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Zirconocene-promoted synthesis of substituted tetrahydropyrans

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Abstract Zirconocene reagents derived from zirconocene dichloride and two equivalents of butyllithium react with allylic, homoallylic diene ethers. Hydrolysis of the reaction products yields substituted tetrahydropyrans. The reaction is postulated to occur via cyclization of the diene to form a zirconacyclopentane. This cyclization occurs without allylic rearrangement.

Introduction

The use of zirconocene reagents to promote reactions in which 1,5- or 1,6-dienes undergo cyclization to form bicyclic zirconacyclopentanes is well precedented [1, 2]. Zirconocenes have also been used to synthesize nitrogen containing heterocycles [3–9]. Analogous reactions in which ether-containing dienes are cyclized to yield oxygen containing heterocycles have been unsuccessful. Cleavage of the allylic ether linkage occurs instead of the cyclization [10–13]. Indeed, zirconocene has been employed as a reagent to deprotect allyl-protected alcohols [14].

As part of our efforts to expand the utility of transition metal complexes in the transformation of organic molecules [15–18], we sought to develop reactions in which zirconium reagents could promote the cyclization of diene ethers to zirconacyclopentanes. It was postulated that a diene ether that contained both allylic and homoallylic, with a methyl substituent on the allylic side, could successfully undergo cyclization without rearrangement. The zirconocene reagent would bind preferentially to the unsubstituted homoallylic side, which would not undergo ether cleavage. It could then bind to the allylic side and undergo cyclization without rearrangement, giving rise to the bicyclic zirconacyclopenetane (Scheme 1).

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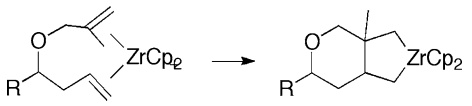
Results and discussion

Several allylic, homoallylic ethers were synthesized and cyclized in the presence of reagents derived from zirconocene dichloride and two equivalents of butyllithium. The products of these reactions were hydrolyzed and characterized. The results are listed in Table 1. These results show that appropriately substituted diene ethers can undergo cyclization without rearrangement.

It is well established that zirconocene cyclizations in which the zirconocene intermediate is generated by alkylating zirconocene dichloride occur by complexation of the Cp_2Zr-butene adduct with one of the reactant alkenes, followed by displacement of butane by the second alkene [1, 2]. The resultant zirconocene-diene complex can undergo cyclization to a zirconacyclopentane.

The presence of a methyl group at the 2-position on the allylic side makes complexation of the unsubstituted homoallylic side faster. It can then complex to the more substituted allylic side. The zirconocene-diene complex can then cyclize to form a zirconacyclopentane. This zirconacycle can be protonated to liberate the cyclized organic product. Deuterolysis of the zirconacycle yields a di-deuteriated organic product (Scheme 2).

Diene substrates were synthesized by addition of allylmagnesium chloride to a carbonyl compound, followed by alkylation with 1-chloro-2-methyl-2-propene (Scheme 3).



Scheme 1 Zirconocene-promoted cyclization

Table 1 Zirconocene-promoted cyclization of allylic, homoallylic dienes

Diene	*R*	Quench	Product	Yield (%)
1	$CH_3CH_2CH_2CH_2$–	H^+/H_2O	2	72
3	–$CH_2CH_2CH_2CH_2$–	H^+/H_2O	4	41
5	C_6H_5–	H^+/H_2O	6	62
5	C_6H_5–	D^+/D_2O	7	72

Conclusions

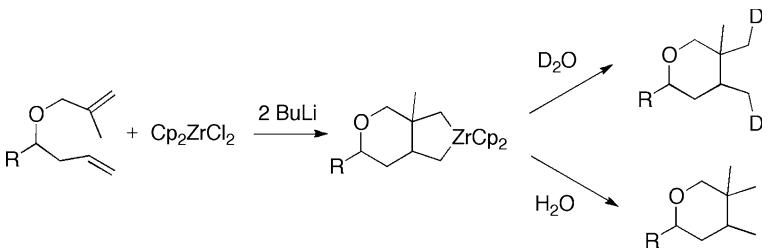
Zirconocene reagents derived from zirconocene dichloride and two equivalents of butyllithium have been used to synthesize substituted tetrahydropyrans from allylic, homoallylic diene ethers. The reaction is postulated to occur via cyclization of the diene to form a zirconacyclopentane, which, upon hydrolysis, yields the organic product.

Experimental

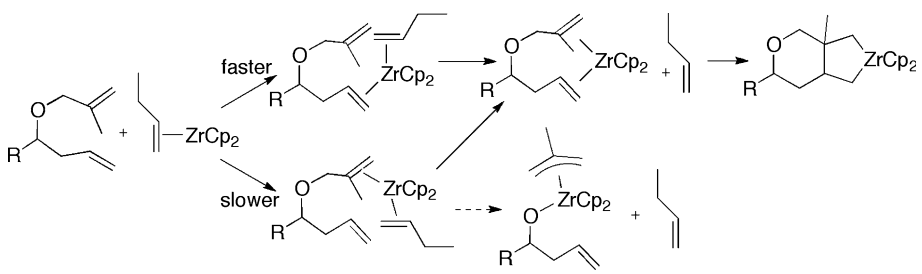
All reactions were carried out under nitrogen gas using standard Schlenk techniques. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. All other solvents were used without further purification. Starting reagents were purchased from Acros Organics and used without further purification. NMR studies were conducted on a Jeol ECX 400 MHz spectrometer.

2-propyl-4,5,5-trimethyltetrahydropyran **(2)**: 1-Heptene-(2-methyl-2-propen-1-yloxy) **(1)** (1.003 g, 5.978 mmoL) and zirconocene dichloride (1.922 g, 6.576 mmoL) were dissolved in dry THF (15 mL) and cooled to −78 °C. BuLi (8.22 mL) was slowly added, causing the mixture to turn yellow and become cloudy with precipitate. The mixture was allowed to stir for 18 h as it was warmed to 0 °C and then slowly to room temperature. The reaction was quenched with H_2O (15 mL). The mixture was dissolved in Et_2O and washed with 2 M HCl and saturated brine. The aqueous layer was back-extracted into Et_2O. The organic layers were collected, dried over magnesium sulfate, and concentrated on a rotary evaporator. The concentrate was dissolved in ethyl acetate, filtered through silica gel, and then concentrated on a rotary evaporator. The concentrate was purified by column chromatography, using a 90 % hexanes/10 % ethyl acetate solution as the eluent to yield the product as a pale oil (0.87 g, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (s, 3H), 0.90 (t, $J = 7.3$, 3H), 0.95, (d, $J = 6.7$, 3H), 1.01 (s, 3H), 1.2-1.6 (m, 8H), 3.22 (d, $J = 11.4$, 1H), 3.34 (d, $J = 11.4$, 1H), 3.5-3.6 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.22, 15.63, 15.85, 17.88, 18.85, 19.03, 22.36, 24.24, 26.41, 32.71, 33.34, 35.10, 35.22, 36.74, 37.20, 38.53, 38.97, 72.12, 72.58, 78.37, 79.88. Anal. Calcd for $C_{11}H_{22}O$: C, 77.6; H, 13.0. Found: C, 77.6; H, 13.0.

6-Oxaspiro[4.5]decane, 9,10,10-trimethyl- **(4)**: 1-(2-propene-1-yl)-1-(2-methyl-2-propen-1-yloxy)-cyclopentane **(3)** (1.000 g, 5.547 mmoL) and zirconocene dichloride (1.784 g, 6.102 mmoL) were dissolved in dry THF (15 mL) and cooled



Scheme 2 Cyclization and quench of the resultant zirconacycle



Scheme 3 Cyclization and allylic rearrangement pathways

to -78 °C. BuLi (8.0 mL) was slowly added, causing the mixture to turn yellow and become cloudy with precipitate. The mixture was allowed to stir for 24 h as it was warmed to 0 °C and then slowly to room temperature. The reaction was quenched with H_2O (15 mL). The mixture was dissolved in Et_2O and washed three times with 2 M HCl and once with saturated brine. The aqueous layer was back-extracted into Et_2O. The organic layers were collected, dried over magnesium sulfate, and concentrated on a rotary evaporator. The concentrate was dissolved in ethyl acetate, filtered through silica gel, and then concentrated on a rotary evaporator. The concentrate was purified by column chromatography, using a 90 % hexanes/10 % ethyl acetate solution as the eluent to yield the product as a pale oil (0.413 g, 41 %). ^{1}H NMR (400 MHz, CDCl3) δ 0.76 (s, 3H), 0.81 (d, $J = 5.6$, 3H), 0.86 (s, 3H), 1.22 (d, $J = 10.1$, 1H), 1.37-1.57 (m, 6H), 1.66-1.77, 4H), 1.89-1.97 (m, 1H), 3.16 (d, $J = 11.5$, 1H), 3.24 (d, $J = 11.5$, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.87, 17.31, 23.33, 24.57, 32.73, 33.16, 36.27, 40.25, 41.47, 74.2, 84.4. Anal. Calcd for $C_{12}H_{22}O$: C, 79.1; H, 12.2. Found: 79.1; H, 12.2.

2H-Pyran, tetrahydro-4,5,5-trimethyl-2-phenyl- **(6)**: 1-(2-methylpropenoxy)-1-phenyl-3-butene **(5)** (2.50 g, 12.36 mmoL) and zirconocene dichloride (3.974 g, 13.59 mmoL) were dissolved in THF (15 mL) and cooled to −78 °C. Butyllithium (1.6 M, 17.0 mL) was added slowly as the reaction warmed to 0 °C. The mixture immediately became cloudy with precipitate and yellow in color. The reaction was warmed to room temperature slowly and stirred for 24 h. The mixture became dark red in color. The reaction was quenched with the addition of 2.0 M HCl (15 mL). The product was extracted into Et_2O and washed with 2.0 M HCl (150 mL) and brine (150 mL). The aqueous phase was back-extracted with Et_2O. The collected aqueous phases were dried over magnesium sulfate and concentrated via rotary evaporation. The crude concentrate was purified by column chromatography to yield a pale yellow oil (1.565 g, 62 % ^{1}H NMR (400 MHz, CDCl3) δ 0.85 (s, 3 H), 1.09 (d, $J = 7.3$ Hz, 3H), 1.12 (s, 3H), 1.55 (m, 1H), 1.68 (m, 1H), 2.12 (m, 1H), 3.35 (d, $J = 11.4$ Hz, 1H), 3.54 (d, $J = 11.4$ Hz, 1H), 4.63 (dd, $J = 3.2$, 9.6 Hz, 1H), 7.38 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.51, 22.65, 26.48, 32.55, 35.79, 36.52, 73.06, 74.38, 126.18, 126.90, 127.21, 128.39, 142.91. Anal. Calcd for $C_{14}H_{20}O$: C, 82.3; H, 9.9. Found: C, 82.3; H, 9.9.

2H-Pyran, tetrahydro-4-methyl-d_1-5-methyl-d_1-5-methyl-2-phenyl- **(7)**: 1-(2-methylpropenoxy)-1-phenyl-3-butene **(5)** (2.50 g, 12.36 mmoL) and zirconocene dichloride (3.974 g, 13.59 mmoL) were dissolved in THF (15 mL) and cooled to –78 °C. Butyl lithium (1.6 M, 17.0 mL) was added slowly as the reaction warmed to 0 °C. The mixture immediately became cloudy with precipitate and yellow in color. The reaction was warmed to room temperature slowly and stirred for 24 h. The mixture became dark red in color. The reaction was quenched with the addition of deuterium oxide (15 mL) and stirred for 2 h. The product was extracted into Et_2O and washed with 2.0 M HCl (150 mL) and brine (150 mL). The aqueous phase was back-extracted with Et_2O. The collected aqueous phases were dried over magnesium sulfate and condensed via rotary evaporation. The concentrate was dissolved in Et_2O, filtered to remove LiCl salts, and then concentrated again. The crude concentrate was purified by column chromatography to yield a pale yellow oil (1.84 g, 72 %) ^{1}H NMR (400 MHz, CDCl3) δ ppm : 7.375 (m, 5H), 4.621 (dd, $J = 3.21$, 10.07 Hz, 1H), 3.54 (d, $J = 11.45$ Hz, 1H), 3.35 (d, $J = 11.45$ Hz, 1H), 2.12 (m, $J = 4.58$, 7.10, 14.2 1H), 1.75 (m, 1H), 1.55 (m, $J = 3.6$, 7.7, 14.2 Hz, 1H), 1.12 (s, 3H), 1.09 (m, $J = 1.83$, 6.87 Hz, 2H), 0.854 (m, $J = 1.83$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) δ ppm: 142.906, 128.394, 127.212, 126.897, 126.182, 74.381, 73.055, 36.509, 35.785, 32.467, 26.479, 22.551, 22.360, 22.169, 15.419, 15.228, 15.037.

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