Pergamon

Tetrahedron Letters, Vol. 38, No. 21, pp. 3785-3788, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00735-1

1,2 Asymmetric Induction in the $TiCl_4$ Mediated Alkylation of α-Methyl-β-Silyloxy Ketones with Grignard Reagents.

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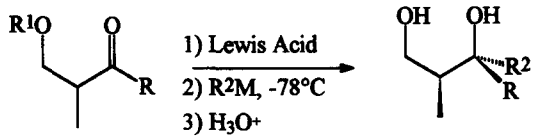
Abstract :Transmetallation of an α-methyl–β-silyloxy ketone with $TiCl_4$ in toluene affords a cyclic chelation complex which undergoes highly stereoselective alkylation from Grignard reagents at the less hindered side. © 1997 Published by Elsevier Science Ltd.

The control on the attack direction of organometallic species to a carbonyl function exerted by a proximal hydroxyl group has been widely exploited in asymmetric organic synthesis[1]. In particular, many efficient protocols have been reported for the synthesis of the important 1,3-diol unit with *syn* or *anti* 1,3-relationship *via* diastereoselective reduction[2] or alkylation[3] of a β–chiral β-hydroxyketone. On the contrary, at present no general solution to the problem of the 1,2-induction starting from β-hydroxy carbonyl compounds having a stereocenter in α position has been proposed. In fact as far as the alkylation process is concerned the reports are restricted to the stereoselective methylation or allylation of α-methyl-β-alkoxy aldehydes with organocuprates[4] or allyltrimethylsilane[5] in the presence of $TiCl_4$ respectively.

On the other hand, alkylation of protected or unprotected α-alkyl substituted β-hydroxyketones like **1** with common organometallic species, such as RLi and $RMgX$[6], gives the corresponding 1,3-diols with poor selectivity and in moderate to good yields (see Table 1, entries 1,2). Moreover we found that alkyl cerium reagents are able to alkylate[7] these compounds in almost quantitative yields (see Table 1, entries 3, 4). However in spite of their claimed chelation ability[8] the diastereoselection doesn't exceed 50% of d.e.. Very likely this is due to some difficulties in organizing the formation of a stable and rigid chelation complex[9] associated with an efficient and simple alkylation procedure. For example the $TiCl_4$ mediated reduction of protected or/and unprotected α-alkyl substituted β-hydroxyketones like system **1** with metallic hydrides has been reported to proceed with high *anti*-diastereoselectivity only when the framework R bonded to the carbonyl function is a phenyl or a *t*-butyl group[10]. Moreover we found that the alkylation of **1a,b** with Grignard reagents in the presence of $TiCl_4$ gives the expected diols **2a,b** in poor yields and with moderate to good diastereoselectivity. In addition an appreciable amount of starting material (20-60%) was recovered, even using a large excess of Grignard reagent and prolonged reaction times (see Table 1, entries 5-8).

Conversely a remarkable improvement was achieved when a rigid chelation complex[11] was formed through transmetallation of *t*-butyl dimethyl silyloxy derivatives **1c-e** with $TiCl_4$ in toluene. In fact the addition of a Grignard reagent in THF[12] to this complex at -78°C affords the corresponding diols **2a,f** in high yields and in excellent diastereomeric purity, independently from the nature of both the R group bonded to the carbonyl and the Grignard reagent alkyl framework. Moreover this procedure works well with both stabilized and not stabilized carbanions.

Table 1 : Experimental conditions, yields and d.e. in diastereoselective synthesis of 1,3-diols.



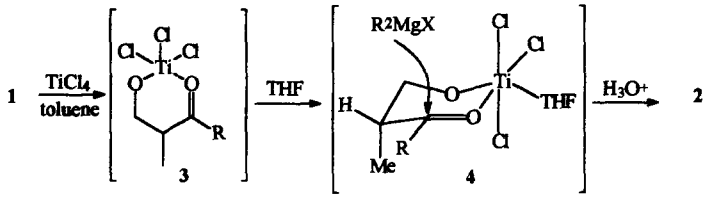
1 **2**

entry	starting material	R	R1	LewisAcid	R2M	product[a]	yield (%)[b]	de (%)[c]
1	**1a**	Me	H	/	EtMgBr	**2a**	34	50
2	**1a**	Me	H	/	EtLi	**2a**	50	2
3	**1a**	Me	H	$CeCl_3$	EtMgBr	**2a**	76	4
4	**1a**	Me	H	/	$EtCeCl_2$	**2a**	98	44
5	**1a**	Me	H	$TiCl_4$	EtMgBr	**2a**	40	60
6	**1a**	Me	H	$TiCl_4$	PhMgBr	**2b**	64	90
7	**1a**	Me	H	$TiCl_4$	PhC≡CMgBr	**2c**	60	40
8	**1b**	Et	H	$TiCl_4$	MeMgBr	**2d**	48	86
9	**1c**	Me	$^tBuMe_2Si$	$TiCl_4$	EtMgBr	**2a**	70	82
10	**1c**	Me	$^tBuMe_2Si$	$TiCl_4$	PhMgBr	**2b**	62	92
11	**1c**	Me	$^tBuMe_2Si$	$TiCl_4$	PhC≡CMgBr	**2c**	89	75
12	**1c**	Me	$^tBuMe_2Si$	$TiCl_4$	$PhCH_2MgBr$	**2e**	98	80
13	**1d**	Et	$^tBuMe_2Si$	$TiCl_4$	MeMgBr	**2d**	95	82
14	**1e**	Ph	$^tBuMe_2Si$	$TiCl_4$	MeMgBr	**2f**	92	96

a) **2a**, **2b**, **2d** and **2f** are known products, configuration of **2c** and **2e** was assigned by analogy with ^1H and ^{13}C NMR of known products[6]; b) yields refer to the diastereomeric mixture after chromatographic purification; c) calculated from ^1H NMR data ; d) Appreciable amount of starting material was also recovered (20-60%).

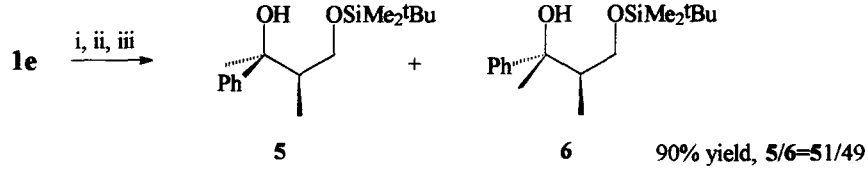
The present method shows high flexibility: it allows to prepare with high diastereoselective purity both diastereoisomers of a given diol simply exchanging the R^2 group in the Grignard reagent with the alkyl group R in the β-silyloxy ketone. For example the (R*, S*)-2-methyl-3-phenyl-butan-1,3-diol[13] **2b** is obtained from **1c** and phenyl Grignard in 80% yield with d.e.=90%. The (R*, R*)-diastereoisomer **2f** is obtained from **1e** and

methyl Grignard in 92% yield and with d.e.%=98. In an analogous manner (R*, S*)- and (R*, R*)-2,3-dimethyl-pentan-1,3-diols **2a** and **2d** can be prepared from **1c** with EtMgBr and **1d** with MeMgBr in 75% and 95% yields respectively, both with d.e.%=82.



Scheme 1 Selectivity of the nucleophilic attack

It's well known that Ti(IV) Lewis acids show a strong preference for a six-coordinate octahedral arrangement[14]. Very likely in our system the five-coordinated complex **3** is rapidly transformed in the six-coordinated **4** by action of THF (Scheme 1). The attack of R^2MgX to the carbonyl function occurs from the less hindered side, i.e. opposite to the α-methyl group. We could assume that **4** is a very stable and rigid complex because it survives in the presence of a strong coordinating agent such as THF. It's a relevant feature, from a practical point of view, since it allows the use of common and commercial metallorganic species as Grignard reagents in THF. The rate of transmetallation is strongly dependent on the nature of the silyloxy ketone **1**: for **1c,d** the reaction goes to completion in few minutes at 0°C ; the same reaction for **1e** requires longer reaction time and higher temperature (1h at 20°C)[15]. If the reaction of **1e** with CH_3MgX is carried out adding $TiCl_4$ at -78°C and, after 30 min, the Grignard reagent at the same temperature, the corresponding diols are isolated as mono silyl derivatives with a very poor diastereomeric purity (d.e.=2%),(Scheme 2).



Scheme 2 *Reagents and conditions*: i, $TiCl_4$ in toluene, -78°C ; ii, CH_3MgX, THF, -78°C ; iii, H_3O^+

In conclusion, a new approach to the synthesis of 1,3-diols with stereodefined 1,2-relationship is given. Studies are in progress to extend this protocol to more complex systems.

Acknowledgments :This work has been carried out in the frame of the "Progetto di Finanziamento Triennale, Ateneo di Bologna".

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12. *Typical procedure*: A toluene solution of $TiCl_4$ (2.6 mmol, 1.3 eq) was added to a solution of the α-methyl-β-silyloxy ketone (2 mmol) in dry toluene, at 0°C. The reaction was allowed to reach room temperature, and stirred until transmetallation was complete, (10-15 min. for **1c,d** and 1h for **1e**). The reaction was then cooled at -78°C and the appropriated Grignard reagent (6 mmol, 3 eq) was added dropwise. After stirring 1h at -78°C, the reaction was left to reach room temperature and then quenched with diluted aqueous HCl. The usual work-up gave the crude product, that was purified by flash cromatography on silica-gel.

13. Descriptors R*, S* indicate that diastereomeric compounds are obtained as racemates. We prefer this terminology to avoid the ambiguities that could arise from the *sin-anti* or erithro-threo ones.

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15. Strong Si-Cl (92Kcal mol^{-1})[16] and Ti-O (115Kcal mol^{-1})[17] bonds are generated in the formation of **3**, but at the expense of comparably strong Si-O (108Kcal mol^{-1})[16] and Ti-Cl (103Kcal mol^{-1})[17] bonds. However, very likely the transmetallation process is completely shifted to **3** owing to the formation of a very stable chelation complex.

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(*Received in UK* 19 *March* 1997; *revised* 14 *April* 1997; *accepted* 18 *April* 1997)