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Highly Stereoselective Asymmetric Construction of an Acyclic Carbon Skeleton Having Two Adjacent Alkyl Substituents by Michael Addition of Optically Active Allenyltitaniums to Alkylidenemalonates

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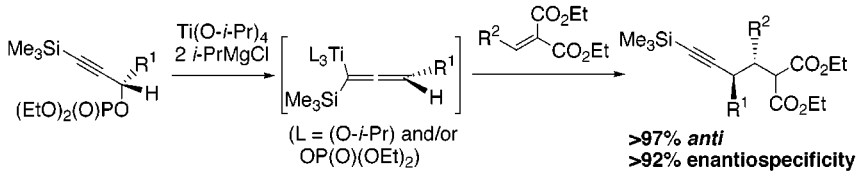
ABSTRACT



Enantio-enriched allenyltitaniums prepared in situ by the reaction of optically active secondary propargyl phosphates with a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl react readily with alkylidenemalonates with excellent regio- and diastereoselectivities to afford the Michael addition products with a high optical purity, thus opening up a new asymmetric method for construction of an acyclic carbon skeleton bearing two adjacent alkyl substituents.

Recently, we reported the synthesis of optically active allenyltitaniums bearing axial chirality by the reaction of optically active secondary propargyl phosphates with a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2*i*-PrMgX (**1**),[1] which proceeds with 97% enantiospecificity.[2a] In our continuing study to utilize the allenyltitaniums thus produced in asymmetric synthesis,[2] we have now found that they react readily with alkylidenemalonates with excellent regio- and diastereoselectivities to afford the Michael addition products with a high optical purity. Thus, the reaction opens up a new asymmetric method for construction of an acyclic carbon skeleton bearing two adjacent alkyl substituents, the structure of which is widely found, as a main unit or subunit, in natural and man-made biologically important compounds.[3] It should be noted that this is the first example of asymmetric Michael addition reaction of an allenylic metal reagent.[4,5]

The allenyltitanium prepared from diethyl (*S*)-1-methyl-3-trimethylsilylprop-2-ynyl phosphate (**2**)[6] and **1** (at −50 to −40 °C for 2 h in ether) reacted smoothly with diethyl ethylidenemalonate (**4**) with excellent regio- and diastereo-

(1) Reviews for synthetic reactions mediated by a Ti(O-*i*-Pr)$_4$/2*i*-PrMgX reagent: Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511−1519. Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753−775. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835−2886. Sato, F.; Okamoto, S. *Adv. Synth. Catal.*, in press.

(2) (a) Okamoto, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4551−4554. (b) An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4555−4558. (c) An, D. K.; Hirakawa, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 3737−3740. (d) Okamoto, S.; Matsuda, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **2001**, *42*, 6323−6326.

(3) For asymmetric synthesis of an acyclic carbon skeleton with two adjacent alkyl groups by conjugate addition of chiral enolates to α,β-unsaturated carbonyl compounds, see: (a) Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025−5028. (b) Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959−962. By conjugate addition of chiral allyllithiums, see: (c) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996−2997. (d) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004−1005. By catalytic asymmetric Michael addition, see: (e) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441−4444 and references therein.

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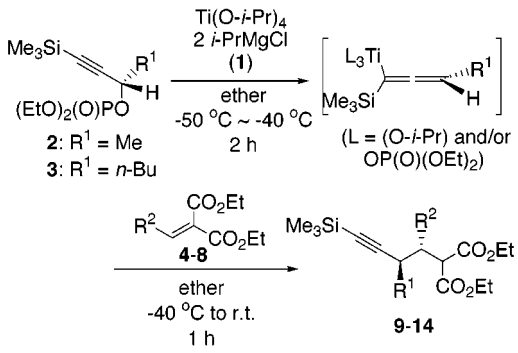
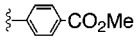
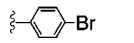
selectivity (at −40 °C to room temperature over 1 h) to afford 92% yield of the corresponding Michael addition product **9** having the structure shown in Scheme 1 and entry 1 in Table

Scheme 1. Generation of Optically Active Allenyltitaniums and Their Reaction with Alkylidenemalonates



1. The enantiomeric ratio (er) of **9** thus obtained was determined to be 96:4 by GC analysis with use of a chiral column after derivatization (vide infra).

Table 1. Michael Addition Reaction of Optically Active Allenyltitaniums with Alkylidenemalonates

Entry	2 or 3[a] R1		4-8 R2		9-14	Yield, %[b]	Anti:Syn[c]	Er[d]
1	Me	**2**	Me	**4**	**9**	92	97:3	96:4[e] (97:3)
2	Me	**2**	*n*-Bu	**5**	**10**	89	98:2	98:2[f] (99:1)
3	Me	**2**	Ph	**6**	**11**	96	~100:0	98:2[g] (99:1)
4	Me	**2**	 **7**		**12**	82	~100:0	96:4[h] (97:3)
5	*n*-Bu	**3**	Me	**4**	**13**	85	97:3	94:6[f] (96:4)
6	*n*-Bu	**3**	 **8**		**14**	97	~100:0	96:4[g,i] (98:2)

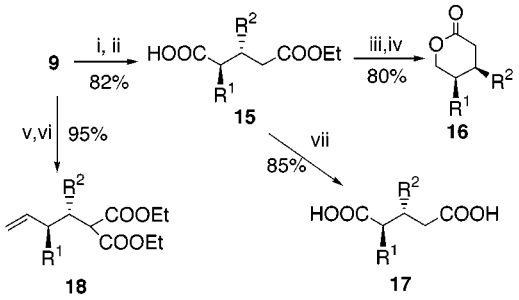
[a] **2**: 97.8% ee. **3**: 95.2% ee. [b] Isolated yield. [c] Ratio was determined by GC analysis. [d] Enantiomeric ratio of the *anti* isomer. The er values given in parentheses are simply extrapolated when the starting propargylic phosphates **2** and **3** are 100% ee. [e] Determined by GC analysis of **15**. [f] Determined by GC analysis of the corresponding acid of the type **15**. [g] Determined by GC analysis of the diol prepared by the reaction of the compound of the type **15** with $LiAlH_4$. [h] Determined by HPLC analysis. [i] Determined by GC analysis of the diol prepared by the reduction with $LiAlH_4$ of the compound of the type **15** in which R^2 is Ph (debromination occurred upon treatment with $LiAlH_4$).

Since we used **2** with 97.8% enantiomeric excess (ee), the overall enantiospecificity from **2** to **9** was calculated to be 94%, and as the enantiospecificity from **2** to the allenyltitanium is 97%,[2a] the degree of enantiospecificity for the Michael addition reaction was estimated to be 97%.

As revealed from entries 2−6 in Table 1, which shows the results of the reaction using **2** or diethyl (*S*)-1-butyl-3-trimethylsilylprop-2-ynyl phosphate (**3**)[6] and alkylidenemalonates **4**−**8**, the reaction appears reasonably general. Thus, the allenyltitanium derived from **2** reacted with, in addition to **4** where R^2 is methyl, alkylidenemalonates in which R^2 is a primary alkyl (**5**, entry 2) and aryl groups (**6** and **7**, entries 3 and 4) to afford the corresponding Michael adduct with more than 97% diastereoselectivity and more than 92% enantiospecificity. Similarly, the reaction of the titanium reagent derived from **3** also proceeded with excellent selectivities (entries 5 and 6). It is noteworthy that the reaction proceeds smoothly with alkylidenemalonates having a functional group such as an ester or a halide group (entries 4 and 6).

The resulting Michael addition products can be readily transformed into a variety of bifunctional compounds such as **15**−**18** by conventional reaction sequences, as represented by the reaction starting with **9**, by taking advantage of the reactivity of the silylacetylene and malonate functionalities present at each of the terminal positions (Scheme 2). The

Scheme 2. Synthetic Transformation Starting with **9** Where R^1 and R^2 Are Me[a]



[a] (i) LiCl, dimethyl sulfoxide/H_2O, 150 °C; (ii) $NaIO_4$, cat. $RuCl_3$, $CCl_4/CH_3CN/H_2O$; (iii) BH_3, tetrahydrofuran; (iv) H_3O^+; (v) *n*-Bu_4NF, tetrahydrofuran; (vi) H_2, $Pd/BaSO_4$/quinoline; (vii) 2 N HCl, reflux.

anti stereochemistry of **9** was confirmed by the production of the known compound **18**[5] and also by the ^1H NMR analysis of δ-lactone **16**.[7] Meanwhile, the absolute configuration of **9** was determined by comparison of the sign of optical rotation of **17** with that reported [$[\alpha]^{29}_D$ −13.8 (*c* 0.60, $CHCl_3$); lit.[3b] $[\alpha]^{24}_D$ −11 (*c* 1.0, $CHCl_3$)].

Determination of the stereochemistries of other products **10**−**14** shown in Table 1 was carried out as follows. The

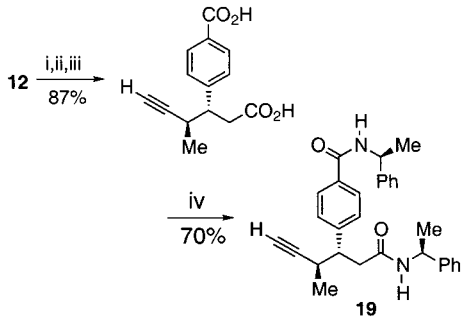
(4) Michael addition reaction of nonchiral or racemic allenylstannanes and allenylsilanes to α,β-unsaturated carbonyl compounds in the presence of Lewis acid have been reported: Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604−1606. Santelli, M.; El Abed, D.; Jellal, A. *J. Org. Chem.* **1986**, *51*, 1199−1206. Haruta, J.; Nishi, K.; Matsuda, S.; Tamura, Y.; Kita, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1065−1066.

(5) Yamamoto reported that Michael addition of allyltitaniums to alkylidenemalonates proceeds with high *anti* stereoselectivity: Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, *53*, 3597−3603. Yamamoto, Y.; Nishii, S.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 386−388.

(6) Optically active propargyl phosphates **2** and **3** could be readily prepared, respectively, from naturally occurring lactates or 2,3-epoxyheptan-1-ol derived from 2-heptenol by Sharpless asymmetric epoxidation. See ref 2 for the synthesis and determination of the optical purities.

anti stereochemistry of all products was confirmed by ^{1}H NMR analysis after converting to the corresponding δ-lactone of the type **16**.[7] X-ray crystallography of the bis-amide **19** derived from **12** and (*S*)-1-phenylethylamine by the procedure shown in Scheme 3 determined the relative and absolute

Scheme 3[a]



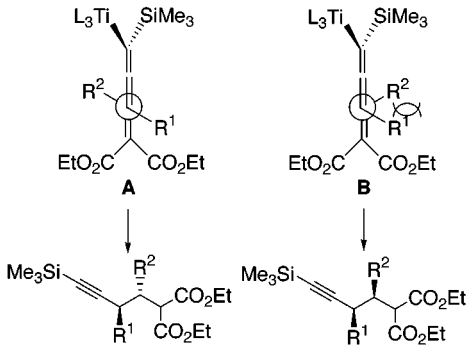
[a] (i) 1 N KOH, MeOH; (ii) H^+; (iii) reflux, 4 h, EtOH; (iv) PyBOP (1*H*-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate), $(i\text{-Pr})_2$NEt, (*S*)-1-Phenylethylamine, DMF.

configurations of **12**.[8] For compounds **10**, **11**, **13**, and **14**, the absolute configuration was assigned from analogy with **9** and **12**.

The stereochemical outcome of the reaction can be rationalized by assuming that the Michael addition reaction of the allenyltitanium with alkylidenemalonate proceeds preferentially via the *anti* coplanar transition structure **A** shown in Scheme 4 rather than **B**, which may be destabilized by the steric repulsion between the substituents R^1 and R^2.[9,10]

Carbon−carbon bond-forming reactions that create two adjacent stereogenic centers with high diastereo- and enantio-

Scheme 4. Proposed Transition Structures for Michael Addition of Allenyltitaniums to Alkylidenemalonates



selectivity in a single step have attracted much interest in organic synthesis. The present one-pot procedure for synthesizing optically active diethyl *anti*-1,2-dialkyl-4-trimethylsilyl-3-butynylmalonates starting from readily available optically active 1-alkyl-3-trimethylsiliy-2-propynyl phosphates and alkylidenemalonates certainly opens up a new efficient method, by taking advantage of the versatile reactivity of the silylacetylene and malonate groups present at each of the terminal positions. Further exploration of the synthetic utility of the reaction is underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization for compounds **9**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The *cis* stereochemistry of δ-lactones of the type **16** was determined on the basis of the ^{1}H−^{1}H coupling constant (3.9−4.2 Hz) and/or the nuclear overhauser enhancement (NOE) between the protons at the β- and γ-positions. Ozegowski, R.; Kunath, A.; Schick, H. *Liebigs Ann.* **1996**, 1443−1448. Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623−5631.

(8) Recrystallization from chloroform provided crystalline **19** as a chloroform-solvate. Crystallographic data (excluding structure factors) for structure **19** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-166668. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (Fax: (44) 1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).

(9) A similar *anti* coplanar transition structure was proposed to explain the predominant production of the *anti* adduct for the conjugate addition of allyltitaniums to alkylidenemalonates; see ref 5.

(10) The cyclic transition structure in which the Ti atom of allenyltitanium is coordinated by one or both of the carbonyl oxygen atom(s) of malonate can be ruled out because it might afford the Michael adduct(s) having an opposite stereochemistry at the propargyl carbon to one obtained here.