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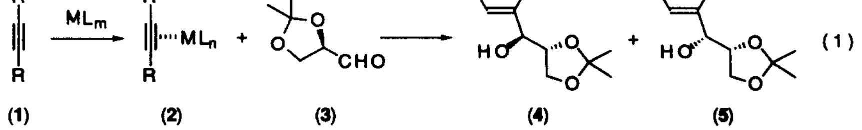
Diastereoselective Addition of (η^2-Alkyne)Ti(O-*i*-Pr)$_2$ Complexes to 2,3-*O*-Isopropylideneglyceraldehyde

Koki Yamashita, Hirokazu Urabe, and Fumie Sato*

Department of Biomolecular Engineering, Tokyo Institute of Technology,
4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226, Japan

Abstract: The title alkyne-titanium complexes, prepared from propargyl ethers, Ti(O-*i*-Pr)$_4$, and *i*-PrMgCl, reacted with 2,3-*O*-isopropylideneglyceraldehyde in good to excellent diastereoselectivities of up to 94:6 to afford the *anti*-adducts, which are useful precursor for the preparation of optically active polyhydroxy compounds. © 1997 Elsevier Science Ltd.

Metal-alkyne complexes **2** have been accepted as a synthetically useful equivalent of vicinal vinylic dianion.[1] Thus, their reaction with an aldehyde followed by trap of the resulting vinylmetal compound with a second electrophile provided a versatile method for the synthesis of a variety of allyl alcohols. Recently, we have reported that new titanium-alkyne complexes **2** (ML$_n$ = Ti(O-*i*-Pr)$_2$), readily prepared from alkynes, Ti(O-*i*-Pr)$_4$, and 2 equiv of *i*-PrMgCl, react with aldehydes in excellent yields to give allyl alcohols.[2] We were interested in asymmetric addition of the titanium complex having chiral alkoxide ligands to carbonyl compounds, which is an intriguing method to prepare optically active allyl alcohols. However, this attempt has so far met with only moderate success at our hands.[2b] Accordingly, we turned our attention to an alternative way, that is, chirality induction via their reaction with a chiral aldehyde such as 2,3-*O*-isopropylideneglyceraldehyde (**3**), which is one of the most widely used chiral aldehydes in the reaction with organometallics due to its versatile array of functional groups as well as its easy availability in both chiral forms.[3,4] In relation to this study, the reactions of alkyne-zirconocene or -tantalum complexes (**2**, ML$_n$ = ZrCp$_2$ or TaL$_n$) with some chiral aldehydes have been recently reported.[5] However, the diastereoselectivity observed for **3** did not fall within a very high range. For example, the reaction of **2** (ML$_n$ = ZrCp$_2$) with **3** unfortunately afforded equal amounts of the two diastereomeric adducts **4** and **5** (eq 1, R = C$_3$H$_7$).

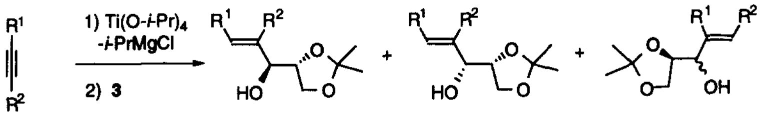


(1)

(**1**) (**2**) (**3**) (**4**) (**5**)

The reaction of the titanium complex generated from 4-octyne or 1-(trimethylsilyl)-1-octyne with (*R*)-**3** was first examined (Table 1). As can be seen from entries 1 and 2, the two expected diastereoisomers were formed in a ratio of 75:25 or 72:28, in addition to the regioisomer in the latter reaction. Thus, the observed diastereoselectivities are considerably improved as compared to the reported value for the $Cp_2Zr(\eta^2$-alkyne) complex and **3** mentioned above. As titanium-propargyl ether complexes, $(\eta^2\text{-RC}\equiv\text{CCH}_2\text{OR'})\text{Ti(O-}i\text{-Pr)}_2$, were known to react with aldehydes in a regioselective manner to give allylic alcohols having an alkoxyalkyl group, thus providing an efficient method to synthesize diol compounds that are otherwise of difficult access,[2c] we then focused our attention on these alkyne complexes. Entries 3-8 in Table 1[6] show that the diastereoselectivities (**4/5**) are generally good irrespective of the substituents of the acetylenes, among which *tert*-butyldimethylsilyl (TBS) ether of (trimethylsilyl)propargyl alcohol (**1d**) showed the highest ***diastereoselectivity*** as well as ***regioselectivity*** (entry 4). As far as the kind of chiral aldehydes is concerned, **3** is much superior to α-(methoxymethoxy)- and α-(*tert*-butyldimethysiloxy)propanal in the reaction with **1d**, the diastereoselectivities decreasing as follows: 94:6 → 78:22 → 65:35. Even in a few cases where the diastereo- and regioselectivities are not excellent, the major diastereoisomer **4** was successfully separated by flash column chromatography on silica gel from the other minor (regio- and diastereo-)isomers (entries 5-7). Particularly, the product **4d**, obtained in a highly regio- and stereoselective manner, would be useful for further synthetic elaboration based on the versatile vinylsilane moiety[7] and the four unprotected and suitably protected hydroxy groups that are easily discriminated from each other.

Table 1. Reactions of $(\eta^2$-Alkyne)titanium Complexes with (*R*)-2,3-O-Isopropylideneglyceraldehyde (**3**)[a]

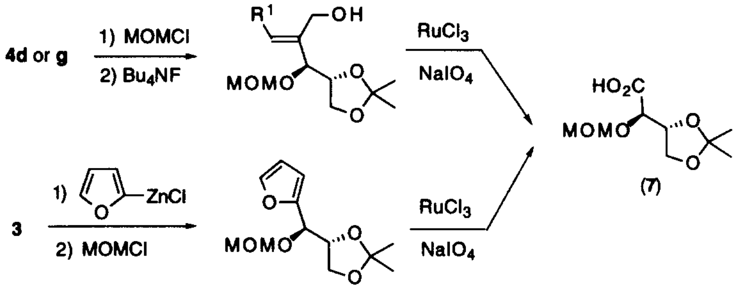


(1) (4) (5) (6)

Entry	1			Regioselectivity[b]	Diastereoselectivity[b]	Isolated yield (%)	
	R1	R2		(4+5)/6	4/5	4+5	4[c]
1	C_3H_7	C_3H_7	a	--	75:25	85	
2	Me_3Si	C_6H_{13}	b	89:11	72:28	71[d]	
3	"	$BnOCH_2$-	c	>98:<2	65:35	52	
4	"	$TBSOCH_2$-	d	>98:<2	94: 6[e]	72	
5	Me_3SiCH_2	"	e	>98:<2	82:18	70	53
6	Ph	"	f	78:22	90:10[e]	68	50
7	C_4H_9	"	g	85:15	80:20	63	48
8	$TBSOCH_2$	"	h	--	76:24	62	

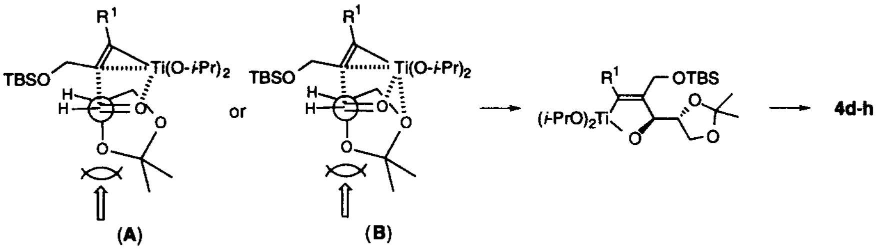
[a] Reactant ratio: $1/\text{Ti(O-}i\text{-Pr)}_4/i\text{-PrMgCl}/3$ = 1.0:1.3: 2.5:2.5. [b] Determined by ^{1}H-NMR analysis of a crude reaction mixture. [c] A pure sample of the major diastereoisomer **4** could be obtained by routine chromatography on silica gel. [d] This yield refers to that of **4+5+6**. [e] GC analysis also confirmed this ratio.

The stereochemistry of the products in these reactions was elucidated in representative cases where the high selectivities were achieved (Scheme 1). Thus, the major isomers **4d** and **g** were oxidatively cleaved to give the carboxylic acid **7**. Its authentic sample was prepared via the *anti*-selective addition of furylzinc to **3**,[8] followed by the same oxidative degradation. These samples of **7** were identical in all respects, indicating that the addition of the acetylene-titanium complex to **3** proceeded preferentially in an *anti* fashion.[9] The other major products in Table 1 are temporarily assigned to have the same configuration.



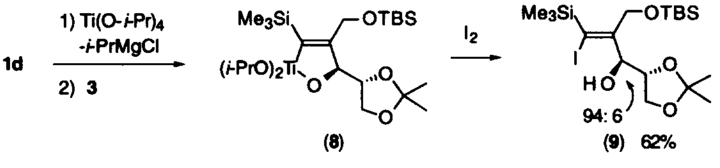
Scheme 1

Interpretation of the stereochemical outcome of the nucleophilic addition to **3** is usually not a straightforward discussion owing to the presence of two α- and β-oxygen atoms in the cyclic structure.[4] In fact, some organotitanium reagents can show both *syn*- or *anti*-preferred addition to **3**, depending upon their organic groups.[10] In the present case, a Felkin-Anh model (**A**)[10,11] or the chelation model (**B**) involving the β-oxygen atom[10] should account for the *anti* selectivity that seems to be enhanced by the sterically demanding substituent R^1 (Me_3Si (**4d**) > Ph (**4f**) > Me_3SiCH_2 (**4e**) > C_4H_9 (**4g**) > $TBSOCH_2$ (**4h**)) (Scheme 2).



Scheme 2

In addition to its simple hydrolysis, the intermediate alkenyltitanium species **8** may be utilized for the reaction with a second electrophile, which was exemplified by the iodinolysis to give **9** without any detectable change in the diastereoselectivity as shown in eq 2. The products obtained herein should be useful precursors for the preparation of optically active oxygenated compounds.[12]



(2)

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6. Preparation of **4d** is typical. To a stirred solution of the TBS ether of 3-(trimethylsilyl)-2-propyn-1-ol (**1d**) (0.111 g, 0.46 mmol) and Ti(O-*i*-Pr)$_4$ (0.171 g, 0.60 mmol) in ether (3.5 mL) was added *i*-PrMgCl (1.60 M in ether, 0.72 mL, 1.15 mmol) at -78 °C under argon. The resulting yellow solution was warmed to -50 °C over 1 h, during which period its color turned brown. After stirring at the same temperature for 2 h, (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**3**) (2.28 M in ether, 0.50 mL, 1.15 mmol) was added at -50 °C and the stirring was continued for 2.5 h at -45 °C. Then the reaction mixture was warmed to 0 °C over 30 min and quenched with water (0.5 mL). To the mixture were added NaF (0.5 g) and Celite (0.6 g). After filtration through a short pad of Celite, the filtrate was concentrated to give an oil, which was purified by chromatography on silica gel to give the title compound (124 mg, 72%) as an oil.
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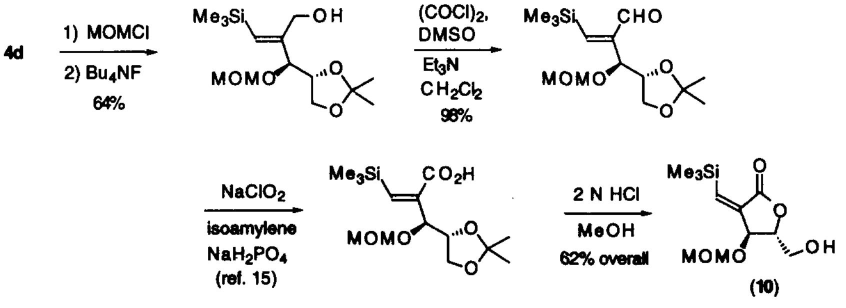
12. A derivatization of **4d** to a functionalized α-alkylidene-γ-butyrolactone **10**, which is a model compound towards the synthesis of litsenolide (ref. 13) and obtusilactone (ref. 14), illustrates such an application.



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