Development of a Chiral Propionaldehyde Homoenolate Equivalent Which Reacts with Imines with Excellent Stereoselectivity: Efficient and Practical Synthesis of Optically Active γ-Amino Carbonyl Compounds

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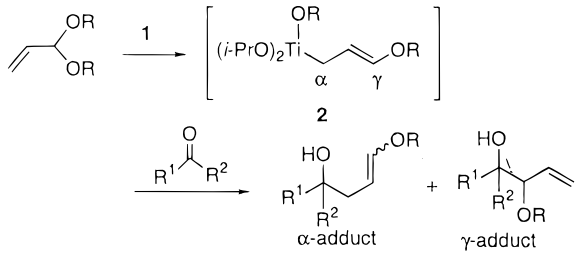
Equivalents of a homoenolate synthon belong to the synthetically important group of umpoled reagents,[1] and recently, much effort has been made for the preparation of their chiral form.[2] However, so far, a chiral homoenolate equivalent which reacts with imines, thus allowing a straightforward access to optically active γ-amino carbonyl compounds, has not been reported.[3] We have now succeeded in developing a chiral propionaldehyde homoenolate equivalent that reacts with imines with excellent selectivity.[4]

Recently, we have reported an efficient method for preparing allyltitanium complexes by the reaction of allylic alcohol derivatives with a divalent titanium reagent (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**), derived from Ti(O-*i*-Pr)$_4$ and 2 equiv of *i*-PrMgX, which proceeds via an oxidative addition pathway.[5,6] The resulting allyltitaniums react with aldehydes at the γ-position exclusively to provide the corresponding homoallylic alcohols. During these studies we found that, while the allyltitanium **2** (R = Et) obtained from **1** and acrolein diethyl acetal reacts with benzaldehyde to afford a γ-addition product (β-ethoxy homoallyl alcohol) exclusively, the complex **2** (R = $CH_2CH_2O^-$) derived from acrolein ethylene acetal provides a mixture of the α- and γ-addition products[7] (Scheme 1). With these results in hand, we searched for a proper acetal which would afford the α-addition product highly predominantly, thus serving as a propionaldehyde homoenolate equivalent. We found that the corresponding dicyclohexylethylene acetal **3** gives a satisfactory result; thus, the corresponding **2** derived from **3** reacts with alkyl and aryl aldehydes and ketones with good to excellent α-selectivity (see Scheme 1). In all cases, the α-addition product consists of a mixture of inseparable *E*- and *Z*-enol ethers; however, the ^{13}C NMR analysis of the mixture indicated that the chiral induction at the newly generated asymmetric center was low (see Supporting Information).

Scheme 1. Reaction of Allyltitaniums Derived from **1** and Acrolein Acetals with Carbonyl Compounds



Acetal	R^1(C=O)R^2	Product(s) α (*E*/*Z*) : γ	Total yield %
OEt, OEt	PhCHO	<2 : >98	93
O, O	PhCHO	39 (71/29) : 61	96
O, O, *c*-Hex., *c*-Hex. (**3**)	PhCHO	90 (75/25) : 10	95
	EtCHO	93 (66/34) : 7	85
	EtC(=O)Et	>97 (87/13) : <3	84

As allyltitaniums also react with imines smoothly, we then turned our attention to the reaction of allyltitaniums derived from **1** and **3** with imines, in anticipation of developing a propionaldehyde homoenolate equivalent which can react with imines for the first time.[3] Furthermore, we had some expectation of attaining high chiral induction because the reaction of allyltitaniums with imines proceeds with far better stereoselectivity than that of the reaction with aldehydes.[5b,d]

The reaction of **2** derived from (*R*,*R*)-**3** with imine **4c**, prepared from 2-methylpropanal and benzylamine, proceeds smoothly and in a regiospecific way to afford 85% yield of the α-addition product **5c** as a mixture of *E*- and *Z*-enol ethers in a ratio of 94:6, and from which pure (*E*)-**5c** was isolated in 70% yield by column chromatography (entry 3 in Table 1). The mixture of (*E*)- and (*Z*)-**5c** itself as well as the pure (*E*)-**5c** was respectively converted into methyl 3-amino-4-methylpentanoate (**6c**) by conventional methods (vide infra), and its enantiomeric excess (ee) was determined. To our surprise as well as to our delight, the ee of **6c** derived from the mixture was 88% and that of pure (*E*)-**5c** was very high, reaching 98%.

As shown in Table 1, the reaction appears to have wide generality. Thus, in addition to secondary alkylimines, methylimines (entry 1) and primary alkylimines (entry 2) and arylimines (entry 4) underwent the addition reaction with similar excellent stereoselectivity. Regarding the *N*-substituent R_2 in **4**, alkyl and aryl groups are acceptable in addition to benzyl group (entries 5 and 6).

In several cases the separation of (*E*)- and (*Z*)-**5** is difficult (entry 1) or not as easy, although possible (entries 2, 4, and 5);

(1) Reviews: Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 441. Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. Ryu, I.; Sonoda, N. *J. Synth. Org. Chem., Jpn.* **1985**, *43*, 112. Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205. Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665. See also: Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932.

(2) Review: Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365.

(3) Even in achiral form, to our best knowledge, only one precedent of homoenolate equivalents which react with imines (but not a propionaldehyde homoenolate equivalent) has been reported: Fang, J.-M.; Chen, S. T.; Chen, I.-H. *J. Organomet. Chem.* **1990**, *398*, 219.

(4) For the asymmetric nucleophilic addition reactions to imines, see reviews: Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun.* **1996**, 999. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. Kleinman, E. F.; Volkmann, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 893. Most recent examples: Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883. Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844. Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614. Itsuno, S.; Watanabe, K.; Matsumoto, T.; Kuroda, S.; Yokoi, A.; El-Shehawy, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2011.

(5) (a) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (b) Gao, Y.; Sato, F. *J. Org. Chem.* **1995**, *60*, 8136. (c) Kasatkin, A.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2848. (d) Hikichi, S.; Gao, Y.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 2867. (e) Teng, X.; Kasatkin, A.; Kawanaka, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8977. (f) Teng, X.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 6927. (g) Matsuda, S.; An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7513.

(6) Reviews for the synthetic utility of **1**: Sato, F.; Urabe, H.; Okamoto, S. *J. Synth. Org. Chem., Jpn.* **1998**, *56*, 424. Sato, F.; Urabe, H.; Okamoto, S. *Synlett*, in press.

(7) It has been reported that allylzirconium compounds derived from $Cp_2Zr(n\text{-}Bu)_2$ and acrolein diethyl acetal or ethylene acetal react with aldehydes to afford β-alkoxy homoallylic alcohols: Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 7873.

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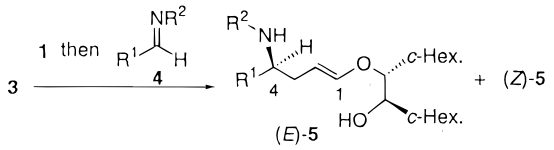
Table 1. Asymmetric Addition Reaction of the Allyltitanium Compound Derived from **1** and **3** with Imines



				adducts **5**[a]				
					isolated yield, %		ee at C-4, %[c]	
	imine **4**				*EZ*	pure		pure
entry		R^1	R^2	E:Z[b]	mixture	(E)-**5**	overall[d]	(E)-**5**
1	**4a**;	Me	Bn	92:8	84		83	
2	**4b**;	*n*-Pr	Bn	94:6	81		85	
3	**4c**;	*i*-Pr	Bn	94:6	85	70	88	98
4	**4d**;	Ph	Bn	93:7	82	40	86	96
5	**4e**;	Ph	*n*-Pr	95:5	85		88	
6	**4f**;	Ph	Ph	95:5	71		>85[e]	

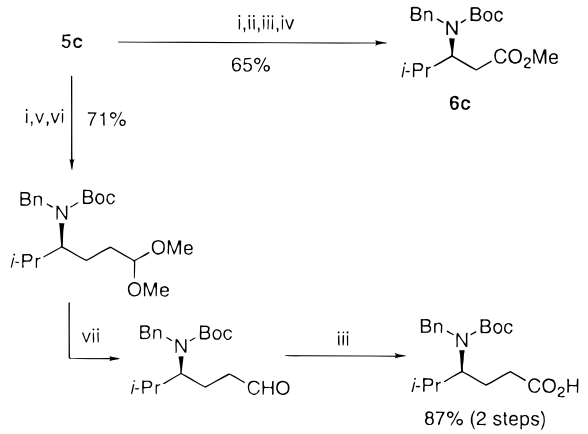
[a] No γ-addition product was observed. [b] Determined by ^{1}H NMR analysis. [c] ee (for entries 1−5) and absolute configuration (for entries 1−4) were determined by converting into the corresponding β-amino ester **6** (see Scheme 2 and Supporting information). [d] ee of **6** derived from the mixture of (*E*)- and (*Z*)-**5**. [e] For determination, see Supporting Information.

however, use of the mixture for further synthetic elaboration might be useful since the enantiomeric purity of the mixture is very high.

By taking advantage of the versatility of the enol ether functionality, the product **5** could be readily transformed into a variety of γ-aminocarbonyl compounds, including γ-amino acids, as represented by Scheme 2.[8] The compound **5** can also be converted to β-amino ester **6** as is also shown in Scheme 2 and in Table 1.

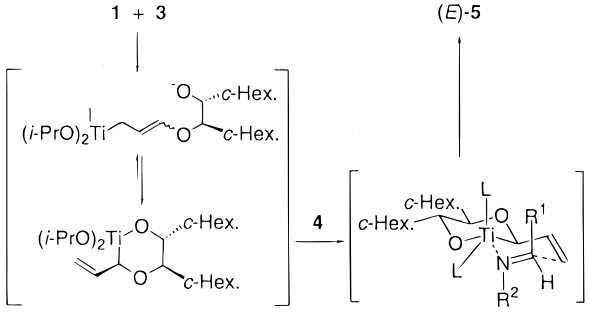
The predominant production of (*E*)-**5** with the absolute configuration depicted in Table 1 can be explained by assuming that the allyltitanium complex generated from **1** and **3** would exist mostly as an internal titanium derivative, which can be stabilized by chelation, rather than as the primary derivative,[9] and the reaction with imines proceeds preferentially via the most stable transition state depicted in Scheme 3, which has a *trans*-fused chair−chair conformation.[10]

Scheme 2[a]



[a] (i) $(Boc)_2O$, Et_3N, THF; (ii) O_3, Me_2S, CH_2Cl_2; (iii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH−H_2O; (iv) MeI, $NaHCO_3$, DMF; (v) Ac_2O, pyr., cat. DMAP; (vi) cat. *p*-TsOH, MeOH; (vii) TFA, CH_2Cl_2−H_2O.

Scheme 3



In summary, we have now succeeded in developing, for the first time, a chiral homoenolate equivalent which reacts with imines with excellent stereoselectivity, thus allowing an efficient preparation of optically active γ-amino carbonyl compounds. Since the reagent is easy to prepare from readily available and inexpensive starting materials, the reaction is practical and will find numerous applications in organic synthesis. The application of the reaction as well as further study to clarify the scope and limitations of the reaction is now in progress.

Supporting Information Available: Experimental procedure and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Synthesis of optically active γ-amino acids attracts current interest: See (a) Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T. A.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867 and references therein. For biological importance of γ-amino acids, see: (b) Nanavati, S. M.; Silverman, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 9341. (c) Burke, J. R.; Silverman, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 9329. See also ref 8a and references therein.

(9) A similar stabilization of allyltitaniums by intramolecular chelation or coordination has been reported, see: Hanko, R.; Hoppe, D. *Angew. Chem.* **1982**, *94*, 378. Weidmann, B.; Seebach, D. *Angew. Chem.* **1983**, *95*, 12. Roder, H.; Helmchen, G.; Peters, E.-M.; Peters, K.; Schnering, H.-G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 898. Zubaidha, P. K.; Kasatkin, A.; Sato, F. *Chem. Commun.* **1996**, 197. See also ref 5f.

(10) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Itoh, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.