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Stereocontrolled Synthesis of Bicyclic Lactone Derivatives via Tungsten-Mediated [3 + 2] Cycloaddition of Epoxides with a Tethered Alkynyl Group

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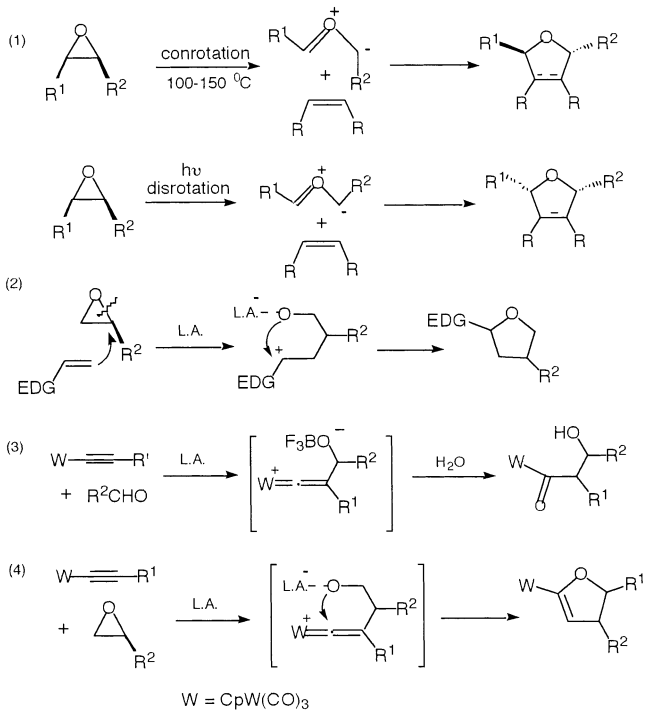
In the presence of $BF_3{\cdot}Et_2O$, alkynyltungsten complexes underwent [3 + 2] cycloaddition with tethered epoxides to give bicyclic γ-lactones efficiently. Only one diastereomeric product was formed despite the presence of three stereogenic centers. A mechanism is proposed that involves formation of a tungsten−vinylidenium species via an S_N2 attack of the epoxide carbon by an alkynyltungsten group to give a tungsten−enol ether species via counterattack at the central tungsten−vinylidenium carbon by the OBF_3^- terminus. Most of the tungsten enol ether species were too unstable for isolation and underwent hydrolysis to give only *cis*-fused γ-bicyclic lactones. This cyclization works for both *cis*- and *trans*-epoxides and tolerates various functional groups. In the case of *trans*-phenyl epoxide, the reaction led to an addition product via a 6-endo attack of epoxide by the tungsten fragment. This method provides a simple enantiospecific synthesis of complex bicyclic lactones if a chiral epoxide is used in the cyclization. It is also applicable to the one-pot synthesis of bicyclic unsaturated γ-lactones if a suitable alkynyltungsten functionality is used.

Introduction

[3 + 2] Cycloaddition of epoxides with alkynes and alkenes is a direct and efficient method for the synthesis of furan derivatives.[1,2] This cycloaddition can be achieved by cleavage of either the C−C bond[3] or C−O bond.[4] The former process is performed by either photochemical or thermal activation to give an oxonium ylide intermediate that can be trapped by electron-deficient olefins and alkynes by 1,3-dipolar cycloaddition (Scheme 1, eq 1).[3] This pathway proceeds with high diastereoselectivity, since rotation of the C−C bond normally follows Woodward−Hoffmann rules. This system has been thoroughly studied and is useful in organic synthesis. An alternative method involves the use of a Lewis acid to cleave the

SCHEME 1



† National Tsing-Hua University.
‡ Yuanpei Institute of Science and Technology.

(1) (a) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: Chichester, 1984; Vol. 2, p 83.

(2) (a) Carruthers, W. *Cycloaddition in Organic Synthesis*; Pergamon: Oxford, 1990. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (c) Togni, A.; Venanzi, L. M. *Angew. Chem., Intl. Ed. Engl.* **1994**, *33*, 497.

(3) Cycloaddition of aziridine with olefin and alkyne with cleavage of the C−C bond; see, for example: (a) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 3211. (b) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523. (c) DeShong, P.; Kell. D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309. (d) Metra, P.; Hemelin, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1038. (e) Gaebert, C.; Siegner, C.; Mattay J.; Toubartz, M.; Steenken, S. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2735. (f) Domingo, L. R. *J. Org. Chem.* **1999**, *64*, 3922. (g) Chou, W.-N.; White, J. B. *Tetrahedron Lett.* **1991**, *32*, 7637. (b) Gaebert, C.; Mattaay, J. *Tetrahedron* **1997**, *53*, 14297. (h) Palomino, E.; Schaap, A. P.; Heeg, M. J. *Tetrahedron Lett.* **1989**. *30*, 6801.

(4) For cycloaddition of aziridine or epoxide with alkene with cleavage of the C−X bond, see: (a) Bergmeier, S. C.; Fundy, S. L.; Seth, P. P. *Tetrahedron* **1999**, *55*, 8025. (b) Schneider, M. R.; Mann, A.; Taddei, M. *Tetrahedron Lett.* **1996**, *37*, 8493. (c) Nakagawa, M.; Kawahara, M. *Org. Lett.* **2000**, *2*, 953. (e) Sugita, Y.; Kimura, Y.; Yokoe, I. *Tetrahedron Lett.* **1999**, *40*, 5877.

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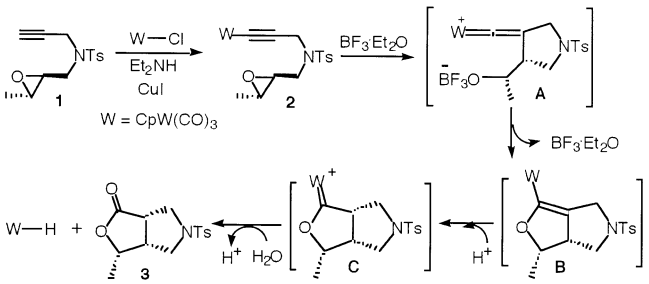
SCHEME 2



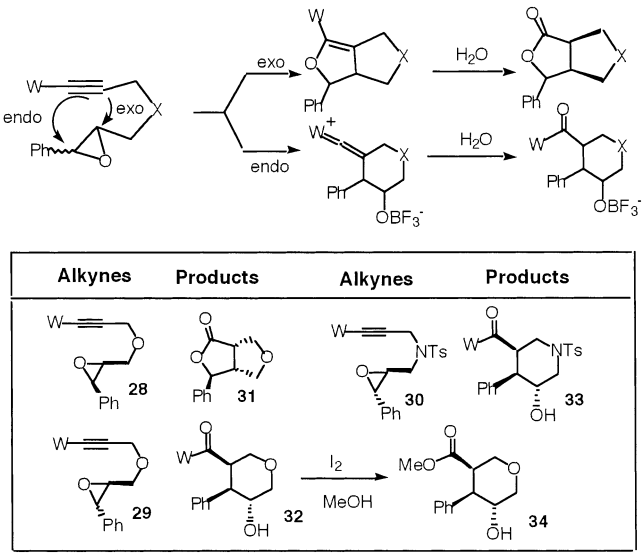
C−O bond of the epoxide to yield a zwitterionic intermediate (Scheme 1, eq 2).[4] This process is not widespread, and only a few cases of special olefins have been reported.[4] Treatment of epoxides with electron-rich olefins normally gives addition products.[5,6] To the best of our knowledge, the cycloaddition of epoxides with alkynes has not yet been reported.

Previously, we reported that alkynyltungsten complexes reacted with aldehydes to generate tungsten vinylidenium intermediate, which undergoes hydrolysis to give acyltungsten complexes[7,8] (Scheme 1, eq 3). The central carbon of metal vinylidenium species is highly electrophilic and suitable for [3 + 2] cycloaddition if epoxides are cleaved with a suitable acid (Scheme 1, eq 4). In this study,[9] we report a new [3 + 2] cycloaddition of alkynyltungsten complexes with epoxides based on this reaction protocol.

Results and Discussion

Cycloaddition of alkynyltungsten species with its tether epoxide appears to be a direct and efficient synthesis of bicyclic lactone because the expected cycloadduct−tungsten enol ethers **B** are prone to hydrolysis to liberate bicyclic lactone efficiently. A representative protocol is shown in Scheme 2. Alkynyltungsten species **2** was synthesized in 78% yield by metalation with $CpW(CO)_3Cl$ (1.1 equiv) and CuI (3 mol %) in Et_2NH.[7a] Treatment of complex **2** with $BF_3{\cdot}Et_2O$ (25 mol %) in CH_2Cl_2 (−40 °C, 8 h) caused the disappearance of complex **2** as shown by monitoring the reaction chromatographically (SiO_2 TLC plate). Subsequent treatment of this mixture with H_2O gave the lactone **3** in 86% yield. The three stereogenic protons of lactone **3** are mutually cis to one another according to proton NOE spectra (see the Experimental Section). Such a stereochemical outcome suggests that ring opening of the epoxide is caused by S_N2 attack of the alkynyltungsten fragment to give tungsten−vinylidenium intermediate **A**.[7a] The enol ether **B**[10] is highly sensitive to the presence of protons, which accelerate its

SCHEME 3



catalytic conversion to tungsten−oxacarbenium **C**[7a] and finally gives *cis*-fused bicyclic lactone **3** in the presence of water.

This one-pot operation provides an easy and stereocontrolled synthesis of bicyclic lactones with three stereogenic centers. We prepared the substrates **4**−**15** to examine the generality of this new approach. In a typical procedure, the alkynyltungsten complex was treated with $BF_3{\cdot}Et_2O$ (25 mol %) in cold CH_2Cl_2 (−40 °C) for 4−12 h before water was added. Entries 1 and 2 show cyclizations of *trans*- and *cis*-epoxides **4** and **5**; the products **16** and **17** have a *cis*-fused bicyclic ring bearing *cis*-methyl and *trans*-propyl groups (entries 1 and 2), respectively. The structures of lactones **16** and **17** are determined by ^1H NOE effects (see the Supporting Information). This reaction also works for *gem*-disubstituted epoxide **6** to give the corresponding lactone **18** in 83% yield. This method was successfully extended to the synthesis of *cis*-fused γ-lactone **19** and **20** bearing a different pyranyl group. It is also applicable to functionalized lactone **21**, which contains an acetate group. Entry 7 shows an additional example for the efficient formation of γ-lactone fused with a pyrrolidinyl ring. Similarly, cyclization of functionalized *cis*- and *trans*-epoxides **11** and **12** led to formation of the corresponding cis-fused lactones **23** and **24**, which contain *trans*-methoxymethyl and *cis*-hydroxymethyl groups, respectively. Entry 10 shows the formation of γ-lactone **25** bearing a piperidinyl group. Both *cis*- and *trans*-fused isomers were obtained and separated on a silica column. The presence of an ester functionality in compounds **14** and **15** did not inhibit cyclization, and bicyclic lactones **26** and **27** were obtained in good yields.

The hybridization of epoxide lies between sp^2 and sp^3[3,11] and both *endo* and *exo* attack in Scheme 3 are likely to occur. The results in Table 1 indicate that the cyclizations exclusively follow *exo*-mode to give [3 + 2] cycloadducts.

(5) For review papers, see: (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) Yamamoto, Y.; Asao N. *Chem. Rev.* **1993**, 2207.

(6) See, for example: (a) Dubiois, S.; Mehta, A.; Toureet, E.; Dodd, R. H. *J. Org. Chem.* **1994**, *59*. 434. (b) Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073.(c) Bennani, Y. L.; Zhu, G. D.; Freeman, J. C. *Synlett* **1998**, 754. (d) Marson, C. M.; McGregor, J.; Khan, A. *J. Org. Chem.* **1998**, *63*, 7833.

(7) (a) Liang, K.-W.; Li,W.-T.; Lee, G.-H.; Peng, S.-Mi.; Liu, R.-S. *J. Am. Chem. Soc.* **1997**, *119*, 4404. (b) Liang, K.-W.; Chandrasekharam, M.; Li, C.-L.; Liu, R.-S. *J. Org. Chem.* **1998**, *63*, 7289. (c) Li, W.-T.; Pan, M.-H.; Wu, Y.-R.; Wang, S.-L.; Liao, F.-L.; Liu, R.-S. *J. Org. Chem.* **2000**, *65*, 6362. (c) Chen, M.-J.; Lo, C.-Y.; Liu, R.-S. *Synlett* **2000**, 1300.

(8) Li, C.-L.; Liu, R.-S. *Chem. Rev.* **2000**, *100*, 3127.

(9) Madhushaw, R.-J.; Li, C.-L.; Shen, K.-H.; Hu, C.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2002**, *123*, 7427.

(10) McDonald, F. E.; Schults, C. C. *J. Am. Chem. Soc.* **1994**, *169*, 9363.

(11) Nicolaou, K. C.; Duggan, M. E.; Huang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359.

TABLE 1. Cycloaddition of Alkynyltungsten Complexes with Tethered Epoxides

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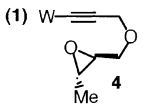
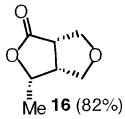
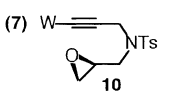
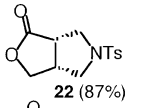
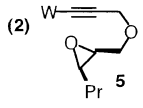
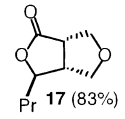
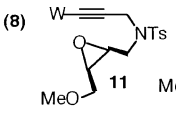
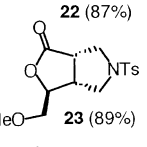
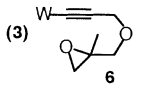
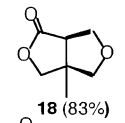
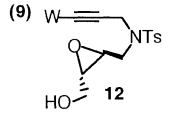
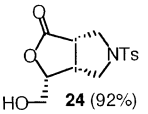
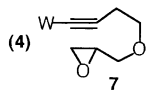
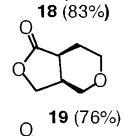
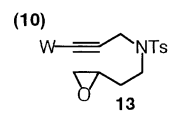
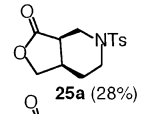
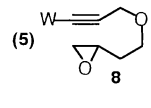
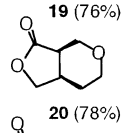
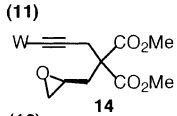
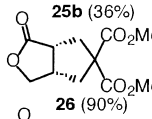
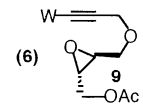
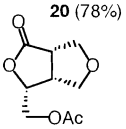
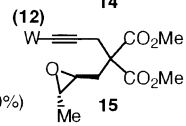
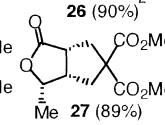
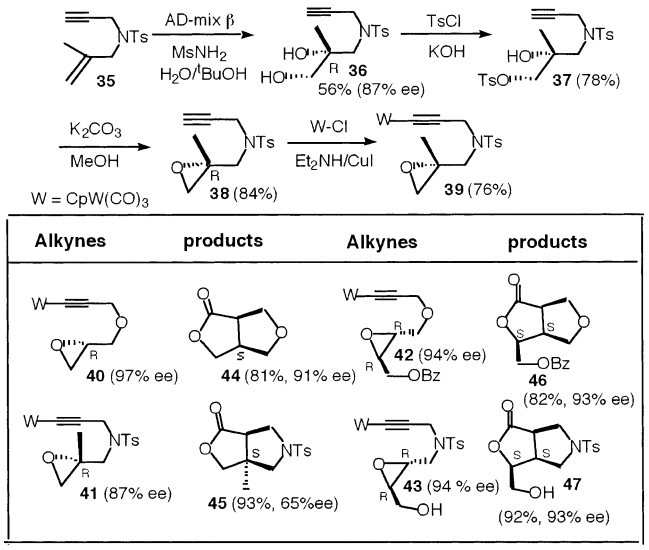
(1) 		(7) 	
(2) 		(8) 	
(3) 		(9) 	
(4) 		(10) 	
(5) 		(11) 	
(6) 		(12) 	

[a] W = $CpW(CO)_3$, $BF_3{\cdot}Et_2O$ (25 mol %), CH_2Cl_2, −40 °C. [b] Yields were reported after purification from preparative silica TLC plates.

To examine the possibility of *endo* attack to form a six-membered ring, we prepared various phenyl-substituted epoxides, which are expected to favor *endo*-attack with the formation of a benzyl carbocation upon opening of the epoxide with $BF_3{\cdot}Et_2O$. The results in Scheme 3 reveal that *cis*-epoxide **28** led to the formation of cycloadduct **31**, whereas *trans*-epoxides **29** and **30** gave six-membered heterocyclic derivatives **32** and **33** in good yields. The structure of **33** was confirmed by an X-ray diffraction study.[12] The preferred *exo*-attack of compound **28** can be explained by steric hindrance as the alkynyltungsten group approaches the phenyl carbon in S_N2-mode. The *cis*-phenyl group makes it difficult for the alkynyl to align with the σ^*-orbital of the PhC−O bond. Oxidative demetalation of compound **32** with I_2 in MeOH (0 °C, 8 h) gave trisubstituted pyrane derivative **34** in 96% yield.

We also prepared chiral epoxides allowing for a conclusive study of enantiospecific cycloaddition. Epoxides **40**, **42**, and **43** (>92% ee) were prepared with high enantiopurity according to Sharpless asymmetric epoxidation,[13] and the synthetic procedures are provided in the Supporting Information. Scheme 4 shows the synthetic protocol of chiral epoxide **39**. Asymmetric dihydroxylation of enyne **35** produced chiral diol in 86% yield with 75% ee. Recrystallization of this solid from ether and hexane increased its enantiopurity to 87% with a final 56% yield. The diol **36** was transformed to tosylate

SCHEME 4



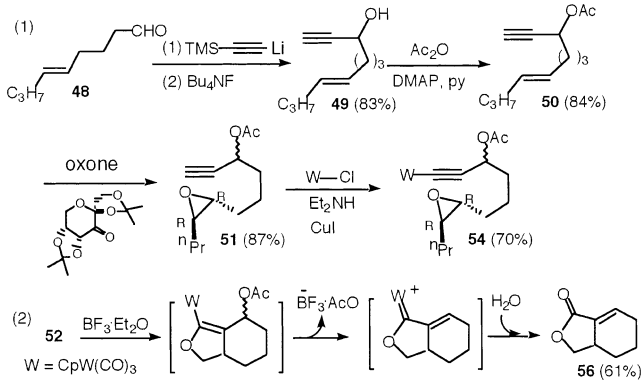
derivative **37** (78%), and then to epoxide **38** (84%), and finally metalated to give alkynyltungsten species **39**. Before cyclization, HPLC analysis of the epoxide **38** showed an enantiopurity of ca. 87%. A small decrease in the ee value is observed for bicyclic lactone **44** (91% ee) derived form the epoxide **40** (97% ee). The [α] value of compound **44** is consistent with that of an authentic sample.[14] A considerable decrease in ee value is found for lactone **45** (65% ee) obtained from chiral *gem*-disubstituted epoxide **41** (87% ee), which suggests the formation of a tertiary carbocation during the opening of the epoxide. In the cyclization of trans-epoxides **42** (94% ee) and **43** (94% ee), no loss of enantiopurity is observed for the resulting products **46** (93% ee) and **47** (93% ee).

This new method was also applicable to the synthesis of various bicyclic unsaturated γ-lactones, and the results are given in Scheme 5. The starting alkynyltungsten complexes **52**−**55** were prepared according to conventional methods. A synthetic protocol for **54** is shown in Scheme 4. Epoxide **51** was prepared with high enantiopurity via a fructose-based catalytic asymmetric epoxidation[15] and each acetate diastereomer showed 90% ee according to HPLC-analysis. This fructose-based epoxidation was also used to prepare chiral epoxide **55** and both of the acetate diastereomers showed 94% ee. The working hypothesis shown in eq 2 involves cleavage of the OAc^- group of the tungsten−enol ether species to form bicyclic unsaturated tungsten−carbenium, which gives the desired lactone **56** (61% yield) upon hydrolysis in air. This approach works well for *cis*-epoxide **53** to give an unsaturated lactone **57** bearing a *trans*-hexyl group. In the cyclization of chiral epoxides **54** and **55**, the resulting lactones **58** and **59** were produced in reasonable yields without loss of enantiopurity. The primary product from alkynyltungsten species **55**, being unstable in reaction medium, was converted to naphthalene derivative **59** upon subsequent oxidation.

In summary, we reported a BF_3-promoted intramolecular [3 + 2] cycloaddition of alkynyltungsten com-

(12) X-ray diffraction data of compound **33** is provided in the Supporting Information.
(13) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
(14) Petit, F.; Furstoss, R. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1341.
(15) Wang, Z.-X.; Yong, T.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

SCHEME 5



plexes with tethered epoxides. This cycloaddition tolerating various functionalities proceeds with high diastereoselectivity to afford, in reasonable yields, bicyclic γ-lactones. The stereochemical outcome of the products suggests that ring-opening of epoxide is initiated by S_N-2 attack of alkynyltungsten group. In most cases, 5-*exo* mode for the attack at epoxide carbon is more preferable than 6-*endo* mode. This new method provides a short enantiospecific synthesis of bicyclic saturated or unsatutated γ-lactones if suitable epoxides are used.

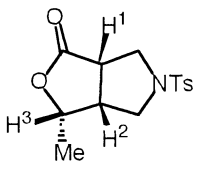
Experimental Section

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Benzene, diethyl ether, tetrahydrofuran, and hexane were dried with sodium benzophenone and distilled before use. Dichloromethane was dried over CaH_2 and distilled before use. $W(CO)_6$, $BF_3{\cdot}Et_2O$, dicyclopentadiene, propargyl bromide, benzyl alcohol, I_2, and sodium were obtained commercially and used without purification. Mass data of tungsten compounds were reported according to ^{184}W. $ClCpW(CO)_3$ were prepared by procedures described in the literature.[16] Spectral data of compounds **4**−**30**, **33**, **35**, **40**−**48,** and **55**−**57** in repetitive experiments are provided in the Supporting Information.

(1) Synthesis of (2*R,3*R**)-3-Methyl-2-[[(4-methylphenyl)(2-propynyl)Sulfonamido]methyl]oxirane (1).** To a CH_2Cl_2 solution (10.0 mL) of enyne (0.50 g, 2.5 mmol) was added *m*-CPBA (0.79 g, 3.75 mmol) at 23 °C, and the mixtures were stirred for 36 h. The solution was concentrated, and the remaining white residues were chromatographed through a short basic alumina column (diethyl ether/hexane = 1/1, R_f = 0.4) to afford epoxide **1** as a colorless oil (0.55 g, 2.0 mmol, 80%): IR (neat, cm^{-1}) 3310 (vs); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 4.20 (ABq, J = 5.6 Hz, 2 H), 3.41 (dd, J = 14.8, 4.0 Hz, 1 H), 3.28 (dd, J = 14.8, 5.2 Hz, 1 H), 2.89−2.88 (m, 2 H), 2.41 (s, 3 H), 2.02 (t, J = 2.4 Hz, 1 H), 1.29 (d, J = 5.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 135.7, 129.5, 127.7, 76.6, 73.9, 57.3, 52.9, 47.9, 37.9, 21.5, 17.0; MS (EI, 75 eV, *m*/*z*) 279 (M^+).

(2) Synthesis of $WCp(CO)_3$[η^1-(2*R,3*R**)-3-methyl-2-[[(4-methylphenyl)(2-propynyl)sulfonamido]methyl]oxirane] (2).** To a Et_2NH solution (15.0 mL) of alkynyltungsten complex **1** (0.50 g, 1.79 mmol) were added $CpW(CO)_3Cl$ (0.66 g, 1.79 mmol) and CuI (34 mg, 0.179 mmol), and the solution was stirred for 3 h to yield a dark yellow solution. The solution was concentrated to ca. 3 mL and eluted through a Et_3N-pretreated silica column to give compound **2** (0.77 g, 1.26 mmol, 70%) as a viscous solid: IR (neat, cm^{-1}) 2016 (s), 1914 (vs); ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H), 5.42 (s, 5 H), 4.30 (ABq, J = 18 Hz, 2 H), 3.42 (dd, J = 14.8, 4.8 Hz, 1 H), 3.25 (dd, J = 14.4, 5.6 Hz, 1 H), 2.89∼2.86 (m, 2 H), 2.40 (s, 3 H), 1.28 (d, J = 5.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 228.8, 211.6, 143.0, 136.4, 129.4, 127.7, 120.3, 91.3, 67.5, 57.3, 53.5, 47.4, 40.7, 21.4, 17.1; MS (75 eV, *m*/*z*) 611 (M^+). Anal. Calcd for $C_{22}H_{22}O_6NWS$: C, 43.15; H, 3.62; N, 2.29. Found: C, 43.11; H, 3.44; N, 2.11.

(3) Synthesis of (3*S,3a*R**,6a*S**)-3-Methyl-5-[(4-methylphenyl)sulfonyl]perhydrofuro[3,4-*c*]pyrrol-1-one (3).** To a CH_2Cl_2 solution (3.0 mL) of alkynyltungsten complex **2** (0.50 g, 0.81 mmol) was added $BF_3{\cdot}Et_2O$ at −40 °C, and the mixtures were stirred for 8 h before addition of water (2.0 mL). The solution was stirred for 6 h, and the organic layer was extracted with diethyl ether. Flash chromatography over a silica bed afforded **3** as a colorless solid (0.21 g, 0.70 mmol, 86%): IR (neat, cm^{-1}) 1774 (vs); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 4.68 (dt, J = 12.8, 6.5 Hz, 1 H), 3.59 (dd, J = 10, 1.8 Hz, 1 H), 3.69−3.30 (m, 1H), 3.25−3.11 (m, 3 H), 3.05−2.98 (m, 1 H), 2.40 (s, 3 H, CH_3), 1.34 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 144.2, 132.1, 129.9, 127.8, 76.3, 50.0, 47.2, 46.0, 42.7, 21.5, 16.2; MS (EI, 75 eV, *m*/*z*) 295(M^+); HRMS calcd for $C_{14}H_{17}NO_4S$ 295.3642, found 295.3646.



3

irradiation	increase
H^2 (δ 3.03)	H^1 δ 3.22 (4.36%)
	H^3 (6.25%)
	Me δ 1.34 (0 %)
H^3 (δ 4.68)	H^2 (2.75%)
	Me (3.59 %)
	H^1 (1.36%)

(4) Synthesis of (3*S,3a*R**,6a*S**)-3-Phenylperhydrofuro[3,4-*c*]furan-1-one (31).** To a CH_2Cl_2 solution (3.0 mL) of alkynyltungsten complex **28** (0.50 g, 0.96 mmol) was added $BF_3{\cdot}Et_2O$ at −40 °C, and the mixtures were stirred for 8 h before addition of water (2.0 mL). The solution was stirred for 6 h, and the organic layer was extracted with diethyl ether. Flash chromatography over a silica bed afforded **31** as colorless oil (0.15 g, 0.71 mmol, 74%): IR (neat, cm^{-1}) 1776 (vs); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.27 (m, 5 H), 5.23 (d, J = 5.4 Hz, 1 H), 4.38 (dd, J = 9.6, 2.0 Hz, 1 H), 4.14 (dd, J = 9.6, 2.0 Hz, 1 H), 3.85−3.80 (m, 2 H), 3.66−3.41 (m, 1 H), 3.13−3.08 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 139.8, 129.0, 128.7, 125.1, 85.9, 74.2, 71.6, 49.2, 46.0; MS (75 eV, *m*/*z*) 204 (M^+); HRMS calcd for $C_{12}H_{12}O_3$ 204.2231, found 204.2230.

(5) Synthesis of $WCp(CO)_3$(η^1-3-Carbonyl-5-hydroxy-4-phenyltetrahydropyran) (32). To a CH_2Cl_2 solution (3.0 mL) of alkynyltungsten complex **29** (0.50 g, 0.96 mmol) was added $BF_3{\cdot}Et_2O$ at −40 °C, and the mixture was stirred for 8 h before addition of water (2.0 mL). The solution was stirred for 4 h, and the organic layer was extracted with diethyl ether. Flash chromatography over a Et_3N-pretreated silica bed

(16) Dub, M. *Organometallic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1966; Vol. 1.

afforded **32** as yellow solid (0.41 g, 0.76 mmol, 79%): IR (neat, cm^{-1}) 2017 (vs), 1939 (vs), 1913 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5 H), 5.22 (s, 5 H, Cp), 4.81−4.72 (m, 1 H), 4.21 (d, J = 12.1 Hz, 1 H), 4.13 (dd, J = 10.8, 5.2 Hz, 1 H), 4.01−3.98 (m, 1 H), 3.48 (dd, J = 12.2, 3.6 Hz, 1 H), 3.08 (dd, J = 10.8, 10.0 Hz, 1 H), 2.68 (dd, J = 10.1, 4.6 Hz, 1 H), 1.75 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 242.1, 226.4, 219.9, 219.2, 139.1, 129.0, 128.5, 126.8, 93.6, 75.8, 72.2, 66.8, 64.6, 52.7; MS (75 eV, *m*/*e*) 538 (M^+). Anal. Calcd for $C_{20}H_{18}O_6W$: C, 44.63; H, 3.37. Found: C, 44.61; H, 3.29.

(6) Synthesis of 5-Hydroxy-4-phenyltetrahydropyran-3-carboxylic Acid Methyl Ester (34). To a CH_2Cl_2 solution containing I_2 (46 mg, 0.185 mmol) wrere added compound **32** (100 mg, 0.185 mmol) and MeOH (2.0 mL) at 0 °C, and the mixture was stirred for 8 h. The reaction mixture was treated with a saturated $Na_2S_2O_3$ solution, and the organic layer was extracted with diethyl ether, dried over $MgSO_4$, and concentrated. The residue was eluted through a silica column (hexane/ether = 1:2) to give compound **34** as a colorless solid (42.0 mg, 0.178 mmol, 96%): IR (neat, cm^{-1}) 2923 (s), 1937 (vs), 1688 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 −7.22 (m, 5 H), 4.82−4.78 (m, 1 H), 4.20−4.16 (m, 1 H), 3.75 (dd, J = 12.0, 3.5 Hz, 1 H), 3.50 (s, 3 H, OCH_3), 3.26 (dd, J = 11.0, 8.5 Hz, 1 H), 3.0−2.98 (m, 1 H), 2.94 (dd, J = 9.5, 5.0 Hz, 1 H), 1.72 (bs, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 138.4, 128.7, 128.5, 127.3, 71.8, 69.3, 64.7, 51.5, 50.6, 47.4; MS (75 eV, *m*/*e*) 236 (M^+); HRMS calcd for $C_{13}H_{16}O_4$ 236.1037, found 236.1035.

(7) Synthesis of 1-[(2*R*)-2,2-Dihydroxy-2-methylpropyl]-1-(2-propynyl)-4-methyl-1-benzensulfonamide (36). To a mixture of water (8.6 mL) and *tert*-butyl alcohol (8.6 mL) were added methyl sulfonamide (0.18 g, 1.89 mmol), β-AD-mix (2.27 g), and compound **35** (0.50 g, 1.89 mmol), and the mixture was stirred at 0 °C for 27 h before quenching with a saturated $Na_2S_2O_3$ solution. The organic layer was extracted with ethyl acetate and dried over $MgSO_4$. The solution was concentrated and chromatographed on a silica column to afford the diol **36** as a solid form (0.48 g, 1.62 mmol, 86%, 75% ee). Recrystallization from a saturated diethyl ether/hexane gave a sample with 87% ee: $[\alpha]_D$ = +4.25 ($CHCl_3$, c = 2.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (2 H, d, J = 11.2 Hz); 7.27 (2 H, d, J = 11.2 Hz), 4.34 (2 H, s), 3.56 (2 H, m), 3.23 (2H, ABq, J = 11.2 Hz), 3.03 (2H, s), 2.30(3H, s), 1.94 (1H, t, J = 3.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 136.0, 129.3, 127.7, 126.8, 90.1, 76.3, 67.2, 52.3, 39.4, 23.4, 21.6; MS (75 eV, *m*/*e*) 297 (M^+); HRMS calcd for $C_{14}H_{19}NSO_4$ 297.1035, found 297.1038.

(8) Synthesis of Toluene-4-sulfonic Acid 2-Hydroxy-2-methyl-3-[prop-2-ynyl(toluene-4-sulfonyl)amino]-propyl Ester (37). To a pyridine solution (5.0 mL) of compound **36** (0.42 g, 1.21 mmol) was added *p*-toluenesulfonyl chloride (0.30 g, 1.41 mmol), and the mixture was stirred for 4 h. To this mixture was added cold water, and the organic layer was extracted with ether. The solution was concentrated and eluted through a silica column to give compound **37** as a colorless solid (0.42 g, 0.94 mmol, 78%): $[\alpha]_D$ = +17.1 ($CHCl_3$, c = 2.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, J = 8.4 Hz); 7.31 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.4 Hz), 4.34 (ABq, J = 11.2 Hz, 2 H), 3.94 (2H, d, J = 1.6), 3.23 (ABq, J = 11.2 Hz, 2H), 2.41 (3H, s), 1.96 (1H, t, J = 3.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 136.0, 129.3, 127.7, 126.8, 90.1, 76.3, 67.2, 52.3, 39.4, 23.4, 21.6; MS (75 eV, *m*/*e*) 451 (M^+); HRMS calcd for $C_{21}H_{25}NS_2O_6$ 451.1123, found 451.1122.

(9) Synthesis of 4-Methyl-*N*-(2-methyloxiranylmethyl)-*N*-prop-2-ynylbenzenesulfonamide (38). To a methanol solution (10 mL) of alcohol **37** (1.00 g, 2.21 mmol) was added potassium carbonate (0.65 g, 4.46 mmol), and the mixtures were stirred for 6 h. To this mixture was added cold water, and the organic layer was extracted with diethyl ether. The solution was concentrated and eluted through a silica column to give compound **38** as a solid (0.52 g, 1.85 mmol, 84%): $[\alpha]_D$ = −24.7 ($CHCl_3$, c = 5.0); IR (neat, cm^{-1}) 2047 (s), 1934(s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, J = 8 Hz), 7.25 (2 H, d, J = 8.0 Hz), 4.21 (ABq, J = 2.8 Hz, 2 H), 3.35 (ABq, J = 14 Hz, 2 H), 2.74 (d, J = 4.4 Hz, 1 H), 2.60 (d, J = 4.4 Hz, 1 H), 2.39 (s, 3H), 1.94 (t, J = 2.8 Hz, 1 H), 1.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 135.8, 129.4, 127.6, 76.3, 73.9, 55.5, 51.4, 50.8, 37.6, 21.4, 18.7; MS (75 eV, *m*/*e*) 279 (M^+); HRMS calcd for $C_{14}H_{17}NSO_3$ 279.0929, found 279.0923.

(10) Synthesis of $WCp(CO)_3$[η^1-4-Methyl-*N*-(2-methyloxiranylmethyl)-*N*-prop-2-ynylbenzenesulfonamide] (39). To a Et_2NH (10 mL) solution of epoxide **38** (1.00 g, 3.77 mmol) were added $CpW(CO)_3Cl$ (1.38 g, 3.77 mmol) and CuI (71 mg, 0.37 mmol), and the solution was stirred for 3 h. The solution was concentrated to 3 mL and eluted through an Et_3N-pretreated silical gel column to give compound **39** as a yellow solid (1.66 g, 2.70 mmol, 76%): $[\alpha]_D$ = −24.7 ($CHCl_3$, c = 5.0); IR (neat, cm^{-1}) 2047 (s), 1931 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (2 H, d, J = 8.0 Hz); 7.26 (2 H, d, J = 8.0 Hz), 5.41(s, 5 H), 4.41 (2 H, dd, J = 16.0, 1.0 Hz), 4.23 (1 H, dd, J = 18, 0.8 Hz), 3.45 (d, J = 14.4 Hz, 1 H), 3.21 (d, J = 14.4 Hz, 1 H), 2.79 (dd, J = 4.8 Hz, 2H), 2.60 (d, J = 4.8 Hz, 1 H), 2.41 (s, 3 H), 1.39 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 228.8, 211.6, 211.6, 142.9, 136.5, 129.3, 127.6, 120.2, 91.2, 67.4, 55.4, 52.1, 50.3, 40.4, 21.4, 19.0; MS (75 eV, *m*/*e*) 611 (M^+). Anal. Calcd for $C_{22}H_{21}WSNO_6$: C, 43.22; H, 3.46; N, 2.29. Found: C, 43.01; H, 3.40; N, 2.00.

(11) General Procedures for Synthesis of Enyne Alcohol (49). To a THF solution (40 mL) of trimethylsilylethyne (6.0 mL, 42.48 mmol) was added *n*-BuLi (42.5 mmol) at −78 °C, and the solution was stirred for 1 h. To this solution was added slowly aldehyde **48** (5.95 g, 42.5 mmol), and the solution was warmed to 23 °C in a period of 5 h. To this mixture was added a saturated ammonium chloride solution, and the organic layer was extracted with diethyl ether, concentrated, and eluted through a silica column to afford a colorless oil (10.2 g, 39.1 mmol, 92%). This oil was treated with a THF solution of TBAF (1 M, 40 mL) at 23 °C, and the mixture was stirred for 1 h. The solution was concentrated and eluted through a silica column to give compound **49** as a colorless oil (5.90 g, 35.6 mmol, 91%): ^1H NMR (400 MHz, $CDCl_3$) δ 5.35−5.33 (m, 2 H), 4.35−4.31 (m, 1 H), 2.4 (s, 1 H), 2.0 −1.84 (m, 4 H), 1.64−1.62 (m, 2 H), 1.45−1.42 (m, 2 H), 1.38−1.22 (m, 2 H), 0.823 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.9, 129.9, 85.5, 72.6, 53.3, 37.3, 34.8, 32.3, 25.2, 22.8, 14.11; MS (75 eV, *m*/*e*) 166.14 (M^+); HRMS calcd for $C_{11}H_{18}O$ 166.1358, found 166.1355.

(12) General Procedures for Synthesis of Ethynyl Acetate Compound (50). To a CH_2Cl_2 (20 mL) of compound **49** (5.50 g, 33.10 mmol) were added dry pyridine (20 mL), acetic anhydride (51.1 mL, 49.7 mmol), and DMAP (360 mg). The solution was washed with 100 mL of 1 N HCl and extracted with ether. The ether extract was concentrated and eluted through a silica column to give compound **50** as a colorless oil (5.78 g, 27.8 mmol, 84%): ^1H NMR (400 MHz, $CDCl_3$) δ 5.39−5.32 (m, 3 H), 2.43 (d, J = 2.4 Hz, 1 H), 2.06 (3 H, s), 1.93−2.02 (m, 4 H), 1.72∼1.76 (m, 2 H), 1.50−1.48 (m, 2 H), 1.37−1.31 (m, 2 H), 0.844 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 131.3, 129.6, 81.4, 73.6, 63.9, 34.7, 34.2, 32.1, 25.0, 22.8, 21.1, 13.8. MS (75 eV, *m*/*e*) 208 (M^+); HRMS calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1456.

(13) Synthesis of 1,3-[(2*R*,3*R*)-3-Oxiran-2-yl]propyl-4-pentynyl Acetate (51). A buffer solution (pH 9−10) was prepared from $Na_2B_4O_7{\cdot}10H_2O$ (1.097 g), Na_2EDTA (1.0 mL, 0.10 M), and water (99 mL). This buffer solution (20 mL) was added with CH_3CN (30 mL), the enyne **50** (0.416 g, 2.0 mmol), chiral fructose-derived ketone (0.31 g, 1.20 mmol), and Bu_4NHSO_4 (0.03 g). To this mixture was added an aqueous K_2CO_3 solution (1.6 g, 13.0 mL water) and a Na_2EDTA solution (4×10^{-4} M, 13.0 mL) of oxone (1.70 g, 2.76 mmol) in a period of 2 h. The mixtures were stirred at 0 °C for an additional 3 h before treatment with pentane (50 mL), dried over $MgSO_4$, and chromatographed through a Et_3N-pretreated silica column to afford compound **51** (0.39 g, 1.74, mmol, 87%) as a colorless oil. HPLC analysis showed a 1:1 diastereomeric mixture product with each one having 90% ee: $[\alpha]_D$ = +18.9 ($CHCl_3$, c

= 0.32); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38−5.30 (m, 1 H), 2.65 (m, 2 H), 2.44 (1 H, d, J = 2.0 Hz), 2.07 (s, 3 H), 1.40−1.86 (m, 8 H), 0.948 (t, J = 4.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 81.1, 73.8, 63.7, 58.7, 58.5, 34.5, 34.3, 31.4, 21.7, 21.1, 19.5, 14.3; MS (75 eV, *m*/*e*) 224.14 (M^+); HRMS calcd for $C_{13}H_{20}O_3$ 224.1424, found 224.1423.

(14) Synthesis of WCp(CO)$_3$[η^1-1,3-[(2*R*,3*R*)-3-propyloxiran-2-yl]propyl-4-pentynyl acetate] (54). To a Et_3N (4.0 mL) solution of epoxide **51** (0.20 g, 0.89 mmol) were added $CpW(CO)_3Cl$ (0.50 g, 1.36 mmol) and CuI (15 mg, 0.37 mmol), and the solution was stirred for 3 h. The solution was concentrated to 3 mL and eluted through a Et_3N-pretreated silica gel column to give the compound as a yellow solid (0.44 g, 0.80 mmol, 70%): $[\alpha]_D$= +7.32 ($CHCl_3$, c = 4.5); IR (neat, cm^{-1}) 1919 (vs), 2015 (vs); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (s, 5 H), 5.30 (t, J = 6.4 Hz, 1 H), 2.50 (d, J = 2 Hz, 2 H), 1.87 (s, 3 H), 1.20−1.60 (m, 10 H), 0.80 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 229.0, 212.0, 212.1, 170.1, 125.4, 91.7, 66.2, 58.5, 35.6, 34.2, 31.6, 22.6, 21.8, 21.4, 19.3, 14.0; MS (EI, 75 eV, *m*/*z*) 555 (M^+). Anal. Calcd for $C_{21}H_{23}O_6W$: C, 45.43; H 4.18. Found: C, 45.33; H, 4.30.

(15) Synthesis of (3*R*,3a*R*)-3-Propyl-1,3,3a,4,5,6-hexahydro-1-isobenzofuranone (58). To a diethyl ether (5.0 mL) solution of tungsten complex **54** (238 mg, 0.43 mmol) was added BF_3·OEt_2 at −78 °C (0.10 mL, 0.43 mmol), and the mixture was stirred for 4 h. To this solution was added water (5.0 mL), and the resulting solution was extracted with diethyl ether and dried over $MgSO_4$. The solution was concentrated and eluted on silica to give compound **58** as colorless oil (50.3 mg, 0.279 mmol, 65%): $[\alpha]_D$ = +69.6 ($CHCl_3$, c = 0.6); IR (neat, cm^{-1}) 1759 (vs), 2015 (vs); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (m, 1 H), 4.66 (dt, J = 9.2, 3.2 Hz, 1 H), 3.1−3.00 (m, 1 H), 2.40−2.32 (m, 1 H), 2.24−2.12 (m, 1 H), 2.00−1.83 (m, 2 H), 1.60−1.20 (m, 6 H), 0.92 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 136.3, 129.8, 81.7, 39.9, 34.0, 25.3, 22.7, 21.3, 18.8, 13.9; HRMS calcd for $C_{16}H_{18}O_3$ 180.1150, found 180.1148.

Acknowledgment. We thank the National Science Council, Taiwan, for financial support of this work.

Supporting Information Available: Experimental procedures and spectral data of compounds **4**−**30**, **33**, **35**, **40**−**48**, and **55**−**57** in repetitive experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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