

Part 1

Regiochemistry of Aryl Radical Cyclization onto Methylenecycloalkanes
and its Application to Syntheses of Calabar Alkaloids

Part 2

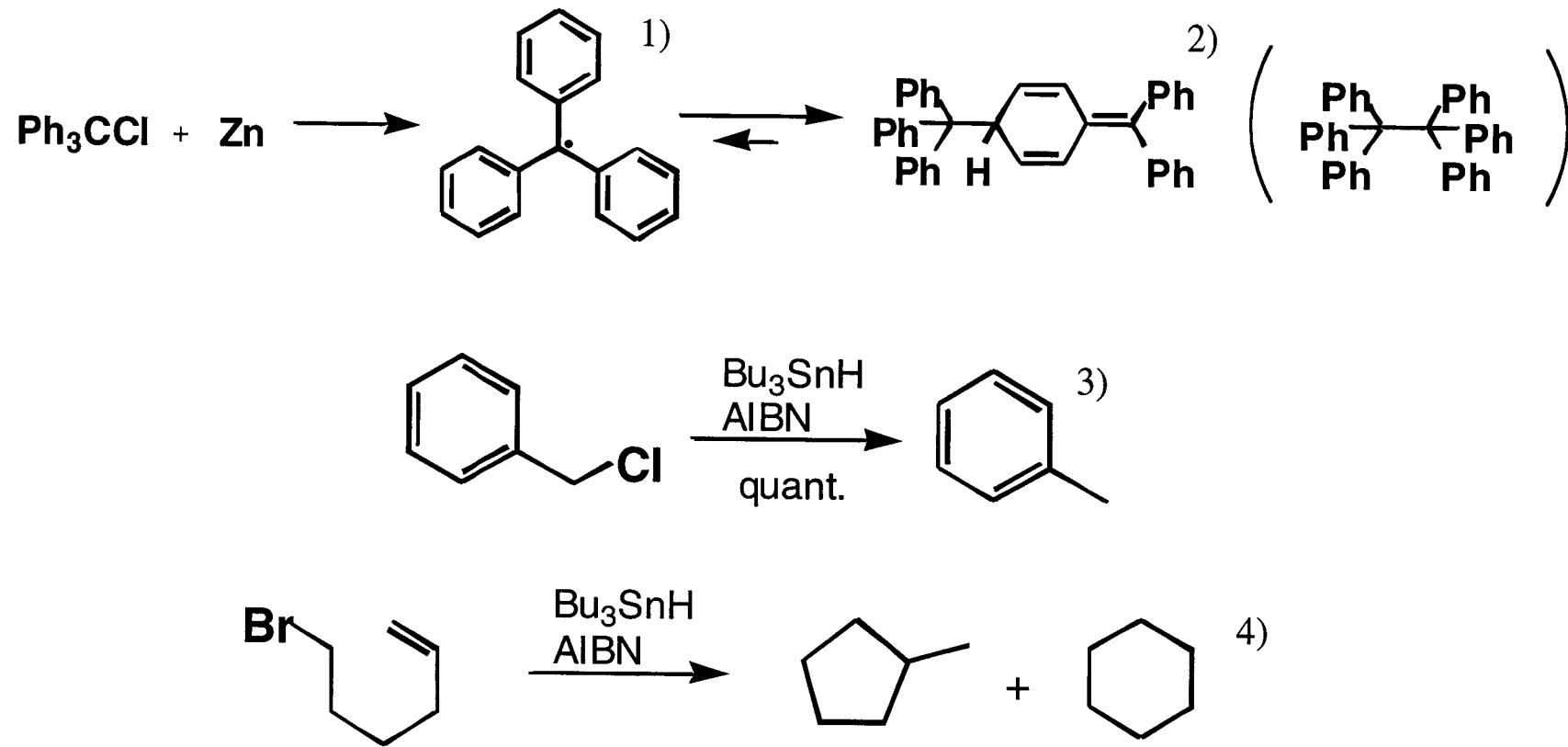
Convenient Synthesis of 3,3,3-Trifluoropropenyl Compounds
by means of Fluoride-Mediated Horner-Wittig Reaction

Tetsuya Kobayashi

Graduate School of Kanazawa University

Professor Hiroyuki Ishibashi

History of Radical Reaction



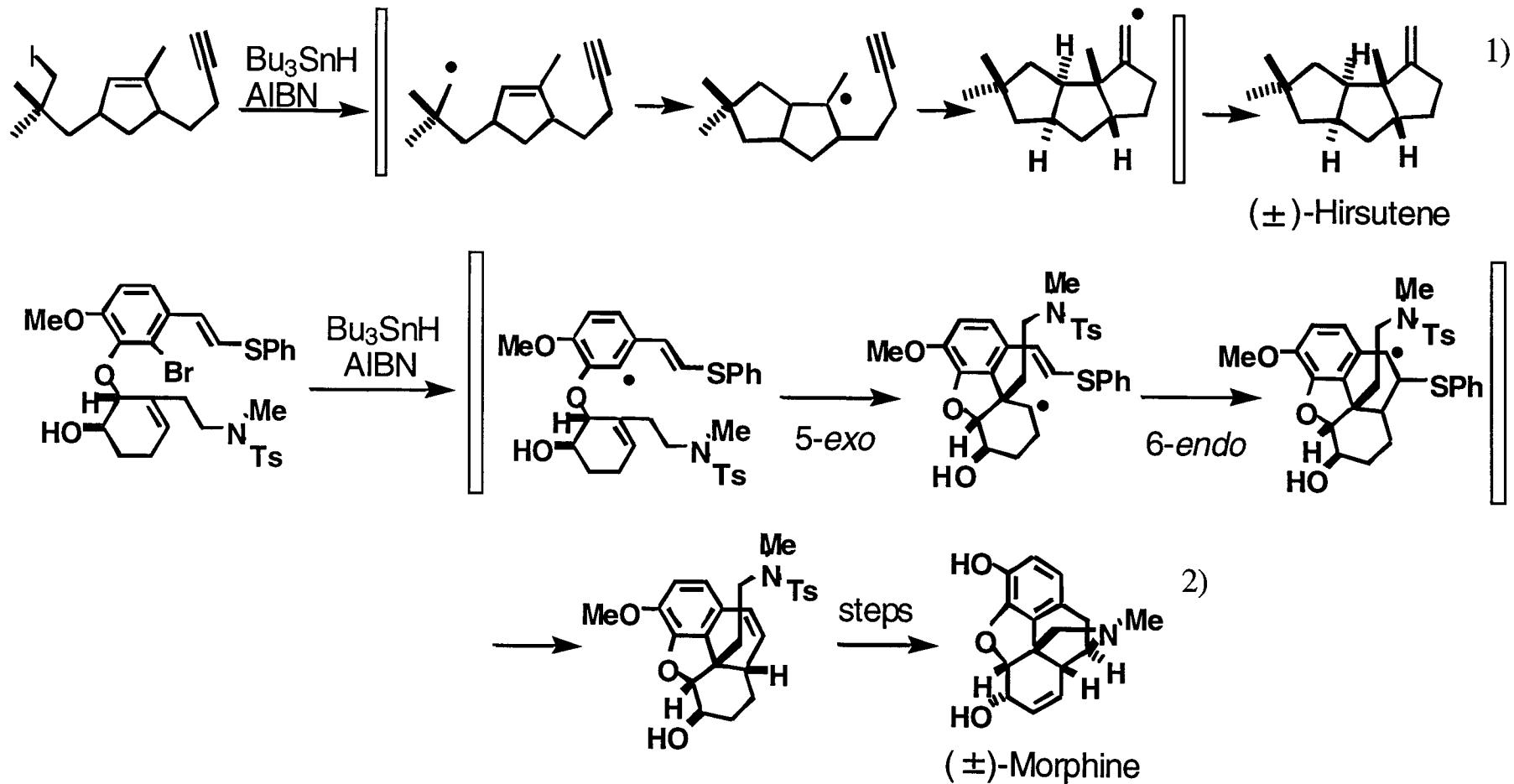
1) M. Gomberg,, *J. Am. Chem. Soc.*, **22**, 757 (1900).

2) H. Lankamp, W. Th. Nanta, and C. Mackeal, *Tetrahedron Lett.*, **1968**, 249.

3) H. G. Kuivila, W. A. Menapace, and C. R. Warner, *J. Am. Chem. Soc.*, **84**, 3584 (1962).

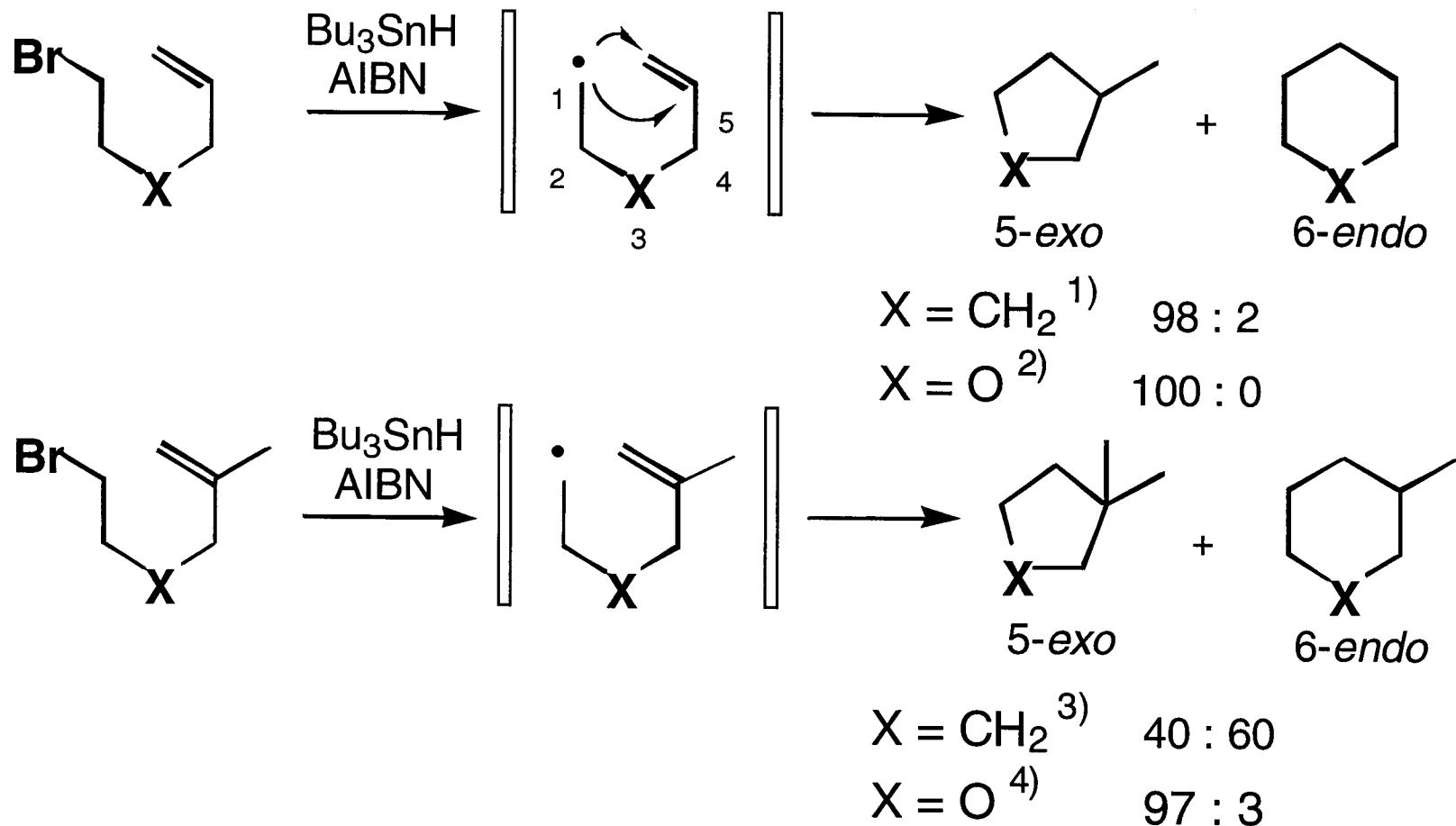
4) C. Walling, J. H. Cooley, A. A. Posnaras, and E. J. Racah, *J. Am. Chem. Soc.*, **88**, 5361 (1966).

Syntheses of Natural Products Using Radical Cyclization



- 1) D. P. Curran and D. M. Rakiewicz, *J. Am. Chem. Soc.*, **107**, 1448 (1985).
 2) K. A. Parker and D. Fokas, *J. Am. Chem. Soc.*, **114**, 9688 (1992).

Regiochemistry of Alkyl Radical Cyclization



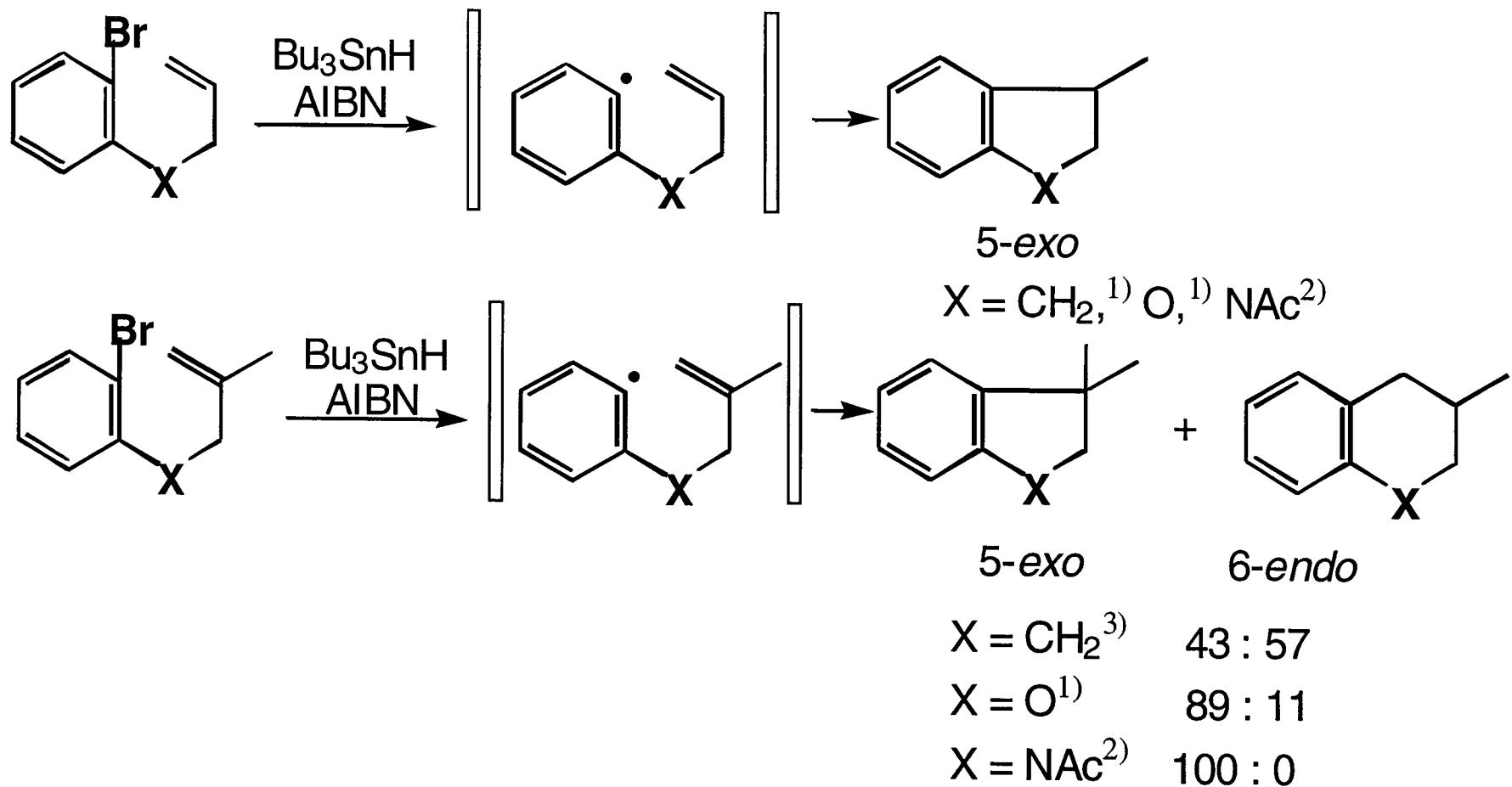
1) A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **41**, 3925, (1985).

2) R. J. Kinney, W. D. Jones, and R. G. Bergman, *J. Am. Chem. Soc.*, **100**, 7902 (1978).

3) A. L. J. Beckwith *Tetrahedron*, **37**, 3073, (1981).

4) T. W. Smith and G. B. Butler, *J. Org. Chem.*, **43**, 6 (1978).

Regiochemistry in Aryl Radical Cyclization

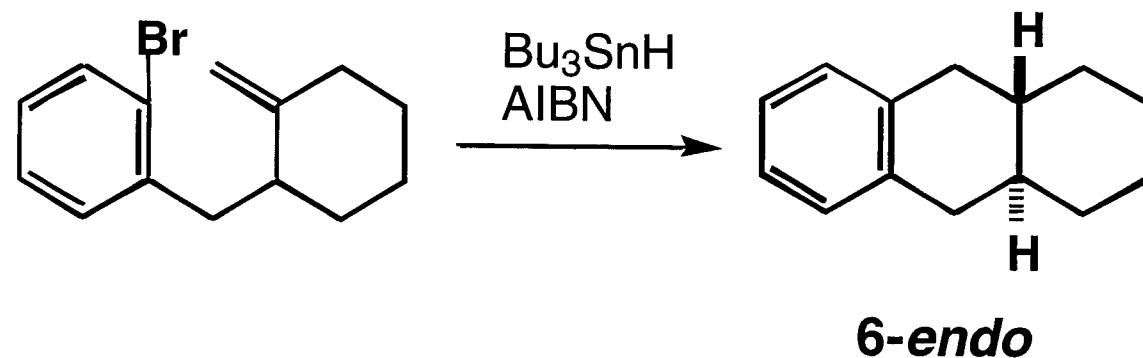
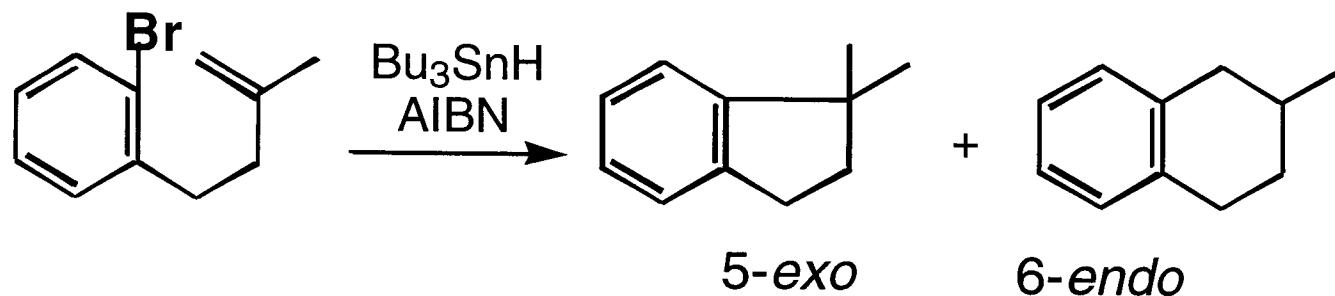
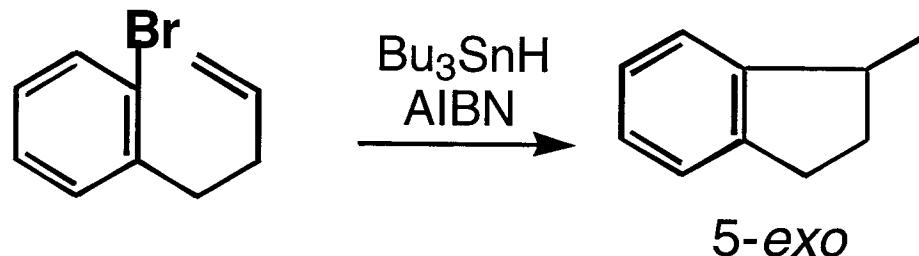


1) A. L. J. Beckwith and W. B. Gara, *J. Org. Chem.*, **52**, 4072 (1987).

2) J. P. Dittami and H. Ramanthan, *Tetrahedron Lett.*, **29**, 45 (1988).

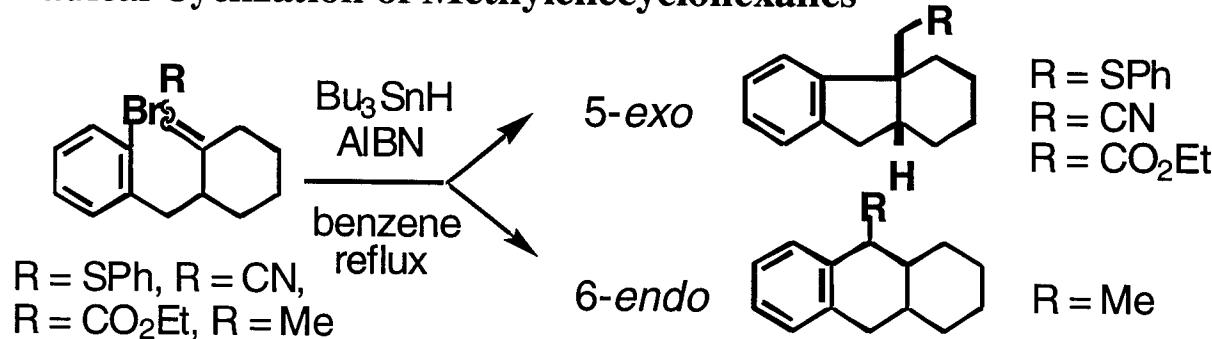
3) P. Rigollier, J. R. Young, L. A. Fowley, and J. R. Stille, *J. Am. Chem. Soc.*, **112**, 9441 (1990).

Regiochemistry in Aryl Radical Cyclization

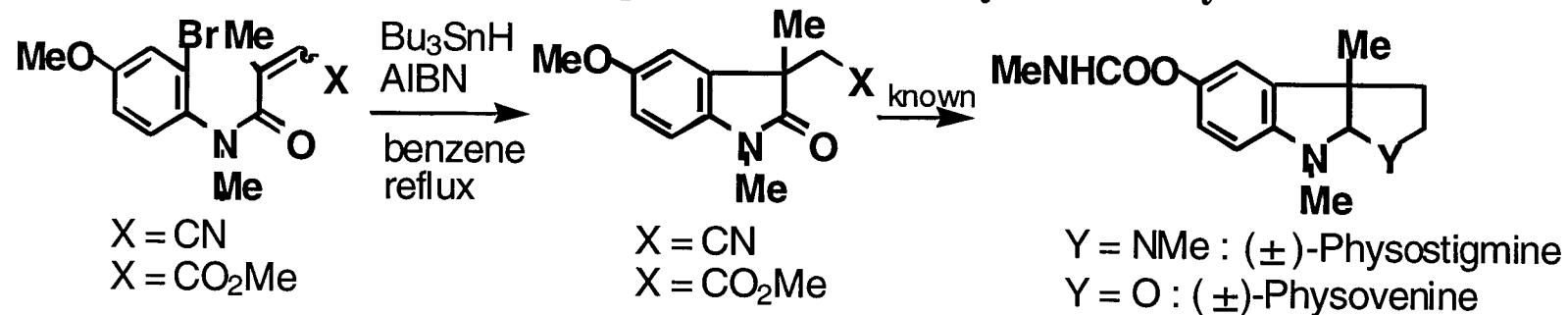


Present Study

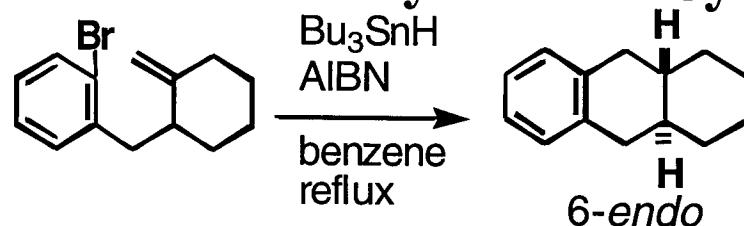
Regiochemistry in Radical Cyclization of Methylenecyclohexanes



Synthetic Study of Calabar Alkaloids Using 5-Exo Selective Aryl Radical Cyclization

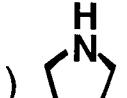


6-Endo Selective Aryl Radical Cyclization



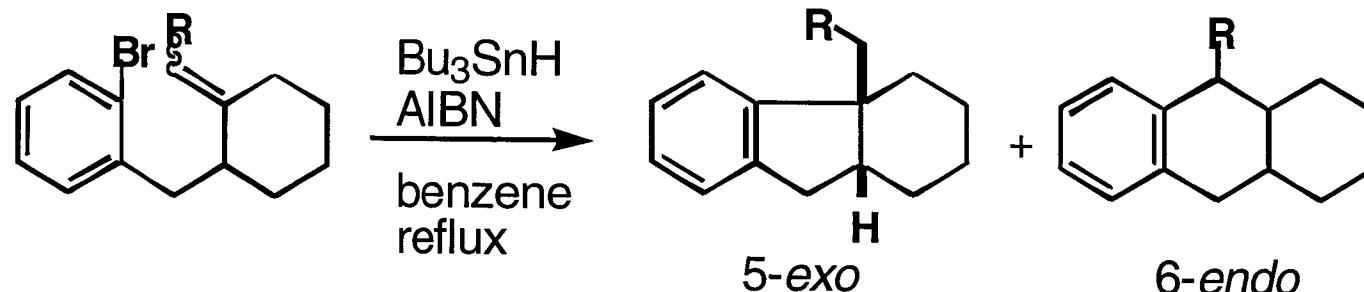
S. Pal, J. K. Mukhopadhyaya, and U. R. Ghatak, *J. Org. Chem.*, **59**, 2687 (1994).

Preparation of Radical Precursors

	Conditions	R	Yield (%)
1) 			
2) 			
3) H ₂ O	Conditions	R	Yield (%)
	Ph ₂ P(O)CH ₂ SPh, BuLi	SPh	91 (<i>E:Z</i> = 22:1)
	(EtO) ₂ P(O)CH ₂ CO ₂ Et, BuLi	CO₂Et	76 (single isomer)
	(EtO) ₂ P(O)CH ₂ CN, BuLi	CN	86 (single isomer)
	Ph ₃ P ⁺ CH ₂ ClCl ⁻ , PhLi	Cl	92 (single isomer)
	Ph ₂ P(O)CH ₂ OMe, BuLi	OMe	72 (<i>E:Z</i> = 5:4)
	Ph ₃ P ⁺ EtI ⁻ , BuLi	Me	76 (<i>E:Z</i> = 1:8)

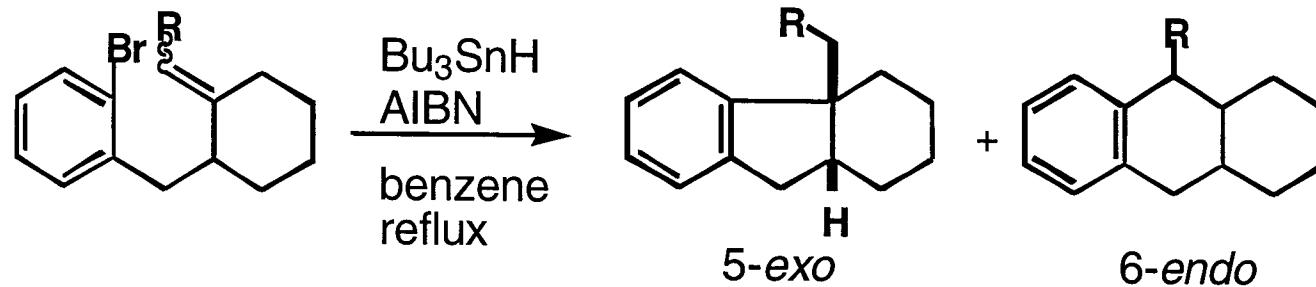
1) S. Pal, J. K. Mukhopadhyaya, and U. R. Ghatak, *J. Org. Chem.*, **59**, 2687 (1994).

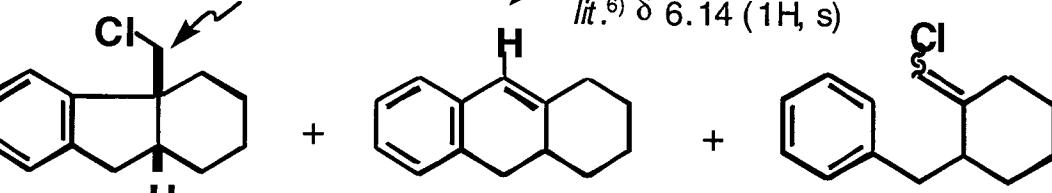
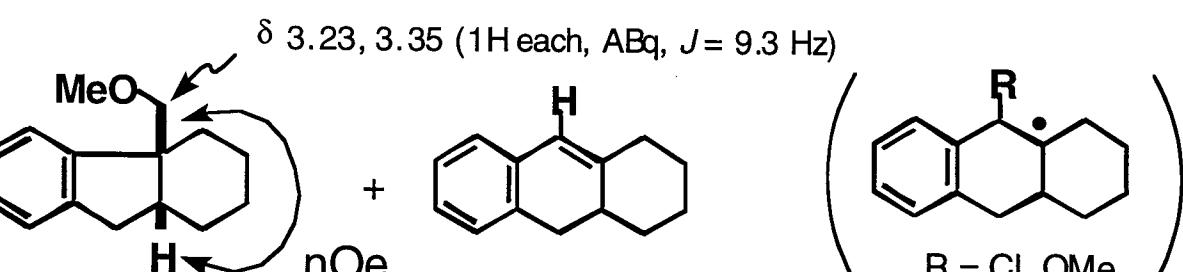
Aryl Radical Cyclization of Methylenecyclohexanes-(I)



Entry	R	Product (Yield)
1	SPh	<p style="text-align: center;">δ 3.13, 3.16 (1H each, ABq, J = 12.2 Hz) (91%)</p>
2	CN	<p style="text-align: center;">δ 2.48, 2.52 (1H each, ABq, J = 16.6 Hz) (81%)</p>
3	CO ₂ Et	<p style="text-align: center;">δ 2.47, 2.53 (1H each, ABq, J = 13.7 Hz) (87%)</p>

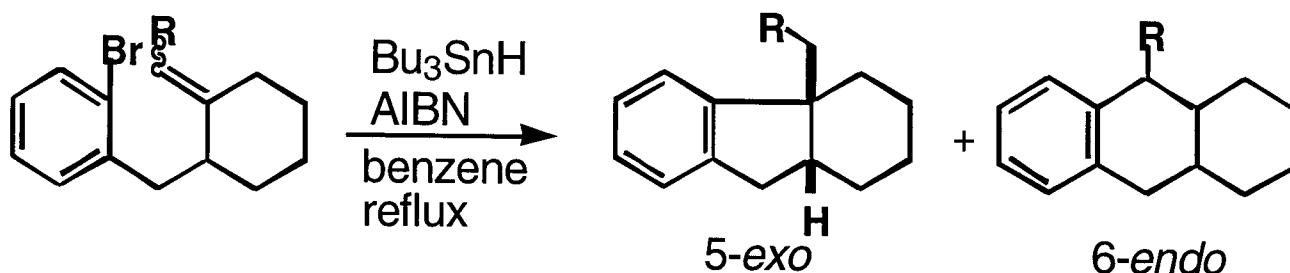
Aryl Radical Cyclization of Methylenecyclohexanes-(II)



Entry	R	Products (Yields)		
4	Cl	δ 3.48, 3.56 (1H each, ABq, J = 9.2 Hz)  <p style="text-align: center;">2 : trace : 1 (ca. 55%)</p>	δ 6.12 (1H, s) <i>lit.</i> ⁶⁾ δ 6.14 (1H, s)	
5	OMe	 <p style="text-align: center;"> δ 3.23, 3.35 (1H each, ABq, J = 9.3 Hz) nOe (55%) (15%) </p>		δ 3.23, 3.35 (1H each, ABq, J = 9.3 Hz) nOe (55%) (15%)

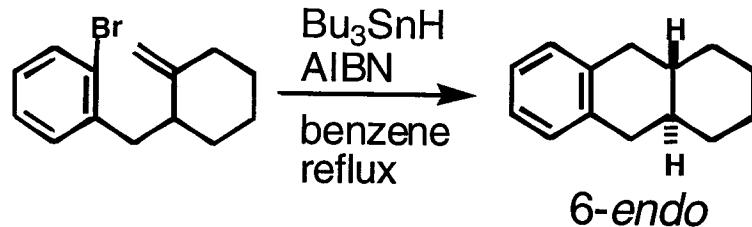
6) D. L. J. Clive, C. Zhang, K. S. K. Murthy, W. D. Hayward, and S. Daigneault, *J. Org. Chem.*, **56**, 6447 (1991).

Aryl Radical Cyclization of Methylenecyclohexanes-(III)



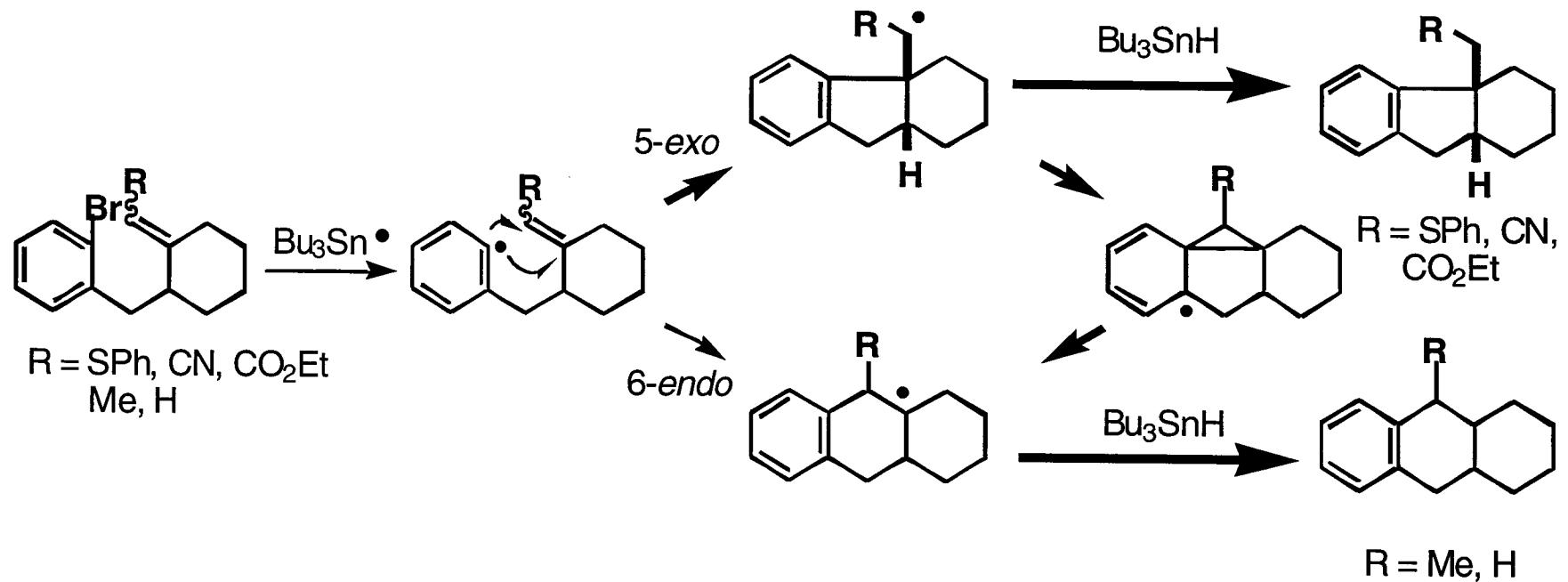
Entry	R	Products (Yields)		
		δ 1.10 (3H, d, $J = 7.3\text{Hz}$) / <i>t.</i> ¹⁾ δ 1.08 (3H, d, $J = 7\text{Hz}$)	δ 1.31 (3H, d, $J = 7.3\text{Hz}$) / <i>t.</i> ¹⁾ δ 1.28 (3H, d, $J = 7\text{Hz}$)	δ 1.32 (3H, d, $J = 7.3\text{Hz}$) / <i>t.</i> ¹⁾ δ 1.31 (3H, d, $J = 7\text{Hz}$)
6	Me	 (trace)	 (79%)	

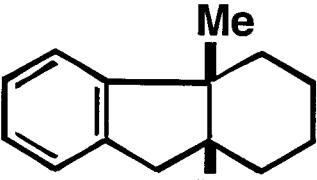
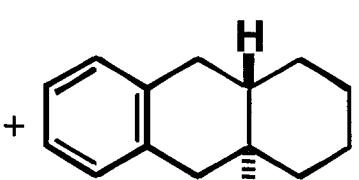
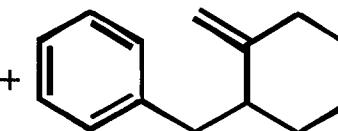
1) S. Hagishita and K. Kuriyama, *Bull. Chem. Soc. Jpn.*, **53**, 3216 (1982).



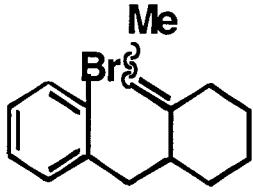
S. Pal, J. K. Mukhopadhyaya, and U. R. Ghatak, *J. Org. Chem.*, **59**, 2687 (1994).

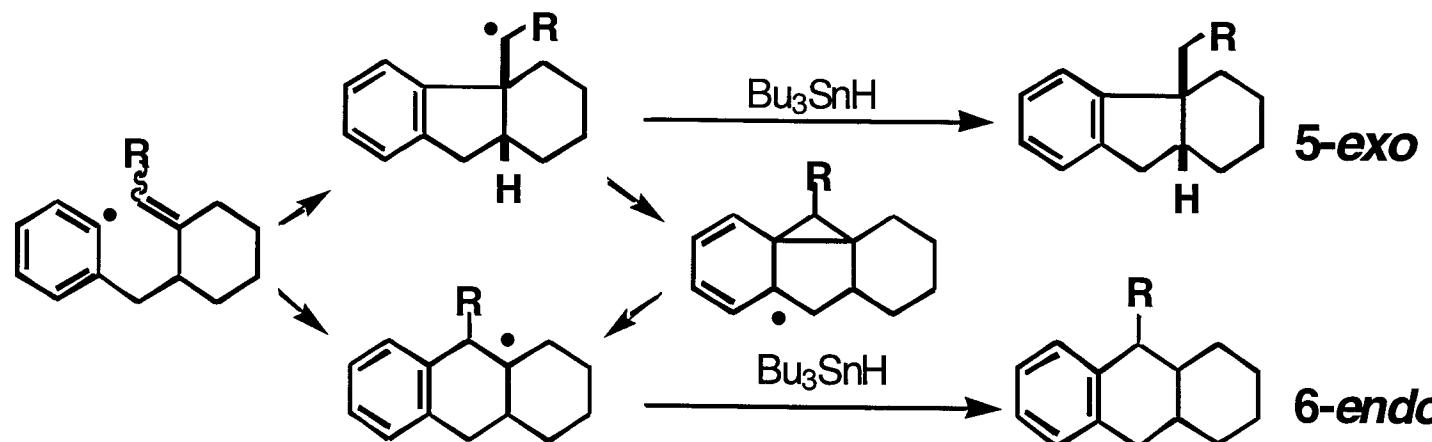
Possible Mechanism of Cyclization



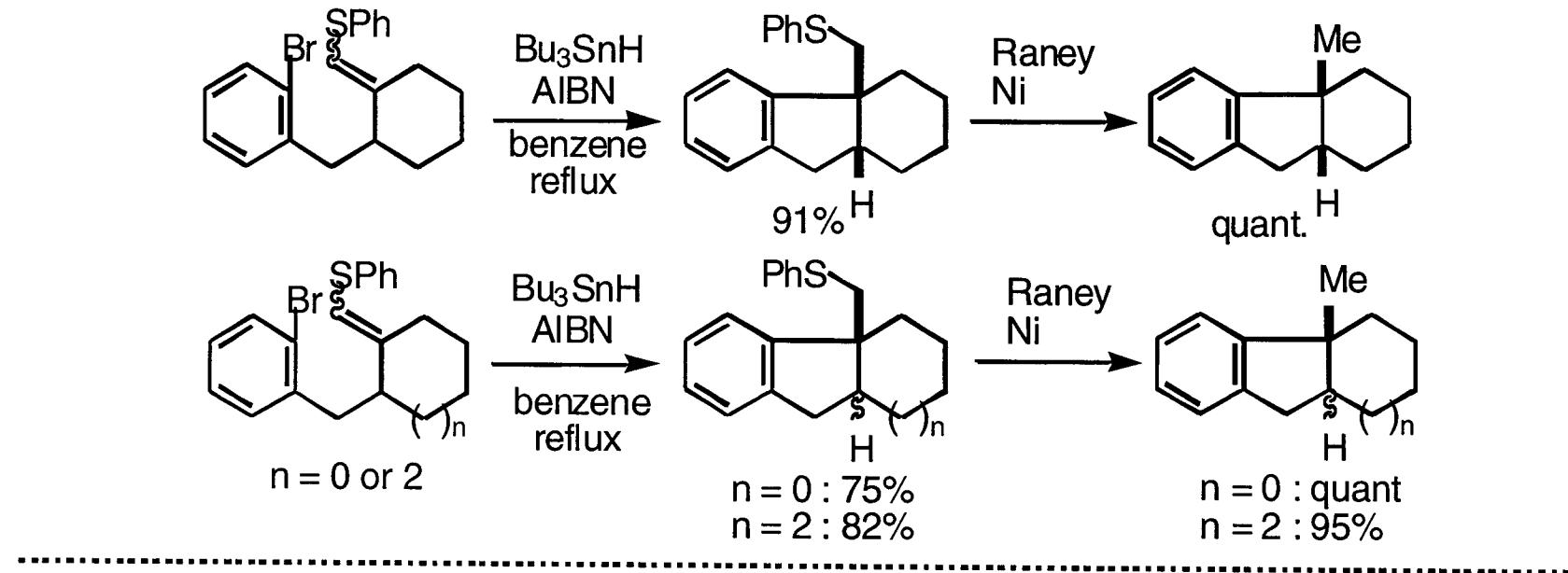
S.M.	Conditions				R.P.
Conditions		Products (Yields)			
Bu ₃ SnH (1.1 eq.,), AIBN (cat.), 0.02 M, benzene, reflux	¹⁾		6-endo : R.P. = 9 : 1 (95%)		
Bu ₃ SnH (1.1 eq.), AIBN (0.15 eq.), 0.1 M, benzene, reflux			5-exo : 6-endo : S.M. = 1 : 7 : 2 (72%)		R.P. (16%)

1) S. Pal, J. K. Mukhopadhyaya, and U. R. Ghatak, *J. Org. Chem.*, **59**, 2687 (1994).

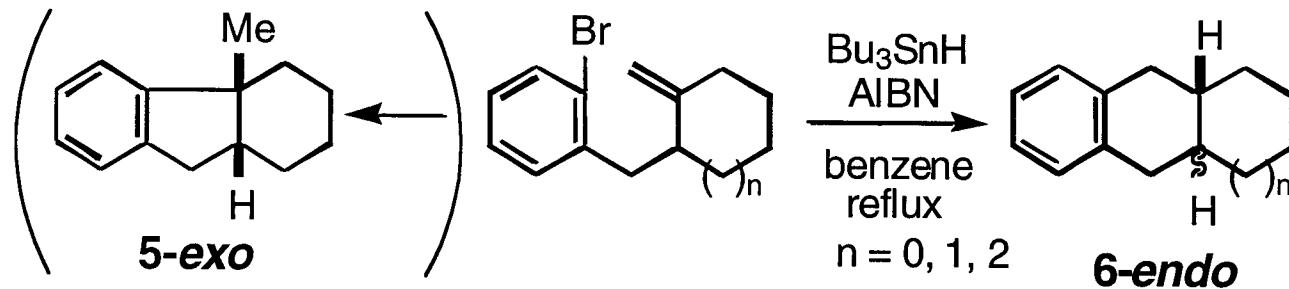
S.M.	Conditions	Products (Yields)
	[Bu ₃ SnH (1.5 eq.,) + AIBN (0.15 eq.)] slow addition, benzene, reflux	6-endo (79%) (5-exo trace)
Bu ₃ SnH (1.2 eq.), Et ₃ B (4.0 eq.), benzene, r.t.		5-exo : S.M. = 6 : 1 (ca. 55%) (6-endo trace)



Aryl Radical Cyclization of (Phenylthio)methylenecycloalkanes (I)

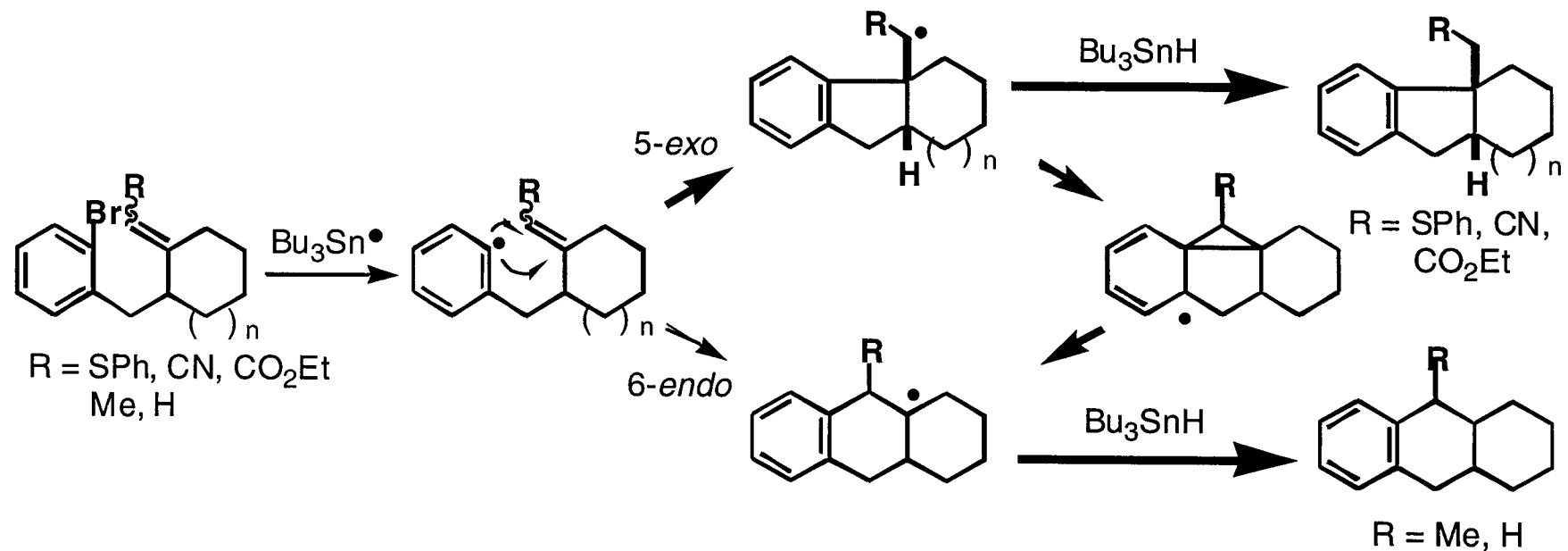


6-Endo Selective Aryl Radical Cyclization

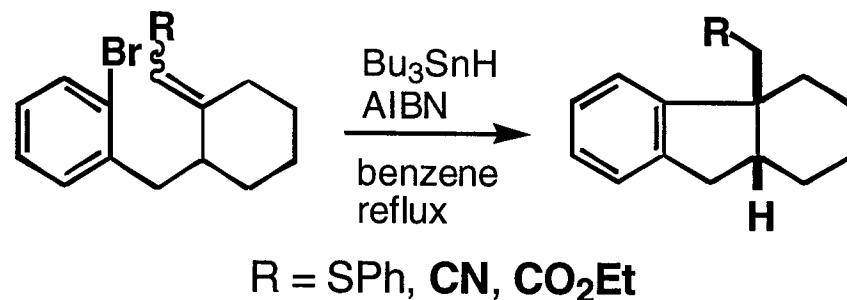
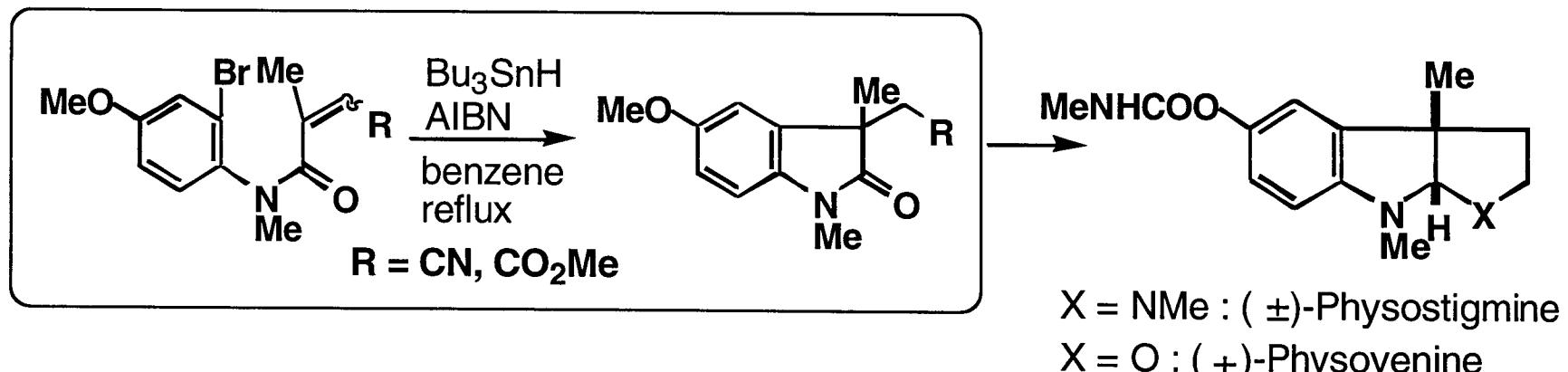


S. Pal, J. K. Mukhopadhyaya, and U. R. Ghatak, *J. Org. Chem.*, **59**, 2687 (1994).

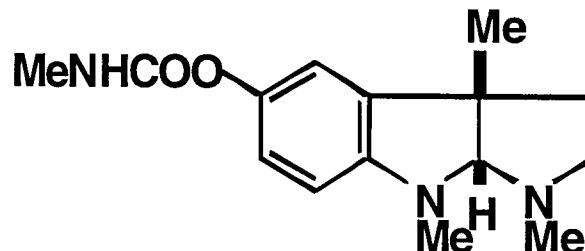
Cyclization of Methylenecycloalkanes



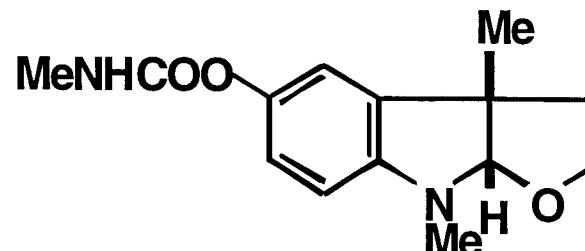
Synthesis of Calabar Bean Alkaloids



Calabar Bean Alkaloids



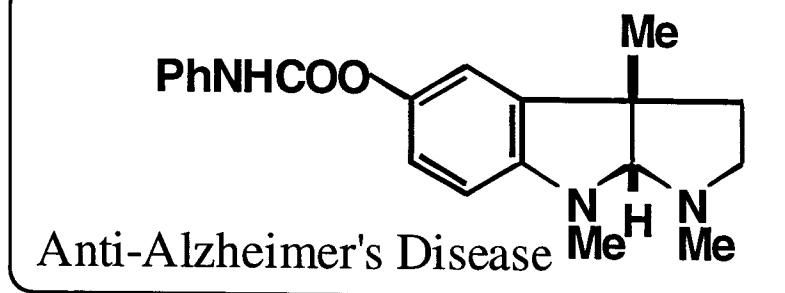
(-)-Physostigmine



(-)-Physovenine

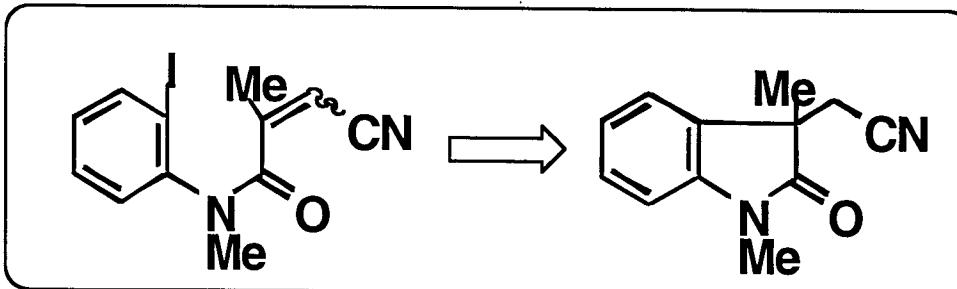
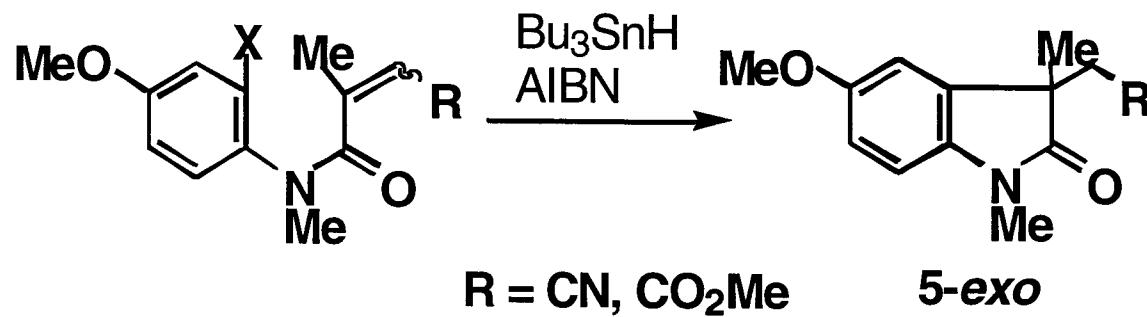
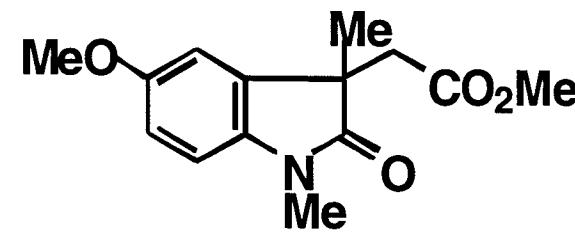
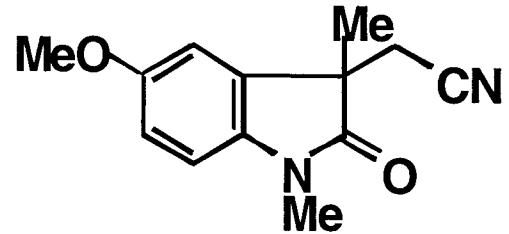
Biological Action : Cholinesterase Inhibition

Clinical Use : Glaucoma Treatment
Myasthenia Gravis Drug

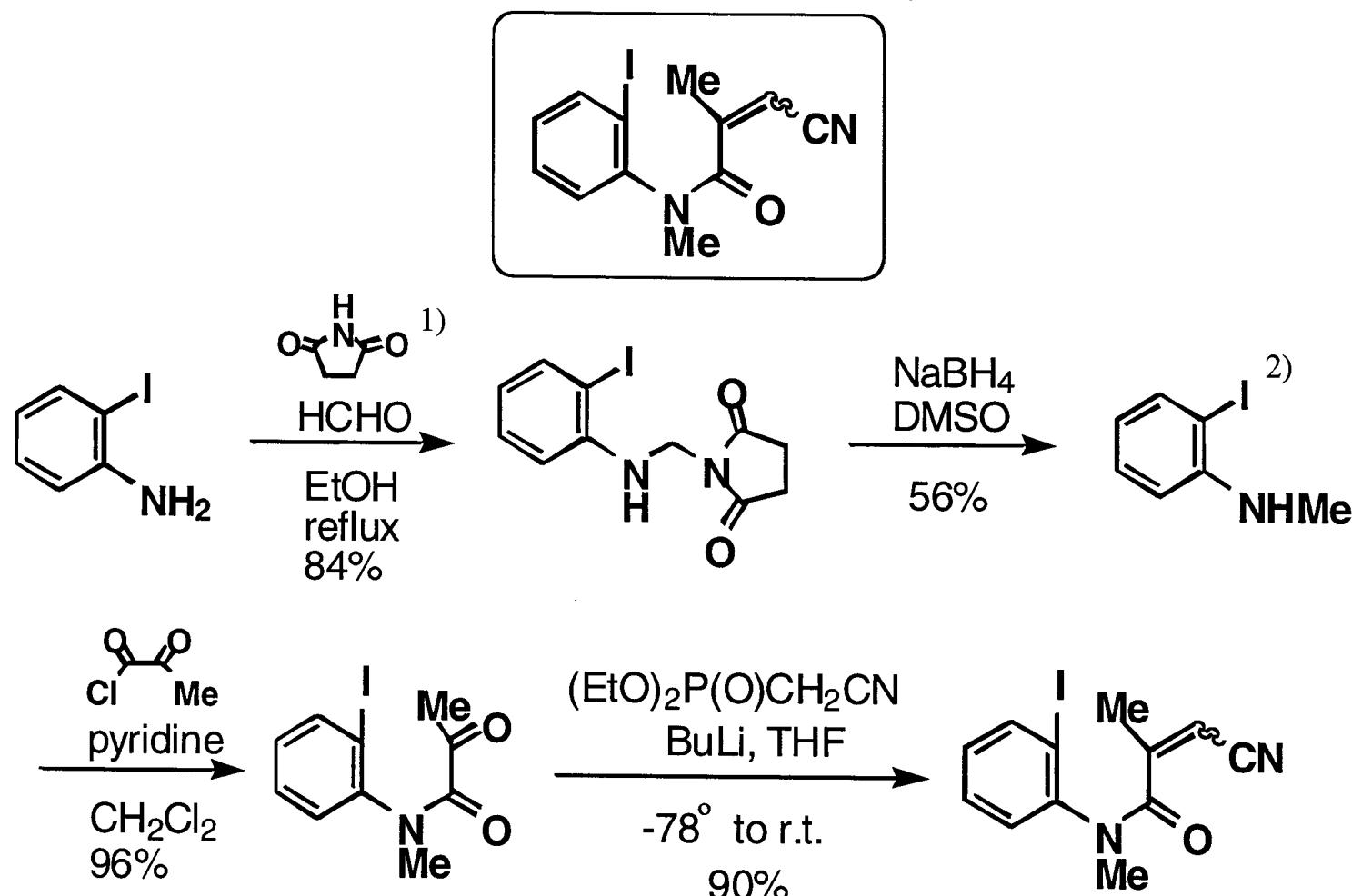


Anti-Alzheimer's Disease

N. H. Greig, X.-F. Pei, T. T. Soncrant, D. K. Ingram,
and A. Brossi, *Med. Res. Rev.*, **15**, 3 (1995).



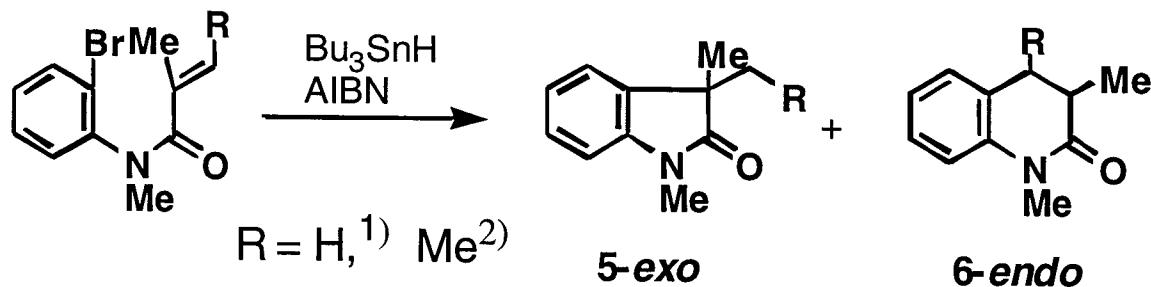
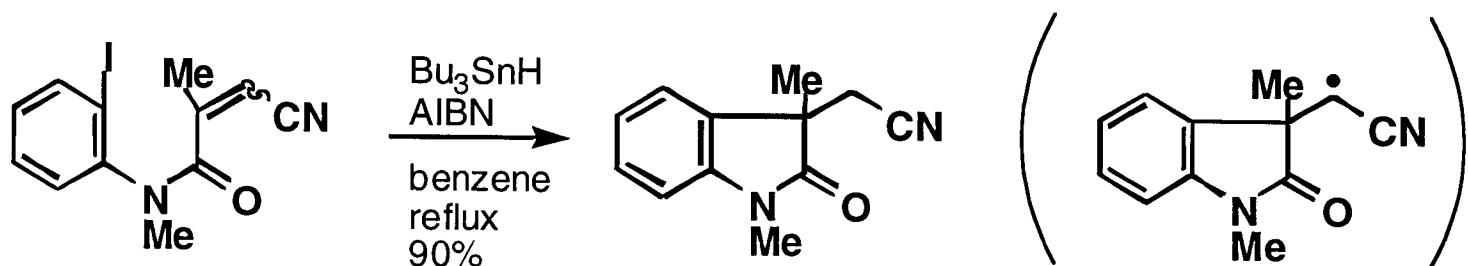
Model Study



1) S. B. Kadin, *J. Org. Chem.*, **38**, 1348 (1973).

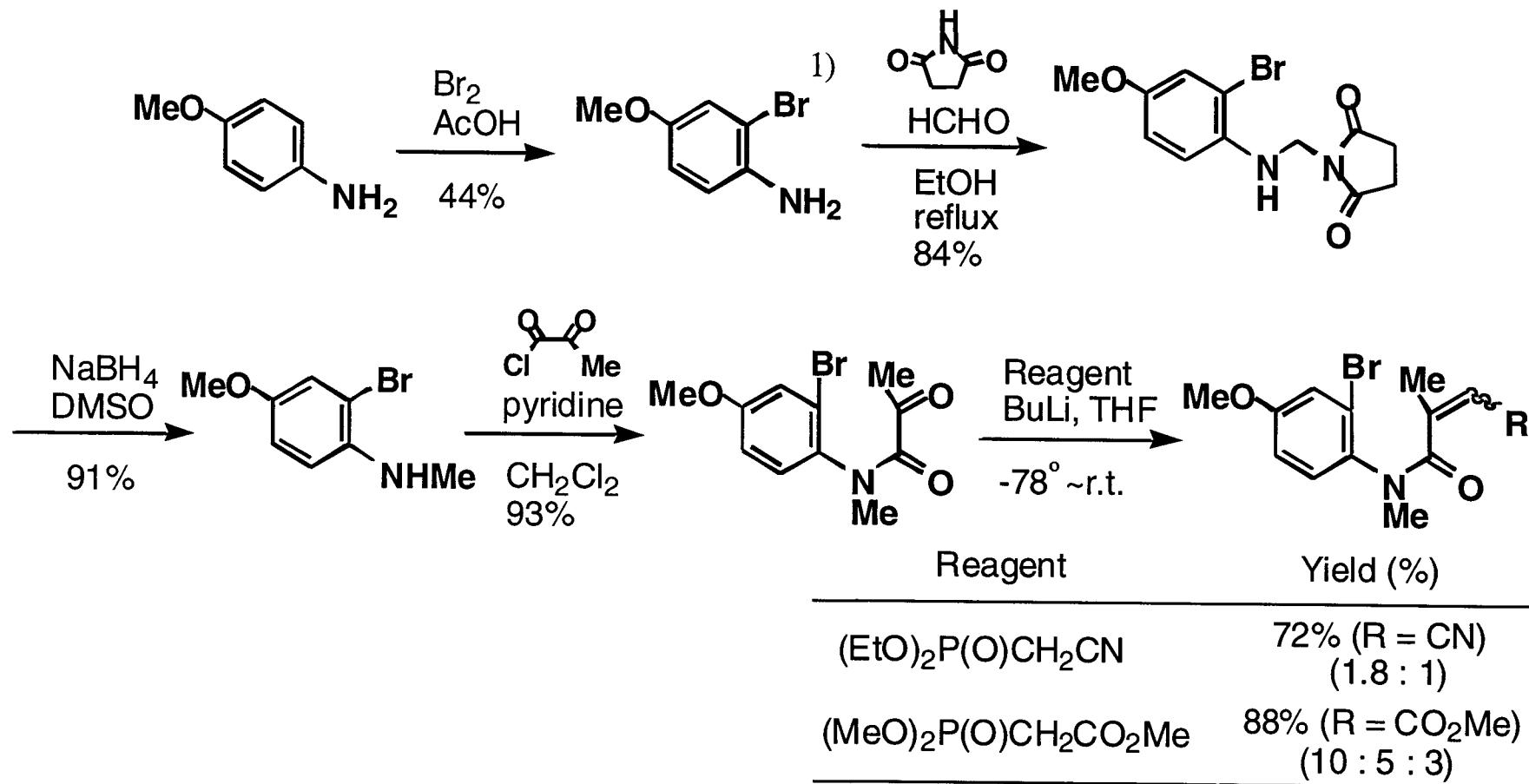
2) M. Kihara, Y. Iwai, and Y. Nagao, *Heterocycles*, **41**, 2279 (1996).

Model Study (*5-Exo* Selective Radical Cyclization)

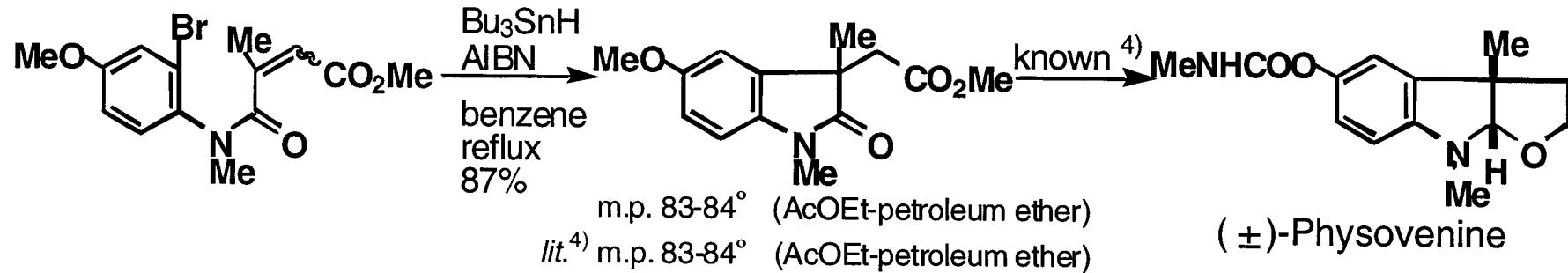
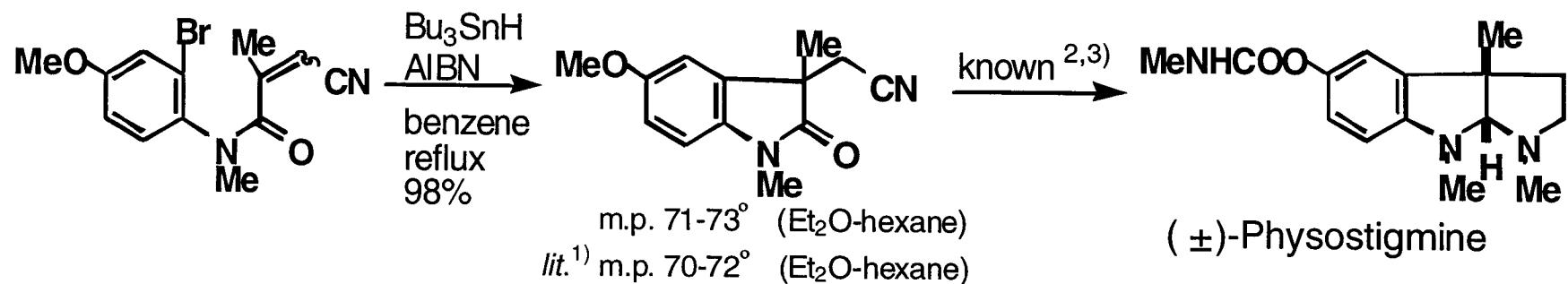


- 1) K. Jones, M. Thompson, and C. Wright, *J. Chem. Soc., Chem. Commun.*, **1986**, 115.
- 2) A. J. Clark and K. Jones, *Tetrahedron Lett.*, **30**, 5485 (1989).

Formal Syntheses of (\pm)-Physostigmine and (\pm)-Physovenine



1) A. J. Clark and K. Jones, *Tetrahedron*, **48**, 6875 (1992).



1) M. S. Morales-Rios, M. A. Bucio, and P. Joseph-Nathan, *Tetrahedron*, **52**, 5339 (1996).

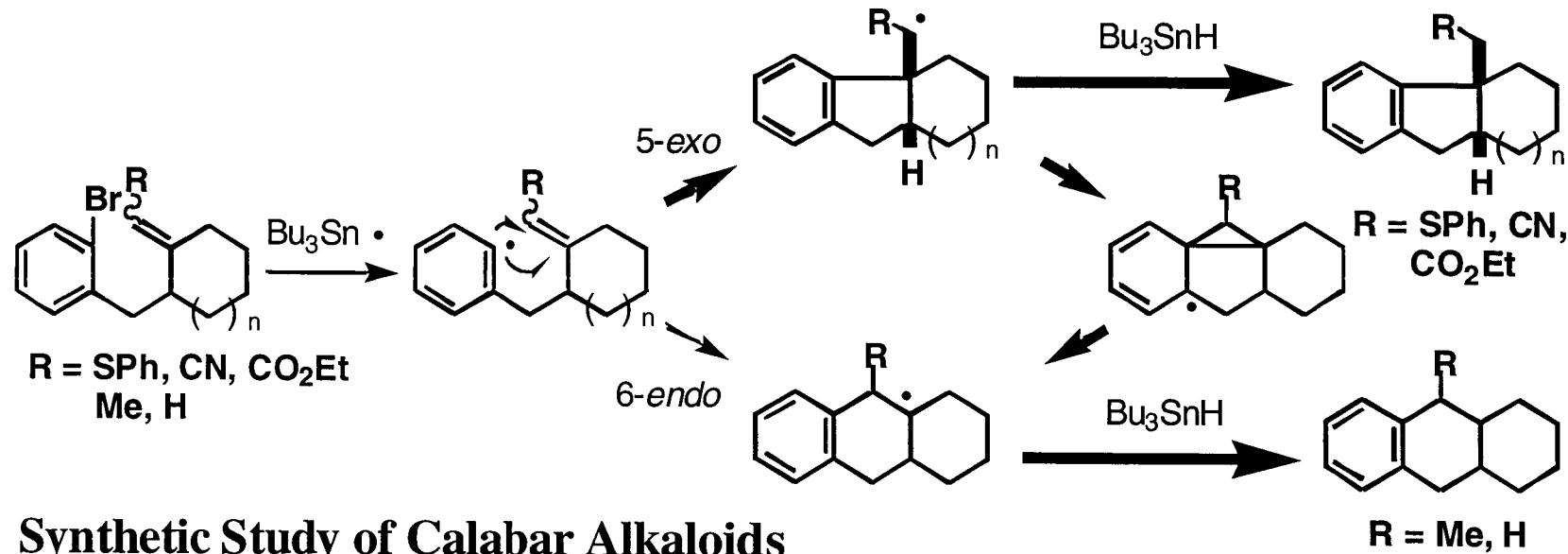
2) Q.-S. Yu, B.-Y. Lu, and X.-F. Pei, *Heterocycles*, **39**, 519 (1994).

3) Q.-S. Yu and A. Brossi, *Heterocycles*, **27**, 1709 (1988).

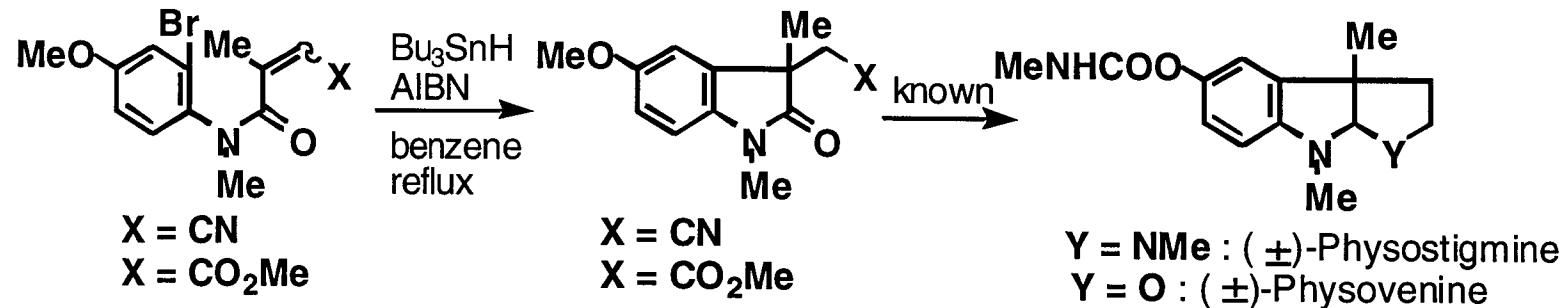
4) Y.-L. Luo, Q.-S. Yu, L. Chrisey, and A. Brossi, *Heterocycles*, **31**, 283 (1990).

Summary

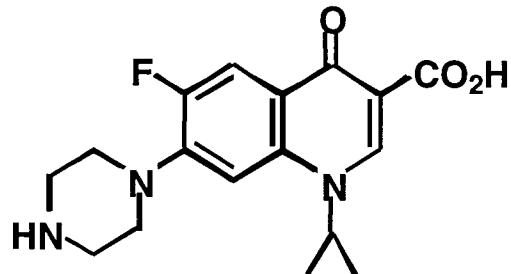
Regiochemistry in Radical Cyclization of Methylenecyclohexanes



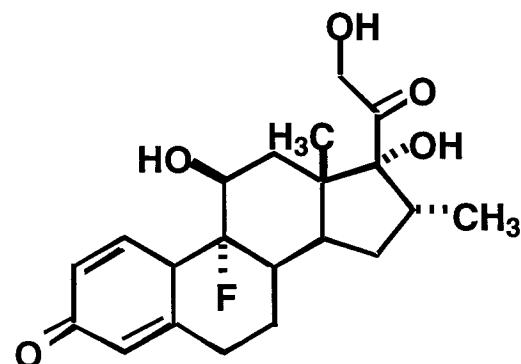
Synthetic Study of Calabar Alkaloids Using 6-Endo Selective Aryl Radical Cyclization



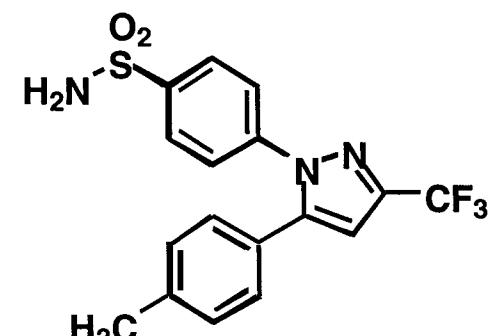
Biologically Active Fluorine-Containing Compounds



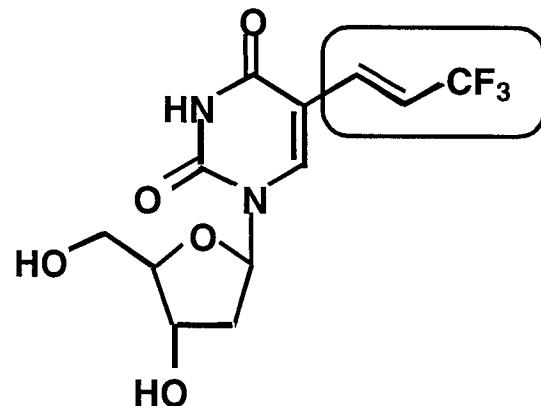
Ciprofloxacin
(Antibacterial Drug)



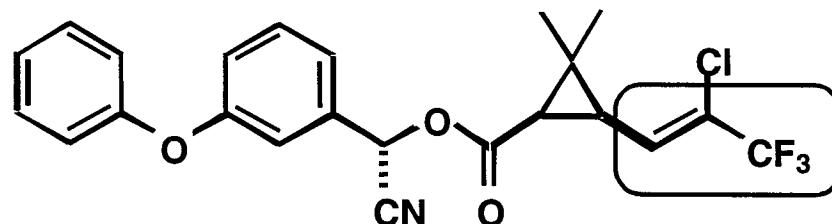
Dexamethasone
(Steroidal Anti-Inflammatory Drug)



Celecoxib
(Selective COX-2 Inhibitor)

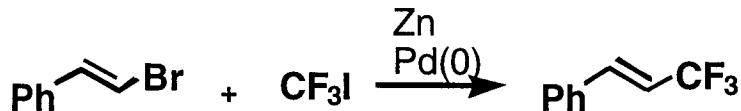


(Antiviral Compound)

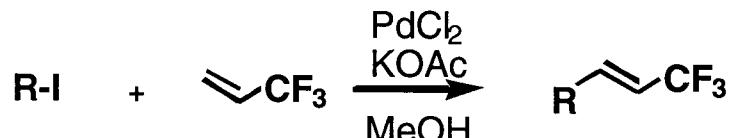


Cyhalothrine
(Pyrethroid Insecticide)

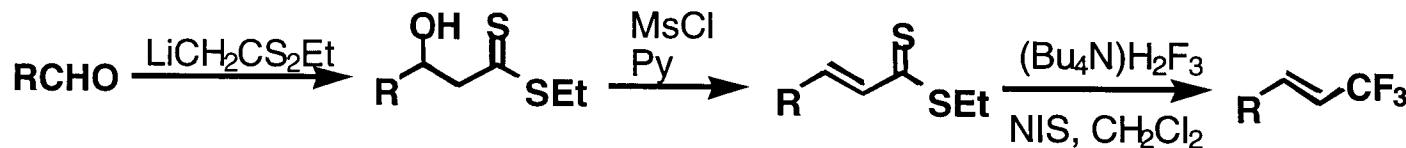
Syntheses of 3,3,3-Trifluoropropenyl Compounds



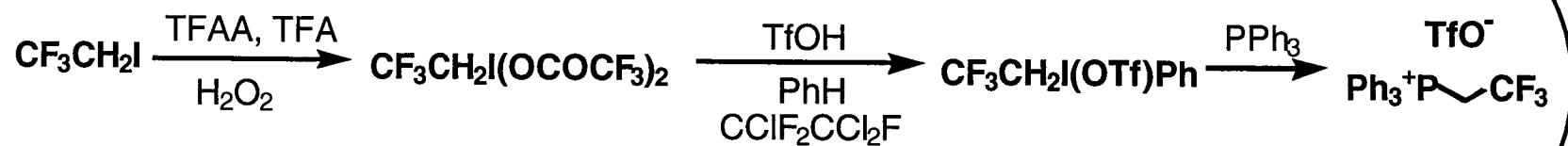
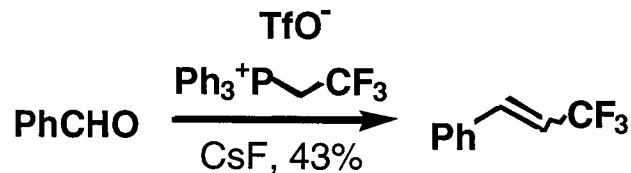
T. Kitazume and N. Ishikawa, *J. Am. Chem. Soc.*, **107**, 5186 (1985).



T. Fuchikami, M. Yatabe, and I. Ojima, *Synthesis*, **1981**, 365.

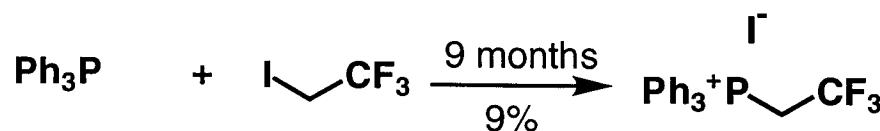
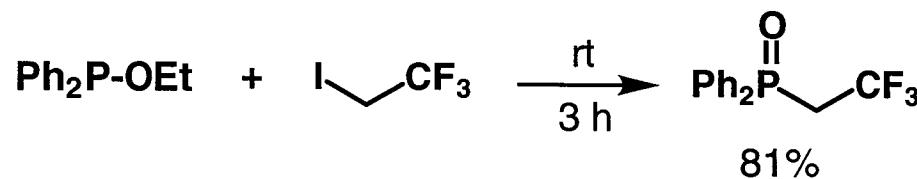
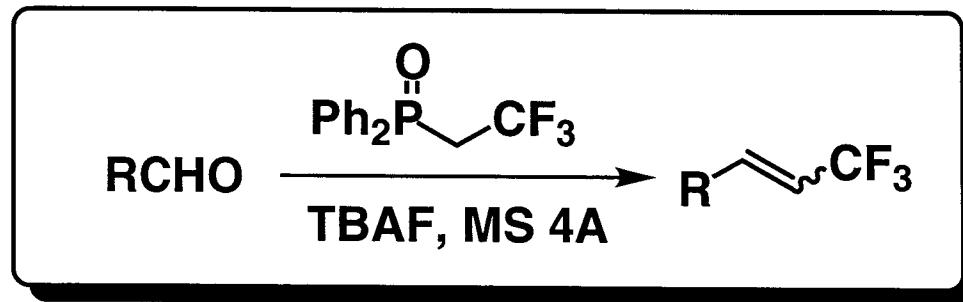


S. Fujita, M. Kuroboshi, and T. Hiyama, *Bull. Chem. Soc. Jpn.*, **72**, 805 (1999).

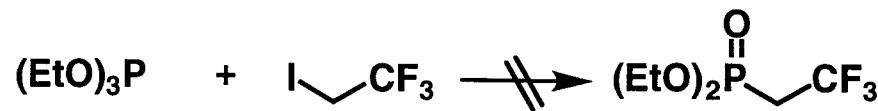


T. Umemoto and Y. Goto, *Bull. Chem. Soc. Jpn.*, **60**, 3307 (1987).
 T. Umemoto and Y. Goto, *Bull. Chem. Soc. Jpn.*, **64**, 2008 (1991).

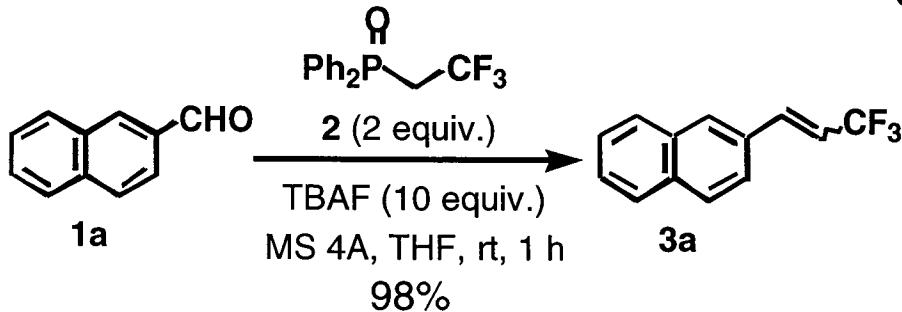
Synthesis of 3,3,3-Trifluoropropenyl Compounds Using Wittig-Type Reaction



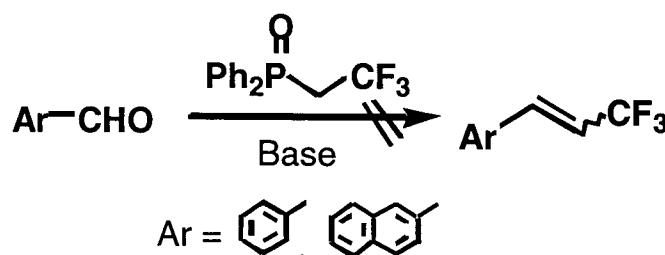
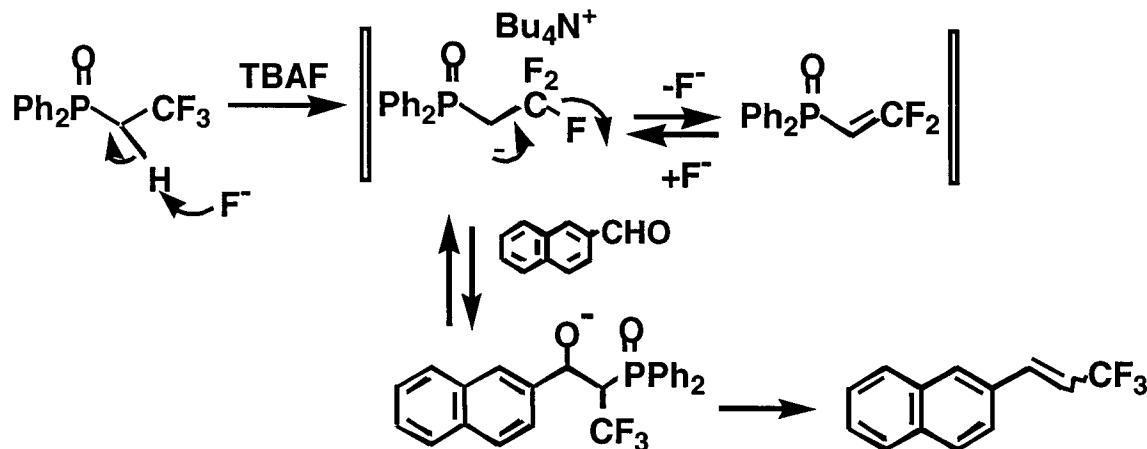
D. J. H. Smith and S. Trippett, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 963.



Fluoride Ion-Mediated Horner-Wittig Reaction

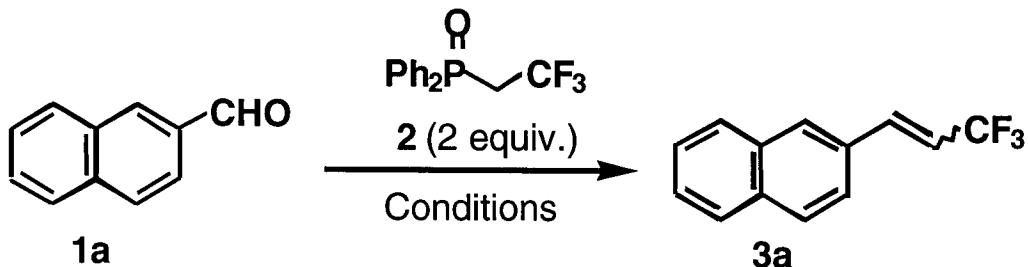


Mechanism



Base = BuLi, KHMDS, Triton® B, KO*t*-Bu, KH

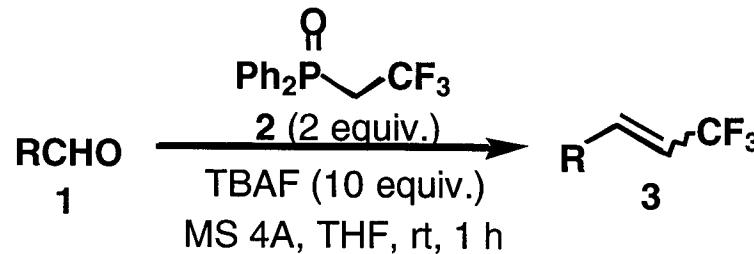
Various Sources of the Fluoride Ion

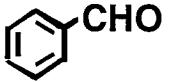
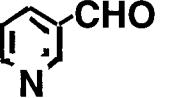
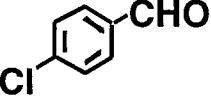
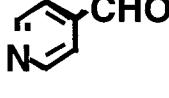
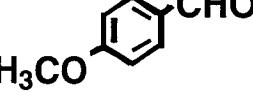
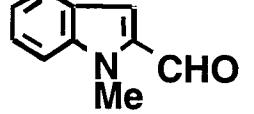


Entry	Conditions	Yield of 3a , % (E/Z)	Recovery of 1a (%)
1	TBAF (10 equiv.) MS 4A , THF, rt, 1 h	98 (85 : 15)	—
2	TBAF (10 equiv.) THF, rt, 24 h	—	86
3	CsF (5 equiv.) DMF, rt, 4.5 h, 100°C, 14 h	1	57
4	HF•Pyridine (10 equiv.) THF, rt, 24 h	—	92
5	TBAT (10 equiv.) THF, 60°C, 1 h reflux, 5 h	—	87

TBAT : $\text{Bu}_4\text{N}^+\text{Ph}_3\text{SiF}_2^-$

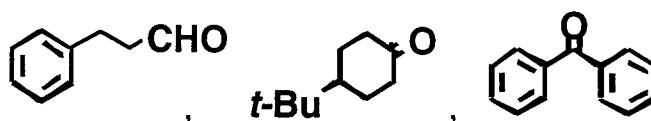
Fluoride Ion-Mediated Horner-Wittig Reaction



RCHO	Yield of 3 , % (<i>E/Z</i>)	RCHO	Yield of 3 , % (<i>E/Z</i>)
 CHO	63 ^a (78 : 22)	 CHO	66 (73 : 27)
 CHO	74 (82 : 18)	 CHO	58 (100 : 0)
 CHO	75 (95 : 5)	 CHO	75 (100 : 0)
			83 (62 : 38)

^a: Volatile compound

No compounds 3 were obtained from these compounds.



Convenient Synthesis of 3,3,3-Trifluoropropenyl Compounds

