Expedient Construction of Multiple Stereogenic Centers in an Acyclic System via the Addition of Aldehydes, Ketones, and Chiral Imines to an Enyne−Titanium Alkoxide Complex

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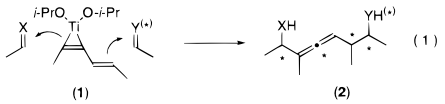
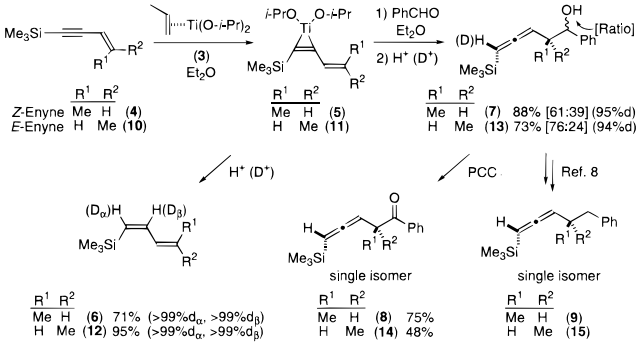
Stereoselective construction of an array of several stereogenic centers in one flask should constitute an important method in organic synthesis,[1] especially when this process could be performed in an asymmetric fashion. Herein we describe a regio- and stereoselective addition reaction of aldehydes, ketones, or imines to one or both of the two carbon−titanium bonds of a conjugated enyne−titanium alkoxide complex **1** (eq 1),[2−4] which creates up to three new consecutive stereo-defined carbon centers as formulated in **1** → **2**. The product **2** has allenic axial chirality, the synthetic utility of which has become more and more appreciated recently,[5] as well as sp^3 chirality due to the substituents on the carbon chain.



(1)

(*Z*)-Enyne **4** (99.5% *Z*) was treated with (η^2-propene)Ti(O-*i*-Pr)$_2$ (**3**) (1.25 equiv), readily prepared from Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl in situ,[6] to generate the enyne-titanium complex **5** (Scheme 1), as evidenced by the protonolysis and deuteriolysis of the complex that cleanly afforded the stereo-defined diene **6** (exclusively *Z*,*Z*-isomer). The addition of the enyne complex **5** to benzaldehyde (0.7 equiv) proceeded in a quite different fashion from a simple (η^2-1-silyl-1-alkyne)Ti(O-*i*-Pr)$_2$ complex reported previously by us.[6b] Thus, the reaction proceeded at the remote olefinic carbon to give the allenyl alcohol **7** as a mixture of only two diastereoisomers out of the four possible ones. The other carbon−titanium bond in **5** not participating in the aldehyde addition was identified by deuteriolysis to give **7**-d_1 with high deuterium incorporation on the allene carbon. Oxidation of **7** afforded the ketone **8** virtually as a single isomer, which shows that the diastereoisomers of **7** as alcohol epimers. This was further confirmed by deoxygenation of the hydroxy group to give known allene **9**[7] as a single isomer,[8] which established the relative stereochemistry of the allene moiety and the methyl group in **7**. The same reaction starting from the isomeric (*E*)-enyne **10** (>99% *E*) afforded exclusively a different set of products as shown by the sequence **10** → **11** → **12**, or **11** → **13** → **14**, or **13** to the known allene **15**[7] (Scheme 1). Thus, the stereochemical integrity of the olefinic portion of the starting enynes was completely transmitted to the series of products, which allows the stereospecific and selective preparation of allene derivatives from the enynes. This reaction has broad applicability with respect to both enynes and aldehydes (or ketones), which is shown in Supporting Information.[8]

Scheme 1. Stereoselective and -specific Addition of Enyne−Titanium Complex to Aldehyde



In place of the simple hydrolytic workup mentioned above, further reaction of the intermediate adduct with an aldehyde or a ketone should broaden the utility of this method. When the titanium complex **5** was first treated with acetone[8] and then with benzaldehyde or heptanal, a single adduct **16** or **17** was obtained (Scheme 2). Diol **16** crystallized from toluene to give large prisms, X-ray crystallography of which unambiguously determined the structure of **16**. Alternatively, complex **5** was intercepted first with benzaldehyde and then with pivalaldehyde[9] to give a 58:42 mixture of two diols **18**, the ratio of which paralleled the mixture of adduct **7** obtained by the simple hydrolysis (61:39, Scheme 1), suggesting that the reaction with pivalaldehyde proceeds with excellent stereoselectivity. This hypothesis was verified by the selective deoxygenation of the benzylic hydroxy group of **18**, which resulted in the formation of the corresponding *tert*-butyl carbinol as a single isomer.[8] The structure of **18** was deduced based on **16**. The same sequence from (*E*)-enyne **10**, acetone,

(1) Although there are numerous methods available for the stereoselective construction of two stereogenic centers, those for more than three in an asymmetric fashion are less common. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. Trost, B. M.; Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 5. Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13159. Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.

(2) For review on group 4 metal−acetylene and −olefin complexes, see: Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047−1058. Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124−130. Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burlakov, V. V.; Rosenthal, U. *Synlett* **1996**, 111−118. Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755−769.

(3) A few group 4 metal-conjugated enyne complexes were reported, but their unique synthetic utility has not been pursued. Stepnicka, P.; Gyepes, R.; Císarová, I.; Horácek, M.; Kubista, J.; Mach, K. *Organometallics* **1999**, *18*, 4869−4880. Takahashi, T.; Xi, Z.; Nishihara, Y.; Huo, S.; Kasai, K.; Aoyagi, K.; Denisov, V.; Negishi, E. *Tetrahedron* **1997**, *53*, 9123−9134.

(4) Cf. group 4 metal−acetylene complexes are known to add to aldehydes, ketones, or imines, but the reaction stops at the stage of mono-addition (see literature cited in references 2, 6, and 10). For the double addition to group 4 metal−*olefin* or −*diene* complexes, see: Thorn, M. G.; Hill, J. E.; Waratuke, S. A.; Johnson, E. S.; Fanwick, P. E.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 8630−8641. Yasuda, H.; Tatsumi, K.; Nakamura, A. *Acc. Chem. Res.* **1985**, *18*, 120−126.

(5) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−5349. Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535−6545. Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 11295−11305. Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5773−5784. Shepard, M. S.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597−2605. Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550−4551. Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367−371. Yoshida, Y.; Okamoto, S.; Sato, F. *J. Org. Chem.* **1996**, *61*, 7826−7831 and references therein. For stereospecific, electrophlic addition to silylallenes, see: Fleming, I.; Dunogués, J.; Smithers, R. In *Organic Reactions*; Kende, A. S., Ed.; Wiley: New York, 1989; Vol. 37, pp 57−575. Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192. Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630−633. The allenes used in these reports were prepared through the S_N2' displacement of propargyl alcohol derivatives. Thus, the conversion of eq 1 should provide a different way to make such allenes.

(6) (a) Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511−1519. (b) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203−3206.

(7) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492−4493.

(8) See Supporting Information.

(9) Pivalaldehyde was chosen as the second aldehyde in order to discriminate between the two hydroxy groups in **18** for structural determination.

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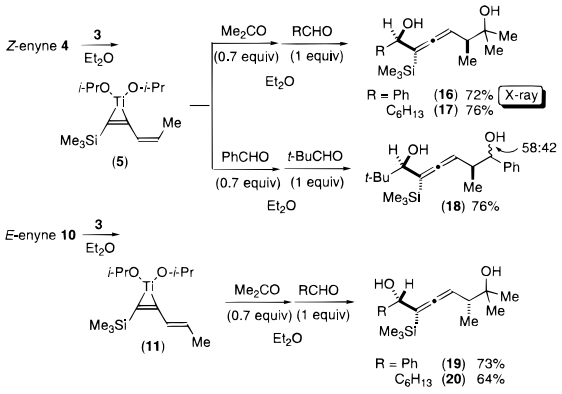
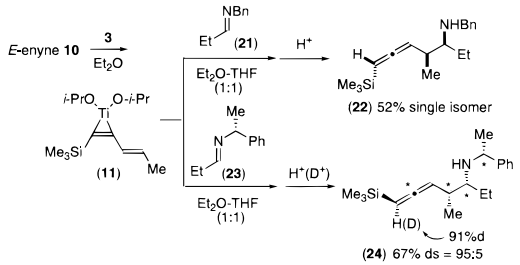
Scheme 2. Sequential Stereospecific and -selective Addition of Two Carbonyl Compounds



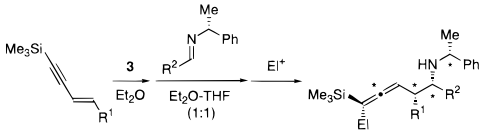
Scheme 3. Addition of Enyne−Titanium Complex to Imines



and an aldehyde afforded virtually a single product **19** or **20**, which proved to be isomeric to **16** or **17**, respectively. The structure of **19** was unambiguously assigned by correlation to **16** of the established structure.[8] These results demonstrated that the tandem addition of aldehydes or ketones to both the carbon−titanium bonds in **1** serves for the construction of three stereogenic centers in an acyclic system.

As far as the coupling partners are concerned, imines impart more advantages to this reaction as regards the selectivity and asymmetric synthesis (Scheme 3). The acetylene complex **11** reacted with an achiral imine **21** to afford an allenylamine **22** virtually as a single isomer.[10] This is in marked contrast to the aforementioned aldehyde addition, which usually gave rise to the formation of a mixture of two isomeric alcohols. The structure assigned to **22** was verified by the comparison with authentic samples.[8] It should be noted that the relative stereochemistry of the allene moiety and the methyl group in **22** is different from that of the corresponding aldehyde adduct **13** obtained from the same *E*-enyne (Scheme 1), suggesting a different stereochemical approach between aldehydes and imines to the enyne-titanium complex. Gratifyingly, extension of this reaction to an asymmetric version starting with *N*-(α-phenylethyl)imines[11] such as **23** turned out to be quite promising. When the complex **11** was allowed to react with **23**, allenylamine **24** was produced as a 95:5 mixture of two isomers unaccompanied with the remaining six possible isomers. The relative and absolute stereochemistry of the major allenylamine **24** was determined by derivatization and correlation to known compounds,[8] which also revealed that the selectivity of 95:5 in this case most likely stems from the asymmetric induction step (i.e., the relative stereochemistry between the phenethylamine part and the remainder of the molecule) rather than the alignment of substituents on the allene chain. More examples, including the carbonyl addition of the intermediate titanium species, are summarized in Table 1, which shows that diastereoselectivities up to 97:3 for the three newly created chiral centers could be achieved by this method.

Table 1. Asymmetric Construction of Three Stereogenic Centers



entry	enyne R¹		imine R²		El⁺	El	product	yield (%)	ds[a]
1	Me	**10**	Et	**23**	H^+	H	**24**	67	95:5
2				**23**	$Me_2C{=}O$	$Me_2C(OH)-$	**25**	45	93:7
3	C_6H_{13}	**26**	Et	**23**	H^+	H	**29**	67	92:8
4	Me	**10**	Me	**27**	H^+	H	**30**	53	93:7
5	Me	**10**	*i*-Bu	**28**	H^+	H	**31**	53	97:3

[a] This value most likely reflects the degree of asymmetric induction.

The above transformations appear to be very practical, because (i) the stereo-defined conjugated enynes are readily accessible by the Sonogashira coupling reaction,[12] (ii) the optically active imines are derived from inexpensive phenylethylamine in one step, and (iii) the reagents, the titanium alkoxide and Grignard reagent, are available at low cost. A preliminary rationalization of stereochemical course of these reactions is presented in Supporting Information; however essential information on the structures of the reacting intermediates as well as the stereo- and regiochemical patterns of the organotitanium reactions is so far not available.[13]

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Supporting Information Available: Addendum to Scheme 1, typical procedures and characterization data for starting materials and products, and rationalization of the stereochemical outcome of the reaction (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The addition to imines must be carried out in ether−THF (1:1) rather than ether (cf. Schemes 1 and 2); otherwise, a mixture of allenylamine and undesired dienylamine is produced. Unfortunately, (*Z*)-enyne complex **5** behaved like a simple acetylene−titanium complex to furnish only dienylamines. For the reaction of the simple acetylene complexes with imines, see: Gao, Y.; Harada, K.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 5913−5916.

(11) Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441−2495. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. Gao, Y.; Sato, F. *J. Org. Chem.* **1995**, *60*, 8136−8137.

(12) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 521−549.

(13) For the reactions of organotitanium compounds, see: Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139−172. Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 1994; pp 195−282.