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Heterosubstituted Chlorohydrins: Knoevenagel Reaction *versus* Epoxide Formation

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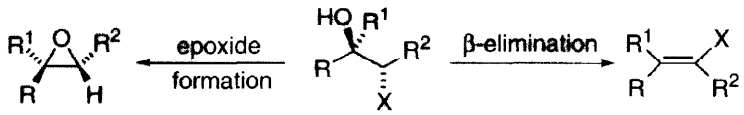
Abstract: Lithiated chloromethyl derivatives **2a–d**, available by deprotonation of 2-(chloromethyl)-1,3-benzothiazole **1a**, -1,3-oxazoline **1b**, -pyridine **1c** and -quinoline **1d**, react with carbonyl compounds to give chlorohydrins **3a–g** and then epoxides **4a–g** upon treatment with NaOH/^{i}PrOH. The same chlorohydrins **3a–g** could be converted into heterosubstituted chloroalkenes **5a–g** with very high *E* stereoselection upon reaction with $MeSO_2Cl/Et_3N$.

Keywords: heterosubstituted chlorohydrin; chloroalkene; Knoevenagel reaction; Darzens condensation; epoxide formation

There are two main reactions halohydrins can undergo under suitable experimental conditions: intramolecular nucleophilic substitution to give an epoxide under basic conditions and β-elimination of H_2O to furnish a haloalkene under acidic conditions (Eq. 1).



Eq. 1

The β-elimination would be expected to be the preferred reaction when the R^1 group at the β-carbon is a strong electron-withdrawing group and OH is converted into a good leaving group. However, there are only a few examples of halohydrins which undergo β-elimination to produce Knoevenagel-type haloalkenes [1,2], and this is usually a minor side reaction [3a–c]. The synthetic potential for di- and trisubstituted haloalkenes which the Knoevenagel reaction would afford stimulated an investigation of this field.

We have recently reported on the reaction of certain heterosubstituted α-chloromethyllithiums with carbonyl compounds leading to epoxides as final products, the heterosubstituent being a heteroaryl or other heterocyclic group [4–9]. We have also found that intermediate halohydrins can be trapped after short reaction times.

We have now studied the competition between the cyclization of these halohydrins to epoxides (Darzens condensation) and the formation of chloroalkenes (Knoevenagel-type reaction).

Treatment of **2a** (Scheme 1), available upon deprotonation of **1a** with LDA at –78 °C, with cyclohexanone and quenching of the reaction mixture with aq. NH_4Cl after 20 h afforded epoxide **4a** [9]. Similarly, lithiation of **1b** and reaction of the resulting lithiated species **2b** with 2-adamantanone led to epoxide **4b**. The reaction of **2a** or **2b** with cyclohexanone and 2-adamantanone, quenched after short reaction time (15 min), provided

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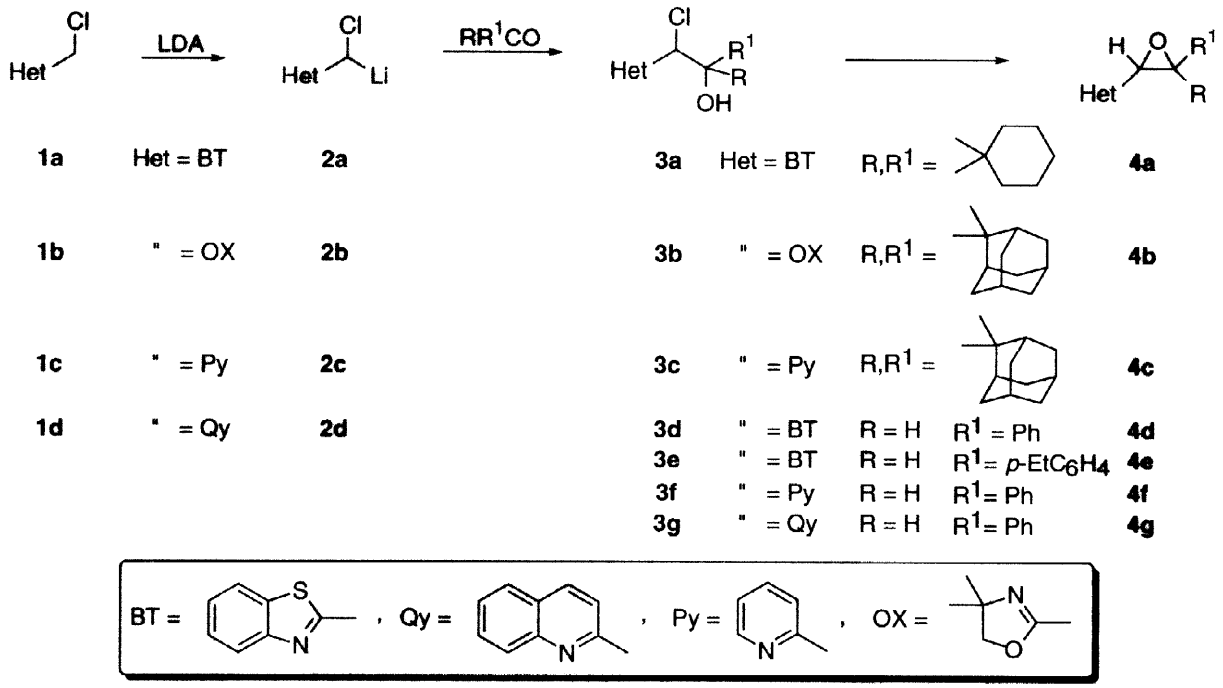
chlorohydrins **3a** (70 %) and **3b** (40 %), respectively, which could be converted into epoxides **4a and 4b upon** treatment with 0.1 N NaOH in ^{i}PrOH [9].

Scheme 1

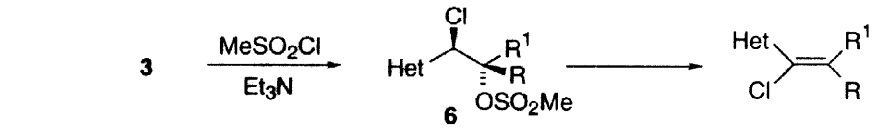


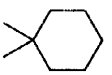
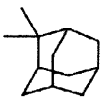
The reaction of **2c** with 2-adamantanone led to chlorohydrin **3c** and then to epoxide **4c** [5]. The reaction of **2a** with benzaldehyde in THF under the above experimental conditions and long reaction time (~ 20 h) afforded epoxide **4d** having almost exclusively the *trans* configuration [9]. The same reaction quenched after 15 min led to the isolation of chlorohydrins **3d** as a 1:1 diastereomeric mixture. Such a mixture, when treated with NaOH/^{i}PrOH, provided a 1:1 *trans/cis* mixture of epoxides **4d**. The lack of diastereoselection of the reaction of **2a** with PhCHO in THF at short reaction time and subsequent cyclization in NaOH/^{i}PrOH, compared with the high *trans* stereoselection of the reaction in THF and long reaction time, could be tentatively explained by taking into consideration the relative rates of the epoxide formation and the chlorohydrin interconversion. It is likely that in a relatively less polar solvent such as THF the chlorohydrin interconversion proceeds faster than the epoxide formation. In THF, therefore, the highly preferential formation of the *trans* epoxide could be explained by the higher propensity of the *anti* chlorohydrin to undergo cyclization to the epoxide with respect to the *syn* isomer. The transition state corresponding to the *anti* chlorohydrin and evolving to the *trans* epoxide should be of lower energy than that leading to the *cis* epoxide and originating from the *syn* halohydrin [3a,10].

When the reaction of **2a** with PhCHO is carried out in THF and quenched after a few minutes the resulting isomeric chlorohydrins have no time to equilibrate. Subsequent cyclization, effected in a polar solvent (^{i}PrOH and NaOH), occurs much faster than the chlorohydrin interconversion. Under these conditions the *trans/cis* ratio between the epoxides reproduces the *anti/syn* ratio between the halohydrins. Comparable results were obtained in the reaction of **2a** with 4-ethylbenzaldehyde: the resulting 1:1 diastereomeric mixture of chlorohydrins **3e** could be quantitatively converted (NaOH/^{i}PrOH) into a 1:1 *trans/cis* mixture of epoxides **4e** at short reaction time. Such a mixture, without isolation, was directly subjected to dehydration to give the Knoevenagel product (see below). Analogously, **2c** and **2d**, derived from **1c** and **1d**, reacted with benzaldehyde

to give chlorohydrins **3f** and **3g** at short reaction times and epoxides **4f** [5] and **4g** [11] at long reaction times. Here again, epoxides **4f** and **4g** of *trans* configuration were obtained at long reaction times, while cyclization of diastereomeric chlorohydrins 3f and **3g**, isolated at short reaction times, gave diastereomeric mixtures of **4e** and **4f** upon treatment with NaOH in ^{i}PrOH.

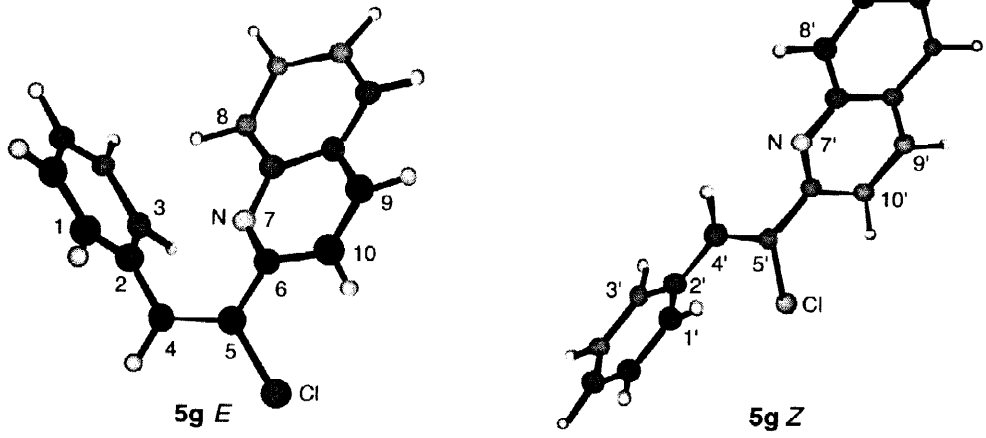
Scheme 2



3a	Het = BT	R,R^1 = 	**5a** (80 %)
3b	" = OX	R,R^1 = 	**5b** (75 %)
3c	" = Py	R,R^1 = 	**5c** (80 %)
3d	" = BT	R = H R^1 = Ph	**5d** (95 %)
3e	" = BT	R = H R^1 = *p*-EtC$_6$H$_4$	**5e** (94 %)
3f	" = Py	R = H R^1 = Ph	**5 f** (50 %)
3g	" = Qy	R = H R^1 = Ph	**5g** (85 %)

It was interesting to observe that chlorohydrins **3a**, derived from the reaction of **2a** with cyclohexanone afforded chloroalkene **5a** (Scheme 2) upon treatment with $MeSO_2Cl/Et_3N$. In a similar way chlorohydrin **3b** afforded chloroalkene **5b** . The sulfonates should be the likely intermediates in the formation of chloroalkenes **5a** and **5b**. This could be proved in the case of chlorohydrins **3g**. Treatment of **3g** with an excess of $MeSO_2Cl/Et_3N$ at room temperature for 30 min gave a 1:1 diastereomeric mixture of the corresponding sulfonates which could not be separated but were identified by ^{1}H NMR spectroscopy and GC–MS. Treatment of the diastereomeric mixture of these sulfonates with Et_3N in CH_2Cl_2 gave (*E*)-2-(2-chlorostyryl)quinoline **5g** and a trace of the *Z* isomer. The configuration of both of the isomers **5g** could be assigned on the basis of a NMR spectral analysis. ^{1}H and ^{13}C chemical shifts for these two isomers could be unambiguously assigned from their ^{1}H-^{1}H homonuclear and ^{1}H-^{13}C heteronuclear correlated 2D NMR spectra. In both of the stereoisomers **5g** the configuration influenced markedly the vinylic proton, H(8) and H(9) chemical shifts as well as the quinolyl and phenyl protons. Ab initio calculations [12] performed for these two isomers justified the observed ^{1}H chemical shifts for the aromatic protons. The results showed that the presence of a small globular substituent (such as a chlorine atom) on the C-C vinylic double bond twisted, in the case of the *Z* isomer, the phenyl ring out of coplanarity by 106.57 °(θ = 1'-2'-4'-5'), while for the quinolyl ring only by 13.6 ° (θ = 4'-5'-6'-7') (Figure 1). On the other hand, the dihedral angles (θ) for the *E* isomer were of 60.3 °(θ= 1-2-4-5) and 51.3 °(θ= 4-5-6-7). Therefore, with reference to these optimized geometries, a *cis* relationship between quinolyl and phenyl rings would mean, first of all, that the H(8) proton should be the one most shielded by the ring current effect of the phenyl ring. Indeed, in the NMR spectrum, the Δδ observed for this proton was the highest: 0.47 (δ 8.13 *vs.* δ 8.60 on going from one isomer to the other). Moreover, the chemical shifts of the vinyl protons for the two isomers (δ 8.13 and δ 8.45) were in good agreement with the values found for similar trisubstituted chloroalkenes [13a-c]. On the basis of such evidence, we assigned the *E* geometry to the isomer showing an upfield shift for all protons.

Figure 1



5g *E* 5g *Z*

In confirmation of this, in a NOESY experiment carried out on the supposed *E* isomer, H(1) and H(3) displayed dipolar interaction with H(10) thus supporting the *E* stereochemisty for this alkene. No such dipolar interaction could be observed in a NOESY experiment performed on the *Z* chloroalkene.

Treatment of the diastereomeric benzothiazolyl chlorohydrins **3d** (1:1 *syn*/*anti* mixture) with $MeSO_2Cl$ /Et_3N, gave chloroalkene **5d** of *E* configuration in a very good yield. Traces of the *Z* isomer were obtained. The *E* geometry of the major product was assigned on the basis of the chemical shift of the vinylic proton (δ 8.04) as with chloroalkene **3g**. Similarly, the reaction of diastereomeric chlorohydrins **3e–f** with $MeSO_2Cl/Et_3N$ afforded chloroalkenes **5e–f** of *E* configuration.

Such an *E* stereoconvergency in the conversion of chlorohydrins **3d–g** to chloroalkenes **5d–g** is difficult to rationalize from a mechanistic viewpoint as there are literature examples of preferential formation of *Z* chloroalkenes resulting from a mesylation-elimination sequence of halohydrins in Knoevenagel-type reactions [1]. At present we can say that the *anti* isomer of chorosulfonates **6** (Het = Qy) should eliminate slower than the *syn* counterpart since we found that when **6** (1:1 diastereomeric mixture) was treated with Et_3N in order to promote the conversion to the corresponding chloroalkenes, an inspection before the elimination was complete clearly indicated an enrichment of the *anti* isomer. However, the *Z* chloroalkene should be expected if an *anti* elimination is occurring. We do not have evidence for the *syn* elimination [1a] that would justify either the higher reactivity of the *syn* isomer in comparison with the *anti* counterpart and the *E* geometry of the resulting chloroalkene. More work is needed to clarify the mechanism of the elimination.

In conclusion, we report here an entry to stereodefined trisubstituted chloroalkenes having functional groups (Cl and the heterocyclic moiety) available for further elaboration [15].

EXPERIMENTAL

^1H NMR spectra were recorded at 90, 200, 300 or 500 MHz in $CDCl_3$; chemical shifts are reported in ppm (δ) from TMS or the residual $CHCl_3$ signal (7.24 ppm). ^{13}C NMR spectra were recorded at 125 MHz and referenced to the center resonance of $CDCl_3$ (77.0 ppm). Absolute values of the coupling constants are reported. IR spectra were recorded on a IR spectrometer. GC-MS spectrometry analyses were performed on a gas cromatograph 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. Column chromatography was

performed by using silica gel (70-230 mesh) with petroleum ether/diethyl ether mixture as the eluent. Microanalyses were performed on a C, H, N analyzer.

Materials:

2-(Chloromethyl)pyridine **2c** and 2-(chloromethyl)quinoline **2d** are sold as hydrochloride salts (Aldrich) from which they can be obtained upon treatment with NaOH 10% solution. 2-(Chloromethyl)-1,3-benzothiazole [16] and 2-(chloromethyl)-4,4-dimethyl-1,3-oxazoline [17] were prepared as reported. Petroleum ether refers to the 40-60 °C boiling fraction. All other chemicals were of commercial grade and used without purification or distilled prior to use.

Preparation of chlorohydrins 3a-g. The preparation of **2-(2-quinolyl)-2-chloro-1-phenylethanol (3g)** is representative. To a solution of LDA, prepared from *n*-BuLi (2.5 M solution in hexanes, 1.2 mmol) and diisopropylamine (1.2 mmol) at 0 °C and cooled at –78 °C, was added dropwise a THF solution of benzaldehyde (1 mmol) and 2-chloromethylquinoline (1 mmol). The reaction mixture was stirred for 30 min, quenched with sat. aq. NH_4Cl, extracted with ether and evaporated under vacuum to give a residue which was column chromatographed on silica gel (Et_2O/petroleum ether: 7/3). Evaporation of the solvent left a solid that was a 1:1 diastereomeric mixture (*syn* + *anti*) [18] of chlorohydrins **3g** (75 % yield). M.p. 85-90 °C. ^1H NMR (200 MHz), δ: 5.25 (d, 1 H, *anti*, J = 6.5 Hz), 5.26 (d, 1 H, *syn*, J = 3.3 Hz), 5.43 (d, 1 H, *anti*, J = 6.5 Hz), 5.58 (d, 1 H, *syn*, J = 3.3 Hz), 5.7 (br s, exchanges with D_2O, 1 H, *syn* + 1 H, *anti*), 7.20–8.20 (m, 11 H, *syn* + 11 H, *anti*); GC-MS *m/z* (rel. int.): (*syn* + *anti*) 179 (M^+ + 2 – PhCHO, 33), 177 (M^+– PhCHO, 100), 142 (60), 128 (8), 115 (10); IR ($CHCl_3$): (*syn* + *anti*) 3300 (br), 3040, 3020, 2950, 2840, 1590, 1490, 1170 cm^{-1}. Elem. anal., found % (calcd for $C_{17}H_{14}ClNO$): C, 72.16 (71.96); H, 5.27 (4.97); N, 5.09 (4.94). When the reaction of **3g** as above was quenched after 24 h the epoxide **4g** of *trans* configuration formed in a 85 % yield [11].

1-[(2-Benzothiazolyl)chloromethyl]cyclohexanol (3a). Oil, 75 % yield. ^1H NMR (90 MHz) δ: 1.60–2.40 (multiplets, 10 H), 3.97 (br s, 1 H, exchanges with D_2O), 5.49 (s, 1 H), 7.50–8.35 (2 m, 4 H). GC-MS *m/z* (rel. int.): 281 (M^+, 3), 263 (1), 185 (33), 183 (100). IR ($CHCl_3$): 3350 (br), 3050, 2960, 2910, 2860, 1600, 1480, 1100 cm^{-1}. Elem. anal., found % (calcd for $C_{14}H_{16}ClNOS$): C, 59.11 (59.67); H, 5.45 (5.72); N, 5.15 (4.97).

2-[(4,4-Dimethyl-2-oxazolin-2-yl)chloromethyl]adamantan-2-ol (3b). M.p. 180-182 °C, 65 % yield. ^1H NMR (200 MHz) δ: 1.10-2.50 (m, 20 H), 2.85 (br s, 1 H, exchanges with D_2O), 3.87–3.97 (m, 2 H), 4.06 (s, 1 H); GC-MS *m/z* (rel. int): 297 (M^+, 4), 295 (10), 269 (34), 267 (100), 232 (53), 133 (35), 91 (69), 77 (33), 55 (36); IR (KBr): 3557 (sharp), 3500–3200 (br), 1636, 1503, 1450, 1350, 1296, 1268, 1064 cm^{-1}. Elem. anal., found % (calcd for $C_{16}H_{24}ClNO_2$): C, 64.43 (64.53); H, 8.20 (8.12); N, 4.85 (4.70).

3'-(4,4-Dimethyl-2-oxazolin-2-yl)spiro[adamantane-2,2'-oxirane] (4 b). M.p. 76–77 °C (hexane), quantitatively obtained from **3b**. ^1H NMR (90 MHz) δ: 1.3 (s, 2 × 3 H), 2.20–1.30 (multiplets, 14 H, adamantyl), 3.40 (s, 1 H), 4.0 (s, 2 H); GC-MS *m/z* (rel. int): 261 (M^+, 1), 232 (24), 206 (37), 176 (100), 133 (18), 91 (62), 81 (15), 79 (31), 41 (53); IR (KBr): 2900, 1645, 1445, 1365, 1290, 970, 910, 755, 655 cm^{-1}. Elem. anal., found % (calcd for $C_{16}H_{23}NO_2$): C, 73.93 (73.53); H, 9.25 (8.87); N, 5.28 (5.36).

2-[(2-Pyridyl)chloromethyl]adamantan-2-ol (3c). M.p. 139–142 °C, 54 % yield. ^1H NMR (200 MHz) δ: 1.31–2.50 (multiplets, 14 H, adamantyl), 5.57 (s, 1 H), 5.60 (s, 1 H, exchanges with D_2O), 7.24–7.41 (2 m, 2 H), 7.66–7.77 (m, 1 H), 8.51–8.59 (m, 1 H); GC-MS *m/z* (rel.int): 279 (M^+ + 2, 0.52), 277 (M^+, 0.64), 276 (2), 242 (165), 224 (270), 151 (138), 129 (337), 127 (1000), 92 (122); IR ($CHCl_3$): 3500–3100 (br), 2890, 1580, 1425 cm^{-1}. Elem. anal., found % (calcd for $C_{16}H_{20}ClNO$): C, 69.35 (69.18); H, 7.10 (7.26); N, 5.20 (5.04).

2-(2-Benzothiazolyl)-2-chloro-1-phenylethanol (3d). M.p. 115–120 °C, 50 % overall yield; 1:1 *syn* + *anti* diastereomeric mixture. ^{1}H NMR (200 MHz), δ: 4.7–4.85 (br s, exchanges with D_2O, 1 H *syn* + 1 H *anti*), 5.29 (d, 1 H, *anti*, J = 7.1 Hz), 5.44 (d, 1 H, *syn*, J = 4.6 Hz), 5.38 (d, 1 H, *anti*, J = 7.1 Hz), 5.52 (d, 1 H, *syn*, J = 4.6 Hz), 7.28–8.03 (m, 9 H, *syn*, + 9 H, *anti*); GC-MS *m/z* (rel. int.): (*syn* + *anti*) 185 (M^+ + 2 – PhCHO, 14.90), 183 (M^+ – PhCHO, 41.83), 148 (100); IR ($CHCl_3$): (*syn* + *anti*) 3580 (br), 3050, 2960, 2920, 2860, 1610, 1500, 1170, 1050 cm^{-1}. Elem. anal., found % (calcd for $C_{15}H_{12}ClNOS$): C, 62.32 (62.17); H, 4.29 (4.17); N, 5.01 (4.83).

2-(2-Benzothiazolyl)-2-chloro-1-(4-ethylphenyl)ethanol (3e). M.p. 103–108 °C, 55% yield, 1:1 *syn* + *anti* diastereomeric mixture. ^{1}H NMR (200 MHz), δ: 1.21 (t, 3 H, *syn* or *anti*, J = 7.5 Hz), 1.28 (t, 3 H, *anti* or *syn*, J = 7.5 Hz), 2.62 (q, 2 × 2 H, *syn* + *anti*, J = 7.5 Hz), 4.65 (br s, exchanges with D_2O, 1 H, *syn* + 1 H, *anti*), 5.26 (d, 1 H, *anti*, J = 7.0 Hz), 5.37 (d, 1 H, *anti*, J = 7.0 Hz), 5.42 (d, 1 H, *syn*, J = 4.1 Hz), 5.47 (d, 1 H, *syn*, J = 4.1 Hz), 7.0–8.0 (m, 8 H, *syn* + 8 H, *anti*); GC-MS *m/z* (rel. int.): (*syn* + *anti*) 185 (M^+ + 2 – *p*-EtC_6H_4CHO, 37.5), 183 (M^+ – *p*-EtC_6H_4CHO, 47.3), 148 (100); IR ($CHCl_3$): (*syn* + *anti*) 3580 (sharp), 3500–3200 (br), 3050, 2960, 2920, 2860, 1610, 1500, 1170, 1050 cm^{-1}. Elem. anal., found % (calcd for $C_{17}H_{16}ClNOS$): C, 64.40 (64.24); H, 5.30 (5.07); N, 4.55 (4.41).

2-(2-Pyridyl)-2-chloro-1-phenylethanol (3f). The 1:1 diastereomeric mixture of chlorohydrins **3e** could be separated by column chromatography. 67 % Overall yield. First eluted diastereomer (*anti*), oil. ^{1}H NMR (200 MHz), δ: 5.05 (d, 1 H, J = 4.2 Hz), 5.2 (br s, exchanges with D_2O, 1 H), 5.38 (d, 1 H, J = 4.2 Hz), 7.20–7.38 (m, 7 H), 7.65 (td, 1 H, J= 8.0, 2.0 Hz), 8.53–8.56 (m, 1 H); GC-MS *m/z* (rel. int.): 198 (M^+ – Cl, 100), 129 (31), 127 (92); IR ($CHCl_3$): 3300 (br), 3025, 2950, 2910, 2850, 1590, 1450, 1050 cm^{-1}. Second eluted diastereomer (*syn*), m.p. 70–72 °C. ^{1}H NMR (200 MHz), δ: 5.05 (d, 1 H, J = 6.0 Hz), 5.28 (d, 1 H, J = 6.0 Hz), 5.5 (br s, exchanges with D_2O, 1 H), 7.20–7.30 (m, 7 H), 7.62 (td, 1 H, J= 8.0, 2.0 Hz), 8.51–8.55 (m, 1 H); GC-MS m/z (rel. int.): 198 (M^+ – Cl, 53), 129 (37), 127 (100); IR ($CHCl_3$): 3300 (br), 3025, 2950, 2910, 2850, 1590, 1450, 1050 cm^{-1}. Elem. anal., found % (calcd for $C_{13}H_{12}ClNO$): C, 66.60 (66.81); H, 5.35 (5.17); N, 5.68 (5.99).

Preparation of chloroalkenes 5a-g. The preparation of **5a** is representative.

An anhydrous CH_2Cl_2 (10 mL) stirred solution of chlorohydrin **3a** (1 mmol) was treated, under N_2, with $MeSO_2Cl$ (2 mmol) and Et_3N (1.2 mmol) at room temperature for 24 h. Then the reaction mixture was quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2 and dried over anhyd. Na_2SO_4. Removal of the solvent under reduced pressure left a solid which was purified by column chromatography (silica gel, Et_2O/petroleum ether 8/2).

2-(Cyclohexylidenechloromethyl)-1,3-benzothiazole (5a). M.p. = 45–47 °C, 80 % yield. ^{1}H NMR (200 MHz), δ: 1.1-1.7 (m, 6 H), 2.6 (t, 2 H, J = 6.4 Hz), 2.8 (t, 2 H, J = 6.4 Hz), 7.34–7.56 (m, 2 H), 7.86–8.05 (2 m, 2 H); GC-MS *m/z* (rel. int.): 265 (M^+ + 2, 23), 263 (M^+, 62), 234 (66), 228 (100); IR ($CHCl_3$): ν 3050, 2920, 2850, 1600, 1490, 1180, 1080 cm^{-1}. Elem. anal., found % (calcd for $C_{14}H_{14}ClNS$): C, 63.53 (63.75); H, 5.61 (5.35); N, 5.10 (5.31).

2[(2-Adamantylidene)chloromethyl]-4,4-dimethyl-1,3-oxazoline (5b). M.p. = 150–152 °C, 75 % yield. ^{1}H NMR (200 MHz), δ: 1.32 (s, 3 H), 1.39 (s, 3 H), 1.10-2.45 (multiplets, 14 H, adamantyl), 3.70–3.82 (m, 2 H); GC-MS *m/z* (rel. int.): 279 (M^+, 8), 244 (100); IR ($CHCl_3$): ν 2950, 1636, 1503, 1450, 1353, 1296, 1200, 1150, 1064 cm^{-1}. Elem. anal., found % (calcd for $C_{16}H_{22}ClNO$): C, 68.92 (68.68); H, 7.70 (7.92); N, 5.18 (5.00).

2-[(2-Adamantylidene)chloromethyl]pyridine (5c). M.p. 133–135 °C, 80 % yield. ^{1}H NMR (200 MHz), δ: 1.81–1.96 (multiplets, 12 H, adamantyl), 2.79 (br s, 1 H), 3.38 (br s, 1 H), 7.17–7.23 (m, 1 H), 7.25–7.35 (m, 1 H), 7.64–7.73 (m, 1 H), 8.63–8.67 (m, 1 H); MS *m/z* (rel. int.): 261 (M^+ + 2, 9), 260 (36), 259 (M^+, 30), 258 (100), 224 (13), 180 (11), 167 (16); IR (film): ν 3060, 2960, 2860, 1600, 1495, 1511, 1420, 1400, 850 cm^{-1}. Elem. anal., found % (calcd for $C_{16}H_{18}ClN$): C, 73.93 (73.98); H, 7.15 (6.98); N, 5.28 (5.39).

(*E*)-2-(2-Chlorostyryl)-1,3-benzothiazole (5d). The diastereomeric mixture of chlorohydrins **3d** was treated as above with $MeSO_2Cl/Et_3N$. M.p. = 85–87 °C, 95 % yield. ^{1}H NMR (200 MHz), δ: 7.35–7.54 (m, 7 H), 7.86–7.90 (m, 1 H), 8.04 (s, 1 H, vinylic proton), 8.03–8.08 (m, 1 H); GC-MS *m/z* (rel. int.): 273 (M^+ + 2, 14), 271 (M^+, 26), 270 (100), 236 (38); IR ($CHCl_3$): ν 3050, 2970, 2900, 2830, 1600, 1150 cm^{-1}. GC-MS rivealed the presence of traces of the *Z* isomer of **5d**. Elem. anal., found % (calcd for $C_{15}H_{10}ClNS$): C, 66.54 (66.29); H, 3.78 (3.71); N, 5.28 (5.15).

(*E*)-2-(2-Chloro-4'-ethylstyryl)-1,3-benzothiazole (5e). It was obtained from the diastereomeric mixture of **3e**. M.p. = 57–58 °C, 94 % yield. ^{1}H NMR (200 MHz), δ: 1.25 (t, 3 H, *J* = 7.5 Hz), 2.67 (q, 2 H, *J* = 7.5 Hz), 7.23–7.28 (m, 2 H), 7.32–7.54 (m, 2 H), 7.79–7.90 (m, 3 H), 8.01 (s, 1 H, vinylic proton), 8.01–8.05 (m, 1 H); GC-MS *m/z* (rel. int.): 301 (M^+ + 2, 14), 299 (M^+, 40), 298 (100), 264 (43), 249 (15), 248 (15); IR ($CHCl_3$): ν 3050, 2980, 2920, 2840, 1610, 1490, 1310, 1150 cm^{-1}. GC-MS showed the presence of traces of the *Z* isomer. The *E/Z* ratio was 96/4. Elem. anal., found % (calcd for $C_{17}H_{14}ClNS$): C, 68.20 (68.10); H, 4.50 (4.71); N, 4.82 (4.67).

(*E*)-2-(2-Chlorostyryl)pyridine (5f). This alkene was obtained from the diastereomeric mixture of halohydrins **3f**. Oil, 50 % yield. ^{1}H NMR (200 MHz), δ: 7.30-7.60 (m, 5 H), 7.70-7.90 (m, 2 H), 8.00-8.40 (m, 2 H), 8.10 (s, 1 H, vinylic proton) 8.80-8.90 (m, 1 H). GC-MS *m/z* (rel. int.): 217 (M^+ + 2, 8), 215 (M^+,18), 214 (63), 180 (100). Elem. anal., found % (calcd for $C_{13}H_{10}ClN$): C, 72.25 (72.39); H, 4.45 (4.67); N, 6.65 (6.49).

(*E*)-2-(2-Chlorostyryl)quinoline (5g). **(*E*)-2-(2-Chlorostyryl)quinoline (5g)**. Treatment of **3g** (diastereomeric mixture) (1 mmol) in 15 mL of anhydrous CH_2Cl_2 with $MeSO_2Cl$ (2 mmol) / Et_3N (1.2 mmol) at rt under N_2 and stirring for 30 min gave a solid that was a 1:1 *syn* + *anti* diastereomeric mixture of the corresponding sulfonates which could not be separated but only purified by column chromatography (silica gel 7/3 petroleum ether/ Et_2O) and identified by ^{1}H NMR and GC-MS. M.p. 117-124 °C. ^{1}H NMR (200 MHz), (*syn* + *anti*) δ: 2.52 (s, 3 H, *syn* or *anti*), 2.83 (s, 3 H, *anti* or *syn*), 5.48 (d, 1 H, *J* = 8.5, *syn* or *anti*), 5.52 (d, 1 H, *J* = 8.5 Hz, *anti* or *syn*), 6.28 (d, 1 H, *J* = 8.5 Hz, *syn* or *anti*), 6.33 (d, 1 H, *J* = 8.5, *anti* or *syn*), 7.37–8.24 (m, 11 H, *syn*, + 11 H, *anti*); GC-MS *m/z* (rel. int.): (*syn* + *anti*) 267 (M^+ + 2 – CH_3SO_3H, 15), 265 (M^+ – CH_3SO_3H, 12), 264 (29), 230 (100), 128 (10); (*syn* + *anti*) IR ($CHCl_3$): ν 3040, 2950, 2840, 1590, 1170 cm^{-1}. Elem. anal., found % (calcd for $C_{18}H_{16}ClNO_3S$): C, 60.00 (59.75); H, 4.25 (4.46); N, 3.58 (3.87). Subjected to reflux in the presence of Et_3N for 12 h, the diastereomeric mixture of the above sulfonates afforded the chloroalkene **5g** which was column chromatographed (silica gel, Et_2O/petroleum ether 3:7) to give mainly (85 % yield) the *E* isomer and a small amount (10 % yield) of the *Z* isomer. (*E* isomer) Oil. ^{1}H NMR (300 MHz), δ: 7.32-7.37 (m, 1 H), 7.40-7.46 (m, 2 H), 7.53 (ddd, 1 H, *J* = 7.5, 7.5, 1.1 Hz), 7.73 (ddd, 1 H, *J* = 7.7, 7.7, 1.5 Hz), 7.81 (dd, 1 H, *J* = 8.1, 1.1 Hz), 7.87-7.90 (m, 2 H), 8.00 (d, 1 H, *J* = 8.7 Hz), 8.14 (dd, 1 H, *J* = 8.6, 1.1 Hz), 8.13 (s, 1 H, =C*H*), 8.21 (d, 1 H, *J* = 8.7 Hz); ^{13}C NMR (125 MHz): δ 118.91, 126.88, 127.54, 127.55, 128.35, 128.65, 129.49, 129.61, 130.07, 130.14, 130.44, 134.97, 136.99, 147.51, 154.82; GC-MS *m/z* (rel. int.): 267 (M^+ + 2, 57), 265 (M^+, 170), 264 (405), 230 (1000), 202 (61), 128 (139), 114 (111), 101 (76), 77 (31); IR ($CHCl_3$): ν 3156, 1643,

1466, 1383, 1096, 905 (strong), 712, 651 cm^{-1}. Elem. anal., found % (calcd for $C_{17}H_{12}ClN$): C, 76.63 (76.84); H, 4.41 (4.55); N, 5.10 (5.27).

(**Z** isomer) Waxy solid. ^1H NMR (500 MHz), δ: 7.35–7.32 (m, 1 H), 7.40–7.37 (m, 2 H), 7.58 (ddd, 1 H, *J*= 7.0, 7.0, 1.1 Hz), 7.80 (ddd, 1 H, *J*= 7.0, 7.0, 1.4 Hz), 7.85 (dd, 1 H, *J*= 8.1, 1.1 Hz), 7.94–7.91 (m, 2 H), 8.02 (d, 1 H, *J*= 8.7 Hz), 8.32 (s, 1 H, =C*H*), 8.41 (d, 1 H, *J*= 8.7 Hz), 8.60 (d, 1 H, *J*= 8.5 Hz); ^{13}C NMR (125 MHz): δ 119.60, 125.64, 127.36, 127.68, 128.31, 128.77, 129.70, 130.53, 132.59, 133.65, 164.82, 141.38, 142.77, 153.08; GC-MS *m/z* (rel. int.): 267 (M^+ + 2, 78), 265 (M^+, 223), 264 (372), 230 (1000), 202 (84), 128 (224), 115 (146), 114 (156), 101 (119), 77 (47); IR ($CHCl_3$): ν 3156, 1637, 1600, 1386 1153, 912, 712, 651 cm^{-1}. Elem. anal., found % (calcd for $C_{17}H_{12}ClN$): C, 76.58 (76.84); H, 4.75 (4.55); N, 5.51 (5.27).

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REFERENCES AND NOTES

[1] Makosza M.; Podraza R.; Bialecki M. *Gazz. Chim. Ital.* **1995**, *125*, 601–603 and Refs. therein.
[2] Rosen T. Comprehensive Organic Synthesis. In: Trost B.M., Ed. Vol. II. Oxford: Pergamon Press, **1991**, 409–439.
[3] [3a] Seyden-Penne J.; Roux-Schmitt M.C.; Roux A. *Tetrahedron* **1970**, *26*, 2649–2656. [3b] Gorog S.; Herenyi B.; Renyei M.; Georgakis A.; Balogh G.; Csehi A.; Gizur T. *Magy. Kem. Foly.* **1989**, *95*, 504–7; *Chem. Abstr.* **1990**, *112*, 216367d. [3c] Zapata A.; Ferrer G. F. *Synth. Commun.* **1986**, *16*, 1611–1615.
[4] Florio S.; Troisi L. *Tetrahedron Lett.* **1992**, *33*, 7953–7956.
[5] Florio S.; Troisi L. *Tetrahedron Lett.* **1994**, *35*, 3175–3178.
[6] Florio S.; Troisi L. *J. Org. Chem.* **1996**, *61*, 4148–4150.
[7] Florio S.; Capriati V.; Luisi R. *Tetrahedon Lett.* **1996**, *37*, 4781–4784.
[8] Florio S.; Capriati V.; Russo V. *Tetrahedron Lett.* **1997**, *38*, 5843–5846.
[9] Florio S.; Capriati V.; Russo V. *Gazz. Chim. Ital.* **1997**, *127*, 587–595.
[10] Berti G.; Bottari F.; Macchia B.; Nuti V. *Ann. Chim. (Rome)* **1964**, *54*, 1253–1269.
[11] Munos M–H.; Mayrargue J.; Fournet A.; Gantier J–C.; Hocquemiller R.; Moskowitz H. *Chem. Pharm. Bull.* **1994**, *42*, 1914–1916.
[12] The structures of **5g** *E* and **5g** *Z* were geometry-optimized using the SPARTAN molecular modeling program version 5.1 (licensed to CNR-M.I.S.O. of Bari), Wavefunction Inc., Irvine, California.
[13] [13a] Kato T.; Katagiri N.; Takahashi T.; Katagiri Y. *J. Het. Chem.* **1979**, *16*, 1575–1578. [13b] Hanack M.; Weber E. *Chem. Ber.* **1983**, *116*, 777–797. [13c] Puciová M.; Solcániova E.; Pronayová N.; Loos D.; Toma S. *Tetrahedron* **1993**, *49*, 7733–7742.
[14] Baciocchi E.; Ruzziconi R. *J. Org. Chem.* **1984**, *49*, 3395–3398 and Refs. therein.
[15] A stereoselective synthesis of trisubstituted chloroolefines had been reported. Minato A.; Suzuki K.; Tamao K. *J. Am. Chem. Soc.* **1987**, *109*, 1257–1258.
[16] Florio S.; Capriati V.; Colli G. *Tetrahedron* **1997**, *53*, 5839–5846.
[17] Breton P.; Andrè-Barres C.; Langlois Y. *Synth. Commun.* **1992**, *22*, 2543–2554.
[18] Diastereomers *syn* and *anti* were identified by their difference in ^1H NMR coupling constants between -C*H*Cl- and C*H*OH- signals (*anti*, 6-8 Hz, *syn* 4-7 Hz) as reported for similar systems. Cabon O.; Buisson D.; Larcheveque M.; Azerad R. *Tetrahedron: Asymmetry* **1995**, *6*, 2199–2210.