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Titanium(III)-induced intramolecular radical cyclization of epoxyallene ethers: an efficient method for synthesis of multifunctional tetrahydrofurans

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Abstract

Ti(III)-mediated intramolecular free radical cyclization of epoxyallene ethers in an *exo*-mode was studied. The reaction afforded an efficient and highly regioselective method of synthetically important 3-vinyl-4-hydroxymethyl tetrahydrofurans.

Keywords: Titanocene monochloride; Radical cyclization; Allene; Multifunctional tetrahydrofurans

Intramolecular radical cyclization has created a new era in recent years for carbon–carbon bond formation, and it reflects its significance as a powerful tool in modern synthetic chemistry.[1] In addition to the reactive nature of carbon radicals, high regioselectivity is frequently achieved in intramolecular reactions. The mildness and regio- and stereoselectivities of 5-hexenyl radical cyclization have extensively been used[2] for the construction of five-membered rings.

Tetrahydrofuran derivatives, especially containing vinyl and hydroxymethyl groups, are versatile precursors for the synthesis of naturally occurring cytotoxic[3]or antiplatelet-aggregation, vascular relaxing and antimutagenic activities[4] and also for the construction of a variety of furfuran lignans[5] and other natural products.[6] However, the synthetic methods for this kind of compounds need either complicated substrates[5b,c,6] or multiple reaction steps,[3,4,5a,b,d,7] so developing a short and efficient method to synthesize this kind of compounds is of interest and value.

The reductive opening of an epoxide via single-electron transfer (SET) to a radical intermediate promoted by titanocene monochloride (Cp_2TiCl) and the subsequent 5-*exo* radical trapping reaction represents a valuable synthetic tool that has been used in intramolecular carbon–carbon bond forming reactions.[8] Thus, epoxides can provide an excellent source of functionalized radicals.[9] The high regioselectivity of the epoxide cleavage via C–O homolysis is guided by the relative stabilities of the intermediate radicals. The trapping groups are usually unsaturated system such as alkenes, alkynes[8e,10] and nitriles.[8g] However, to the best of our knowledge, very little is known concerning the Ti(III)-mediated intramolecular free radical addition to the allenes. Radical reactions of allenes have been paid much attention because of the unique bonding character,[11] and are of current interest.[12] To expand upon the aforementioned chemistry, intramolecular cyclizations of epoxyallene ethers were investigated. In addition to achieving a new approach for constructing functional oxygen heterocycles, this investigation also presents an opportunity to address the regioselectivity issue in radical processes involving allenes, which is not a well-resolved problem.[13]

The *exo*-cyclization (path a) of radical intermediate **2** would lead to a vinyl radical **3**, and *central*-cyclization

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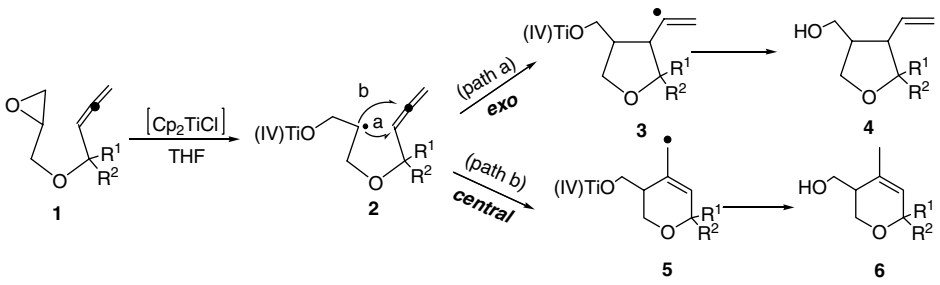


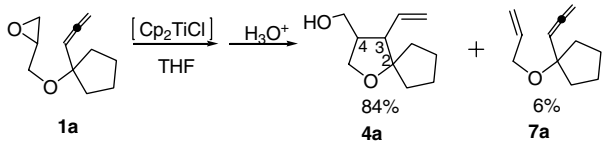
Scheme 1. Probable reaction pathways.

(path b) would give the energetically more favoured allyl radical **5** (Scheme 1). Since this is an intramolecular radical process, *endo*-cyclization might be prohibited due to geometric constrains. With these issues in mind, we report here a highly regioselective radical cyclization of epoxyallene ethers for the synthesis of multifunctional tetrahydrofurans.

The first substrate we examined for this reaction was cyclopentyl epoxyallene ether[14] (**1a**). The radical cyclization of **1a** using Cp_2TiCl in THF[15] under nitrogen for 1 h afforded the cyclization product **4a** containing a vinyl group at C-3 and hydroxymethyl group at C-4 position in 84% yield, along with 6% of deoxygenation product[15] **7a** indicating that the radical cyclization was conducted with high regioselectivity in an *exo*-mode (Scheme 2). The central-cyclized product **6a** was not found.

On the basis of this promising result, the Ti(III)-mediated cyclization of a variety of epoxyallene ethers was tested.[16] The results are summarized in Table 1. From Table 1, similar results were obtained for both monosubstituted and disubstituted epoxyallene ethers. For the ring substituted substrates **1a**–**e**, the multifunctional oxaspirocompounds **4a**–**e** were isolated in good yields (entries 1–5). And for the two same alkyl substituted substrates **1f**,**g**, **4f**,**g** were obtained in similarly good yields (entries 6 and 7). Compared with the two same substituted substrates, the different substituted and racemic substrates **1j**,**k** also afforded the corresponding cyclized products in good yields (entries 10 and 11). However, to our surprise, when both the substituted groups were hydrogen and phenyl, an unidentified mixture was obtained (entries 8 and 9).

As indicated in Table 1, products **4a**–**g** were obtained in an inseparable mixture of diastereoisomers with the ratio range as 56:44 to 70:30. The ratio of diastereoisomers of each compounds **4a**–**g** was determined by ^1H NMR based on the splitting pattern for hydrogen atom at C-3 position.



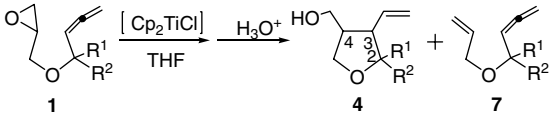
Scheme 2. The formation of multifunctional tetrahydrofuran **4a**.

Compared with the literature,[10b,c] our results indicated that the major isomer of products was the one with the vinyl and hydroxymethene groups at *cis*-position.[17]Attempts to separate products **4j**,**k** by HPLC to provide the ratios of stereoisomers did not yield good separation results.[18]

Besides the ethereal substrates, this radical cyclization can also be extended to synthesize multifunctional pyrrolidines. As shown in Scheme 3, when the *N*-tosyl containing epoxide **8** was subjected to the reaction conditions, the corresponding *N*-tosyl pyrrolidine **9** was isolated in 80% yield, the ratio of two inseparable diastereoisomers as 55:45.[19] It is important to note that substituted pyrrolidines are important structural features in many natural products.

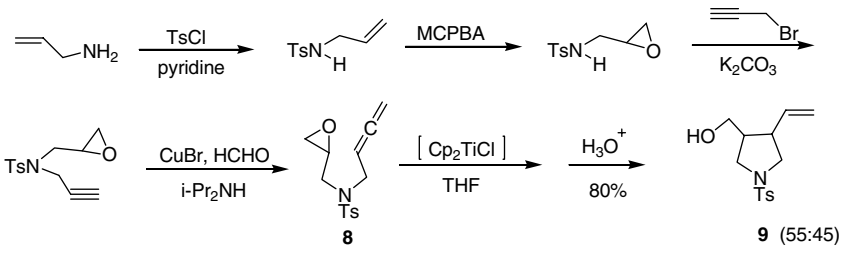
In conclusion, we have developed the radical cyclization of epoxyallene ethers induced by titanocene monochloride (Cp_2TiCl) with high regioselectivity in an *exo*-mode. This reaction also provided a useful way for the synthesis of 3-vinyl-4-hydroxymethyl tetrahydrofuran derivatives. Further studies of titanocene monochloride mediated radical cyclization of epoxyallenes are ongoing in our laboratory.

Table 1
Ti(III)-mediated radical cyclization of epoxyallene ethers



Entry	R^1	R^2	Yields[a] of **4**/**7** (%)	Ratio of diastereoisomer[b]
1 (**1a**)		–$(CH_2)_4$–	84(**4a**)/6	64:36
2 (**1b**)		–$(CH_2)_5$–	72(**4b**)/8	64:36
3 (**1c**)		–$(CH_2)_6$–	76(**4c**)/8	63:37
4 (**1d**)		–$(CH_2)_7$–	71(**4d**)/7	62:48
5 (**1e**)		–$(CH_2)_2CH(CH_2)_2$– (CH_3)	72(**4e**)/8	60:40
6 (**1f**)	C_2H_5	C_2H_5	75(**4f**)/8	70:30
7 (**1g**)	*n*-C_3H_7	*n*-C_3H_7	77(**4g**)/7	70:30
8 (**1h**)	H	H	—(**4h**)[c]	—
9 (**1i**)	C_6H_5	C_6H_5	—(**4i**)[c]	—
10 (**1j**)	H	C_6H_5	80(**4j**)/7	—
11 (**1k**)	CH_3	$CH_3OC_6H_4CH_2$	74(**4k**)/8	—

[a] Isolated yield.
[b] The ratio was determined by ^1H NMR of the isolated product.
[c] Unidentified mixture was obtained.



Scheme 3.

Acknowledgement

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14. The epoxyallene ethers were prepared from the corresponding allenyl alcohols treated with NaH, then added epichlorohydrin and refluxed.
15. The radical initiator Cp_2TiCl was generated in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and Zn dust in tetrahydrofuran under nitrogen. See Ref. 8a and references cited therein.
16. *Typical procedure for radical cyclization reaction. Preparation of* **4a**: A solution of titanocene dichloride (0.5 g, 2 mmol) in dry tetrahydrofuran (15 mL) was stirred with activated zinc dust (0.39 g, 6 mmol) for 1 h under nitrogen (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 N HCl and thoroughly washing with water and finally with dry acetone and then drying in vacuo). The resulting green solution was then added dropwise to a stirred solution of epoxide **1a** (0.18 g, 1 mmol) in dry tetrahydrofuran (10 mL) at room temperature under nitrogen during 15 min. The reaction mixture was stirred for an additional 1 h and quenched with 10% H_2SO_4 (15 mL). Most of the solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (4×15 mL). The ether layer was washed with saturated $NaHCO_3$ (2×10 mL) and dried (Na_2SO_4). After removal of solvent, the crude residue was purified by column chromatography over silica gel (25% ethyl acetate/light petroleum) to afford alcohol **4a** (0.15 g, 84%) as a viscous liquid. Compound **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76–5.62 (m, 1H), 5.08–5.04 (m, 2H), 3.95–3.89 (m, 1H), 3.68–3.63 (m, 1H), 3.61–3.57 (m, 1H), 3.52–3.47 (m, 1H), 2.71–2.66 (m, 0.36 H), 2.59–2.54

(m, 0.36H), 2.35–2.30 (m, 0.64H), 2.29–2.24 (m, 0.64H), 2.15 (s, 1H, OH), 1.75–1.41 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.99, 135.50, 117.49, 117.17, 94.17, 93.98, 68.24, 67.81, 64.12, 62.34, 53.60, 53.51, 47.15, 45.45, 37.92, 36.48, 33.97, 32.06, 24.12, 23.93, 23.56, 23.23. IR(neat): 3418, 2956, 1639, 1428, 1018, 916 cm^{-1}; MS (EI): *m*/*z* (%) = 80 (100), 151 (43), 165 (26), 182 (M^+, 9), 183 (M^++1, 51). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.45; H, 10.01.

17. The observed cis-isomer as the major isomer was in accordance with the Beckwith-Houk rules, see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996; (b) Backwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925; (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
18. HPLC conditions: CH_3CN/H_2O = 1:1, ODS column.
19. *The spectra data of compound* **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.69 (m, 2H), 7.35–7.32 (m, 2H), 5.68–5.49 (m, 1H), 5.06–5.02 (m, 2H), 3.62–3.35 (m, 4H), 3.25–3.12 (m, 2H), 3.02–2.92 (m, 0.45H), 2.87–2.75 (m, 0.55H), 2.52–2.40 (m, 0.45H), 2.44 (s, 3H), 2.37–2.26 (m, 0.55H), 2.16 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.52, 143.50, 136.76, 134.09, 133.41, 133.18, 129.62, 127.44, 127.35, 117.27, 117.12, 62.25, 61.06, 52.56, 51.96, 50.46, 49.61, 46.11, 44.65, 44.19, 44.00, 21.42. IR(neat): 3523, 3078, 2929, 1597, 1400, 1340, 1161, 924 cm^{-1}; MS (EI): *m*/*z* (%) = 42 (100), 91 (56), 126 (55), 155 (18), 184 (14), 251 (21), 282 (M^++1, 2). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81. Found: C, 59.53; H, 6.93.