Lithiation of Cinnamyl Chloride: Stereoselective Synthesis of Propargylic Oxiranes and Aziridines

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Propargylic oxiranes **4a–e** and aziridines **8a–c** have been prepared from cinnamyl chloride through lithiation–alkylation with α-halo carbonyl compounds and α-chloro imines, respectively. The reaction with substituted α-halo carbonyl compounds and α-chloro imines proved to be highly *E* diastereoselective.

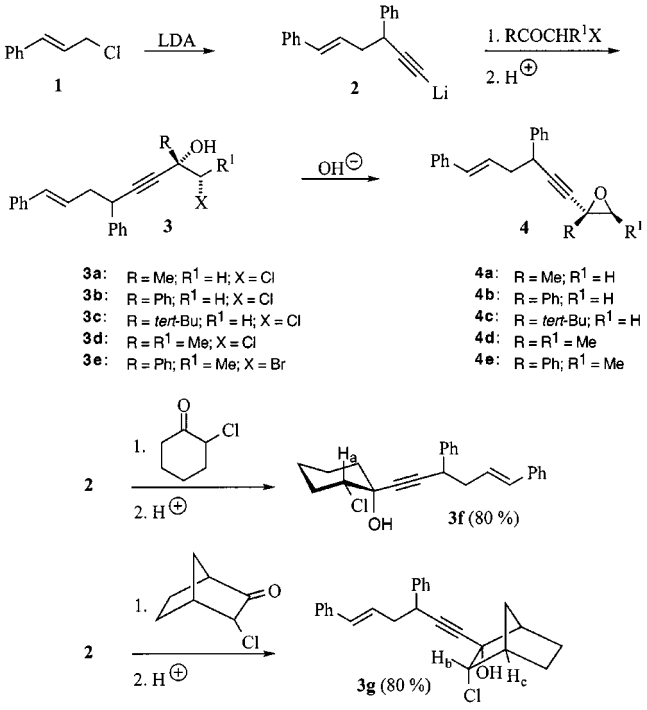
Introduction

Propargylic oxiranes, which are particularly useful synthetic intermediates for the preparation of a variety of substances through elaboration of both the C−C triple bond and the oxiranyl moiety,[1a−1e] are currently prepared by oxidation of the corresponding enynes with *m*-CPBA[2a,2b] or oxone®.[3] The preparation of γ-amino α-acetylenic epoxides based on the reaction of lithium aminoacetylide with α-halo ketones has been reported.[4] Asymmetric syntheses of ethynyl epoxides from epoxybutanols[5] as well as based on the oxiranyl anion methodology[6] have also been developed. A stereoselective access to propargylic oxiranes[7a] and propargylic aziridines[7b] based on the metallation of 3-trimethylsilyl propargyl chloride has been described quite recently.

In the present paper, we report on a stereoselective synthesis of certain enynyl oxiranes and aziridines based on the deprotonation of cinnamyl chloride and reaction with α-halo carbonyl compounds and α-chloro imines.

Results and Discussion

Lithiation of *trans*-cinnamyl chloride **1** (Scheme 1) with lithium diisopropylamide (LDA) in THF at −78 °C followed by the addition of chloroacetone furnished the chlorohydrin **3a** in very good yield (Table 1). The explanation for the formation of this chlorohydrin is that, owing to its carbenoid character,[8a−8c] lithiated cinnamyl chloride dimerizes or couples with its precursor, to give acetylide **2**.[9] It is the latter that undergoes addition of chloroacetone to give **3a**, which may then be quantitatively converted to the enynyl oxirane **4a** by treatment with NaOH in *i*PrOH. In a similar way, chlorohydrin **3b** and oxirane **4b** could be prepared from α-chloroacetophenone. In the case of 1-chloro-3,3-dimethyl-2-butanone, oxirane **4c** was straightforwardly obtained (Table 1).[10]



Scheme 1. Reaction of lithium acetylide **2** with α-halo carbonyl compounds to give propargylic oxiranes **4a−e** and *syn* chlorohydrins **3f** and **3g**

Table 1. Reaction of lithium acetylide **2** with α-halo carbonyl compounds in THF at −78 °C

α-Halo carbonyl	Halohydrin (% yield)[a]	Propargylic oxirane (% yield)[a]
CH_3COCH_2Cl	**3a** (80)	**4a** (quant.)
$PhCOCH_2Cl$	**3b** (60)	**4b** (quant.)
t$BuCOCH_2Cl$	**3c** (−)	**4c** (60)
$CH_3COCHClCH_3$	**3d** (82)[b]	**4d** (95)[b]
$PhCOCHBrCH_3$	**3e** (−)	**4e** (95)
2-Chlorocyclohexanone	**3f** (80)	**4f** (−)
3-Chloro-2-norbornanone	**3g** (80)	**4g** (−)

[a] Isolated yields. − [b] Inseparable mixture of optical diastereomers 42:58 by GC.

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Interestingly, upon treatment with $MeSO_2Cl/Et_3N$, chlorohydrin **3b** underwent a Knoevenagel-type reaction leading to the dienynyl chloride **5b** (65%)[11] (Figure 1).

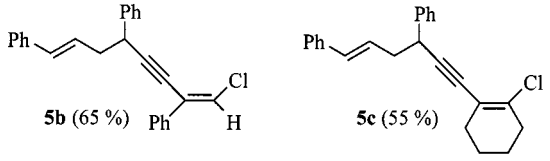
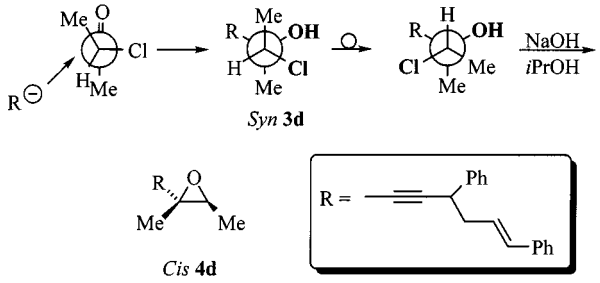


Figure 1. Dienynyl chlorides **5b** and **5c**

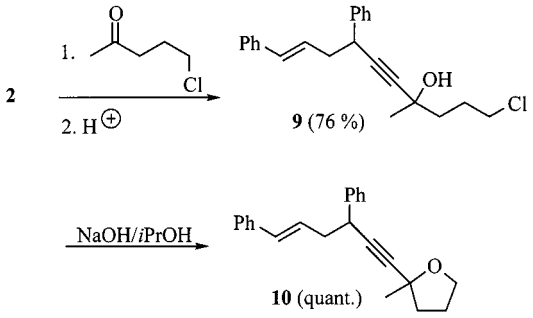
The reaction of **2** with 3-chloro-2-butanone proceeded diastereoselectively yielding exclusively the *syn* chlorohydrin **3d** (Scheme 2). Treatment of **3d** with NaOH/*i*PrOH afforded the *cis* epoxide **4d** as a result of a stereospecific cyclization. The configuration of the epoxide **4d** could be assigned on the basis of the vanishingly small long-range $^3J_{CH}$ coupling constant ($^3J_{CH_3\text{-}H} \approx 0$ Hz) between the oxirane ring proton and the methyl group on the adjacent ring carbon atom, which proves that these groups are on opposite sides, as reported for similar trisubstituted epoxides.[4,12a−12c]



Scheme 2. Stereoselective synthesis of *cis* epoxide **4d**

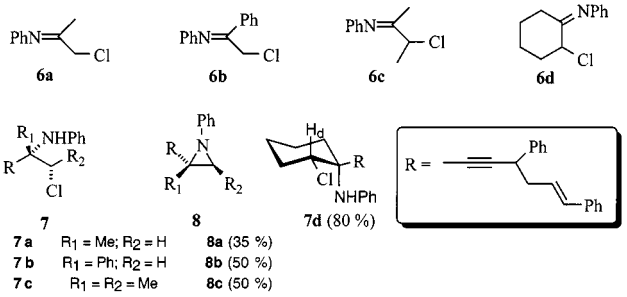
Such diastereoselectivity could be accounted for in terms of a modified Felkin−Anh model[13] by assuming that when acetylide **2** adds to the diastereotopic faces of the carbonyl function of 3-chloro-2-butanone, it preferentially attacks the face whereby the chlorine atom is pushed away to give the *syn* chlorohydrin **3d**. After adopting the appropriate antiperiplanar conformation, this then cyclizes to the *cis* epoxide **4d** (Scheme 2).

That nucleophiles stereoselectively attack the carbonyl group of α-halo ketones to give *syn* chlorohydrins and then *cis* epoxides has precedent.[14] Similarly, the addition of **2** to the α-bromopropiophenone led straightforwardly to the epoxide **4e**[15] (Scheme 1, Table 1). The addition of **2** to 2-chlorocyclohexanone led exclusively to the expected *syn* chlorohydrin **3f**[16] (Scheme 1). However, treatment with NaOH in *i*PrOH under mild conditions (room temp. for 3 h) did not furnish the corresponding epoxide **4f** since, in this case, the required antiperiplanarity of the OH and Cl groups cannot be achieved. Accordingly, the reaction of 3-chloro-2-norbornanone with the lithio derivative **2** ended with the formation of *syn* chlorohydrin **3g**[16] (Scheme 1). Treatment of chlorohydrin **3f** with $MeSO_2Cl/Et_3N$ furnished the dienynyl chloride **5c** (55%) (Figure 1). The synthetic utility of acetylide **2** was also demonstrated by its conversion to enynyl tetrahydrofuran **10** (Scheme 3) through reaction with 5-chloro-2-pentanone via the chloro alcohol **9**.



Scheme 3. Synthesis of enynyl tetrahydrofuran **10**

We have also found that the lithio derivative **2** adds to α-chloro imines.[17a][17b] Indeed, **2** reacted cleanly with α-chloro imines **6a**,**b** to straightforwardly afford the propargylic aziridines **8a**,**b** (Scheme 4).



Scheme 4. Synthesis of propargylic aziridines **8a**−**d** and α-chloro amine **7d**

Moreover, the reaction of **2** with α-chloro imine **6c** gave *cis* aziridine **8c**,[15] while that with α-chloro imine **6d** ended with the formation of *syn* chloro amine **7d**. The latter could not cyclize to the corresponding aziridine for the same reason that chlorohydrin **3f** did not cyclize to the corresponding epoxide[18] (Scheme 4).

Conclusion

In conclusion, we have described a facile synthesis of certain enynyl oxiranes and aziridines based simply on the lithiation of cinnamyl chloride and reaction with α-halo carbonyl compounds and α-chloro imines.

Experimental Section

General: Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Diisopropylamine was distilled from finely powdered calcium hydride. α-Chloro ketones, $MeSO_2Cl$, Et_3N, and all other chemicals were of commercial grade (Aldrich) and were used without further purification. Petroleum ether refers to the 40−60 °C boiling fraction. A commercial solution of *n*BuLi in hexanes (Aldrich) was titrated with *N*-pivaloyl-*o*-toluidine prior to use.[19] − NMR: Bruker (200 MHz and 50.3 MHz, for ^1H and ^{13}C, respectively); for ^1H NMR, $CDCl_3$ as solvent, $\delta_H = 7.24$, TMS as internal standard; for ^{13}C NMR,

$CDCl_3$, δ_C = 77.0. − IR: Perkin−Elmer 283. − GC-MS analyses were performed on an HP 5890 II gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm *i.d.*) equipped with a mass-selective detector operating at 70 eV (EI). − Melting points are uncorrected. − TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished by means of UV light (254 nm). − Column chromatography was performed on silica gel (70−230 mesh) using petroleum ether/diethyl ether mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe/septum cap techniques.

General Procedure for the Preparation of Halohydrins 3a,b, 3d, 3f,g, Chloro Alcohol 9, Propargylic Oxiranes 4a−e, Propargylic Aziridines 8a−c, and Enynyl Tetrahydrofuran 10: A solution of lithium diisopropylamide (LDA) (2.4 mmol) [prepared from diisopropylamine (0.33 mL) and 1.6 M *n*BuLi (1.5 mL) in dry THF (15 mL)] was stirred under N_2 at 0 °C for 30 min. To this solution, cooled to −80 °C by means of a methanol/liquid nitrogen bath, a solution of cinnamyl chloride (304 mg, 2.0 mmol) in dry THF (2.0 mL) was added dropwise. The mixture was slowly allowed to warm to 0 °C (over ca. 1 h), then cooled to −80 °C once more, whereupon a solution of the α-halo carbonyl compound (or the α-chloro imine) (2.0 mmol) in dry THF (2.0 mL) was added dropwise. After 10 min., the resulting mixture was quenched at low temperature with satd. aq. NH_4Cl solution and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude chlorohydrin (or the α-chloro amine **7d**) was purified by column chromatography (silica gel, petroleum ether/Et_2O, 9:1) and then quantitatively cyclized to the corresponding epoxide with NaOH/*i*PrOH.[12c] The aziridines **8a**, **8b**, and **8c** were straightforwardly obtained from the α-chloro imines **7a**, **7b**, respectively, and purified as described above for the chlorohydrins. It is noteworthy that if the reaction mixtures were allowed to warm to room temp. and quenched after 2 h, only epoxides (or the enynyl tetrahydrofuran **10**) as opposed to chlorohydrins could be isolated. On the other hand, the chlorohydrins **3c** and **3e** could not be isolated even after short reaction times.

1-Chloro-2-methyl-5,8-diphenyl-7-octen-3-yn-2-ol (3a): Oil; 519.74 mg, 80%. − ^{1}H NMR (200 MHz): δ = 1.6 (s, 3 H), 2.66 (t, *J* = 7.0 Hz, 2 H), 2.74 (br. s, 1 H, exchanges with D_2O, OH), 3.60 (d, *J* = 10.9 Hz, 1 H), 3.70 (d, *J* = 10.9 Hz, 1 H), 3.82 (t, *J* = 7.0 Hz, 1 H), 6.18−6.5 (m, 2 H), 7.24−7.38 (m, 10 H). − ^{13}C NMR (50.3 MHz): δ = 24.8, 27.8, 38.8, 42.6, 55.2, 68.4, 86.6, 126.8, 127.5, 127.6, 127.9, 128.1, 129.2, 133.1, 138.0, 141.4. − GC-MS (70 eV): *m*/*z* (%) = 324 (0.9) [M^+], 231 (16.1), 117 (100.0), 115 (20.2). − IR ($CHCl_3$): $\tilde{\nu}$ = 3550 (br., OH) cm^{-1}, 3060, 3020, 2980, 2240, 1600, 1490, 1460, 1330, 1260, 1120, 1070.

1-Chloro-2,5,8-triphenyl-7-octen-3-yn-2-ol (3b): M.p. 62−63 °C (ligroin); 464.29 mg, 60%. − ^{1}H NMR (200 MHz): δ = 2.71−2.74 (m, 2 H), 3.03 (br. s, 1 H, exchanges with D_2O, OH), 3.74 and 3.81 (2 × d, *J* = 11 Hz, 2 H), 3.80−4.05 (m, 1 H), 7.23−7.69 (m, 15 H). − ^{13}C NMR (50.3 MHz): δ = 28.9, 30.0, 41.2, 52.5, 70.0, 84.5, 126.4, 127.7, 127.9, 128.0, 128.3, 128.7, 128.8, 129.5, 131.8, 130.0, 133.5, 133.8, 139.8. − GC-MS (70 eV): *m*/*z* (%) = 295 (2.2) [M^+ − 91], 232 (10.3), 155 (12.4), 117 (100.0). − IR ($CHCl_3$): $\tilde{\nu}$ = 3500 (br., OH) cm^{-1}, 3060, 3020, 1600, 1490, 1450, 1060, 750, 695. − $C_{26}H_{23}ClO$ (386.92): calcd. C 80.71, H 5.99; found C 80.68, H 5.95.

***syn*-2-Chloro-3-methyl-6,9-diphenyl-8-nonen-4-yn-3-ol (3d):** Oil (inseparable mixture of optical diastereomers in a 42:58 ratio by GC); 555.75 mg, 82%. − ^{1}H NMR (200 MHz): δ = 1.35 (d, *J* = 5.5 Hz, 2 × 3 H), 2.65 (t, *J* = 6.8 Hz, 2 × 2 H), 2.78 (br. s, 2 × 1 H, exchanges with D_2O, 2 × OH), 3.84 (dd, *J* = 7.0 Hz, 2 × 1 H), 4.05 (q, *J* = 5.5 Hz, 2 × 1 H), 6.20−6.50 (m, 2 × 2 H), 7.17−7.40 (m, 2 × 10 H). − ^{13}C NMR (50.3 MHz): δ = 20.7, 26.7, 28.0, 38.0, 45.0, 58.0, 67.0, 86.0, 126.0, 126.7, 127.0, 127.4, 128.2, 128.4, 128.6, 132.4, 137.0, 140.8. − GC-MS (70 eV): *m*/*z* (%) = 275 (3.3) [M^+ − CH_3CHCl], 231 (5.2), 117 (100.0), 115 (36.2). − IR ($CHCl_3$): $\tilde{\nu}$ = 3420 (br., OH) cm^{-1}, 3060, 3020, 2980, 2240, 1600, 1490, 1450, 1070, 1050, 970, 930, 750, 700.

***syn*-2-Chloro-1-(5-hexen-1-yne-3,6-diphenyl-1-yl)cyclohexanol (3f):** Oil; 583.86 mg, 80%. − ^{1}H NMR (200 MHz): δ = 1.20−2.15 (m, 8 H), 2.50 (br. s, 1 H, exchanges with D_2O, OH), 2.62 (t, *J* = 7.0 Hz, 2 H), 3.80 (t, *J* = 7.0 Hz, 1 H), 4.17 (dd, *J* = 4.0, 9.0 Hz, 1 H), 6.15−6.44 (m, 2 H), 7.16−7.38 (m, 10 H). − ^{13}C NMR (50.3 MHz): δ = 22.7, 27.0, 39.6, 37.3, 38.1, 39.2, 62.7, 68.2, 69.4, 85.7, 126.0, 126.7, 126.8, 126.9, 127.0, 127.3, 128.4, 132.3, 137.3, 140.8. − GC-MS (70 eV): *m*/*z* (%) = 364 (0.8) [M^+], 329 (2.3), 311 (3.2), 232 (10.4), 141 (15.3), 117 (100.0). − IR (film): $\tilde{\nu}$ = 3420 (br., OH) cm^{-1}, 3060, 3020, 2940, 2860, 1600, 1490, 1450, 1160, 1115, 1060, 970, 740, 690.

***syn*-3-Chloro-2-(5-hexen-1-yne-3,6-diphenyl-1-yl)norbornan-1-ol (3g):** Oil; 603.07 mg, 80%. − ^{1}H NMR (200 MHz): δ = 1.20−2.40 (m, 8 H), 2.58 (br. s, 1 H, exchanges with D_2O, OH), 2.60−2.76 (m, 2 H), 3.82 (t, *J* = 7.0 Hz, 1 H), 4.02 (d, *J* = 2.2 Hz, 1 H), 6.15−6.45 (m, 2 H), 7.18−7.35 (m, 10 H). − ^{13}C NMR (50.3 MHz): δ = 20.6, 25.6, 34.2, 42.1, 46.7, 59.3, 63.4, 74.8, 86.2, 126.05, 126.8, 127.1, 127.3, 128.4, 128.5, 128.6, 132.4, 134.3, 137.2. − GC-MS (70 eV): *m*/*z* (%) = 376 (3.3) [M^+], 341 (3.1), 269 (10.5), 195 (15.2), 117 (100.0). − IR (film): $\tilde{\nu}$ = 3500 (br., OH) cm^{-1}, 3060, 3020, 2960, 2860, 1600, 1500, 1300, 1170, 1060, 740, 690.

1,2-Epoxy-2-methyl-5,8-diphenyl-7-octen-3-yne (4a): Oil; 461.41 mg, quantitative conversion from **3a**. − ^{1}H NMR (200 MHz): δ = 1.56 (s, 3 H), 2.63 (t, *J* = 7.0 Hz, 2 H), 2.73 (d, *J* = 5.5 Hz, 1 H), 3.0 (d, *J* = 5.5 Hz, 1 H), 3.77 (t, *J* = 7.0 Hz, 1 H), 6.15−6.44 (m, 2 H), 7.20−7.35 (m, 10 H). − ^{13}C NMR (50.3 MHz): δ = 26.1, 26.8, 38.0, 58.5, 64.0, 68.5, 84.0, 126.0, 126.6, 126.8, 127.0, 128.0, 128.5, 128.6, 133.7, 138.0, 141.0. − GC-MS (70 eV): *m*/*z* (%) = 288 (80.2) [M^+], 197 (92.3), 171 (40.4), 153 (35.2), 128 (55.5), 115 (70.2), 91 (100.0). − IR ($CHCl_3$): $\tilde{\nu}$ = 3060 cm^{-1}, 3020, 2980, 2240, 1600, 1490, 1450, 1340, 1250, 1070, 970, 860.

1,2-Epoxy-2,5,8-triphenyl-7-octen-3-yne (4b): Oil; 420.54 mg, quantitative conversion from **3b**. − ^{1}H NMR (200 MHz): δ = 2.71 (t, *J* = 7.0 Hz, 2 H), 3.02 (d, *J* = 4.0 Hz, 1 H), 3.39 (d, *J* = 4.0 Hz, 1 H), 3.94 (t, *J* = 7.0 Hz, 1 H), 6.20−6.50 (m, 2 H), 7.12−7.50 (m, 15 H). − ^{13}C NMR (50.3 MHz): δ = 29.7, 31.0, 52.5, 62.0, 71.0, 85.0, 127.6, 128.0, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.9, 132.0, 133.1, 133.3, 133.5, 139.0. − GC-MS (70 eV): *m*/*z* (%) = 350 (40.1) [M^+], 259 (43.2), 233 (40.3), 215 (50.1), 115 (60.4), 91 (100.0). − IR ($CHCl_3$): $\tilde{\nu}$ = 3060 cm^{-1}, 3020, 2970, 2240, 1605, 1450, 1450, 1350, 1230, 960.

2-*tert*-Butyl-1,2-epoxy-5,8-diphenyl-7-octen-3-yne (4c): Oil; 396.55 mg, 60%. − ^{1}H NMR (200 MHz): δ = 1.03 (s, 9 H), 2.65 (t, *J* = 7.0 Hz, 2 H), 2.85 (d, *J* = 5.5 Hz, 1 H), 2.91 (d, *J* = 5.5 Hz, 1 H), 3.81 (t, *J* = 7.0 Hz, 1 H), 6.14−6.45 (m, 2 H), 7.15−7.38 (m, 10 H). − ^{13}C NMR (50.3 MHz): δ = 25.6, 26.0, 27.0, 30.0, 52.0, 66.0, 68.0, 83.0, 127.0, 128.4, 128.7, 128.9, 129.3, 129.5, 130.0, 133.0, 134.0, 140.0. − GC-MS (70 eV): *m*/*z* (%) = 330 (25.2) [M^+], 273 (30.3), 239 (23.0), 213 (25.4), 91 (100.0). − IR ($CHCl_3$): $\tilde{\nu}$ = 3060 cm^{-1}, 3020, 2960, 2870, 2240, 1600, 1450, 1220, 1170, 740, 695.

***trans*-2,3-Epoxy-3-methyl-6,9-diphenyl-8-nonen-4-yne (4d):** Oil (inseparable mixture of optical diastereomers in a 42:58 ratio by GC);

471.76 mg, 95% from **3d**. − ^{1}H NMR (200 MHz): δ = 1.29 (d, *J* = 5.5 Hz, 2 × 3 H), 1.49 (s, 2 × 3 H), 2.63 (t, *J* = 7.0 Hz, 2 × 2 H), 3.19−3.29 (2 × q, overlapping, *J* = 5.5 Hz, 2 × 1 H), 3.76 (t, *J* = 7.0 Hz, 2 × 1 H), 6.04−6.44 (m, 2 × 2 H), 7.17−7.50 (m, 2 × 10 H). − ^{13}C NMR (50.3 MHz): δ = 20.3, 27.0, 38.0, 40.0, 64.0, 65.0, 66.7, 86.3, 125.9, 126.0, 126.7, 126.8, 127.3, 128.4, 128.5, 132.3, 137.2, 141.0. − GC-MS (70 eV): *m*/*z* (%) = 302 (70.0) [M$^+$], 259 (16.1), 211 (83.2), 185 (92.3), 91 (100.0). − IR ($CHCl_3$): ṽ = 3060 cm^{-1}, 3020, 2960, 2920, 2240, 1600, 1450, 1250, 1070, 970, 745, 695.

***trans*-2,3-Epoxy-3,6,9-triphenyl-8-nonen-4-yne (4e):** Oil; 692.51 mg, 95%. − ^{1}H NMR (200 MHz): δ = 1.76 (d, *J* = 6.6 Hz, 3 H), 2.67 (t, *J* = 7.2 Hz, 2 H), 3.55−3.60 (m, 1 H), 3.86 (t, *J* = 6.6 Hz, 1 H), 6.15−6.53 (m, 2 H), 7.20−8.10 (m, 10 H). − ^{13}C NMR (50.3 MHz): δ = 21.0, 25.2, 31.0, 53.0, 59.5, 71.0, 84.5, 127.8, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 129.9, 132.0, 132.5, 133.5, 133.6, 133.8, 139.0. − GC-MS (70 eV): *m*/*z* (%) = 364 (100.0) [M$^+$], 321 (25.2), 243 (64.3), 217 (41.2), 202 (30.1). − IR ($CHCl_3$): ṽ = 3060 cm^{-1}, 3020, 2970, 2920, 2240, 1600, 1450, 1350, 1250, 960.

1-Chloro-4-methyl-7,10-diphenyl-9-decen-5-yl-4-ol (9): Oil; 536.41 mg, 76%. − ^{1}H NMR (200 MHz): δ = 1.50 (s, 3 H), 1.80 (t, *J* = 8 Hz, 2 H), 1.90−2.05 (m, 2 H), 2.65 (t, *J* = 6.5 Hz, 2 H), 3.49 (t, *J* = 6.5 Hz, 2 H), 3.6 (br. s, 1 H, exchanges with D_2O, OH), 3.78 (t, *J* = 7.4 Hz, 1 H), 6.15−6.46 (m, 2 H), 7.19−7.35 (m, 10 H). − ^{13}C NMR (50.3 MHz): δ = 25.0, 28.0, 39.0, 40.5, 42.0, 68.0, 75.0, 85.0, 87.0, 126.7, 127.4, 127.7, 127.8, 128.0, 129.0, 133.0, 138.0, 142.1. − GC-MS (70 eV): *m*/*z* (%) = 352 (2.2) [M$^+$], 334 (2.1), 232 (13.2), 117 (100.0), 115 (35.3), 91 (25.3), 43 (25.4). − IR (film): ṽ = 3400 (br., OH) cm^{-1}, 3060, 3030, 2960, 2940, 2240, 1600, 1490, 1450, 1375, 1120, 1100.

2-Methyl-2-(5-hexen-1-yne-3,6-diphenyl-1-yl)tetrahydrofuran (10): Oil; 481 mg, quantitative conversion from **9**. − ^{1}H NMR (200 MHz): δ = 1.56 (s, 3 H), 1.72−2.20 (m, 4 H), 2.57−2.64 (m, 2 H), 3.78 (t, *J* = 7.4 Hz, 1 H), 3.88−3.96 (m, 2 H), 6.17−6.44 (m, 2 H), 7.16−7.40 (m, 10 H). − ^{13}C NMR (50.3 MHz): δ = 68.0, 68.03, 75.5, 126.7, 127.4, 127.7, 127.8, 128.1, 129.1, 138.2, 142.0. − GC-MS (70 eV): *m*/*z* (%) = 316 (2.1) [M$^+$], 301 (2.3), 225 (30.0), 199 (16.1), 171 (35.2), 117 (80.4), 85 (100.0). − IR (film): ṽ = 3060 cm^{-1}, 3020, 2980, 2930, 2230, 1600, 1490, 1450, 1370, 1100, 1025, 740, 690.

***syn*-2-Chloro-1-(5-hexen-1-yne-3,6-diphenyl-1-yl)-1-phenylamino-cyclohexane (7d):** Oil; 704.03 mg, 80%. − ^{1}H NMR (200 MHz): δ = 1.50−2.20 (m, 8 H), 2.51 (br. s, 1 H, exchanges with D_2O, NH), 2.60−2.67 (m, 2 H), 3.82 (t, *J* = 7.4 Hz, 1 H), 4.19 (dd, *J* = 4.3, 9.0 Hz, 1 H), 6.16−6.64 (m, 2 H), 7.20−7.40 (m, 15 H). − ^{13}C NMR (50.3 MHz): δ = 20.9, 31.7, 36.6, 38.0, 41.9, 42.0, 68.3, 68.4, 69.5, 126.0, 126.8, 126.9, 126.95, 127.1, 127.4, 127.5, 128.5, 132.3, 132.4, 137.4, 137.3, 140.8. − GC-MS (70 eV): *m*/*z* (%) = 441 (23.1) [M$^+$ + 2], 439 (72.0) [M$^+$], 404 (20.1), 362 (100.0), 117 (90.5). − IR (film): ṽ = 3560 (NH) cm^{-1}, 3020, 2940, 2860, 2250, 1600, 1210.

2-Methyl-2-(5-hexen-1-yne-3,6-diphenyl-1-yl)-1-phenylaziridine (8a): Oil; 254.44 mg, 35%. − ^{1}H NMR (200 MHz): δ = 1.58 (s, 3 H), 2.64 (t, *J* = 7.0 Hz, 2 H), 3.62 (pseudo t, *J* = 10.8 Hz, 1 H), 3.76−3.87 (m, 2 H), 6.20−6.50 (m, 2 H), 7.20−7.40 (m, 15 H). − ^{13}C NMR (50.1 MHz): δ = 27.0, 38.0, 41.9, 67.7, 74.9, 84.0, 86.5, 119.0, 126.0, 126.8, 126.9, 127.0, 127.1, 127.4, 128.4, 128.5, 129.0, 132.4, 132.5, 137.0, 141.0. − GC-MS (70 eV): *m*/*z* (%) = 363 (90.2) [M$^+$], 362 (70.1), 286 (10.2), 348 (30.3), 117 (100.0). − IR (film): ṽ = 3060 cm^{-1}, 3040, 2990, 2940, 2240, 1600, 1500, 1450.

2-(5-Hexen-1-yne-3,6-diphenyl-1-yl)-1,2-diphenylaziridine (8b): Oil; 425.56 mg, 50%. − ^{1}H NMR (200 MHz): δ = 2.61 (t, *J* = 7.1 Hz, 2 H), 3.40−3.70 (2 m, overlapped, 3 H), 6.10−6.60 (m, 2 H), 7.00−7.70 (m, 20 H). − ^{13}C NMR (50.1 MHz): δ = 37.7, 42.0, 67.7, 68.2, 83.0, 84.0, 119.0, 126.2, 126.5, 126.6, 126.8, 126.9, 127.0, 127.1, 127.2, 127.8, 128.4, 128.5, 128.7, 129.0, 132.5, 132.7, 141.0. − GC-MS (70 eV): *m*/*z* (%) = 425 (100.0) [M$^+$], 424 (73.2), 348 (12.2), 117 (70.0). − IR (film): ṽ = 3060 cm^{-1}, 3025, 2965, 2870, 2240, 1600, 1450, 1340.

(*E*)-2-(5-Hexen-1-yne-3,6-diphenyl-1-yl)-2,3-dimethyl-1-phenyl-aziridine (8c): Oil; 377.52 mg, 80%. − ^{1}H NMR (200 MHz): δ = 1.57 (s, 3 H), 1.62 (d, *J* = 7.0 Hz, 3 H), 2.60−2.70 (m, 2 H), 3.80−3.90 (m, 1 H), 4.05 (q, *J* = 7.0 Hz, 1 H), 6.20−6.50 (m, 2 H), 7.20−7.40 (m, 15 H). − ^{13}C NMR (50.1 MHz): δ = 20.0, 26.0, 38.0, 42.0, 67.0, 71.0, 83.0, 86.0, 119.0, 126.0, 126.8, 126.9, 127.0, 127.1, 127.4, 128.4, 128.5, 129.0, 132.4, 132.5, 137.0, 141.0. − GC-MS (70 eV): *m*/*z* (%) = 377 (30.2) [M$^+$], 376 (10.0), 362 (100.0), 300 (25.2), 117 (75.1). − IR (film): ṽ = 3060 cm^{-1}, 3040, 2990, 2940, 2870, 2240, 1600, 1500, 1450, 1350, 1150.

General Procedure for the Preparation of Dienynyl Chlorides 5b and 5c: To a stirred solution of **3b** or **3f** (1.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added $MeSO_2Cl$ (15.0 mmol) and Et_3N (10 mmol). The resulting mixture was stirred overnight at room temperature and then poured into H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to dryness in vacuo. The crude product was purified by column chromatography (silica gel, petroleum ether/Et_2O, 8:2) to give **5b** or **5c**, which were characterized as follows:

1-Chloro-2,5,8-triphenylocta-1,7-dien-3-yne (5b): M.p. 62−63 °C (hexane); 359.68 mg, 65%. − ^{1}H NMR (200 MHz): δ = 2.76−2.83 (m, 2 H), 4.13 (pseudo t, *J* = 6.5 Hz, 1 H), 6.33−6.57 (m, 2 H), 6.83 (s, 1 H), 7.14−7.57 (2 m, 15 H). − ^{13}C NMR (50.1 MHz): δ = 39.3, 42.1, 79.6, 100.6, 123.2, 123.3, 126.2, 126.9, 127.09, 127.15, 127.6, 128.4, 128.47, 128.55, 132.5, 136.0, 137.4, 140.7. − GC-MS (70 eV): *m*/*z* (%) = 370 (5.8) [M$^+$ + 2], 368 (16.1) [M$^+$], 333 (95.1), 251 (92.8), 215 (100.0), 117 (57.1), 91 (15.2). − IR (film): ṽ = 3060 cm^{-1}, 3020, 2230, 1600, 1490, 1440, 750, 690. − $C_{26}H_{21}Cl$ (368.90): calcd. C 84.65, H 5.74; found C 85.05, H 5.65.

2-Chloro-1-(5-hexen-1-yne-3,6-diphenyl-1-yl)cyclohexene (5c): Oil; 286.18 mg, 55%. − ^{1}H NMR (200 MHz): δ = 1.54−1.77 (m, 4 H), 2.22−2.40 (m, 4 H), 2.68 (t, *J* = 6.6 Hz, 2 H), 3.94 (t, *J* = 7.1 Hz, 1 H), 6.28−6.47 (m, 2 H), 7.15−7.45 (m, 10 H). − ^{13}C NMR (50.1 MHz): δ = 21.8, 23.4, 31.1, 33.6, 39.1, 42.2, 82.5, 95.3, 117.9, 126.1, 126.8, 127.0, 127.3, 127.6, 128.4, 132.2, 136.2, 137.5, 141.3. − GC-MS (70 eV): *m*/*z* (%) = 348 (2.3) [M$^+$ + 2], 346 (6.3) [M$^+$], 311 (30.5), 229 (100.0), 178 (14.4), 165 (13.9), 115 (14.1), 91 (8.8). − IR (film): ṽ = 3060 cm^{-1}, 3020, 2230, 2930, 1600, 1490, 1450, 1330, 740, 690.

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[1] [1a] Propargylic epoxides are useful precursors of homopropargylic alcohols, see: N. Bernard, F. Chemla, N. Normant, *Tetrahedron Lett.* **1998**, *39*, 6715−6718. − [1b] D. Grandjean, P. Pale, J. Chuche, *Tetrahedron* **1993**, *49*, 5225−5236. − [1c] D. Grandjean, J. Chuche, P. Pale, *Bull. Soc. Chim. Belg.* **1992**, *101*, 415.

– [1d] A. R. Katritzky, J. Li, *J. Org. Chem.* **1995**, *60*, 638−643. – [1e] J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180−7184.

[2] [2a] R. G. Carlson, W. W. Cox, *J. Org. Chem.* **1977**, *42*, 2382−2386. – [2b] A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677−1696.

[3] G.-A. Cao, Z.-X. Wang, J. Tu, Y. Shi, *Tetrahedron Lett.* **1998**, *39*, 4425−4428 and refs. therein.

[4] D. Bernard, A. Doutheau, J. Gore, J. Moulinoux, V. Quemener, J. Chantepie, G. Quash, *Tetrahedron* **1989**, *45*, 1429−1439.

[5] D. Grandjean, P. Pale, J. Chuche, *Tetrahedron Lett.* **1992**, *33*, 5355−5358.

[6] D. Grandjean, P. Pale, J. Chuche, *Tetrahedron Asymmetry* **1993**, *4*, 1991−1994.

[7] [7a] F. Chemla, N. Bernard, J. F. Normant, *Tetrahedron Lett.* **1999**, *40*, 75−78. – [7b] F. Chemla, V. Hebbe, J. F. Normant, *Tetrahedron Lett.* **1999**, *40*, 8093−8096.

[8] [8a] G. Kobrich, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 473−485. – [8b] U. H. Brinker, *Methoden der Organischen Chemie (Houben Weyl)*, Georg Thieme Verlag, Stuttgart, New York, **1989**, Vol. E19b/Teil 1, pp. 337−663. – [8c] H. Siegel, *Top. Curr. Chem.* **1982**, *106*, 55−78.

[9] S. Florio, L. Troisi, *Tetrahedron Lett.* **1996**, *37*, 4777−4780.

[10] The homocoupling reaction between cinnamyl chloride (α-attack) and its lithiated derivative (γ-attack) proceeded regioselectively so that the geometry about the C−C double bond remained unchanged in **2** and consequently in the chlorohydrin **3** and the epoxide **4** as well.

[11] The chemical shift found for the olefinic proton of **5b** (δ = 6.83) is in excellent agreement with the value estimated (δ = 6.81) for a *Z* geometry utilizing Simon's additive shielding parameters for the prediction of NMR shifts, as reported by U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, S. Sternhell, *Tetrahedron* **1969**, *25*, 691−697.

[12] [12a] S. Florio, G. Ingrosso, L. Ronzini, E. Epifani, *Tetrahedron* **1991**, *47*, 3365−3374. – [12b] C. A. Kingsbury, D. L. Durham, R. Hutton, *J. Org. Chem.* **1978,** *43*, 4696−4700. – [12c] S. Florio, V. Capriati, V. Russo, *Gazz. Chim. Ital.* **1997**, *127*, 587−595.

[13] The chloro substituent has been chosen as the "large" group on the basis of frontier molecular orbital arguments that the ligand with the lowest-lying σ* orbital, rather than the sterically most demanding group, is perpendicular to the carbonyl plane and *anti* to the attacking nucleophile (E. P. Lodge, C. H. Heathcock, *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361). On the other hand, the chlorine atom has almost the same van der Waals volume as the methyl group (A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441−451).

[14] S. Florio, L. Troisi, V. Capriati, *Tetrahedron Lett.* **1998**, *39*, 7951−7954.

[15] The stereochemistries of epoxide **4e** and aziridine **8c** were confirmed on the basis of their NOESY spectra.

[16] It is noteworthy that proton H_a in chlorohydrin **3f** (Scheme 1) and proton H_d in chloro amine **7d** (Scheme 4) are always axial protons, as indicated by the magnitude of their coupling constants with the protons attached to the adjacent carbon atoms ($^3J_{\text{axial-axial}}$ = 9.0 Hz, $^3J_{\text{axial-equat.}}$ = 4.0−4.3 Hz) as reported by A. Gaudemer in: *Stereochemistry − Fundamentals and Methods: Determination of Relative Configurations by NMR Spectroscopy* (Ed.: B. H. Kagan), **1977**, vol. 1, pp. 95−108. In the case of chlorohydrin **3g**, the vicinal coupling constant $^3J_{H_bH_c}$ (see Scheme 1) indicates very clearly the relative configuration of these coupled protons. In fact, according to the Karplus−Conroy equation ($^3J_{HH} = a\cos2\theta - 0.28$; up to θ = 90°, *a* = 8.5; above θ = 90°, *a* = 9.5) for a dihedral angle $\theta_{H_bCCH_c}$ = 52° (calculated on a Dreiding model with H_c *exo*-orientated), the $^3J_{H_bH_c}$ calculated (2.9 Hz) is very close to the $^3J_{H_bH_c}$ found (2.2 Hz), considering that electronegative substituents (such as a chlorine atom) on the coupling path reduce the magnitude of $^3J_{HH}$. Therefore, H_a should be synclinal to H_c.

[17] α-Halo imines can easily be synthesized from α-halo ketones and primary amines as reported: [17a] K. Taguchi, F. H. Westheimer, *J. Org. Chem.* **1971**, *36*, 1570−1572. – [17b] N. De Kimpe, W. De Cock, C. Stevens, *Tetrahedron* **1992**, *48*, 2739−2760.

[18] Chloro amines **7a**−**c**, which are the probable intermediates en route to the formation of aziridines **8a**−**c**, could not be isolated.

[19] J. Suffert, *J. Org. Chem.* **1989**, *54*, 509−512.

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