NaOH/*i*-PrOH.[11] The epoxides were purified by flash chromatography (silica gel; petroleum ether–AcOEt, 6:4).

Reaction of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline Lithium derivative (3) with Schiff's Bases; General Procedure for the Synthesis of the Oxazolinylaziridines 17a–f

Procedure for a 2 mmol scale: A solution of 2.4 mmol of LDA (from diisopropylamine (347 μL) and of 2.5 M *n*-BuLi (960 μL) in anhyd THF(10 mL)) was prepared under N_2 and stirred at 0 °C for 15 min. To this solution, cooled to –80 °C, 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline (**2**) (323 mg, 2.0 mmol) in anhyd THF (5 mL) was added dropwise and the resulting yellow solution stirred at this temperature for 20 min. The Schiff's base (2.0 mmol in 5 mL of anhyd THF) was then added dropwise over 20 min at –80 °C and the resulting solution stirred for a time variable between 3–5 h (TLC monitoring). The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 × 30 mL). Combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was separated by flash-chromatography (silica gel; petroleum ether–Et_2O, 1:1) to give oxazolinylaziridines **17a–f**.

(1*R*,4'*S*,5'*S*/1*S*,4'*S*,5'*S*)-2-(1-Chloroethyl)-4-methoxymethyl-5-phenyl-2-oxazoline (15a)

Chlorination of the 2-ethyl derivative **14**[12] was carried out as reported in ref.[4] to give oxazoline **15a** as a mixture of diastereoisomers after flash chromatography (petroleum ether–AcOEt, 4:1).

Colorless oil, 92% yield.

IR (film): 3064, 1667, 1496, 1397, 1129, 1086, 699 cm^{-1}.

^1H NMR: δ = 1.77 (d, 3 H, *J* = 7.5 Hz), 1.83 (d, 3 H, *J* = 7.5 Hz), 3.40 (s, 3 H), 3.43–3.58 (m, 1 H), 3.60–3.70 (m, 1H), 4.10–4.80 (2 × q, 1 H, *J* = 7.5 Hz), 5.40 (d, 1 H, *J* = 7.3 Hz) 7.25–7.45 (m, 5 H).

^{13}C NMR: δ = 22.0, 48.6, 48.8, 59.3, 73.8, 74.4, 74.5, 84.1, 125.3, 127.6, 128.2, 128.8, 140.2, 140.3, 166.3.

GC–MS (70 eV) *m/z* (%): 254 (4, M^+), 208 (34), 146 (26), 119 (53), 112 (69), 91 (62), 77 (27), 45 (100).

Reaction of (1*R*,4'*S*,5'*S*/1*S*,4'*S*,5'*S*)-2-(1-chloroethyl)-4-methoxymethyl-5-phenyl-2-oxazoline Lithium Derivative (15b) with Carbonyl Compounds; General Procedure for the Synthesis of the Oxazolinylepoxides 16a–c

Procedure for a 2 mmol scale: A solution of 2.4 mmol of LDA (from diisopropylamine (347 μL) and 2.5 M *n*-BuLi (960 μL) in anhyd THF (10 mL)) was prepared under N_2 and stirred at 0 °C for 15 min. To this solution, cooled to –78 °C, oxazoline **15a** (507 mg, 2.0 mmol) in anhyd THF (5 mL) was added dropwise and the resulting yellow solution was stirred at this temperature for 20 min. The carbonyl compound (2.4 mmol in 5 mL of anhyd THF) was then added dropwise at –78 °C and the resulting solution stirred for 1 h and warmed to r.t. The reaction mixture was quenched with sat aq. NH_4Cl and extracted with AcOEt (3 × 30 mL). Combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was flash-chromatographed (silica gel; petroleum ether–AcOEt, 6:4) to give pure epoxides **16a–c**.

Addition of Grignard Reagents to the Oxazolinylepoxide 6c; General Procedure for the Synthesis of Oxazolidines 7a–h

Procedure for a 1 mmol scale: To a solution of the oxazolinylepoxide **6c** (245 mg, 1 mmol) in anhyd THF (2 mL) under N_2 at 0 °C, methyl triflate ($CH_3SO_3CF_3$, 170 μL, 1.5 mmol) was added. After 30 min, to the resulting *N*-methyloxazolinium salt, the Grignard reagent (1.1 mmol) mixed with hexamethylphosphorous triamide (HMPT, 400 μL, 2.2 mmol) in anhyd THF (2 mL) was added dropwise at r.t. The reaction mixture was stirred for 50 min, quenched with sat aq. NH_4Cl and extracted with Et_2O (3 × 10 mL). Combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by flash-chromatography (silica gel; petroleum ether–Et_2O, 9:1) to give **7a–h**.

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