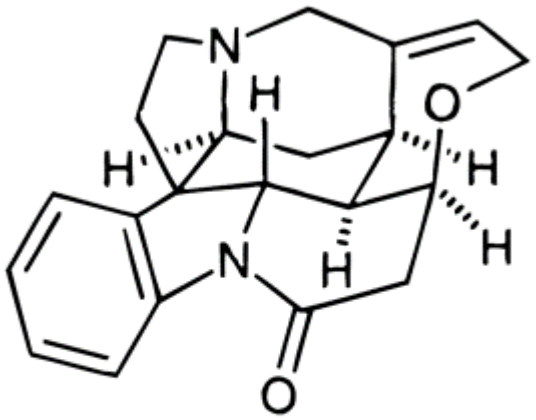
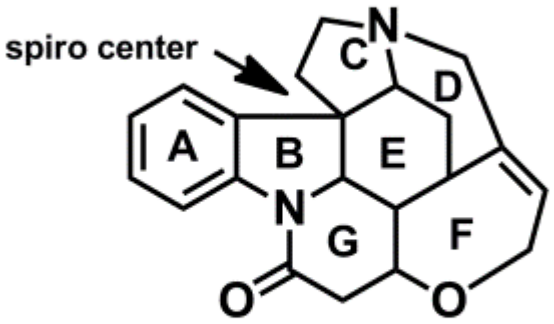
Total synthesis of Strychnine

2011. 8.30. Shota Kato



Strychnine



1. Introduction

♦isolation
The seeds and barks of Strychnos nux vomica in 1818

♦total synthesis
R. B. Woodward (1954, racemic)- *J. Am. Chem. Soc.*, 1954, 76, 4749
Larry E. Overman (1993)- *J. Am. Chem. Soc.*, 1993, 115, 9293
Masakatsu Shibasaki (2002)- *J. Am. Chem. Soc.*, 2002, 124, 14546
Tohru Fukuyama (2004)- *J. Am.Chem. Soc.*, 2004, 126, 10246
David W. C. MacMillan (2011)- *Nature, 475,* 183
Christopher D. Vanderwal (2011)- *Chem. Sci.*, 2011, *2*, 649

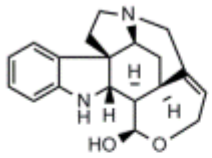
Magnus(1992, racemic), Stork(1992, racemic), Kuehne(1993, racemic), Rawal(1994, racemic), Martin(1996, racemic), Bosch(1999), Vollhardt (2000, racemic), Bodwell(2002, racemic), Mori(2002), Padwa(2007, racemic), Andrade(2010, racemic), Reissig(2010, racemic)

♦Bioactivity
notorious poison(50 mg is lethal for an adult human), which blocks postsynaptic inhibition in the spinal cord where it antagonizes the transmitter glycine

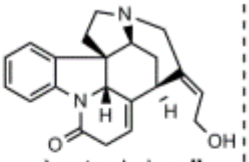
♦Stumbling blocks in the synthesis
i) the generation of the spirocenter
ii) the assembling of the bridged framework of the alkaloid (CDE core ring)

Robert Robinson said "For its molecular size it is the most complex substance known".....

Biosynthetic and degradative product of strychnine



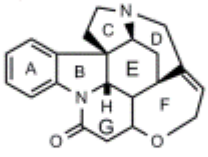
Wieland-Gumlich aldehyde- **I**



Isostrychnine- **II**

$CH_2(CO_2H)_2$, Ac_2O
NaOAc, AcOH, 110°C — 68%

20% — KOH, EtOH, 85°C



Strychnine

All case of total synthesis has been attained through WGA or Isostrychnine

Saxton, J. E. *J. Chem. Soc.* 1952, 982
Taylor, W. I. *Helv. Chim. Acta* 1948, *31*, 2244

Features of some total synthesis

R. B. Woodward - A →AB →ABC→ ABCG→ ABCEG →ABCDEG → **II**
steps 29: ,total yield: 0.000105%

Larry E. Overman - A →AD→ ACDE→ ABCDE → ABCDEF → **I**
steps: 24, total yield: 2.4%

Masakatsu Shibasaki - E→ AE →ABDE →ABCDE → **I**
steps: 31, total yield: 1.4%

Tohru Fukuyama - AB →ABCDE →ABCDEF → **I**
steps: 25, total yield: 1.1%

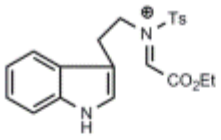
David W. C. MacMillan - AB →ABCE →ABCDEF → **I**
steps: 12, total yield: 6.3%

Christopher D. Vanderwal - AB →ABCE → **I**
steps: 6, total yield: 3.1%

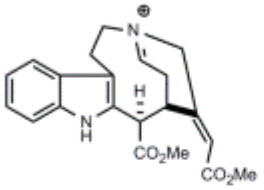
Stumbling blocks in the synthesis

i) the generation of the spirocenter

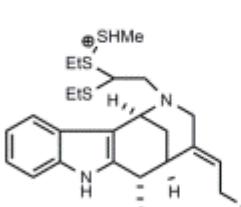
taking advantage of indole reactivity



Woodward

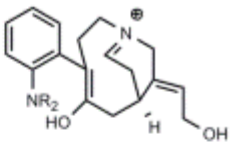


Fukuyama

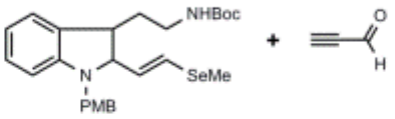


Shibasaki

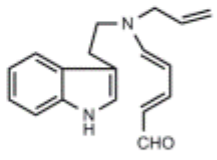
other than that



Overman - Mannich reaction



Macmillan - Diels-alder



Vanderwal - Intramolecular Diels-alder

ii) the assembling of CDE core ring

Forming D-ring after forming spirocenter
: Woodward, Macmilan, Vanderwal

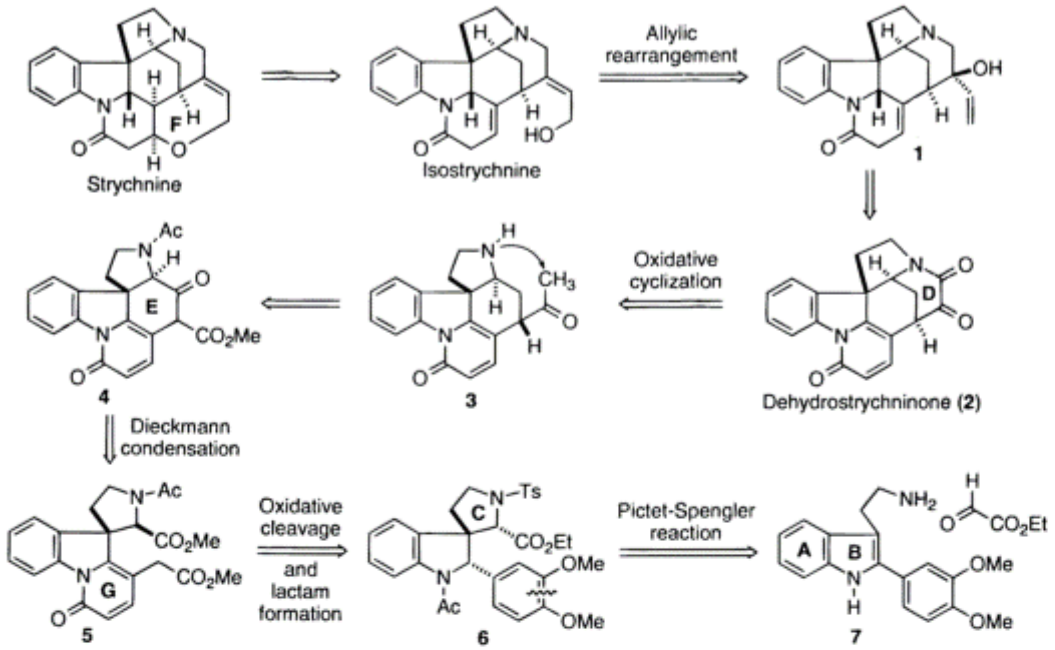
Forming spirocenter after forming D-ring
: Overman, Shibasaki

Forming both at the same time
: Fukuyama

2. Woodward's total synthesis

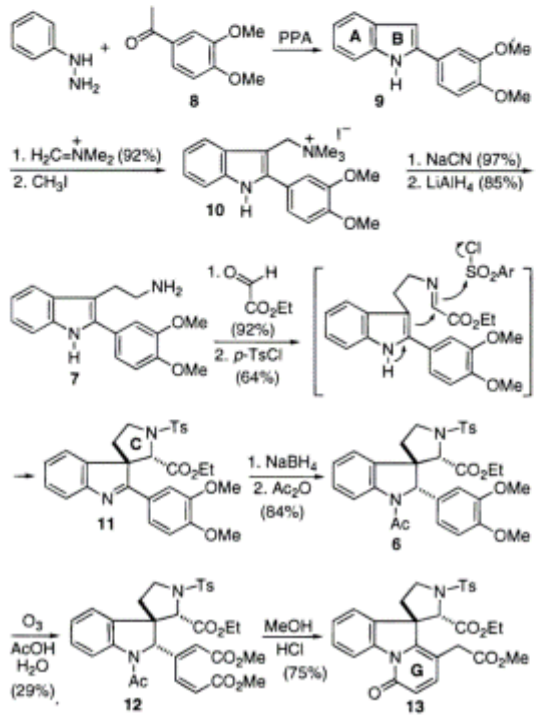
J. Bonjoch *et al.*,*Chem. Rev*. 2000, *100*, 3455-3482

Retrosynthesis



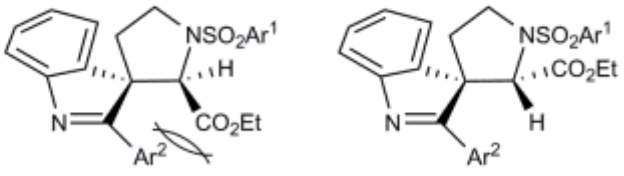
Total synthesis

Closure of Rings C and G: Synthesis of Intermediate 13



⟸ Formation of A-B ring by Ficher-indole

the structure of **11** and the epimer

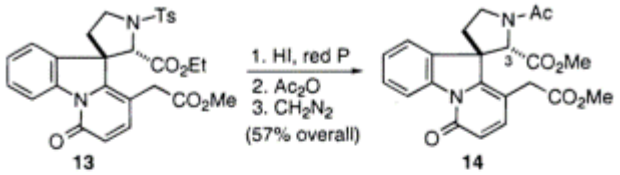


⟸ **11** is less steric hindrance than the epimer

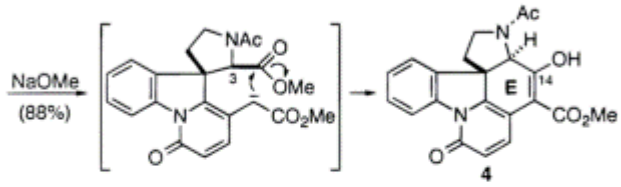
Formation of C ring by Pictet-Spemgler reaction

⟸ Formation of C ring by formation of amide

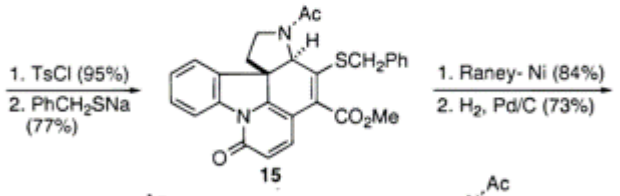
Closure of Ring E: Synthesis of Intermediate 17



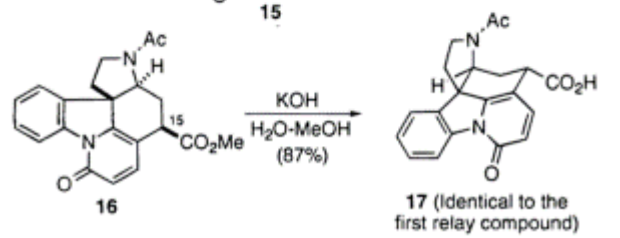
⟸ ester was converted to carboxylic acid by HI
N-Ts was reducted to N-H by red P in condotion 1



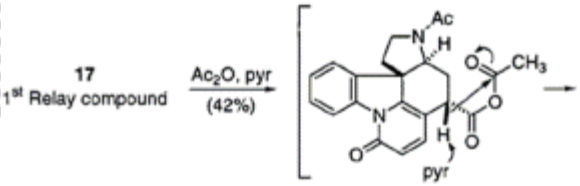
⟸ epimerization at C-3, Formation of E ring by Diekman-condensation



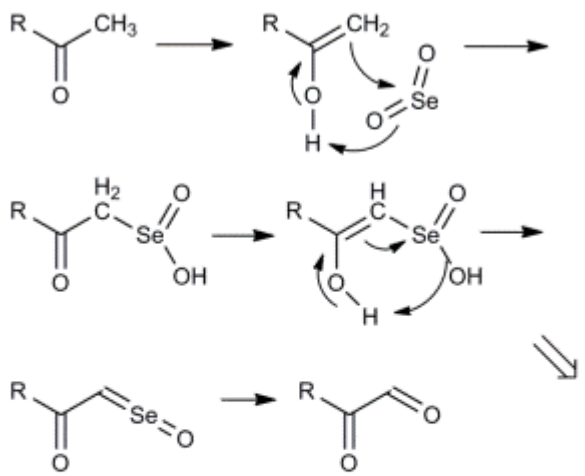
⟸ epimerization at C-15

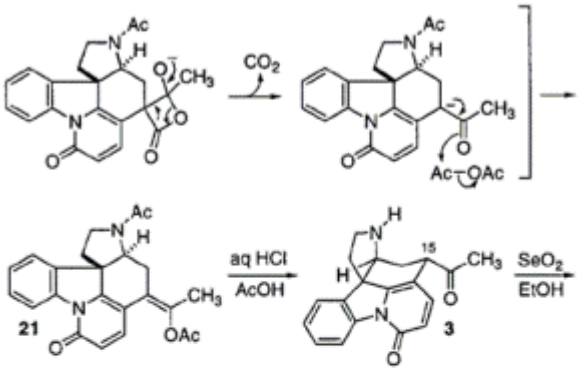


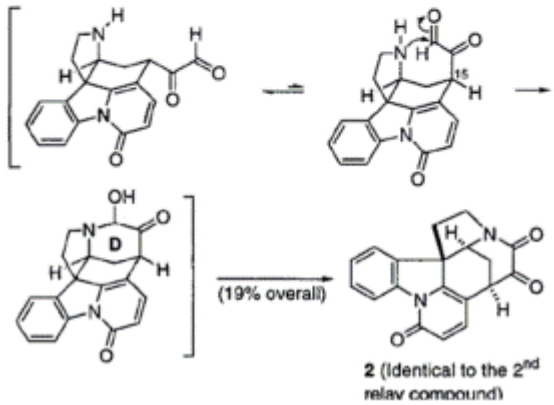
Closure of Ring D: Synthesis of Intermediate 2



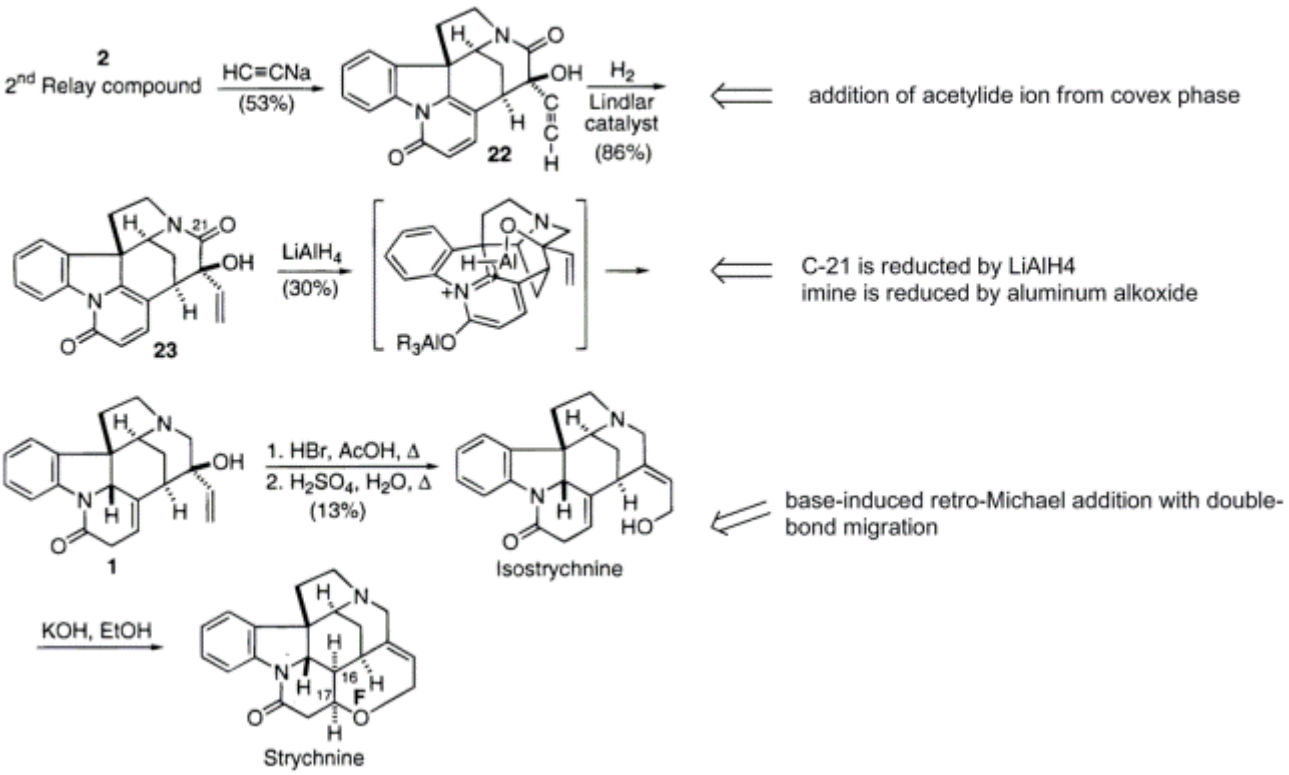
SeO_2 oxidation of 3







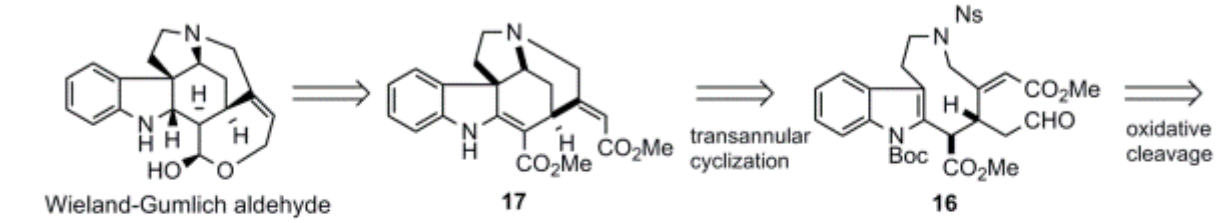
Introduction of the Hydroxyethylidene Side Chain



3. Fukuyama's total synthesis

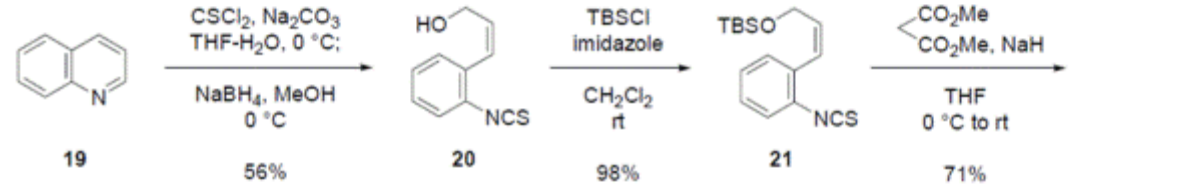
T. Fukuyama *et al.*, *J. Am. Chem. Soc.*, 2004, *126*, 10246

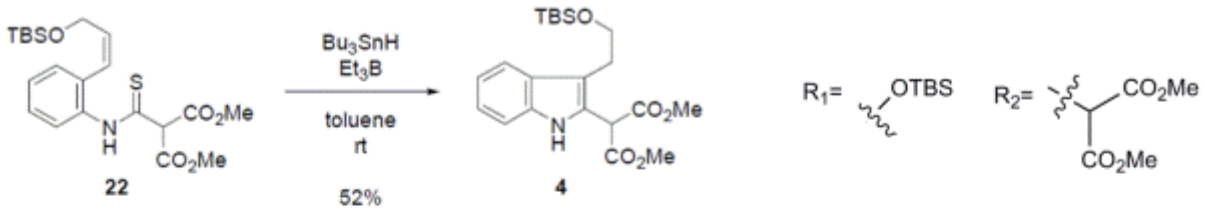
Retrosynthesis



Total Synthesis

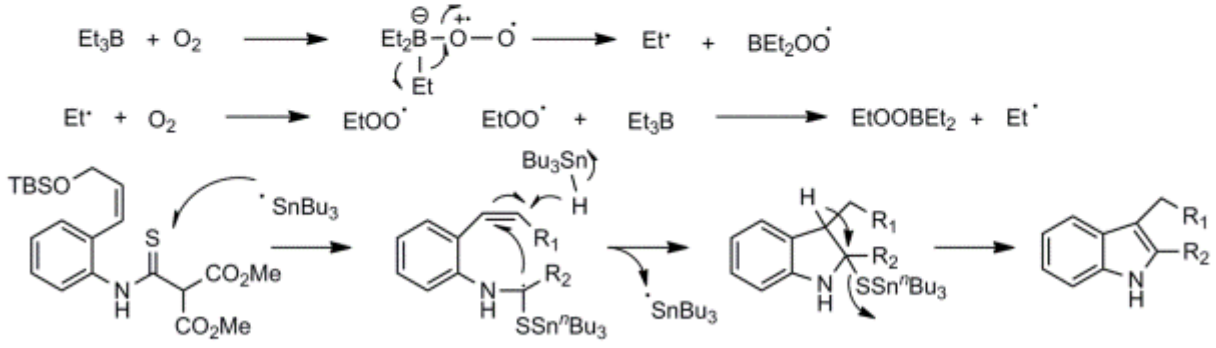
Formation of Indole 4





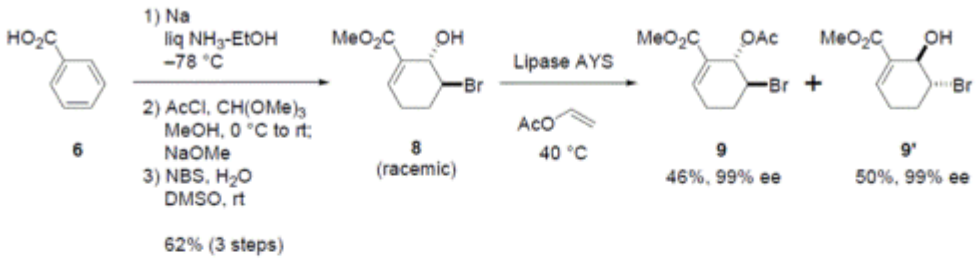
Fukuyama indole synthesis: to 4 from 22

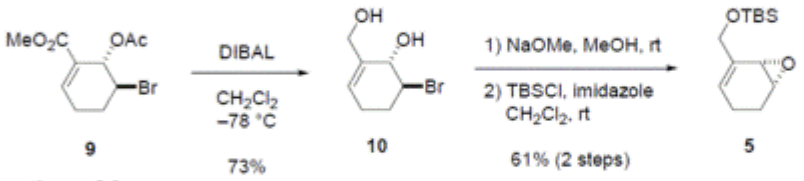
T. Fukuyama *et al. J. Am. Chem. Soc.* 1999, *121*, 3791



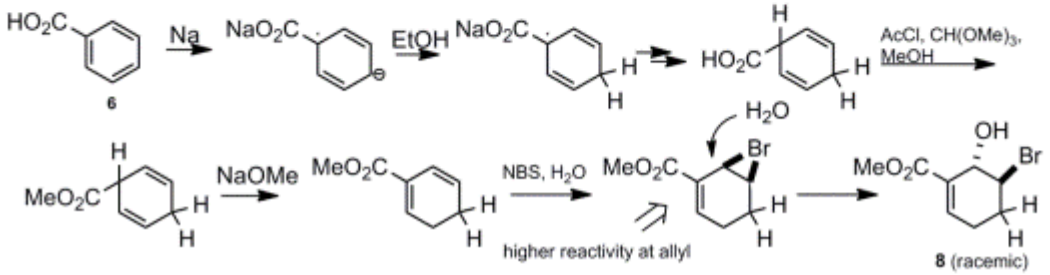
Formation of Vinyl Epoxide5

T. Fukuyama *et al.*, *J. Am. Chem. Soc.*, 2004, *126*, 10246

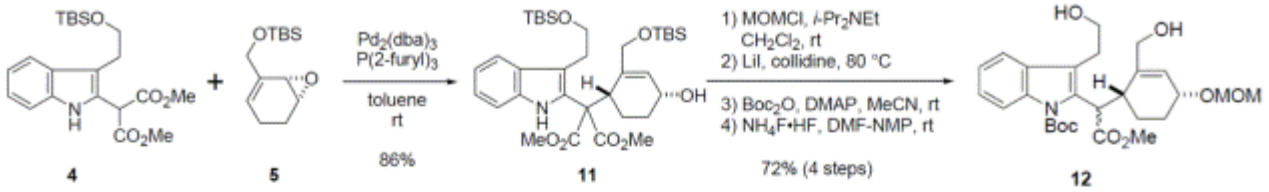




Formation of 8

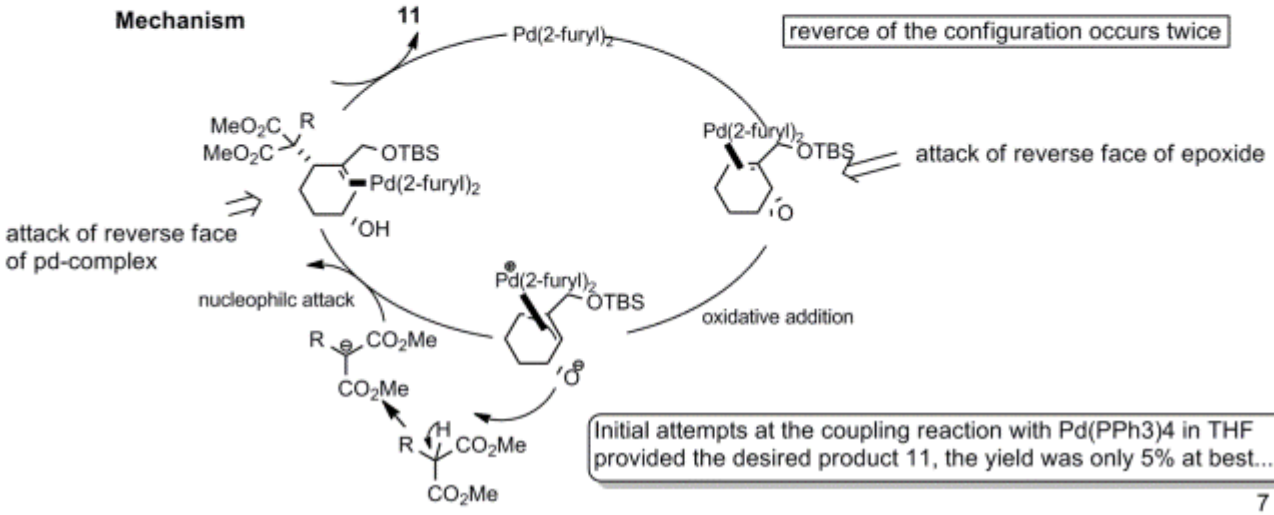


Formation of 12



Tsuji-Trost reaction: to 11 from 4 and 5

Mechanism

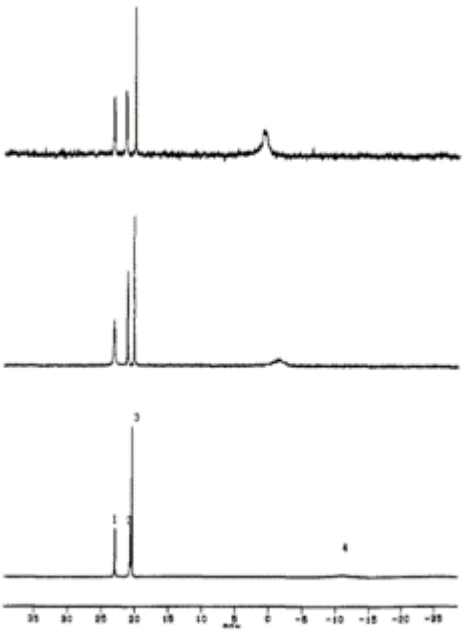


Initial attempts at the coupling reaction with Pd(PPh3)4 in THF provided the desired product 11, the yield was only 5% at best.....

Ligand effect by ^{31}P NMR (compared to PPh_3)

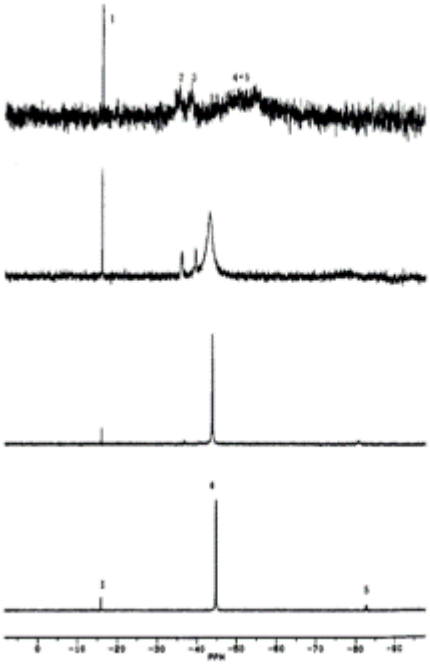
13 mM Pd_2dba_3, in THF with 4 equiv of PPh_3 or TFP per Pd

X) ^{31}P NMR study of Pd(0)-PPh_3 complexes:



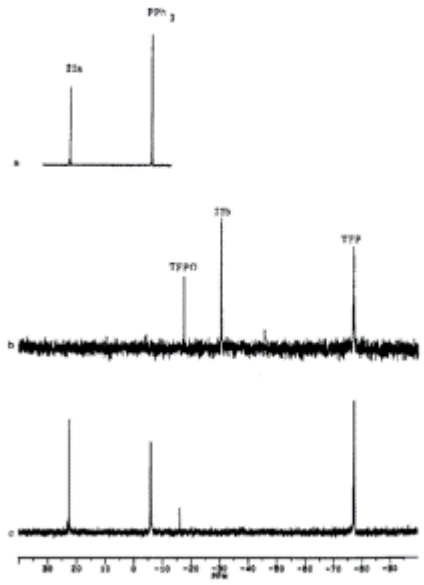
1,2 = Mixed Pd/dba/PPh_3 complexes; 3 = PPh_3 oxide;
4 = average of $Pd(PPh_3)_2$,$Pd(PPh_3)_3$, $Pd(PPh_3)_4$ and PPh_3,
Temperature:(a) 24 °C; (b) -23 °C (c) -78 °C.

Y) ^{31}P NMR study of Pd(0)-TFP complexes:



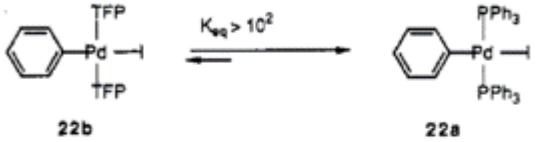
1 = TFP oxide; 2,3 = mixed Pd/dba/TFP complexes;
4 = $Pd(TFP)_4$;5 = TFP.
Temperature:(a) 24 °C; (b) -23 °C; (c) -43 °C; (d) -60 °C.

Z) ^{31}P NMR study of oxidative addition



[Pd] = ca. 25 mM in THF. Solutions:
(a) 1 equiv of PhI + 0.5 equiv of Pd_2dba_3 + 4 equiv of PPh_3,
(b) 1 equiv of PhI + 0.5 equiv of Pd_2dba_3, + 4 equiv of TFP;
(c) 4 equiv of PPh_3, added to solution b.

W) the equilibrium constant within 22b and 22a



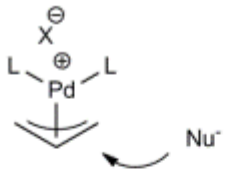
22b **22a**

These experimental results (X and Y) show that TFP binds Pd(0) more tightly than does PPh_3 .
And Z and W show PPh_3 binds Pd(II) more tightly than does TFP .
So, PPh_3 behaves as a effective σ-donor and poor π-acceptor while TFP does the reverse

V. Farina *et al. J. Am. Chem. SOC.* 1991, *113,* 9585

Ligand effect 2

Rahman *et al*. *Organometallics*, 1989, 8, *1*



Ligand of poor σ-donor and strong π-acceptor is suitable for being attacked by Nu^- because bond between PdL2 and allyl compound is weak

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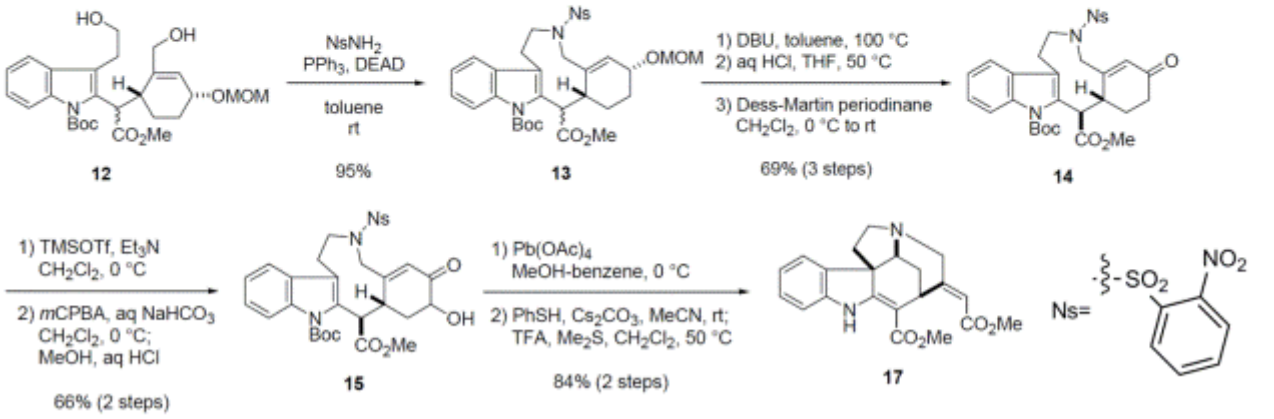
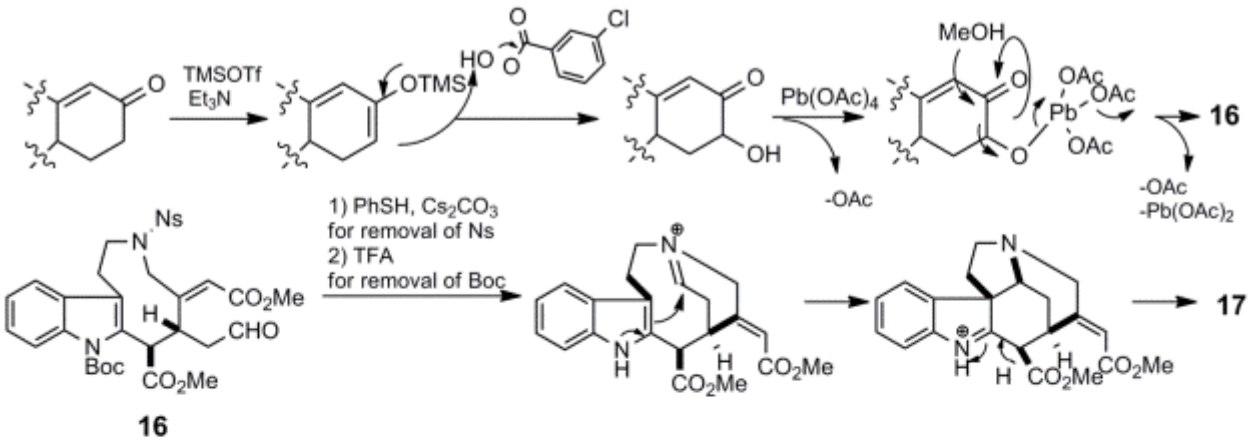
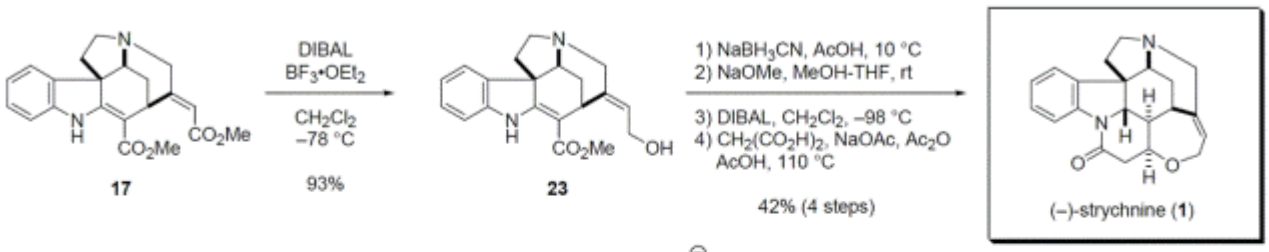
Formation of 17

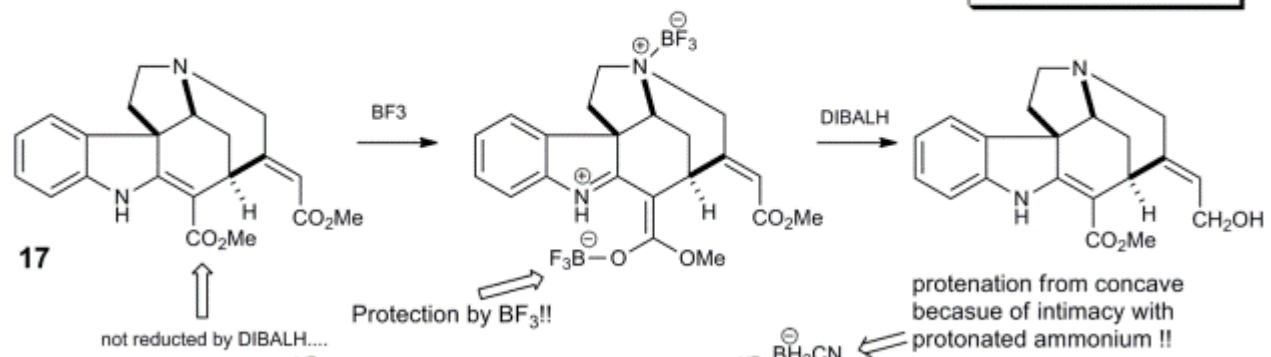


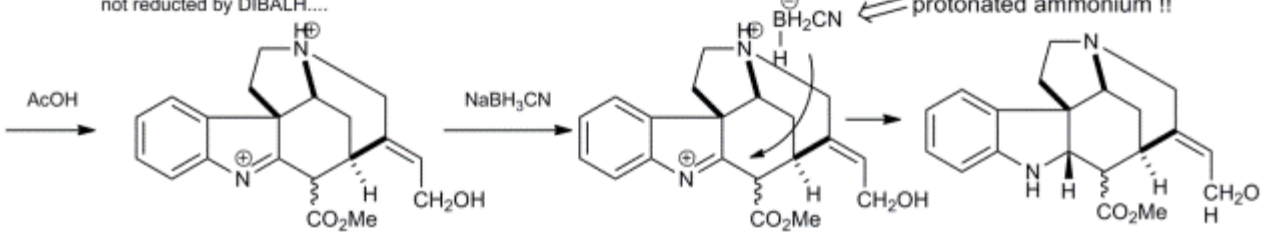


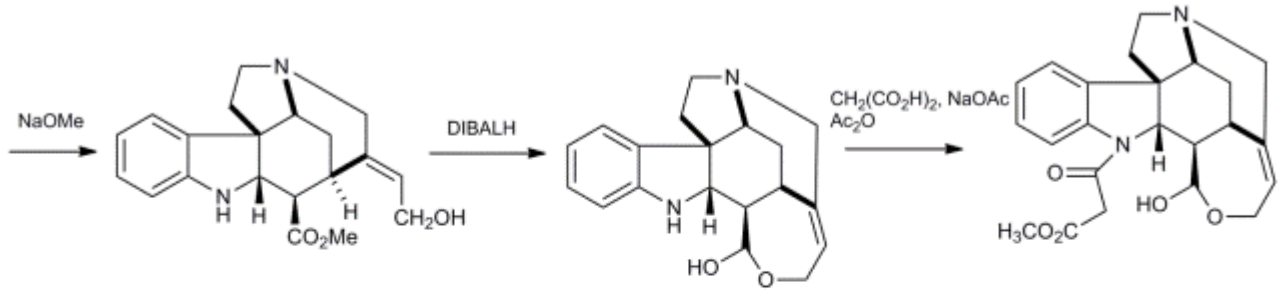
Formation of strychnine(1)

E. Kuehne *et al.*, *J. Org. Chem.* 1998, *63*, 9427
E. Kuehne *et al.*, *J. Org. Chem.* 1993,*58*, 7490

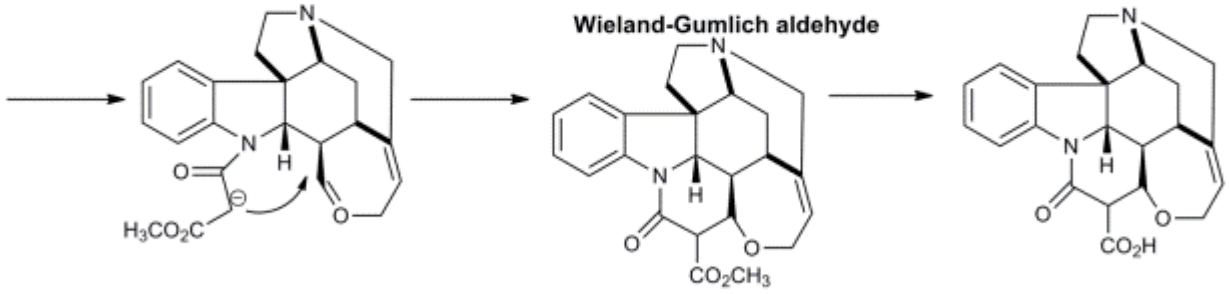








Wieland-Gumlich aldehyde

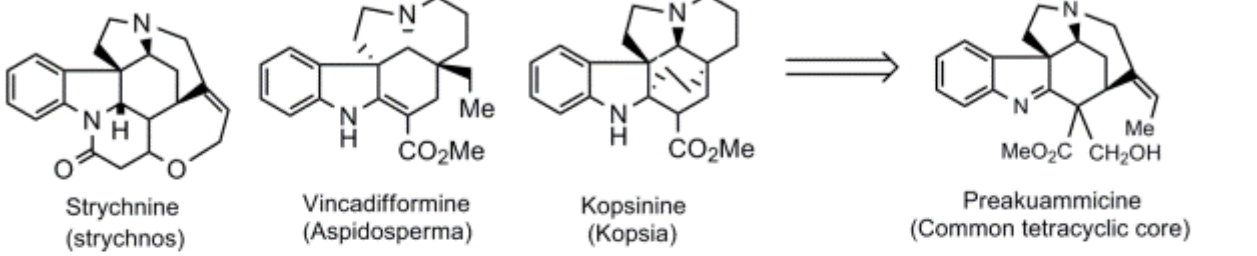


→ **(-)-Strychnine (1)**

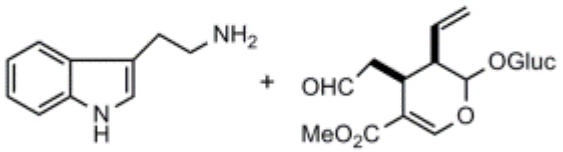
4. Macmillan's total synthesis

Macmillan *et al.*, *Nature*, *475*, 183

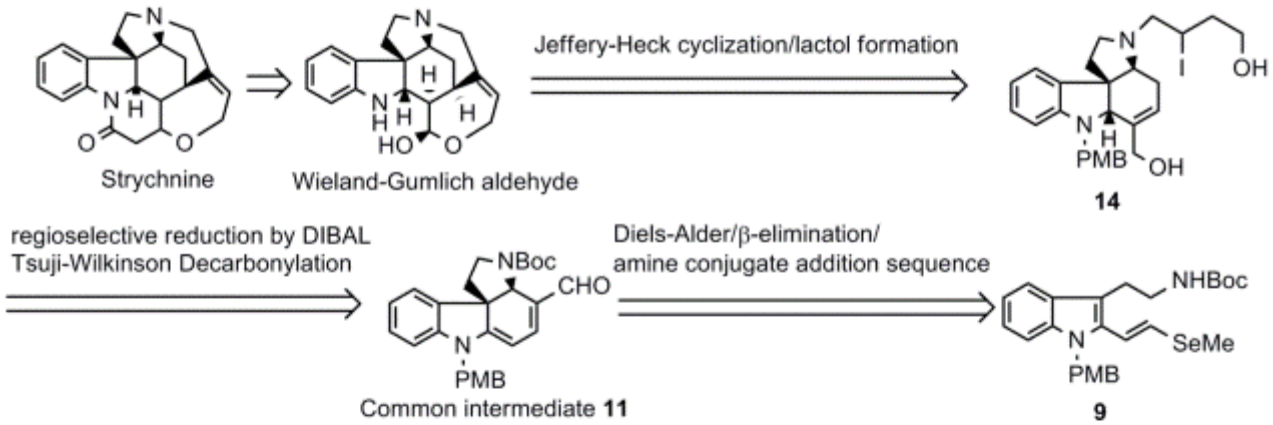
Background



preakuammicine is believed to share a biosynthetic precursor with a range of prominent Strychnos, Aspidosperma and Kopsia alkaloids. This common intermediate arises biosynthetically through a controlled enzymatic cascade involving a coupling of the precursors tryptamine and secologanin



Retrosynthesis



Total synthesis

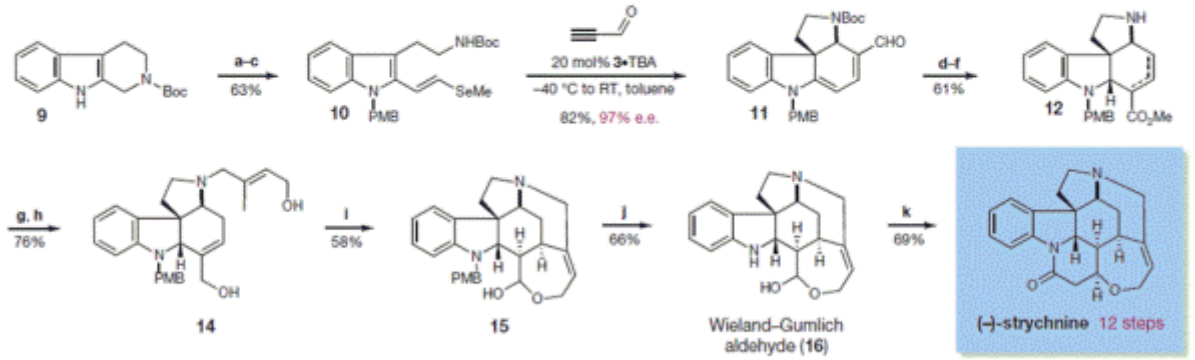
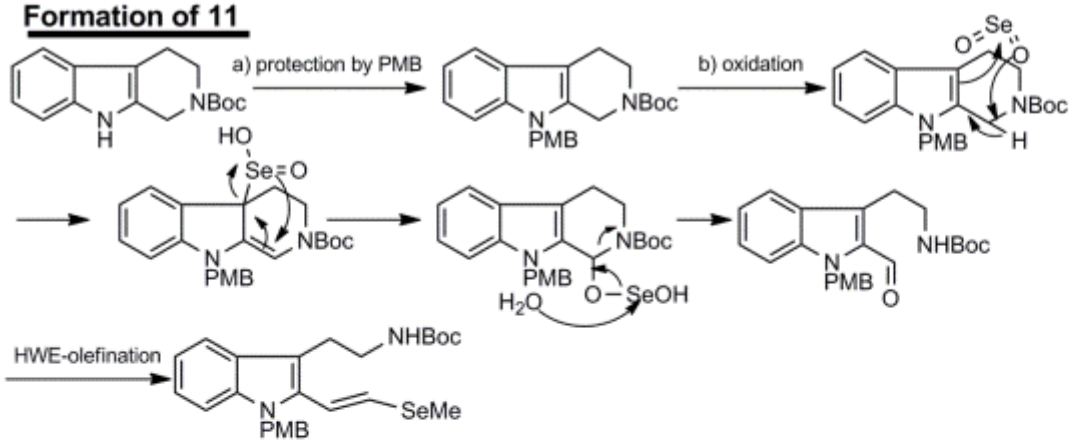
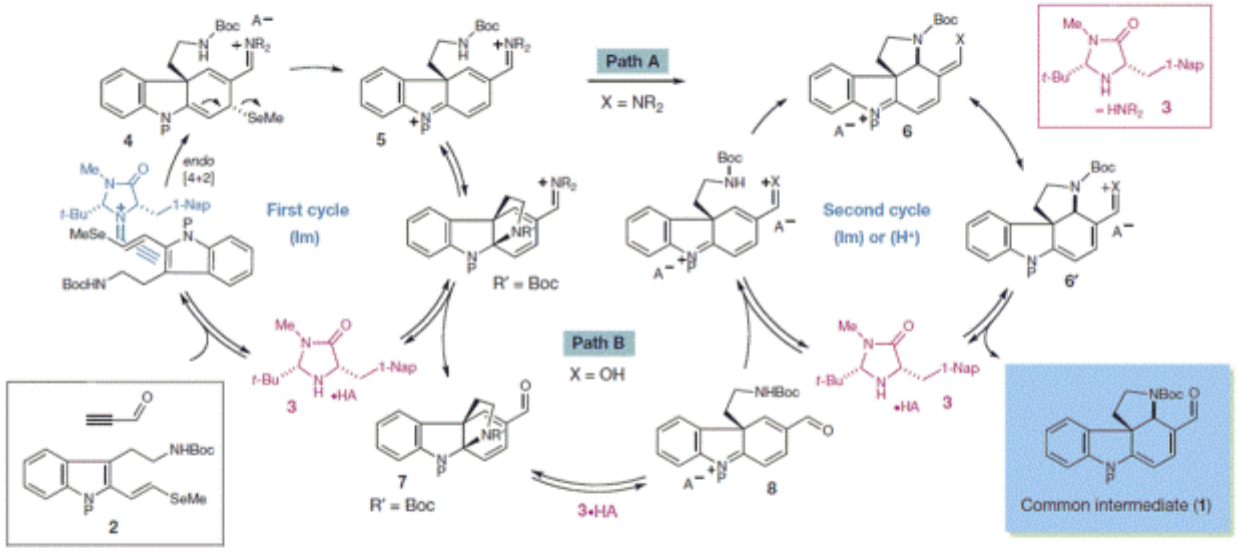


Figure 4 | Twelve-step enantioselective total synthesis of (−)-strychnine. Reagents and conditions are as follows. a, NaH, PMBCl, dimethylformamide (DMF), 0 °C. PMB, *para*-methoxybenzyl. b, SeO_2, dioxane, H_2O, 100 °C. c, $(EtO)_2P(O)CH_2SeMe$, 18-crown-6, potassium bis(trimethylsilyl)amide (KHMDS), tetrahydrofuran (THF), −78 °C to room temperature (RT, 23 °C). e.e., enantiomeric excess. d, $(Ph_3P)_3RhCl$, toluene, PhCN, 120 °C. e, $COCl_2$, Et_3N, toluene, −45 °C to RT, then MeOH, −30 °C to RT. f, DIBAL-H, CH_2Cl_2, −78 °C to RT, then trifluoroacetic acid (TFA), −78 °C to RT. g, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), K_2CO_3, DMF, (*Z*)-4-bromo-3-iodobut-2-enyl acetate (13), RT. h, DIBAL-H, CH_2Cl_2, −78 °C. i, 25 mol% $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, EtOAc, RT. j, PhSH, TFA, 45 °C. k, NaOAc, Ac_2O, AcOH, malonic acid, 120 °C. Ac, acetyl.

Formation of 11



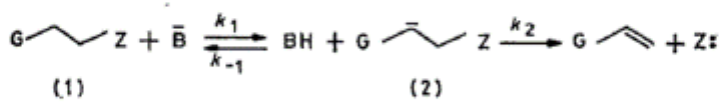
Formation of common intermediate ~Proposed mechanism of organocascade cycles



An organocascade reaction is expected to proceed through an organocatalytic Diels.Alder/β-elimination/amine conjugate addition sequencealong path A, involving iminium ion catalysis, or path B, involving Bronsted acid catalysis.

Pottential of leaving group

M. Stirling *et al.*, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1130



(1) (2)

SCHEME

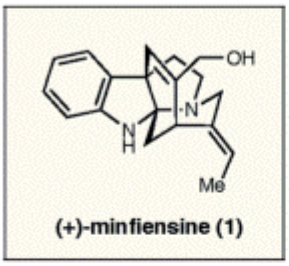
$$Rank = \log k_{obs} - \log k_1 = \log k_2 - \log k_{-1}$$

TABLE

Leaving-group ranks in elimination from carbanions [a]

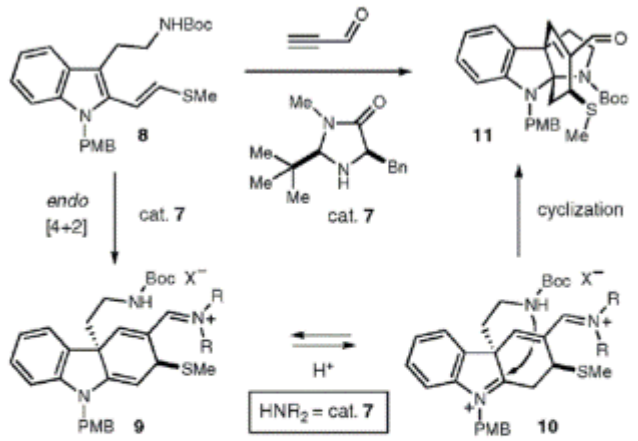
Z	$k_{obs.}$ [b]	$\log k_1$	Rank [c,d]
$\overset{+}{N}Me_2Ph$	1.21×10^4	4.5 [f]	10.7
SePh	3.5×10^{-1}	0.25 [g]	10.0
SPh	1.04×10^{-2} [j]	1.09 [h]	7.9

Cf) Pottential of leaving group ~Synthesis of minfiensine(1) by Macmillan



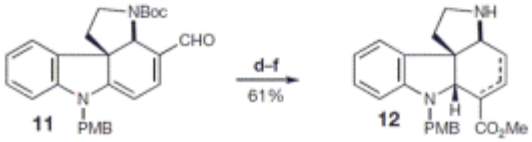
In case of β-SMe, not leaving!!! ⟹

Scheme 2. Enantioselective Catalytic Cascade Sequence to Core



Macmillan *et al*., *J. AM. CHEM. SOC.* 2009, *131*, 13606

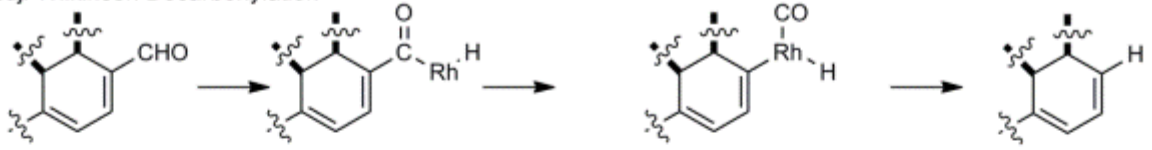
Regioselective reduction by DIBAL and Tsuji-Wilkinson Decarbonylation



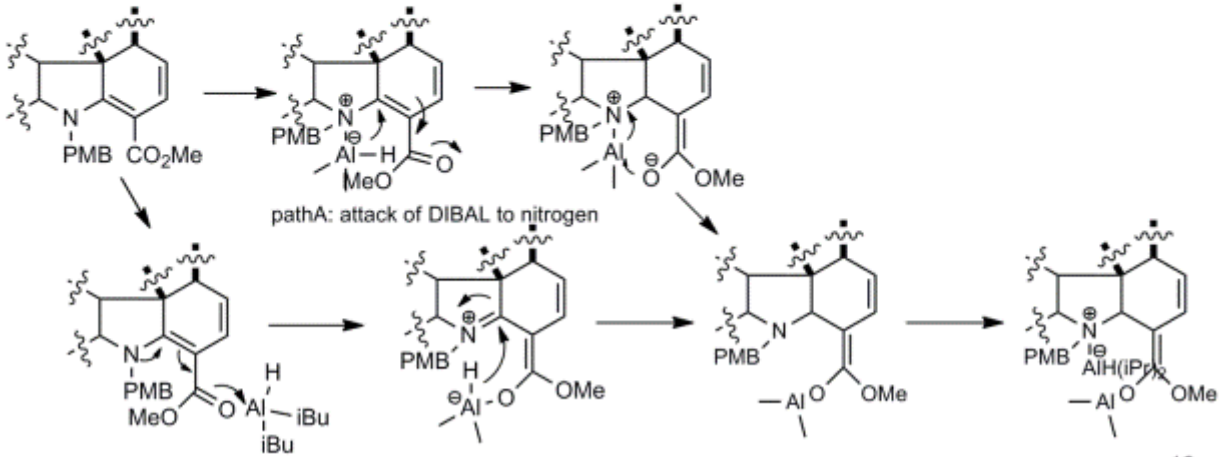
d, $(Ph_3P)_3RhCl$, toluene, PhCN, 120 °C.
e, $COCl_2$, Et_3N, toluene, −45 °C to RT, then MeOH, −30 °C to RT.
f, DIBAL-H, CH_2Cl_2, −78 °C to RT, then trifluoroacetic acid (TFA), −78 °C to RT.

d) Tsuji-Wilkinson Decarbonylation

J. Tsuji *et al*., *J. Am. Chem. Soc*. 1968, *90*, 99

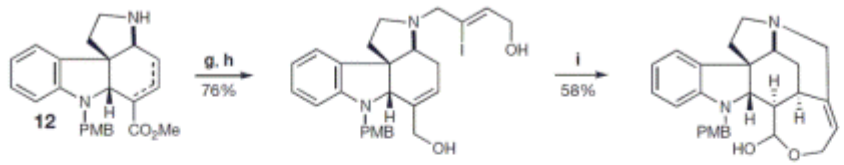


f) Regioselective reduction by DIBAL



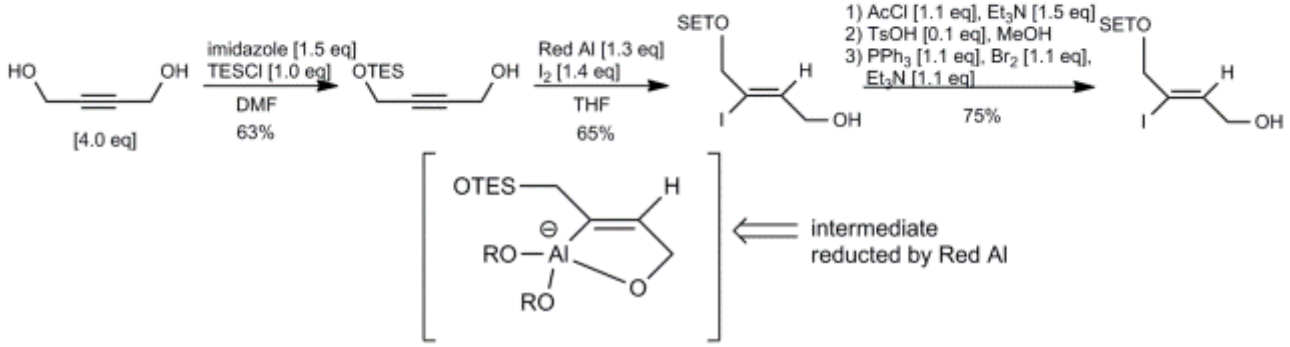
pathB: attack of DIBAL to carbonyl

Formation of 15

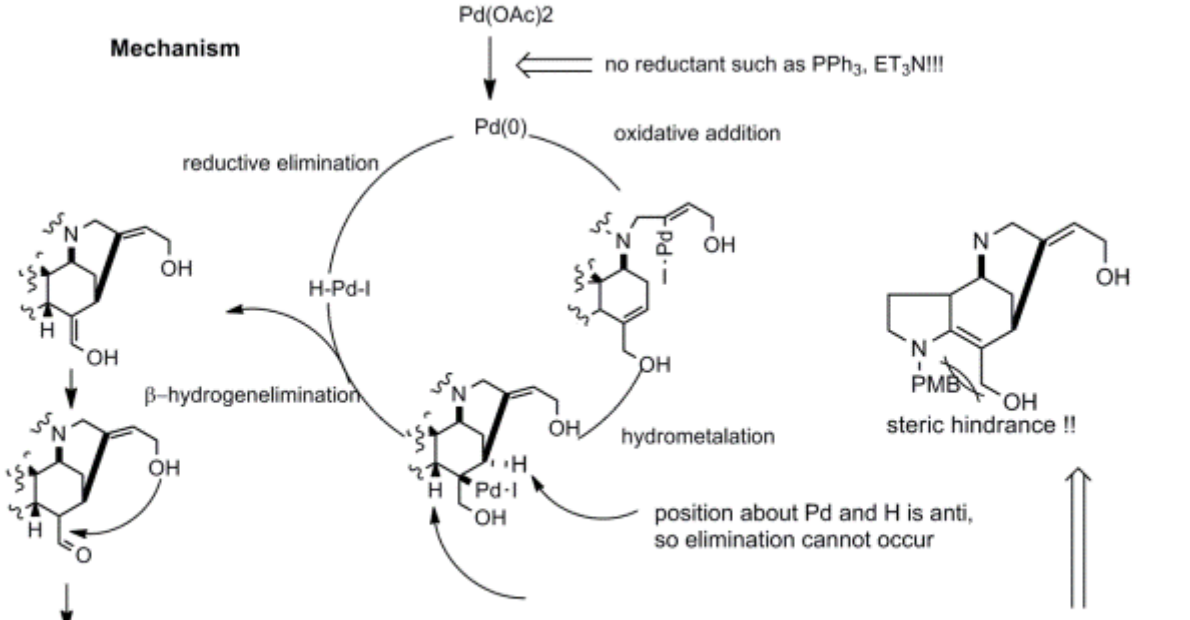


g, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), K_2CO_3, DMF, (Z)-4-bromo-3-iodobut-2-enyl acetate (**13**), RT.
h, DIBAL-H, CH_2Cl_2, −78 °C.
i, 25 mol% $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, EtOAc, RT.

Synthesis of (Z)-4-bromo-3-iodobut-2-enyl acetate (13)



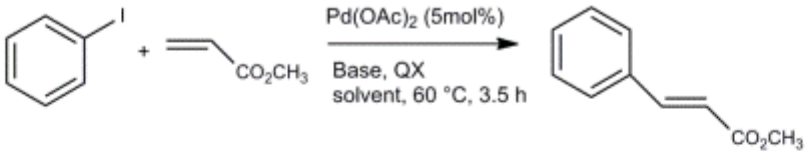
Jeffery-Heck cyclization/lactol formation



the PMB protecting group was critical in facilitating regioselective β-hydride elimination. Such a high degree of regiocontrol presumably arises from the allylic strain that accompanies formation of the N-PMB-substituted enamine, a destabilizing element

Jeffery condition

T. Jeffery *et al.*, *Termhedron*.1996, *52*,10113



Effect of Tetraalkyiammonium Salts on Pd-catalysed Arylation of Methyl Acrylate in the presense of phosphine ligand

Entry	Base	Solvent [b]	QX	Molecular sieves	Yield (%) [c]
1	$NaHCO_3$	CH_3CN	-	no	10
2	$NaHCO_3$	CH_3CN	$n\text{-}Bu_4NCl.xH_2O$ [d]	no	57
3	$NaHCO_3$	CH_3CN	$n\text{-}Bu_4NCl$ [e]	no	70
4	$NaHCO_3$	CH_3CN	$n\text{-}Bu_4NCl$ [e]	yes	99
5	$NaHCO_3$	CH_3CN	$n\text{-}Bu_4NHSO_4$	yes	98
6	$KHCO_3$	CH_3CN	$n\text{-}Bu_4NHSO_4$	yes	99
7	$KHCO_3$	CH_3CN	$n\text{-}Bu_4NBr$	yes	67
8	$NaHCO_3$	DMF	-	yes	16
9	$NaHCO_3$	DMF	$n\text{-}Bu_4NCl$ [e]	yes	99
10	$NaHCO_3$	DMF	$n\text{-}Bu_4NHSO_4$	yes	99
11	$KHCO_3$	DMF	$n\text{-}Bu_4NHSO_4$	yes	93
12	$KHCO_3$	DMF	$n\text{-}Bu_4NBr$	yes	80

a) See General Procedure (Method I). b) HPLC grade solvents. c) determined by GLC against an internal standard. d)"Tetrabutylammonium chloride hydrate 98%" from Aldrich. e) "Tetra-n-butylammonium chloride 98%" from Lancaster.

Effect of Tetraalkyiammonium Salts on Pd-catalysed Arylation of Methyl Acrylate in the absence of phosphine ligand. ($NaHCO_3$ as base,all Entry in Molecular sieves)

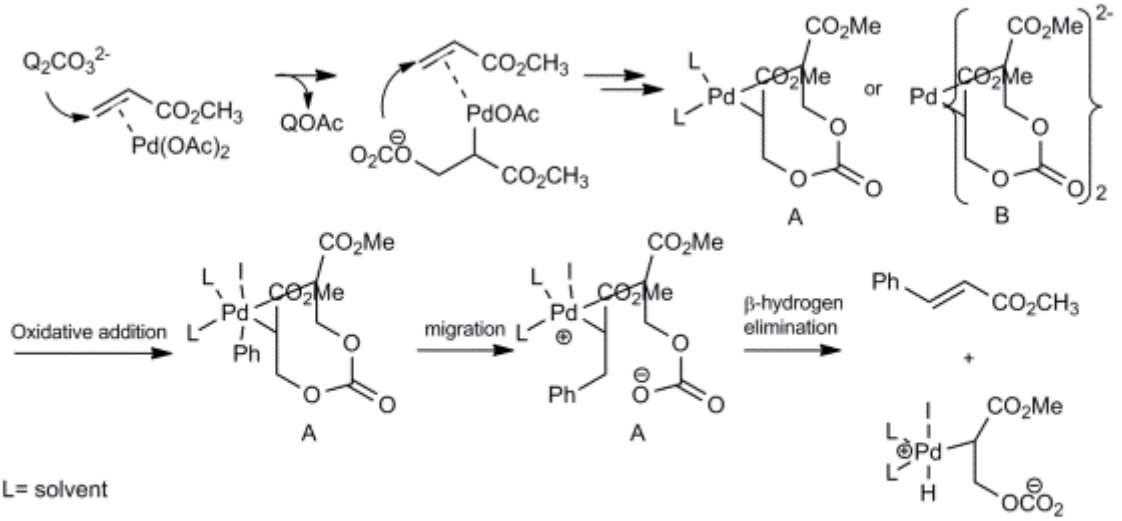
Entry	Solvent	QX	Yield (%) [b]
1	CH_3CN	-	3
2	CH_3CN	$n\text{-}Bu_4NCl$ [c]	90
3	CH_3CN	$n\text{-}Bu_4NHSO_4$	45
4	CH_3CN	$n\text{-}Bu_4NBr$	20
5	DMF	-	5
6	DMF	$n\text{-}Bu_4NCl$ [c]	99
7	DMF	$n\text{-}Bu_4NHSO_4$	99
8	DMF	$n\text{-}Bu_4NBr$	62

a) See General Procedure (Method I, with 4Å molecular sieves). b) determined by GLC against an internal standard. c) "Tetra-n-butylammonium chloride 98%" from Lancaster.

Jeffery found that Heck reaction proceeded in the absence of phosphine ligand.

Proposed Mechanism (Pd(II)↔Pd(IV))

L. Shaw., *New J. Chem*., 1998, 77



L= solvent

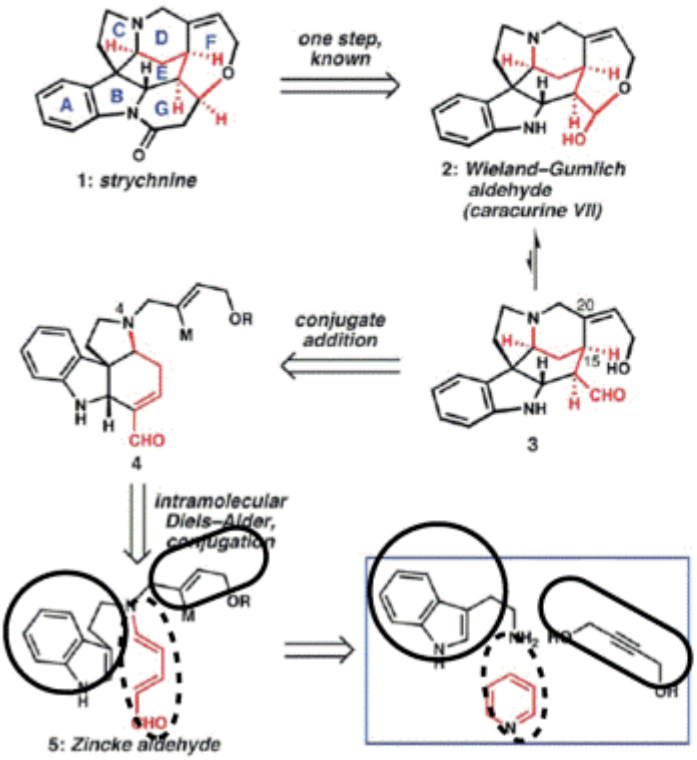
At first, carbonate attack C=C bonds, generate complex A or B.
After that, Oxidative addition, migration with loss of the carbonate ion and β-hydrogen elimination proceeds.

But,the substrate in synthesis by Macmillan is different from methyl acrylate in nature of olefin.
So, I think that proposed mechanism is not applicable to this case

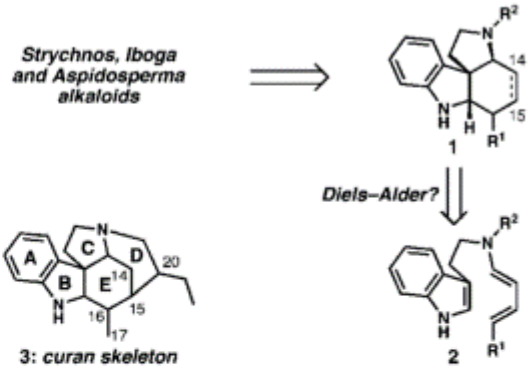
5. Vanderwal's total synthesis

Retrosynthesis

D. Vanderwal *et al.*, *Chem. Sci.*, 2011, *2*, 649



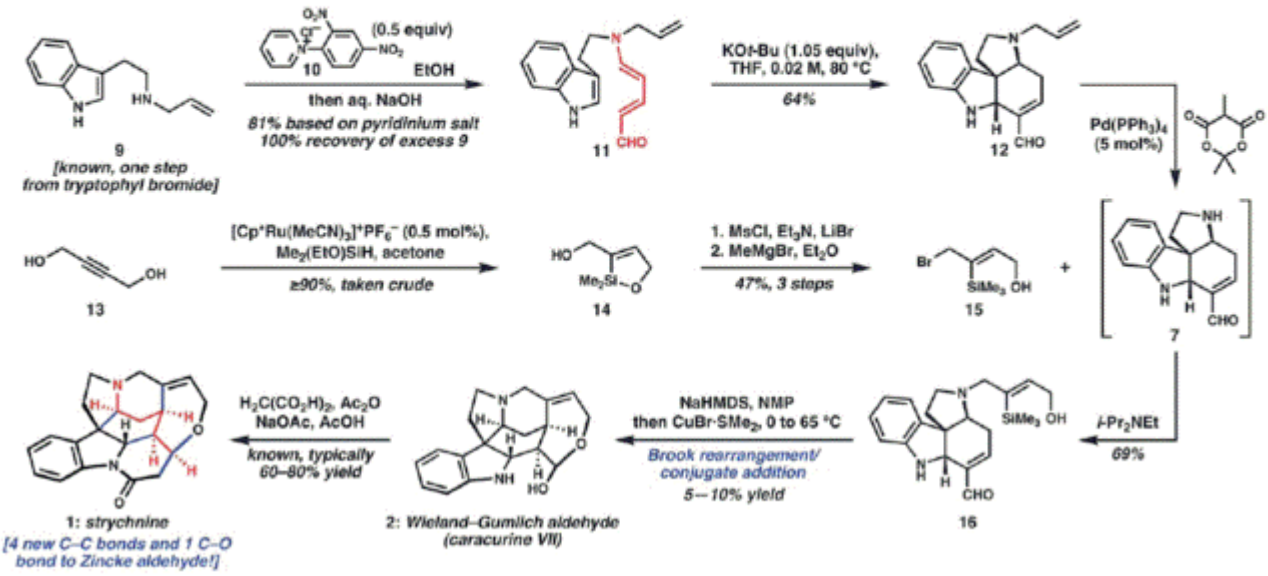
direct synthesis of important core structure 1



it constitutes the ABCE ring system of the curan skeleton (3) common to most Strychnos alkaloids. Obscured by the lack of unsaturation at the C14-C15 bond of these alkaloids is the possibility of a direct synthesis of this important core structure via an intramolecular Diels-Alder reaction of a tryptamine-derived aminodiene such as 2. Such an approach is confrontedby two major challenges: (1) indoles are notoriously poor dienophilic components for [4 + 2] cycloadditions; (2) most aminodienes are electron-rich and would be poorly reactive toward the electronrich indole.2 For an approach of this type, an ideal strategy avoids indole protection and places an electron-deficient C-atom at R1 to allow for straightforward elaboration toward natural product targets.A tryptamine-derived Zincke aldehyde fulfills these criteria.

D. Vanderwal *et al.*, J. AM. CHEM. SOC. 2009, 131, 3472

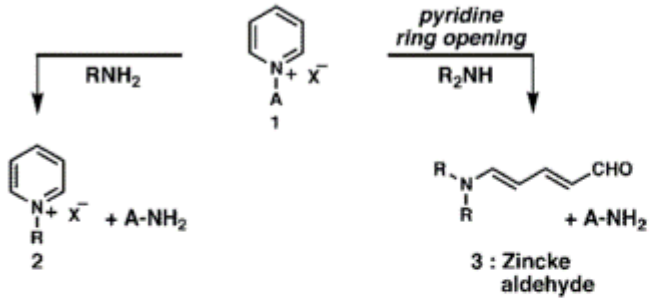
Total synthesis



Zinkle aldehyde

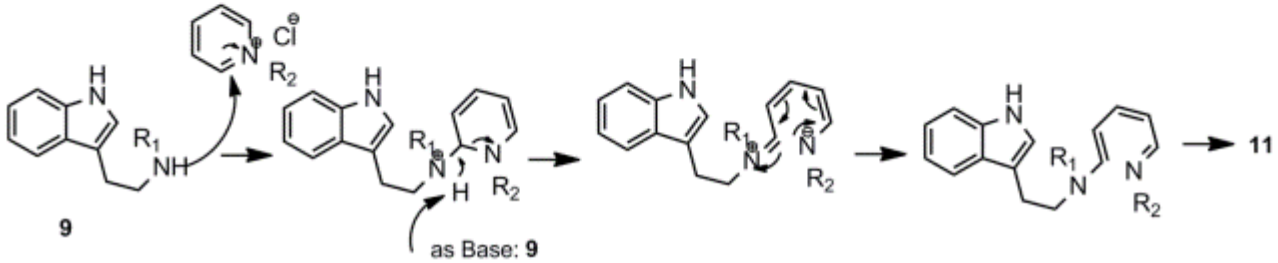
D. Vanderwal *et al., J. AM. CHEM. SOC.* 2009, *131*, 3472

Figure. Aminolysis of pyridinium salts. A = activating group.



The ring-opening reaction of pyridinium salts dates back over a century to the pioneering work of Zincke and Konig. Activation of pyridines as their pyridinium salts followed by treatment with primary amines, leads to the formation of new pyridinium salts (2), while the use of secondary amines cleanly affords the products of ring opening.

Mechanism of pyridine ring opening



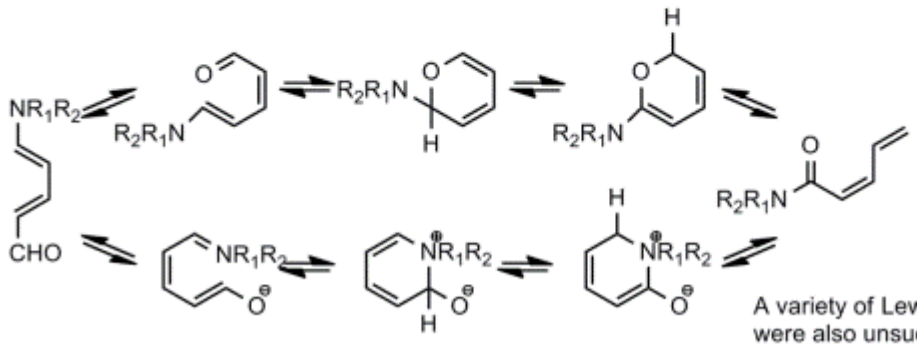
Intramolecular Diels-Alder

Try In condition of 160 °C

D. Vanderwal *et al., J. Am.Chem. Soc.* 2008, *130*, 7560

Attempted Intramolecular Diels-Alder Cycloaddition of 11 Yielded Unexpected Rearrangement Product A.....

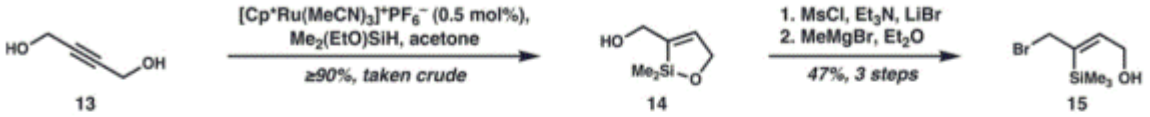
Two Reasonable Pericyclic Cascade Mechanisms



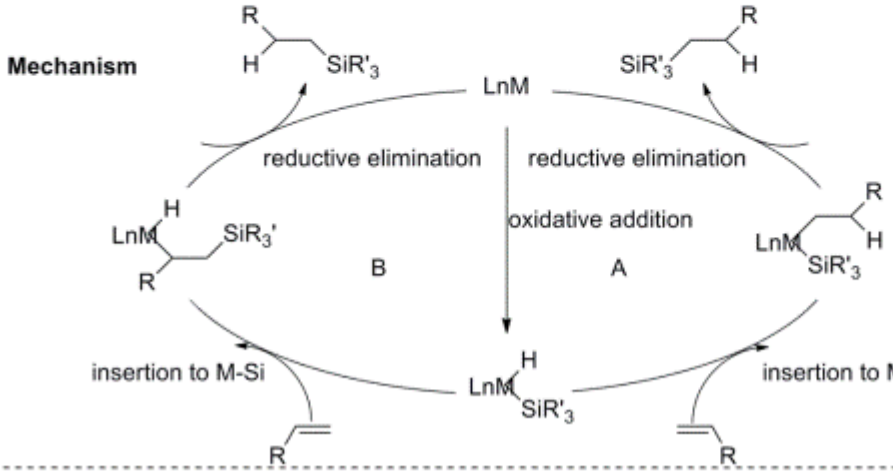
A variety of Lewis acids and protic acids were also unsuccessful in promoting the desired cycloaddition.....

Hydrosilylation using Cationic Ruthenium Complex

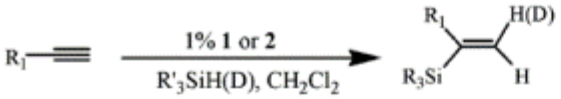
M. Trost *et al. J. AM. CHEM. SOC.* 2003, *125*, 11578



Two mechanisms of hydrosilylation have been widely accepted,the Chalk-Harrod and the modified Chalk-Harrod mechanisms. Linear anti-Markovnikov products are obtained and the products is almost syn addition of silane. The reaction tend to proceed via cycleA using Pd,Pt catalyst, and via cycleB using Ru,Rh catalyst

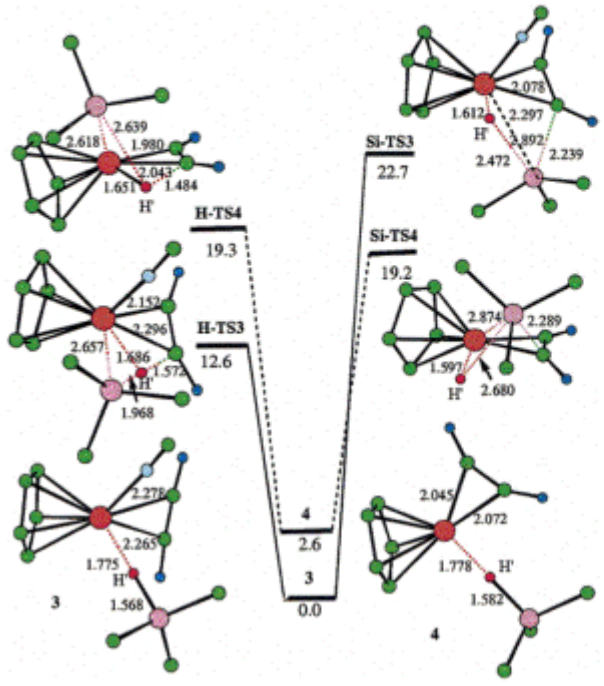


But, using [CpRu(MeCN)3]PF6 (1) and [Cp*Ru-(MeCN)3]PF6 (2).....

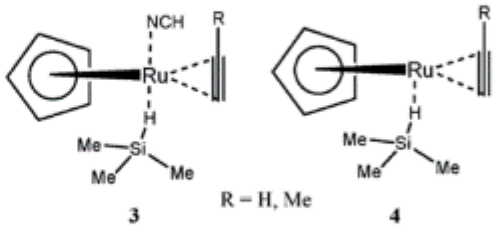


produce the branched, Markovnikov and trans-addition of silane products!!!

Investigations on the hydrosilylation of system 3 and 4 using density functional theory calculations.



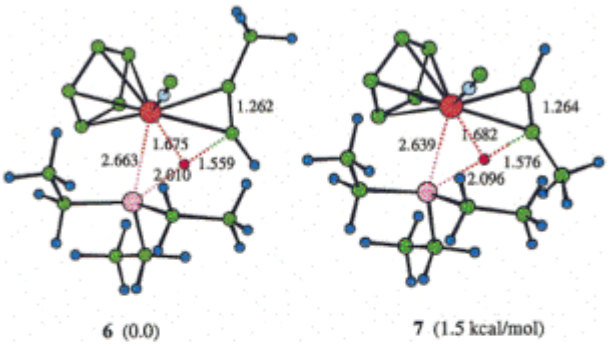
In system 3 and 4,Which is H-insertion and Si-insertion more favored?



⟸ Hydride insertion is favored with a nitrile ligand, while silyl insertion is favored in the absence of a nitrile. Overall, hydride insertion (H-TS3) is much favored over silyl insertion.

Figure 1. Calculated precursor complexes (**3**, **4**, R = H) and transition structures resulting from hydride and silyl insertion with relative free energies (kcal/mol) and selected bond distances (Å). Methyl, nitrile, and Cp hydrogen atoms are omitted for clarity.

Markovnikov and anti- transition structure



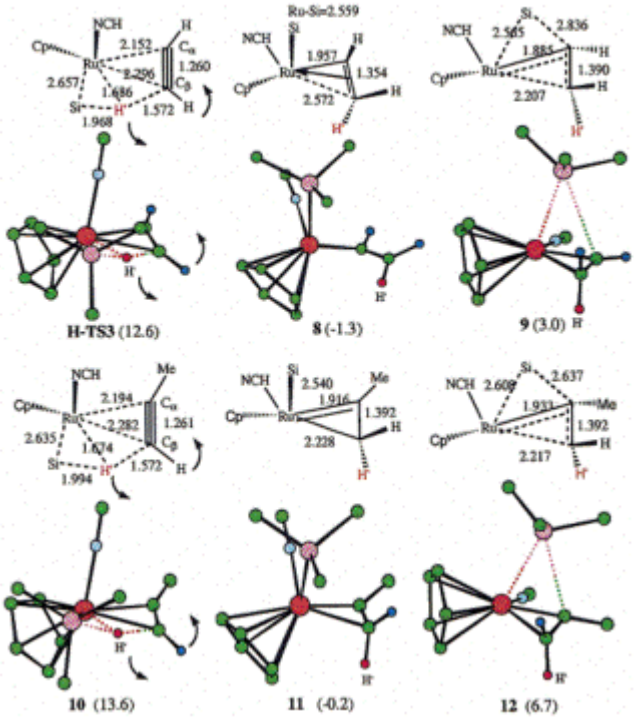
6 (0.0) **7** (1.5 kcal/mol)

Figure 2. The calculated hydride-insertion transition structures for the reaction of triethylsilane with propyne. The hydrogen atoms of the Cp group and nitrile are omitted for clarity.

⇑

Structure 7 is apparently destabilized by the steric interaction between the bulky silyl group and the propyne methyl group. Markovnikov product is calculated to be more stable than transition structure 7, which gives the anti- product, by about 1.5 kcal/mol.

trans-addition of silane by a counterclockwise rotation of the Cα-Cβ bond



H-TS3 (12.6) **8** (-1.3) **9** (3.0)

10 (13.6) **11** (-0.2) **12** (6.7)

Figure 3. Calculated hydride-insertion transition structures (**H-TS3** and **10**), η^2-vinylruthenium (**8**) and metallacyclopropene (**11**) intermediates, and α-silyl migration transition structures (**9** and **12**) for the reaction of Cp-Ru(HCN) trimethylsilane with acetylene and propyne (**3**, R = H and Me). The values in parentheses are calculated relative free energies with respect to their precursor complexes. The hydrogen atoms of the Cp and methyl groups and nitrile are omitted for clarity.

After transferring of the H' to Cβ so that a planar η1-vinylruthenium structure is formed, the formation of both 8 and 11 was accompanied by a counterclockwise rotation of the Cα-Cβ bond so that the transferring hydride became anti to the silyl group. ⟹

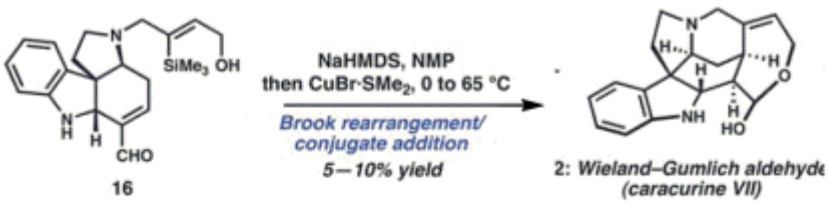
Table 2. Calculated Geometrical Parameters and Relative Energies (kcal/mol) of Structures on the Potential Energy Surface of $C_\alpha-C_\beta$ Bond Rotation of the Metallacyclopropene Intermediate (**11**) (Distances Are in Angstroms and Angles Are in Degrees)

H′CCRu	−91° (**14**)	−60°	−30°	−7° (**13**)	30°	60°	85° (**11**)
RuC_α	1.909	1.947	1.992	2.078	1.986	1.940	1.926
RuC_β	2.228	2.385	2.564	2.451	2.519	2.345	2.228
$C_\alpha C_\beta$	1.392	1.370	1.351	1.313	1.356	1.376	1.392
CpRuN[a]	125	127	128	129	126	122	121
CpRuSi	111	107	106	109	111	113	114
$CpRuC_\alpha$	122	124	124	119	126	135	139
$CpRuC_\beta$	148	148	149	135	119	119	118
$C_\beta C_\alpha RuSi$	13	7	3	−27	−59	−65	−68
$CpRuC_\alpha C_\beta$	145	146	151	129	88	79	74
$r_{H/H}$[b]	2.33 (2.36)	2.29 (2.33)	2.26 (2.31)	2.38	2.88	2.57	2.44
E_{rel}[c]	1.0	3.7	6.2	9.8	3.8	1.2	0.0

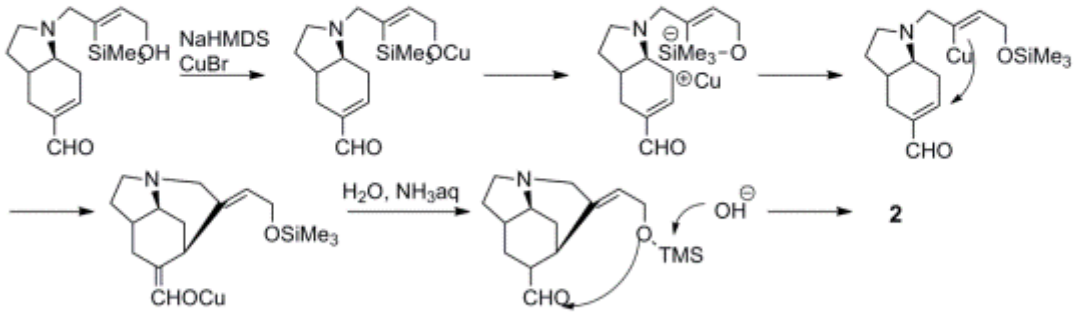
[a] Cp is the centroid of the Cp ring. [b] The shortest H/H distance between the trimethylsilyl and C_bH_2 groups. [c] The relative energy is in terms of electronic energy.

⟸ **13** is the planar structure. the counterclockwise rotation of the Cα-Cβ bond (-7°, 30°, 60°, 85°) more favored than the Cα-Cβ bond rotates in a clockwise manner(-7°, -30°, -60°, -91°).

Brook rearrangement/conjugated addition

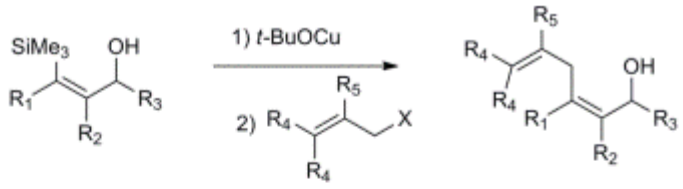


Mechanism

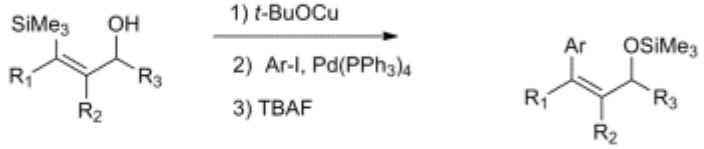


The authors believe that the conversion of 16 to 2 is self-limiting in the sense that the presence of acidic protons in the substrate and/or product leads to quenching of the key reactive organometallic reagent, resulting in an inefficient and rather irreproducible reaction.
Because the mass balance consists largely of the product of protodesilylation, which likely occurs by Brook rearrangement/hydrolysis of the resulting vinyl metal.

Precedents



Takeda *et al.*, *J. Org. Chem.*, 2002, *67*, 8450



6. Summary

Reports of 18 total synthesis (11 racemic syntheses, 7 asymmetric syntheses) have been presented.

> "Admittedly, by one whose special familiarity with the intricacies of its structure and behavior might excuse a certain prejudice, but with six nuclear asymmetric centers and seven rings constituted from only twenty-four skeletal atoms, the case is a good one" - R. B. Woodward et al,. *Tetrahedron*, 1963, *19*, 247