HETEROCYCLES, Vol. 74, 2007, pp. 191 - 197. © The Japan Institute of Heterocyclic Chemistry
Received, 29th August, 2007, Accepted, 28th September, 2007, Published online, 2nd October, 2007. COM-07-S(W)48

AN ALTERNATIVE REGIOSELECTIVE RING-OPENING OF EPOXIDES TO CHLOROHYDRINS MEDIATED BY CHLOROTITANIUM(IV) REAGENTS

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Abstract – A regioselective cleavage of various epoxides to *vic*-chlorohydrin isomers by using $TiCl_4$ or $TiCl_4$-Ti(O-*i*-Pr)$_4$ complex was investigated. The less substituted alcohols, C2-attack products, were formed by the use of $TiCl_4$ in CH_2Cl_2. On the other hand, the less substituted chlorides, C1-attack products, were formed by using TiCl(O-*i*-Pr)$_3$ in DMF. These regioselectivities depend on both the acidity of the Lewis acids and the polarity of the solvents.

INTRODUCTION

In the course of synthetic studies directed toward the naturally occurring terpenoid lactones containing the α-methylene-δ-lactone moiety, we have found that the regioselectivity of the cleavage of the terminal epoxide to chlorohydrins depended on the reagents used.[1] We have observed that an intramolecular cyclization of epoxy-allylsilane (**1**) by using BF_3•OEt_2 afforded a good yield of 5-exo cyclization product (**4**), however, chlorotitanium(IV) reagents reacted with only the epoxy group to give chlorohydrins regioselectively. When epoxy-allylsilane (**1**) was treated with titanium tetrachloride in dichloromethane, chlorohydrins (**2** and **3**) were obtained in a ratio of 88:12. On the other hand, treatment with a titanium tetrachloride-titanium tetraisopropoxide mixture (1:1) gave **2** and **3** in a ratio of 19:81. Vicinal chlorohydrins have attained great importance in organic synthesis.[2] The regioselective ring-openings of epoxides have been reviewed by Bonini and Righi.[3] The regioselective ring-openings using ionic liquids such as [Hexmim]/MX,[4] [AcMim]X,[5] or [Bmim]PF_6/LiX[6], using additive DDQ/Bu_4NX-Ph_3P[7] or

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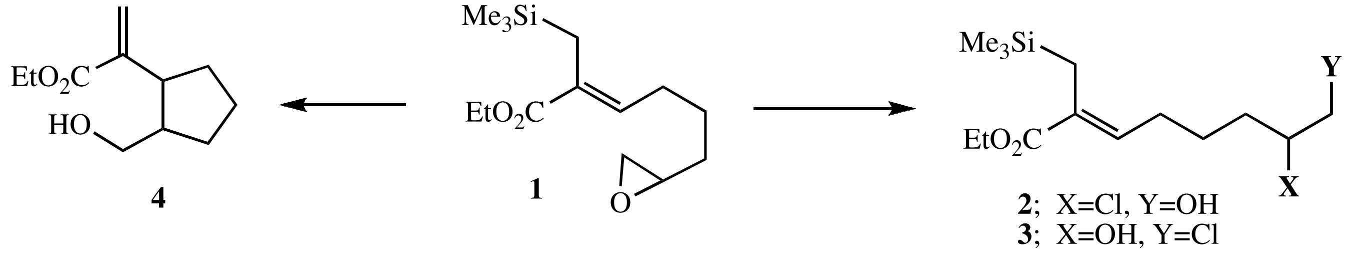
This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

β-CD/MX[8] and using rare metals $NbCl_5$[9] or zirconocene-TMSCl[10] are recently reported. There have been a large number of reports on the regioselective ring-opening of terminal epoxides by using titanium reagents, such as $TiCl_4$, Ti(O-*i*-Pr)$_4$-*i*-Bu_2AlCl,[11] $TiCl_4$-DBU,[12] $TiCl_4$-LiX,[13] Ti(O-*i*-Pr)$_4$-NH_4X,[14] or Ti(O-*i*-Pr)$_4$-X_2.[15] The reaction of terminal epoxides with $TiCl_4$-LiCl in THF afforded C-1-opening primary chlorides (**7**),[13] while that using $TiCl_4$ in heptane selectively afforded C-2-opening secondary chlorides (**8**).[11] Regioselective cleavage of epoxides by the use of a $TiCl_n$(O-*i*-Pr)$_{4-n}$ reagent, however, has not been reported yet. We would like to report the regioselective cleavage of various epoxides by using $TiCl_4$-Ti(O-*i*-Pr)$_4$ reagents, and their solvent effects.



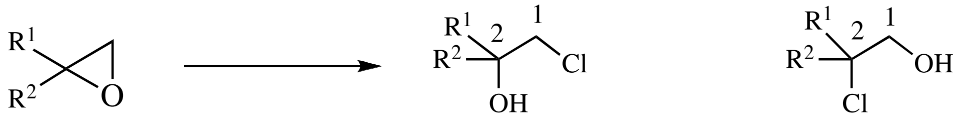
Scheme 1

RESULTS AND DISCUSSION

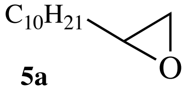
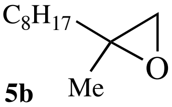
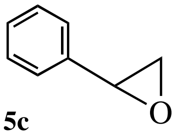
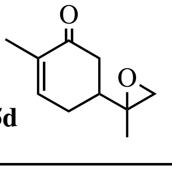
We selected 1,2-epoxydodecane (**5a**), 2-methyl-1,2-epoxydecane (**5b**) and styrene oxide (**5c**) as terminal epoxides, 2,3-epoxydodecane(**6a**) as a 1,2-disubstitutedepoxide, and 2-methyl-2,3-epoxyundecane (**6b**) as a trisubstituted epoxide. 2,3-Epoxydodecane (**6a**) was prepared by epoxidation of 2-undecene (*Z*/*E*=8/1) which was derived from decylaldehyde by the Wittig reaction with triphenylphosphonium ethylide. 3-Methyl-2-undecene oxides (**6b**) were prepared from 2-decanone *via* the Wittig reaction with triphenylphosphonium ethylide followed by an epoxidation reaction.

Reaction of Terminal Epoxides The extent of epoxy ring-opening of 1,2-epoxides (**5a-d**) by using $TiCl_4$-Ti(O-*i*-Pr)$_4$ in CH_2Cl_2 or DMF, and the resulting ratio of chlorohydrins, **7** (C-1 attack) and **8** (C-2 attack), are summarized in Table 1. The reaction of the epoxide (**5a**) with $TiCl_4$ at -76°C gave **7a** and **8a** in a ratio of 6:94 (entry 1). The epoxide (**5a**) was also cleaved by using a 1:1 mixture of $TiCl_4$ and Ti(O-*i*-Pr)$_4$ to yield **7a** and **8a** in a ratio of 37:63, while the TiCl(O-*i*-Pr)$_3$ reagent[16] gave **7a** and **8a** in a ratio of 84:16 (entries 7 and 8). As for the nature of the solvent, a polar solvent such as DMF significantly increased the ratio of C-1 attack (**7**) to C-2 attack (**8**) in both reactions using $TiCl_4$ or TiCl(O-*i*-Pr)$_3$. A dramatic shift in regioselectivity toward C-1 attack was especially found in the reaction by the use of $TiCl_4$. Epoxy ring-opening of **5a** by using $TiCl_4$ in CH_2Cl_2 produced **7a** and **8a** in a ratio of 6:94, but in DMF in a ratio of 93:7 (entries 1 and 6). The formation of the primary chloride, C-1 attack, was increased with the polarity of the solvent (DMF/CH_2Cl_2 from 1/50 to 1/2, entries 3-5). When **5a** was treated with

Table 1. Cleavage of Terminal Epoxides (**5a**-**d**)



5 **7**; C_1 attack **8**; C_2 attack

Entry	Epoxide	Reagent (equiv) and Conditions	Yield [a)] (%)		Ratio C_1 / C_2
			7	**8**	
1		$TiCl_4$(1.2) / CH_2Cl_2 / -76°C/ 0.3h	4.0	64.7	**6 : 94**
2		$TiCl_4$(1.2) / THF / -76 to -60°C/ 0.3h	13.5	5.3	72 : 28
3	**5a**	$TiCl_4$(1.2) / DMF-CH_2Cl_2 (1/50) / 0°C /0.3h	38.5	30.0	56 : 44
4		$TiCl_4$(1.2) / DMF-CH_2Cl_2 (1/9) / 0°C/ 0.5h	62.7	10.5	86 : 14
5		$TiCl_4$(1.2) / DMF-CH_2Cl_2 (1/2) / 0°C/ 0.3h	87.3	12.9	88 : 12
6		$TiCl_4$(1.2) / DMF / -70 to 0°C/ 1.4h	75.1	5.4	**93 : 7**
7		$TiCl_2(Oi\text{-}Pr)_2$(1.2) / CH_2Cl_2 / -76 to -30°C/ 2.3h	24.4	42.0	**37 : 63**
8		$TiCl(Oi\text{-}Pr)_3$(1.2) / CH_2Cl_2 / 0°C/ 17.7h	59.0	11.5	84 : 16
9		$TiCl(Oi\text{-}Pr)_3$(1.2) / THF / -76 to r.t./ 22.5h	9.8	7.5	57 : 43
10		$TiCl(Oi\text{-}Pr)_3$(1.2) / DMF / 0°C/ 15h	71.0	0.8	**99 : 1**
11		$TiCl_4$(1.2) / CH_2Cl_2 / -78°C/ 1.2h	0	42.0	**0 : 100**
12	**5b**	$TiCl_4$(1.2) / DMF / 0°C/ 0.3h	53.4	17.0	76 : 24
13		$TiCl(Oi\text{-}Pr)_3$(1.2) / CH_2Cl_2 / -78°C/ 6.5h	10.1	35.0	22 : 78
14		$TiCl(Oi\text{-}Pr)_3$(1.2) / DMF / 0 to rt / 42.7h	69.6	5.9	**92 : 8**
15		$TiCl_4$(1.2) / CH_2Cl_2 / -78°C/ 0.3h	0	96.4	**0 : 100**
16	**5c**	$TiCl(Oi\text{-}Pr)_3$(1.2) / DMF / 0 to rt / 46h	60.9	31.4	**66 : 34**
17		$TiCl_4$(1.2) / CH_2Cl_2 / -78°C/ 0.3h	0	81.7	**0 :100**
18	**5d**	$TiCl(Oi\text{-}Pr)_3$(1.2) / DMF / 0 °C/ 19h	79.4	0	**100 : 0**

a) Isolated yield.

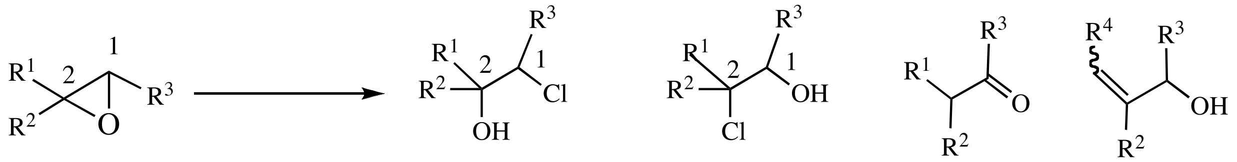
$TiCl(O\text{-}i\text{-}Pr)_3$ in DMF, the primary chloride (**7a**) was almost exclusively obtained (entry 10). In THF or hexane, however, the chlorohydrins were obtained in poor yields. Ring-opening of the 2,2-disubstituted epoxide, 1,2-epoxy-2-methyldecane (**5b**), by using $TiCl_4$ in CH_2Cl_2 exclusively gave a C-2 attack product (**8b**). In contrast, the reaction using $TiCl(O\text{-}i\text{-}Pr)_3$ in DMF selectively gave a C-1 attack product (**7b**) in a ratio of 92:8 (**7b**:**8b**) (entries 11 and 14). In the case of a styrene oxide, C-1 opening product (**8c**) was exclusively obtained, however, using TiCl(O-*i*-Pr)$_3$ in DMF yielded the C-1 attack chloride (**7c**) in a moderate selectivity, **7c**:**8c**=66:34 (entry 16). Our method can also be applied to epoxides derived from monoterpens. Carvone oxide (**5d**) exclusively yielded a tertiary chloride (**8d**) by using TiCl$_4$ in CH$_2$Cl$_2$ but, on the contrary, a primary chloride (**7d**) was exclusively obtained by using TiCl(O-*i*-Pr)$_3$ in DMF.[17]

Reaction of Internal Epoxides Little regioselectivity was observed in the opening of 1,2-disubstituted epoxide, 2,3-epoxydodecane (**6a**), by using TiCl$_4$ or TiCl(O-*i*-Pr)$_3$ in CH$_2$Cl$_2$ or DMF, as expected (entries 1-3 in Table 2). Treatment of the trisubstituted epoxide, 3-methyl-2,3-epoxyundecane(**6b**), with TiCl$_4$ or TiCl$_4$-TiCl(O-*i*-Pr)$_4$ (1:1) in CH$_2$Cl$_2$ exclusively gave a tertiary chloride (**10b**), and the reaction using TiCl(O-*i*-Pr)$_3$ gave an 18:82 mixture of **9b** and **10b** (entry 7). When DMF was used as a polar solvent for this TiCl$_4$- or TiCl(O-*i*-Pr)$_3$-mediated reaction, the formation of the C-1 attack product (**9b**)[18] was somewhat improved in a ratio of **9b**:**10b**=1.1:1 (entries 5 and 8). The C-1 attack of the chlorine anion may partly be prevented in terms of the steric hindrance. Treatment of the trisubstituted epoxide (**6d**) derived from geraniol by using TiCl$_4$ in CH$_2$Cl$_2$ gave chlorohydrin (**10d**) exclusively, and that by using TiCl(O-*i*-Pr)$_3$ in DMF gave **9d** and **10d** in a ratio of 63:37. The reaction of limonene oxide (**6c**), which is 1:1 mixture of *cis* and *trans* isomers, with TiCl(O-*i*-Pr)$_3$ in DMF yielded a mixture of chlorohydrins (**9c** and **10c**) in a ratio of 1:1. This result would strongly depend on a stereochemical reason, in which the *axial* opening of the epoxy-ring is predominant. Treatment of **6c** with TiCl$_4$ in CH$_2$Cl$_2$ did not give any chlorohydrins but a complex mixture, presumably because of participation of the remaining double bond, that would have come from the reaction between the epoxy group and the isopropenyl group.[19]

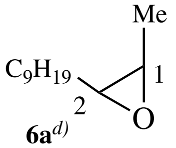
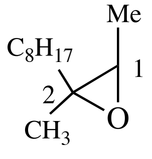
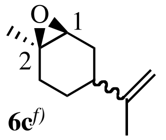
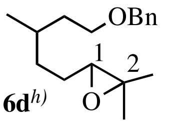
All compounds gave satisfactory spectral data (IR, MS, HRMS, ^{1}H-NMR and ^{13}C-NMR). Especially, the structural elucidation of these chlorohydrins was confirmed by means of ^{1}H-NMR and ^{13}C-NMR analysis. The multiplicity of the hydroxyl proton signals, coupled with the protons on the α-carbon of the hydroxyl group, elucidate the primary, secondary or tertiary alcohol moiety. For example, the hydroxyl proton of **7b** showed a singlet signal at δ 1.86, and that of **8b** showed a triplet signal at δ 1.99. In the ^{1}H-NMR spectra of the chlorohydrins having a methyl group at the C-X (X=Cl or OH) (**7b**,**d**, **8b**,**d**, **9a**,**b**,**c**,**d** and **10a**,**b**,**c**,**d**), the methyl groups of C$\underline{H}_3$-C-Cl are observed in a lower field than those of C$\underline{H}_3$-C-OH. For example, **9b** shows singlet a signal of $\underline{CH}_3$-C-OH at δ 1.25 and a doublet signal of $\underline{CH}_3$-CH-Cl at δ 1.54, and **10b** shows a singlet signal of $\underline{CH}_3$-C-Cl at δ 1.54 and a doublet signal of $\underline{CH}_3$-CH-OH at δ 1.25.

The regioselectivity of the cleavage of the epoxides can thus be summarized as follows. A chlorine atom attacks at the more substituted carbon of the epoxides (C-2 attack) with the strongly acidic TiCl$_4$, but attacks at the less substituted carbon (C-1 attack) with less acidic TiCl(O-*i*-Pr)$_3$ in CH$_2$Cl$_2$. In a polar solvent such as DMF, a chlorine atom attacks at the less substituted carbon in a regioselective manner.

Table 2. Cleavage of Internal Epoxides **(6a-d)**[a]



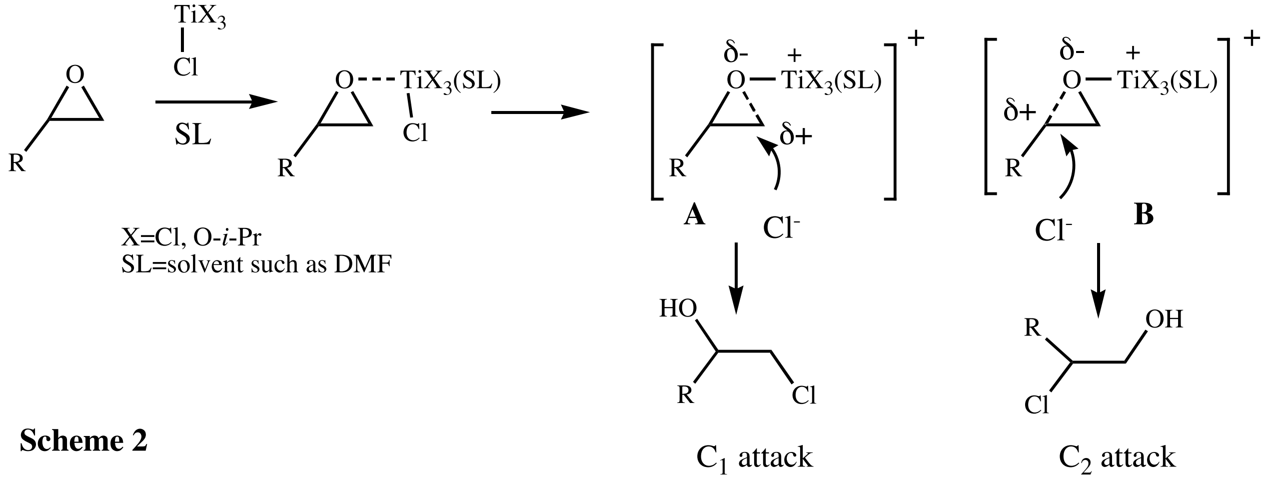
6 **9** C_1 attack **10** C_2 attack **11**[b] **12**[b]

Entry	Epoxide	Reagent (equiv) and Conditions	Yield[c] (%) **9**	**10**		Ratio C_1 / C_2
1	 **6a**[d]	$TiCl_4$(1.2) / CH_2Cl_2 / -78°C/ 0.3h	40.0	21.0		66 : 34
2		$TiCl_2(O\textit{i}\text{-}Pr)_2$(1.2) / CH_2Cl_2 / -60 to -30°C/ 2.1h	37.6	36.7		51 : 49
3		$TiCl(O\textit{i}\text{-}Pr)_3$(1.2) / DMF / 0°C/ 37h	30.1	28.2		52 : 48
4	 **6b**[e]	$TiCl_4$(1.2) / CH_2Cl_2 / -78°C/ 0.3h	0	67.3	**11**: 9.4	0 : 100
5		$TiCl_4$(1.2) / DMF / -78 to 0°C/ 1.4h	18.2	16.0		53 : 47
6		$TiCl_2(O\textit{i}\text{-}Pr)_2$(1.2) / CH_2Cl_2 / -72 to -60°C/ 0.3h	0	57.0	**11**: 2.2	0 : 100
7		$TiCl(O\textit{i}\text{-}Pr)_3$(1.2) / CH_2Cl_2 / -78 to -62°C/ 2.8h	4.8	21.7	**12**: 6.6	18 : 82
8		$TiCl(O\textit{i}\text{-}Pr)_3$(1.2) / DMF / 0 to rt / 42.4h	43.2	29.9		59 : 41
9	 **6c**[f]	$TiCl_4$(1.2) / CH_2Cl_2 / -78°C/ 0.3h	complex mixture			
10		$TiCl(O\textit{i}\text{-}Pr)_3$(1.2) / DMF / 0 to rt / 29.1h	almost quant. as a mixture			1 : 1[g]
11	 **6d**[h]	$TiCl_4$(1.2) / CH_2Cl_2 / -78°C/ 0.2h	0	77.2		0 : 100
12		$TiCl(O\textit{i}\text{-}Pr)_3$(1.2) / DMF / 0 to rt / 18.0h	41.8	24.2		63 : 37

a) The C-1 and the C-2 respectively represent here the less substituted and the more substituted carbon atoms of both the epoxides and the chlorohydrins as a matter of convenience. *b)* This compound should arise from the C-2 opening of the epoxide. *c)* Isolated yield. *d)* A mixture of the *cis* and *trans* (8:1) isomers. *e)* A mixture of the *E* and *Z* (1:1) isomers. *f)* A mixture of the *cis* and *trans* (1:1) isomers. *g)* By ^{1}H-NMR analysis. *h)* A mixture of the diastereomers.

Mechanisms Regiochemical models for cleaving epoxides by various metal halides have been proposed by Eisch *et al.*[11] They rationalized the regioselectivity depending on the nature of the Lewis acids in terms of the competition between the model transition states **A** and **B** in Scheme 2.

Our results of the cleavage of the epoxides by using the $TiCl_4$ or $TiCl_4$-Ti(O-*i*-Pr)$_4$ system in CH_2Cl_2 or DMF also can be rationalized by these models. The strong Lewis acid $TiCl_4$ in CH_2Cl_2 should foster the electrophilic opening of the epoxy ring through an *SN* 1-like mechanism *via* the more stable carbenium ion (**B**), and then the chlorine atom attacks at the more substituted C-2 carbon. The chlorine anion attacks at the less substituted C-1 carbon of the epoxy ring through transition model **A**, an *SN* 2-like mechanism, when weaker Lewis acid, $TiCl(O\text{-}i\text{-}Pr)_3$ in DMF, was used. Even if the reaction of the 2,2-disubstituted epoxides or styrene oxide, in which the transition state C-1 carbenium ion should be strongly stabilized by aryl or alkyl groups, the less substituted chlorides were preferentially obtained by using $TiCl(O\text{-}i\text{-}Pr)_3$ in DMF. The solvent effect was not clear, but *N*,*N*-dimethylformamide may coordinate the titanium(IV) reagents to decrease the acidity of the reagents. In the case of substituted cyclohexene oxide, the selectivity of the epoxy ring cleavage would depend not only on the mechanism (*S*N 1 or *S*N 2) but also stereochemical demand.



X=Cl, O-*i*-Pr
SL=solvent such as DMF

Scheme 2

Thus our epoxy ring-opening method provides one of the efficient tools for the regioselective preparation of chlorohydrins, depending on the selection of Lewis acids, $TiCl_4$ or $TiCl(O\text{-}i\text{-}Pr)_3$, and the polarity of the solvents.

General procedure for the ring-opening reaction. Titanium(IV) chloride ($TiCl_4$) or triisopropoxy titanium chloride ($TiCl(O\text{-}i\text{-}Pr)_3$) (1.2 mmol) is added to a chilled solution of the epoxide (1.0 mmol) in anhydrous CH_2Cl_2 or DMF (10 mL). This solution is stirred at the temperature shown in Tables 1 and 2. The reaction is then monitored by TLC until the starting material disappears on the plate. After addition of aqueous $NaHCO_3$, the organic phase is separated. The aqueous phase is extracted with Et_2O twice. The combined organic layers are dried with $MgSO_4$, and then concentrated *in vacuo*. The resulting products are isolated by flush column chromatography using EtOAc-hexane.

ACKNOWLEDGEMENTS

The authors are grateful to Mrs. F. Hasegawa of this faculty for her MS spectral measurements.

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17. P. Bovicelli, E. Mincione, and G. Ortaggi, *Tetrahedron Lett.*, 1991, **32**, 3719. They reported that treatment of carvone oxide (**5d**) with $ClBH_2$-Me_2S gave a 77% yield of **7d** and **8d** in a 96:4 ratio.
18. The C-1 and the C-2 respectively represent here the less substituted and the more substituted carbon atoms of both the epoxides and the chlorohydrins as a matter of convenience.
19. Epoxy ring-opening of limonene oxide (**6c**) with $TiCl_4$-DBU gave a 46% yield of **10c**,[12] and with $ClBH_2$-Me_2S gave a 68% yield of **11c** and **10c** in a 64:34 ratio.[17]