NEW SYNTHESIS OF PIPERIDINE DERIVATIVES *VIA* THE CHROMACYCLOBUTANE

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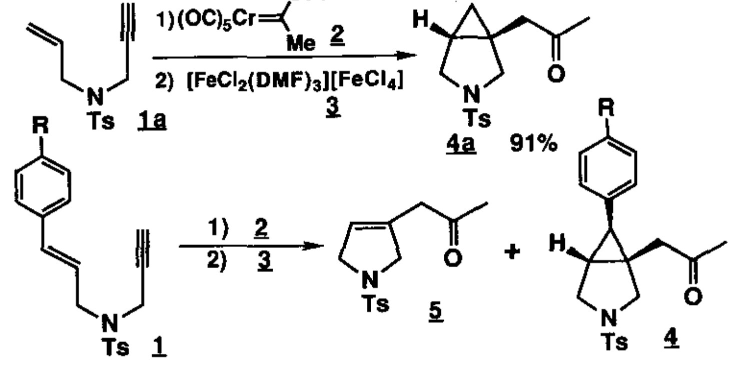
Abstract-----Piperidine derivatives were synthesized from the enynes and Fischer chromium carbene complex *via* chromacyclobutanes in moderate yields and the reaction course was controlled by the substituents on the double bond of the enynes.

It has been well established that acetylenes are far more reactive than olefins with the heteroatom-stabilized carbene complexes.[1] Recent reports described that the lack of reactivity of unactivated olefins for the hetero-atom stabilized complexes can be overcome in the reaction of an enyne.[2] We also reported that the reaction of enyne (**1**) with chromium carbene complex (**2**) afforded the pyrrolidine derivatives in good yields.[3] In this reaction, various pyrrolidine derivatives (**4**) and (**5**) were obtained. It was quite interesting that the reaction course was controlled by the substituents on the double bond of enyne (**1**). Now we want to report the synthesis of piperidine derivatives using chromium carbene complex (**2**) *via* chromacyclobutane (**11**).

Scheme 1



	R	5	4
1b	Me	62%	—
1c	NO_2	4%	73%

Dedicated to Professor E. C. Taylor on the occasion of his 70th birthday.

A solution of enyne (**9**), prepared from the aldehyde (**8**), and chromium carbene complex (**2**) in MeCN was warmed at 70 °C for 4 h followed by treatment with $[FeCl_4][Fe(DMF)_3Cl_2]$ (**3**)[4] afforded the piperidine derivative (**10**)[5] *via* the chromacyclobutane (**11**) in 46% yield. The result was very interesting because Harvey has recently reported that the reaction of enyne (**12**) having oxygen in the tether with molybdenum carbene complex did not afford the desired cyclized product.[6] The reaction of **9** with **2** was carried out under the various conditions and the most suitable solvent was MeCN. Subsequently, compound (**13**)[7] was treated with the chromium carbene complex to give the piperidine derivative (**14**) in 40% yield.

Scheme 2

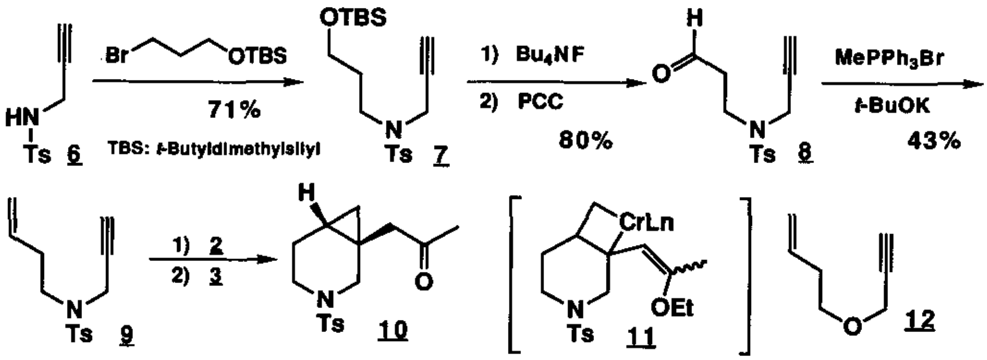
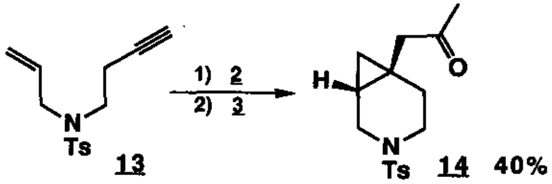


Table 1 Reaction of 9 with 2

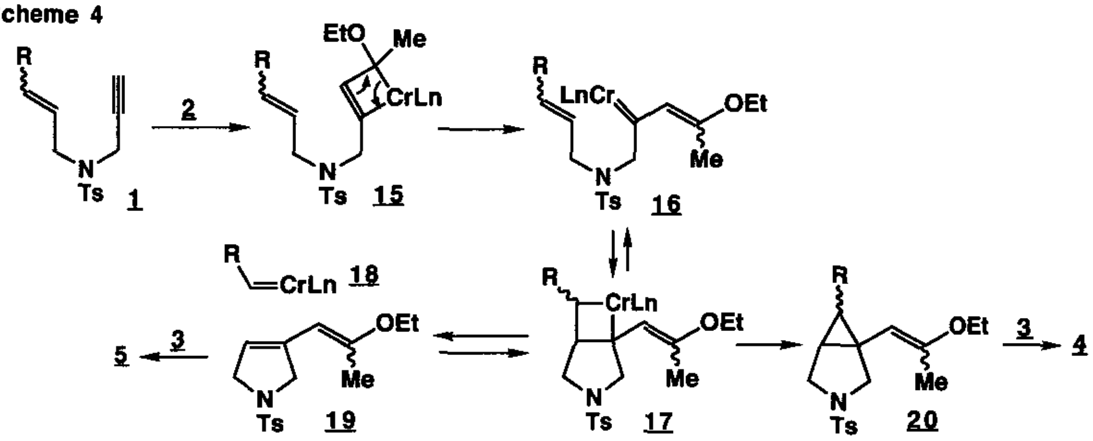
Solvent	Temp	10	6
MeCN	70°C	46%	—
THF	reflux	36%	12%
Benzene	70°C	39%	15%

Scheme 3



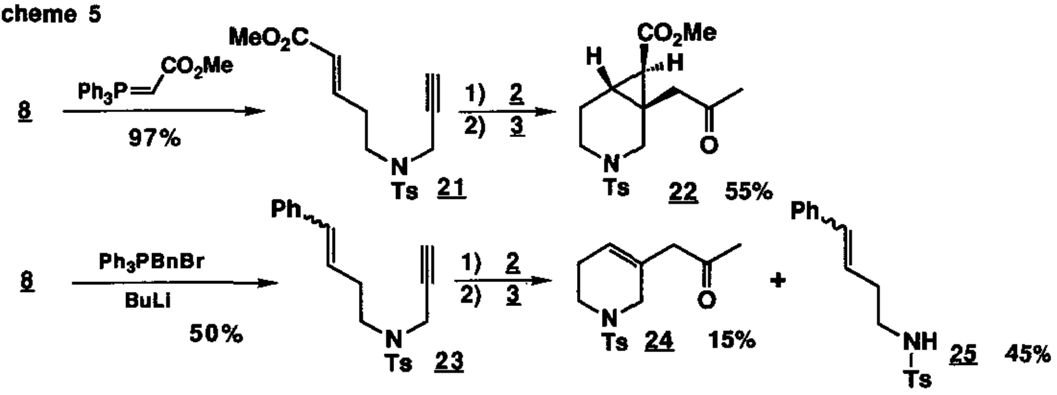
We have already mentioned that the reaction course for the formation of the various pyrrolidine derivatives was controlled by the substituents on the double bond of enyne (**1**). Chromacyclobutane (**17**) generated from enyne (**1**) having an electron withdrawing groups on the double bond would afford the cyclopropane (**20**). On the other hand, the electron donating groups on the double bond would favor the metathesis process because of the stabilization of the alkylidene carbene complex (**18**) generated from the chromacyclobutane (**17**). Thus, the metathesis product (**19**) was obtained.

Scheme 4



On the basis of the considerations of the previously mentioned reaction mechanism, the electron withdrawing group on the double bond should predominantly afford the piperidine derivative fused cyclopropane ring. Thus, compound (8) was converted to 21 by the Wittig reaction, which was treated with chromium carbene complex (2) in MeCN under the same reaction conditions, to give the cyclized product (22) in 55% yield. On the other hand, if the phenyl group was introduced on the double bond, the metathesis process should be favored. Thus, compound (23) was prepared from 8 by the Wittig reaction, which was treated with chromium carbene complex (2) in MeCN under the same reaction conditions. The desired metathesis product (24) was obtained though the yield was low (15% yield). In this reaction, the main product was the tosylamide (25). The reason why the propargyl group was eliminated under these reaction conditions is not clear.

Scheme 5



These results suggest that the reaction of the enyne having nitrogen in the tether with the Fischer chromium carbene complex is a useful method for the synthesis of the pyrrolidine and piperidine derivatives. It has also become apparent that the reaction course is controlled by the substituents on the double bond of the enyne during the formation of the piperidine ring similar to that for the pyrrolidine ring. Further studies are in progress.

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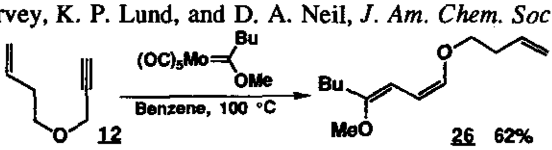
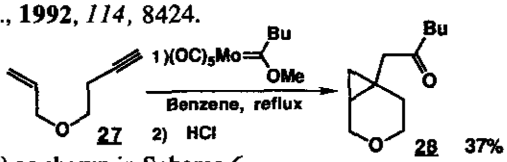
5. All new compounds were fully characterized by ^{1}H-nmr, ^{13}C-nmr, ir, ms, and hr-ms spectra.

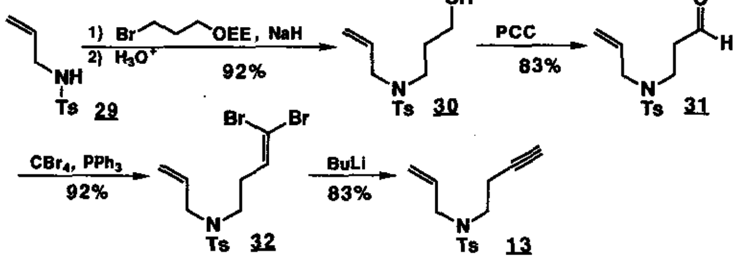
6. The importance of the oxygen substituent in the four-atom tether was examined by Harvey *et al.* Though the reaction of an enyne (27) with molybdenum carbene complex afforded the desired product (28) in 37% yield, similar treatment of compound (12) with molybdenum carbene complex did not afford the desired cyclized product. They claimed that the oxygen substituent activates the α-hydrogens of alkyne. D. F. Harvey, K. P. Lund, and D. A. Neil, *J. Am. Chem. Soc.*, **1992**, *114*, 8424.





7. Compound (13) was easily prepared from tosylamide (29) as shown in Scheme 6.

Scheme 6



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