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Substituent Effects on the *Z/E*-Selectivity in Cross-Metathesis of Conjugated Enynes

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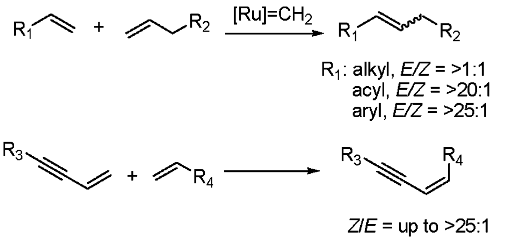
Cross-metathesis of a range of conjugated enynes with alkenes turns out to proceed with preferential formation of *Z*-isomers over *E*-isomers up to >25:1. Careful studies including substrate modification and control experiments revealed that the reaction proceeds under kinetic rather than thermodynamic control. Driving forces for this substrate-dependent Z-selectivity are attributed to the steric hindrance between substituents on the reacting enynes and NHC ligand of the ruthenium catalyst in the putative metallacyclobutane, as well as chelation effects of suitably positioned functional groups to Ru, which is strongly supported by ab initio calculations.

Introduction

Olefin methathesis has become one of the most useful reactions in organic chemistry for its efficiency and selectivity.[1] Whereas ring-closing metathesis (RCM) is established as a routine synthetic method, cross-metathesis (CM) has found increasing synthetic utility only recently.[2] To apply CM in synthetic chemistry in more predictable ways, the development of general conditions providing high stereoselectivity and reactivity in a variety of substrate types is highly desirable.[3] Using the well-known Mo or Ru carbene catalysts, *E*-olefinic alkenes are produced favorably from most CMs, the extents of which vary depending on the steric and electronic nature of the reacting partners (eq 1).



(1)

In the course of our studies on olefin metathesis,[4] we recently reported the first example of cross-metathesis of conjugated enynes with alkenes, giving moderate to excellent *Z*-selectivity.[5] The high *Z*-selectivity observed from the studies was unusual considering the thermodynamic nature of olefin metathesis,[6] and herein we present detailed investigations to elucidate the properties (or nature) of the reverse stereoselectivity on the basis of experimental data and quantum chemical calculations.[7]

Results and Discussions

It is generally considered that olefin metathesis including CM proceeds mainly under the kinetic control at the initial stages, and as the reaction progresses, thermodynamics take over to afford *E*-isomeric products predominantly at the end of the reaction.[8]

In case of conjugated enyne, the reaction of 4-hexen-2-ynyl benzoate and allyltrimethylsilane under the CM conditions with ruthenium carbene catalysts $(PCy_3)_2(Cl)_2$-

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[1] For selected recent reviews, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (f) Grubbs, R. H. *Handbook of Olefin Metathesis*; Wiley-VCH: Weinheim, Germany, 2003.

[2] For recent representative reports on cross-metathesis, see: (a) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

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[4] (a) Jo, E.; Na, Y.; Chang, S. *Tetrahedron Lett.* **1999**, *40*, 5581. (b) Lee, W.-W.; Chang, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4473. (c) Park, S.-H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621. (d) Lee, W.-W.; Shin, H. J.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 29. (e) Chang, S.; Na, Y.; Shin, H. J.; Choi, E.; Jeong, L. S. *Tetrahedron Lett.* **2002**, *43*, 7445. (f) Kang, B.; Chang, S. *Tetrahedron* **2004**, *60*, 7353.

[5] Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041.

[6] Although the detailed explanations were not presented, it was shown that CM of acrylonitrile afforded high Z-selectivity: Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162.

[7] For a recent report on cross-metathesis of conjugated enynes and related mechanistic discussions, see: Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035.

[8] For mechanistic studies of olefin metathesis, see: (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887. (b) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204. (c) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543. (d) Cavallo, L. *J. Am. Chem. Soc.* **2002**, *124*, 8965. (e) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103. (f) Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* **2004**, *126*, 3496. (g) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225. (h) Vyboishchikov, S. F.; Bühl, M.; Thiel, W. *Chem. Eur. J.* **2002**, *8*, 3962.

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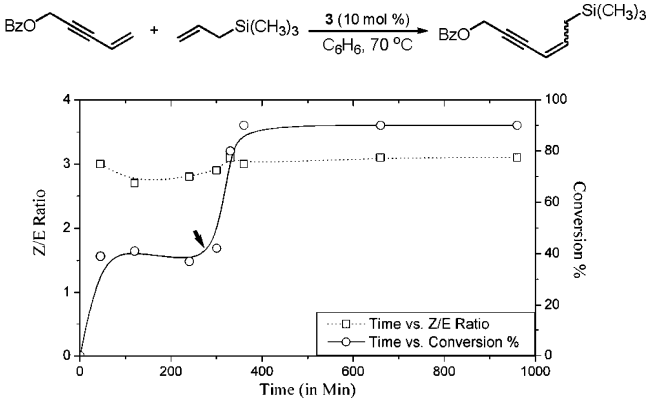
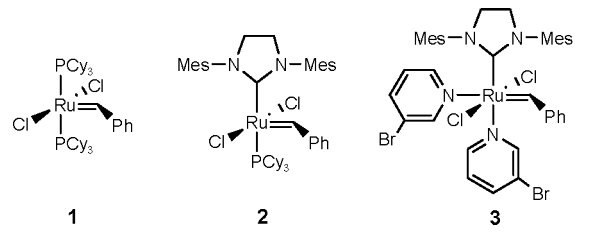


FIGURE 1. *Z*/*E* ratio of the produced enynes over conversion. The arrow indicates where the additional 5 mol % catalyst **3** was added.

SCHEME 1. Ruthenium Carbene Catalysts

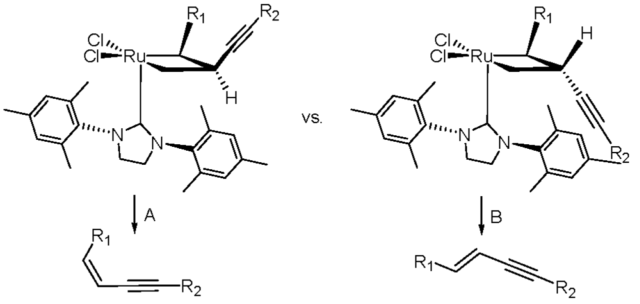


Ru=CHPh (**1**), $(H_2IMes)(PCy_3)(Cl)_2$ Ru=CH Ph (**2**), or $(H_2IMes)(3\text{-}Br\text{-}py)_2(Cl)_2Ru{=}CHPh$ (**3**)[9] (Scheme 1) showed a fast initiation rate of the reaction (the catalyst was added in two portions 4.5 h apart) and little isomerization of the double bond of products over time when applying the resulting products to the reaction condition, maintaining the initial *Z*/*E* ratio (Figure 1).[10] In addition, no metathesis reaction occurred when the internal enyne was allowed to react with other alkenes under the previously employed reaction conditions.[5] This observation strongly suggests that *Z*-enynes generated from CM are kinetic products in nature and that they are inert to the putative subsequent and reversible metathesis cycles probably as a result of low reactivity of the compounds. The inertness to the subsequent CM cycles and the preferential formation of *Z*-isomers may suggest that the conjugated enynes belong to a category *different* from olefins, alkynes, or dienes as substrates in CM catalyzed by ruthenium carbenes.

Given the general acceptance of the Chauvin mechanism in olefin metathesis,[11] it is reasonable to apply this scenario also in the CM of conjugated enynes, of which the stereochemistry-determining step is the formation of a metallacyclobutane intermediate (Scheme 2, where catalyst **2** or **3** is employed).

The initial stereoselectivity of CM is better understood using a kinetic rationale based only on the relative energy differences of the corresponding metallacyclobutane adducts. It could assume that a large *N*-heterocyclic carbene (NHC) ligand blocking one side of the metallacyclobutane may force both substituents to approach the reaction center from the opposite side of the bulky NHC ligand, which was described by others.[7] This bias may lead to the preferential formation of *Z*-enynes as an initial product under the kinetic control (pathway A). It is obvious that unfavorable steric interactions exist between the NHC and one of two substituents in the metallacyclobutane if the two groups are positioned *trans* to each other, ultimately leading to *E*-isomeric products (pathway B). On the basis of the observation that generated enynes do not participate in the subsequent reversible metathesis cycles, the *initially produced* kinetic isomers, predominantly *Z*-enynes, are isolated maintaining the initial *Z*/*E* ratios.[12]

SCHEME 2. Proposed Intermediates Leading to *Z*- and *E*-Isomeric Products from CM of Conjugated Enynes



From the previous study,[5] we noticed that CM of enynes bearing some functional groups in certain positions provided especially high *Z*/*E* ratios, implying that there might be substituent effects on the selectivity. To examine the relationship between pendent groups of enynes and resulting stereoselectivity, a series of conjugated enynes substituted with some several groups of varying distance were prepared and subjected to the metathesis conditions. As surmised, *Z*/*E*-selectivity turned out to be dependent on both the nature and the position of functional groups (Table 1). With the use of **3** (10 mol %), a series of *O*-benzyl enynyl ethers were reacted smoothly in benzene (reflux, 12 h) with alkenes represented by *trans*-3-hexene (**A**, internal olefin) and allyltrimethylsilane (**B**, terminal olefin) to afford the corresponding enynes in good yields (entries 1−5). Stereochemistry of the newly formed double bond was determined on the basis of ^1H NMR of the crude reaction mixture (J_Z = 10−11 Hz and J_E = 15−20 Hz). Whereas the catalyst **3** exhibits good activity for CMs, other ruthenium catalysts such as **1** and **2** show much lower efficiency (e.g., 30% conversion from a substrate of entry 2 with catalyst **2**) in these cases. However, the observed *Z*/*E*-selectivity remains exactly the same regardless of the ruthenium catalyst precursors used, implying that the reaction proceeds via a common active ruthenium species regardless of the different initiation rates depending on the catalyst precursors.

It is noteworthy that the extent of the selectivity turned out to be influenced by the types of the conjugated enynes examined. A higher ratio of *Z*/*E* was produced from CM of enynyl ether with a longer linker length between the alkynyl and benzyloxy groups, although it

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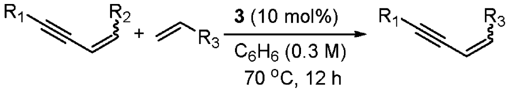
[9] Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035.

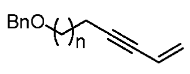
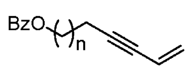
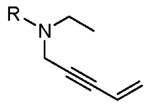
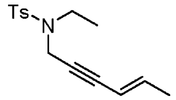
[10] The detailed experiment procedure is available in Supporting Information.

[11] Hérrisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161.

[12] For a previous example of kinetically controlled CM leading to preferential formation of *E*-olefins, see: Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209.

TABLE 1. Cross-Metathesis of Conjugated Enynes with Alkenes[a]



entry	enyne		alkene[b]	yield (%)[c]	*Z*/*E*[d]
1		n = 0	**A**	71	5.3:1
2		n = 2	**A**	78	7.5:1
3		n = 8	**A**	91	7.4:1
4		n = 0	**B**	58	2.6:1
5		n = 2	**B**	54	5.2:1
6		n = 0	**A**	72	2.8:1
7		n = 2	**A**	78	8.8:1
8		n = 8	**A**	89	8.4:1
9		n = 0	**B**	83	3.0:1
10		n = 2	**B**	50	5.1:1
11		R = Bz	**A**	69	15:1
12		R = Ts	**A**	64	15:1
13		R = Ts	**B**	57	>25:1
14			**A**	56	12:1
15			**B**	51	>25:1

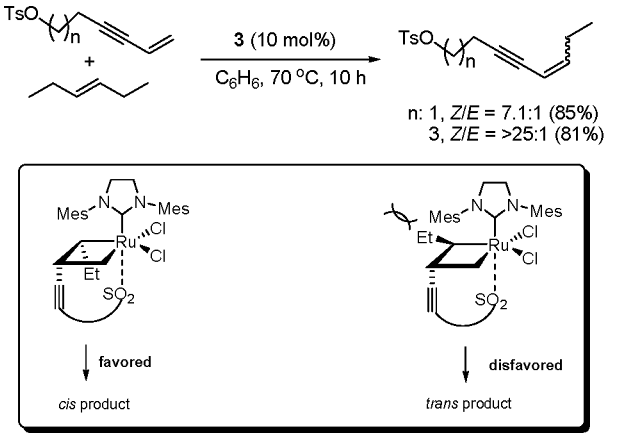
[a] Enyne (1.0 equiv), alkene (3.0 equiv), and **3** (10 mol %) in benzene (0.3 M) at 70 °C for 10 h. [b] **A** = *trans*-3-hexene; **B** = allyltrimethylsilane. [c] Combined isolated yields of two isomers. [d] *Z*/*E* ratios determined by ^{1}H NMR of crude reaction mixture.

reached soon a plateau after a certain length of the linker. Dependence of the ratio on the linker length was more noticeable with a terminal alkene such as **B** (compare entries 4 and 5). With benzoylated enynes under the reaction condition,[13] the ratio *Z*/*E* varied depending on the linker length, favoring more *Z*-isomers with longer methylene linkers between the triple bond and the benzoyl group with both an internal olefin (entries 6–8) and a terminal olefin (entries 9 and 10) in the presence of catalyst **3**.

More significantly, much higher *Z*-selectivity was obtained with *N*-disubstituted propargylic amino adducts, which may be useful in synthetic chemistry (entries 11–13). For example, a metathesis reaction between *N*-benzoyl *N*-ethyl aminomethyl enyne and *trans*-3-hexene (**A**) provided the *Z*-isomeric product in good yields with an excellent selectivity (*Z*/*E* = 15:1, entry 11). Changing the *N*-substituents from benzoyl to tosyl group had little effects on the preference for the *Z*-selectivity (entry 12). Almost exclusive formation of *Z*-isomer was observed from the metathesis of *N*-tosylamido enyne with **B** under the same conditions albeit in moderate yield (entry 13). The noticeable *N*-susbtituent effects were also observed when a conjugated internal enyne was employed (entries 14 and 15).

Enynyl tosylates with different linker length between two functional groups were synthesized and subjected to the metathesis conditions in the presence of *trans*-3-hexene (Scheme 3). As expected, stereochemistry of the newly generated double bond exhibited a high preference for *Z*-isomers in both cases, and again, the degree of the selectivity was significantly increased in the substrate with longer chain length between the triple bond and the tosyl group (n = 3).

SCHEME 3 Proposed Model of Chelation-Based Metathesis Reaction between Enynyl Tosylates and *trans*-3-Hexene



It is proposed that a chelation of the sulfonyl oxygen to the ruthenium metal center secures the disposition of two substituents in the metallacyclobutane structure *cis* to each other and *trans* with respect to the NHC ligand.[14] The degree of the ligation would be related to the conformational flexibility of the suggested transition state. Because a 10-membered chelating ring resulting from the shorter substrate (n = 1) bears relatively high ring strain due to the presence of a linear triple bond, it is expected that the chelation would be less likely in this case, giving just a moderate *Z*/*E* ratio (*Z*/*E*, 7.1:1). In contrast, a substrate bearing the longer chain linker (n = 3) is anticipated to provide a chelation geometry more readily because of relatively lower ring strain, thus resulting in almost exclusive formation of the *Z*-isomer.[15]

To estimate the validity of our speculation that the degree of the chelation significantly affects the distribution of *Z*/*E* isomers in the CM of conjugated enynes, ab initio calculations were carried out to optimize geometries of the metallacyclubuatne intermediates.[16] Based on the reaction of 5-octyn-7-enyl tosylate (n = 3, in Scheme 3) with *trans*-3-hexene, the geometries of the plausible intermediates for the cases of both the chelation and the nonchelation were estimated from the MM+ force field

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[13] Conjugated enynes were readily prepared by the reaction of vinyl or propenyl bromide with the corresponding alkynes under the Sonogashira conditions.

[14] For an analogous explanation of observed stereochemistry in polymerization metathesis, see: Krause, J. O.; Zarka, M. T.; Anders, U.; Weberskirch, R.; Nuyken, O.; Buchmeiser, M. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 5965.

[15] For previous examples involving chelation-based metathesis structures, see: (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (b) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651. (c) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (d) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277. (e) Courchay, F. C.; Sworen, J. C.; Wagener, K. B. *Macromolecules* **2003**, *36*, 8231.

[16] For the mechanistic studies of olefin metathesis using quantum molecular dynamics, see: (a) Aagaard, O. M.; Meier, R. J.; Buda, F. *J. Am. Chem. Soc.* **1998**, *120*, 7174. (b) Hansen, S. M.; Rominger, F.; Metz, M.; Hofmann, P. *Chem. Eur. J.* **1999**, *5*, 557. (c) Suresh, C. H.; Koga, N. *Organometallics* **2004**, *23*, 76.

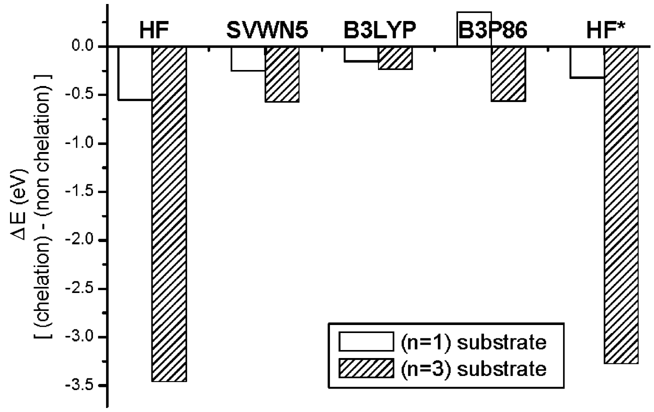

FIGURE 2. Energy difference between chelation and nonchelation intermediates for the reaction in Scheme 2, based on the energy values[22] calculated from a putative reaction: $RuO_3 + O \rightarrow RuO_4$, $\Delta E = -1.07$ eV (calculated by HF/3-21G**), and others were derived from the HF/3-21G** optimized geometry.

calculations.[17] These two geometries were further optimized at the Hartree−Fock (HF) level with the 3-21G** basis set.[18] At the HF optimized geometries, density functional theory (DFT)[19] calculations were performed with the 3-21G** basis set, and HF calculations were repeated with a larger basis set, the DGDZVP basis set that contains the extra polarization and diffuse functions.[20] In the methods utilized, the nonchelation form was less stable than the chelation one, although the magnitude of the stability varies depending on the calculation methods (Figure 2). The energy differences are especially significant from the substrate being $n = 3$, where the chelation model shows much higher stability compared with the nonchelation for two sets of HF calculations, with different basis sets.[21] The energy differences are much smaller for DFT results, suggesting that the electron correlations may reduce the energy difference of HF calculations. Since HF calculations usually yield reasonable geometries, the chelated form is likely to be more stable than the nonchelated one in more accurate calculations but with substantially smaller energy difference than the HF results.

Conclusions

We have shown that cross-metathesis of conjugated enynes proceeds under kinetic rather than thermodynamic control, favorably affording *Z*-isomeric products. The trend of the product distribution over a series of substrates indicates that steric interactions between two substituents in the putative metallacyclobutane intermediate and the bulky NHC ligand are mainly responsible for the *Z*-selectivity. Chelation of a functional group in enynyl substrates to the ruthenium metal center also seems to have influence on the selectivity, which is supported by ab initio calculations.

Experimental Section

Representative Experimental Procedure of Enyne Metathesis. To a solution of 7-octen-5-yne-1-yl *p*-toluenesulfonate (111 mg, 0.39 mmol) in benzene (1.0 mL) was added *trans*-3-hexene (0.15 mL, 1.1 mmol) followed by catalyst **3** (18 mg, 0.019 mmol) in benzene (1.5 mL). The reaction mixture was stirred for 5 h at 70 °C under nitrogen atmosphere. Then catalyst **3** (18 mg, 0.019 mmol) in benzene (1.5 mL) was added again, and the mixture was stirred for another 5 h at the same temperature. After removal of organic solvent under reduced pressure, the residue was purified by a column chromatography on silica gel (ethyl acetate/hexane, 1:7) to afford the corresponding enyne as an analytically pure isomer, [(*Z*)-7-decen-5-ynyl] tosylate (Scheme 2, $n = 3$) (99 mg, 82%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 2H, $J = 8.3$ Hz), 7.30 (d, 2H, $J = 8.2$ Hz), 5.77 (dt, 1H, $J = 10.6, 7.3$ Hz), 5.32 (d, 1H, $J = 10.7$ Hz), 4.02 (t, 2H, $J = 6.2$ Hz), 2.41 (s, 3H), 2.28 (td, 2H, $J = 6.9, 2.1$ Hz), 2.21 (qd, 2H, $J = 7.5, 1.2$ Hz), 1.71−1.78 (m, 2H), 1.49−1.56 (m, 2H), 0.95 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 144.3, 132.9, 129.7, 127.7, 108.3, 92.9, 77.8, 69.9, 27.8, 24.5, 23.4, 21.5, 18.7, 13.3; HRMS (EI) calcd for $C_{17}H_{22}O_3S$ [M^+] 306.1290, found 306.1292.

Acknowledgment. This work was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare (01-PJ1-PG1-01CH12-0002).

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

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(18) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265.

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(20) Sosa, C.; Andzelm, J.; Elkin, B. C.; Wimmer, E.; Dobbs, K. D.; Dixon, D. A. *J. Phys. Chem.* **1992**, *96*, 6630.

(21) Detailed values of the calculation performed in this study are presented in Supporting Information.

(22) For the reference of the energy values, see: Dobbs, K. D.; Hehre, W. J. *J. Comput. Chem.* **1987**, *8*, 861.