JOC Note

A Novel Titanium-Catalyzed Cyclization of Olefinic Iodoethers to Tetrahydrofurans

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Abstract: A catalytic reductive cyclization of olefinic iodo-ethers was achieved by use of cat. Cp_2TiCl_2 in the presence of Mn and Me_3SiCl. This protocol provides a versatile method for the selective formation of multisubstituted tetrahydrofurans.

The explosive growth in free radical chemistry in recent years reflects its significance as a powerful tool in modern synthetic chemistry.[2] Although the stereo- and chemoselectivity of the substrate-controlled reactions have reached a high level,[3] little attention has been paid to the reagent-controlled catalytic transformation of radicals not proceeding via chain reactions.[4] Low-valent titanium compounds have been used as a useful one-electron reductant, but more than stoichiometric amounts of the reductant are usually required to accomplish the reduction reactions, which is clearly disadvantageous from a synthetic viewpoint.[5] Construction of a catalytic system is of great importance. It has been recently reported that the use of a chlorosilane in combination with a catalytic amount of early transition metal compound such as titanium or vanadium and a stoichiometric co-reductant successfully effects the catalytic reagent-controlled pinacol coupling and reductive epoxide opening reactions.[4, 6]

The 5-hexenyl radical cyclization has been extensively investigated for the construction of carbocyclic as well as oxacyclic skeletons, leading to cyclopentane and tetrahydrofuran derivatives, respectively.[7] Although some

TABLE 1. Intramolecular Cyclization of 1a with Various Reductants[a]

entry	catalyst	time (h)	yield (%) 2a	3a
1	Cp_2TiCl_2	36	35	10
2	Cp_2VCl_2	24	45	trace
3[b,c]		24	16	trace
4[c]		24	22	trace
5	Cp_2TiCl_2[d]	3	86	trace
6[b]	$PbCl_2$	4		
7	$PbCl_2$	96		
8[b,c,e]	$PbCl_2$	24	trace	36
9[c,e]	$PbCl_2$	24	trace	15

[a] Reaction conditions: **1a** (0.25 mmol), catalyst (10 mol %), Mn (2 mmol), Me_3SiCl (0.5 mmol), THF (5 mL) unless otherwise stated, and room temperature. [b] Me_3SiCl (5 μL) was used. [c] The reaction was conducted at 65 °C. [d] Cp_2TiCl_2 (0.25 mmol) was used. [e] THF (4 mL) and DMF (2 mL) were used.

intramolecular radical cyclization reactions prior to anion formation through further one-electron reduction have been achieved by using a stoichiometric amount of metallic reductant,[8,9] only a few examples have been found for the catalytic reaction.[10] With this consideration in mind, we here wish to report a novel intramolecular cyclization of olefinic iodides induced by a titanium or vanadium catalytic system.

The cyclization of the olefinic iodide **1a** was examined with the catalytic system (Table 1). When a catalytic amount of Cp_2TiCl_2 or Cp_2VCl_2 was employed as a catalyst in the presence of Mn and Me_3SiCl (freshly distilled over CaH_2), a moderate yield of the cyclization product **2a** was obtained as shown in eq 1 (entries 1 and

$$(1)$$
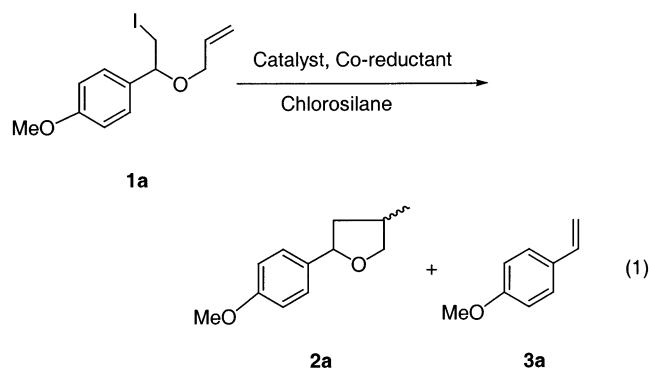
2). It should be noted that the reaction in the absence of Cp_2TiCl_2 led to a much lower yield of **2a** (entries 3 and 4). Furthermore, use of a stoichiometric amount of Cp_2TiCl_2 resulted in a higher yield (entry 5). Although the $PbCl_2$/Mn/Me_3SiCl reduction system has been reported to be effective in radical carbon−carbon bond-forming reactions,[11] the cyclization reaction of **1a** did not proceed with this system in the presence of a catalytic or even excess amount of Me_3SiCl (entries 6−9). These

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TABLE 2. Effect of Solvent, Reaction Temperature, Additive, and Co-reductant Metal on the Cyclization of 1a[a]

entry	additive	solvent	metal	time (h)	yield (%) 2a	3a
1[b]	Me₃SiCl	DME	Zn	1		78
2[b]	Me₃SiCl	DMF	Mn	48	33	
3[b]	Me₃SiCl	THF	Mn	36	35	
4	Me₃SiCl	DMF	Mn	24	58	trace
5	Me₃SiCl	THF-DMF[c]	Mn	24	46	12
6	Me₃SiCl	THF	Mn	24	87	trace
7[d]	Me₃SiCl	THF	Mn	23	62	
8	Me₃SiCl	THF	Zn	1.5		81
9	Me₃SiCl	THF	Al	48		
10	Me₃SiCl	THF	Mg	24	15	
11		THF	Mn	24	trace	
12	Me₂PhSiCl	THF	Mn	24	67	6
13	collidinium chloride	THF	Mn	24	42	6

^{a} Reaction conditions: **1a** (0.25 mmol), Cp₂TiCl₂ (10 mol %), Mn (2 mmol), Me₃SiCl (0.5 mmol), solvent (5 mL), 65 °C unless otherwise stated. ^{b} Room temperature was employed. ^{c} THF (4 mL) and DMF (2 mL) were used. ^{d} Cp₂VCl₂ (10 mol %) was employed as a catalyst.

findings suggest the involvement of the titanium catalyst in the cyclization reaction.

Solvent or reaction temperature effect was next studied as shown in Table 2. With DME as a solvent, the desired product **2a** was not detected with formation of only the β-elimination product **3a** (entry 1). The formation of **2a** was observed with DMF or THF as a solvent at room temperature (entries 2 and 3). When the reaction was conducted at 65 °C in DMF or THF-DMF, the yield was improved (entries 4 and 5). Furthermore, a better result was obtained in THF at this reaction temperature (entry 6). Cp₂TiCl₂ was found to be superior to Cp₂VCl₂ as a catalyst under these reaction conditions (entry 7). The effect of additive and co-reductant metal was also studied as shown in Table 2. Although the cat. Cp₂TiCl₂/Me₃SiCl/ Zn system works well for the diastereoselective cyclization of ketonitriles,[12] no desired cyclization product of **1a** was detected with Zn, only giving the β-elimination product **3a** (entry 8). The reaction with Al or Mg as a co-reductant was sluggish with a very poor result, although the elimination product was not detected (entries 9 and 10). Noteworthy is that only a trace amount of **2a** was formed in the absence of Me₃SiCl as an additive (entry 11). Me₂PhSiCl was inferior to Me₃SiCl (entry 12).

However, use of collidinium chloride, which is an effective additive in the reagent-controlled catalytic pinacol coupling reaction,[4a] resulted in the lower yield (entry 13). These results indicate that the chlorosilane serves an important role in the cyclization reaction.

The optimized reaction conditions were employed for the intramolecular cyclization of various olefinic iodides **1**. The reaction of **1** induced by the cat. Cp₂TiCl₂/Me₃SiCl/ Mn system in THF afforded the desired multisubstituted tetrahydrofuran **2** stereoselectively as shown in Table 3. The corresponding olefinic chloro analogue of **1a** did not undergo the reaction. An interesting feature is that the stereoselectivity of **2** was enhanced in comparison to the reported one with a stoichiometric amount of initiator.[9f] This observation is suggestive of a similar transition state in the cyclization step as described in the free radical reaction. β-Alkoxy elimination products were nearly undetectable in the reaction mixture. Thus, the halogen– metal exchange might not take place in the cat. Cp₂TiCl₂/ Me₃SiCl/Mn induced reactions.[13] Generally, radical reactions offer suitable methods for generating quaternary carbon atoms, and this is indeed the case as observed in entries 6 and 9. Bicyclic product **2g** was also formed successfully.

A plausible reaction path is as follows. Reduction of Cp₂TiCl₂ with manganese powder affords a low-valent titanium species, which is able to reduce **1**. The thus-generated 3-oxa-5-hexenyl radical intermediate **4** undergoes the carbon–carbon bond-forming cyclization to **5**, which is finally converted to **2**. Chlorosilanes appear to contribute to the catalytic reaction in various ways, which involve the liberation of the Ti^IV species from the cyclization product as one of the possibilities.[4] When the radical **4** is further reduced to the anionic species **6**, β-elimination leads to the olefinic compound **3**. This process was mostly observed when active zinc powder was used as a co-reductant.[14]
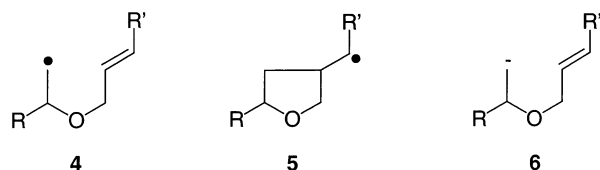
In conclusion, the cyclization of olefinic iodoethers was promoted by using cat. Cp₂TiCl₂ in the presence of Mn and Me₃SiCl in THF at 65 °C. This synthetic method has the potential to construct multisubstituted tetrahydrofurans selectively.

Experimental Section

¹H NMR or ¹³C NMR spectra were recorded in chloroform-*d* with tetramethylsilane or residual chloroform as an internal standard. Mass spectra were recorded with LRMS and HRMS. TLC was carried out on aluminum sheets precoated with silica gel 60 F₂₅₄ (E. Merck). Column chromatography was performed on silica gel 60 (E. Merck). Me₃SiCl and Me₂PhSiCl were freshly distilled under argon over calcium hydride before use. All reagents were of commercial quality and were used without

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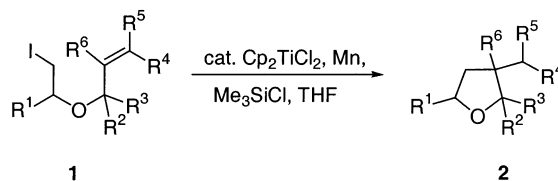
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TABLE 3. Intramolecular Cyclization of 1 with cat. Cp$_2$TiCl$_2$/Me$_3$SiCl/Mn System^a

entry	1	R^1	R^2	R^3	R^4	R^5	R^6	time (h)	2	yield (%) (trans:cis)^b
1	**1a**	*p*-MeOC$_6$H$_4$	H	H	H	H	H	24	**2a**	83 (80:20)
2	**1b**	*p*-MeOC$_6$H$_4$	Me	Me	H	H	H	24	**2b**	64 (85:15)
3	**1c**	*p*-MeOC$_6$H$_4$	H	H	H	Pr	H	24	**2c**	63 (80:20)
4	**1d**	*p*-MeOC$_6$H$_4$	H	H	Pr	H	H	24	**2c**	61 (71:39)
5	**1e**	*p*-MeOC$_6$H$_4$	Me	H	H	H	H	28	**2e**	59^c
6	**1f**	*p*-MeOC$_6$H$_4$	H	H	H	H	Me	48	**2f**	56
7	**1g**	*p*-MeOC$_6$H$_4$	H	$-$(CH$_2$)$_3-$		H	H	36	**2g**	59^d
8	**1h**	BuO	Me	Me	H	H	H	30	**2h**	73 (69:31)
9	**1i**	BuO	H	H	H	H	Me	36	**2i**	45
10	**1j**	BuO	H	H	H	H	H	30	**2j**	70 (60:40)

^{a} Reaction conditions: **1** (0.5 mmol), Cp$_2$TiCl$_2$ (10 mol %), Mn (4 mmol), Me$_3$SiCl (1 mmol), THF (8 mL), 65 °C. ^{b} The ratio was determined by ^{1}H NMR. ^{c} Obtained as a mixture. ^{d} Obtained as a mixture of exo and endo isomers (60:40).

purification. All dry solvents were freshly distilled under argon over an appropriate drying agent. The reactions were carried out under argon, using the syringe and Schlenk-type technique.

General Procedure for the Preparation of 1a–j. The olefinic iodide **1** was prepared according to the literature procedure.[15] Under argon, an allyl alcohol (7.52 mmol) was added to a solution of an olefin (3.76 mmol) in dry CH$_2$Cl$_2$ (25 mL) at room temperature. After being stirred for 5 min, the reaction mixture was cooled to −78 °C. *N*-Iodosuccinimide (1.27 g, 5.64 mmol) was then added to the mixture, which was allowed to reach 0 °C within 6 h. A saturated aqueous solution of Na$_2$S$_2$O$_3$ was added to the reaction mixture, which was stirred vigorously for 5 min. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/Et$_2$O (20:1−1:1) to give the iodide **1**.

Representative Procedure for the Intramolecular Cyclization of 1a. To a mixture of Cp$_2$TiCl$_2$ (12.5 mg, 0.050 mmol) and manganese powder (220 mg, 4.0 mmol) in THF (6 mL) was added Me$_3$SiCl (0.13 mL, 1.0 mmol) at room temperature under argon. After the mixture was stirred for 30 min, a solution of **1a** (0.5 mmol) in THF (3 mL) was added. The mixture was kept at the indicated temperature with magnetic stirring for the time indicated in the table. Then, the reaction mixture was subjected to workup with 1 M HCl (3 mL) and ether (50 mL). The organic layer was washed with saturated aqueous Na$_2$S$_2$O$_3$ (10 mL),

water (10 mL), and brine (10 mL), dried over MgSO$_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g; eluent, hexane/ethyl acetate = 50:0, 48:2, 46:4, 44:6, 42:8, 40:10, 38:12, 35:15, 32:18, 28:22, 25:25, 50 mL × each), giving **2a**:[15] colorless oil. Trans: ^{1}H NMR (CDCl$_3$) δ 1.09 (d, 3H, *J* = 6.9 Hz), 1.85−2.04 (m, 2H), 2.36−2.50 (m, 1H), 3.45 (dd, 1H, *J* = 8.1, 6.9 Hz), 3.80 (s, 3H), 4.20 (dd, 1H, *J* = 8.4, 6.9 Hz), 4.97 (t, 1H, *J* = 6.9 Hz), 6.85−6.89 (m, 2H), 7.23−7.29 (m, 2H); ^{13}C NMR (CDCl$_3$) 17.9, 33.3, 42.6, 55.2, 75.5, 79.7, 113.5, 126.7, 135.6, 158.5 ppm. Cis: ^{1}H NMR (CDCl$_3$) δ 1.10 (d, 3H, *J* = 6.9 Hz), 1.88−2.04 (m, 1H), 2.39−2.50 (m, 2H), 3.57 (t, 1H, *J* = 8.1 Hz), 3.80 (s, 3H), 4.07 (t, 1H, *J* = 8.1 Hz), 4.86 (dd, 1H, *J* = 10.0, 5.7 Hz), 6.85−6.89 (m, 2H), 7.23−7.29 (m, 2H); ^{13}C NMR (CDCl$_3$) 17.6, 34.9, 43.8, 55.2, 75.2, 81.3, 113.6, 126.8, 135.1, 158.6 ppm. MS (EI): 192 (M$^+$, 64), 191 (73), 161 (35), 135 (100). HRMS (EI) Calcd for C$_{12}$H$_{16}$O$_2$ (M$^+$): 192.1150. Found: 192.1144.

Supporting Information Available: Experimental procedure as well as ^{1}H NMR, ^{13}C NMR, MS, and HRMS data for the products **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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