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A Novel Stereocontrolled Synthesis of Cis-Fused Bicyclic Lactams via [3 + 2]-Cycloaddition of Alkynyltungsten Complexes with Tethered Aziridines

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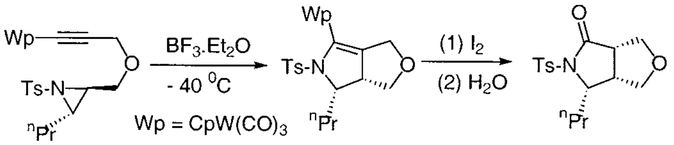
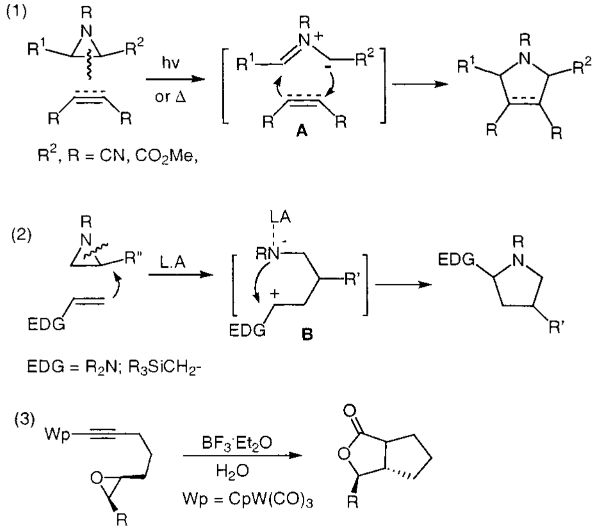
ABSTRACT



Treatment of alkynyltungsten complexes with tethered aziridines in the presence of $BF_3{\cdot}Et_2O$ led to [3 + 2]-cycloaddition reactions, affording bicyclic tungsten–enamine species stereoselectively. The stereochemistry of the resulting product reveals that ring opening of aziridine is initiated by S_N2 attack of the tungsten fragment. Decomplexation of these organometallics with I_2 in CH_2Cl_2, followed by hydrolysis, afforded only cis-fused bicyclic lactams efficiently.

[3 + 2]-Cycloaddition of aziridine with alkynes and alkenes is a useful method for synthesis of pyrrolidine derivatives.[1−9] The cycloaddition can be achieved via two pathways, involving cleavage of the C−C[2−7] or C−N[8,9] bonds of aziridines as shown in Scheme 1. Thermal or photolytic activation of aziridines of special types (R^2, R = CN, CO, Ph) generates azomethine ylides **A** that can be trapped with electron-deficient olefins or alkynes by 1,3-dipolar cycloaddition.[2−7] This system has been thoroughly studied and is

Scheme 1



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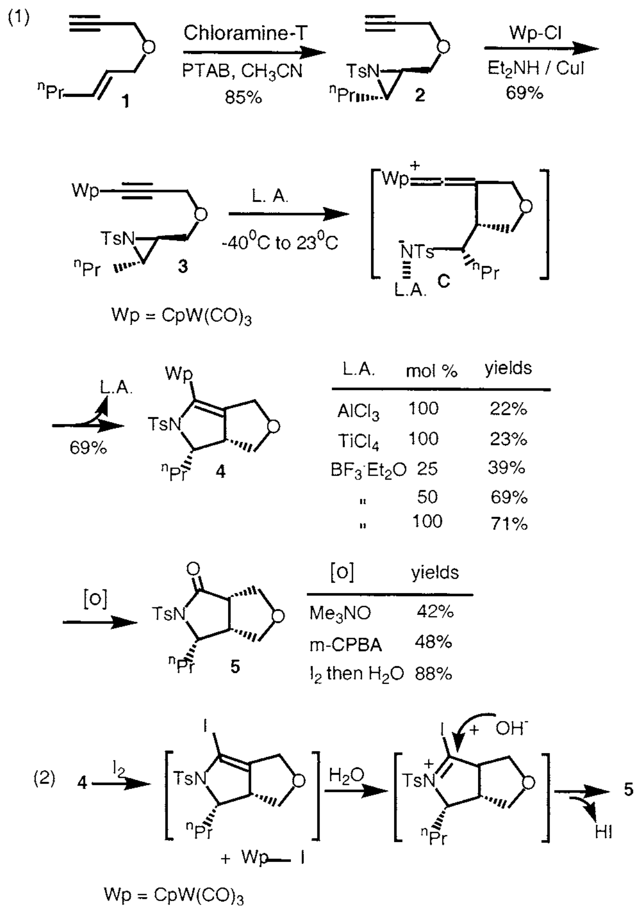
10.1021/ol0201862 CCC: $22.00

Scheme 2



L.A.	mol %	yields
$AlCl_3$	100	22%
$TiCl_4$	100	23%
$BF_3 \cdot Et_2O$	25	39%
"	50	69%
"	100	71%

[o]	yields
Me_3NO	42%
m-CPBA	48%
I_2 then H_2O	88%

widely used for synthesis of complex nitrogen-containing molecules such as marine alkaloid Sarain −A.[7] An alternative approach[8,9] involves use of a Lewis acid to generate zwitterionic intermediate **B**. Despite its synthetic significance, this method works for only limited cases of electron-rich olefins such as allylsilanes and enamines.[8] Cycloaddition of aziridines with functionalized alkynes via cleavage of C−N bond still remains unknown in the literature. Recently, we reported a novel acid-promoted [3 + 2]-cycloaddition of alkynyltungsten functionality with tethered epoxides via a reactive tungsten−vinylidenium intermediate.[10,11] This method provides a facile synthesis of bicyclic lactones (Scheme 1, eq 3). In the present work, we report a facile synthesis of cis-fused bicyclic lactams via extension of our approach to tethered aziridines.

Scheme 2 shows a synthetic protocol of alkynyltungsten complex **3** tethered with an aziridine group. Conversion of allyl propargyl ether **1** to its aziridine derivative **2** was accomplished in 85% using Chloramine-T and phenyl trimethylammonium tribromide (PTAB).[12] Metalation[13] of aziridine **2** with $CpW(CO)_3Cl$ (1.1 equiv) with CuI catalyst (5 mol %) in Et_2NH solvent afforded alkynyl tungsten complex **3** in 69% yield.

Among several Lewis acids, $BF_3 \cdot Et_2O$ was found to be the most active in cyclization. $AlCl_3$ and $TiCl_4$ gave low yields (22−23%) of desired adduct **4**. Treatment of complex **3** with $BF_3 \cdot Et_2O$ (50 mol %) in CH_2Cl_2 at −40 °C, followed by warming to 23 °C, gave bicyclic tungsten−enamine species **4** in 69% yield after workup. The cyclization is proposed to involve a tungsten−vinylidenium species,[14,15] **C**, via ring opening of the aziridine group by S_N2 attack of tungsten fragment. ^1H NOE[17] of the cycloadduct **4** shows a cis configuration of the structure, consistent with our hypothesis. Oxidative demetalation of tungsten−enamine **4** was best performed with I_2-oxidation in CH_2Cl_2 to afford cis-fused bicyclic lactam **5** and $CpW(CO)_3I$ in 88 and 94% yields, respectively. Oxidative demetalation of complex **4** in CH_2Cl_2 with Me_3NO and *m*CPBA gave lactam **5** in 42 and 48% yields, respectively. Cis-fused lactam **5** was presumbly produced upon hydrolysis of an unstable bicyclic iodoenamine precursor,[16] followed by protonation at the enamine bond from the less hindered face (Scheme 2, eq 2).

Table 1 shows additional instances of formation of bicyclic tungsten−enamines and their corresponding lactams. The cyclization and demetalation exactly followed preceding procedures. Entry 1 shows an additional example for synthesis of tungsten−enamine **14** (64%) fused with a five-membered oxacyclic ring. Decomplexation of complex **14** with I_2, followed by hydrolysis, gave cis-fused lactam **22** in 84% yield. Entries 2 and 3 show two examples for formation of tungsten−enamines **15** (54%) and **16** (58%) comprising a fused six-membered oxacyclic ring that further afforded bicyclic lactams **23** and **24** in 90% and 89% yield, respectively, on I_2-promoted demetalation. This [3 + 2]-cycloaddition is also applicable to synthesis of tungsten−enamines **17** and **18** comprising five- and six-membered carbocyclic rings, respectively. I_2-Oxidation of complexes **17** and **18** efficiently produced bicyclic lactams **25** and **26**, respectively. We also prepared functionalized alkynyltungsten complexes **11** that underwent cycloaddition to form tungsten−enamine **19** smoothly and further gave bicyclic lactam **27** after demetalation. Cyclization of complex alkynyltungsten species **12** yielded cis-fused tricyclic lactam **20** in 61% yield. Isolation of the corresponding tungsten−enamine species was unsuccessful because it is prone to hydrolysis. The three protons on the stereogenic centers of compounds **22**, **23**, and **26** are mutually cis to one another according to ^1H NOE spectra,[17] indicative of inversion of stereochemistry at the aziridine carbon during cycloaddition. Hydrolysis in the I_2-demetalation of tungsten−enamines only led to a cis-fused

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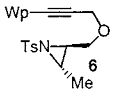
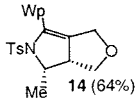
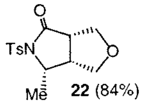
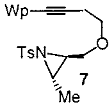
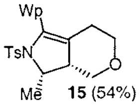
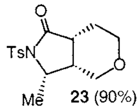
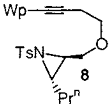
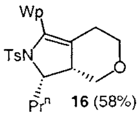
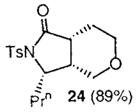
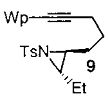
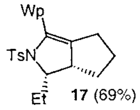
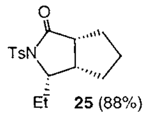
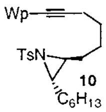
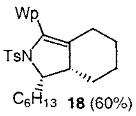
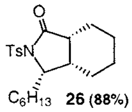
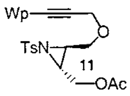
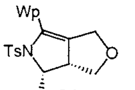
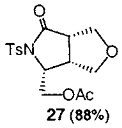
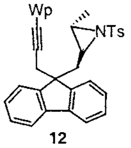
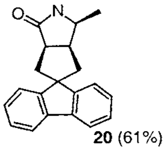
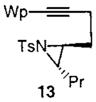
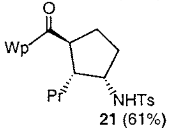
(17) ^1H NOE NMR data of key compounds are provided in Supporting Information.

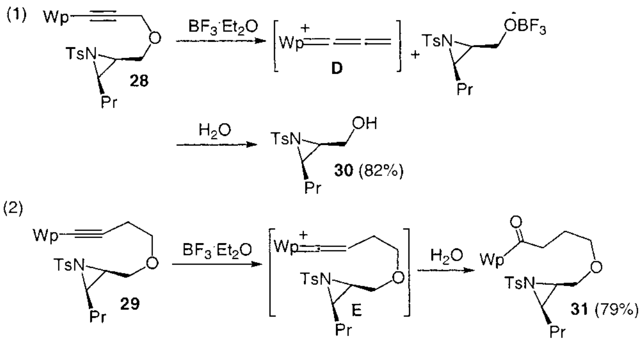
Table 1. [3 + 2]-Cycloaddition of Alkynyltungsten Group with Tethered Aziridine

entries	alkynyltungsten	products[a,b]	I_2-demetallation[b,c]
1	 **6**	 **14** (64%)	 **22** (84%)
2	 **7**	 **15** (54%)	 **23** (90%)
3	 **8**	 **16** (58%)	 **24** (89%)
4	 **9**	 **17** (69%)	 **25** (88%)
5	 **10**	 **18** (60%)	 **26** (88%)
6	 **11**	 **19** (72%)	 **27** (88%)
7	 **12**	 **20** (61%)	—
8	 **13**	 **21** (61%)	—

[a] Conditions: Wp = $CpW(CO)_3$; 50 mol% $BF_3 \cdot Et_2O$, CH_2Cl_2, from −40 to 23 °C, then $NAHCO_3$. [b] Yields were reported after column chromatography. [c] I_2 (1.0 equiv), CH_2Cl_2, 23 °C, 12 h, water.

configuration of products. Treatment of alkynyltungsten complex **13** with $BF_3 \cdot Et_2O$ (50 mol %) gave a tungsten−acyl complex **21** in 61% yield. The stereochemistry of compound **21** was determined from ^1H NOE NMR spectra.[17] This information indicates that 5-endo attack of aziridine is also likely to occur and is preferable to 4-exo attacks.

Scheme 3



Unlike *trans*-aziridines, *cis*-aziridines do not undergo cyclization under similar conditions. Treatment of *cis*-aziridine derivative **28** with $BF_3 \cdot Et_2O$ (50 mol %) gave alcohol **30** in 82% yield (Scheme 3, eq 1). $BF_3 \cdot Et_2O$ may cleave the ether C−O bond of compound **28** over a prolonged period to form tungsten−allenylidenium species **D**.[18] *cis*-Aziridine species **29** yielded tungsten−acyl complex **31** in 79% yield, and the intermediate likely involves vinylidenium species **E** (Scheme 3, eq 2). A small amount of water in the reaction system is expected to generate protons in the presence of $BF_3 \cdot Et_2O$. The inactivity of *cis*-aziridine is attributed to steric hindrance as tungsten−alkynyl group undergoes S_N2 attack at the aziridine group. The cis-propyl group makes it difficult for the alignment of alkynyltungsten group toward the σ^*-bonding orbital of the aziridine group.

In summary, we present a new [3 + 2]-cycloaddition of alkynyltungsten functionality with its tethered aziridine, and the intermediate involves tungsten−vinylidenium species. Both the cycloaddition and demetalation proceed with high diastereoselectivity. This reaction pathway provides an efficient synthesis of bicyclic lactams.

Acknowledgment. We thank National Science Council, Taiwan, for financial support.

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

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