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Diastereoselective Allylations of Allyl–Propargyl Hybrid Cations: Synthesis of Conjugated 1,5-Dien-7-yne Frameworks Bearing C(4)-Stereogenic Centers

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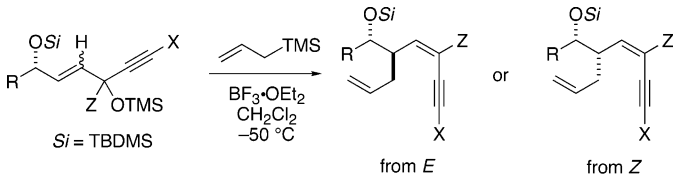
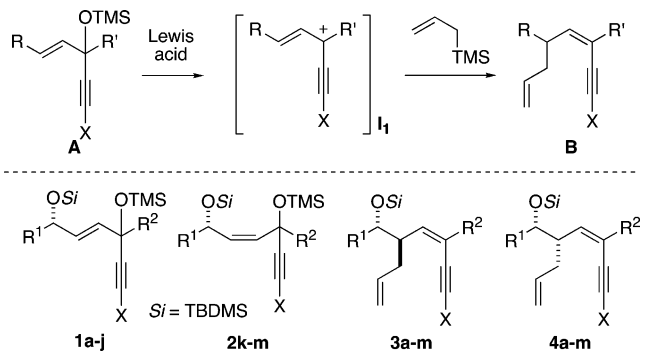
ABSTRACT



Chiral C(4)-substituted (*E*)- or (*Z*)-1-alkynyl-1-trimethylsilyloxy-2-butene systems provide anti-(*Z*) or syn-(*Z*) conjugated dienyne, with a very high level of stereocontrol, on treatment with BF_3·OEt_2 in CH_2Cl_2 at −50 °C in the presence of allyltrimethylsilane. The Cieplak conformation for (*E*)-substrates and neighboring-group participation for (*Z*)-substrates are considered to be responsible for the stereochemical consequences.

Lewis acid-promoted nucleophilic allylations using allylsilanes have found widespread application in organic synthesis.[1] Among them, cyclic acetal-based oxonium ions have succeeded in allylation with a high level of diastereocontrol, for which general stereoelectronic models[2] have been proposed. On the other hand, no stereoselective allylation of acyclic allylic cations has been reported so far.[3] Fortunately, a clue that deserves consideration about such a synthetically meaningful system has recently been provided which features the intervention of an allyl−propargyl hybrid cation (**I_1**) generated from 1-(alkynyl)propen-2-yl silyl ethers (**A**) by the action of Lewis acid (Scheme 1).[4] The subsequent allylation with allyltrimethylsilane proceeded in a totally regioselective manner to furnish dienynes involving conju-

Scheme 1



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(1) For reviews for allylation using allyltrimethylsilane, see: (a) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200−206. (b) Sakurai, H. *Pure Appl. Chem.* **1985**, *57*, 1759−1770. (c) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto H., Eds.; Springer-Verlag: Berlin, Heidelberg, 1999; Vol. II, Chapter 27.

(2) (a) Schmitt, A.; Ressig, H.-U. *Synlett* **1990**, 40−42. (b) Powell, S. A.; Tenenbaum, J. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 12648−12649. (c) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209. (d) Kudo, K.; Hashimoto, Y.; Sukegawa, M.; Hasegawa, M.; Saigo, K. *J. Org. Chem.* **1993**, *58*, 579−587.

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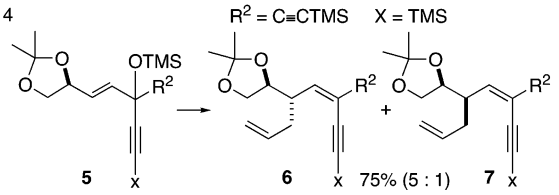
gated (*Z*)-enyne functionality (**B**). Thus, if the substituent R involves a stereogenic center as in **1** or **2**, the allylation may proceed in a diastereomerically biased manner. If realized, this may provide a useful way for synthesizing chiral conjugated 1,5-dien-7-yne backbones with new C(4)-stereogenic centers such as **3** or **4**.

This idea led to fruitful results which are summarized in Table 1: BF_3·OEt_2-promoted allylations of **1a**−**j** or **5** (*E*-isomers) and **2k**−**m** (*Z*-isomers) with allyltrimethylsilane smoothly proceeded (CH_2Cl_2, −50 °C, 10 min) to afford anti- (**3a**−**j** or **6**) and syn-products (**4k**−**m**) in good yields, respectively, depending on the geometry of the substrates. Absolute configurations for induced stereogenic centers of **3** and **6** or **4** and **7** were determined by ^{1}H NMR analysis based on NOE data observed for tetrahydrofuran derivatives **8** or **9** derived from these products, respectively, via deprotection and iodo-etherification (Figure 1).[5]

Table 1. Diastereoselective Allylation of (*E*)- and (*Z*)-Substrates[a]

entry	sub	R^1	R^2	X	yield/%	**3** : **4** [b]
	E-isomer					
1	**1a**	Me	C≡CPh	Ph	96	5.5 : 1
2	**1b**	Me	C≡CPr	Pr	88	5.5 : 1
3	**1c**	Me	C≡CTMS	TMS	83	5.5 : 1
4	**1d**	$TBSOCH_2$	C≡CTMS	TMS	71	2.5 : 1
5	**1e**	*i*-Pr	C≡CTMS	TMS	78	> 99 : 1
6	**1f**	$PhCH_2$	C≡CTMS	TMS	76	10 : 1
7	**1g**	*i*-Pr	Me	TMS	56 [c]	> 99 : 1
8	**1h**	*i*-Pr	Ph	TMS	88	> 99 : 1
9	**1i**	*i*-Pr	*i*-Pr	TMS	80	> 99 : 1
10	**1j**	$PhCH_2$	*i*-Pr	TMS	63	9.5 : 1
	Z-isomer					
11	**2k**	Me	C≡CTMS	TMS	70	1 : 5.5
12	**2l**	*i*-Pr	Ph	TMS	73	> 1 : 99
13	**2m**	$PhCH_2$	*i*-Pr	TMS	56	1 : 10

14



[a] Conditions: allyltrimethylsilane (150 mol %), BF_3·OEt_2 (100 mol %), CH_2Cl_2, −50 °C, 10 min. [b] **3c** = **3k**, **4c** = **4k**, **3h** = **3l**, **4h** = **4l**, **3j** = **3m**, **4j** = **4m**. [c] *Z*/*E* = 8/1.

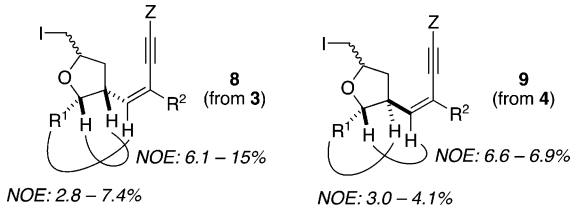
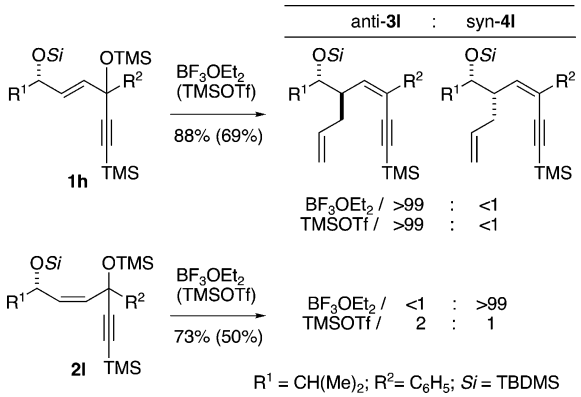


Figure 1.

The level of diastereoselectivity seems to be controlled by the steric bulkiness of R^1, showing the highest ratio >99:1 when R^1 = *i*-Pr for both *E*- and *Z*-isomers (entries 5, 7−9, and 12). For entries 7−10, 12, and 13, a high level of control was simultaneously achieved over not only two contiguous stereogenic centers but also the geometry of the conjugated enyne moieties.[6] It should be noted that mixtures of diastereoisomers of 1:1 to 3:1 ratios with regard to the propargylic stereogenic centers were used as substrates in these cases. Furthermore, each diastereoisomer isolated from such a mixture by a silica gel column chromatography led to the same product as that obtained from the mixture of propargylic epimers. These facts clearly suggest a typical S_N1 nature of the reaction and also the dominant role of the TBDMSO-linked stereogenic center as a stereocontrol element. Although entry 4 (**1d**) shows unacceptable selectivity (2.5:1), entry 14, employing an acetonide protection (**5**), may provide a practical replacement for it, giving anti- (**6**) and syn-isomer (**7**) in a ratio of 5:1.

The choice of Lewis acids was highly important for the reaction to be successful. Trimethylsilyl triflate (TMSOTf), for instance, exhibited remarkable effects on not only chemical yields but also syn/anti selectivity. Representative examples are shown in Scheme 2. In general, TMSOTf lowered chemical yields for both **1h** and **2l**. The syn/anti selectivity was kept intact for (*E*)-isomer **1h** irrespective of

Scheme 2. Effect of Lewis Acid on Diastereoselective Allylation for Representative (*E*)- and (*Z*)-Isomers[a]



[a] Conditions: allyltrimethylsilane (150 mol %), Lewis acid (100 mol %), CH_2Cl_2, −50 °C, 10 min.

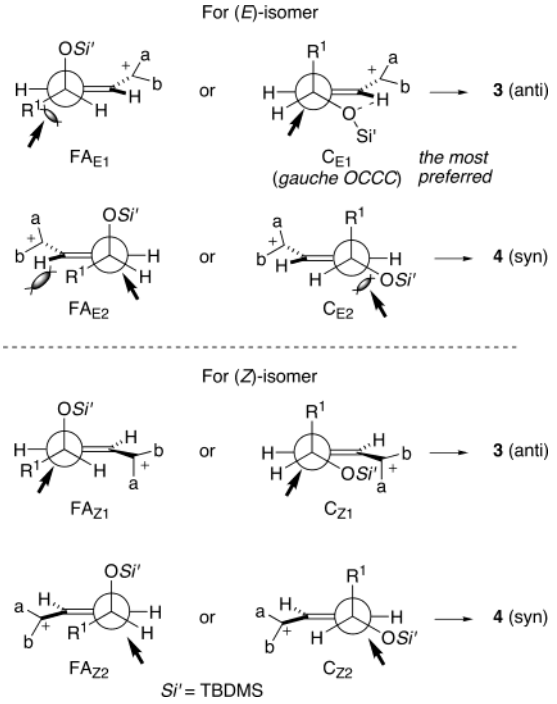
(3) For synthetically useful allylations of allyl, propargyl, or benzyl cations with no stereochemical consequences, see: (a) Cella, J. A. *J. Org. Chem.* **1982**, *47*, 2125−2130. (b) Mayr, H.; Pock, R. *Tetrahedron* **1986**, *42*, 4211−4214. (c) Murakami, M.; Kato, T.; Mukaiyama, T. *Chem. Lett.* **1987**, 1167−1170. (d) Hayashi, M.; Inubushi, A.; Mukaiyama, T. *Chem. Lett.* **1987**, 1975−1978. (e) Mayr, H.; Gorath, G.; Bauer, B. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 788−789. (f) Yokozawa, T.; Furuhashi, K.; Natsume, H. *Tetrahedron Lett.* **1995**, *36*, 5243−5246. (g) Kaur, G.; Kaushik, M.; Trehan, S. *Tetrahedron Lett.* **1997**, *38*, 2521−2524. (h) Rubin, M.; Gevorgyan, V. *Org. Lett.* **2001**, *3*, 2705−2707.

(4) Ishikawa, T.; Okano, M.; Aikawa, T.; Saito, S. *J. Org. Chem.* **2001**, *66*, 4635−4642: see also Ishikawa, T.; Aikawa, T.; Mori, Y.; Saito, S. *Org. Lett.* **2003**, *5*, 51−54.

Lewis acids, but for (*Z*)-isomer **2l**, a reversal of the stereochemical outcome was observed for TMSOTf (2:1 in preference to anti-isomer **3l**) in marked contrast to BF_3·OEt_2 (>99% syn). These results strongly suggest that the steric course for the (*E*)- and (*Z*)-substrates should be different from each other,[7] and the way by which the syn products result from **2** might involve some dynamic process which is specific for **2** and is lacking for **1** as is discussed later (vide infra).

We tried to explain the selectivity observed for **1** and **2** on the basis of Felkin−Ahn models taking the Cieplak effect[8] into account.[9] Thus, as shown in Scheme 3, four models such as Felkin−Ahn (FA_{E1} and FA_{E2}) and Cieplak (C_{E1} and C_{E2}) types for (*E*)-isomers and their (*Z*)-versions (FA_{Z1}, FA_{Z2}, C_{Z1}, and C_{Z2}) deserve consideration.

Scheme 3. Felkin−Ahn and Cieplak Stereochemical Models

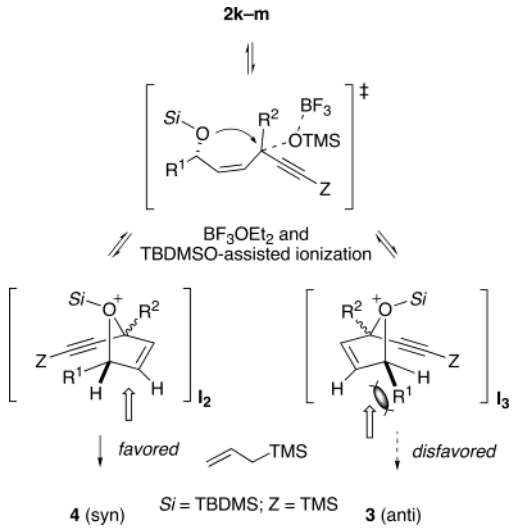


The model C_{E1} should be responsible for selective formation of anti-isomers **3** from **1** because this is free from nonbonded interactions between the incoming nucleophile and either R^1 or *Si′*O substituents whereas the remaining three models (FA_{E1}, FA_{E2}, and C_{E2}) may suffer from this disadvantage. In addition, C_{E1} would expect stabilizing electrostatic interaction stemming from the gauche-OCCC arrangement.[10] The ion-pairing with TfO^- would not change the situation for these models because such a non-nucleophilic counteranion should locate far away from both R^1 and *Si′*O substituents or from an incoming nucleophile.

On the other hand, it seems difficult to interpret the highly syn-selective nature for allylation of (*Z*)-isomers (entries 11−13) on the basis of these four models (FA_{Z1}, FA_{Z2}, C_{Z1}, and C_{Z2}). Every conformation seems to lack enough stabilization to override the others. Therefore, as already mentioned above, the reaction should involve a certain dynamic process in which the TBDMSO-linking stereogenic center can act as a stereocontrolling element.

The most plausible mechanism may involve the 1,5-participation[11] of the TBDMSO group by which BF_3·OEt_2-promoted ionization should be assisted. The outline of such a process is illustrated in Scheme 4.

Scheme 4. Siloxy Participation Mechanism for (*Z*)-Substrates



The BF_3·OEt_2-promoted and TBDMSO-participating ionization may involve an entropically advantageous five-membered transition state structure leading to two possible cationic intermediates such as $\mathbf{I_2}$ and $\mathbf{I_3}$.[12] Although the energy difference between these two intermediates might be small due to the small size of the alkynyl group, the R^1 group necessarily interferes with approach of allyltrimethylsilane toward $\mathbf{I_3}$, whereas $\mathbf{I_2}$ may be free from such a steric constraint. Thus, the reaction would lead to syn-product **4**.

(5) See the Supporting Information for details.

(6) The sterically less demanding nature of an alkyne unit should be responsible for the Z-selective conjugated enyne formation; see ref 4.

(7) The difference for stereochemical outcomes between (*E*)- and (*Z*)-substrates when TMSOTf was employed might be rationalized by assuming that the TMSOTf leads to a stable ion-pair intermediate between allyl−propargyl hybrid cation and TfO^-.

(8) (a) Cieplak, A. S. *J. Am. Chem. Soc*. **1981**, *103*, 4540−4552. (b) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc*. **1984**, *106*, 3880−3882. See also: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994; pp 876−886.

(9) For discussion pertinent to this issue, see: (a) Yamamoto, Y.; Chounan, Y.; Nishi, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc*. **1992**, *114*, 7652−7660. (b) Kim. J. D.; Zee, O. P.; Jung, Y. H. *J. Org. Chem*. **2003**, *68*, 3721−3724.

(10) (a) Wu, T.-C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem*. **1987**, *52*, 4819−4823. (b) Houk, K. N.; Eksterowicz, J. E.; Wu, Y.-D.; Fuglesang, C. D.; Mitchell, D. B. *J. Am. Chem. Soc*. **1993**, *115*, 4170−4177.

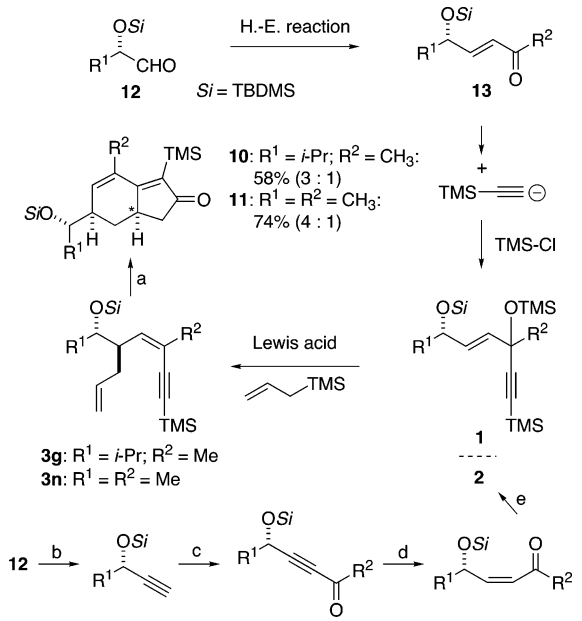
(11) Perst, H. *Oxonium Ion in Organic Chemistry*; Verlag Chemie: Weinheim, 1971.

(12) One of reviewers suggested on the basis of the reviewer's own DFT calculations using the Gaussian program that the cyclic oxonium ion has much lower energy than the open-chain *Z* carbocation but, contrary to our structure, it is totally planar. Our own efforts for this issue are now being made using the Gaussian 03 program.

Since every process involved in Scheme 4 may occur with minimum structural change,[13] no geometrical isomerization from **2** to **1** could be allowed.[14]

Optically pure bicyclic carbon frameworks bearing a linear conjugated dienone function such as **10** (44% yield together with the separable β-epimer 14%) or **11** (59% together with the separable β-epimer 15%) was directly obtained from conjugated 1,5-dien-7-yne frameworks **3g** or **3n**[15] through a Pauson−Khand reaction (Scheme 5). Considering the ready

Scheme 5. Synthetic Applications[a]



[a] Conditions: (a) (1) Co_2CO_8/CH_2Cl_2, (2) CH_3CN, 65 °C, 15 h; (b) CBr_4, PPh_3, NEt_3; (c) (1) BuLi, (2) R^2CHO, (3) SO_3·Py, NEt_3; (d) H_2, Lindlar; (e) (1) TMSCC, BuLi, (2) TMSCl, imidazole.

availability of **1** from commercially available chiral carbon sources,[16] the present work may significantly serve organic synthesis. For instance, starting from optically pure aldehyde **12**, derived from the corresponding L-amino acid (R^1 = *i*-Pr/L-valine),[17] **1h** was prepared via an intermediate such as **13**. For preparation of the corresponding (*Z*)-isomer, the common intermediate **12** was convenient and led to **2** (Scheme 5, bottom)[5] through a series of routine transformations involving Corey's procedure for formyl to ethynyl conversion,[18] the generation of the corresponding acetylide anion and its addition to aldehydes, oxidation of the thus-obtained ynol to the ynone, hydrogenation of the triple bond using the Lindlar catalyst to the enone, and final addition of trimethylsilylacetylide anion to the enone followed by treatment of the resulting ynol with chlorotrimethylsilane.

In conclusion, we have disclosed the novel BF_3·OEt_2-promoted diastereoselective allylations of chiral allyl-propargyl hybrid cations generated from acyclic precursors leading to highly functionalized carbon frameworks of synthetic interest. For (*E*)-substrates, the Cieplak conformation with the gauche-OCCC arrangement[10] should play an important role in determining the stereochemical outcomes. On the other hand, ionization assisted by the combination of the Lewis acid and the neighboring TBDMSO-group attached to the stereogenic center should be crucial for the diastereofacial differentiation of the (*Z*)-substrates.

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Supporting Information Available: Experimental procedures and spectroscopic data including stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For the principle of least motion, see: (a) Hine, J. *J. Org. Chem.* **1966**, *31*, 1236−1246. (b) Tee, O. S. *J. Am. Chem. Soc.* **1969**, *34*, 7144−7149. (c) Jochum, C.; Gasteiger, J.; Ugi, I. *Angew. Chem, Int. Ed. Engl.* **1980**, *7*, 495−574.

(14) When **1j** or **2m** was subjected to the reaction conditions without allyltrimethylsilane, these substrates were recovered unchanged. However, such substrates in which a TBDMS group of **1j** or **2m** was replaced with a TMS group were subjected to the conditions as just mentioned above, hydride shift from the stereogenic center to the neighboring sp^2 carbon took place to give β,γ-unsaturated ketones in a significant amount. These results suggest, though are not necessarily direct evidence, that we cannot completely ruled out the possibility of the 1,2-participation by the TBDMSO-group even for (*E*)-substrates.

(15) This compound was prepared from ethyl (*S*)-lactate through a series of reactions involving TBDMS protection, DIBALH reduction, Horner−Emmons reaction, and appropriate transformations directed to **3** as shown in Scheme 5.

(16) Optically pure α-amino acids, α-hydroxycarboxylic acids, or glyceraldehyde were used for the preparation of **1** and **2**: see the Supporting Information.

(17) A series of routine transformations from α-amino acids involving deamination, esterification, *O*-protection, and reduction led to **1l**.

(18) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.