Diastereoselective Titanocene-Catalyzed Oxidative Cyclization of Bishomoallylic Alcohols

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Abstract: Bishomoallylic alcohols are converted in good yields and diastereoselectivity into tetrahydrofuranols and tetrahydropyranols by Cp_2TiCl_2/*t*-butyl hydroperoxide/activated 4Å molecular sieves system.

Key words: epoxidation, cyclization, metallocenes, tetrahydrofuranols, tetrahydropyranols

Metallocenes are commonly used catalysts for C-C bond forming reactions[1], while only few examples have been reported in oxidation processes[2] and in particular a very low conversion to products has been showed when employed in the epoxidation of unfunctionalised alkenes.

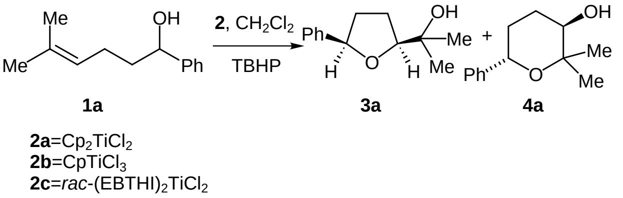
Very recently we have disclosed a synthetically useful catalytic activity of metallocenes in the epoxidation of allylic alcohols[3] with *t*-butyl hydroperoxide (TBHP) and in the asymmetric sulfoxidation of prochiral sulfides using (*R*)-BINOL as chiral ligand[4].

Prompted by these results we decided to investigate the reactivity of bishomoallylic alcohols in the presence of Cp_nTiX_m/TBHP systems. This research was devoted to the achievement of a new and efficient procedure for the oxidative cyclization of bishomoallylic alcohols to tetrahydrofuranols and tetrahydropyranols.

Rhenium[5], chromium[6], thallium[7], vanadium[8] complexes have been employed in some oxidative cyclizations of bishomoallylic alcohols, affording the cyclic ethers with the regio and diastereoselectivity dependent on the pattern of substitution of the alkenols and the oxidation system. As these oxacyclic compounds are widely found in many natural products, such as polyether antibiotics[9] and are valuable building blocks in synthetic organic chemistry[10] new methods for their synthesis are in demand.

Initially, we investigated the oxidation of model compound 1-phenylhexenol **1a** with catalytic amounts of some commercial titanocene chlorides and TBHP as oxygen donor.

When the reaction was carried out at room temperature (entry 1) in catalytic mode (5%mol of Cp_2TiCl_2) compound **1a** was poorly converted to the tetrahydrofuranol **3a** and the tetrahydropyranol **4a**. The main product **3a** was isolated in high *cis*/*trans* ratio, **4a** showed an appreciable diastereoselectivity[11], while no trace of epoxide was detected. When refluxing the reaction mixture (entry 2) the conversion was greatly improved and the *cis*/*trans* ratios were maintained. Catalyst **2b** afforded similar results. The sterically hindered titanocene **2c** [(±)Ethylen(4,5,6,7-tetrahydro-1-indenyl)dichlorotitanium(IV)], more sensitive to moisture, was employed in the presence of activated 4Å molecular sieves.



Scheme 1

Table 1 Oxidation of **1a** by **2**/TBHP Systems[a]

Entry	Catalyst	T(°C)	t(h)	Yield[c] **3a**(%)	*cis*/*trans*[d] **3a**	Yield[c] **4a**(%)	*cis*/*trans*[d] **4a**
1	**2a**	r.t.	26	27	92/8	8	26/74
2	"	40	22	47	92/8	21	24/76
3	**2b**	"	"	59	91/9	16	24/76
4[b]	**2c**	"	"	32	94/6	22	30/70
5[b]	-	"	24	-	-	-	-
6[b]	**2a**	"	6	66	93/7	25	27/73

[a]Molar ratios employed: **1a**/**2**/TBHP/ 1/0.05/1.5. [b]In this reaction activated 4Å molecular sieves were added. [c]Isolated yields. [d]The diastereoisomeric ratios were determined by ^1H NMR analysis.

It was less reactive compared to **2a,b** and the diastereoselectivity was marginally inverted.

The blank experiment (entry 5) confirmed that molecular sieves do not catalyze the oxidative cyclization but their presence is beneficial (entry 6) as the reaction time was remarkedly reduced (compare with entry 2) and almost all the starting material consumed.

The different steric hindrance and electronic properties of the titanocene chlorides had a limited influence on the outcome of the reaction. Comparable yields and diastereoselectivities were observed with **2a** and **2b**. However, in view of its cheapness we felt it appropiate to carry on our investigation using **2a** in the presence of activated molecular sieves.

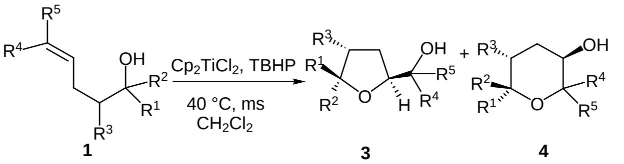
A screening of different solvents (Table 2) showed a decrease of the conversion to the ethers and the diastereoselectivity of tetrahydrofuranol **3a** in apolar media (*n*-hexane, toluene). Halogenated solvents and in particular CH_2Cl_2 seemed to be the most suitable to perform the transformation[12].

Table 2 Effect of Solvent on the Oxidative Cyclization of **1a**[a]

Entry	Solvent	T(°C)	t(h)	Yield[b] **3a**(%)	*cis*/*trans*[c] **3a**	Yield[b] **4a**(%)	*cis*/*trans*[c] **4a**
1	*n*-hexane	60	6	45	89/11	19	24/76
2	toluene	"	"	63	"	26	24/76
3	$CHCl_3$	40	"	66	"	26	28/72
4	CH_2Cl_2	"	"	66	93/7	25	27/73

[a]Molar ratios employed: **1a**/**2a**/TBHP/ 1/0.05/1.5 and activated 4Å molecular sieves (400mg). [b]See note c in Table 1. [c]See note d in Table 1.

In order to evaluate the range of application of the system Cp_2TiCl_2/TBHP/4Å ms in the oxidative cyclization, some bishomoallylic alcohols[13] were submitted to the conditions reported in Scheme 2.



Scheme 2

Table 3 Cp_2TiCl_2/TBHP/4Å Molecular Sieves Catalyzed Oxidative Cyclization of Alcohols **1**[a]

Entry	R^1	R^2	R^3	R^4	R^5	t(h)	Yield **3a**(%)[d]	*c*/*t* **3a**[e]	Yield **4a**(%)[d]	*c*/*t* **4a**[e]
1	Ph	H	H	Me	Me	6	66	93/7	25	27/73
2[b]	Me	"	"	"	"	7	58	80/20	32	31/69
3		"	"	"	"	3	63	86/14	15	17/83
4[c]	"	"	"	"	"	22	57	82/18	15	21/79
5	H	H	Ph	"	"	13	69	19/81	15	<2/98
6	H	H	H	H	H	24	-	-	-	-
7	Me		"	Me	Me	46	55	53/47	15	50/50

[a]See note a in Table 2. [b]Conversion estimated by ^1H NMR. [c]1% mol of **2a** was used. [d]See note c in Table 1.[e]See note d in Table 1.

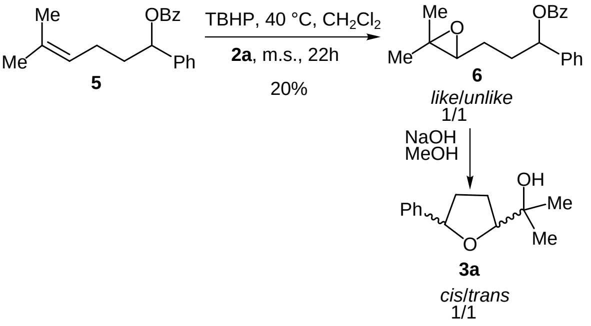
The level of diastereoselectivity observed for tetrahydrofuranols **3** is dependent to a certain extent on the nature of the substituent R^1 proximal to the hydroxy group (first three entries). When R^1 = cyclohexyl good *cis*/*trans* ratios were achieved for both the regioisomers. The reaction can be carried out even with quite low catalyst loading (1%mol) furnishing after a longer reaction time comparable conversion and stereoselectivities (entry 4). Interestingly, when (R^3 = Ph) (entry 5) the *trans* tetrahydropyranol **4** was exclusively obtained. The electron-poor terminal alkenol in entry 6 did not react at all under the conditions applied. It is worth pointing out that linalool (entry 7) was regioselectively converted only to the cyclic ethers without traces of the allylic epoxidation product.

These findings indicate that the selectivity in the epoxidation is dominated by the electron density of the double bond.

From a mechanistic point of view, it seems reasonable a reaction pathway that involves chloride/*t*-butyl hydroperoxide ligand exchange leading to the formation of a titanocene *t*-butylperoxy complex as postulated by Halterman in a previous report[14].

The stereochemical outcome of the overall process can be explain through the coordination of the unsaturated alcohol to the metal centre, followed by oxygen transfer to give an epoxyalcohol intermediate in a diastereoselective way, which then undergoes fast cyclization to five- and six-membered products.

A confirmation to this proposition has been supported by the following experiment.



Scheme 3

The model compound **1a** was *O*-benzoylated and then submitted to the same reaction conditions. After 22h a 1/1 mixture of *like* and *unlike* epoxides **6** were isolated in 20% yield. This low conversion was not surprising because titanocene chlorides are known to be poor catalysts for the epoxidation of unfunctionalized olefins[2] and this result clearly showed the decisive role of coordination in favouring the epoxidation of the double bond. Then, the hydrolysis of the epoxyester **6** yielded tetrahydrofuranol **3a** in 1/1 *cis*/*trans* ratio pointing out the complete different regio and stereochemical outcome of the reaction.

In conclusion, we have disclosed an interesting and preparatively useful catalytic activity of titanocenes. The system Cp_2TiCl_2/TBHP/4Å molecular sieves can be a mild and selective alternative to the literature precedents for the oxidative cyclization of bishomoallylic alcohols having an electron rich double-bond. In particular, as regards rhenium oxide reagents we wish to point out that Re_2O_7/H_5IO_6[5a,b] system and $ReO_3(OCOCF_3)$[5c] are characterized by significant acidity so that a base such as pyridine or 2,6-lutidine is necessary in order to prevent the formation of acid catalyzed (non oxidative) cyclohydration by-products.

Then, Re_2O_7 is economically less convenient than Cp_2TiCl_2 and in general has to be used in more than stoichiometric amounts. Furthermore, methyl trioxorhenium/H_2O_2 system[5f] has proven to be particular efficient for the conversion of suitable hydroxy alkenes into tetrahydrofuran derivatives; however, no diastereoselectivity was found in the formation of *cis*/*trans* isomers.

Acknowledgement

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(11) Compound **1a** is oxidatively cyclized to **3a** and **4a** by the system $VO(acac)_2$/TBHP[8c] (10%mol) in CH_2Cl_2 at r.t. furnishing **4a** within 48h in 19% yield and without diastereoselection.

(12) Coordinating and polar solvents such as: THF, DMF, CH_3CN, diethyl ether were not investigated. We had previously observed in the epoxidation of allylic alcohols using titanocenes/TBHP system[3] (unpublished results) that these solvents led to a small conversion to epoxyalcohols (in some cases they prevented the reaction to occur). A strong coordination of the solvent to the catalytic complex might be responsible of the suppressed reactivity.

(13) **Typical experimental procedure:** To a solution of dry CH_2Cl_2 under argon atmosphere at r.t. are sequentially added: **2** (5%mol), activated 4Å ms (400mg) and the bishomoallylic alcohol **1** (1 mmol). After stirring for 10 min, TBHP (1.5 mmol, 5.5 M solution in decane) is added and the reaction mixture refluxed. The reaction was monitored by TLC. At the end of the reaction the solvent is concentrated under vacuum and the crude mixture is purified by silica gel column chromatography by elution with light petroleum/diethyl ether mixtures. The spectroscopic data of compounds **3** and **4** matched with ones reported in the literature: Michael, J. P.; Nkwelo, M. M. *Tetrahedron* **1990**, *46*, 2549; Mischitz, M.; Hackinger, A.; Francesconi, I.; Faber, K. *Tetrahedron* **1994**, *50*, 8661; Méou, A.; Bouanah, A.; Archelas, A.; Zhang, X. M.; Guglielmetti, R.; Furstoss, R. *Synthesis* **1990**, 752; Méou, A.; Bouanah, A.; Archelas, A.; Zhang, X. M.; Guglielmetti, R.; Furstoss, R. *Synthesis* **1990**, 681; ref. 8c and 7.

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