Tungsten-Promoted [3+2]- and [3+3]-Cycloaddition of Epoxides with Alkynes. A Facile Enantiospecific Synthesis of Bicyclic Lactones

Reniguntala J. Madhushaw, Chien-Le Li, Kuo-Hui Shen, Chu-Chen Hu, and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University Hsinchu, Taiwan, ROC

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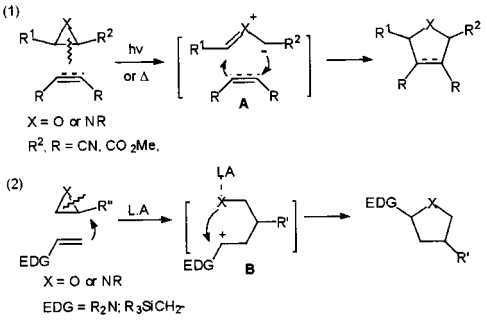
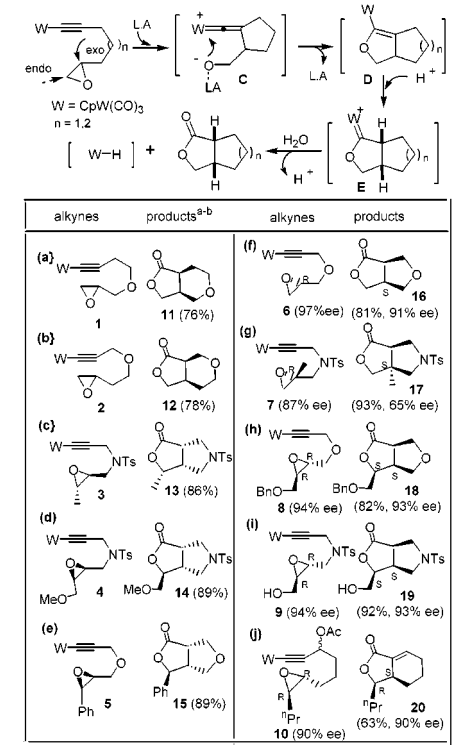
The cycloaddition of alkynes and alkenes with organic substrates is widely used for the synthesis of carbocyclic and heterocyclic compounds.[1,2] Epoxides and aziridines are important substances, and the cycloaddition of these molecules with alkenes and alkynes is an interesting topic in organic synthesis. Scheme 1 shows two types for [3+2]-cycloaddition of alkenes and alkynes with epoxides or aziridines via cleavage of their C−C and C−X bonds, respectively.[3,4] The former (eq 1) involves 1,3-dipolar cycloaddition of electron-deficient alkynes and alkenes with a zwitterionic intermediate **A** produced by the thermal and photolytic activation of epoxides and aziridines. The presence of an electron-withdrawing group R^2 (R^2 = CN, CO_2R) is crucial for formation of this intermediate.[3,4] This system has been thoroughly studied and is useful in organic synthesis. An alternative route[5] involves the use of a Lewis acid to cleave of the C−X bond, to give the intermediate **B** (eq 2). Despite its synthetic significance, there have been very few successful examples of this system despite its synthetic significance. It is only applicable to special types of functionalized olefins.[5] Yamamoto[6] recently reported the synthesis of tetrahydrofuran derivatives from vinyloxirane with activated alkenes using palladium catalyst. Normally, addition products are formed exclusively when epoxides and aziridienes are treated with activated alkenes or alkynes in the presence of a Lewis acid.[7,8] [3+2]-Cycloaddition of epoxides and aziridines with alkynes remains unknown to our best knowledge. In this study, we describe two new cycloadditions for common epoxides and functionalized alkynes. These methods are applicable to the enantiocontrolled synthesis of complex bicyclic lactones.

Scheme 1



Scheme 2



[a] $BF_3{\cdot}Et_2O$ (25 mol %), CH_2Cl_2, −40 °C. [b] Yields were reported after purification from preparative silica TLC plate. [c] ee values were determined from HPLC (Merck Chiral Sphere column.

Scheme 2 shows a working hypothesis for the [3+2]-cycloaddition of alkynyltungsten and epoxide. The mechanism involves a tungsten-vinylidenium[9] cation **C**. A catalytic amount of Lewis acid is sufficient for the reaction. The enol ether **D** is highly sensitive to the presence of a proton which accelerates its catalytic conversion to oxacarbenium **E**,[10] and finally to cis-fused bicyclic lactone selectively if water is present.[9] The success of this cycloaddition relies on exo-attack at the epoxide, which normally is considered to be problematic because the hybridization of epoxide is somewhere between sp^2 and sp^3.[11]

Scheme 2 also shows the syntheses of various lactones based on this mechanism. Alkynyltungsten complexes **1**−**10** were prepared in yields of 75−86% from $CpW(CO)_3Cl$, Et_2NH, and the corresponding alkyne.[9] In a typical reaction, a CH_2Cl_2 solution of alkynyltungsten species was treated with $BF_3{\cdot}Et_2O$ (20 mol

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(8) See the following examples: (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.

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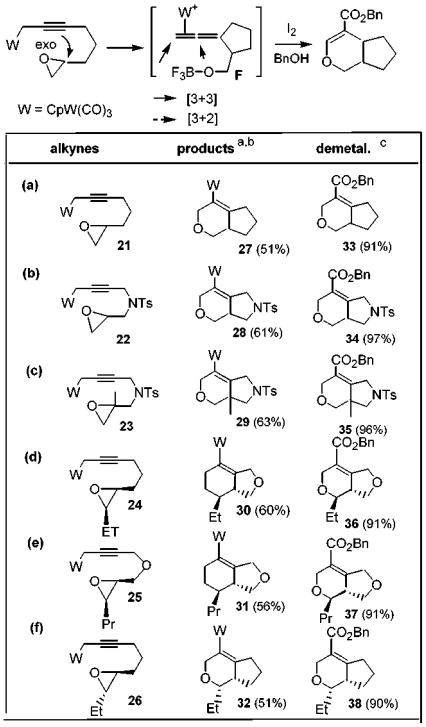
%) at −40 °C for 2−8 h before water was added. Entries a and b show two examples of the efficient synthesis of *cis*-γ-lactones **11** and **12** fused with six-membered oxaocycles, respectively. The cis-configurations of **11** and **12** were determined by ^{1}H NOE NMR spectra.[12] In the cyclization of *trans*- and *cis*-epoxides **3** and **4** (entries c and d), the cis-fused products **13** and **14** have *cis*-methyl and *trans*-propyl groups, respectively, based on ^{1}H NMR analysis.[12] This information suggests that opening of the epoxide proceeds via an inversion of stereochemistry. We also prepared the styrene epoxide **5** which could favor the endo-attack via the formation of a benzyl carbocation,[11] but the exo-attack is still the dominant route to yield the bicyclic lactone **15** exclusively. Two chiral epoxides **6** (97% ee) and **7** (87% ee) were prepared to study the enantioselective cycloadditions as depicted in entries f and g. A small decrease in the ee value is observed for the lactone **16** (91% ee), while a significant decrease is seen for compound **17** (65% ee). The latter may involve a tertiary carbocation during ring-opening of the epoxide. The absolute configuration and [α]-value of **16** are consistent with those reported in the literature.[13] Enantiopure bicyclic lactones can be synthesized smoothly from chiral 1,2-disubstituted epoxides[14] **8** and **9** in a one-pot operation. Entries h and i show the enantiospecific synthesis of functionalized bicyclic lactones **18** and **19** with BF_3·Et_2O as the catalyst. Only one stereoisomer was formed even through three stereogenic centers are present. The enantiopurities of **18**−**19** agree with those of the starting epoxides **8**−**9**. We also prepared chiral epoxide **10** as a 1:1 mixture of acetate diastereomers, and each isomer has 90% ee according to HPLC analysis; the resulting unsaturated lactone **20** was obtained in 63% yield with 90% ee.

BF_3·Et_2O catalyst also effected a novel [3+3]-cycloaddition of epoxides with propargyltungsten groups; the results are summarized in Scheme 3. The propargyltungsten complexes **21**−**26** were prepared[15] in yields of 87−95% from $NaCpW(CO)_3$ and the corresponding chloropropargyl chlorides comprising an epoxide. In a typical reaction, the propargyl complex was treated with BF_3·Et_2O (25 mol %) catalyst in cold CH_2Cl_2 (−40 °C) for 4−10 h before treatment with a saturated $NaHCO_3$ solution. The products **27**−**32** were obtained in 51−63% yields. Structural assignment of the products was made based on spectroscopic data. This cyclization induces 1,2-migration of the tungsten fragment. Subsequent demetalation of **27**−**32** with I_2 (1.1 equiv) and benzyl alcohol (2.0 equiv) gave benzyl esters **33**−**38** in high yields (90−97%). Entries a and b show the synthesis of tungsten−pyranyl complexes **27** and **28** fused with five-membered carbocycles and azacycles. This cyclization also works well for gem-disubstituted epoxide **23** to yield compound **29** in 63% yield. Cyclizations of cis epoxides **24** and **25** afforded *trans*-pyranyl compounds **30** and **31** in reasonable yields. Trans epoxide **26** gave the *cis*-pyranyl complex **32** in 51% yield.

The preference for [3+3]-cycloaddition can be rationalized by the mechanism proposed in Scheme 3, which involves a tungsten-η^2-allene cation[16] **F** produced by exo-attack on the epoxide.

Scheme 3



[a] BF_3·Et_2O (25 mol %), CH_2Cl_2 (−40 °C). [b] Yields were reported after purification from silica TLC plate. [c] BnOH (2.0 equiv), I_2 (1.1 equiv), CH_2Cl_2, −40 °C.

Notably, the BF_3O^- terminus of species **F** attacks the terminal allene carbon rather than the expected central carbon.[17] This contradicts those of free allenes comprising a similar alcohol.[17] The exact nature of this cyclization is uncertain at this stage. We tentatively propose that it may be due to coordination of $CpW(CO)_3$ to the external $=C=CH_2$ group to alter the carbon hybridization close to sp^3 character. This effect disfavors a [3+2]-cycloaddition pathway given from a 5-endo-trig ring-closure.[18]

In summary, we have reported two tungsten-promoted [3+2]- and [3+3]-cycloadditions of alkynes and epoxides. These two types of cycloadditions involve the exo ring-opening of epoxide, followed by counterattack of OBF_3^- of the intermediate at its central vinylidenium carbon and its terminal allene carbon, respectively. These cyclizations proceed having high diastereo- and enantiospecificity to give bicyclic heterocycles with multiple stereogenic centers in a one-pot operation. Further applications of these cycloadditions to the syntheses of natural lactones with high enantiopurities is under investigation.

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Supporting Information Available: Experimental procedures for the syntheses and spectral data of new compounds **1**−**38** and the key chiral epoxides (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) ^{1}H-NOE NMR spectra of key compounds are provided in the Supporting Information.

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(14) Syntheses of chiral epoxides **6**−**10** are provided in the Supporting Information.

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