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1,5-Asymmetric Induction in Addition Reaction of Aldehydes with Chiral Allyltitaniums Having an Amino Group at the Stereogenic Center. Synthesis of Optically Active 2,6-*cis*-Disubstituted Piperidines

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Abstract

Chiral allyltitaniums prepared from cyclic carbamate of optically active 4-aminoalk-1-en-3-ols and a Ti(O-*i*-Pr)4/2*i*-PrMgCl reagent react with aldehydes with good to excellent regio- and stereoselectivity to afford optically active 1,5-amino alcohols, from which optically active 2,6-*cis*-disubstituted piperidines are synthesized. © 1998 Elsevier Science Ltd. All rights reserved.

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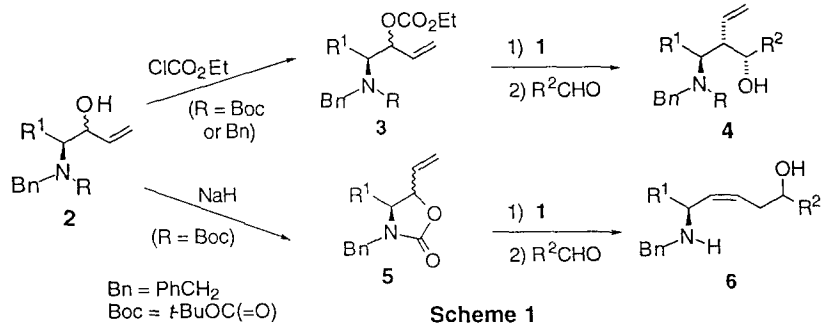
Recently, we have developed a new efficient entry to allyltitanium compounds by the reaction of allylic alcohol derivatives such as halides, carbonates and acetates with a Ti(O-*i*-Pr)4/2*i*-PrMgCl reagent (**1**) which proceeds *via* an oxidative addition pathway [1]. The resulting allyltitaniums react selectively with aldehydes and imines, thus providing an efficient method for synthesizing homoallylic alcohols or amines [1,2]. In these previously reported examples, it was found that optically active 4-aminoalk-1-en-3-ols (**2**) reacted, after converting to the ethyl carbonate **3**, with **1** to afford the corresponding chiral allyltitaniums and which in turn react with aldehydes regio- and stereoselectively to afford β-vinyl-γ-aminoalkanols **4** (R = Bn or Boc) having the structure depicted in Scheme 1 [2d]. We have



Scheme 1

PII: S0040-4039(98)01455-5

Table 1. The Addition Reaction of Allyltitaniums Derived from **5** with Aldehydes[a]

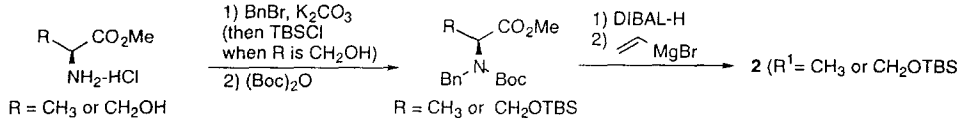
Entry	Substrates: 5[c]	Substrates: R^2CHO	Product(s)[b]: 6[d]	Diastereoselectivity[e]	Yield, %[f]
1	$R^1 = CH_3$	*n*-PrCHO	**6a**	5 : 1[g]	81
2	R^1 = *n*-Pr	EtCHO	**6b**	14 : 1	79
3	$R^1 = CH_2OTBS$	MeCHO	**6c**	14 : 1	83
4		EtCHO	**6d**	18 : 1[g]	82
5		PhCHO	**6e**	20 : 1	79
6			**6f**	11 : 1	81

[a]A mixture of **5** (1.0 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (1.5 equiv), and *i*-PrMgCl (3.0 equiv) in ether was stirred for 1.5 h at -50~-40 °C, and then the mixture was allowed to warm to 0 °C and stirred for 2 h. After cooling to -78 °C, to this was added an aldehyde (1.5 equiv). [b]The reaction afforded a mixture of **6** and its regioisomer **4** (R = H) in a ratio of more than 12:1 in all cases. The ratio was determined by ^1H and/or ^{13}C NMR. [c]**5** was prepared from **2** (R=Boc) by treatment with NaH in THF (88~92% yield). A mixture of two diastereomers in a ratio of 4:1 for entry 1 and entry 2, 7:3 for entries 3-6 was used. [d]>98% (*Z*)-olefin geometry in all cases. [e]Determined by ^1H and/or ^{13}C NMR analysis after separation of **4**. [f]Combined yield of two diastereomers of **6**. [g]Stereochemistry was confirmed by converting to the corresponding piperidine, see Scheme 2.

now found that allyltitaniums derived from cyclic carbamates **5** (prepared easily from **2**[1] (R=Boc) by treatment with NaH) react with aldehydes to afford another regioisomer, 1,5-amino alcohols **6**, highly selectively (Scheme 1, Table 1).

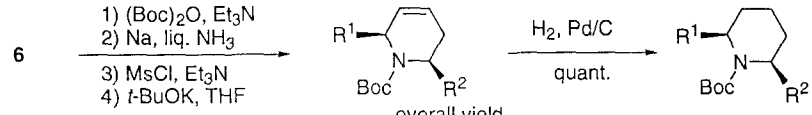
As shown in Table 1, the reaction of the allyltitaniums generated *in situ* from **5** and **1** with aldehydes afforded 1,5-amino alcohols **6** and their regioisomers **4** (R = H) in a ratio of more than 12:1. The 1,5-amino alcohols **6** thus produced consisted of two diastereomers having *Z*-geometry with respect to the olefin moiety; the isomer having *E*-olefin geometry was not detected. The diastereoselectivity associated with the 1,5-asymmetric induction was somewhat dependent on the steric bulkiness of R^1 in **5** and, when R^1 is a methyl group, it was 5:1 (entry 1) while it was better than 11:1 in the case where the bulkiness of R^1 is larger than that of the methyl group. The stereochemistry of the main diastereoisomer was verified as shown in Table 1 by ^1H NMR analysis after derivatization to the corresponding piperidine derivative in several representative cases (*vide infra*). It should be noted that in these reactions, although the regioisomers **4** and **6** could be readily separated from each

[1]The compound **2** (>94% e.e.) where R^1 is CH_3 or CH_2OTBS was synthesized from the corresponding L-amino acid by the conventional reaction sequences shown below. Meanwhile, the compound **2** where R^1 is *n*-Pr (95% e.e.) was prepared from readily available optically active 2,3-epoxy-1-hexanol: see ref. 2d.



other by column chromatography, two stereoisomers of **6** were inseparable. However, since the diastereoselectivity is very high except for the case where R^1 is a methyl group, the value of the reaction as synthetic methodology of **6** would not be detracted[2].

With a convenient method for synthesizing optically active **6** in hand, we carried out their conversion into piperidine derivatives in several representative cases. Thus, as illustrated in Scheme 2, 2,6-disubstituted 3,4-didehydropiperidines (1,2,5,6-tetrahydropyridines) **7a** and **7d**[3] were synthesized in good overall yields from the corresponding **6** by the following reaction sequence: (1) protection of the amino group with Boc using $(Boc)_2O$ and Et_3N in THF at room temperature, (2) removal of the benzyl group using Na / liq. NH_3 at -70 ~ -40 °C, (3) mesylation of the alcohol group using MsCl and Et_3N in CH_2Cl_2 at ambient temperature, and (4) cyclization reaction using *t*-BuOK in THF at 0 °C. The unsaturated piperidines **7** thus obtained were hydrogenated (H_2, Pd/C, EtOH, room temp.) quantitatively to saturated 2,6-disubstituted piperidines **8**, the *cis*-stereochemistry of which was confirmed by ^1H NMR analysis[4]. It should be noted that a new asymmetric entry has now been opened up to saturated and unsaturated *cis*-2,6-disubstituted piperidines, the structure of which frequently occurs as a subunit of alkaloids and biologically active compounds [3,4].



a; $R^1 = CH_3$, $R^2 = n$-Pr
d; $R^1 = CH_2OTBS$, $R^2 = Et$

overall yield
7a ; 60%
7d ; 61%

Scheme 2

The regio- and stereochemistry of the aldehyde addition reaction of the allyltitanium derived from **5** and **1** can be explained by the preference for the secondary allyltitanium **10**

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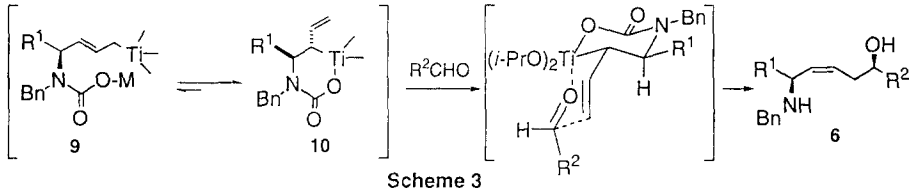
[2]The characteristic ^1H NMR data of **6** (300MHz, $CDCl_3$): for **6a**: δ 1.17 (d, *J* = 6.0 Hz, 0.5H, $C\underline{H}_3CHN$, minor), 1.18 (d, *J* = 6.3 Hz, 2.5H, $C\underline{H}_3CHN$, major), 3.51-3.68 (m, 2H, CHN, C<u>H</u>OH), 5.41-5.63 (m, 2H, C<u>H</u>=C<u>H</u>CH_2). for **6b**: δ 3.36-3.46 (m, 1H, CHN), 3.51 (quintet, *J* = 6.0 Hz, 1H, C<u>H</u>OH), 5.41 (t, *J* = 10.2 Hz, 1H, C<u>H</u>=CHCH_2), 5.63 (dt, *J* = 10.8, 7.8 Hz, 1H, CH=C<u>H</u>CH_2). for **6c**: δ 3.50-3.85 (m, 4H, TBSOC<u>H</u>$_2$C<u>H</u>N, C<u>H</u>OH), 5.43-5.52 (m, 1H, C<u>H</u>=CHCH_2), 5.68 (dt, *J* = 7.8, 11.1 Hz, 1H, CH=C<u>H</u>CH_2). for **6d**: δ 3.45-3.65 (m, 4H, TBSOC<u>H</u>$_2$C<u>H</u>N, C<u>H</u>OH), 5.42-5.51 (m, 1H, C<u>H</u>=CHCH_2), 5.68 (dt, *J* = 7.8, 11.1 Hz, 1H, CH=C<u>H</u>CH_2). for **6e**: δ 3.43-3.61 (m, 3H, TBSOC<u>H</u>$_2$C<u>H</u>N), 4.68 (dd, *J* = 4.5, 8.1 Hz, 1H, C<u>H</u>OH), 5.52 (dd, *J* = 7.8, 10.8 Hz, 1H, C<u>H</u>=CHCH_2), 5.70 (ddd, *J* = 7.8, 8.4, 10.8 Hz, 1H, CH=C<u>H</u>CH_2). for **6f**: δ 3.48-3.65 (m, 3H, TBSOC<u>H</u>$_2$, CHN), 4.04 (q, *J* = 6.3 Hz, 1H, C<u>H</u>OH), 5.40-5.55 (m, 2H, C<u>H</u>=CHCH_2, C<u>H</u>=C<u>H</u>CH_3), 5.60-5.73 (m, 2H, CH=C<u>H</u>CH_2, CH=C<u>H</u>CH_3).

[3]The characteristic ^1H NMR data of *cis*-**7** (300 MHz, $CDCl_3$, 65 °C): **For 7a** δ 1.93 (dd, *J* = 6.3, 17.1 Hz, 1H, CH=CHC<u>H</u>$_2$), 2.23-2.37 (m, 1H, CH=CHC<u>H</u>$_2$), 4.28-4.43 (m, 2H, 2CHN), 5.54 (dt, *J* = 10.2, 3.3 Hz, 1H, olefinic proton), 5.63-5.74 (m, 1H, olefinic proton). **For 7d** δ 1.95 (dd, *J* = 6.3, 17.4 Hz, 1H, CH=CHC<u>H</u>$_2$), 2.22-2.36 (m, 1H, CH=CHC<u>H</u>$_2$), 3.44 (t, *J* = 9.0 Hz, 1H, OCH_2), 3.78 (dd, *J* = 4.5, 9.0 Hz, 1H, OCH_2), 4.18-4.38 (m, 2H, 2CHN), 5.70-5.79 (m, 1H, olefinic proton), 5.88 (dt, *J* = 10.2, 3.0 Hz, 1H, olefinic proton).

[4]The *cis*- and *trans*-**7** (or **8**) were inseparable by column chromatography. The ratios determined by ^1H NMR analysis were as follows: for **7a** or **8a**: *cis* : *trans* = 4.8 : 1; for **7d** or **8d**: *cis* : *trans* = 11:1. The *cis*-stereochemistry of the major isomer of **8a** was confirmed by comparing the NMR data with those reported in the literature (Beak P, Lee WK. J. Org. Chem. 1993;58:1109-1117). The *cis*-stereochemistry of **8d** was confirmed by ^1H NMR NOE-difference experiments between protons at the C-2 and C-6 position of the piperidine ring. The characteristic ^1H NMR data of **8d** (300 MHz, $CDCl_3$, 65 °C): δ 3.50 (dd, *J* = 5.1, 9.6 Hz, 1H, OCH_2), 3.57 (t, *J* = 9.6 Hz, 1H, OCH_2), 3.92-4.04 (m, 1H, $CH_3CH_2C\underline{H}N$), 4.09-4.21 (m, 1H, $OCH_2C\underline{H}N$).

over the primary ones **9** and its reaction with aldehydes through a six-membered chair-like transition state as shown in Scheme 3. Usually, substituted allyltitanium exists as the primary titanium derivative over the more congested secondary ones which provided a basis for the production of **4** from the reaction of the allyltitaniums derived from **3** and **1** with aldehydes (see Scheme 1) [2d]; however, in the present case the equilibrium might be shifted in favor of **10** because it has a stable six-membered cyclic structure [5].



Scheme 3

It should be noted that there is a precedent for highly selective 1,5-asymmetric induction in the addition reaction of aldehydes with allylmetal complexes having an amino group at the stereogenic center; Thomas *et al.* have reported that the reaction of tributyl(4-dibenzylaminopent-2-enyl)stannane with aldehydes proceeds with excellent selectivity to afford 1,5-amino alcohols having a similar structure to that of **6** [6]. They explained the stereoselectivity of the reaction by a similar transition state model to that shown in Scheme 3.

References

[1] Kasatkin A, Nakagawa T, Okamoto S, Sato F. J. Am. Chem. Soc. 1995;117:3881-3882.

[2] (a) Gao Y, Sato F. J. Org. Chem. 1995;60:8136-8137. (b) Kasatkin A, Sato F. Angew. Chem., Int. Ed. Engl. 1996;35:2848-2849. (c) Hikichi S, Gao Y, Sato F. Tetrahedron Lett. 1997;38:2867-2870. (d) Teng X, Kasatkin A, Kawanaka Y, Okamoto S, Sato F. Tetrahedron Lett. 1997;38:8977-8980.

[3] For recent reviews on natural products having a *cis*-2,6-disubstituted piperidine moiety, see: Numata A, Ibuka I. The Alkaloids, Brossi A. editor, New York, Academic Press: 1987;Vol. 31:193-315. Takahata H, Momose T. The Alkaloids, Cordell GA. editor, San Diego, Academic Press, 1993;Vol. 44:189-256. For recent syntheses of optically active *cis*-2,6-disubstituted piperidines, see: Munchhof MJ, Meyers AI. J. Am. Chem. Soc. 1995;117:5399-5400. Hirai Y, Watanabe J, Nozaki T, Yokoyama H, Yamaguchi S. J. Org. Chem. 1997;62:776-777. Momose T, Toyooka N, Jin M. J. Chem. Soc., Perkin Trans. 1, 1997; 2005-2013 and references cited therein.

[4] For representative examples of natural products having a 2,6-disubstituted tetrahydropyridine moiety, see: Lotter HL, Abraham DJ, Turner CE, Knapp JE, Schiff PL, Slatkin DJ. Tetrahedron Lett. 1975; 2815-2818. Nader B, Bailey TR, Franck RW, Weinreb SM. J. Am. Chem. Soc. 1981;103:7573-7580. Colau B, Hootelé C. Can. J. Chem. 1983;61:470-472. Wasserman HH, Leadbetter MR, Kopka IE. Tetrahedron Lett. 1984;25:2391-2394. Natsume M, Ogawa M. Chem. Pharm. Bull. 1984;32:3789-3791. Bailey TR, Garigipati RS, Morton JA, Weinreb SM. J. Am. Chem. Soc. 1984;106:3240-3245. For syntheses of 2,6-disubstituted tetrahydropyridines, see: Bonin M, Romero JR, Grierson DS, Husson HP. J. Org. Chem. 1984;49:2392-2400. Wuts PGM, Jung YW. J. Org. Chem. 1988;53:1957-1965. Comins DL, Weglarz MA. J. Org. Chem. 1991;56:2506-2512. Ahman J, Somfai P. J. Am. Chem. Soc. 1994;116:9781-9782. Huwe CM, Velder J, Blechert S. Angew. Chem., Int. Ed. Engl. 1996;35:2376-2378. Bubnov YN, Klimkina EV, Ignatenko AV, Gridnev ID. Tetrahedron Lett. 1997;38:4631-4634. Craig D, McCague R, Potter GA, Williams MRV. Synlett, 1998;55-57 and references cited therein.

[5] Hanko R, Hoppe D. Angew. Chem. 1982;94:378-379. Weidmann B, Seebach D. Angew. Chem. 1983;95:12-26. Zubaidha PK, Kasatkin A, Sato F. Chem. Commun. 1996;197-198.

[6] Stanway SJ, Thomas EJ. J. Chem. Soc., Chem. Commun. 1994;285-286.