J|A|C|S
COMMUNICATIONS

The Effect of Alkynyl Groups on Torquoselectivity. Highly Stereoselective Olefination of Alkynyl Ketones with Ynolates

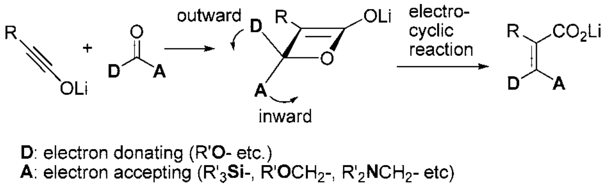
Takashi Yoshikawa,† Seiji Mori,‡ and Mitsuru Shindo*,¶

Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasuga-koen, Kasuga 816-8580, Japan, Faculty of Science, Ibaraki University, Mito, Ibaraki 310-8512, Japan, Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga-koen, Kasuga 816-8580, Japan

Received December 8, 2008; E-mail: shindo@cm.kyushu-u.ac.jp

In electrocyclic ring-opening reactions of cyclobutene analogues, the geometry of the dienyl products is controlled by torquoselectivity. Houk and co-workers have revealed the effects of various kinds of substituents on the torquoselectivity of the ring opening of cyclobutenes, including several heteroatoms.[1] It has been shown experimentally and theoretically that in the transition states, the orbital interactions between the breaking C−C σ or σ^* orbitals and the appropriate bonding and/or antibonding orbitals of the substituents on the ring strongly influence the torquoselectivity.[2] Recently, we have developed a new olefination method for carbonyl compounds with ynolates giving multisubstituted alkenes with high stereoselectivities[3] in which the β-lactone enolate intermediates, i.e., oxetenes, are ring-opened with unusually high torquoselectivity. In particular, acylsilanes,[4] α-oxy- and α-amino ketones,[5] and esters[6] were olefinated to afford tetrasubstituted olefins with excellent stereoselectivity.[7] This high torquoselectivity is attributed to the strong orbital interactions between the nonbonding orbital of the oxygen on the oxetene as well as the breaking C−O σ bond with antibonding orbitals such as the Si−C σ^* orbitals, C−X (X = O, N) σ^* orbitals in the case of the acylsilanes and the α-oxy- and α-amino ketones. In other words, electron donating substituents rotate outward, whereas electron-accepting substituents rotate inward to afford the stereodefined products (Scheme 1).[8]

Scheme 1. Heteroatom-Assisted Torquoselective Olefination

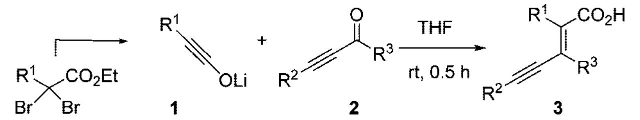


These results are all based on heteroatom-assisted olefinations. Since the effect of nonpolarized carbon substituents on torquoselectivity has not yet been established, the efficient torquoselective olefination without heteroatoms on the substituents has not been achieved. Although Houk and co-workers predicted that the alkynyl group favors outward rotation ($\Delta E^{\ddagger}_{\text{(in-out)}} = 7.6$ kcal/mol) in the ring opening of 3-ethynylcyclobutene, no experimental results are presently available.[9−11] Herein, we describe the strong substituent effect of alkynyl groups on the torquoselectivity and the highly stereoselective olefination of alkynyl ketones with ynolates.

Ynolate **1a**, prepared from ethyl 2,2-dibromopropionate with *t*-BuLi,[12,13] reacted with 1-phenyl-1-heptyn-3-one (**2a**) at room temperature for 30 min to afford the tetrasubstituted olefin **3a** in a *Z*/*E* ratio of 91:9 (Table 1, entry 1). Encouraged by this result, we decided to examine the olefination of several kinds of alkynyl ketones as substrates, as shown in Table 1. The ketones with an alkyl substituent on the terminal ethynyl group afforded the olefins with excellent selectivity (entries 2 and 3), while the silylethynyl ketone provided *E*-olefins along with a small amount of the minor *Z*-isomers (entries 4, 5, and 6), but the acylsilane and the styryl alkynyl ketone afforded single isomers without any stereoisomers (entries 8 and 9). Even the highly stereocongested alkene (**3f**) could be generated using the *tert*-butyl substituted ynolate, owing to the "compact" and highly nucleophilic properties of ynolates. These results therefore illustrate the first highly stereoselective olefination of alkynyl ketones resulting in tetrasubstituted olefins. Furthermore, in this electrocyclic reaction, the alkynyl group prefers outward rather than inward rotation over the alkyl and alkenyl groups, and the substituent on the terminal position of the ethynyl group has a slight effect on the torquoselectivity. However, the olefination of the alkynyl phenyl ketones (**2h**, **2i**) did not show selectivity (entries 10 and 11), with the alkynyl and phenyl groups rotating outward to a similar extent.

To clarify the high torquoselectivity, B3LYP/6-31G(d)[14] level calculations were carried out for the ring-opening transition states of the oxetene (β-lactone lithium enolate which is coordinated by two molecules of dimethyl ether). The most stable transition states

Table 1. Olefination of Alkynyl Ketones with Ynolates



entry	R^1	1	R^2	R^3	2	yield (%)	*Z*:*E*^{a}
1	Me	**1a**	Ph	*n*-Bu	**2a**	69 (**3a**)	91:9
2	Me	**1a**	*t*-Bu	*n*-Bu	**2b**	88 (**3b**)	95:5
3	Me	**1a**	MPMO(CH$_2$)$_2$	*n*-Bu	**2c**	85 (**3c**)	>99:1
4	Me	**1a**	TBS	*n*-Bu	**2d**	69 (**3d**)	90:10
5	Ph	**1b**	TBS	*n*-Bu	**2d**	50 (**3e**)	96:4
6	*t*-Bu	**1c**	TBS	*n*-Bu	**2d**	39 (**3f**)	95:5
7	Me	**1a**	TMS	Me	**2e**	76^b (**3g**)	95:5
8	Me	**1a**	TBS	TMS	**2f**	75 (**3h**)	>99:1
9	Me	**1a**	TBS	*trans*-PhCH=CH	**2g**	81 (**3i**)	>99:1
10	Me	**1a**	Ph	Ph	**2h**	98 (**3j**)	50:50
11	Me	**1a**	*t*-Bu	Ph	**2i**	97 (**3k**)	68:32

^{a} The stereochemistry was determined by NOE experiments of the products or the corresponding derivatives. See Supporting Information. ^{b} The product was 2,3-dimethylpent-2-en-4-yne without the trimethylsilyl substituent.

[†] Interdisciplinary Graduate School of Engineering Sciences, Kyushu University.
[‡] Ibaraki University.
[¶] Institute for Materials Chemistry and Engineering, Kyushu University.

10.1021/ja809592q CCC: $40.75

leading to the *E*- and the *Z*-forms are shown in Figure 1.[15] According to the calculated $\Delta\Delta G^{\ddagger}$, the TSE1 is 8.3 kJ/mol more stable than TSZ1, which is consistent with the experimental results. The NBO (natural bond orbital) analysis[16] revealed the secondary orbital interactions between the π-orbital of the alkyne and the σ^*-orbital of the breaking C−O bond (**A** in Figure 2), and between the π^*-orbital of the alkyne and the σ-orbital of the breaking C−O bond (**B** in Figure 2). While the orbital interaction **A** in TSE1 is 13.7 kJ/mol larger than the corresponding interaction in TSZ1, the interaction **B** in TSE1 is 3.7 kJ/mol smaller. The interaction between the σ^*-orbital of the C−H bond in the methyl group and the σ-orbital of the breaking C−O bond (**C** in Figure 2) also contributes to the *E*-selectivity. Consequently, the orbital interaction **A** dominates the torquoselectivity.[17]

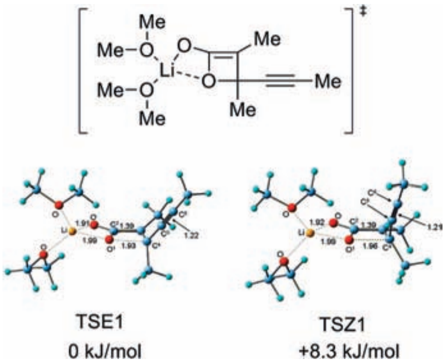


Figure 1. The most stable transition states leading to the *E*- and *Z*-forms.

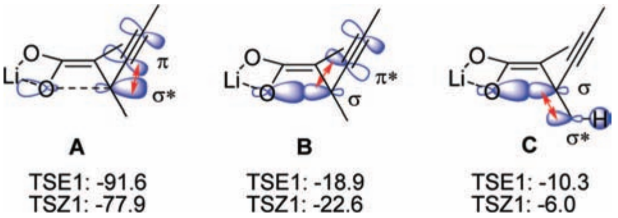
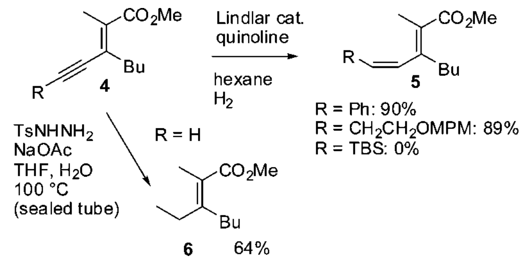


Figure 2. Secondary orbital interactions with their energies in kJ/mol by NBO analysis.

The triple bond of the resulting conjugate enyne compounds could be converted into various functionalities. As an example, the triple bond was partially reduced via hydrogenation with the Lindlar catalyst to afford the corresponding conjugate dienes. This hydrogenation being dependent on the substituents, the sterically hindered TBS-substituted alkene was thus inert. The nonsubstituted alkyne was hydrogenated by diimide to provide the tetrasubstituted alkene. Since these products would not be easy to generate stereoselectively by other methods, our results demonstrate the synthetic utility of the olefination.

In conclusion, we have shown the first experimental evidence of the alkynyl substituent effect on torquoselectivity and succeeded in effecting the highly torquoselective olefination of alkynyl ketones to provide functionalized tetrasubstituted olefins. The triple bond acts as an electron donating substituent in the torquoselective olefination of alkynyl ketones. This is the first general and successful example of a carbon-function-controlled torquoselective olefination.

Scheme 2



Acknowledgment. This research was partially supported by Grant-in-Aid for Scientific Research on Priority Areas (19020052 and 20038005) and (B) (19390007). T.K. also acknowledges the support of the JSPS. We thank RCCS at Okazaki, Japan, for computational time.

Supporting Information Available: General procedures, computational procedures, characterization data of new compounds, ^{1}H and ^{13}C NMR spectra of new compounds, and Cartesian coordinates of transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471–477. (b) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1871–1872. (c) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989–7991. (d) Kallel, E. A.; Wang, Y.; Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 6759–6763.

(2) (a) Murakami, M.; Miyamoto, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 189–190. (b) Murakami, M.; Miyamoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6441–6442. (c) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072–5079. (d) Murakami, M.; Hasegawa, M.; Igawa, H. *J. Org. Chem.* **2004**, *69*, 587–590. (e) Murakami, M.; Hasegawa, M. *J. Org. Chem.* **2007**, *72*, 3764–3769.

(3) (a) Shindo, M; Mori, S. *Synlett* **2008**, 2231–2243. (b) Shindo, M.; Mori, S. *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 28–38.

(4) (a) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840–6841. (b) Shindo, M.; Matsumoto, K.; Shishido, K. *Tetrahedron* **2007**, *63*, 4271–4277.

(5) Shindo, M.; Yoshikawa, T.; Itou, Y.; Mori, S.; Nishii, T.; Shishido, K. *Chem.—Eur. J.* **2006**, *12*, 524–536.

(6) Shindo, M.; Kita, T.; Kumagai, T.; Matsumoto, K.; Shishido, K. *J. Am. Chem. Soc.* **2006**, *128*, 1062–1063.

(7) Stereoselective synthesis of tetrasubstituted olefins is a topic of current interest. For a review, see: Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698–4745.

(8) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945–3948.

(9) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072–5079.

(10) The para-substituted acetophenones are olefinated with good to moderate torquoselectivity; see:(a) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2000**, *65*, 5443–5445. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857–4860. (c) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912–3916.

(11) The ring-opening reactions of 3,4-bisalkynylcyclobutenes were reported without description of the torquoselectivity. Huth, A.; Straub, H.; Muller, E. *Tetrahedron Lett.* **1973**, *284*, 5–2848, and references therein.

(12) (a) Shindo, M. *Tetrahedron Lett.* **1997**, *38*, 4433–4436. (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411–2422. (c) Shindo, M.; Matsumoto, K.; Shishido, K. *Org. Synth.* **2007**, *84*, 11–21.

(13) The preparative method has been improved slightly (see Supporting Information).

(14) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley; New York, 1986. and references cited therein.

(15) TSE2 was very similar to TSE1 (see Supporting Information).

(16) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, version 5.0; University of Wisconsin: Madison, WI, 2007.

(17) For the natural steric analysis, see: (a) Badenhoop, J. K.; Weinhold, F. *J. Chem. Phys.* **1997**, *107*, 5406–5421. The contribution of the repulsion between the alkynyl π-orbital and the C-O σ orbital is small according to the natural steric analysis. (b) Min, S.-J.; Jones, G. O.; Houk, K. N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10078–10079.

JA809592Q