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Synthesis of Chiral Allyltitaniums Having an Amino Group at the C-4 Position and Their Diastereoselective Addition Reaction with Aldehydes

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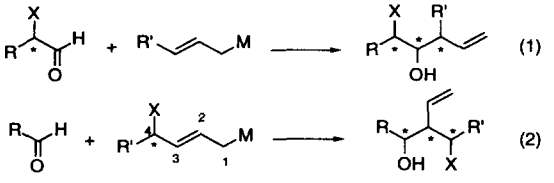
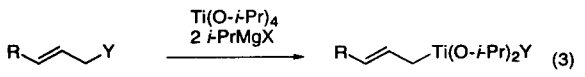
Abstract: *Chiral allyltitaniums having an amino substituent at the C-4 position are prepared from optically active allylic alcohol derivatives 1 and a Ti(O-i-Pr)4/2i-PrMgCl reagent, which, in turn, react with aldehydes regio- and stereoselectively to afford 3-amino-2-vinylalkanols in excellent yields.* © 1997 Elsevier Science Ltd.

Reactions of substituted allylmetals with aldehydes play an important role in stereoselective synthesis since, in one step, plural stereogenic centers can be generated and the resulting homoallyl alcohols can be used for further chemical transformations. Much effort has been paid to applying the reaction for the construction of three consecutive stereogenic centers. In consequence, there have been developed a variety of reactions of allylic metal compounds with chiral aldehydes as shown in eq 1 which proceed highly selectively with respect to the new stereocenters generated in concert with the new C-C bond formation (simple diastereoselectivity) as well as the stereocenter induced by the chiral center in the aldehyde (diastereofacial selectivity).[1] Diastereoselective addition reaction of achiral aldehydes with chiral allylmetals possessing a stereocenter at the C-4 position as shown in eq 2 might afford another attractive methodology. However, investigations so far reported from the standpoint of application of the reaction for acyclic stereocontrol have been limited in regard to both the metal and the allylic moiety,[2] and further research is needed to gain recognition of the reaction as useful methodology like the reaction of eq 1. This restricted research work is presumably due to the difficulty of access to a variety of allylmetals having a heteroatom substituent at C-4, the presence of which seems to be highly desirable for attaining excellent diastereoselectivity and also for further synthetic elaboration of the reaction products.[3]



Recently, we have developed a new method for synthesizing allyltitanium complexes by the reaction of allyl halides or allyl alcohol derivatives with a Ti(O-*i*-Pr)4/2*i*-PrMgX reagent (eq. 3).[4] Herein we report the

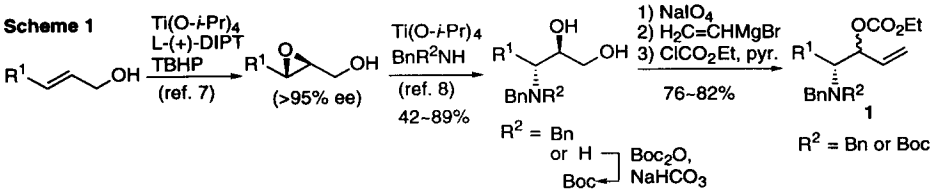


Y = Cl, Br, I, OAc, OCO_2Et, OSO_2Me, $OP(=O)(OEt)_2$, OPh

synthesis of allyltitaniums having an amino group at C-4 from allylic alcohol derivatives **1** containing an α-(1-amino)alkyl group and a Ti(O-*i*-Pr)4/2*i*-PrMgX reagent and their highly selective reaction with an aldehyde.

Optically active substrates **1a~d**[5] were readily prepared starting with primary allylic alcohols according to the conventional reaction sequence shown in Scheme 1. The carbonates **1** thus synthesized were treated with a Ti(O-*i*-Pr)4/2*i*-PrMgX reagent and then with propanal and/or benzaldehyde. The stereoselectivity of the reaction was determined by GC, ^1H NMR and ^{13}C NMR analysis of the crude hydrolysis products, while stereochemistries of the main product(s) were verified by ^1H NMR analysis after derivatization to the corresponding β-lactam and β-lactone by using the conventional reaction sequence.[6] The results are summarized in Table 1.

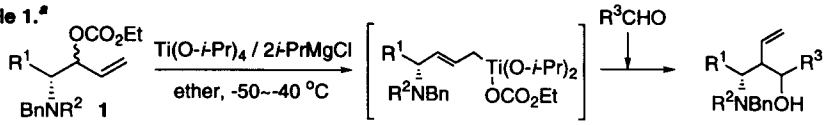
Scheme 1

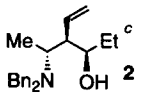
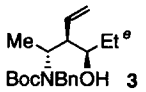
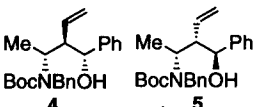
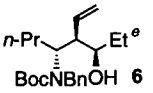
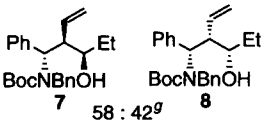


As can be seen from Table 1, allyltitanium compounds having an amino group at C-4 are readily prepared from **1** and a Ti(O-*i*-Pr)4/2*i*-PrMgX reagent and, in turn, they react with an aldehyde to afford the expected γ-addition products in excellent yields. The diastereoselectivity of the reaction depends on whether R^1 in **1** is an alkyl or aryl and whether R^3 in the aldehyde is an alkyl or aryl; however, in the case of another substituent R^2 on the N-atom the effect is not serious. Allyltitanium complexes derived from **1** where R^1 is *an alkyl* such as **1a**, **1b**, and **1c** react with *an alkyl aldehyde* to afford one product with the structure shown in Table 1 highly predominantly among four possible diastereomers (entries 1, 2 and 4). The total stereoselectivity (simple diastereoselectivity and diastereofacial selectivity) of more than 90% attained here is higher than the simple diastereoselectivity observed in the reaction of crotyltitanium and propanal which provides two possible diastereomers in a ratio of 75:25.[4] In the case of either starting with **1** where R^1 is an aryl group (entry 5) or using an aryl aldehyde (entry 3), the diastereofacial selectivity induced by the stereogenic center at C-4 was very low. In these cases, although the stereochemistry with regard to the new C-C bond forming reaction was highly controlled, to our surprise, the sense of this simple diastereoselectivity was different between the reactions of entries 3 and 5.

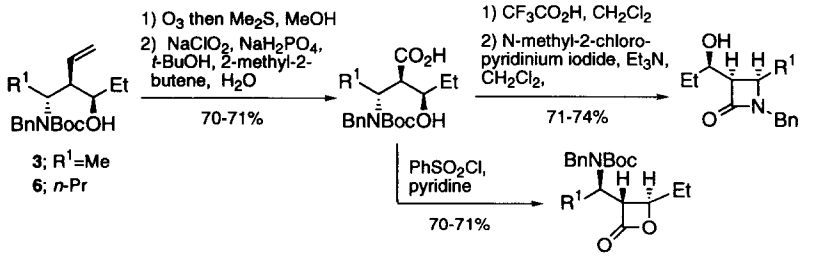
The excellent stereoselectivity attained in the reaction of allylic titanium complexes derived from **1a**, **1b**, or **1c** with an alkyl aldehyde can be explained by assuming that the reaction proceeds *via* the six-membered chair-like transition state **a** (Fig. 1) which is most favorable according to the Felkin-Ahn model because the steric repulsion between the sterically most demanding amino moiety and the R^3-group is minimized.[9] In the case of entry 5, the reaction might proceed *via* the transition states **a** as well as **b** due to the small difference in the steric requirement between the amino and the phenyl (R^1) group, thus eventually resulting in low diastereofacial selectivity. The simple diastereoselectivity observed in entry 3 can be explained by assuming that severe gauche repulsion between both the sterically demanding phenyl group (R^3) and the allyl substituent does

Table 1.[a]



Entry	1		R^3CHO	Products		
	R^1	R^2		Main Diastereomer(s)	Ratio [main(s) : others]	Yield[b] %
1	**a** ; Me	Bn	EtCHO	 **2**	[92 : 8][d]	88
2	**b** ; Me	Boc	EtCHO	 **3**	[91 : 9][d]	88
3	**b** ; Me	Boc	PhCHO	 **4** 45 : 55[f] **5**	[>95 : <5]	79
4	**c** ; *n*-Pr	Boc	EtCHO	 **6**	[91 : 9][d]	89
5	**d** ; Ph	Boc	EtCHO	 **7** 58 : 42[g] **8**	[>95 : <5]	83

[a]Reaction procedure: To a solution of **1** (1.0 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (592 μL, 2.0 mmol) in ether (10 mL) was added *i*-PrMgCl (1.0~1.5 M in ether, 4.0 mmol) at -50 °C. After being stirred for 1.5 h at -50 ~ -40 °C, aldehyde (1.5 mmol) was added at -50 °C and the resulting mixture was warmed to 0 °C over 1 h followed by usual extractive workup. [b]Total yield. [c]The structure was confirmed by comparison with authentic **2** derived from **3** by treatment with CF_3CO_2H and then BnBr. [d]Three diastereomers were detected on NMR and/or GC analysis (ratio = 92 : 2 : 6 for entry 1, 91 : 2 : 7 for entry 2, 91 : 3 : 6 for entry 4). [e]Stereochemistry was confirmed by derivatization to the corresponding β-lactam and β-lactone according to the scheme shown below.[6] [f]Similar derivatization provided a *cis* and *trans* mixture of the corresponding β-lactam, while the β-lactones obtained have *cis*-configuration. [g]Similarly, a mixture of *cis* and *trans* β-lactams were obtained. Treatment of the β-hydroxycarboxylic acid derived from **7** or **8** under the Mitsunobu reaction conditions (PPh_3, DEAD, THF) afforded 1-amino-1-phenyl-2-pentene with (*Z*)-stereochemistry[11] (lactonization by using $PhSO_2Cl$/pyridine provided a complex mixture).



not allow the reaction to proceed *via* a transition state like **a** or **b**; the reaction thus proceeds *via* **c** in which the phenyl group occupies the axial position.[10]

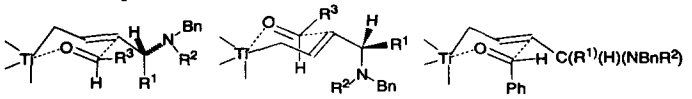


Fig. 1

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2. Allylic chromium compounds having an alkoxymethyl group at the C-4 position reacted with benzaldehyde with diastereoselectivity of around 83%; the presence of another stereocenter at the C-5 position increased the selectivity significantly to 90%: (a) Mulzer, J.; Kattner, L.; Strecker, A. R.; Schröder, C.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 4218-4229. Reaction of [(*E*)-4-Benzyloxy-2-pentenyl]tributylstannane with *p*-nitrobenzaldehyde at 150 °C afforded two diastereomers in a ratio of 73 : 27 (48% yield): (b) Gung, B. W.; Peat, A. J. *Synth. Commun.* **1991**, *21*, 1797-1802. (c) McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1990**, *31*, 6239-6242. (d) Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.* **1988**, *29*, 2479-2482. The reaction of these allyltin compounds with aldehydes in the presence of Lewis acid gave another regioisomer: (e) McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1992**, *33*, 1369-1372. (f) Bradley, G. W.; Hallett, D. J.; Thomas, E. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2579-2582. The reaction of 4-substituted (*E*)-1-trimethylsilyl-2-pentene with aldehydes in the presence of Lewis acid gave four diastereomers: (g) Nativi, C.; Palio, G.; Taddei, M. *Tetrahedron Lett.* **1991**, *32*, 1583-1586. Highly diastereoselective intramolecular cyclization reactions of an allylic metal compound having both a carbonyl group and a substituent at the C-4 position have been reported. Allylzirconiums: (h) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835-8836. (i) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1993**, *34*, 7639-7640. Allylsilanes: (j) Asao, K.; Iio, H.; Tokoroyama, T. *Tetrahedron Lett.* **1989**, *30*, 6397-6400. (k) Ranasinghe, M. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **1989**, *111*, 779-782.
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4. Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881-3882.
5. The compounds **1a~d** were obtained as a mixture of two diastereomers with a 3 : 2 ~ 9 : 1 ratio. In each case, both diastereomers have >95% ee which was confirmed by ^{1}H NMR analysis of MTPA-esters of the 4-(*N*,*N*-dibenzylamino)- or 4-(*N*-methyl-*N*-benzylamino)-1-alken-3-ol derived from the corresponding **1** by treatment with $LiAlH_4$ in tetrahydrofuran.
6. The reaction provides an attractive method for synthesizing optically active β-lactone and β-lactam, the synthesis of which has attracted considerable interest. Especially, the β-lactam having a (1-hydroxy)alkyl group at the α-position is found widely in therapeutically important β-lactam antibiotics: Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M. Eds.; Springer-Verlag: Berlin Heidelberg; 1990; pp 565-612.
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