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Ti(III)-catalyzed radical cyclization of 6,7-epoxygeranyl acetate

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Abstract—The reductive cyclization of epoxygeranyl acetate (**1**) was investigated using a catalytic amount of Cp_2TiCl with various additives. The newly developed Cp_2TiCl–Mn–lutidine · HCl–BEt_3 system was found to be as effective as the reported stoichiometric system to afford the cyclized dehydro products **4** and **5** with 72% selectivity.

Stereo- and regio-selective cyclization of epoxy-alkenes can generate cycloalkanols.[1] Barrero reported the Ti(III)-mediated cyclization of various geraniol derivatives.[2] We have also reported that the Ti(III)-mediated radical cyclization of 6,7-epoxygeranyl acetate derivatives provided important synthetic intermediates for both the A and C ring synthons in the synthesis of paclitaxel.[3] In the synthesis, a stoichiometric amount of Cp_2TiCl was used; therefore, the work-up process was very tedious due to a large amount precipitated Ti-salts. A catalytic cycle, however, had only been reported for the reductive opening of epoxides using a novel Cp_2TiCl–Mn–collidine · HCl system by Gansäuer,[4] until Barrero recently demonstrated the Ti(III)-catalyzed transannular cyclization of an epoxy-alkene in a germacrane skeleton using Cp_2TiCl–Mn–collidine · TMSCl.[5] We wish to report that the catalytic cyclization of 6,7-epoxygeranyl acetate was efficiently achieved by using Cp_2TiCl–Mn–lutidine · HCl–BEt_3.

A plausible mechanism for the Ti(III)-catalyzed radical cyclization of 6,7-epoxygeranyl acetate (**1**) is shown in Scheme 1. Reductive opening of the epoxide with $Cp_2Ti(III)Cl$, followed by *endo*-trig cyclization via a chair-like transition state would form **2**. According to Gansäuer's method, transformation of the Ti(IV) of $Cp_2Ti(OR)Cl$ **2** can be carried out by a Cp_2TiCl–Mn–collidine · HCl system to afford $Cp_2Ti(III)Cl$ and **3**. Then, disproportionation of the radical of **3** with $Cp_2Ti(III)Cl$ would provide a double bond in the product **4** and **5** and concomitantly produce a similar species to $Cp_2Ti(IV)HCl$. In order to accomplish a catalytic cycle of Ti(IV) to Ti(III), another transformation of this Ti(IV) species to Cp_2TiCl is necessary. This process may be possible by addition of Et_3B because that would reduce the Cp_2ZrHCl into Cp_2ZrCl.[6] It will be very important whether these systems are compatible in the same reaction flask.

We initially investigated the effect of the additives, Et_3B, 2,6-lutidine · HCl, 2,4,6-collidine · HCl (Table 1, entries 2, 3 and 5) using 10 mol% of Cp_2TiCl and 4 equiv of Mn. The results are shown in Table 1. In the absence of additives, only 10% conversion of **1** was observed. A catalytic process was achieved when 2,6-lutidine · HCl (99%) and 2,4,6-collidine · HCl (71%) were added, respectively (entries 3 and 5). Addition of only Et_3B was not effective (entry 2). However, addition of Et_3B and 2,6-lutidine · HCl gave better selectivities than that of 2,6-lutidine itself to afford the desired **4** and **5** (entry 4). Addition of Et_3B was slightly more effective with the use of 2,4,6-collidine · HCl (entry 6 vs entry 5). Presumably, Et_3B promotes a smooth catalytic cycle to result in efficient supply of Cp_2TiCl for disproportionation rather than the protonated termination by HCl salt.[7] To avoid the protonated termination, addition of TMSCl was attempted instead of lutidine salt.[8] However, unwanted chlorohydrin **8** was mostly formed (entry 7). The recently reported Cp_2TiCl–Mn–lutidine · TMSCl system[5] was not effective in this cyclization yielding at most 55% conversion (entry 8). The best result was obtained using Cp_2TiCl–Mn–lutidine · HCl–BEt_3 (entry 4). This is as good as the results obtained using the stoichiometric system reported previously (entry 9).[2,3]

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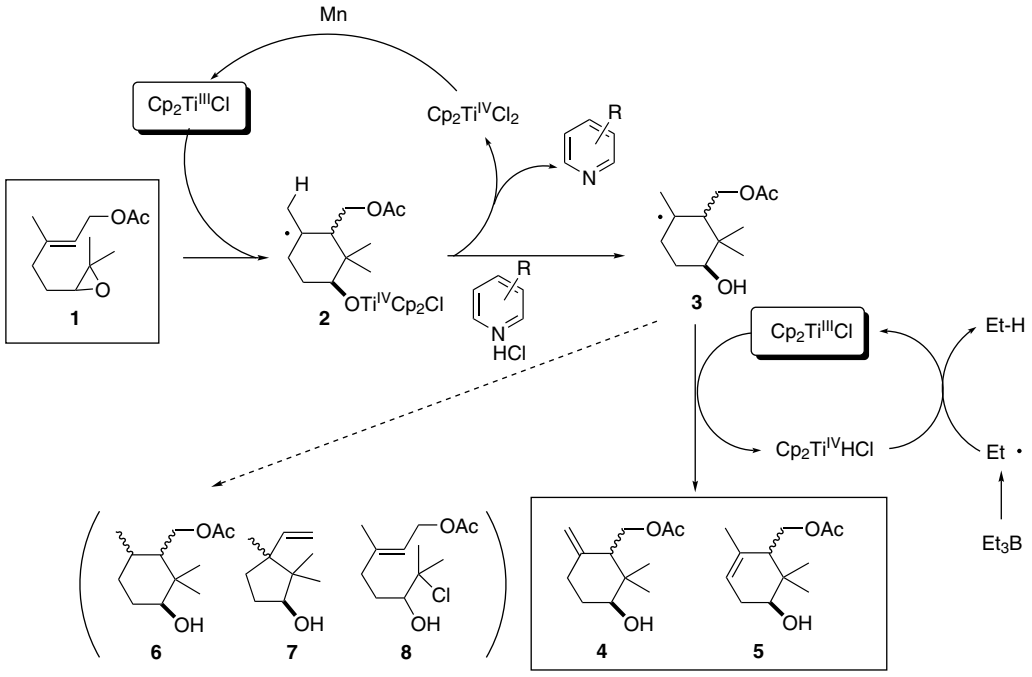

Scheme 1. Plausible mechanism of Ti(III)-catalyzed reductive cyclization of epoxygeranyl acetate (**1**).

Table 1. The Cp_2TiCl-catalyzed radical cyclization of **1** using various additives[a]

Entry	Cp_2TiCl/mol%	Additives (1.5 equiv)	Time/h	Conversion/%	**4** (RT^b/min) (57 for *cis* and 87 for *trans*)	**5** (RT^b/min) (51 for *cis* and 82 for *trans*)	**6** (RT^b/min) (47, 70, and 78)[c]	**7** (RT^b/min) (21 and 24)	**8** (RT^b/min) (41)
1	10	None	9	10	5	1			4
2	10	BEt_3	9	30	6	2	3		1
3	10	2,6-Lutidine·HCl	9	99	43 (3:1)	12 (5:1)	17		7
4	10	BEt_3, 2,6-lutidine·HCl	4	99	56 (3:1)	16 (7:1)	12		
5	10	2,4,6-Collidine·HCl	9	71	30 (3:1)	5	18		11
6	10	BEt_3, 2,4,6-collidine·HCl	9	86	35 (3:1)	9	19	6	5
7	10	TMSCl	4	89	20 (3:1)	6	8	2	41
8[d]	20	2,4,6-Collidine·TMSCl[e]	24	55	25 (5:1)	5	6		
9[f]	300	None	2	99	64 (3:1)	2		15	9

[a] The reaction was carried out in THF with 4 equiv of Mn at room temperature. The conversion and ratio of the products were determined by HPLC analysis with RI intensities (Silica-3301-N 8ϕ×300 mm, 13% ethyl acetate in hexane, 2.0 mL/min).
[b] RT = retention time.
[c] Three of four possible diastereomers were observed.
[d] Ref. 5.
[e] 4 equiv.
[f] Refs. 2 and 3.

We have demonstrated that the reductive cyclization of 6,7-epoxygeranyl acetate was accomplished using a catalytic amount of Cp_2TiCl with Mn, lutidine·HCl, and BEt_3 as additives. A larger scale reaction is underway in our laboratory toward a key synthetic intermediate of paclitaxel.

Experimental procedure of the Ti(III)-catalyzed cyclization of (**1**). A mixture of Cp_2TiCl_2 (211 mg, 0.848 mmol) and manganese (62 mg, 1.1 mmol), and 10 mL of THF was stirred under argon. The supernatant of Cp_2TiCl was transferred via a cannular to a mixture of 2,6-lutidine·HCl (1.84 g, 12.8 mmol, pre-dried at 60 °C under 600 Pa), manganese (1.80 g, 33.9 mmol), and 6,7-epoxygeranyl acetate (**1**) (1.80 g, 8.48 mmol) in 40 mL of dry THF. Then, the mixture was treated with a 0.1 M THF solution of BEt_3 (12.7 mL, 12.7 mmol) and was stirred at room temperature under argon. After 4 h, 1 M HCl was added at 0 °C. Usual work-up and flash column chromatography on silica gel afforded the alcohols **4**–**6** (1.77 g) as a colorless oil.

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