Highly Selective Asymmetric Synthesis of Homoallylic Amines with and without a β-Substituent by the Reaction of Allylic Titanium Compounds with Chiral Imines

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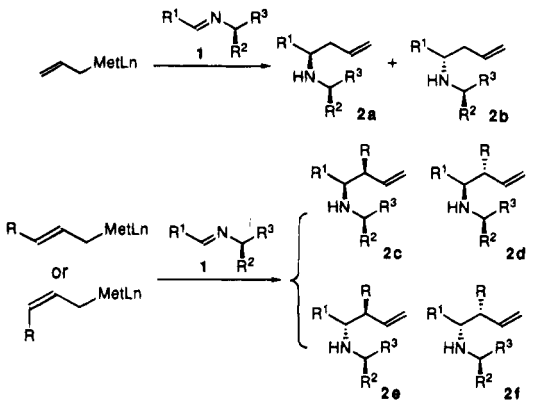
Reactions of allylic organometallic compounds with chiral imines have attracted considerable interest because they might provide synthetically useful methodology for preparing nitrogen-containing compounds such as natural products and pharmaceutically important compounds. The diastereoselective addition of allylic metal compounds to imines **1**, prepared by the condensation of aldehydes with optically active amines, can provide an effective synthetic method for preparing homoallylic amines in a chiral form.[1-4] A major goal of research in this area has been the development of allyl and substituted allyl organometallic reagents that provide highly selective access to each of the homoallylic amines indicated in Scheme 1. While several highly selective methods for preparing each of the two possible β-unsubstituted homoallyl amines **2a** and **2b** have been developed,[2] the issue of synthesizing each of the four possible β-substituted homoallyl amines **2c–f** has remained unsolved.[2a,p] We have now found that allylic titanium compounds can solve the problem, thus affording an efficient and practical method for the synthesis of chiral β-substituted homoallyl amines.

The reaction of allylic titanium compounds with chiral imines has been investigated by several research groups but not in a systematic fashion.[2a-c] Our recent synthesis

Scheme 1



of various allylic titanium compounds[5] prompted us to revisit the reactions shown in Scheme 1. We selected the imines **1** (R^2 = CH_3, R^3 = Ph), prepared by the reaction of aldehydes with 1-phenylethylamine, for investigating the reactions in Scheme 1, because both enantiomers of 1-phenylethylamine are readily available and this auxiliary group is easily removed after the reaction. It should be noted that among the allyl metal compounds so far investigated, allyl-9-borabicyclo[3.3.1]-nonane compounds (allyl-9-BBN) afforded the highest stereoselectivity in reactions with **1**.[2a,b]

To a mixture of $Ti(O\text{-}i\text{-}Pr)_4$ and allylic halides or alcohol derivatives in ether was added 2 equiv of *i*-PrMgCl at −50 °C. After the reaction mixture was stirred for 1 h at −40 to −50 °C, the chiral imine **1a** or **1b** was added at the same temperature and the reaction mixture was warmed gradually to −10 °C over 2 h to provide the corresponding homoallylic amine in the yield and with the stereoselectivity shown in Table 1.

The reaction of allyltitanium compounds with **1a** and **1b** proceeded with very high 1,3-asymmetric induction to provide the Cram product[2a] predominantly (Table 1, entries 1–4). This diastereoselectivity is somewhat superior to that attained by using allyl-9-BBN. It can also be seen that the diastereoselectivity was not dependent on the nature of the allylic compound used for synthesis of the allyltitanium compound. Especially noteworthy is the very high diastereoselectivity attained by the reaction of crotyl titanium compound with **1a**. Thus, as can be seen from entries 5 and 6 (Table 1), the reaction of the crotyltitanium compound with **1a** provided the Cram-*syn* and Cram-*anti* isomers in the ratio of 94:6. Exclusive production of the Cram product in the reaction with **1a** was attained by using crotyl-9-BBN, but in this case the *syn*:*anti* ratio was 75:25.[2a] Thus, to the best of our knoweledge, this is the first example to succeed in synthesizing one of the four possible stereoisomers highly selectively by the reactions shown in Scheme 1. Very high stereoselectivity was also attained in the reaction of the titanium compound derived from methyl 1-phenyl-2-propenyl carbonate that provided the Cram-*syn* product predominantly (Table 1, entry 7). Since both enantiomers of **1** are readily available and the auxiliary group is easily removed, the present finding opens an easy and practical route to both enantiomers of primary β-substituted homoallylic amines bearing *syn* substituents.

(1) For recent reviews, see: (a) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 975. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 1.

(2) (a) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778. (b) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. (c) Tanaka, H.; Inoue, K.; Pokorski, U.; Taniguchi, M.; Torii, S. *Tetrahedron Lett.* **1990**, *31*, 3023. (d) Wu, M.-J.; Pridgen, L. N. *Synlett* **1990**, 636. (e) Laschat, S.; Kunz, H. *Synlett* **1990**, 51. (f) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883. (g) Neumann, W.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, *32*, 5865. (h) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. (i) Dembélé, Y. A.; Belaud, C.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511. (j) Dembélé, Y. A.; Beland, C.; Hitchcock, P.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 351. (k) Beuchet, P.; Le Marrec, N.; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959. (l) Beresford, K. J. M.; Howe, G. P.; Procter, G. *Tetrahedron Lett.* **1992**, *33*, 3355. (m) Giammaruco, M.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1993**, *34*, 3635. (n) Bhuyan, P. J.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1993**, *34*, 7975. (o) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766. (p) Hashimoto, Y.; Takaoki, K.; Sudo, A.; Ogasawara, T.; Saigo, K. *Chem. Lett.* **1995**, 235.

(3) For analogous asymmetric allylation of nitrones, cyclic iminium ions, and hydrazones: (a) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3475. (b) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. (c) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (d) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868. (e) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294. (f) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858. (g) Ukaji, Y.; Tsukamoto, K.; Nasada, Y.; Shimizu, M.; Fujisawa, T. *Chem. Lett.* **1993**, 221. (h) Denmark, S. E.; Nicaise, O. *Synlett* **1993**, 359. (i) Enders, D.; Schankat, J.; Klatt, M. *Synlett* **1994**, 795.

(4) Enatioselective addition of chiral allylboron reagents to achiral imines has been reported; see: Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1531.

(5) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881.

(6) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

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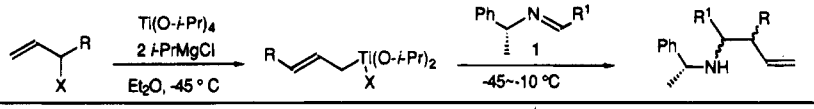
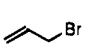
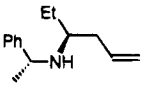
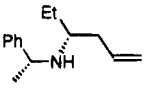
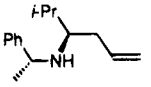
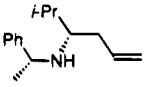
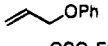
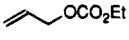
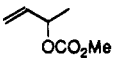
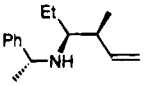
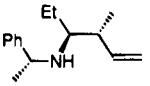
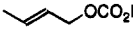
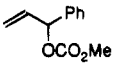
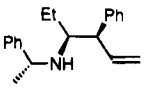
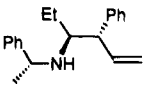
Table 1[a]

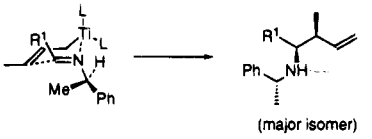


Entry	Allyl compound	Imine	Product[b] Major	Minor	Diastereo selectivity[c]	Isolated yield (%)
1		R^1 = Et **1a**			95:5	88
2	"	R^1 = *i*-Pr **1b**			96:4	87
3		"	"	"	"	80
4		"	"	"	"	78
5[d]		**1a**			94:6	92
6[d]		"	"	"	"	87
7[e]		"			92:8	83

[a] The reaction was carried out at −45 to −10 °C for 2−3 h with a reactant ratio of allylic compounds:Ti(O-*i*-Pr)$_4$:*i*-PrMgCl:imine **1** = 1:1:2:1. [b] Stereochemistries of the products shown in entries **1**−**6** were determined by comparison with authentic samples prepared according to the procedure reported by Yamamoto.[2a] The stereochemistry of the major isomer in entry **7** was confirmed by converting it to (3*S*,4*R*)-*N*-(4-phenylhex-3-yl)(trifluoromethyl)sulfonamide (H_2/Pd−C and then $(CF_3SO_2)_2O$), and comparing the ^{1}H, ^{13}C NMR spectra and $[\alpha]_D$ value with an authentic sample prepared from (2*S*-*trans*)-3-phenyloxiranemethanol[6] using conventional reactions (see the supporting information). [c] Determined by ^{1}H NMR. [d] The reactant ratio was allylic compound:Ti(O-*i*-Pr)$_4$:*i*-PrMgCl:imine **1** = 1.6:1.6:3.2:1. [e] The reactant ratio was allylic compound:Ti(O-*i*-Pr)$_4$:*i*-PrMgCl:imine **1** = 1.2:1.2:2.4:1.

The predominant production of Cram-*syn* products in the reactions of crotyl titanium compounds with chiral imines can be explained with the six-membered chairlike transition state[1c,7] shown in eq 1 in which the imine R^1 group occupies an axial position as proposed by Yamamoto.[2a]

The reaction of allylic titanium compounds with the readily available chiral imines **1** reported here represents a practical and efficient method for the synthesis of nitrogen-containing compounds. This method has the advantageous feature of easy access to various allylic titanium compounds from readily available and inexpensive starting materials, i.e., allylic alcohol derivatives, Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl.



(1)

Supporting Information Available: A typical procedure for generating allylic titanium compounds and subsequent reactions with chiral imines, structural determination of the major isomer shown in entry 7 (Table 1), and physical properties of homoallylic amines (4 pages).

JO951803L

(7) Reactions of allyltitanium compounds with aldehydes have been proposed to proceed via six-membered chairlike transition state; see: (a) Reetz, M. T. In *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; p 165. (b) Widler, L.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1085. (c) Sato, F.; Iijima, S.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 243.