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Reaction of oxazirconacycloheptenes with aldehydes mediated by CuCl: one-pot synthesis of tetrahydrofuran derivatives from four different components involving two molecules of the same or different aldehydes, an ethylene and an alkyne☆

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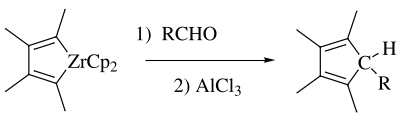
Abstract—Reaction of zirconacyclopentenes with 2 equiv. of the same aldehydes in the presence of 1 equiv. of CuCl from −78 °C to room temperature afforded tetrahydrofuran derivatives in good isolated yields upon hydrolysis with aqueous 3 N HCl. Oxazirconacycloheptenes, generated in situ from zirconacyclopentenes with one aldehyde was found to be the reactive intermediate. When treated with a second aldehyde and CuCl, an oxazirconacycloheptene gave a tetrahydrofuran derivative comprised of four different components involving an alkyne, an ethylene and two different aldehydes, thus providing the first one-pot synthesis of important tetrahydrofuran derivatives from four components. When bulky aldehydes were used, hydrolysis of the above reaction mixtures afforded 2-hexen-1,6-diols, which could be quantitatively transformed to their corresponding tetrahydrofuran derivatives when treated with stronger aqueous acid (12 N HCl).

1. Introduction

Zirconacyclopentadienes **1** and zirconacyclopentenes **2** can be readily prepared via cross-coupling of two alkynes or pair-selective coupling of an alkyne with an ethylene on low valent zirconocene species, respectively.[1,2] In order to develop synthetically useful methods by combining the transition-metal-mediated C–C bond forming reaction with the Lewis acids-mediated organic transformation reaction,[3–10] we studied Lewis acids-mediated reaction of these readily available zirconacycles with unsaturated organic substrates such as aldehydes.[11,12] In the presence of classical Lewis acids such as $AlCl_3$ and BF_3, reaction of zirconacyclopentadienes **1** with a wide variety of aldehydes afforded multiply substituted cyclopentadienes, via a novel deoxygenation of the C=O double bond of aldehydes (Eq. 1).[11] When a zirconacyclopentene **2** was treated with two molecules of an aldehyde, Oppenauer-type oxidation took place to give homoallylketones **3** and alcohols (Eq. 2).[12] Only one of the two aldehydes was incorporated into the product. The second molecule of aldehyde was reduced to an alcohol. Interestingly, as shown in Eq. 3, when the Lewis acid was changed from $AlCl_3$ to CuCl, tetrahydrofuran derivatives (THF derivatives for short) **4** were obtained in good yields from the reaction of zirconacyclopentenes with two molecules of aldehydes.[13] Both of the two molecules of aldehydes were incorporated into the products. In this paper, we report a full investigation of this useful preparation of THF derivatives,[14–20] including (1) preparation of THF derivatives from an alkyne, an ethylene, and two molecules of the same aldehydes, (2) preparation of THF derivatives from an alkyne, an ethylene, and two different aldehydes (Scheme 1), and (3) mechanistic aspects.



1 (1)

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2003.10.095

Keywords: Aldehydes; Alkynes; Ethylene; Four-component synthesis; Tetrahydrofuran derivatives; Zirconacyclopentenes; Oxazirconacycloheptenes; CuCl.

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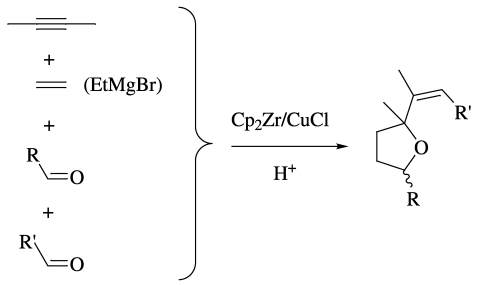
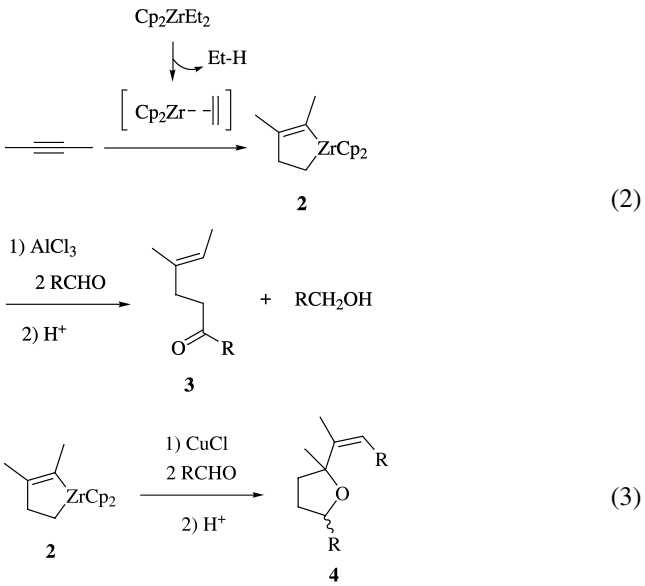


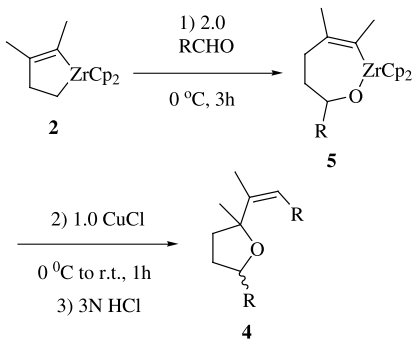
Scheme 1. One-pot synthesis of THF derivatives from four different components.



2. Results and discussion

2.1. Preparation of 1-alkenyl tetrahydrofuran derivatives from an alkyne, an ethylene and two of the same aldehydes

Reaction of Cp_2ZrEt_2 with an alkyne from −78 to 0 °C forms a zirconacyclopentene **2** in high yields via a pair-selective coupling of the alkyne with the in situ generated zirconocene–ethylene complex, as developed by Takahashi and co-workers.[1,2] When a zirconacyclopentene is treated with aldehydes, insertion of an aldehyde into the Zr-sp3 C bond takes place to afford the corresponding seven-membered oxazirconacycloheptene **5**.[21] Hydrolysis of the reaction mixtures of oxazirconacycloheptenes with 3 N HCl gave the corresponding alcohols.[21] It is noteworthy that oxazirconacycloheptenes do not react with the second molecule of aldehydes. However, interestingly, our preliminary results have demonstrated that, in the presence of 1 equiv. of CuCl, oxazirconacycloheptenes do react with a second molecule of aldehyde, leading to the unexpected THF derivatives upon hydrolysis of the reaction mixture with either aqueous 3 N HCl or saturated aqueous $NaHCO_3$ (Scheme 2).[13] Several ways of adding aldehydes and CuCl to zirconacyclopentenes have been tested, and THF derivatives can be obtained in most cases. Scheme 2 shows the best reaction condition (including addition order of aldehydes and CuCl) for the formation of THF



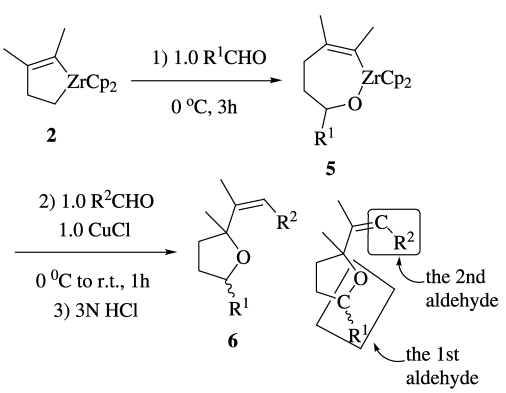
Scheme 2.

derivatives. Representative results are given in Table 1. The stereochemistry of the vinyl moiety in **4e** was determined by NOE measurement. NOESY cross-peaks were observed between the vinyl hydrogen and the methyl hydrogen, thereby establishing the trisubstituted olefin geometry (see Supporting Information). Aromatic aldehydes could generally afford THF derivatives in good yields. When aliphatic aldehydes were used, although the corresponding oxazirconacycloheptenes **5** could be formed cleanly,[21] the next reaction step involving CuCl was messy.

2.2. Preparation of 1-alkenyl tetrahydrofuran derivatives from an alkyne, an ethylene and two different aldehydes

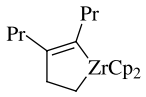
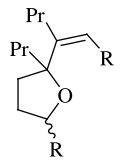
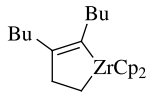
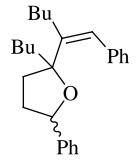
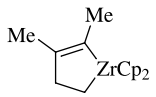
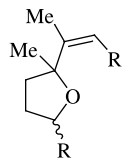
Since oxazirconacycloheptenes **5** were formed in situ from zirconacyclopentenes with an aldehyde and were the reactive intermediates for the formation of THF derivatives (Scheme 2), we assumed a different aldehyde could be used as the second aldehyde to react with oxazirconacycloheptenes **5**, thus affording THF derivatives from two different aldehydes. As given in Scheme 3 and Table 2, THF derivatives could be prepared highly chemoselectively from two different aldehydes; the first aldehyde was highly regioselectively incorporated into the α-position of the THF skeletons, while the second aldehyde was perfectly transformed to be the alkenyl moiety in the product.

Interestingly, when bulky aldehydes were used, 2-hexen-1,6-diols **7** were obtained as the only products after the reaction mixtures were hydrolyzed with aqueous 3 N HCl. Particularly interesting, when two different bulky aldehydes were added step by step, the first aldehyde was incorporated



Scheme 3.

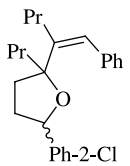
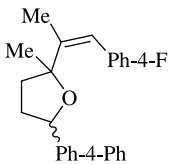
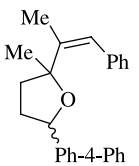
Table 1. Formation of THF derivatives from two molecules of the same aldehydes, one alkyne and one ethylene

Entry	Zircona-cyclopentene	Aldehyde	Product **4**		Yield of **4** (%)[a]
1		RCHO		**4a**[b]	71 (44)
2				**4b**[c]	(42)
3				**4c**[d]	(54)
4		PhCHO		**4d**[e]	(48)
5		RCHO		**4e**[f]	(56)
6				**4f**[g]	(55)

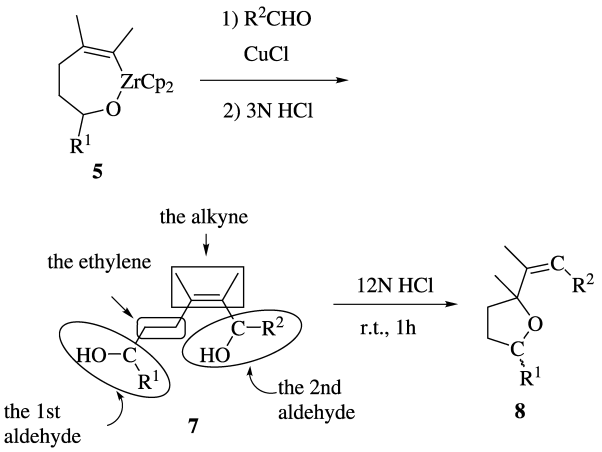
[a] Combined GC yields. Combined isolated yields are given in parentheses.
[b] R=phenyl, two isomers in 2:1.
[c] R=4-methylphenyl, two isomers in 1:1.
[d] R=4-F-phenyl, two isomers in 2:1.
[e] Two isomers in 7:5.
[f] R=phenyl, two isomers in 3:2.
[g] R=2,4,6-trimethylphenyl, two isomers in 1:1.

in the diols **7** at the 6 position, while the second aldehyde made a C–C bond with the alkenyl carbon to form an allylic alcohol moiety (Scheme 4). Representative results are given in Table 3. The structure of **7c** was determined by single crystal X-ray analysis (see Supporting Information). These diols **7** could be quantitatively transformed to THF derivatives **8a**–**c** when treated with aqueous 12 N HCl at room temperature for 1 h (Fig. 1). Similarly, these THF

Table 2. Formation of THF derivatives from two different aldehydes, one alkyne and one ethylene

Alkyne	First aldehyde	Second aldehyde	Product **6**		Yield of **6** (%)[a]
Pr—≡—Pr	2-Cl–PhCHO	PhCHO		**6a**[b]	55
Me—≡—Me	4-Ph–PhCHO	4-F–PhCHO		**6b**[c]	56
Me—≡—Me	4-Ph–PhCHO	PhCHO		**6c**[d]	52

[a] Combined isolated yield.
[b] Two isomers in 5:4.
[c] Two isomers in 2:1.
[d] Two isomers in 3:2.

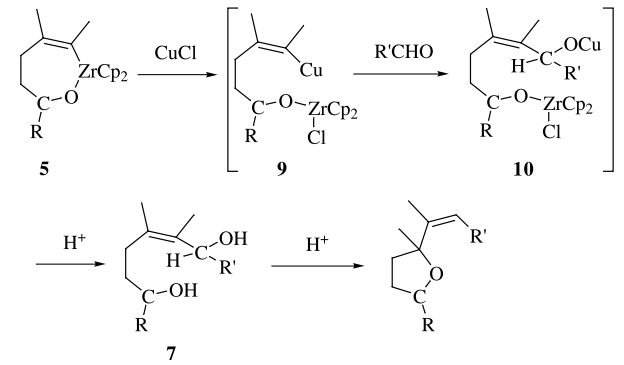


Scheme 4.

derivatives **8a–c** were obtained also as a mixture of two isomers.

2.3. Mechanistic aspects

Two pathways are proposed for the formation of THF derivatives from the CuCl-mediated reaction of oxazirconacycloheptenes **5** with aldehyde. Transmetallation of the Zr–C bond in oxazirconacycloheptenes **5** is assumed to be the first step to form cuparate **9** (Scheme 5).[22] This organocopper compound adds to the carbonyl C=O bond of aldehyde,[23] which upon hydrolysis gives 2-hexen-1,6-diols. Cyclization is then accomplished in acidic media with allylic inversion to afford the final THF derivatives.



Scheme 5.

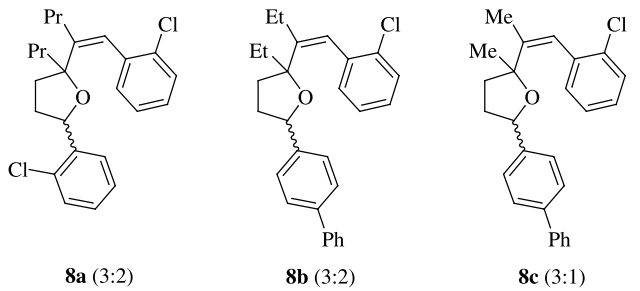
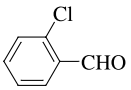
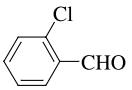
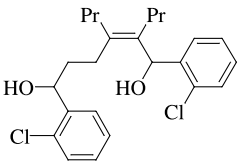
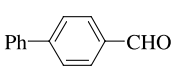
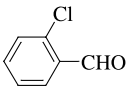
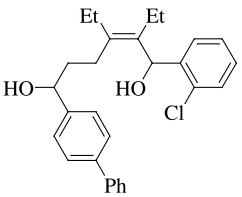
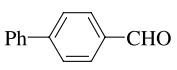
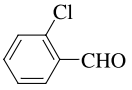
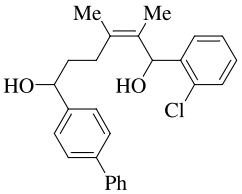


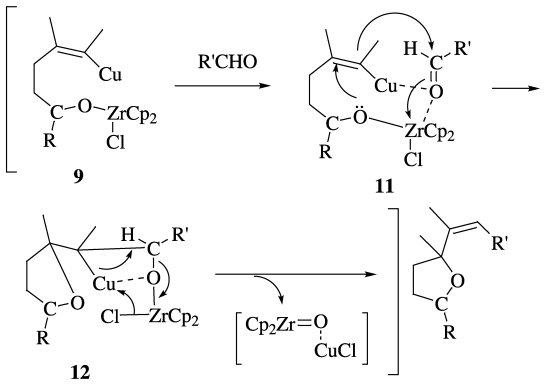
Figure 1.

Although the above pathway seems more likely, the following mechanism cannot be ruled out, since formation of THF derivative **4a** was observed in the reaction mixture by NMR without hydrolysis. A concerted addition and sequential release of $Cp_2Zr{=}O{\cdot}CuCl$ is proposed (Scheme 6). Intramolecular nucleophilic attack by an oxygen atom on

Table 3. Isolation of diols by hydrolysis of the reaction mixtures of oxazirconacycles with aldehydes in the presence of CuCl

Alkyne	First aldehyde	Second aldehyde	Product **7**		Yield of **7** (%)[a]
Pr—≡—Pr				**7a**[b]	56
Et—≡—Et				**7b**[c]	47
Me—≡—Me				**7c**[d]	48

[a] Combined isolated yield.
[b] Two isomers in 5:1.
[c] Two isomers in 4:3.
[d] Two isomers in 1:1.



Scheme 6.

a suitable activated carbon center has been a common approach.

3. Conclusions

Development of synthetically useful methods for the preparation of THF derivatives is of great interest since tetrahydrofuran skeletons are frequently found in important natural products. In this paper, we report the first example of one-pot four-component synthesis of THF derivatives via a novel CuCl-mediated reaction of oxazirconacycloheptenes with aldehydes. When four different components involving one alkyne, one ethylene, and two different aldehydes, THF derivatives could be also formed highly selectively.

4. Experimental

4.1. General methods

All reactions were conducted under a slightly positive pressure of dry, prepurified nitrogen using standard Schlenk line techniques when appropriate. Unless otherwise noted, all starting materials were commercially available and were used without further purification. Tetrahydrofuran (THF) was refluxed and distilled from sodium/benzophenone under a nitrogen atmosphere. EtMgBr and *n*-BuLi were obtained from Kanto Chemicals Co. Ltd.

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.4 MHz, respectively, in $CDCl_3$ unless stated otherwise. GC yields were determined using suitable hydrocarbons as internal standards.

4.2. Typical procedure for preparation of 1-alkenyl tetrahedron derivatives from an alkyne, an ethylene and two of the same aldehydes (4a–4f)

A 50-mL Schlenk tube under dried nitrogen was charged with Cp_2ZrCl_2 (0.59 g, 2 mmol) and THF (20 mL). To this mixture was added ethylmagnesium bromide (1.0 M THF solution, 4 mmol, 4 mL) at −78 °C. After 1 h of stirring, alkyne (2 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h. Then to the reaction mixture was added aldehyde (4 mmol), the reaction mixture was continued to stir at 0 °C for 3 h, and CuCl (200 mg, 2 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 1 h. The above reaction mixture was then quenched with 3 N HCl and extracted with ether. The extract was washed with sat. $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a light yellow liquid. The liquid was subjected to silica gel column using petroleum ether and dichloromethane (3:1) as the eluent. The final product was obtained as a colorless liquid.

4.2.1. THF derivative (4a). Light yellow liquid, GC yield 71%, isolated yield 44% (293 mg), mixture of isomers (2:1). ^{1}H NMR (TMS, $CDCl_3$) δ=0.88 (t, J=7.5 Hz, 3H), 0.95 (t, J=7.5 Hz, 3H), 1.18–2.33 (m, 8H), 4.96–5.03 (m, 1H), 6.68 (s) 6.75 (s) (total 1H), 7.16–7.44 (m, 10H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.51, 14.60, 14.75, 14.82, 17.74, 22.62, 22.73, 31.38, 31.67, 34.10, 35.22, 36.54, 36.70, 41.41, 42.53, 80.26, 80.39, 89.24, 89.39, 123.82, 125.03, 125.82, 126.01, 126.28, 127.12, 127.14, 128.13, 128.15, 128.23, 128.29, 128.58, 138.64, 138.76, 143.22, 143.67, 145.82, 146.10; HRMS calcd for $C_{24}H_{30}O$: 334.2297, found: 334.2296.

4.2.2. THF derivative (4b). Light yellow liquid, isolated yield 42% (306 mg), mixture of isomers (1:1). ^{1}H NMR (TMS, $CDCl_3$) δ=0.86–0.98 (m, 6H), 1.26–1.52 (m, 4H), 1.69–2.28 (m, 8H), 2.32 (s, 3H), 2.33 (s, 3H), 4.91–4.96 (m, 1H), 6.62 (s) 6.69 (s) (total 1H), 7.10–7.32 (m, 8H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.52, 14.60, 14.76, 14.81, 17.74, 21.11, 22.60, 22.71, 31.44, 31.73, 34.15, 35.18, 36.54, 36.72, 41.53, 42.63, 80.13, 80.37, 89.21, 89.31, 123.64, 124.86, 125.84, 126.33, 128.51, 128.85, 128.87, 128.90, 128.96, 135.54, 135.57, 135.72, 135.83, 136.69, 136.70, 140.27, 140.73, 145.21, 145.50; HRMS calcd for $C_{26}H_{34}O$: 362.2610, found: 362.2603.

4.2.3. THF derivative (4c). Light yellow liquid, isolated yield 54% (400 mg), mixture of isomers (2:1). ^{1}H NMR ($CDCl_3$, TMS) δ=0.84–0.97 (m, 6H), 1.27–1.59 (m, 4H), 1.67–1.87 (m,3H), 1.94–2.0 (m, 1H), 2.10–2.32 (m, 4H), 4.92–5.00 (m, 1H), 6.62 (s) 6.66 (s), (total 1H), 6.97–7.05 (m, 4H), 7.17–7.25 (m, 2H), 7.32–7.39 (m, 2H); ^{13}C NMR δ=14.48, 14.57, 14.73, 14.79, 17.74, 22.54, 22.66, 31.26, 31.56, 34.04, 35.25, 36.53, 36.63, 41.37, 42.55, 79.72, 79.77, 89.28, 89.40, 115.01 (d, J=21.0 Hz, J_2CF), 115.09 (d, J=21.0 Hz, J_2CF), 122.84, 124.05, 127.40 (d, J=8.0 Hz, J_3CF), 127.88 (d, J=7.5 Hz, J_3CF), 130.00, 130.10, 134.63, 134.67, 134.71, 138.92, 138.96, 139.28, 139.31, 145.70, 145.72, 146.07, 161.28 (d, J=242.9 Hz, JCF), 162.09 (d, J=242.9 Hz, JCF); HRMS calcd. for $C_{24}H_{28}OF_2$: 370.2108, found: 370.2113.

4.2.4. THF derivative (4d). Light yellow liquid, isolated yield 48% (346 mg), mixture of isomers (7:5). ^{1}H NMR (TMS, $CDCl_3$) δ=0.82–0.95 (m, 6H), 1.20–1.53 (m, 8H), 1.73–2.05 (m, 1H), 4.97–5.04 (m, 1H), 6.67 (s) 6.75 (s) (total 1H), 7.18–7.44 (m, 10H); ^{13}C NMR (TMS, $CDCl_3$) δ=13.76, 14.18, 23.17, 23.20, 23.37, 23.38, 26.60, 26.63, 28.84, 29.14, 31.33, 31.48, 34.13, 35.21, 36.66, 36.82, 38.10, 39.90, 80.29, 80.37, 89.25, 89.44, 123.80, 124.94, 125.85, 126.01, 126.31, 127.13, 127.16, 128.12, 128.13, 128.23, 128.30, 128.64, 128.66, 138.67, 138.78, 143.22, 143.70, 145.84, 146.21; HRMS calcd. for $C_{26}H_{34}O$: 362.2610, found: 362.2609.

4.2.5. THF derivative (4e). Light yellow liquid, isolated yield 56% (311 mg), mixture of isomers (3:2). ^{1}H NMR (TMS, $CDCl_3$) δ=1.52 (s), 1.58 (s) (total 3H), 1.91–2.41 (m, 7H), 5.08 (t, J=7.2 Hz,) 5.14 (t, J=6.9 Hz) (total 1H), 6.77 (s) 6.81 (s) (total 1H), 7.17–7.59 (m, 14H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.97, 15.97, 26.63, 27.09, 34.38, 35.04, 36.82, 37.08, 80.21, 80.41, 86.38, 86.77, 122.29, 123.20, 126.02, 126.30, 126.67, 127.05, 127.08, 127.10, 127.14, 128.03, 128.73, 129.06, 129.09, 138.53, 138.57, 140.18, 140.21, 141.04, 141.11, 142.01, 142.18, 142.61, 142.66; HRMS calcd for $C_{20}H_{22}O$: 278.1676, found: 278.1671.

4.2.6. THF derivative (4f). Light yellow liquid, isolated yield 55% (400 mg), mixture of isomers (1:1). ^{1}H NMR (TMS, $CDCl_3$) δ=1.47–1.58 (m, 6H), 1.98–2.47 (m, 22H), 5.36 (t, J=7.5 Hz), 5.50 (t, J=8.1 Hz) (total 1H), 6.49 (s, 1H), 6.80–6.86 (m, 4H); ^{13}C NMR (TMS, $CDCl_3$) δ=13.60, 14.60, 20.08, 20.75, 20.89, 20.97, 25.15, 26.90, 30.49, 30.91, 30.94, 36.20, 36.94, 75.20, 75.99, 85.66, 85.81, 120.86, 121.51, 127.87, 130.01, 130.14, 133.70, 133.99, 134.61, 134.80, 135.53, 135.62, 136.56, 136.57, 136.61, 136.66, 141.68, 142.72; HRMS calcd. for $C_{26}H_{34}O$: 362.2610, found: 362.2595.

4.3. Typical procedure for preparation of 1-alkenyl tetrahedron derivatives from an alkyne, an ethylene and two of the different aldehydes (6a–6c)

A 50-mL Schlenk tube under dried nitrogen was charged with Cp_2ZrCl_2 (0.59 g, 2 mmol) and THF (20 mL). To this mixture was added ethylmagnesium bromide (1.0 M THF solution, 4 mmol, 4 mL) at −78 °C. After 1 h of stirring, the alkyne (2 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h. Then to the reaction mixture was added the first aldehyde (2 mmol), the reaction mixture was continued to stir at 0 °C for 3 h, and CuCl (200 mg, 2 mmol) and the second aldehyde (2 mmol) were added and the reaction mixture was warmed to room temperature and stirred for 1 h. The above reaction mixture was then quenched with 3 N HCl and extracted with ether. The extract was washed with sat. $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a light yellow liquid. The liquid was subjected to silica gel column using petroleum ether and dichloromethane (3:1) as the eluent. The final product was obtained as a colorless liquid.

4.3.1. THF derivative (6a). Light yellow liquid, isolated yield 55% (405 mg), mixture of isomers (5:4). ^{1}H NMR (TMS, $CDCl_3$) δ=0.87–1.00 (m, 6H), 1.26–2.61 (m, 12H), 5.29–5.38 (m, 1H), 6.67 (s), 6.79 (s) (total 1H), 7.12–7.36 (m, 8H), 7.68–7.74 (m, 1H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.48, 14.63, 14.74, 14.80, 17.69, 17.92, 22.62, 22.80, 31.33, 31.66, 32.78, 33.28, 35.98, 36.15, 40.48, 42.37, 76.75, 77.08, 89.33, 89.69, 124.33, 125.00, 126.07, 126.12, 126.71, 126.79, 126.81, 127.04, 127.94, 128.17, 128.19, 128.60, 128.63, 129.15, 129.19, 131.63, 131.66, 138.57, 138.64, 141.52, 141.65, 145.10, 145.86; HRMS calcd for $C_{24}H_{29}OCl$: 368.1907, found: 368.1912.

4.3.2. THF derivative (6b). Light yellow liquid, isolated yield 56% (416 mg), mixture of isomers (2:1). ^{1}H NMR ($CDCl_3$, TMS) δ=1.51 (s), 1.58 (s) (total, 1H) 1.89–2.41 (m, 7H), 5.07 (t, J=6.9 Hz), 5.14 (t, J=6.9 Hz) (total, 1H), 6.73 (s) 6.76 (s) (total 1H), 6.98–7.60 (m, 13H); ^{13}C NMR δ=14.91, 15.25, 26.59, 27.08, 34.29, 35.05, 36.85, 37.05, 80.18, 80.49, 86.29, 86.69, 114.86 (J=21.1 Hz, J_2CF) 121.19, 122.15, 126.29, 126.66, 126.72, 126.95, 127.08 (d, J=1.8 Hz, J_3CF), 127.14, 128.73, 129.49, 130.48 (d, J=2.5 Hz, J_4CF), 130.58 (d, J=2.5 Hz, J_4CF), 134.45, 134.50, 140.22, 140.25, 141.00, 141.07, 141.92, 142.16, 142.50, 142.61, 161.20 (J=244.6 Hz, JCF); HRMS calcd for $C_{26}H_{25}OF$: 372.1889, found: 372.1896.

4.3.3. THF derivative (6c). Light yellow liquid, isolated yield 52% (368 mg), mixture of isomers (3:2). ^{1}H NMR ($CDCl_3$, TMS) δ=1.52 (s) 1.58 (s) (total 3H), 1.91–2.41 (m, 7H), 5.08 (t, J=7.2 Hz) 5.14 (t, J=6.9 Hz) (total 1H), 6.77 (s), 6.81 (s) (total 1H), 7.17–7.59 (m, 14H); ^{13}C NMR δ=14.97, 15.31, 26.63, 27.09, 34.38, 35.04, 36.82, 37.08, 80.21, 80.41, 86.38, 86.77, 122.29, 123.20, 126.02, 128.03, 128.73, 129.06, 129.09, 138.53, 138.57, 142.61, 142.66; HRMS calcd for $C_{26}H_{26}O$: 354.1984, found: 354.1974.

4.4. Typical procedure for preparation of 2-hexen-1.6-diol derivatives (7a–7c)

A 50-mL Schlenk tube under dried nitrogen was charged with Cp_2ZrCl_2 (0.59 g, 2 mmol) and THF (20 mL). To this mixture was added ethylmagnesium bromide (1.0 M THF solution, 4 mmol, 4 mL) at −78 °C. After 1 h of stirring, the alkyne (2 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h. Then to the reaction mixture was added the first aldehyde (2 mmol), the reaction mixture was continued to stir at 0 °C for 3 h, and CuCl (200 mg, 2 mmol) and the second aldehyde (2 mmol) were added and the reaction mixture was warmed to room temperature and stirred for 1 h. The above reaction mixture was then quenched with 3 N HCl and extracted with ether. The extract was washed with sat. $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a light yellow solid. The solid was subjected to silica gel column using petroleum ether and ether (1:1) as the eluent. The final product was obtained as a colorless solid.

4.4.1. 2-Hexen-1.6-diol derivative (7a). Colorless solid, isolated yield 55% (405 mg), mixture of isomers (5:1). For the major, ^{1}H NMR ($CDCl_3$, TMS) δ=0.65 (t, J=7.2 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H), 1.26–2.21 (m, 9H), 2.96–3.11 (m, 1H), 4.03 (s, br 1H) 4.23 (s, br 1H), 5.00–5.12 (m, 1H), 5.86 (s) 6.03 (s) (total 1H), 7.08–7.28 (m, 6H), 7.42 (d, J=7.5 Hz) 7.42 (d, J=7.5 Hz) (total 1H), 7.62 (d, J=7.5 Hz) 7.63 (d, J=7.5 Hz) (total 1H); ^{13}C NMR ($CDCl_3$, TMS) δ=14.23, 14.53, 21.49, 23.52, 25.62, 30.53, 32.59, 35.37, 68.59, 70.24, 126.41, 126.96, 127.03, 127.75, 127.96, 128.14, 129.06, 129.23, 131.41, 132.30, 134.06, 138.64, 140.72, 142.36. Elemental analysis calcd for $C_{24}H_{30}O_2Cl_2$: C 68.40, H 7.13, found: C 68.40, H7.17.

4.4.2. 2-Hexen-1.6-diol derivative (7b). Colorless solid, isolated yield 47% (409 mg), mixture of isomers (4:3). ^{1}H NMR (TMS, $CDCl_3$) δ=0.55 (t, J=7.5 Hz) 0.82 (t, J=7.5 Hz) (total 3H), 0.94 (t, J=7.5 Hz) 0.99 (t, J=7.5 Hz) (total 3H), 1.65–2.08 (m, 5H), 2.19–2.31 (m, 2H), 2.93–3.04 (m, 1H), 3.60–4.20 (s, br, 2H), 4.58–4.71 (m, 1H), 5.97 (s) 6.00 (s) (total 1H)), 7.07–7.62 (m,

13H); ^{13}C NMR (TMS, $CDCl_3$) δ=7.95, 13.18, 13.69, 14.63, 20.89, 21.27, 23.59, 25.40, 33.60, 33.67, 36.54, 37.15, 69.81, 71.79, 75.09, 78.60, 126.19, 126.20, 126.41, 126.48, 126.96, 126.98, 127.03, 127.11, 127.14, 127.20, 127.83, 127.85, 127.87, 127.90, 128.69, 128.73, 128.88, 128.97, 132.27, 132.34, 134.83, 134.94, 139.27, 139.35, 140.03, 140.25, 140.51, 140.54, 140.76, 140.80, 143.73, 143.72; FAB-MS: $C_{28}H_{31}O_2^{35}Cl$ 441(M+Li). Elemental analysis calcd for $C_{28}H_{31}O_2Cl$: C 77.33, H 7.19, found: C 77.07, H 7.24.

4.4.3. 2-Hexen-1.6-diol derivative (7c), (1*R*,6*R*) and (1*S*,6*S*). Colorless solid, mp 99–102 °C, isolated yield 24% (193 mg); ^{1}H NMR (TMS, $CDCl_3$) δ=1.35 (s, 3H), 1.70 (s, 3H), 1.84–1.94 (m, 2H), 2.01–2.13 (m, 1H), 3.07–3.17 (m, 1H), 3.74 (s, br, 1H), 4.09 (s, br, 1H), 4.57–4.66 (m, 1H), 6.04 (s, 1H), 7.09–7.60 (m, 13H). ^{13}C NMR (TMS, $CDCl_3$) δ=13.51, 18.20, 29.21, 36.06, 69.38, 71.51, 126.13, 126.28, 126.91, 126.94, 127.10, 127.74, 128.02, 128.65, 128.98, 129.20, 131.69, 132.50, 139.99, 140.36, 140.70, 143.72; FAB-MS: $C_{26}H_{27}O_2^{35}Cl$ 413 (M+Li). Elemental analysis calcd for $C_{26}H_{27}O_2^{35}Cl$: C 76.70, H 6.69, found: C 76.20, H 7.04.

4.4.4. 2-Hexen-1.6-diol derivative (7c), (1*S*,6*R*) and (1*R*,6*S*). Colorless solid, mp 82–85 °C, isolated yield 24% (197 mg). ^{1}H NMR (TMS, $CDCl_3$) δ=1.39 (s, 3H), 1.67 (s, 3H), 1.87–1.94 (m, 2H), 2.12–2.22 (m, 1H), 2.71–2.78 (m, 1H), 3.21 (s, br, 2H), 4.69 (t, J=6.3 Hz, 1H), 5.93 (s, 1H), 7.11–7.64 (m, 13H); ^{13}C NMR (TMS, $CDCl_3$) δ=13.71, 18.97, 30.98, 37.43, 69.87, 74.88, 126.19, 126.45, 126.99, 127.13, 127.19, 127.98, 128.22, 128.70, 129.17, 131.94, 134.00, 140.31, 140.55, 140.73, 143.67; FAB-MS $C_{26}H_{27}O_2^{35}Cl$ 413 (M+Li). Elemental analysis calcd for $C_{26}H_{27}O_2^{35}Cl$: C 76.70, H 6.69, found: C 76.21, H 7.09.

4.5. Typical procedure for preparation of compounds 8a–8c

2-Hexen-1.6-diol derivative (1 mmol) was dissolved in 10 mL THF, to the solution was added 10 mL conc. HCl dropwise at 0 °C in 10 min, then the mixture was warmed to room temperature and stirred for 1 h, and the mixture was extracted with ether, the combined extract was washed with sat. $NaHCO_3$, water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a light yellow liquid.

4.5.1. THF derivative (8a). Light yellow liquid, mixture of isomers (3:2). ^{1}H NMR (TMS, $CDCl_3$) δ=0.72–1.02 (m, 6H), 1.27–2.60 (m, 12H), 5.34–5.42 (m, 1H), 6.66 (s) 6.80 (s) (total 1H), 7.15–7.40 (m, 7H), 7.69 (d, J=7.5 Hz), 7.81 (d, J=7.8 Hz) (total 1H); ^{13}C NMR (TMS, $CDCl_3$), 14.54, 14.69, 14.77, 17.70, 17.97, 22.56, 22.65, 30.97, 31.45, 32.76, 33.14, 35.65, 36.01, 40.62, 42.21, 76.93, 89.09, 89.54, 122.81, 122.96, 126.27, 126.30, 126.70, 126.74, 126.80, 127.23, 127.59, 127.65, 127.88, 127.93, 129.07, 129.16, 129.21, 130.03, 130.14, 131.57, 133.74, 133.78, 137.54, 137.59, 141.41, 141.78, 146.15, 146.93; HRMS calcd for $C_{24}H_{28}OCl_2$: 402.1517, found: 402.1515.

4.5.2. THF derivative (8b). Light yellow liquid, mixture of isomers (3:2). ^{1}H NMR (TMS, $CDCl_3$) δ=0.91 (t, J=7.5 Hz), 0.92 (t, J=7.5 Hz) (total 3H), 1.00 (t, J=7.5 Hz), 1.07 (t, J=7.5 Hz) (total 3H), 1.54–2.55 (m, 8H), 5.04–5.11 (m, 1H), 6.68 (s), 6.76 (s) (total 1H), 7.14–7.60 (m, 13H); ^{13}C NMR (TMS, $CDCl_3$) δ=8.86, 8.92, 13.88, 13.97, 21.42, 21.81, 31.47, 32.59, 34.10, 34.94, 35.99, 36.18, 79.93, 80.21, 89.29, 89.43, 122.25, 123.10, 126.19, 126.24, 126.61, 126.41, 126.69, 126.79, 126.82, 126.89, 126.96, 127.04, 127.15, 127.24, 127.35, 127.53, 128.63, 129.10, 130.09, 130.17, 133.60, 133.63, 137.51, 137.63, 139.95, 139.97, 140.94, 140.97, 142.15, 142.68, 147.75, 147.99; HRMS calcd for $C_{28}H_{29}OCl$: 416.1907; found: 416.1883.

4.5.3. THF derivative (8c). Light yellow liquid, mixture of isomers (3:1). ^{1}H NMR (TMS, $CDCl_3$) δ=1.51 (s) 1.58 (s) (total 3H), 1.74 (s) 1.79 (s) (total 3H), 1.82–2.00 (m, 2H), 2.11–2.40 (m, 2H), 5.09–5.16 (m, 1H),6.78 (s), 6.86 (s) (total 1H), 7.07–7.57 (m, 14H); ^{13}C NMR (TMS, $CDCl_3$) δ=14.58, 15.13, 26.59, 26.88, 34.28, 34.73, 36.51, 37.06, 80.32, 86.10, 86.52, 120.24, 120.86, 126.09, 126.11, 126.26, 126.94, 126.99, 127.07, 127.53, 128.64, 128.68, 128.74, 129.16, 130.70, 130.76, 133.85, 133.89, 136.87, 136.89, 140.03, 140.04, 140.90, 140.94, 141.81, 142.61, 143.71, 144.20; HRMS calcd. for $C_{26}H_{25}OCl$: 388.1594, found: 388.1610.

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