ORGANIC LETTERS

2003
Vol. 5, No. 12
2145−2148

# Asymmetric Synthesis of Allyl- and α-Allenylamines from Chiral Imines and Alkynes via ($\eta^2$-Imine)Ti(O-*i*-Pr)$_2$ Complexes

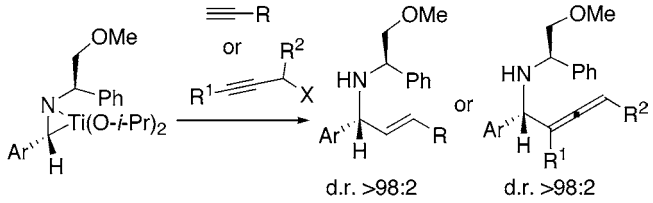
**Kohki Fukuhara, Sentaro Okamoto,[†] and Fumie Sato***

*Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan*

*fsato@bio.titech.ac.jp*

**Received April 6, 2003**

## ABSTRACT




**The reaction of a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2*i*-PrMgX with optically active arylaldimines derived from arylaldehydes and *O*-methylphenylglycinol provided, in a highly diastereoselective manner, chiral ($\eta^2$-imine)Ti(O-*i*-Pr)$_2$ complexes, which in turn reacted with 1-alkynes or propargyl compounds to give optically active allyl- and α-allenylamines, respectively.**

The synthesis of unsaturated amines such as allylamines[1] and α-allenylamines (2,3-alkadienylamines)[2] has attracted much interest, because they are important compounds in organic synthesis. Although a variety of synthetically useful methods to access optically active allylamines has been developed,[3] asymmetric synthesis of α-allenylamines has scarcely been reported.[2b,c]

We recently reported that a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX (**1**) reacts with arylaldimines to provide the corresponding azatitanacyclopropanes ($\eta^2$-imine)Ti(O-*i*-Pr)$_2$ that, in turn, react with 1-alkynes to provide allylamines after hydrolysis of the resulting azatitanacyclopentene complexes as exemplified in path a in Scheme 1.[4−6] With these results, we envisioned that the reaction of the azatitanacyclopropane complexes with propargyl halides might afford α-allenylamines through the $\beta$-elimination reaction of the resulting azatitanacyclopentene intermediate and found that this expectation was realized as exemplified by the reaction shown in path b in Scheme 1. With these findings in hand, we were interested in carrying out these reactions in an asymmetric way starting with optically active imines, and reported herein is the successful result.

First, we investigated the reaction of **1** with several chiral imines **2a**−**5a** prepared from the corresponding α-substituted

[†] Current address: Department of Applied Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama, 221-8686, Japan. E-mail: okamos10@kanagawa-u.ac.jp.

(1) For a review on methods for synthesis of allylamines, see: Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. See also ref 3.

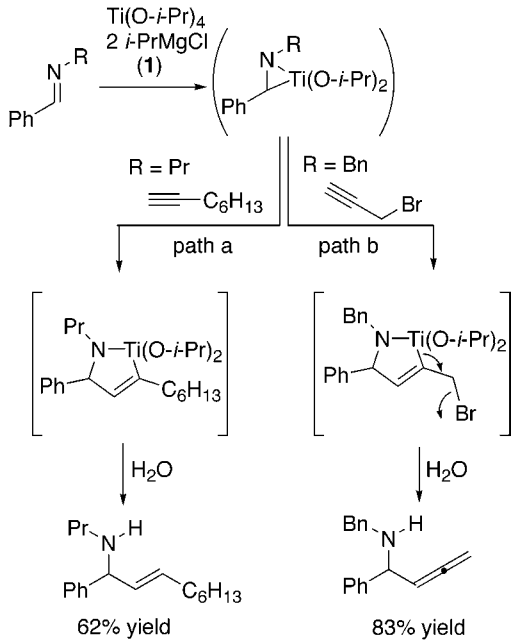
(2) For recent leading references, see: (a) Billet, M.; Schoenfelder, A.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2002**, *43*, 1453. (b) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855. (c) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904.

(3) For recent leading references, see: (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (b) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225. (c) Konno, T.; Nagata, K.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2002**, *67*, 1768. (d) Martín, R.; Alcón. M.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2002**, *67*, 6896. (e) Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478. (f) Evans, P. A.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269. (g) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. (h) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847. (i) Yadav, J. S.; Bandyopadhyay, A.; Reddy, B. V. S. *Tetrahedron Lett.* **2001**, *42*, 6385. (j) Chao, B.; Dittmer, D. C. *Tetrahedron Lett.* **2001**, *42*, 5789. (k) Yadav, J. S.; Bandyopadhyay, A.; Reddy, B. V. S. *Synlett* **2001**, 1608.

(4) Gao, Y.; Yoshida, Y.; Sato, F. *Synlett* **1997**, 1353.

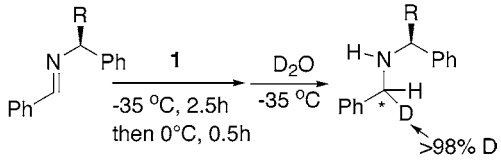
10.1021/ol034599u CCC: $25.00 
**Published on Web 05/21/2003**

**Scheme 1**




benzylamine and benzaldehyde and saw the diastereofacial selectivity of the formation of azatitanacyclopropane complexes by their deuteriolysis product. As shown in Scheme 2, the titanium complexes derived from **2a** and **3a** provided

**Scheme 2**

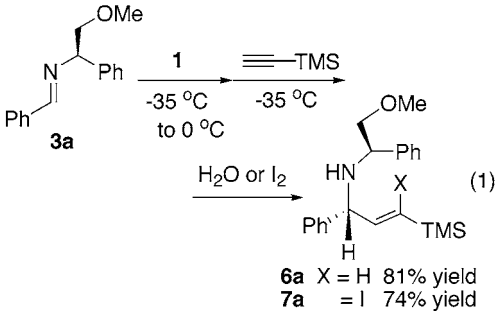



| imine | d.r.[a] | yield, % |
|---|---|---|
| **2a**: R = Me | 64:36 | 80 |
| **3a**: R = $CH_2OMe$ | >97 : 3 | 81 |
| **4a**: R = $CH_2OSi$-$BuMe_2$ | n.d.[b] | 25 |
| **5a**: R = $CO_2Me$ | complex mixture[b] | |

[a] By $^1H$ NMR. [b]Not determined.

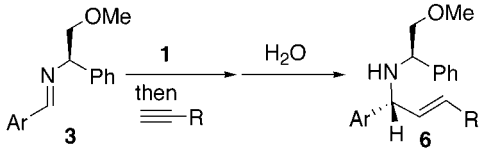
the corresponding amine with quantitative deuterium incorporation in excellent yield. While **2a** provided two possible diastereomers in a ratio of 64:36, to our satisfaction, **3a**, which has a 2-methoxy-1-phenylethyl group as the N-substituent, afforded one diastereomer with excellent selectivity of >97:3, indicating the highly diastereoselective formation of the azatitanacyclopropane from **3a**, though its absolute stereochemistry was not determined. Meanwhile, **4a** furnished the corresponding azatitanacyclopropane in low yield presumably due to the larger steric bulkiness of OSi*t*-$BuMe_2$ than that of the OMe group, and **5a** gave a complex mixture.

With the finding that **3a** afforded a good result, we carried out the reaction of the azatitanacyclopropane derived from it with trimethylsilylacetylene. Thus, the titanium complex prepared by adding 2 equiv of *i*-PrMgCl to a mixture of **3a** and Ti(O-*i*-Pr)$_4$ was treated with trimethylsilylacetylene (1.5 equiv) at −35 °C to afford, after hydrolysis or iodinolysis, the corresponding allylamine **6a** and **7a** in 81 and 74% yields, respectively.[7] The diastereomeric ratio of **6a** thus obtained was found to be >97:3 by $^1H$ NMR analysis, and the absolute structure of the major product was confirmed as depicted in eq 1 (vide infra).




The results of the reaction with other representative 1-alkynes are summarized in Table 1. It can be seen that the

**Table 1**



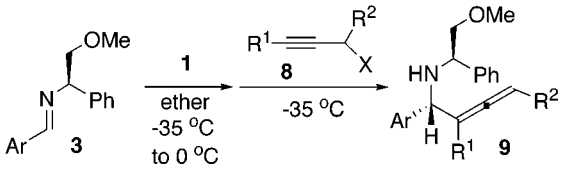

| entry | 3 Ar | R-C≡CH | 6 | d.r.[a] | yield[b] |
|---|---|---|---|---|---|
| 1 | Ph (**3a**) | R = $SiMe_3$ | **6a** | >97:3 | 81% |
| 2 | " | =*n*-$C_6H_{13}$ | **6b** | >98:2 | 82% |
| 3 | " | = Ph | **6c** | >98:2 | 84% |
| 4 | " | = $CO_2Et$ | **6d** | >96:4 | 63% |
| 5 | " | = $SO_2Tol$ | **6e** | >94:6 | 28% |
| 6 |  (**3b**) | = $SiMe_3$ | **6f** | >98:2 | 63% |

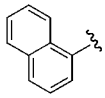
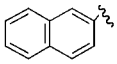
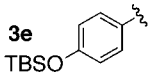
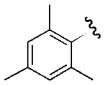
[a] Determined by $^1H$ and $^{13}C$ NMR analyses. No regioisomer was detected. [b] isolated yield.

reaction is reasonably general. An alkyl- and phenylacetylene reacted with excellent selectivity as shown in entries 2 and 3. Ethyl propiolate could be used equally well to give the desired allylamine **6d**. Sulfonylacetylene also provided the expected allylamine **6e**, albeit in low yield. The present reaction appears to allow preparation of optically active

(5) We also reported that the ($\eta$2-alkyne)Ti(O-*i*-Pr)$_2$ complexes derived from **1** and internal alkynes react with imines to provide the corresponding $\beta,\gamma$-disubstituted allylamines: Gao, Y.; Harada, K.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 5913.

**Table 2**




| entry | 3 | Ar | 8 | 9[a] | d.r.[b] | yield[c] |
|---|---|---|---|---|---|---|
| 1 | **3a** | Ph | $R^1 = R^2 = H$, X = Br (**8a**) | **9aa** | >98:2 | 74% |
| 2 | **3b** |  | | **9ba** | >98:2 | 61% |
| 3 | **3c** |  | | **9ca** | >98:2 | 59% |
| 4 | **3d** |  | | **9da** | >98:2 | 67% |
| 5 | **3e** |  | | **9ea** | >98:2 | 62% |
| 6 | **3f** |  | | **9fa** | 93:7 | 45% |
| 7 | **3a** | Ph | $R^1$= *n*-$C_6H_{13}$, $R^2$= H, X= OP(O)(OEt)$_2$ (**8b**) | **9ab** | >98:2 | 49% |
| 8 | **3a** | Ph | $R^1$ = Ph, $R^2$ = H, X= OP(O)(OEt)$_2$ (**8c**) | **9ac** | >98:2 | 62% |
| 9 | **3a** | Ph | $R^1$ = H, $R^2$ = *n*-$C_6H_{13}$, X = OAc (**8d**) | **9ad** | >98:2 (62:38)[d] | 56% |
| 10 | **3a** | Ph | $R^1$ = H, $R^2$ = Ph, X = OAc (**8e**) | **9ae** | >98:2 (55:45)[d] | 63% |

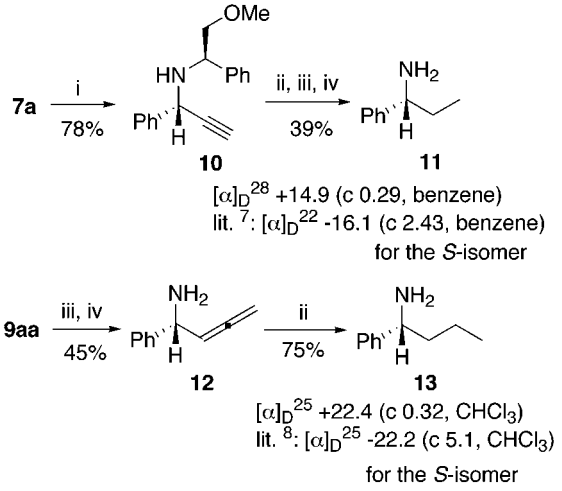
[a] Stereochemistry was determined for **9aa**. That of other compounds was assigned from analogy with **9aa**. [b] Determined by $^1$H and $^{13}$C NMR analyses. [c] Isolated yield. No regioisomer was detected. [d] Ratio of diastereomer regarding the allenyl moiety determined by $^1$H NMR.

allylamines having other aromatic substituents than phenyl at the α-position as exemplified by the preparation of **6f** (entry 6, see also Table 2). Thus, in conclusion, a new attractive entry to an optically active α-arylallylamines has been developed. It should be noted that the preparation of an optically active $Cp_2Zr(\eta^2$-imine) complex from $Cp_2Zr(\eta^2$-butene) and **3a** and its highly diastereoselective reaction with trimethylsilylacetylene providing the corresponding

(6) Recent reviews for synthetic reactions mediated by a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl: Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 319−354. Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

(7) No regioisomer was detected.[4]

**Scheme 3**[a]




[a] (i) *n*-$Bu_4NF$, DMF. (ii) $H_2$, $Pd(OH)_2$/C, MeOH. (iii) $BBr_3$, $CH_2Cl_2$. (iv) $H_5IO_6$, $MeNH_2$,MeOH−$H_2O$.

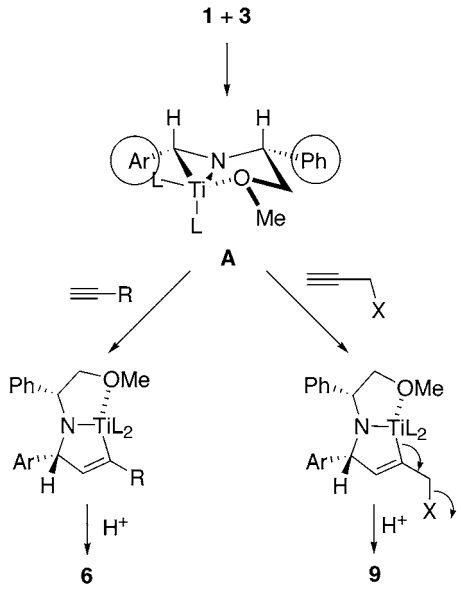
optically active allylamine has been reported previously.[8,9] However, the scope of the reaction was not explored.

We next carried out the reaction of the azatitanacyclopropanes derived from **3** with propargyl compounds **8** and found that the reaction afforded the expected optically active α-allenylamines highly selectively. Thus, the titanium complex prepared from **1** and **3a** was treated with propargyl bromide (**8a**) (1.5 equiv) at −35 °C to afford α-allenylamine **9aa** in 74% isolated yield. The diastereomeric ratio of **9aa** thus obtained was found to be >98:2 by $^1$H NMR analysis, while the absolute configuration of the major isomer was determined as depicted in the equation shown in Table 2 (vide infra).

This highly diastereoselective formation of α-aryl-α-allenylamines from chiral imines of type **3** and propargyl compounds appears to be reasonably general, and additional results are collected in Table 2. Optically active α-allenylamines having 1- and 2-naphthyl groups (entries 3 and 4), a 4-siloxy-phenyl group (entry 5), or a mesityl group (entry 6) as an α-aryl moiety can be prepared starting with the corresponding **3**. As mentioned above (see entry 6 in Table 1), an aromatic iodide survives these reductive conditions so that 2-iodophenyl imine **3b** gave the desired **9ba** without any complication (entry 2). As can be seen from entries 7−10, propargyl phosphates (**8b**,**c**) and acetates (**8d**,**e**) in addition to the halides can be used as a propargylic substrate. The results shown in these entries also indicate that the propargyl substrate having a substituent at the 1- or 3-position proceeded with similar excellent diastereoselectivity to afford allenylamines having an allenyl substituent, though in the case where the product has an axial allenyl chirality such as **9ad** and **9ae**, two diastereomers regarding the allenyl portion were produced.

The stereochemistry of **7a** and **9aa** thus obtained was determined by converting to the known compounds **11**[10] and **13**,[11] respectively, as shown in Scheme 3. The stereochem-

**Scheme 4**




istry of other products shown in Tables 1 and 2 was assigned from analogy with **7a** or **9aa**, respectively.

The stereochemical outcome of the reaction shown in Tables 1 and 2 can be explained by assuming that the reaction proceeds through the azatitanacyclopropane complex shown in Scheme 4, which has the six-membered chair-like titanacyclic structure **A** in which the oxygen is coordinated to the titanium and two aryl groups (Ar and Ph) are situated at the equatorial position.[12]

In summary, we have developed a one-pot method for synthesizing optically active allyl- and α-allenylamines from arylaldimines **3** and 1-alkynes or propargyl compounds via the chiral azatitanacyclopropanes. Although the present method is restricted to preparation of allyl- and α-allenylamines having an α-aryl group, the method might find wide utility because of the ready availability of all reagents used and the operational simplicity of the reaction.

**Acknowledgment.** K.F. is thankful for the Grant of the 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology, Japan, for financial support.

**Supporting Information Available:** Experimental procedures and spectroscopic data for **6**, **7a**, and **9**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett*. **1992**, *33*, 4469.

(9) Enantioselective synthesis of allylamines by the reaction of optically active azazirconacyclopropanes derived from (*ansa*-bistetrahydroindenyl)-$ZrMe_2$ and amines with alkynes was reported: Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2321.

(10) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2423.

(11) Yamamoto, Y.; Shimoda, H.; Oda, J.; Inoue, Y. *Bull. Chem. Soc. Jpn*. **1976**, *49*, 3247.

(12) Insertion of an alkyne is expected to proceed with retention of configuration at the imine carbon atom similarly to that proposed for the zirconocene system.[8,9]