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The first one-pot synthesis of alkoxycyclopropanes via cyclometalation of styrene with Cl_nAlEt_{3-n} and RCO_2R' mediated by Cp_2ZrCl_2

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ABSTRACT

The one-pot cyclopropanation of styrene using Cl_nAlEt_{3-n} (Et_2AlCl, $EtAlCl_2$, $AlCl_3$) and carboxylic esters in the presence of Cp_2ZrCl_2 as catalyst gives rise to alkoxycyclopropanes.

The work reported in this Letter is a continuation of our earlier studies on chemical transformations of organoaluminum compounds (OACs) such as aluminacyclopentanes,[1–4] aluminacyclopentenes,[5,6] aluminacyclopentadienes,[7] and aluminacyclopropanes.[8,9] In order to elaborate an efficient, catalytic, one-pot method for the synthesis of substituted cyclopropanes based on α-olefins, alkylchloroalanes, and carboxylic esters, we investigated the model reactions between styrene and Et_2AlCl, $EtAlCl_2$, or $AlCl_3$ in the presence of ethyl acetate mediated by metallic Mg as an acceptor of chloride ions and a catalytic amount of Cp_2ZrCl_2.

Our idea was based on the previously obtained results on cycloalumination of aryl ethylenes using $EtAlCl_2$ to give aluminacyclopropanes under the action of Ti complexes.[8] The formation of phenyltitanacyclopropane from 'Cp_2Ti' and styrene was the key step in this reaction. We assumed that under the chosen conditions the coordinatively unsaturated zirconocene 'Cp_2Zr' would coordinate the styrene molecule providing intermediate phenylzirconacyclopropane **1**, transmetalation of which in situ by the OAC or $AlCl_3$ would then afford aluminacyclopropane **2**. Subsequent reaction of **2** with RCO_2R' at the active Al–C bond and further hydrolysis of the reaction mixture would yield phenylcyclopropane-type compounds such as 1-ethoxy-1-methyl-2-phenylcyclopropane **3** and 1-methyl-2-phenylcyclopropanol **4** (Scheme 1).

The reaction of styrene and Et_2AlCl (1:2 ratio) catalyzed by Cp_2ZrCl_2 (10 mol %) in the presence of metallic Mg and ethyl acetate (THF, 8 h, ~20 °C styrene/[Al]/CH_3CO_2Et/Mg/[Zr] = 1:2:1:1.5:0.1) was shown to afford, after hydrolysis, stereoisomeric *cis*/*trans*-1-ethoxy-1-methyl-2-phenylcyclopropanes, *cis*-**3a** and *trans*-**3a**, in a ratio of ~1:1 and 52% yield (styrene conversion was 80%) (Scheme 2).[10]

The ^1H and ^{13}C NMR spectra of the mixture of *cis*-**3a** and *trans*-**3a** showed signals due to the ethoxy and phenyl groups as well as two characteristic singlets assigned to the methyl group [δ (CH_3), 1.16 and 1.54, δ (CH_3), 16.13 and 21.7].

For a reliable assignment of the signals in the NMR spectra and in order to establish the structures of the stereoisomers, homonuclear (HH COSY) and heteronuclear (HSQC and HMBC) two-dimensional experiments were performed. As reference signals, the observed methyl proton resonance at 1.54 ppm correlated with the signals of the quaternary C1 carbon atom (δ 62.89), the methine C2 carbon atom (δ 30.6), and the methylene C3 carbon atom (δ 21.0) in the HMBC experiment. In contrast, the upfield methyl group (δ 1.16) interacted with the relevant carbon signals at 62.4, 29.7, and 18.0 ppm, respectively. These signals correspond to the carbon atoms of the two possible stereoisomeric *cis*- and *trans*-1-ethoxy-1-methyl-2-phenylcyclopropanes. The stereo assignments of the signals in the ^1H NMR spectra of 1,1,2-trisubstituted cyclopropanes, according to specific magnitudes of the vicinal spin-spin interaction constant (SSIC) between three protons, appeared to be rather difficult because each of the isomers should display both the *cis* (8–10 Hz) and the *trans* (3–5 Hz) vicinal con-

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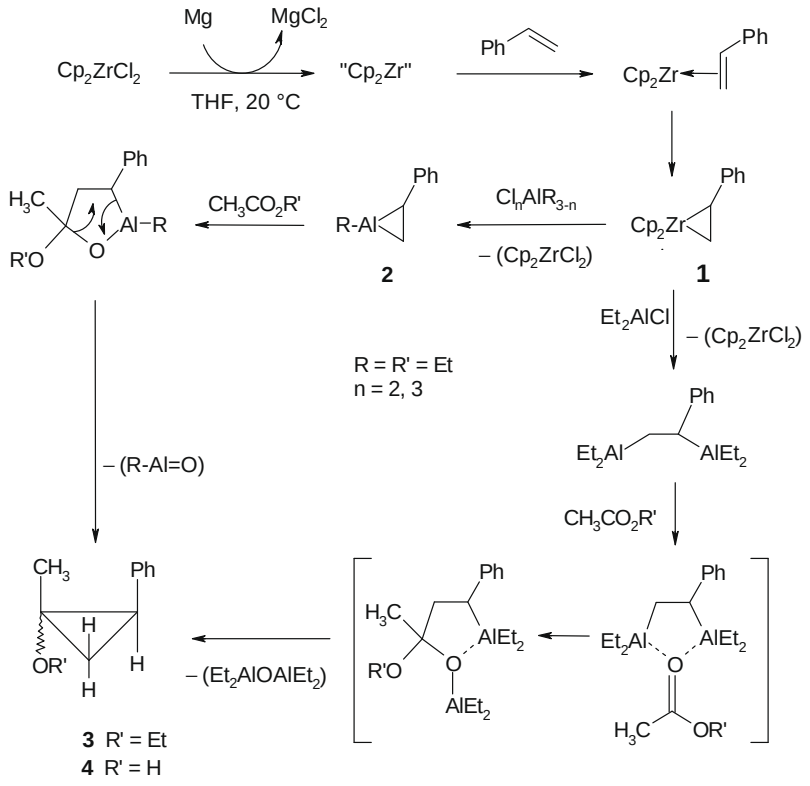
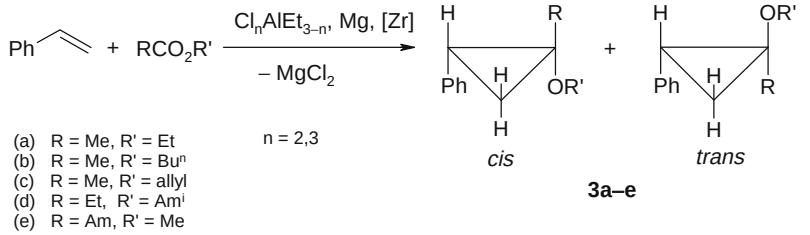


Scheme 1.



Scheme 2.

stants.[11] In this context, we examined the ^{1}H NMR data of *cis*-**3a**, which drew attention to the rather unusual signals of the methylene protons of the ethoxy group. Diastereotopic splitting of the methylene protons [δ (H_aH_bC–O) 3.04 (quin, $^2J \approx {}^3J$ = 7.2 Hz) and 3.52 (quin, $^2J \approx {}^3J$ = 7.2 Hz)] apparently occurs due to blocked rotation of the C–O–CH_2 bonds ascribed to the anisotropic shielding effect of the bulky phenyl group in the cis isomer.

Such splitting was not observed in the NMR spectra of *trans*-**3a** due to free rotation of the *trans* ethoxy group. High-field shielding of the methyl carbon atom [δ (CH_3) 16.1] by the phenyl substituent characterizes *trans*-**3a** compared with *cis*-**3a** [δ (CH_3) 21.7]. The methyl chemical shift value for *cis*-**3a** correlates with the chemical shift value [δ (CH_3) 20.6] for *cis*-1-hydroxy-1-methyl-2-phenylcyclopropane **4** previously obtained via the Kulinkovich reaction.[12]

In order to clarify the mechanism of the styrene cyclopropanation reaction using Et_2AlCl and ethyl acetate, additional experiments were undertaken, which demonstrated the requirement for mediation by Mg and Cp_2ZrCl_2.

In view of these results, the mechanistic proposals assume that in the presence of styrene the generation of a coordinatively unsaturated complex 'Cp_2Zr' occurs through reduction of Cp_2ZrCl_2 by Mg[13,14] with simultaneous formation of 2-phenylzirconacyclopropane **1**.[15] Subsequent transmetalation of **1** with Et_2AlCl in the presence of ethyl acetate led to a 2-oxoaluminacyclopentane and regeneration of Cp_2ZrCl_2. Carbocyclization of the 2-oxoaluminacyclopentane followed by carbonyl deoxygenation of ethyl acetate apparently acts as the driving force[16,17] for the formation of cyclopropane ether **3**. Without ethyl acetate the reaction affords 1,4-dialuminiobutanes.[18]

These specific conditions (10 mol % Cp_2ZrCl_2, 20 °C, THF, 8 h, styrene/$AlCl_3$/ester/Mg = 1:2:2:1.5) appeared to favor styrene cyclopropanation in the presence of other alkyl carboxylates, namely *n*-butyl acetate, allyl acetate, isoamyl propionate, and methyl caproate to afford the corresponding stereoisomeric cyclopropane ethers *cis*-**3b**–**e** and *trans*-**3b**–**e** (cis/trans ≈ 1:1) in 40–52% yield.[19]

In conclusion, we have developed a new and efficient method for the cyclopropanation of styrene assisted by Et_nAlCl_{3-n} and alkyl carboxylates to afford the corresponding alkoxycyclopropanes. Systematic investigations of this reaction aim to clarify the proposed mechanism and the scope of unsaturated compounds and carbonyl compounds amenable to this process.

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10. Alkoxycyclopropanation of styrene with Cl_nAlEt_{3-n} and RCO_2R' catalyzed by Cp_2ZrCl_2. A glass reactor, under a dry argon atmosphere at 0 °C, was charged under stirring with THF (5 ml), Cp_2ZrCl_2 (1.0 mmol), Mg (15 mg, powdered), styrene (10 mmol), alkyl carboxylate (10 mmol) (ethyl acetate, *n*-butyl acetate, allyl acetate, isoamyl propionate, or methyl caproate), and $AlCl_3$ (20 mmol) (Et_2AlCl or $EtAlCl_2$). The temperature was raised to 20 °C and the mixture was stirred for an additional 8 h. After addition of hexane (5 ml), the reaction mixture was quenched with a 5–8% aqueous solution of HCl. The organic layer was separated. The aqueous layer was extracted twice with diethyl ether. The combined organics were washed with Na_2CO_3 (until neutral) and dried over $MgSO_4$. The final products were isolated by column chromatography with hexane as eluent. (*cis*/*trans*)-1-Ethoxy-1-methyl-2-phenylcyclopropane (**3a**). Yield 52%. R_f 0.64 (hexane/ether, 1:1). IR (ν, cm^{-1}): 1520, 1490, 1305, 1290, 1220, 1170, 1105, 1055. MS, *m/z*: 176 (M^+). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.62; H, 9.07. (*cis*)-1-Ethoxy-1-methyl-2-phenylcyclopropane (*cis*-**3a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.2 Hz, 3H, CH_3), 1.07 (dd, ^2J = 6.0 Hz, ^3J = 9.6 Hz, 1H, CH_2), 1.34 (dd, $^2J \approx {}^3J$ = 6.0 Hz, 1H, CH_2), 1.54 (s, 3H, CH_3), 1.94 (dd, $^3J_{trans}$ = 6.0 Hz, $^3J_{cis}$ = 9.6 Hz, 1H, CH), 3.04 (quin, $^2J \approx {}^3J$ = 7.2 Hz, 1H, O–CH_2), 3.52 (quin, $^2J \approx {}^3J$ = 7.2 Hz, 1H, O–CH_2); 7.18–7.34 (m, 5H, Ph); ^{13}C NMR (100 MHz, C_6D_6): δ 15.24, 20.96, 21.69, 30.57, 62.15, 62.89, 125.94, 128.16, 128.54, 138.62. (*trans*)-1-Ethoxy-1-methyl-2-phenylcyclopropane (*trans*-**3a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (dd, $^2J \approx {}^3J$ = 6.0 Hz, 1H, CH_2), 1.16 (s, 3H, CH_3), 1.26 (t, J = 7.2 Hz, 3H, CH_3), 1.33 (m, 1H, CH_2), 2.38 (dd, $^3J_{trans}$ = 5.3 Hz, $^3J_{cis}$ = 9.8 Hz, 1H, CH), 3.64 (quin, J = 7.2 Hz, 2H, CH_2), 7.18–7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz, C_6D_6): δ 15.74, 16.13, 17.97, 29.70, 61.85, 62.43, 127.63, 127.71, 129.54, 138.78.
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19. (*cis*/*trans*)-1-Butoxy-1-methyl-2-phenylcyclopropane (**3b**): Yield 50%. R_f 0.62 (hexane/ether, 1:1). IR (ν, cm^{-1}): 1510, 1490, 1255, 1105, 1070. MS, *m/z*: 204 (M^+). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.18; H, 9.83. (*cis*)-1-Butoxy-1-methyl-2-phenylcyclopropane (*cis*-**3b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, J = 7.2 Hz, 3H, CH_3), 1.05 (dd, ^2J = 6.0 Hz, ^3J = 9.2 Hz, 1H, CH_2), 1.16–1.64 (m, 5H, CH, $2CH_2$), 1.53 (s, 3H, CH_3), 1.95 (dd, $^3J_{trans}$ = 7.0 Hz, $^3J_{cis}$ = 8.8 Hz, 1H, CH), 3.04 (q, $^2J \approx {}^3J$ = 7.2 Hz, 1H, CH_2), 3.42 (q, $^2J \approx {}^3J$ = 7.2 Hz, 1H, CH_2), 7.19–7.33 (m, 5H, Ph); ^{13}C NMR (100 MHz, C_6D_6): δ 13.83, 19.51, 20.55, 21.62, 30.66, 32.22, 62.64, 66.37, 125.89, 128.13, 128.53, 138.62. (*trans*)-1-Butoxy-1-methyl-2-phenylcyclopropane (*trans*-**3b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (m, 1H, CH), 0.96 (t, J = 7.2 Hz, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.16–1.64 (m, 5H, CH, $2CH_2$), 2.36 (dd, $^3J_{trans}$ = 7.0 Hz, $^3J_{cis}$ = 10.0 Hz, 1H, CH), 3.58 (t, J = 7.2 Hz, 2H, CH_2), 7.19–7.33 (m, 5H, Ph); ^{13}C NMR (100 MHz, C_6D_6): δ 13.94, 16.10, 18.05, 19.20, 29.70, 31.95, 62.46, 66.33, 125.38, 127.69, 127.77, 138.62. (*cis*/*trans*)-1-(Allyloxy)-1-methyl-2-phenylcyclopropane (**3c**): Yield 40%. R_f 0.62 (hexane/ether, 1:1). IR (ν, cm^{-1}): 1515, 1495, 1270, 1220, 1100, 1025, 980. MS, *m/z*: 147 (M^+–allyl). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.74; H, 8.48. (*cis*)-1-(Allyloxy)-1-methyl-2-phenylcyclopropane (*cis*-**3c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (dd, ^2J = 6.0 Hz, ^3J = 9.2 Hz, 1H, CH_2), 1.31–1.39 (m, 1H, CH_2), 1.57 (s, 3H, CH_3), 1.98 (dd, $^3J_{trans}$ = 7.2 Hz, $^3J_{cis}$ = 9.2 Hz, 1H, CH), 3.58 (dd, ^2J = 12.0 Hz, ^3J = 5.2 Hz, 1H, O–CH_2), 3.94 (dd, ^2J = 12.0 Hz, ^3J = 5.6 Hz, 1H, O–CH_2), 5.01–5.38 (m, 2H, CH=CH_2), 6.0 (m, 1H, CH=CH_2), 7.20–7.35 (m, 5H, Ph). ^{13}C NMR (100 MHz, C_6D_6): δ 20.71, 21.72, 30.66, 63.22, 68.15, 116.23, 126.00, 127.80, 128.54, 135.24, 138.40. (*trans*)-1-(Allyloxy)-1-methyl-2-phenylcyclopropane (*trans*-**3c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (dd, $^2J \approx {}^3J$ = 6.0 Hz, 1H, CH_2), 1.19 (s, 3H, CH_3), 1.31–1.39 (m, 1H, CH_2), 2.43 (dd, $^3J_{trans}$ = 7.6 Hz, $^3J_{cis}$ = 10.0 Hz, 1H, CH), 4.15 (d, J = 5.6 Hz, 2H, O–CH_2), 5.01–5.38 (m, 2H, CH=CH_2), 5.68 (m, 1H, CH=CH_2), 7.20–7.35 (m, 5H, Ph). ^{13}C NMR (100 MHz, C_6D_6): δ 16.29, 18.03, 29.78, 62.96, 68.00, 116.49, 125.51, 127.80, 128.18, 134.82, 138.48. (*cis*/*trans*)-1-Isoamyloxy-1-ethyl-2-phenylcyclopropane (**3d**): Yield 49%. R_f 0.66 (hexane/ether, 1:1). IR (ν, cm^{-1}): 1510, 1490, 1220, 1100, 1055. MS, *m/z*: 232 (M^+). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.72; H, 10.32. (*cis*)-1-Isoamyloxy-1-ethyl-2-phenylcyclopropane (*cis*-**3d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81–1.82 (m, 16H, CH, $3CH_2$, $3CH_3$), 2.01 (m, 1H, CH–Ph), 3.05 (m, 1H, O–CH_2), 3.43 (m, 1H, O–CH_2); 7.26–7.33 (m, 5H, Ph). ^{13}C NMR (100 MHz, C_6D_6): δ 9.55, 19.01, 22.11, 22.33 (2C), 24.82, 27.80, 29.95, 38.80, 64.62, 67.14, 125.41, 127.74, 127.87, 138.67. (*trans*)-1-Isoamyloxy-1-ethyl-2-phenylcyclopropane (*trans*-**3d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81–1.82 (m, 16H, CH, $3CH_2$, $3CH_3$), 2.45 (m, 1H, CH–Ph), 3.60–3.65 (m, 2H, O–CH_2), 7.26–7.33 (m, 5H, Ph). ^{13}C NMR (100 MHz, C_6D_6): δ 9.90, 16.96, 22.72 (2C), 22.83, 25.06, 29.89, 39.12, 64.62, 66.82, 125.89, 127.87, 128.54, 138.67. (*cis*/*trans*)-1-Methyloxy-1-amyl-2-phenylcyclopropane (**3e**): Yield 40%. R_f 0.38 (hexane/ether, 1:1). IR (ν, cm^{-1}): 1510, 1480, 1280, 1100, 1060. MS, *m/z*: 218 (M^+). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.38; H, 10.09. (*cis*)-1-Methyloxy-1-amyl-2-phenylcyclopropane (*cis*-**3e**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98–1.12 (m, 4H, CH, CH_3), 1.28–1.93 (m, 9H, CH, $4CH_2$), 2.06 (m, 1H, CH), 3.18 (s, 3H, O–CH_3), 7.16–7.31 (m, 5H, Ph). ^{13}C NMR (100 MHz, C_6D_6): δ 14.09, 19.08, 22.51, 25.02, 30.09, 31.93, 34.09, 53.72, 66.92, 125.56, 127.92, 128.53, 138.54. (*trans*)-1-Methyloxy-1-amyl-2-phenylcyclopropane (*trans*-**3e**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98–1.12 (m, 4H, CH, CH_3); 1.28–1.93 (m, 9H, CH, $4CH_2$); 2.46 (m, 1H, CH); 3.48 (s, 3H, O–CH_3); 7.16–7.31 (m, 5H, Ph). ^{13}C NMR (100 MHz, C_6D_6): δ 14.22, 17.33, 22.91, 25.52, 28.51, 29.47, 32.01, 54.08, 66.77, 125.98, 128.19, 128.53, 138.59.