N-heterocyclic compounds via Radical Cyclization Reactions: Chemistry of The Imidoyl Radical

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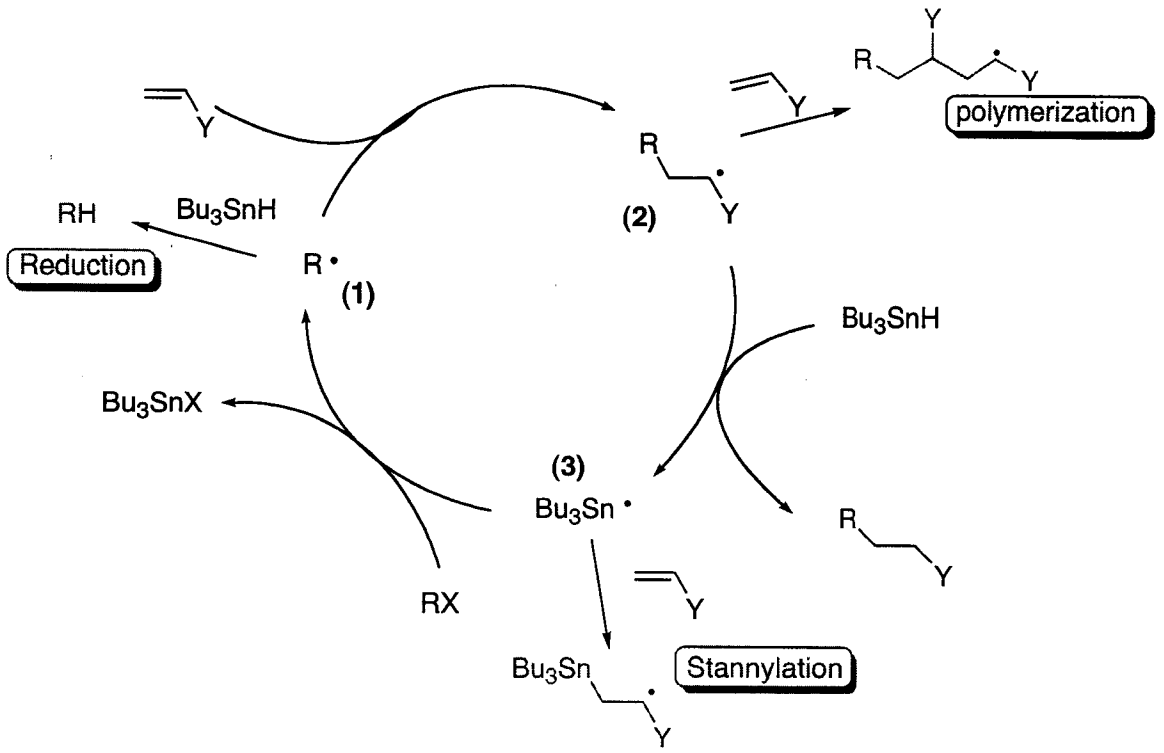
SED Group Meeting

04/12/05

Radical Cyclizations: Introduction

- Radical chain reactions:

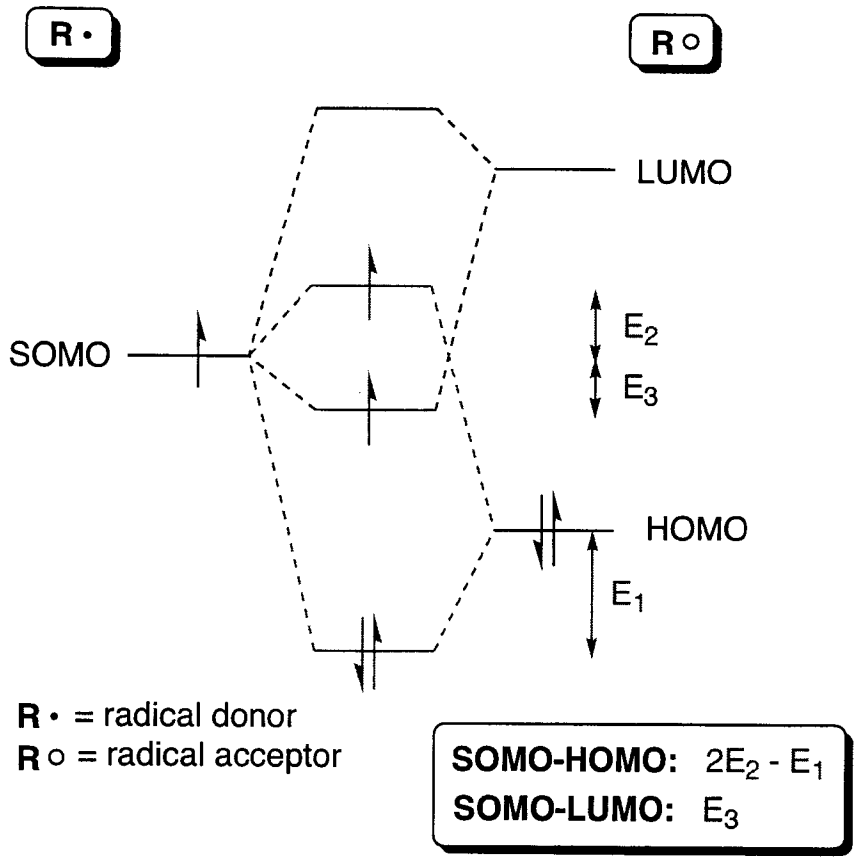


- Two conditions for successful radical chain reaction

    1. The seletivities of the radicals in chain must differ from one another.

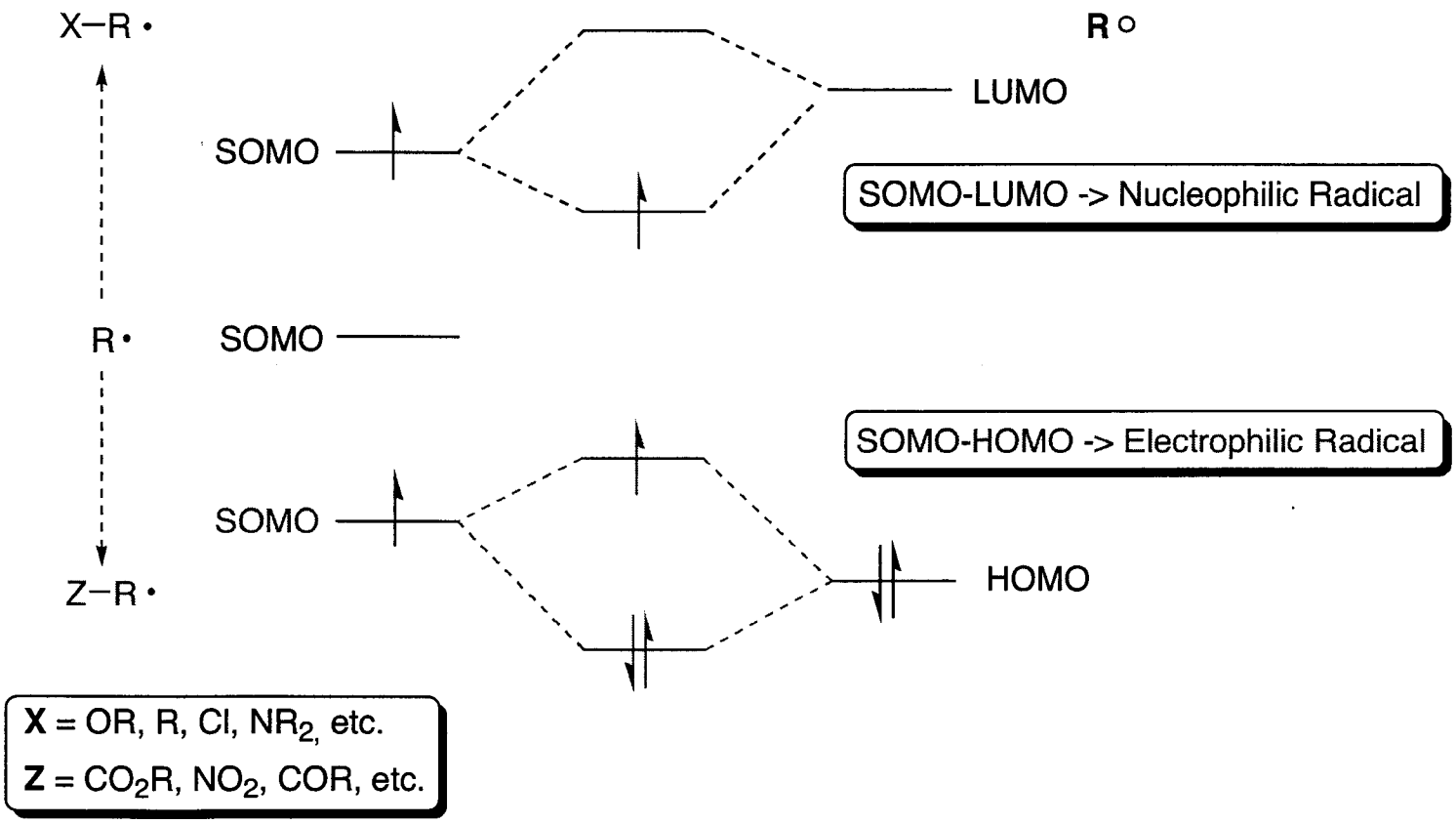
    2. Reactions between radical/non-radicals must be faster than radical/radical reactions

Radical Cyclizations: FMO Analysis



- Both SOMO-HOMO and SOMO-LUMO interactions are stabilizing
- The nature of the radical is determined by the strongest interaction between the respective Frontier molecular orbitals

Radical Cyclizations: FMO Analysis

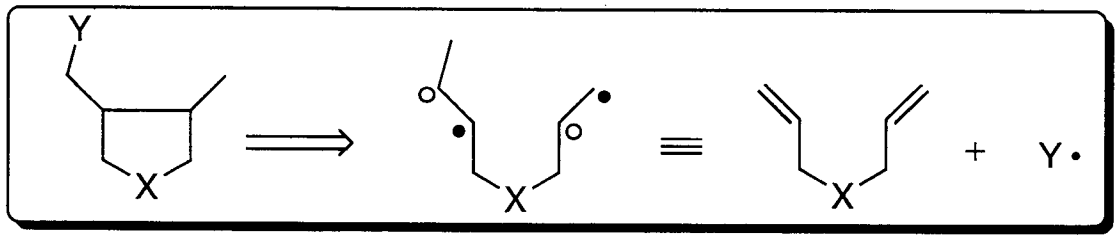


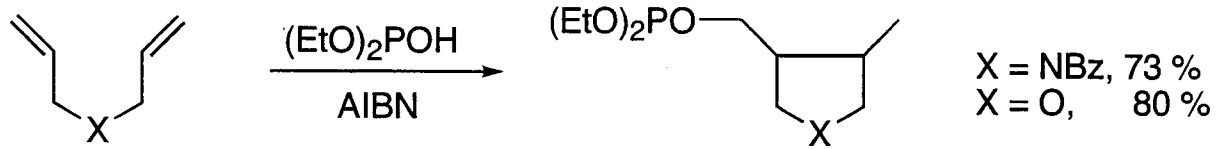
- Radicals with a high-energy SOMO exhibit nucleophilic character
- Radicals with a low-energy SOMO exhibit electrophilic character

Radical Cyclizations: Formation of Heterocycles

- Limited number of ways to construct heterocycles using radical cyclizations.

<u>Case 1:</u> Heteroatom linker in the radical chain



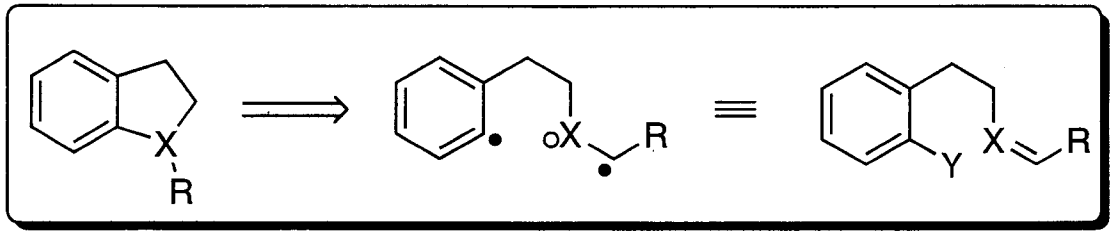


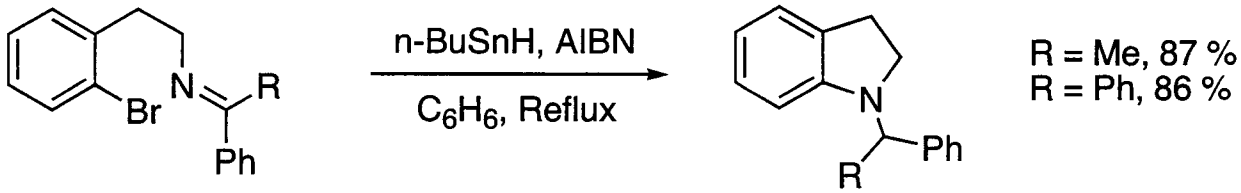
Parsons, A.F.; et.al. *Tetrahedron*, **2003**, 44, 479

- Open dot represents a radical acceptor
- Closed dot represents radical donor

Radical Cyclizations: Formation of Heterocycles

Case 2: Heteroatom as the radical acceptor

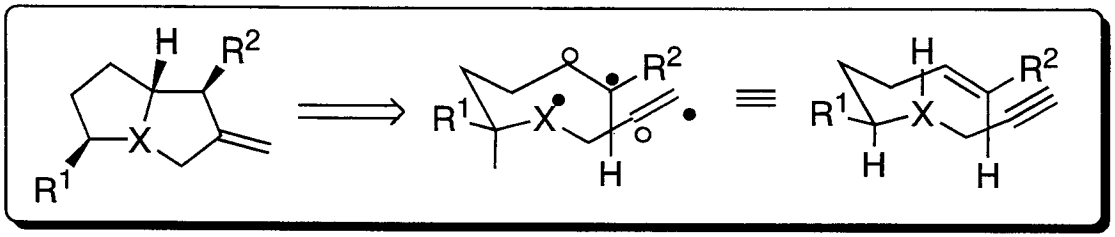


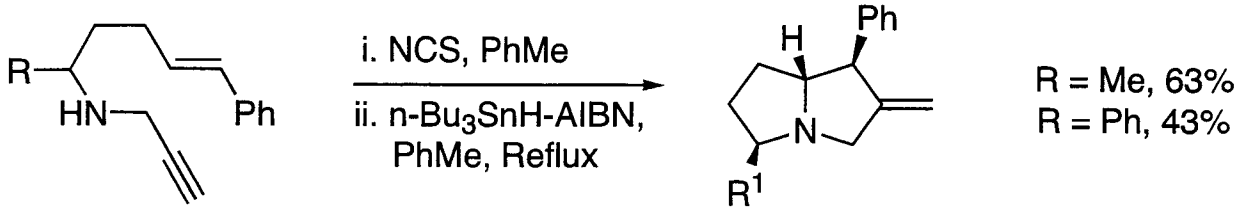


Viswanathan, R.; et.al. *J.Am.Chem.Soc.* **2003**, 125, 163

Radical Cyclizations: Formation of Heterocycles

Case 3: Heteroatom as the radical donor





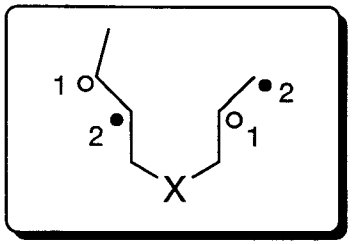
Tokuda, M.; et.al. *Tetrahedron* **2003**, 59, 827

- Method also highlights a tandem radical cyclization

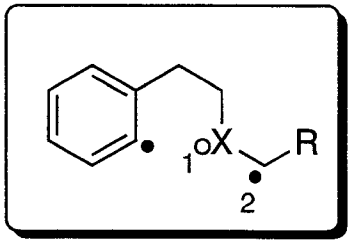
Radical Cyclizations: Formation of Heterocycles

- Common theme to all three cases is the vicinial relationship between the radical acceptor and radical donor

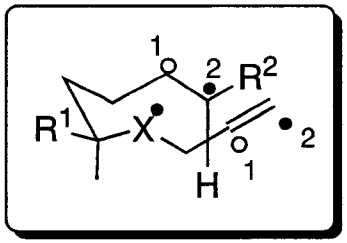
Case 1:



Case 2:



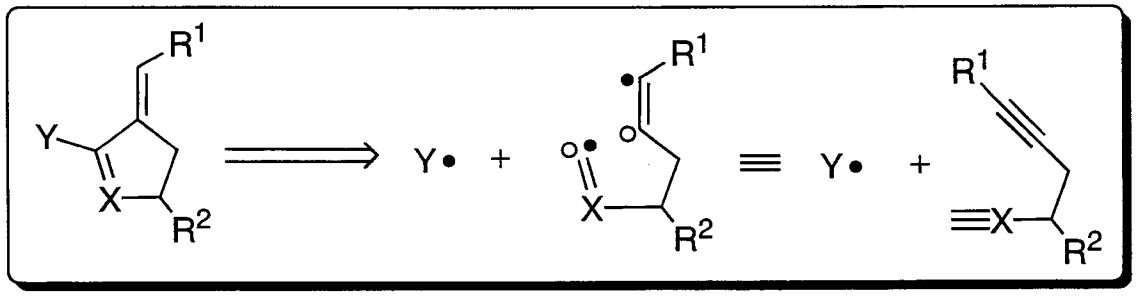
Case 3:

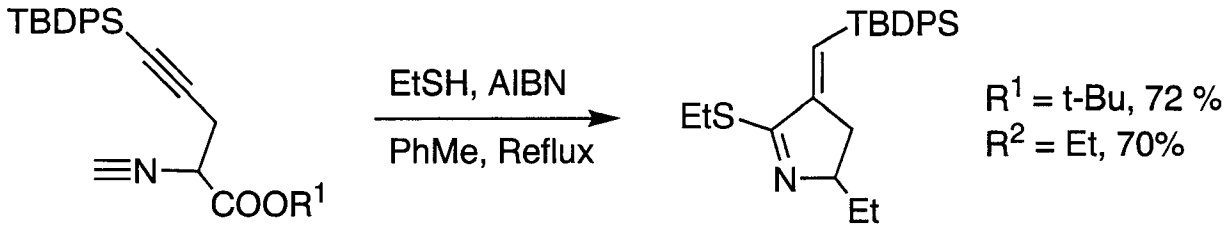


- What about geminial radical acceptor/radical donor groupings?

Radical Cyclizations: Formation of Heterocycles

Case 4: Geminal radical acceptor/radical donor synthon



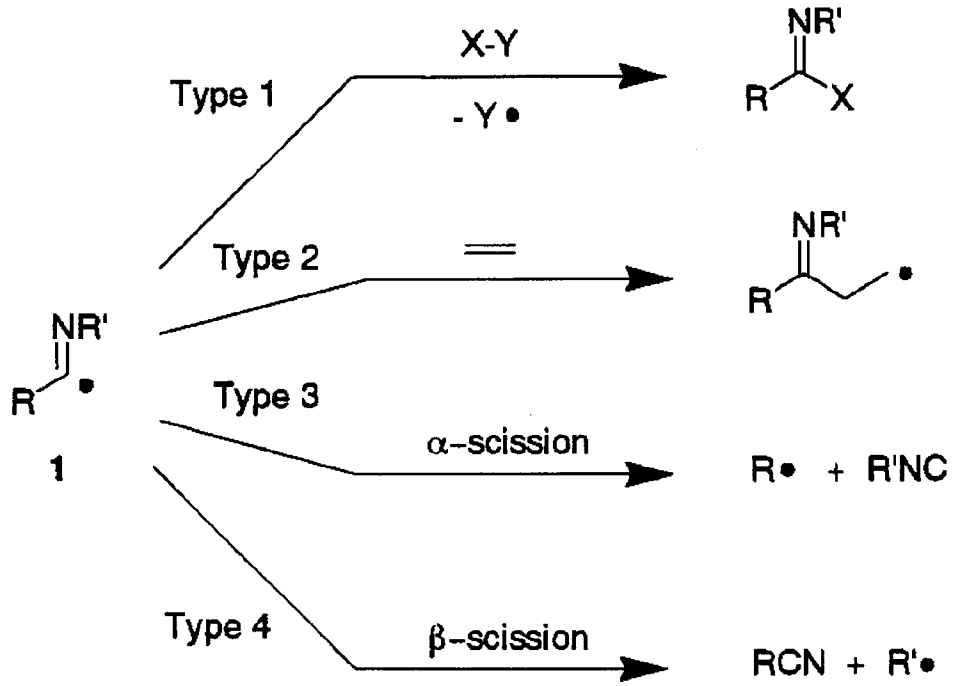


Bachi, M.D.; et.al. *J.Org.Chem.* **1994**, 59, 7752

- Isonitrile and carbon monoxide variants have both been studied
- Focus of this talk will be on the isonitrile variants

Radical Cyclizations: Imidoyl Radical

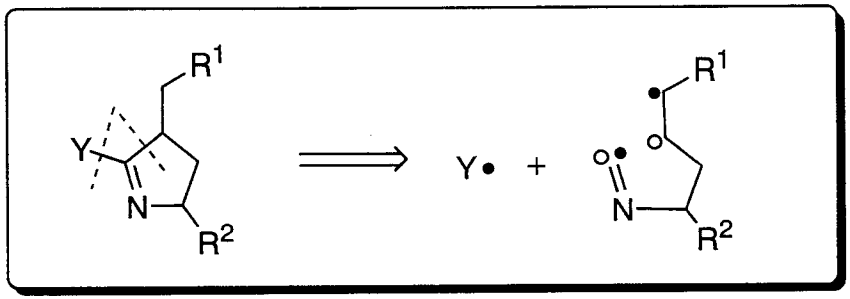
- Reaction pathways available to imidoyl radicals



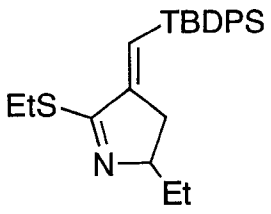
Fujiwara S., et.al. *J.Org.Chem.* **2001**, 66, 2183

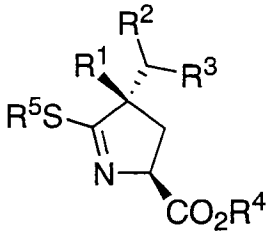
Radical Cyclization: Pyrrolines and Pyroglutamates

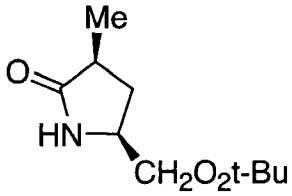
- The pyrroline ring can be broken into two radical synthons



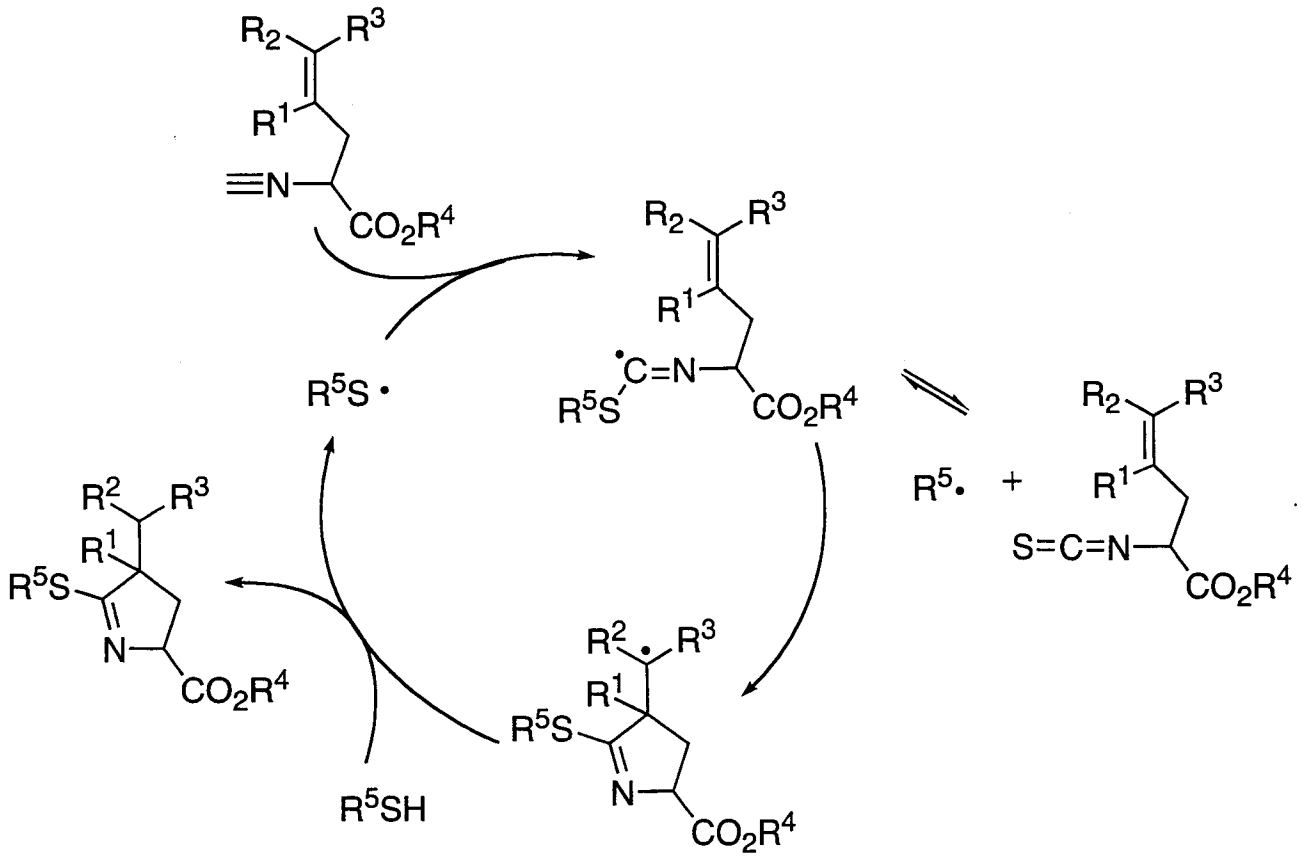
- Bachi and co-workers used this general scheme for the synthesis of several pyrroline and pyroglutamates derivatives





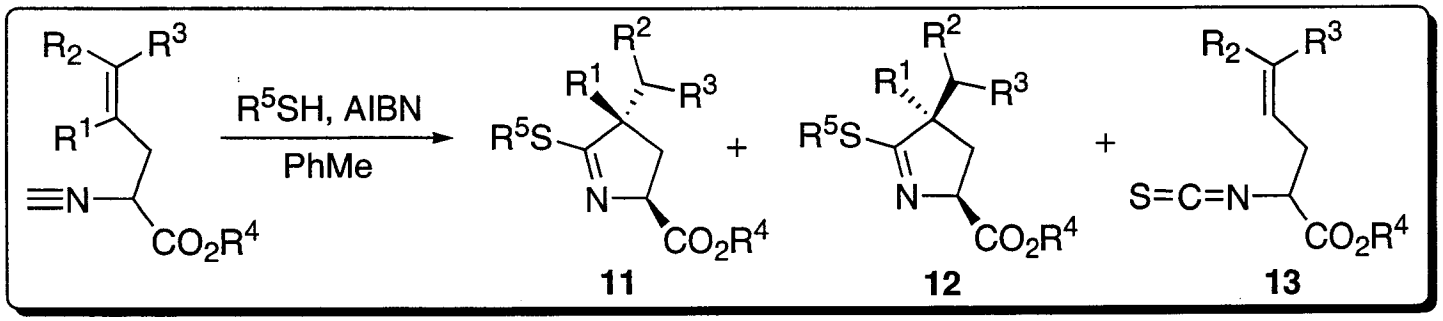


Radical Cyclization: Pyrrolines



- Thioisocynate formation results when R^5 is a stable radical

Radical Cyclization: Pyrrolines

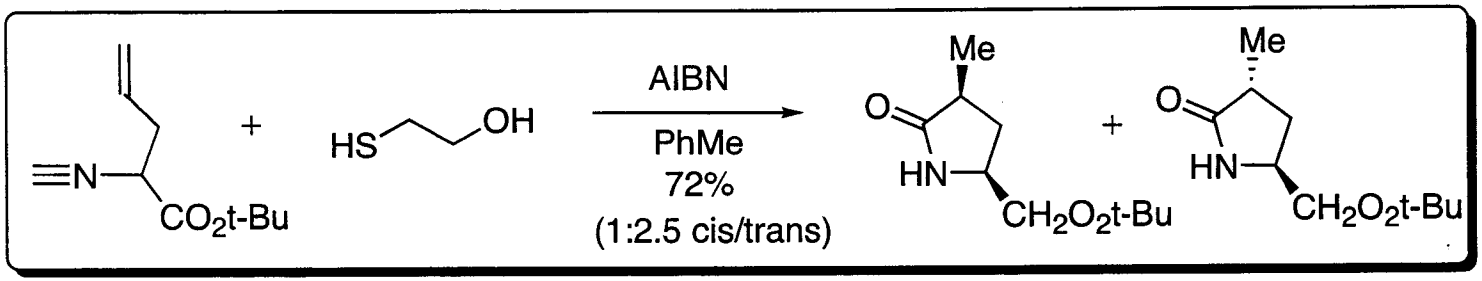


temp, °C	time, h		pyrrolines 11 + 12 R¹	R²	R³	R⁴	R⁵	yield, %	11/12 ratio[b]		isothiocyanate 13 R¹	R²	R³	R⁴	yield, %
110	1.0	**k**	H	H	H	^{t}Bu	Ph	74	1:1.1	–					–
110	1.5	**l**	H	H	H	^{t}Bu	Et	83	1.4:1	–					–
40	1.5	**m**	H	H	H	Et	Et	85	1.2:1	–					–
40	1.5	**n**	H	Me	Me	Et	Et	83	1.4:1	–					–
85	2.0	**o**	H	Me	Me	Et	$(CH_2)_3$-CO_2Me	84	1:1	–					–
40	1.5	**p**	Me	H	H	^{t}Bu	Ph	traces	–	–					–
110	1.5	**p**						30	–						–
40	3.5	**q**	Me	H	H	^{t}Bu	Et	56	–	**d**	Me	H	H	^{t}Bu	–
110	2.5	**q**						50	–	**d**					10
45	3.0	**r**	H	Me	Me	Et	CH_2CO_2Me	38	1:1	**c**	H	Me	Me	Et	57
5[c]	2.0	**r**						58	1:1	**c**					36
−20[c]	4.5	**r**						70	1:1	**c**					28
−60[c]	8.5	**r**						78	1:1	**c**					2

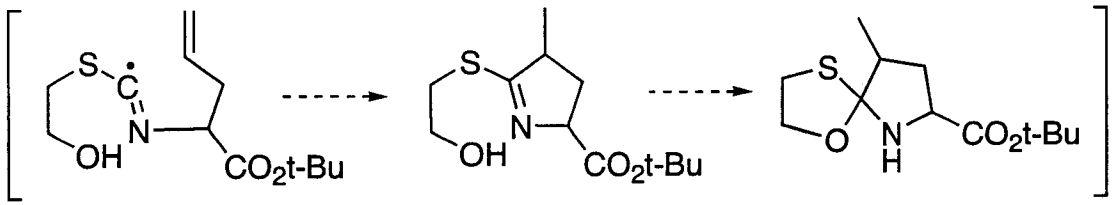
Bachi, M.D., et.al. *J.Org.Chem.* **1994**, 59, 7752

Radical Cyclization: Pyroglutamates

- The authors found that pyroglutamates could be obtained in high yield with the use of mercaptoethanol.



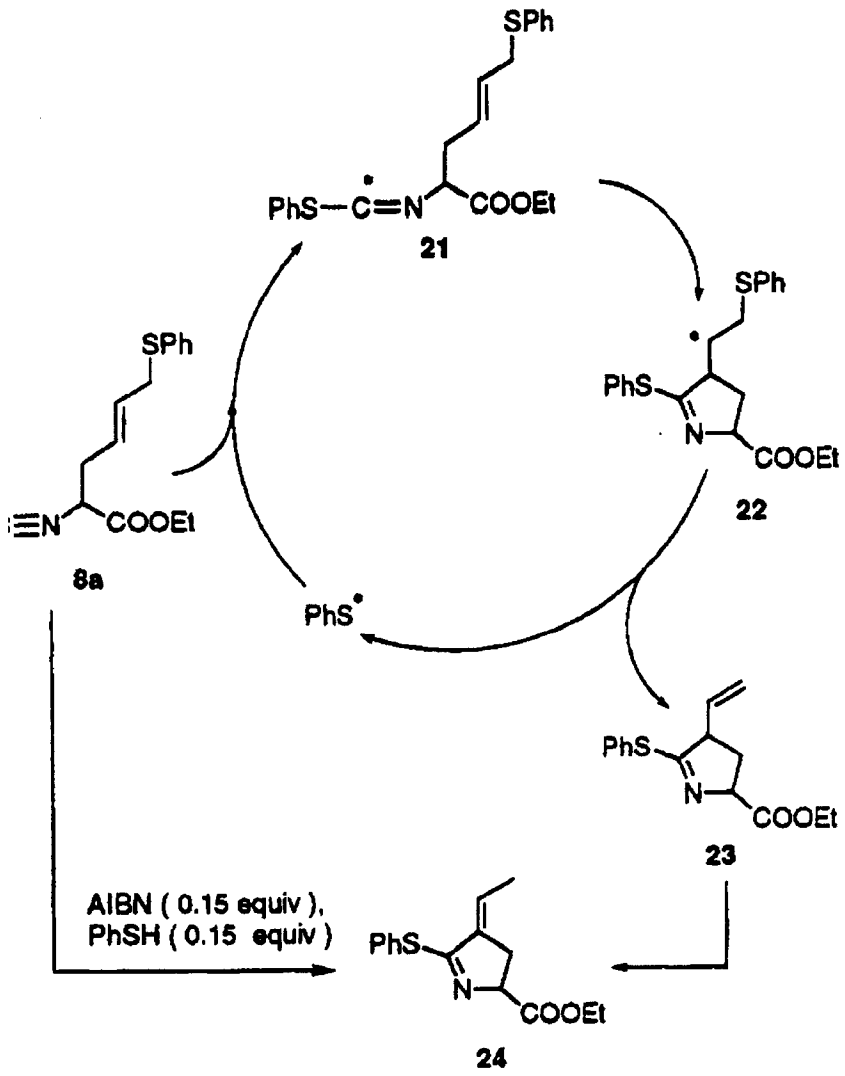
- The authors proposed that the pyroglutamates were forming through the following intermediates.



Radical Cyclization: Catalytic Method

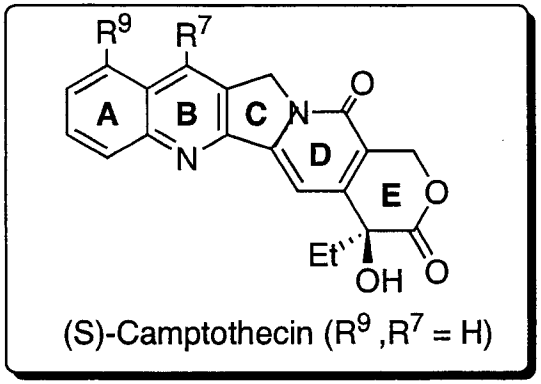
- Placement of a cleavable phenylthiyl radical in the substrate allowed for a "catalytic" process to occur.

- Product 24 was obtained after isomerization to give a conjugated pyrroline in 85% yield.



Radical Cyclization: Quinoline Derivatives

- Quinoline structure is present in a a variety of natural products including the anti-tumor candidate (S)-camptothecin



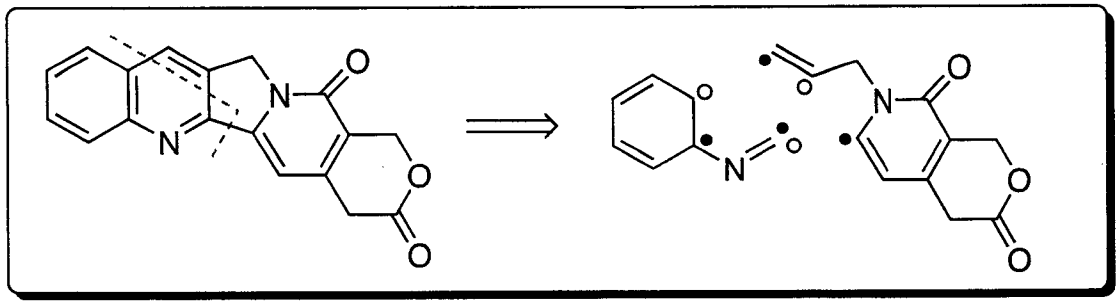
- Researchers have found that substituents at the 7 and 9 position on the quinoline ring favorable modulate the activity of the drug.

- Methods for making the 7,9-substitution pattern are limited.

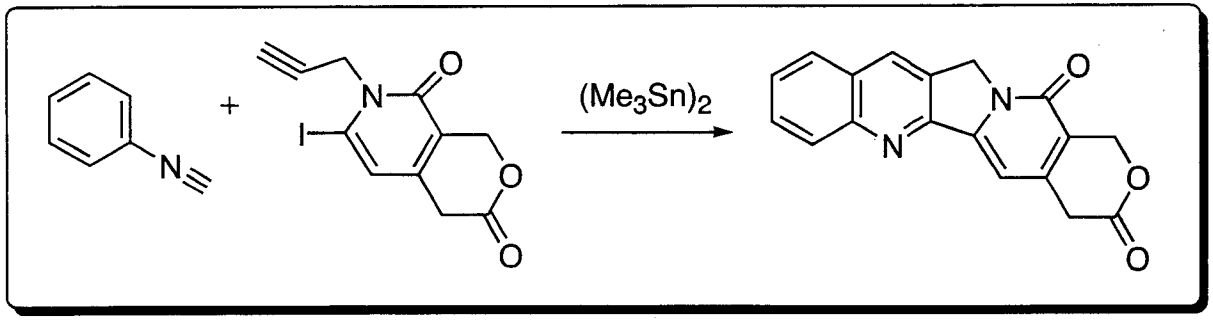
Curran, D.P.; Du, W. *Synlett* **2003**, 1299

Radical Cyclization: Quinoline Derivative

- The breaking apart camptothecin core reveals possibility for a radical cyclization reaction



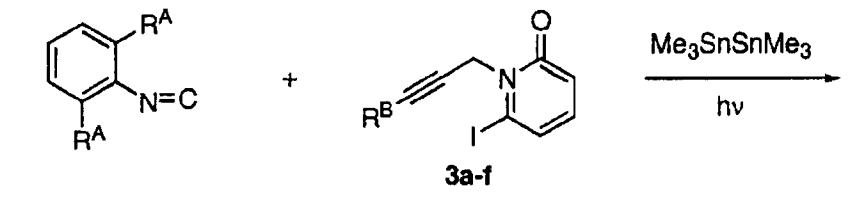
- Curran and co-workers envisioned a radical cyclization between phenyl isonitrile and a N-propargyl-6-iodo-pyridone derivative

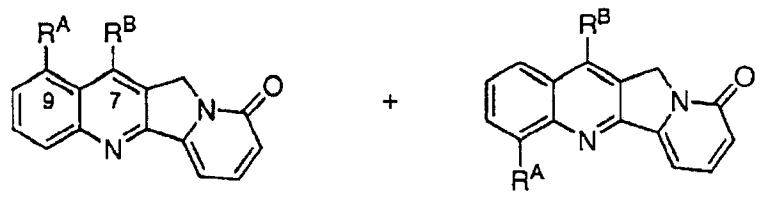


Radical Cyclization: Quinoline Derivatives

- In the 7,9 isomer the orientation of R^A has changed from ortho to meta.

- Increasing the size of the o-aryl substituents gives rise to the more crowded 7,9-isomer.





7,9-isomer **9a-d** **11c,e,f**

R^A = *i*-pr

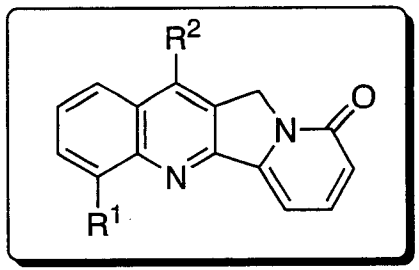
R^A = Et

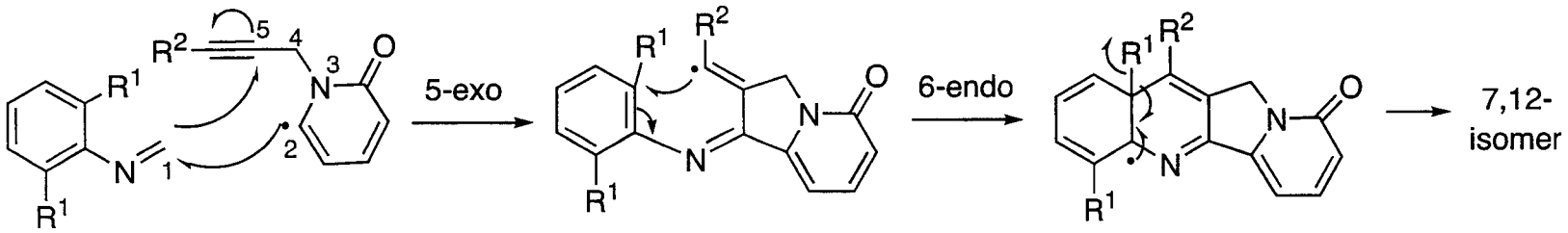
7,12-isomer **10a-d** **12c,e,f**

Entry	R^A	R^B	Ratio **9/10** or **11/12**	Yield[a]
1	*i*-Pr	H	**9b/10b**, 3/1	53%
2	*i*-Pr	TMS	**9c/10c**, 7/1	43%
3	*i*-Pr	Et	**9a/10a**, 8/1	53%
4	*i*-Pr	*t*-Bu	**9d** only	59%
5	Et	TMS	**11c/12c**, 3.1/1	66%
6	Et	TES	**11e/12e**, 2.7/1	70%
7	Et	TBS	**11f/12f**, 0.9/1	79%

Radical Cyclization: Quinoline Derivative

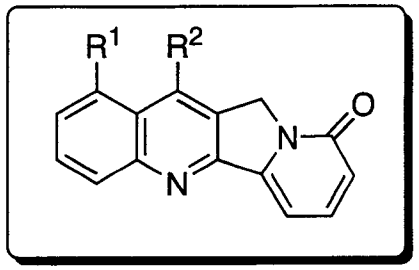
- Proposed Mechanism: 7,12-isomer

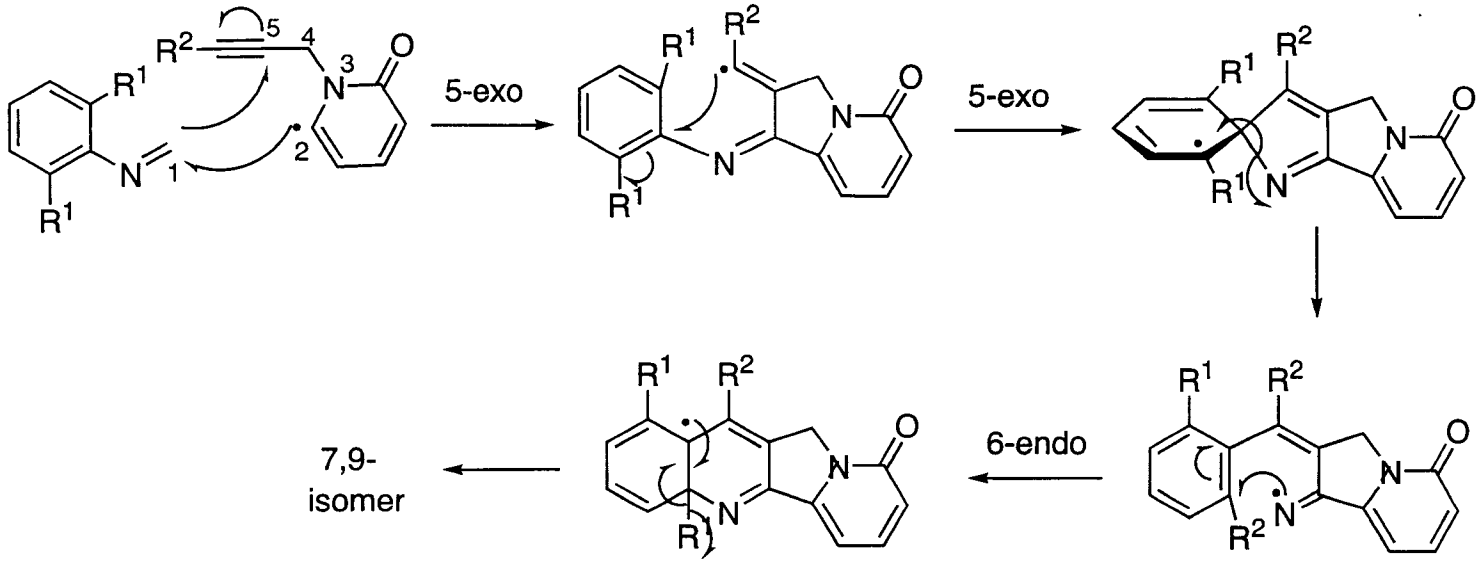




Radical Cyclization: Quinoline Derivatives

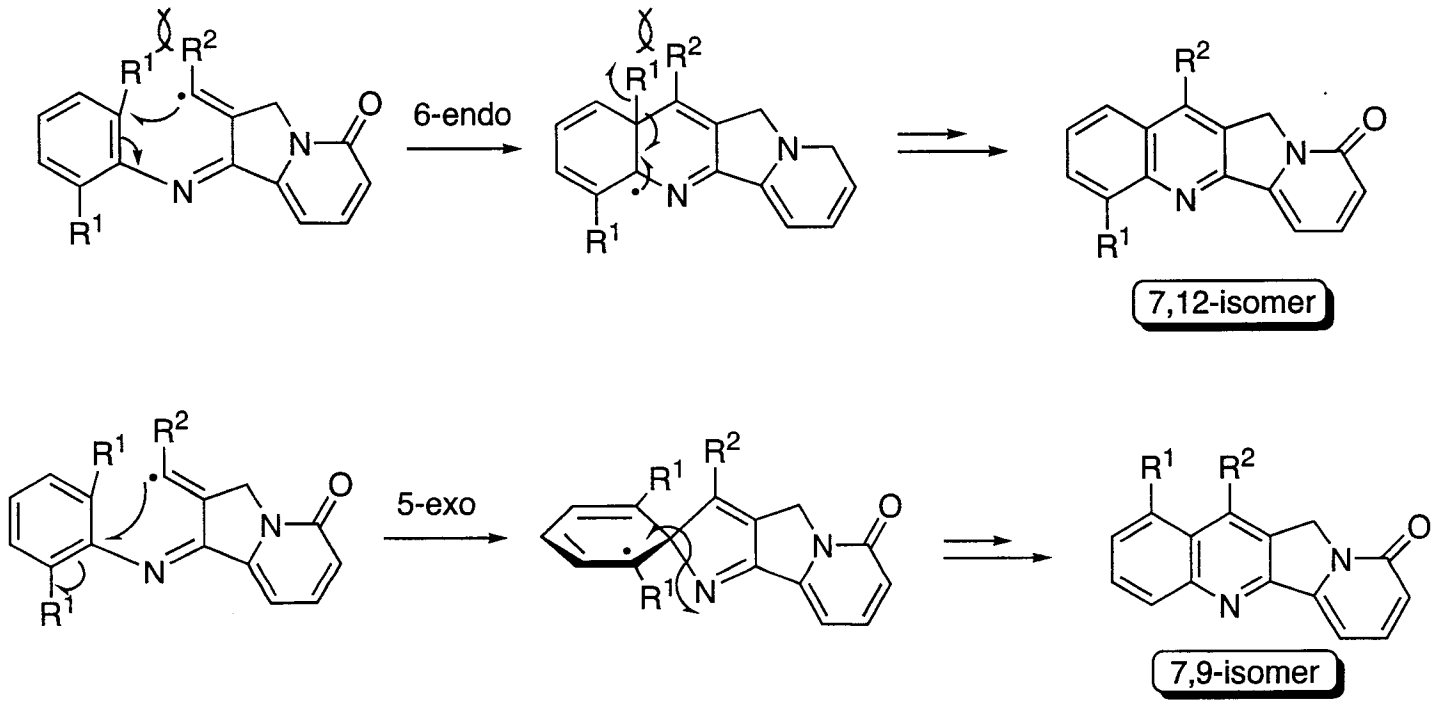
- Proposed Mechanism 7,9-isomer



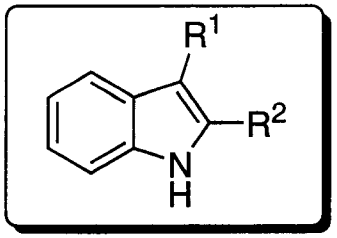


Radical Cyclization: Quinoline Derivatives

- 7,9-Isomer favored when R^1 is large
- Authors contend this could result from unfavorable steric interaction during 6-endo cyclization



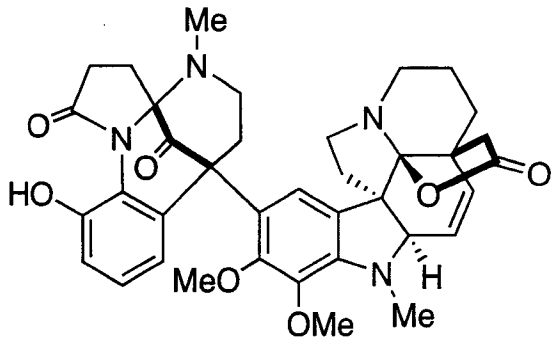
Radical Cyclization: 2,3-Substituted Indoles



- Indole and indoline rings can be found throughout a wide range of alkaloid natural products

- Few practical methods are available for the construction of 2,3-substituted indoles

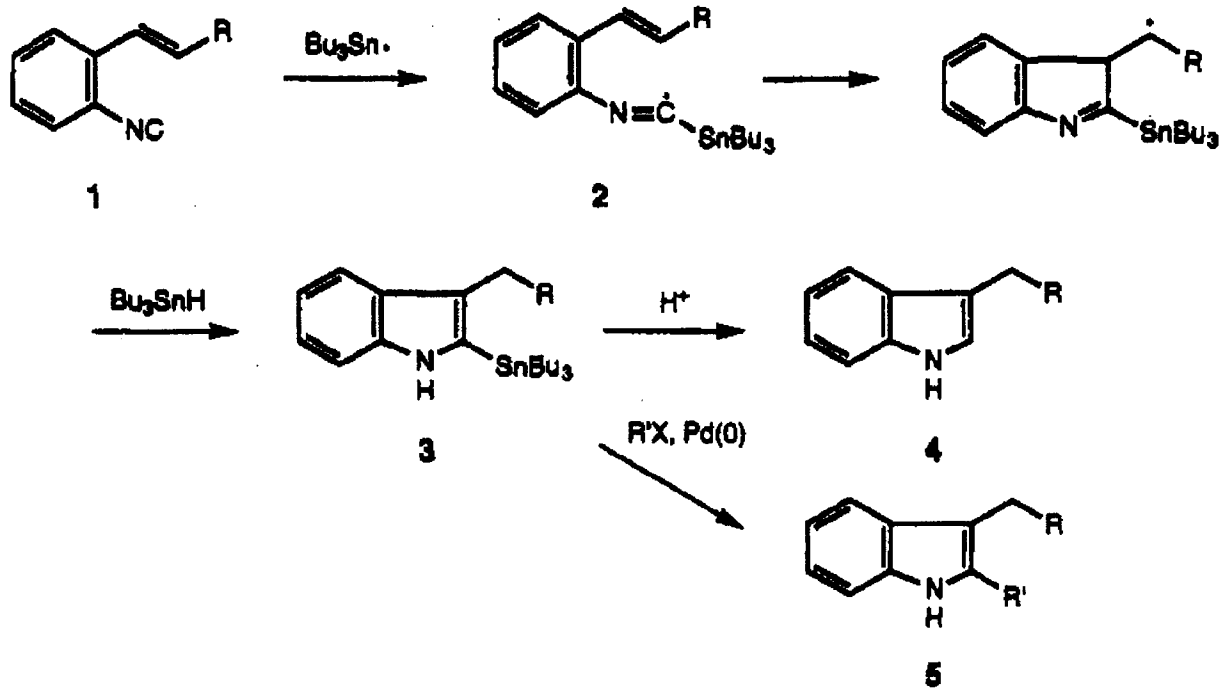
- Fisher indole synthesis is not compatible with acid labile functionalities.



Haplophytine

Radical Cyclization: 2,3-Substituted Indoles

General Method:

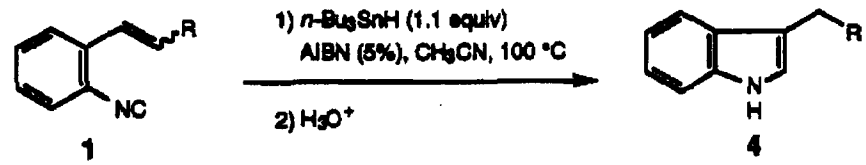


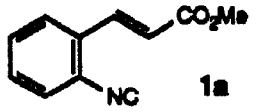
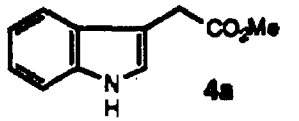
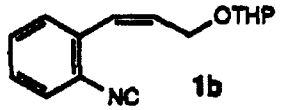
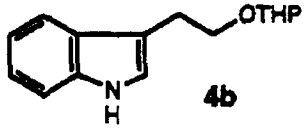
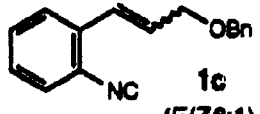
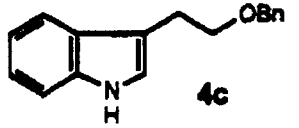
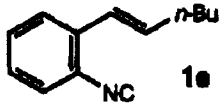
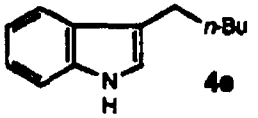
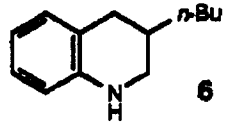
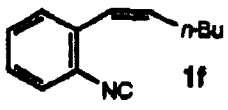
- Allows for both 3-substituted and 2,3-substituted indole rings
- 2-stannylindoles are further reacted through Still conditions to give 2,3-substituted indoles.

Radical Cyclization: 3-substituted indoles

- E/Z double bonds tolerated in most cases.

- Formation of tetra-hydroquinoline (6) could be avoided by use of Z-double bond

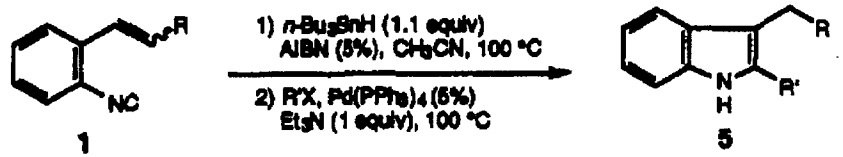


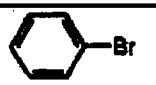
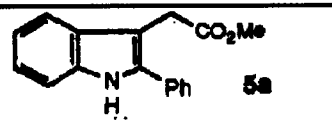
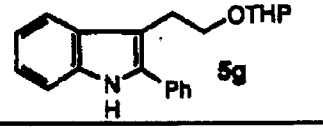
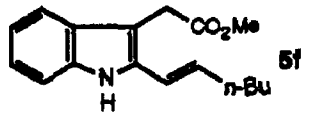
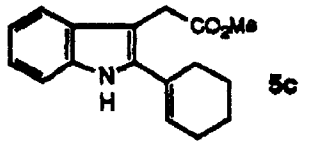
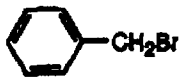
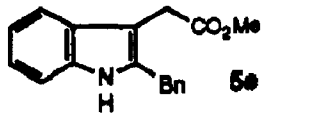
entry	substrate	product	isolated yield,%
1	 1a	 4a	91
2	 1b	 4b	83
3	 1c (E/Z 6:1)	 4c	68
5	 1e	 4e	51
		 6	33
6	 1f	4 e	72
		6	18

Radical Cyclization: 2,3-substituted indoles

- Decreasing the radical stabilizing ability of the R-group resulted in decreased yields

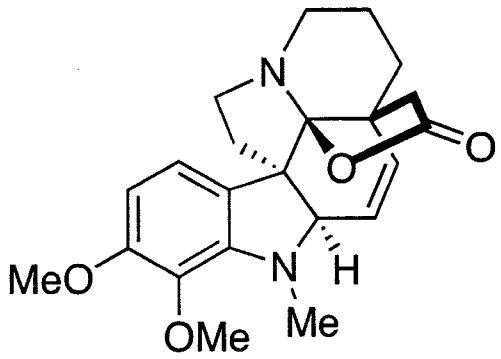
- Substrate scope of coupling partner in Stille reaction was high.



R'X	equiv	time (h)	product	yield (%)
	1.2	5	 5a	82
	3.0	11	 5g	63
	3.0	8	 5f	71[c]
	3.0	8	 5c	58
	3.0	1	 5e	71[b]

Radical Cyclization: (-) Aspidophytine

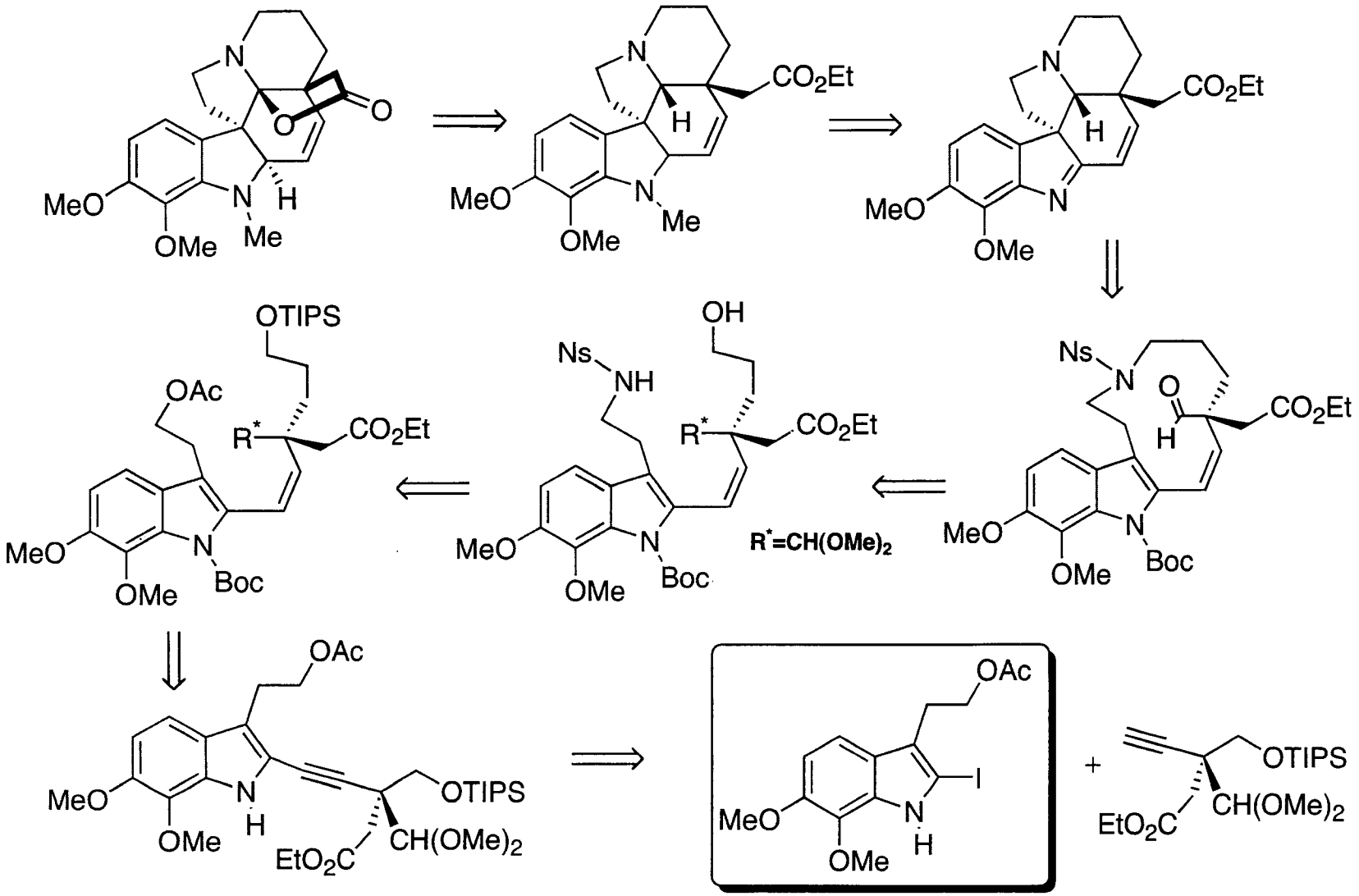
- Fukuyama showcased his radical cyclization methodology in the synthesis of (-)-Aspidophytine



(-)-Aspidophytine

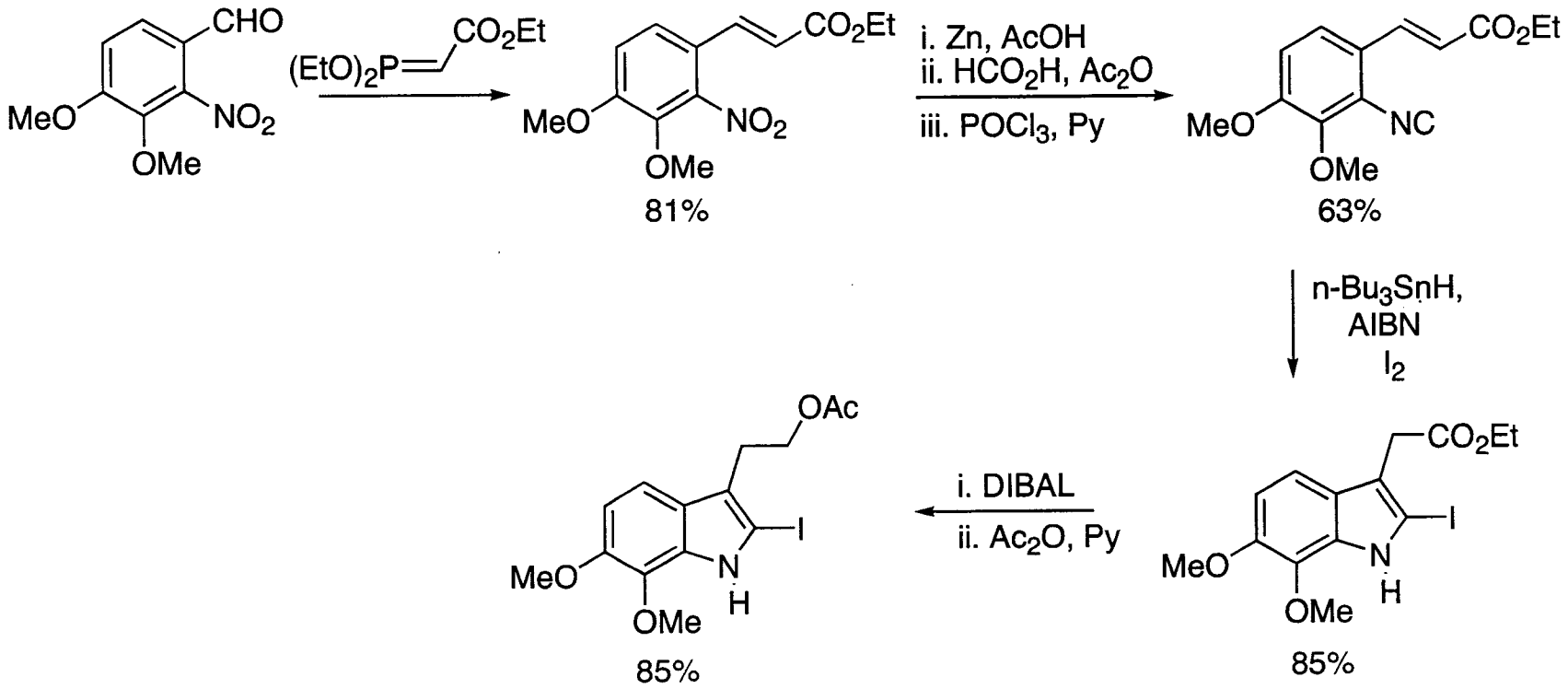
Fukuyama, T., et.al. *Tetrahedron* **2003**, 59, 8571

Radical Cyclizations: (-)-Aspidophytine



Radical Cyclizations: (-)-Aspidophytine

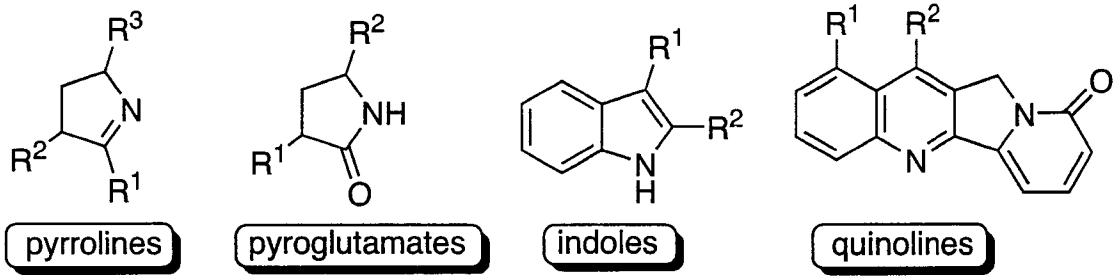
- Synthesis of indole core



- 7 manipulations, 37% overall yield

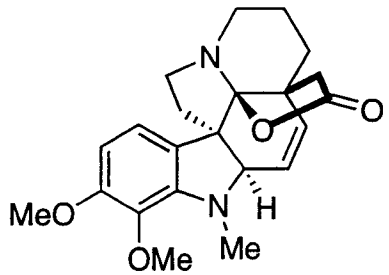
Radical Cyclization: Concluding Remarks

- The radical cyclization chemistry of the imidoyl radical has been used for the synthesis of a variety of N-heterocyclic compounds in moderate to high yields

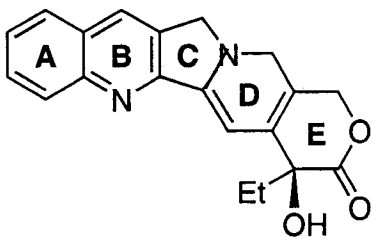


Radical Cyclization: Concluding Remarks

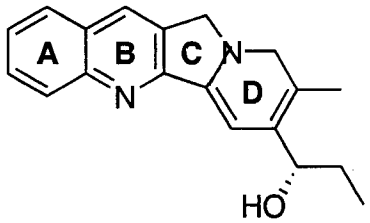
- Applications in total synthesis have led to the successful construction of (-)-aspidophytine as well as derivatives of the camptothecin and mappicine families.



(-)-Aspidophytine



(S)-camptothecin



(S)-mappicine

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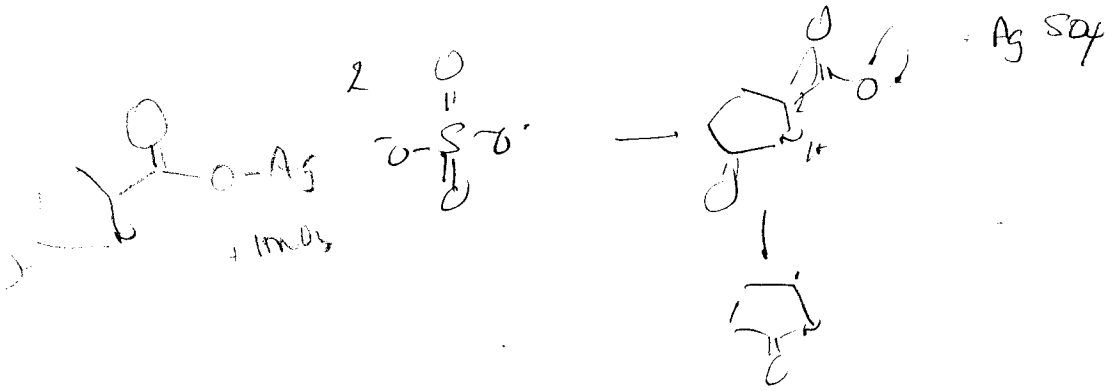
2
Ag SO4