

## **$\alpha$ -Carbonyl Radical Cyclization: Application Toward Total Syntheses of Natural Products**

**Chin-Kang Sha,\* Shih-Jung Huang, Rei-Torng Chiu, Shinn-Horng Lih, Chen-Tso Tseng, K. C. Santhosh, S. Danialdoss, Ching-Jung Chang, An-Wei Hong, Pyng-Chang Cherng, Wei-Hong Tseng, Wen-Yueh Ho, Fu-Shing Wang and Tzung-Huei Jeng**

*Department of Chemistry, National Tsing Hua University, Hsinchu 300, Taiwan, R. O. C.*

*Abstract:*  $\alpha$ -Carbonyl radicals generated from the corresponding  $\alpha$ -iodo ketones or enones underwent cyclization onto the tethered trimethylsilylacetylenic side chain to afford the bicyclic vinylsilane ketone or enones. The radicals generated from  $\gamma$ -bromo vinylogous derivatives cyclize preferentially at the  $\gamma$ -position. Based on the  $\alpha$ -carbonyl radical cyclization methodology, enantioselective total synthesis of (-)-dendrobine is accomplished.

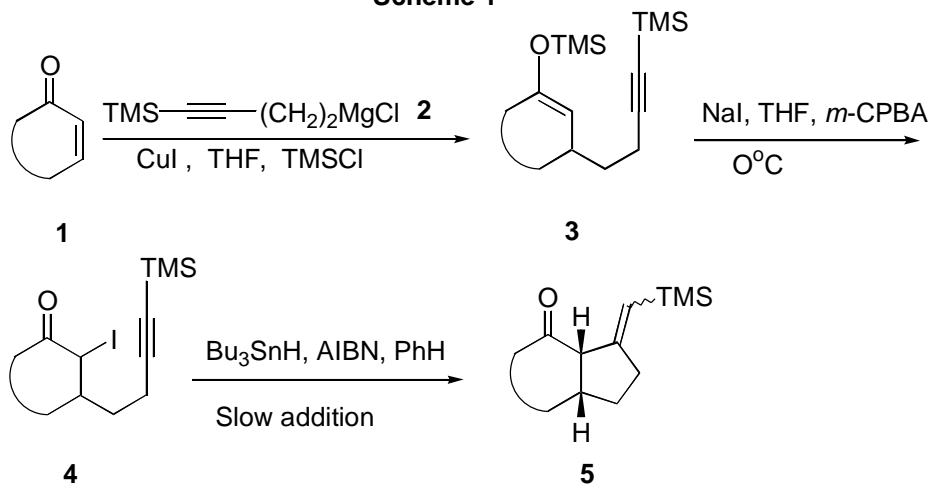
Radical reactions have emerged as one of the most useful synthetic methodologies in the formation of carbon-carbon bonds. Especially, the intramolecular radical cyclization has been extensively used in the synthesis of spiro and fused carbo- and heterocyclic structures<sup>1</sup>. We have developed three methodologies involving radical cyclization of  $\alpha$ -iodo ketones,  $\alpha$ -iodo enones and  $\gamma$ -bromo enones for the synthesis of bicyclic ketones and enones.<sup>2,3</sup>

According to our method,  $\alpha$ -carbonyl radicals were generated with tributyltin hydride from the corresponding  $\alpha$ -iodo ketones<sup>2a</sup> and  $\alpha$ -iodo enones.<sup>2b</sup> The tethered acetylenic side chain in **3** was introduced by 1,4-addition to cycloalkenone **1**. Thus, CuI-mediated conjugate addition of Grignard reagent **2** to **1** followed by trapping of the resultant enolate with chlorotrimethylsilane gave trimethylsilyl enol ether **3**. Iodination of **3** with sodium iodide and *m*-chloroperoxybenzoic acid afforded  $\alpha$ -iodo ketone **4**. Treatment of **4** with tributyltin hydride and AIBN on slow addition gave bicyclic vinylsilane ketone **5**, Scheme 1.

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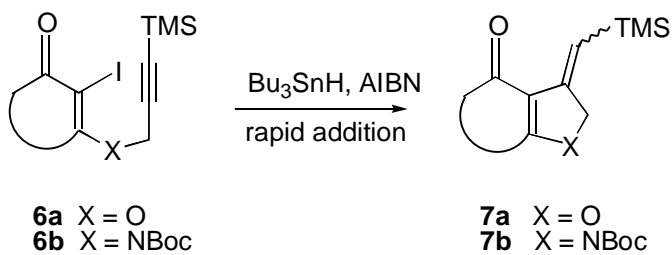
\*Invited lecture presented at the International Conference on Biodiversity and Bioresources: Conservation and Utilization, 23–27 November 1997, Phuket, Thailand. Other presentations are published in *Pure Appl. Chem.*, Vol. 70, No. 11, 1998.

**Scheme 1**

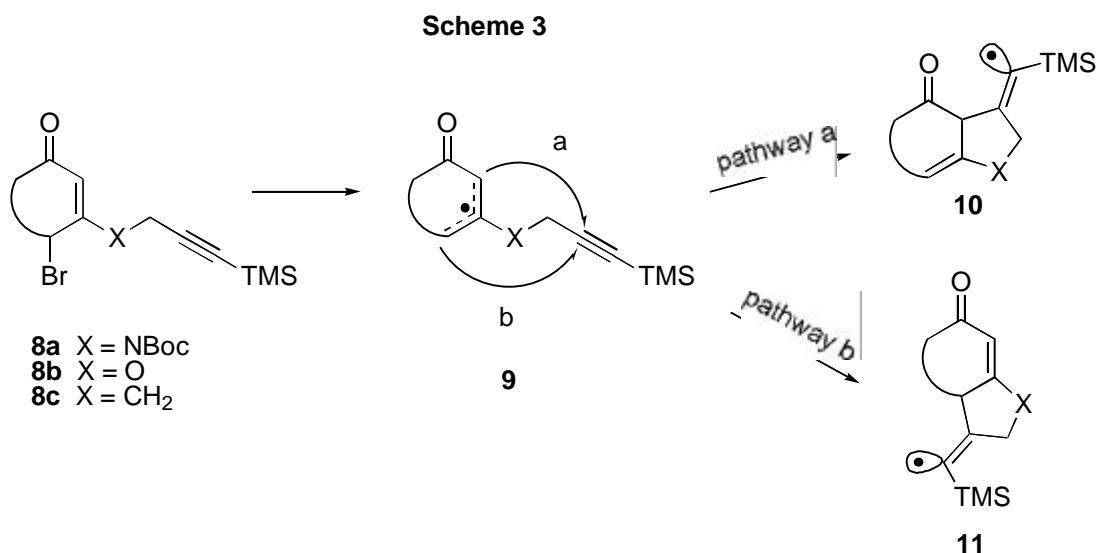


$\alpha$ -Iodo enones were prepared by literature methods.<sup>4,5</sup> Treatment of **6a** with tributyltin hydride and AIBN on rapid addition afforded cyclized product **7a**. *t*-Boc protected vinylogous amide **6b** under similar radical conditions furnished **7b**, Scheme 2.

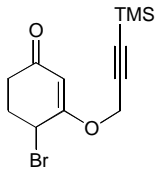
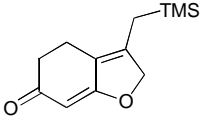
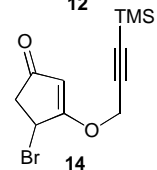
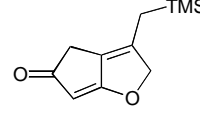
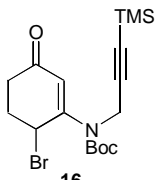
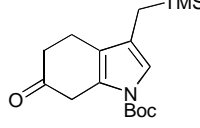
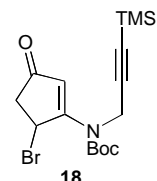
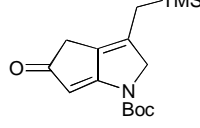
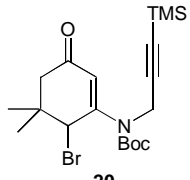
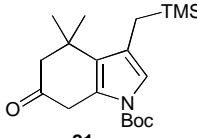
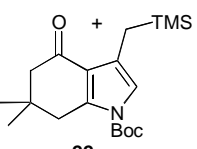
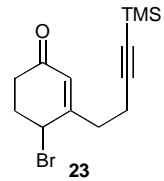
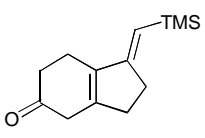
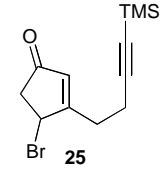
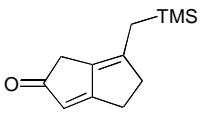
**Scheme 2**



As an extension of this work, 4-bromo vinylgous esters, amides and enones were subjected to similar radical cyclization conditions.<sup>3</sup> The regiochemistry of the cyclization (pathway a or b) of the allylic radicals **9** was investigated, Scheme 3. The required starting materials **8** were prepared by literature methods.<sup>6</sup> We found that radicals **9** generated from these  $\gamma$ -bromo enones underwent cyclization preferentially at the  $\gamma$  position. Only in entry 5 when the  $\gamma$ -position is sterically hindered, the allylic radical cyclizes both at  $\alpha$  and  $\gamma$  position. The results are summarized in Table 1.



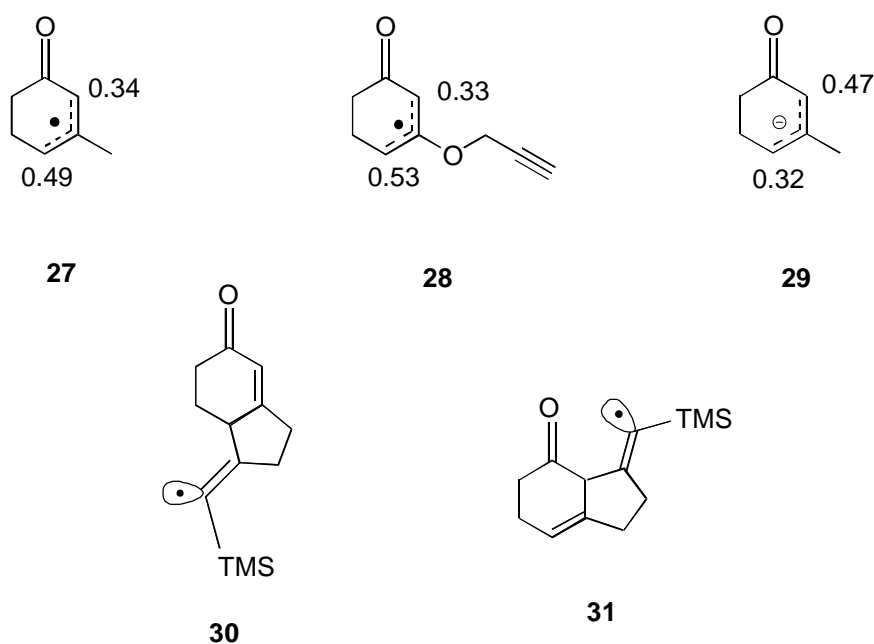
**Table 1. Radical Cyclization of 4-Bromo Vinylous-Amides, Vinylous-Esters and Enones**

Entry	4-Bromo Compound	Cyclized Product	Cyclization (%)	Reduction (%)
1			68 <sup>a</sup>	--
2			42 <sup>a</sup>	52
3			70 <sup>b</sup>	--
4			51 <sup>c</sup>	23
5			50 <sup>b</sup>	--
			( 21:22 = 1:2.5 )	
6			31	31
7			0	85

<sup>a</sup>The reaction was carried out in refluxing toluene. <sup>b</sup>The unstable crude cyclization product was treated with I<sub>2</sub> and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give pyrrolo compound, which was isolated by flash column chromatography (florisil, 6:1, hexane-ethyl acetate). <sup>c</sup>The reaction was carried out in refluxing xylene. <sup>d</sup>The geometry of vinylsilyl group in **24** was assigned tentatively as *E*.

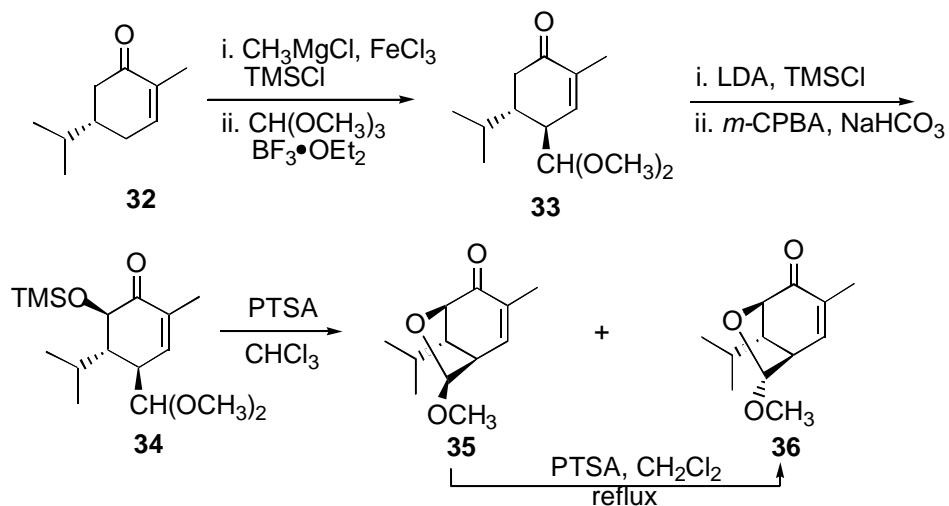
To understand the unusual regioselectivity we performed PM3 calculations on model radical systems **27** and **28**. Spin densities at the  $\alpha$  and  $\gamma$  positions expressed as the square of atomic orbital coefficients in SOMO are 0.34 and 0.49 for **27** and 0.33 and 0.53 for **28**. For the reaction under kinetic control, these coefficients are in accordance with the experimental observation. Whereas the HOMO electron densities of the corresponding anionic species **29** at the  $\alpha$  and  $\gamma$  position are 0.47 and 0.32 which are opposite to that of radical species. We have also calculated the relative stability of the intermediates **30** and **31** which were formed via the  $\alpha$  or  $\gamma$  cyclization, Scheme 4. We found that **30** is 4.5 kcal mol<sup>-1</sup> more stable than **31**.

Scheme 4



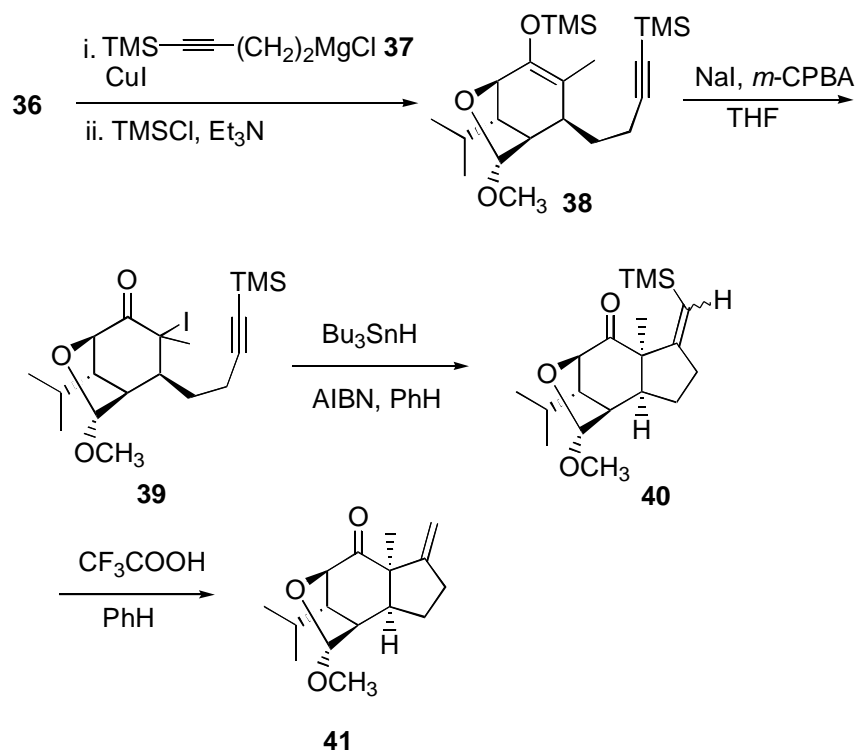
After successful development of these radical cyclization reactions, we exploited  $\alpha$ -carbonyl cyclization methodology for the enantioselective total synthesis of (-)-dendrobine (**51**).<sup>7</sup> Thus, (s)-carvotanacetone (**32**) was treated sequentially with methylmagnesium chloride, ferric chloride and chlorotrimethylsilane and then a mixture of trimethyl orthoformate and boron trifluoride etherate to give acetal **33**(55%).<sup>8</sup> Reaction of **33** with lithium diisopropylamide (LDA) and chlorotrimethylsilane generated the corresponding trimethylsilyl enol ether which without purification was reacted with *m*-chloroperoxybenzoic acid (*m*-CPBA) to give siloxy enone **34**(71%). Cyclization of **34** in presence of *p*-toluenesulfonic acid afforded bicyclic acetal enones **35**(14%) and **36**(79%). Compound **35** was separated and isomerized to required enone **36** using *p*-toluenesulfonic acid (55% yield with 25% **35** recovered), Scheme 5. CuI-mediated conjugate addition of Grignard reagent **37** from the less hindered  $\beta$ -face of **36** followed by trapping of the

Scheme 5



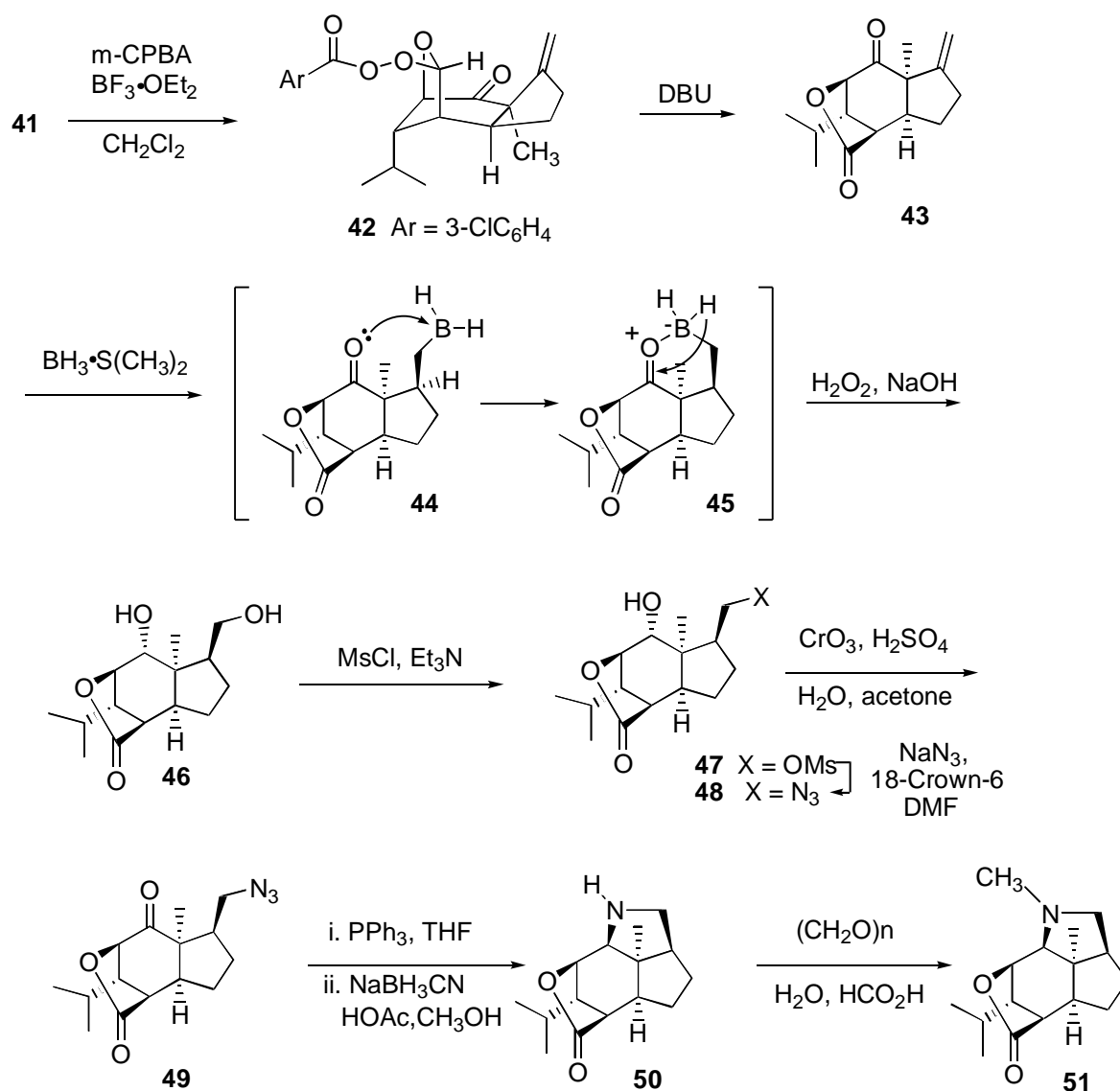
resultant enolate with chlorotrimethylsilane furnished **38**. Reaction of crude **38** with an iodination reagent, generated by mixing sodium iodide and *m*-chloroperoxybenzoic acid in THF, gave  $\alpha$ -iodo ketone **39** (82% from **36**). Intramolecular radical cyclization of **39** with tributyltin hydride and AIBN yielded the tricyclic ketone **40** (69%, *E:Z* = 1:9) as a viscous liquid with a minor amount of uncyclized product (25%). The TMS group in **40** was removed by trifluoroacetic acid to afford acetal **41** (84%), Scheme 6.

Scheme 6

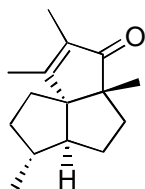


Oxidation of the acetal **41** with *m*-chloroperoxybenzoic acid and  $\text{BF}_3 \cdot \text{OEt}_2$  gave peroxy compound **42**.<sup>9</sup> Treatment of **42** with DBU furnished lactone **43** (62% from **41**). Stereoselective hydroboration of **43** with basic  $\text{H}_2\text{O}_2$  workup gave diol **46** (60%) via intermediates **44** and **45**. Conversion of the diol **46** into azido alcohol **48** (80%) followed by Jones oxidation afforded the azido ketone **49** (94%). Treatment of **49** with  $\text{PPh}_3$  followed by reduction of the resulting imine moiety by sodium cyanoborohydride afforded amine **50**. Finally, methylation of the crude amine with paraformaldehyde and formic acid furnished enantiomerically pure (-)-dendrobine **51** (42% from **49**), Scheme 7.

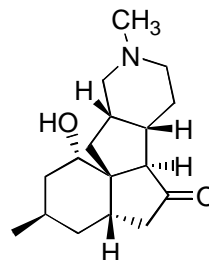
Scheme 7



In conclusion, we have developed efficient radical cyclization reactions of  $\alpha$ -iodo ketones,  $\alpha$ -iodo enones and  $\gamma$ -bromo enones. Utilizing this methodology an enantioselective total synthesis of (-)-dendrobine (**51**) is accomplished. Recently the methodology has been extended for the total synthesis (-)-5-oxosilphiperfol-6-ene (**52**) and paniculatine (**53**) and the results will be published in due course.



**52**



**53**

## ACKNOWLEDGEMENT

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