C-H Activation in Total Synthesis

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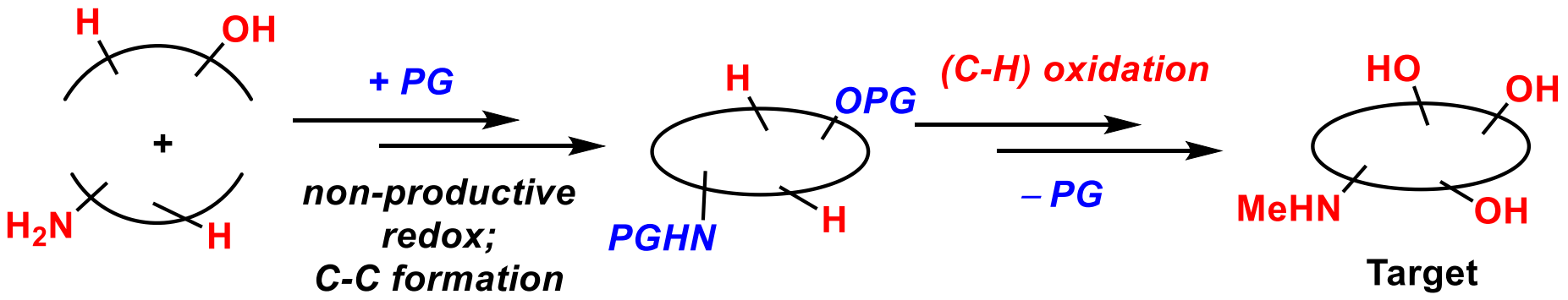
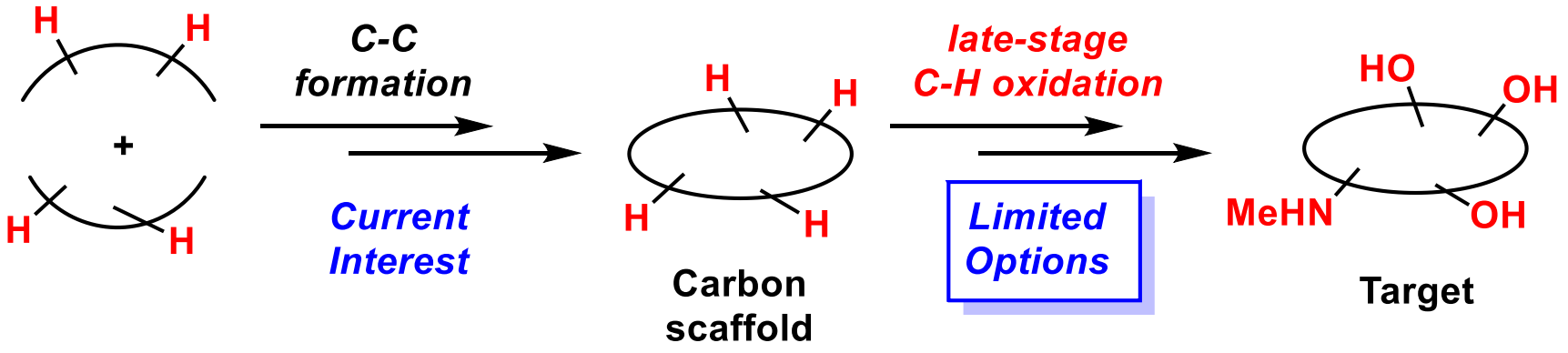
21st Jun. 2014

Does a late-stage activation of unactivated C-H bond shorten a total synthesis ??

Conventional approach (with or without C-H Functionalization)



Baran's 2-Phase Route (*Nature* 2009, 459, 824)



Contents

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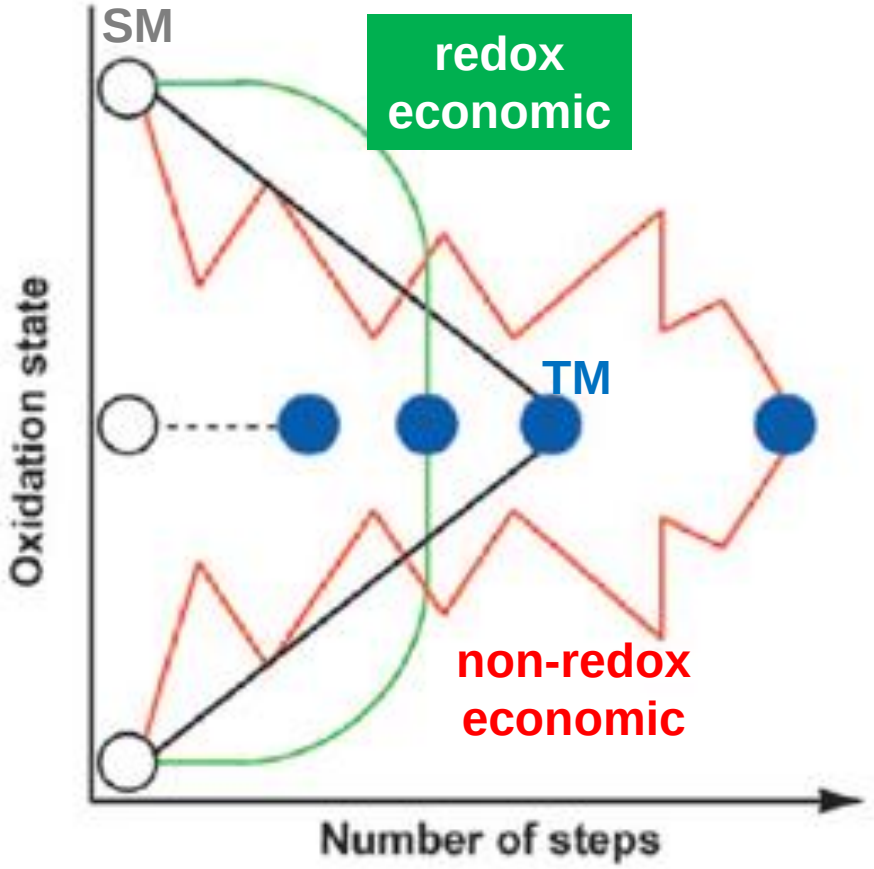
How to reduce redox steps ?



Baran, P. S. *et al.*
Angew. Chem. Int. Ed. **2009**, *48*, 2854.

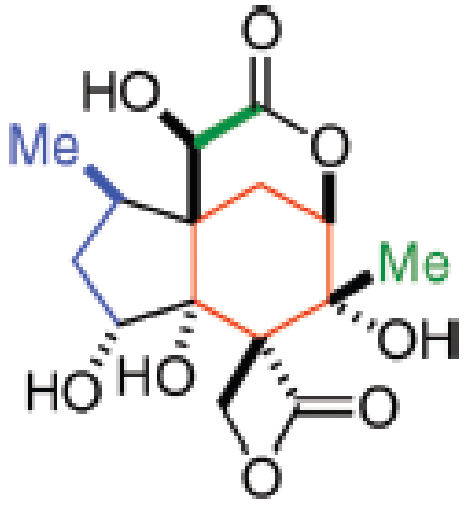
Redox Steps =

- **Difficult to scale up**
- **Noxious byproducts**

" Linear elevation of oxidation state is good."

How about starting from SM with higher oxidation state ?

Total Synthesis of (-)-Anisatin



anisatin

Synthetic challenges

- **8 contiguous stereogenic centers**
- **oxabicyclo [3,3,1] skelton**
- **spiro β-lactone**

Total Synthesis

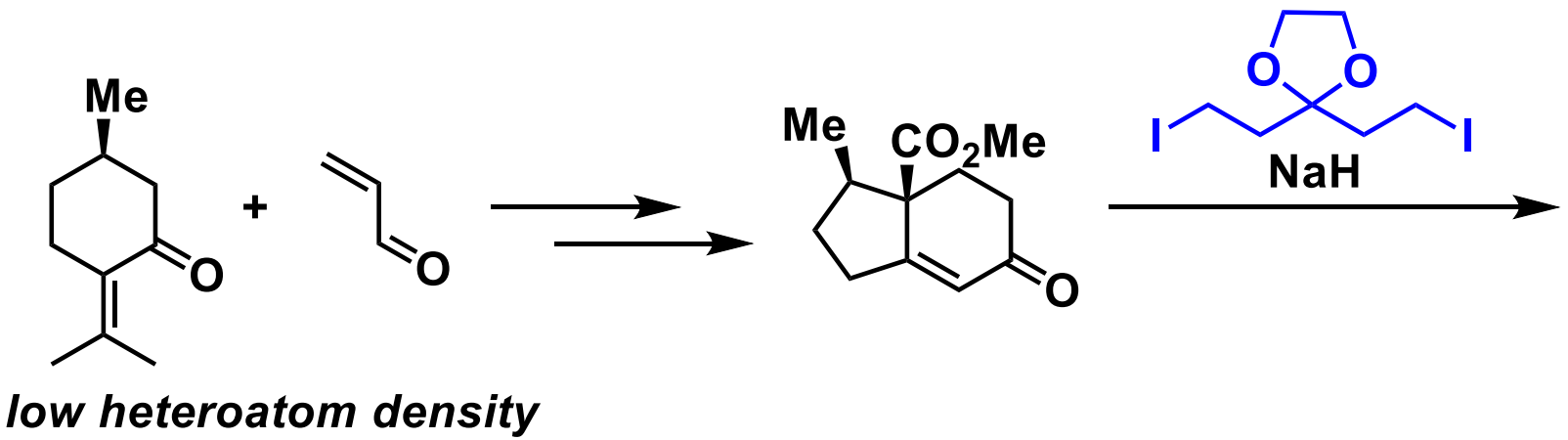
Yamada K
(*J. Am. Chem. Soc.* 1990, 112, 9001.)

SM with low [O]-state

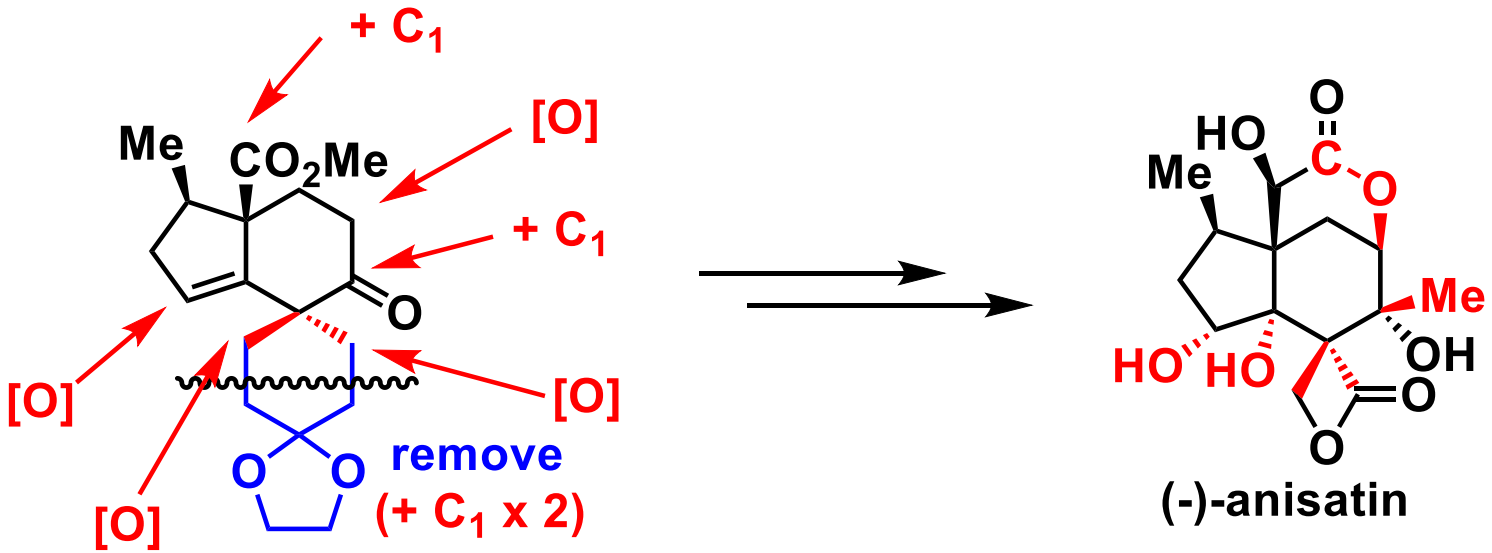
Fukuyama T
(*Org. Lett.* 2012, 14, 1632)

SM with high [O]-state

Total Synthesis of (-)-Anisatin

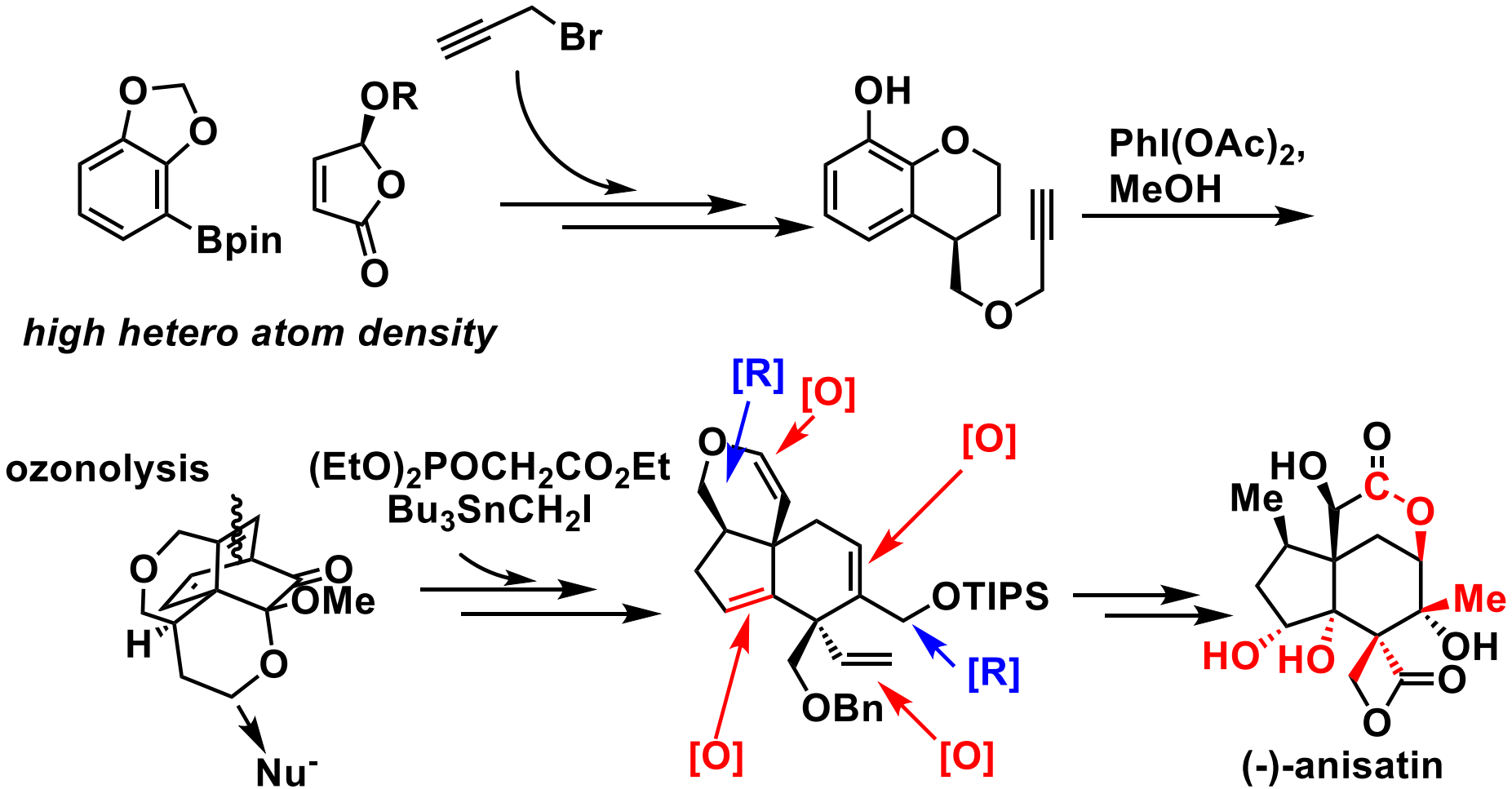


low heteroatom density



Yamada, K. *et al. JACS* 1990, 112, 9001.

Total Synthesis of (-)-Anisatin



Fukuyama, T. *et al. OL* 2012, 14, 1632

Total Synthesis of (-)-Tetrodotoxin

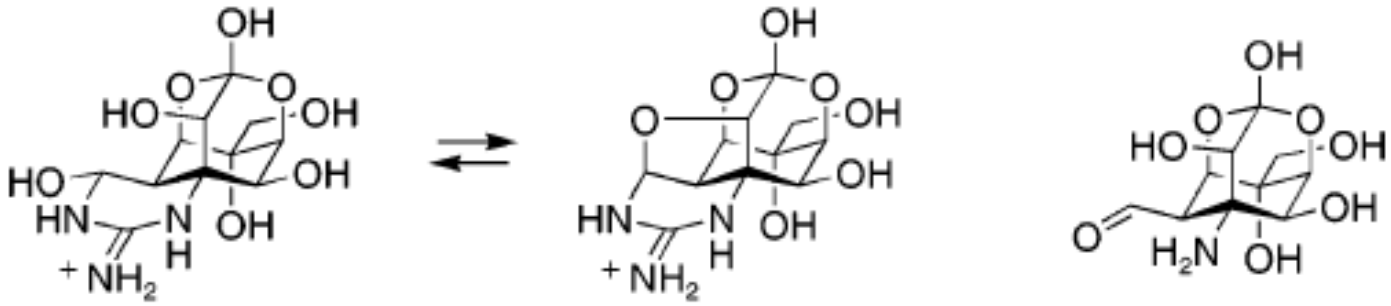


Figure 1. (−)-TTX, the active poison of the Japanese *fugu*.

Total Synthesis

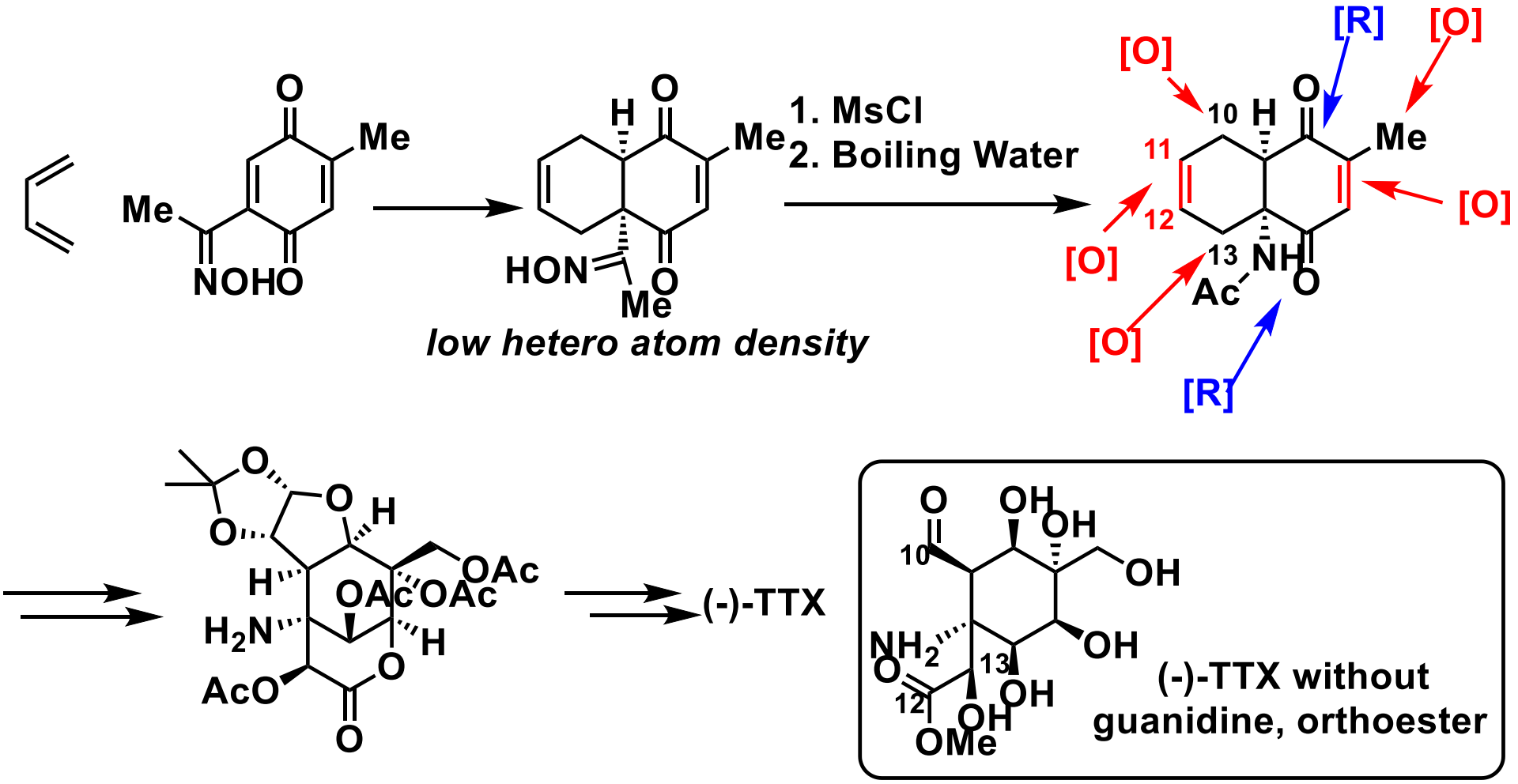
Kishi, Y
(*J. Am. Chem. Soc.* 1972, 94, 9219.)

SM with low [O]-state

Du Bois
(*J. Am. Chem. Soc.* 2003, 125, 11510)

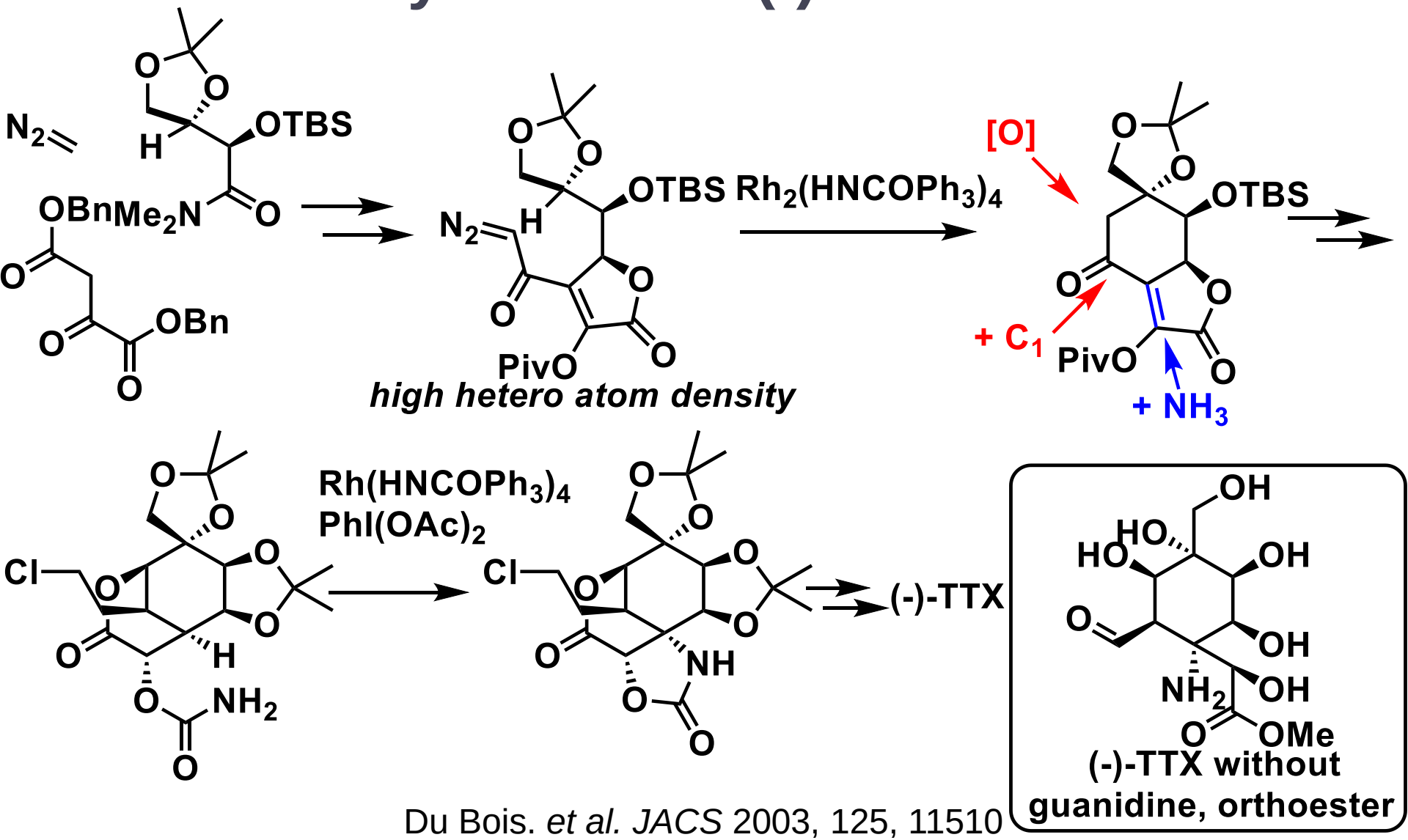
SM with high [O]-state

Total Synthesis of (-)-Tetrodotoxin



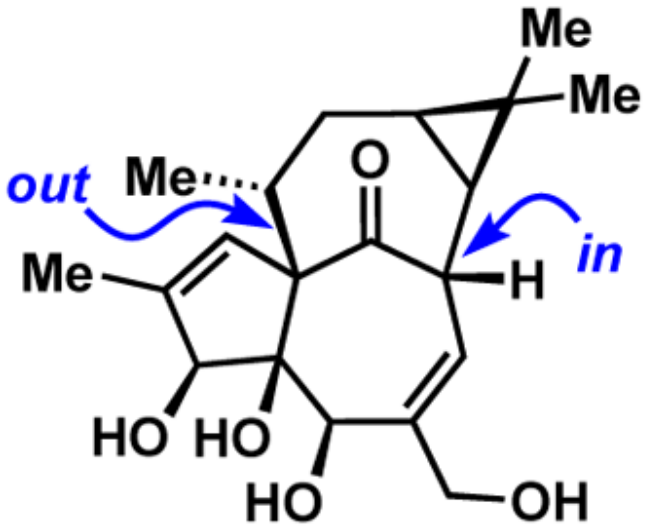
Kishi, Y. *et al. JACS* 1972, 94, 9219

Total Synthesis of (-)-Tetrodotoxin



Du Bois. *et al. JACS* 2003, 125, 11510

Total Synthesis of (-)-Ingenol



ingenol (**1**)

Total Synthesis

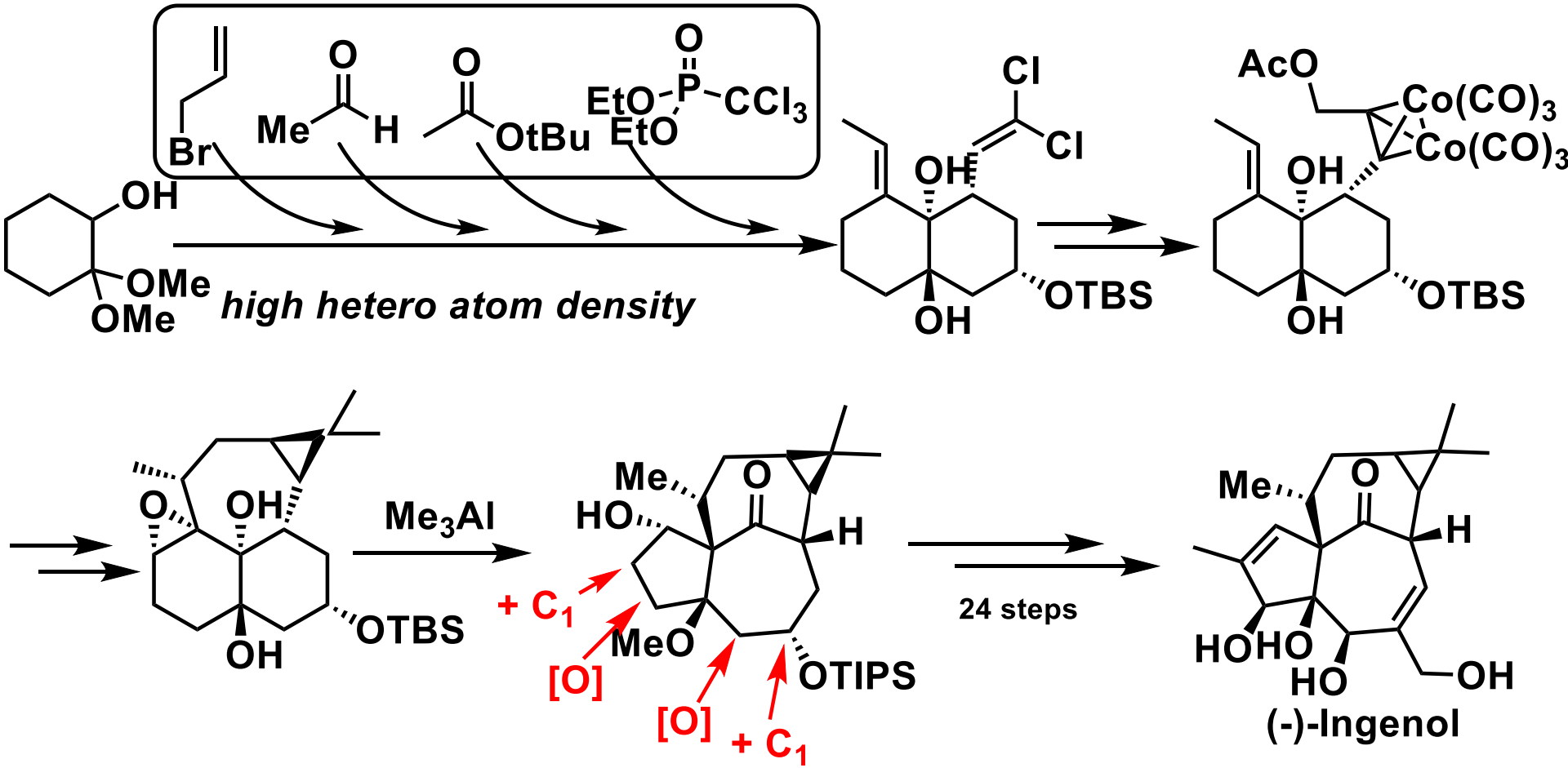
Kuwajima
(*J. Am. Chem. Soc.* 2003, 125, 1498-1500)

SM = high [O]-state

Baran
(*J. Am. Chem. Soc*. 2014, 136, 5799)

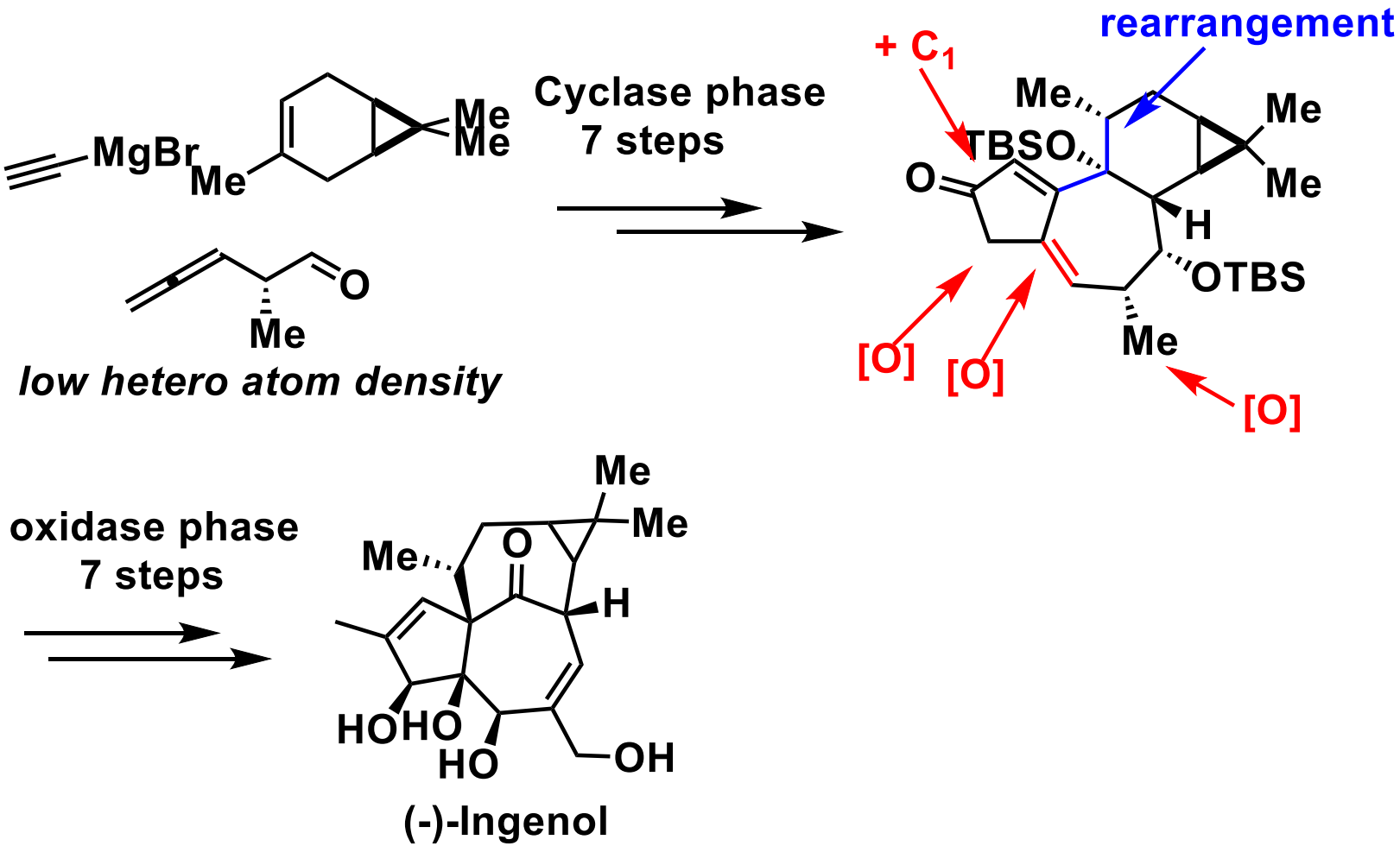
SM = low [O]-state

Total Synthesis of (-)-Ingenol



Kuwajima *et al. JACS* 2003, 125, 1498

Total Synthesis of (-)-Ingenol



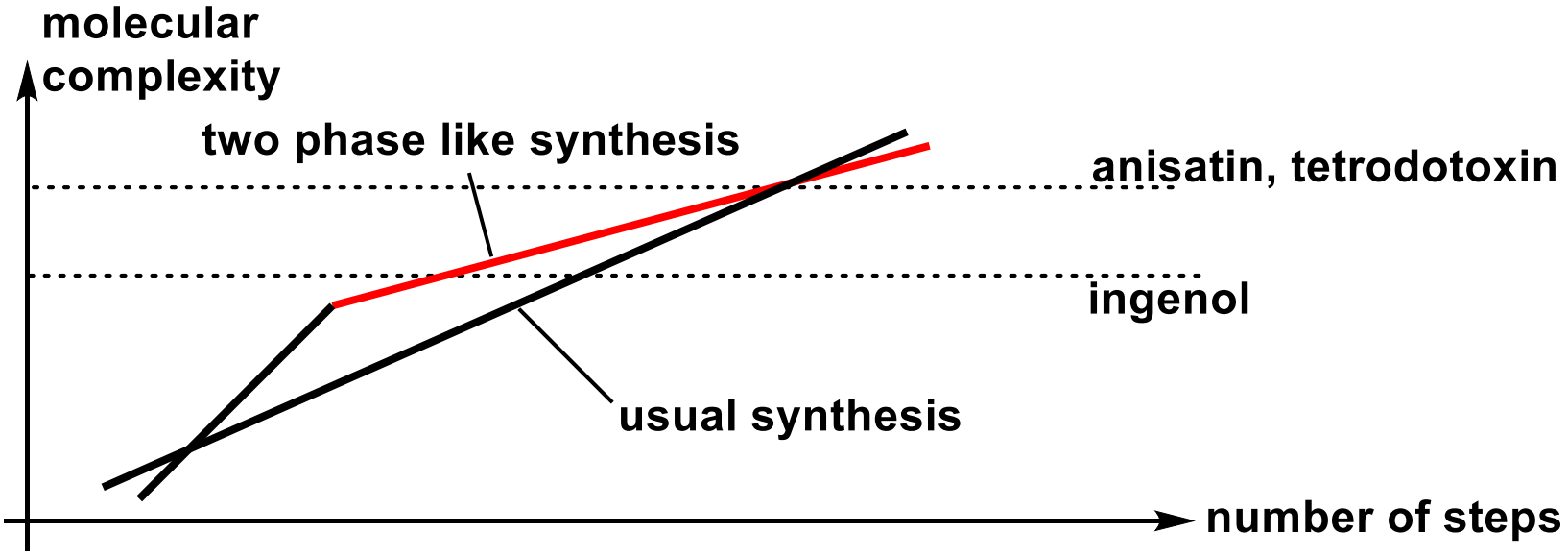
Baran *et al. JACS* 2014, 136, 5799

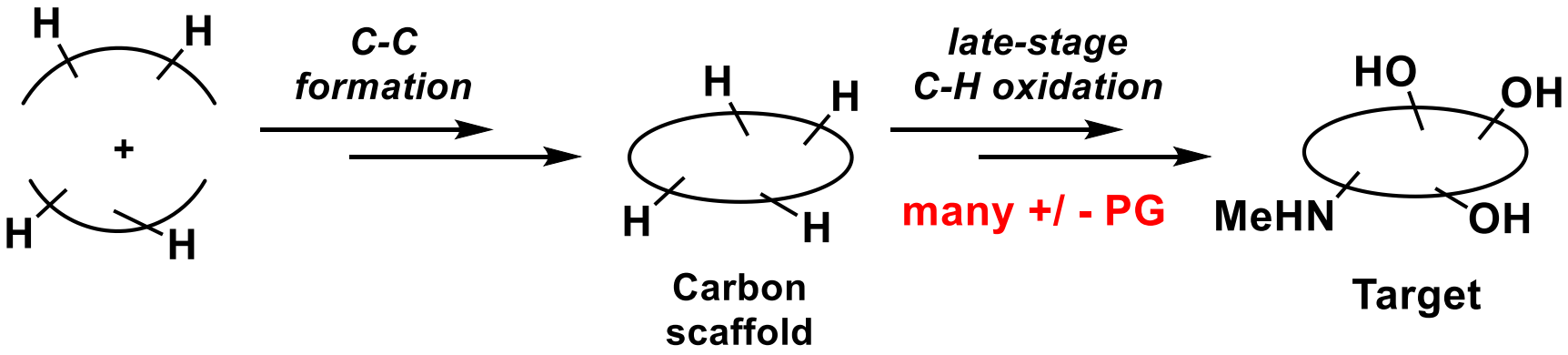
Summary

N.P.	Chemist	[O]-state of SM	Total Steps	C-C	C-hetero	oxi	red	+/– PG
Anisatin (high [O])	Yamada	low	40	5	5	15	3	11
	Fukuyama	high	40	5	6	8	7	10
Tetrodo -toxin (high [O])	Kishi	low	32	1	9	8	3	12
	Du Bois	high	28	4	2	4	3	6
Ingenol (low [O])	Baran	low	14	4	4	5	0	3
	Kuwajima	high	45	11	2	8	3	12

Efficiency of two phase like synthesis depends on [O]-state of N.P.

Summary

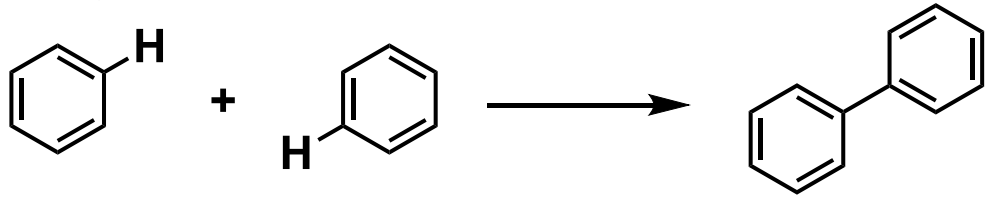




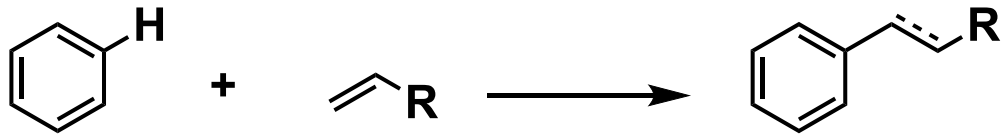
Methods for efficient C-hetero atom bond forming reaction are needed.

Contents

1) Aromatic C-H Arylation



2) Aromatic C-H Alkenylation and Alkylation



3) C(sp^3)-H Activation (C-C Bond Formation)

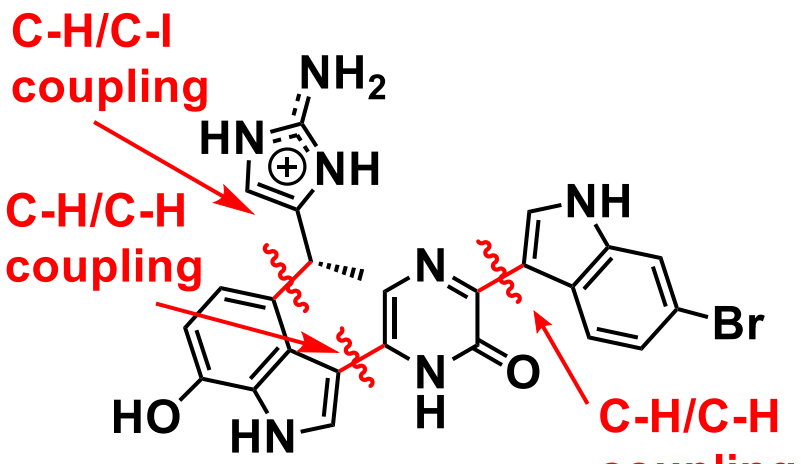
4) C(sp^3)-H Activation (C-Hetero Bond Formation)

(X= O, N)

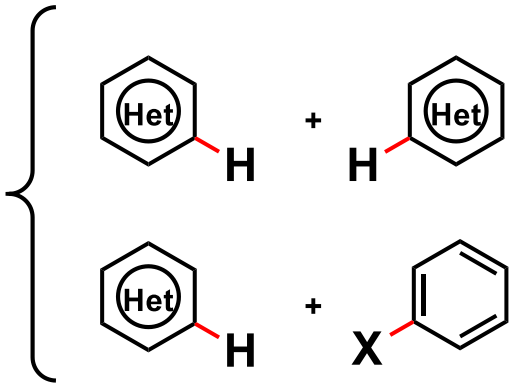
For further readings
***Angew. Chem. Int. Ed.* 2012, 51, 8960**
***Chem. Soc. Rev.*, 2011, 40, 1976**

C-H activation is mainly applied to
C-C Bond or intramolecular C-hetero Bond formation.

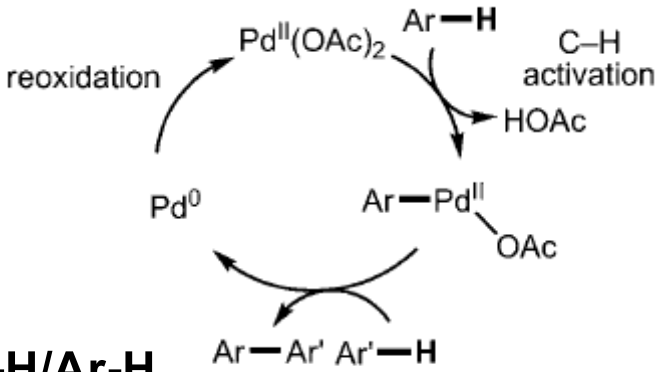
1) Aromatic C-H Arylation



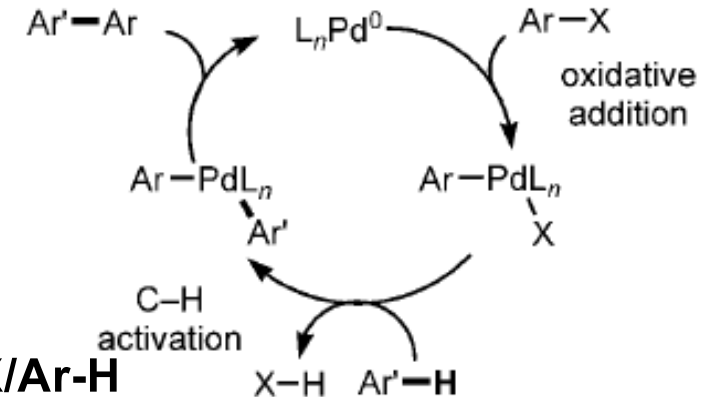
Dragmadine D



Many exaples can be found.
Relatively high regioselectivity can be obtained.



Ar-H/Ar-H coupling

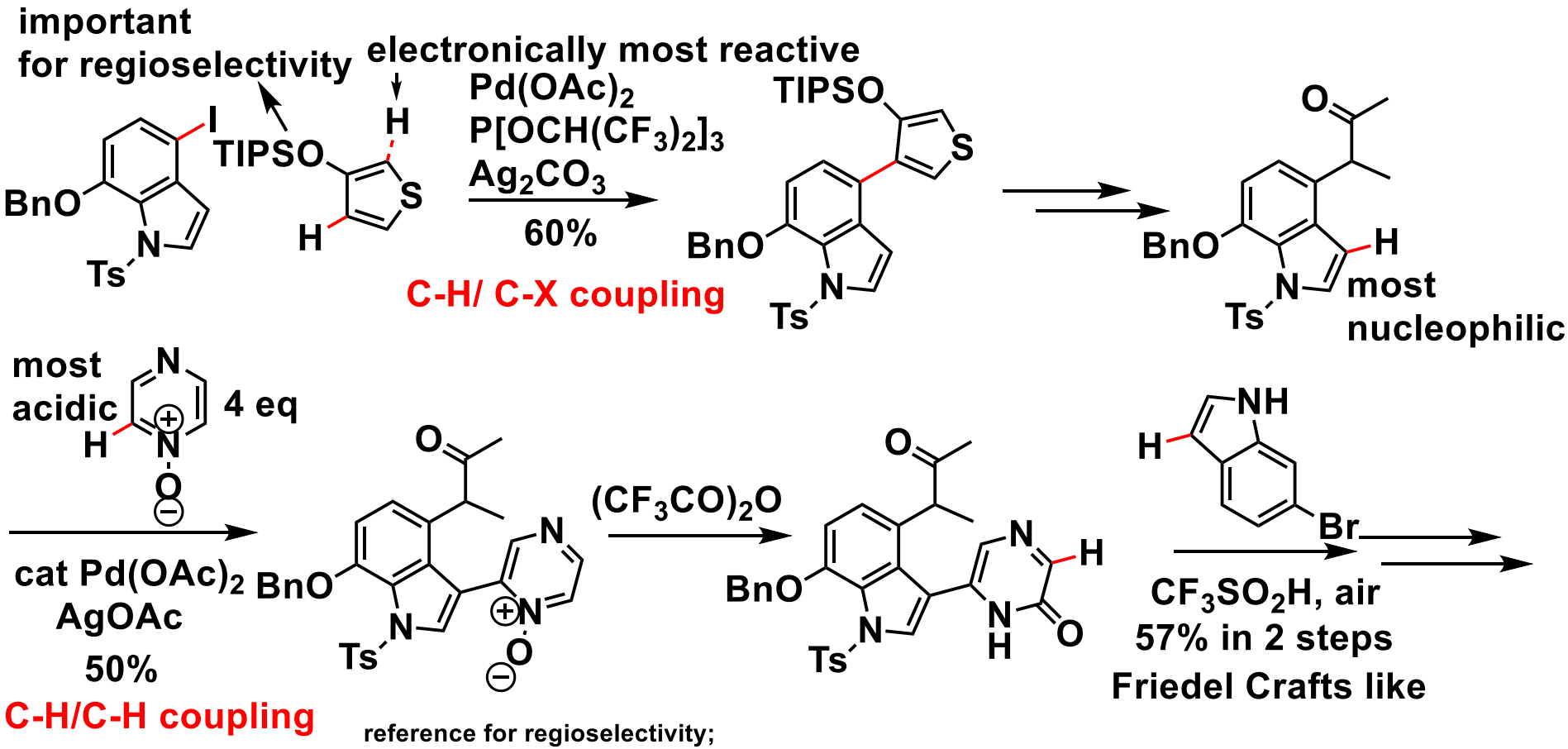


Ar-X/Ar-H coupling

Angew. Chem. Int. Ed. 2009, 48, 5094

1) Aromatic C-H Arylation

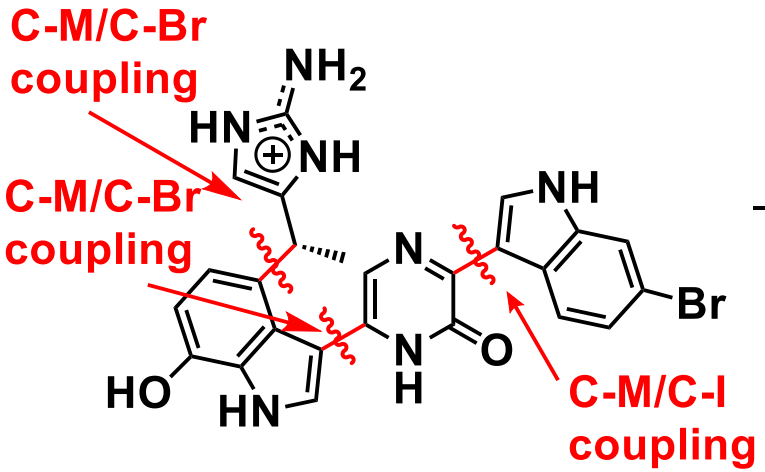
Total Synthesis of Dragmadin D (Itami *et. al*. *JACS*. 2011. 133, 19660)



reference for regioselectivity;
1)J. Am. Chem. Soc. 2006, 128, 11748 2)*J. Am. Chem. Soc.* 2008, 130, 9254 *3)Chem. Lett.* 2011, 40, 555

1) Aromatic C-H Arylation

cf) Total Synthesis of Dragmadin D (Stoltz *et. al*. *JACS*. 2002, 124, 13179)

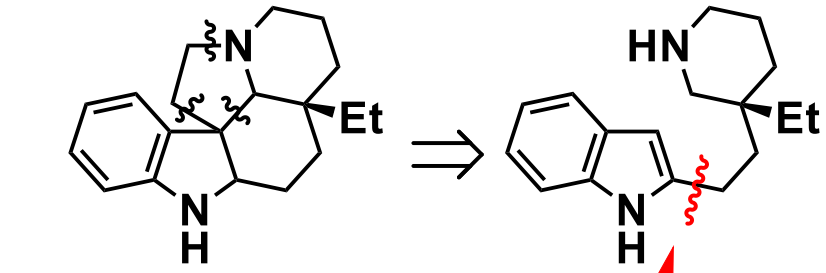


Dragmadine D

	coupling	C-M, X / total
Itami	C-H activation	1/ 15 steps
Stoltz	classical coupling	7/ 25 steps

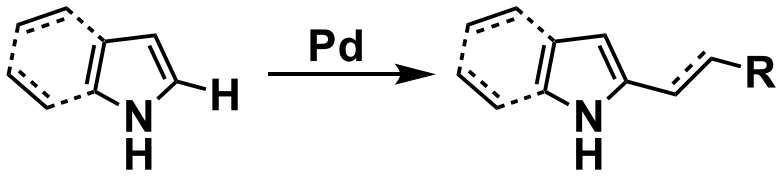
2) Aromatic C-H Alkenylation and Alkylation

Total Synthesis of (±)-Aspidospermidine (Bach *et. al. JACS.* 2012, 134, 14563)



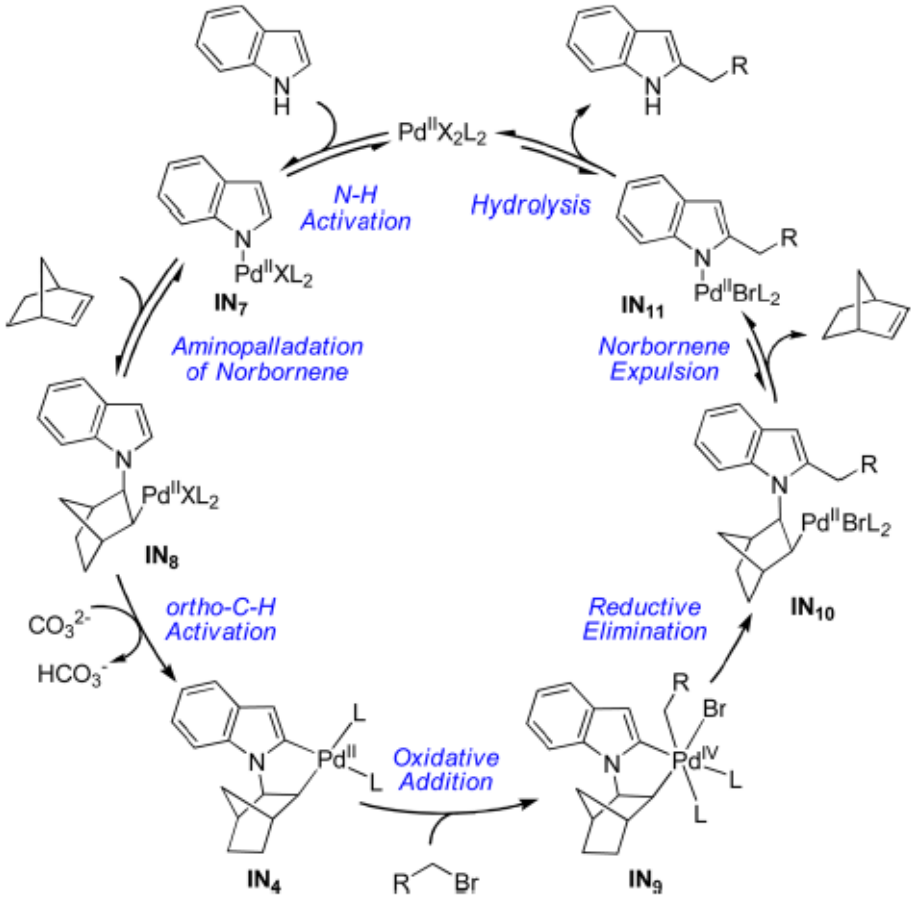
(±)-Aspidospermidine

alkylition of indole



pyrrole, indole alkylation, alkenylation

ex) Rhazinicine (*JACS.* 2013, 135, 9318.)
Ibogamine (*JACS.* 1978,100,3930.)
Okaramine (*JACS.* 2003, 125, 5628.)



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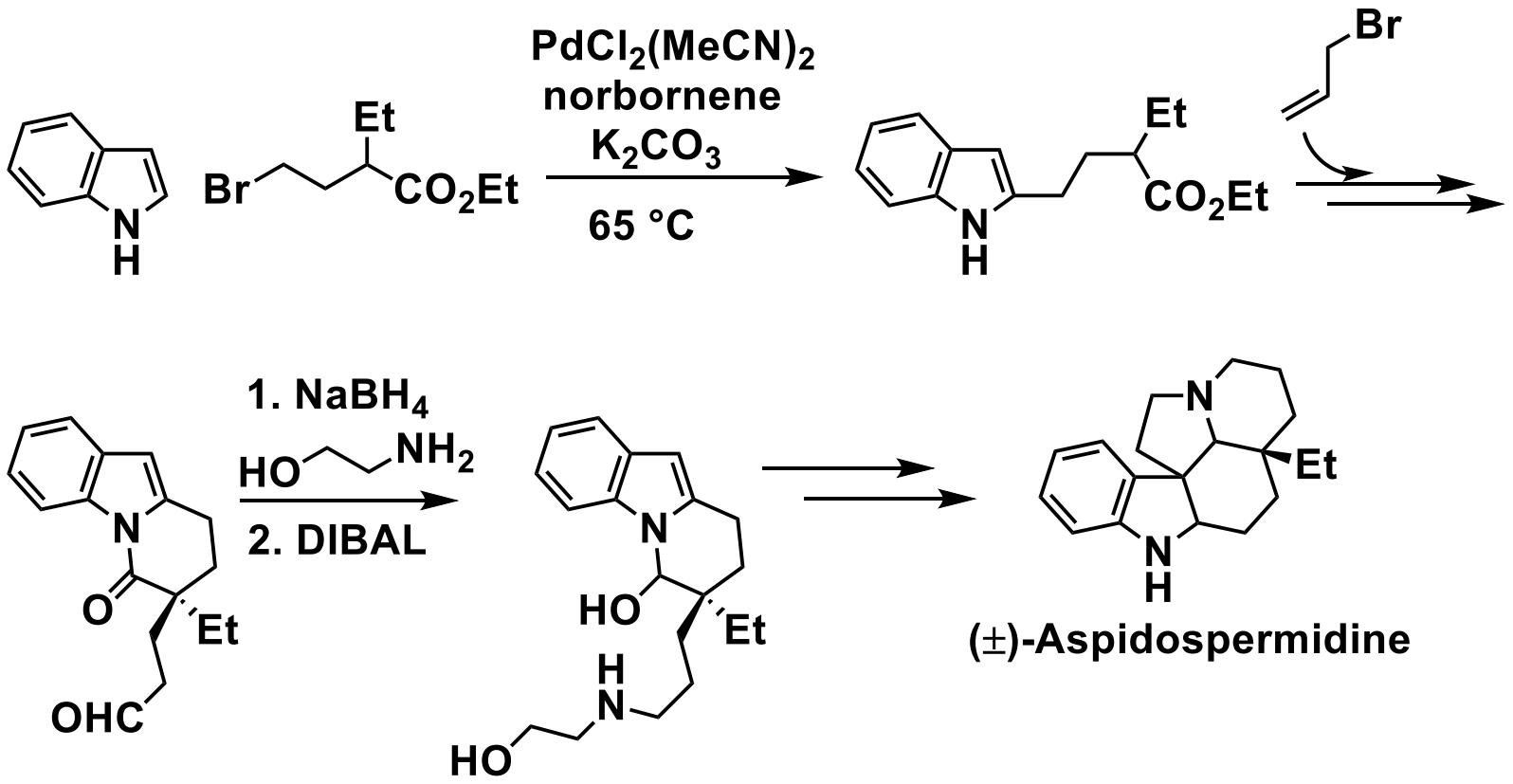
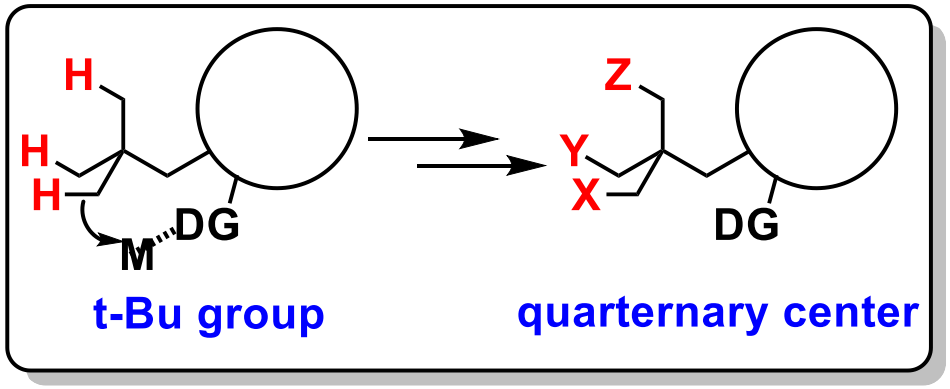
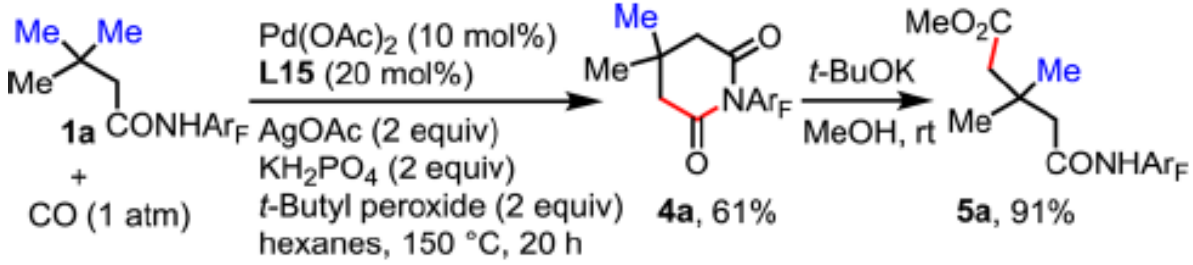
Total Synthesis of (±)-Aspidospermidine (Bach *et. al. JACS.* 2012, 134, 14563)

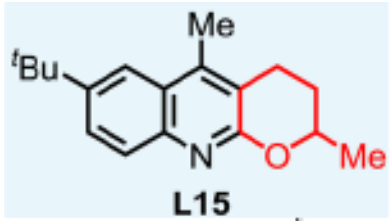


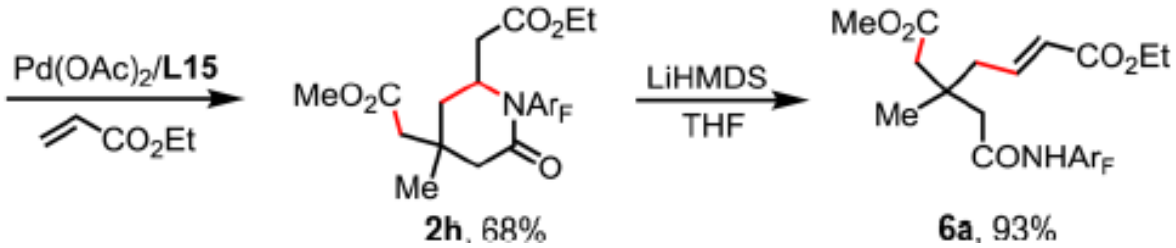
3) C(sp^3)-H Activation (C-C Bond Formation)



related example
*Angew. chem. Int. Ed.*2014, 53, 3115



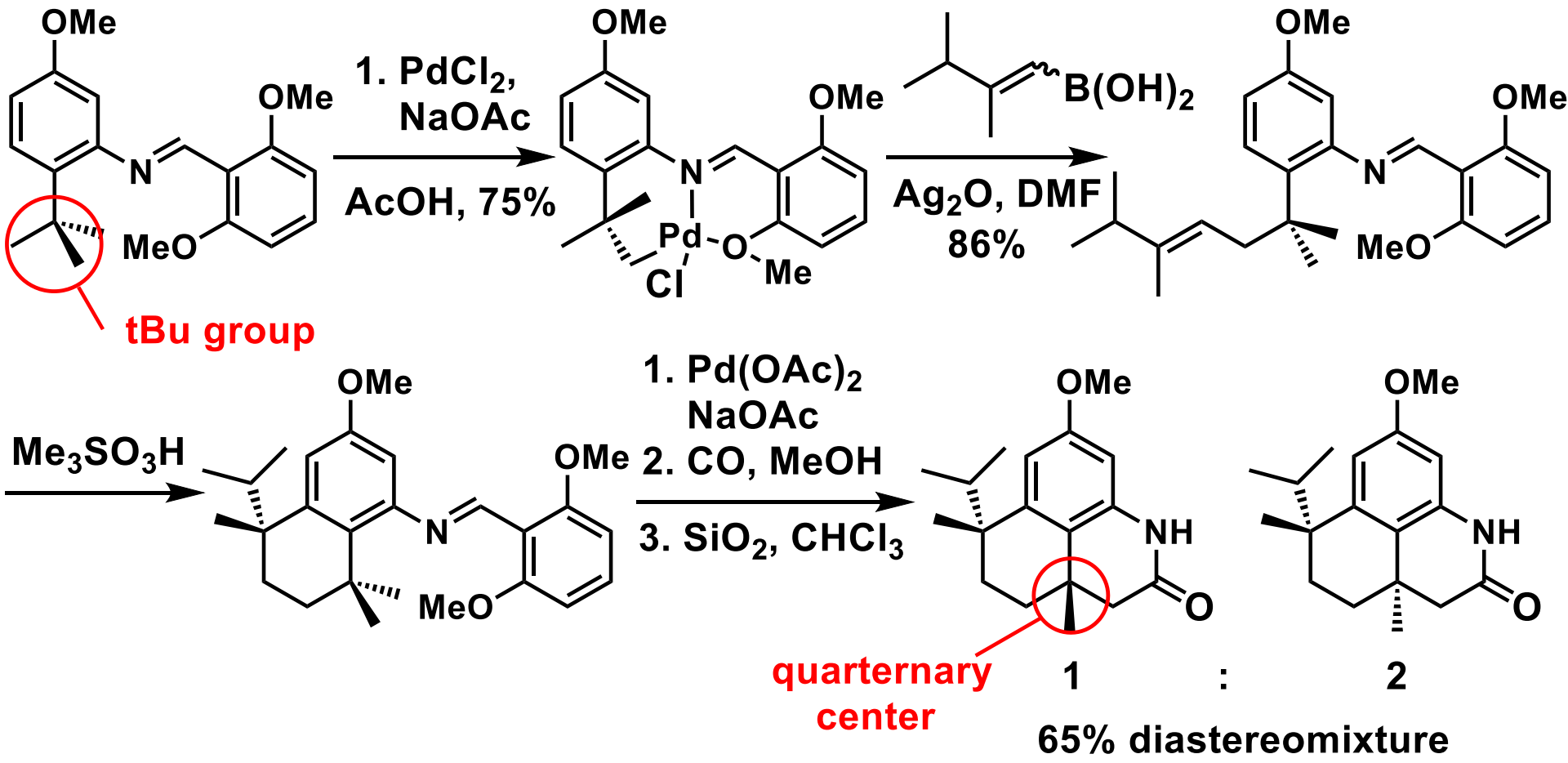




Jin *et. al. J. Am. Chem. Soc.* 2014, 136, 5267

3) C(sp^3)-H Activation (C-C Bond Formation)

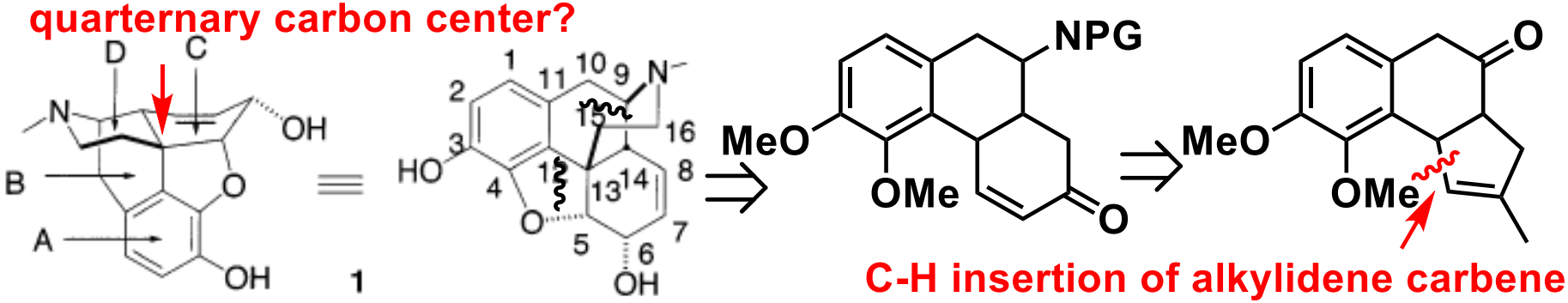
Teleocidin B_4 core (Sames *JACS*. 2002, 124, 11856)



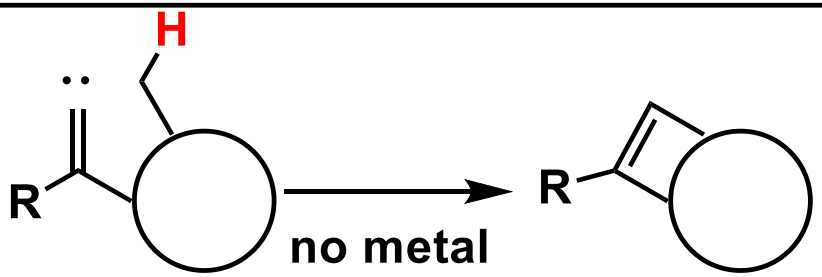
3) C(sp^3)-H Activation (C-C Bond Formation)

Total synthesis of Molphine (Taber *et. al. JACS*. 2002, 124, 12416)

How to constract this quarternary carbon center?



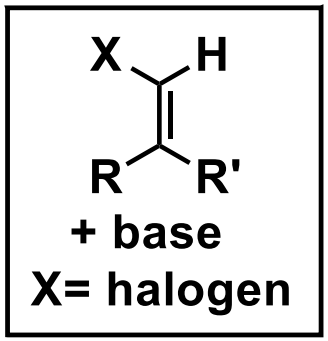
C-H insertion of alkylidene carbene

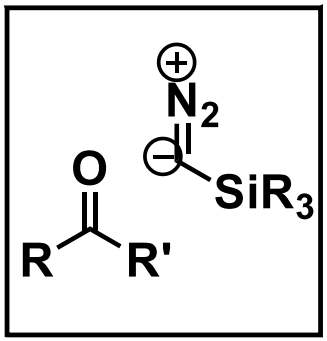


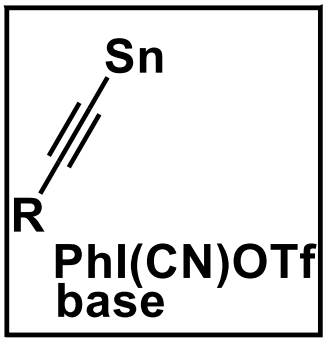
examples

Agelastatin A (*JOC*. 2002, 67, 7096)
Fumagillin (*JACS*. 1999, 121, 5589)
Isonitrin B (*JACS*. 1998, 120, 13285)
.....many examples

Preparation of alkylidene carbene







Angew. Chem. Int. Ed. 2012, 51, 8960

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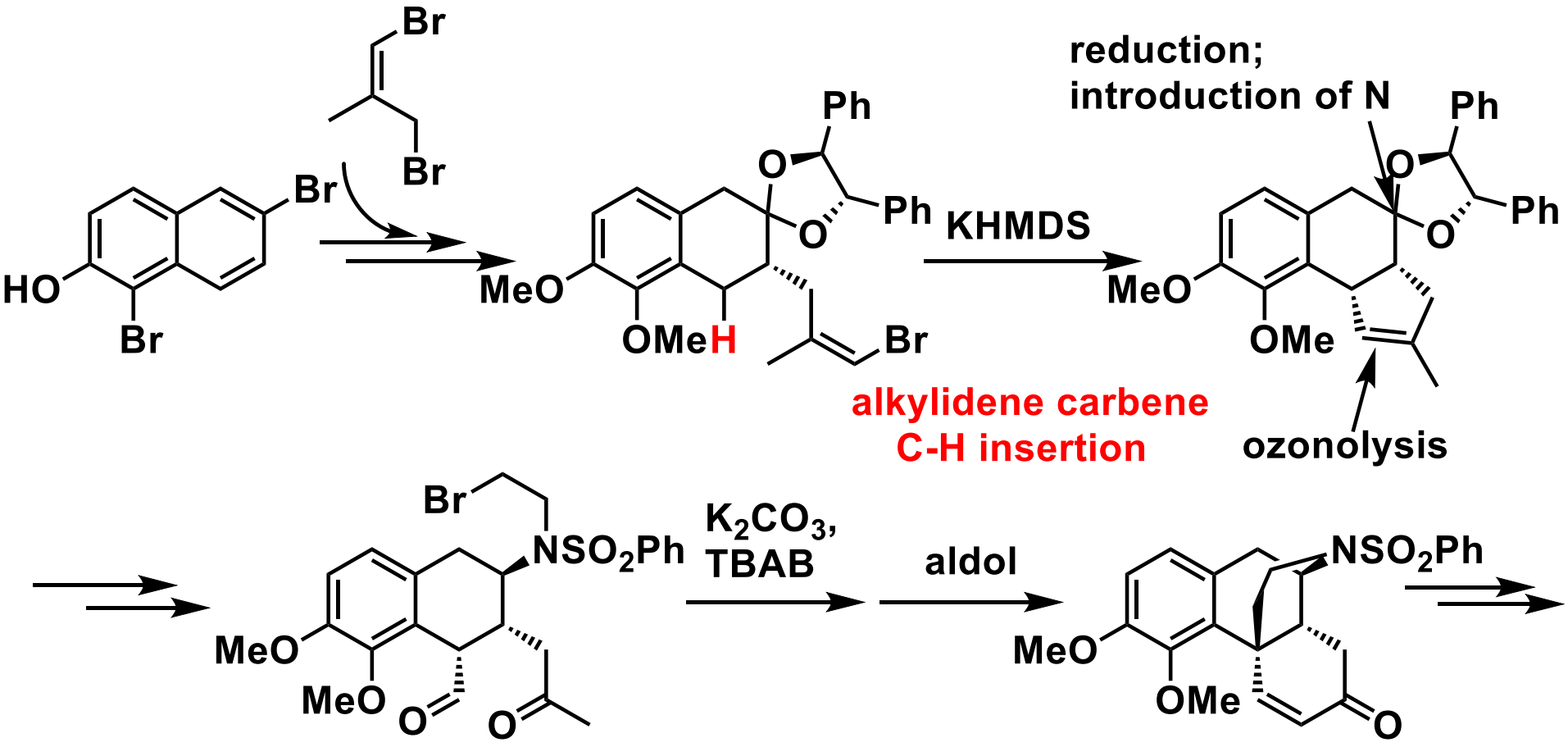
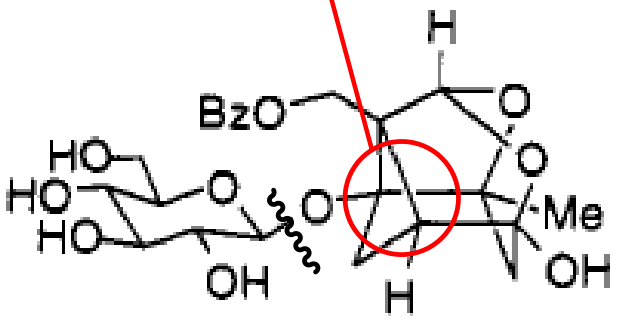


4) C(sp^3)-H Activation (C-Hetero Bond Formation)

Total Synthesis of Paeoniflorin (Hatakeyama *et. al. JACS*. 1994, 116, 4081)

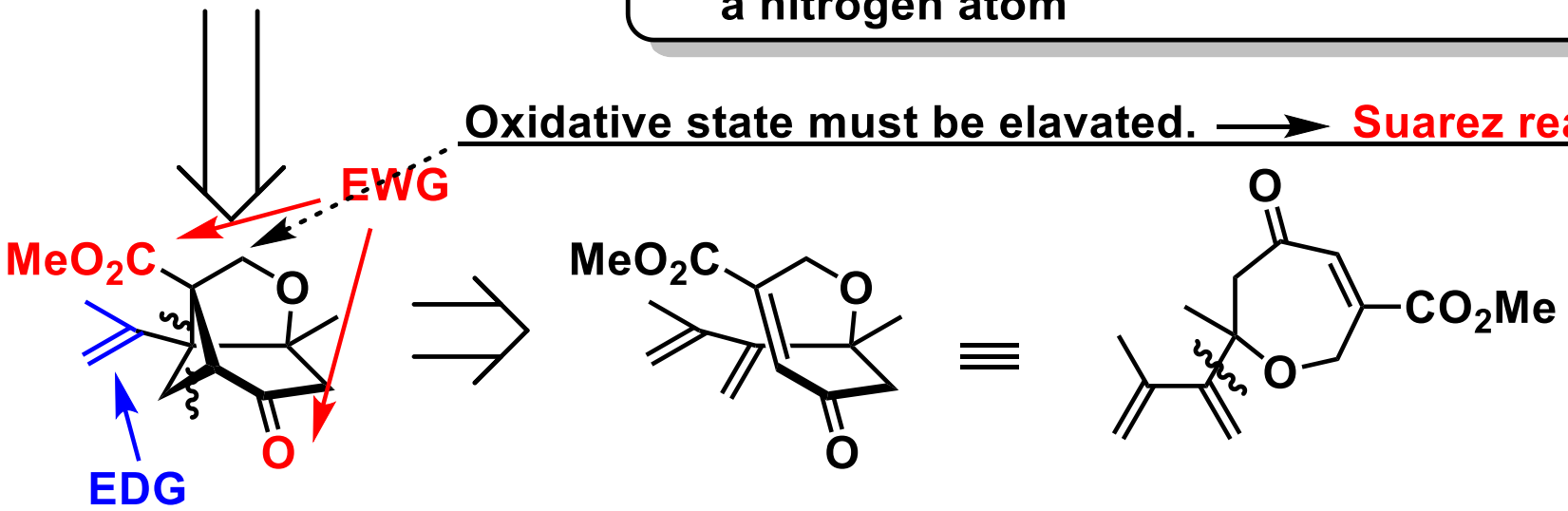
How to constract this 4-membered ring?



C-Hetero Bond Formation

1. C-H amination of Nitrene or Nitrenoid
2. HLF and Suarez type reaction
3. metal catalyzed C-H amination, oxidation
4. C-H oxidation on a carbon atom bearing a nitrogen atom

Oxidative state must be elavated. → Suarez reaction



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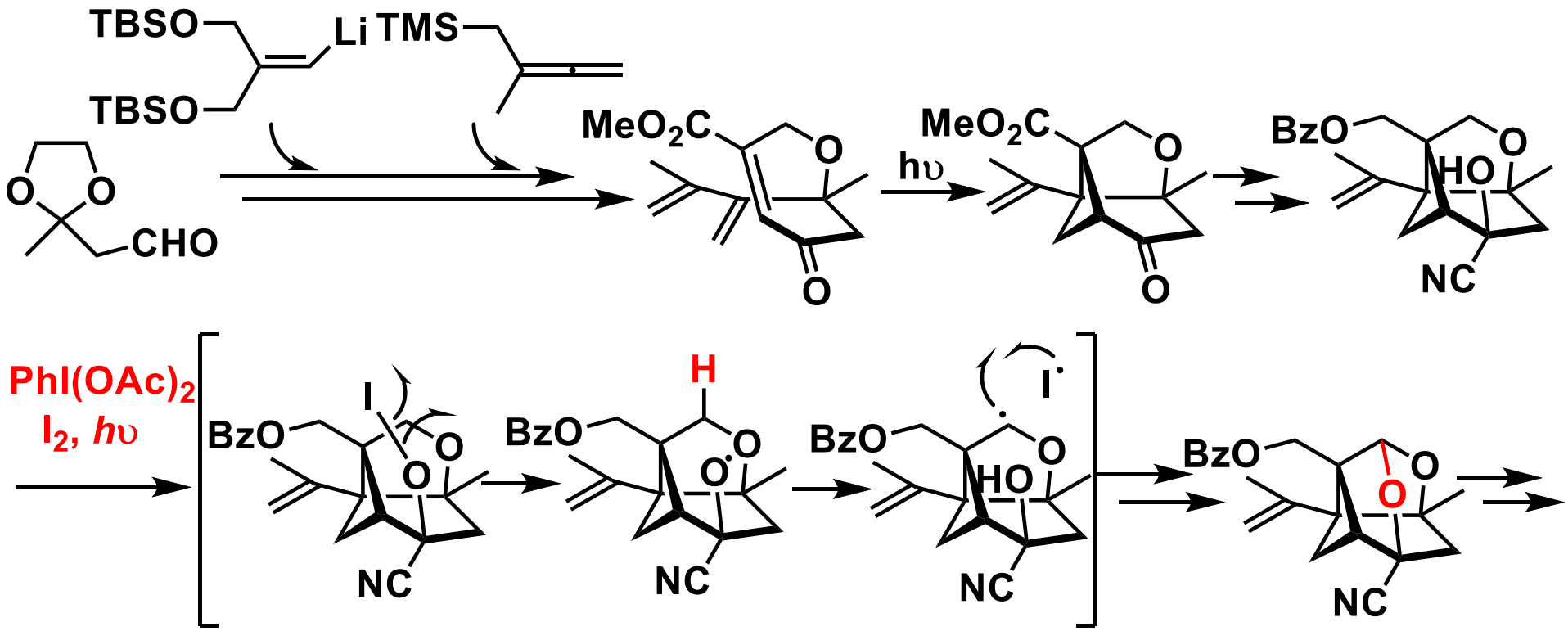
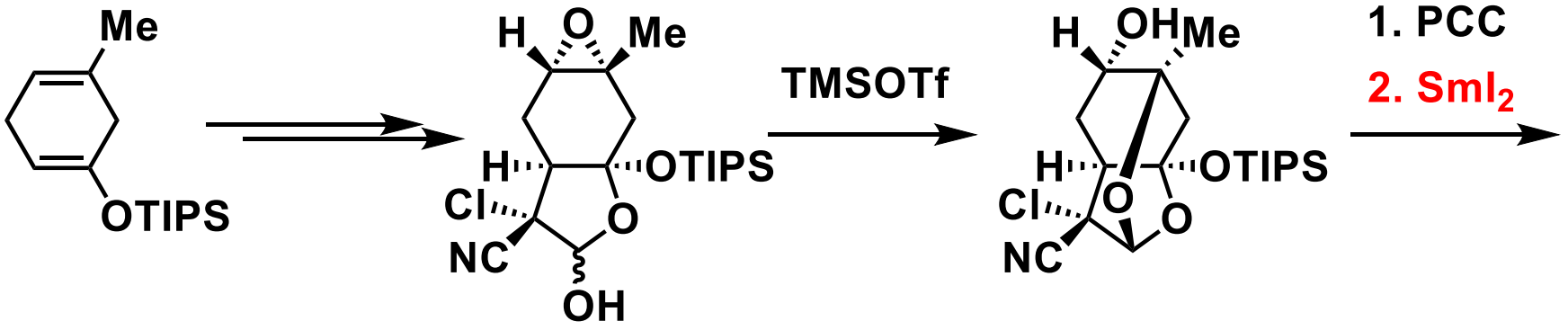
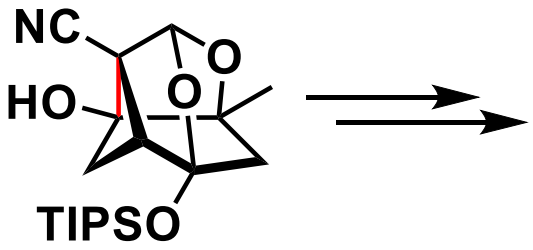
Total Synthesis of Paeoniflorin (Hatakeyama *et. al. JACS*. 1994, 116, 4081)



4) C(sp^3)-H Activation (C-Hetero Bond Formation)

cf) Total Synthesis of Paeoniflorin (Corey *et. al. JACS*. 1993, 115, 8871)





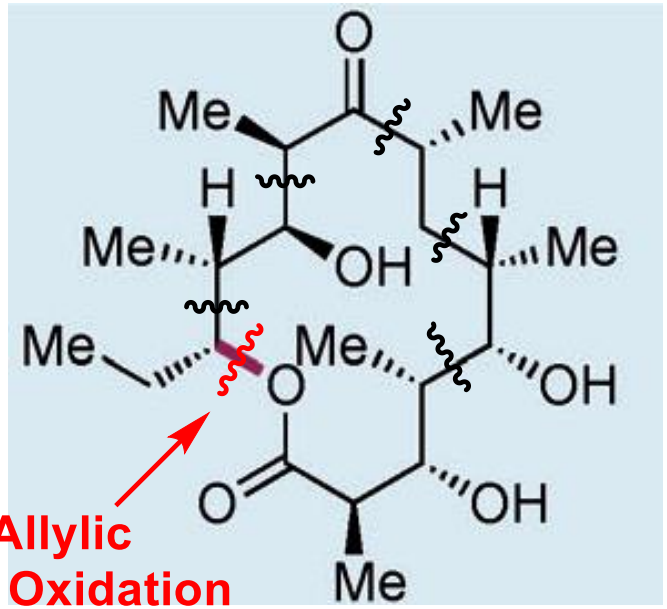
Method for 4-membered ring

	Reaction	non productive/ total
Hatakeyama	[2 + 2]	17/ 24 steps
Corey	Pinacol	9/ 15 steps

Forming carbon scafold with less steps of functionalization is most important.

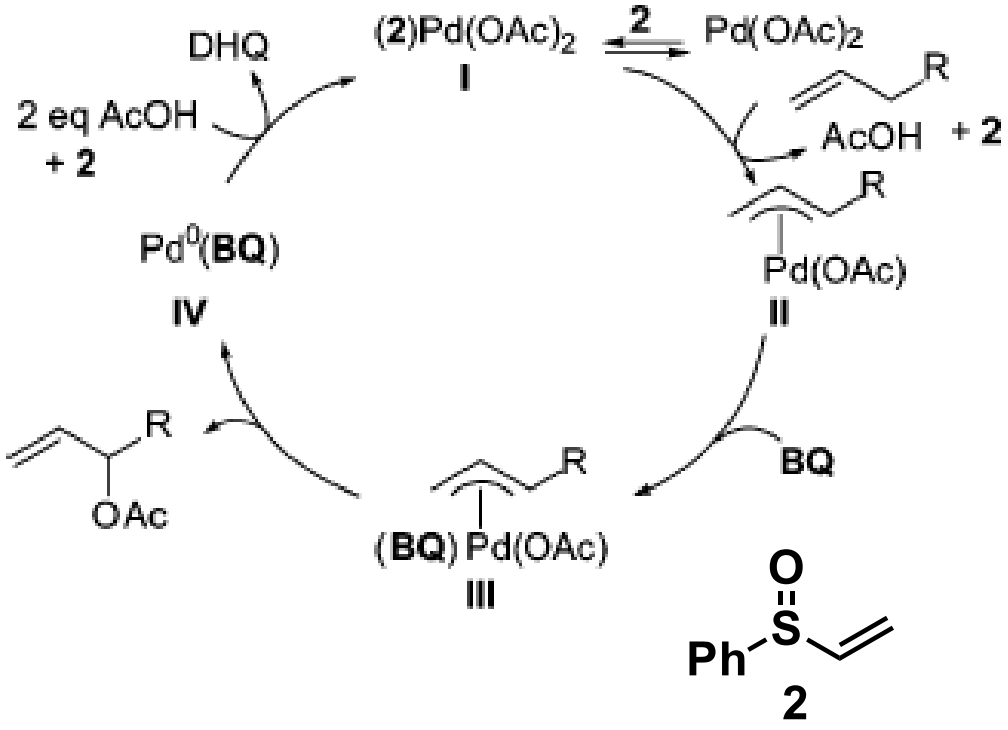
4) C(sp^3)-H Activation (C-Hetero Bond Formation)

Total Synthesis of 6-deoxyerythronolide (White *et. al. Nat. Chem*. 2009, 1, 157)



〰 aldol or alkylation of enolate

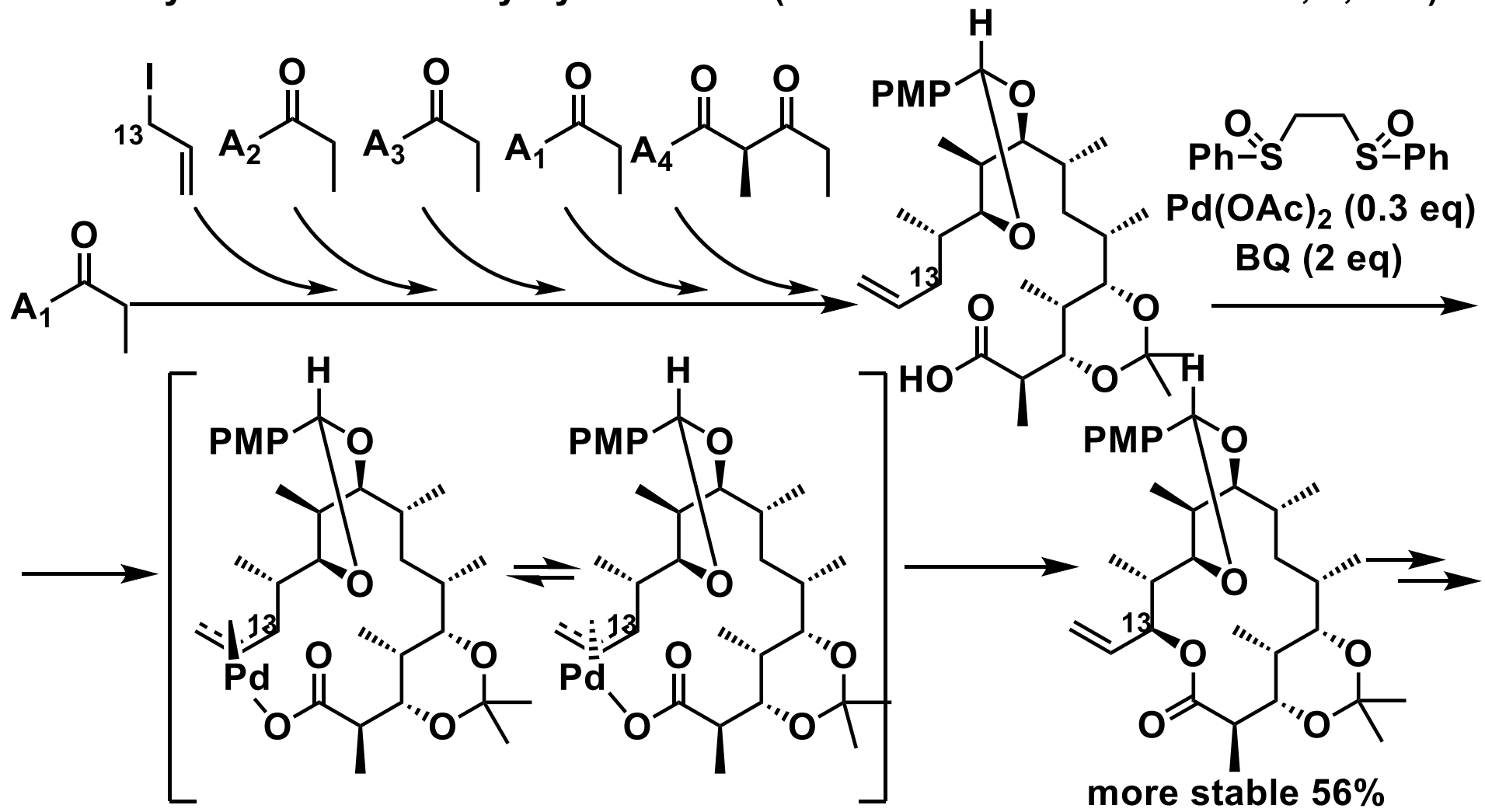
Reaction Mechanism



JACS. 2005, 127, 6970

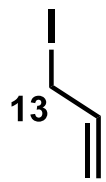
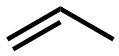
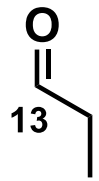
4) C(sp^3)-H Activation (C-Hetero Bond Formation)

Total Synthesis of 6-deoxyerythronolide (White *et. al. Nat. Chem*. 2009, 1, 157)



4) C(sp^3)-H Activation (C-Hetero Bond Formation)

Total Synthesis of 6-deoxyerythronolide (White *et. al. Nat. Chem*. 2009, 1, 157)

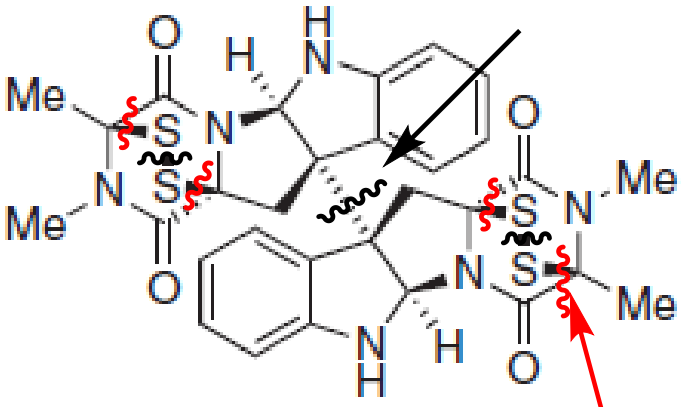
electronphile	required steps		advantages
	oxidative macrolactonizaton		less -[O] group = less side reaction
	reduction of 	2 steps	(high yield in total) (atom economical)
	+/ - PG macrolactonizaton	3 steps	(more promising)

Only a limited advantages

4) C(sp^3)-H Activation (C-Hetero Bond Formation)

Total Synthesis of (+) - 11,11'-Dideoxyverticillin A
(Movassaghi *et. al. Science* 2009, 324, 238)

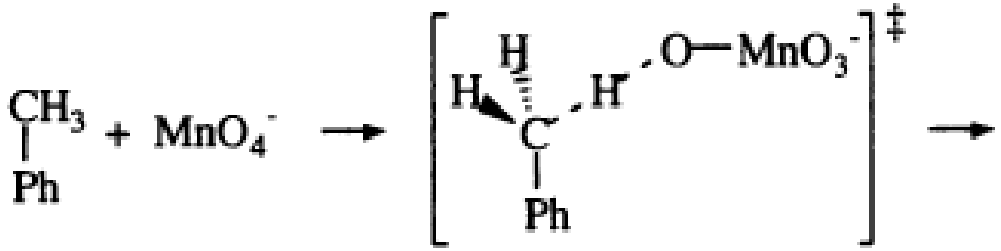
[R]-dimerization



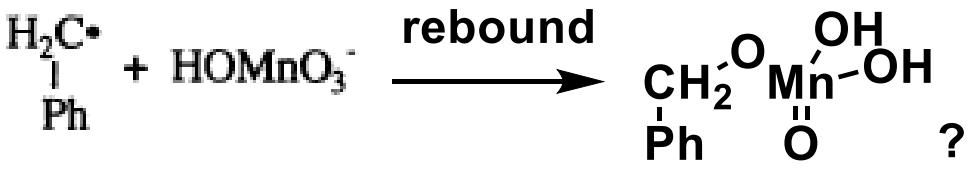
(+)-11,11'-dideoxyverticillin A (1)

C-H oxidation

Proposed Reaction Mechanism for C-H Oxidaton by Permangante



BDE value is important

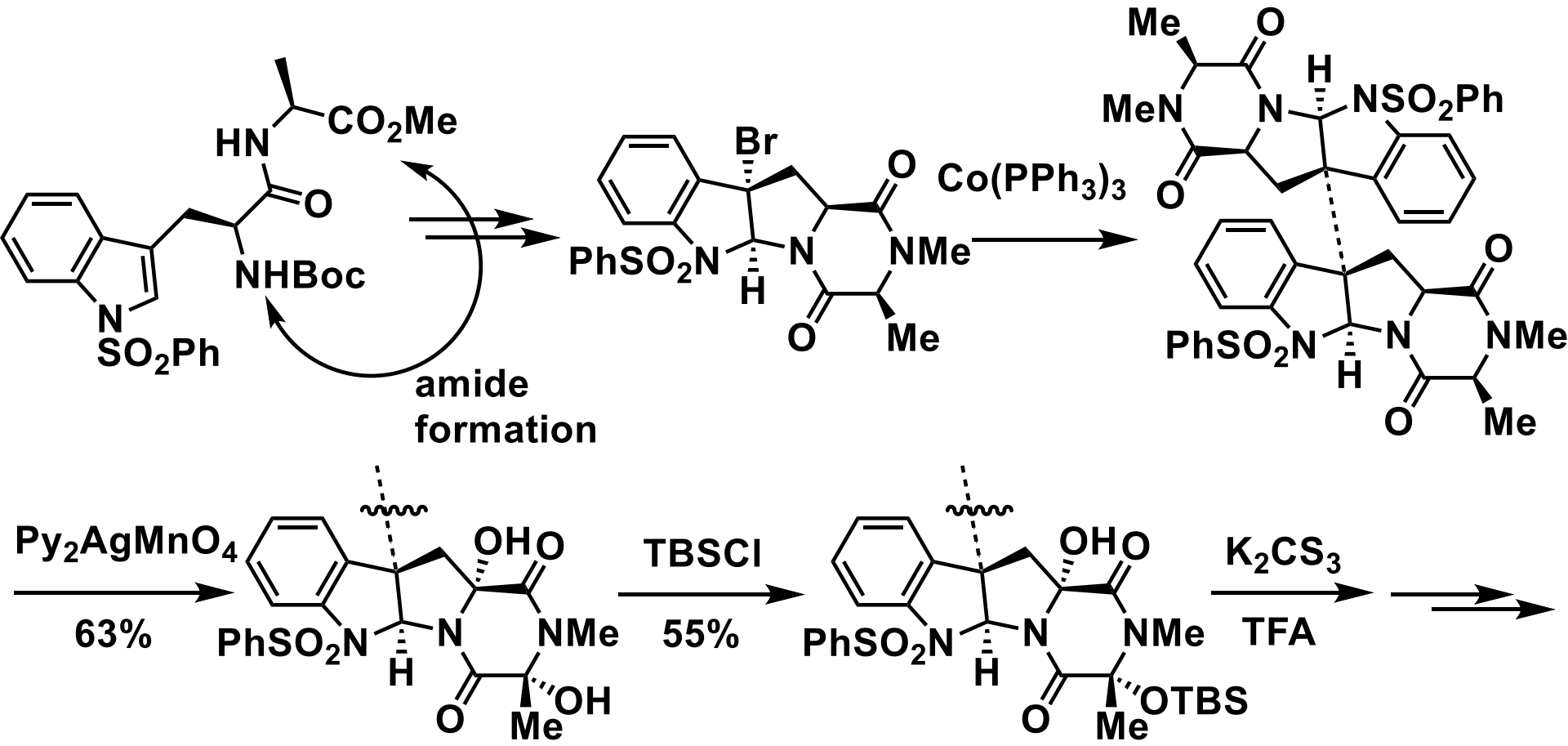


$PhCH_2OH$

Mayer *et. al. Science* 1995, 269,
Houk *et. al. JACS.* 2000, 122, 7821

4) C(sp^3)-H Activation (C-Hetero Bond Formation)

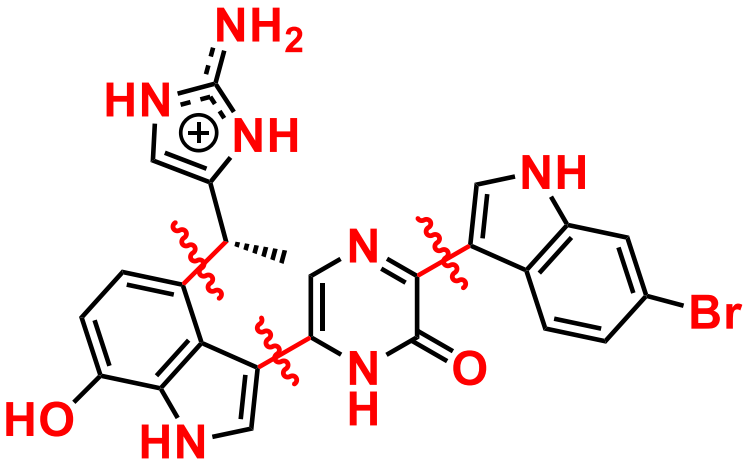
Total Synthesis of (+) - 11,11'-Dideoxyverticillin A
(Movassaghi *et. al. Science* 2009, 324, 238)



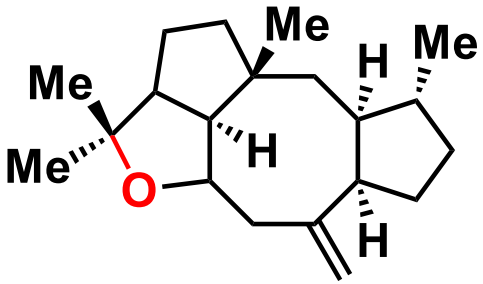
5) Summary

C-H Activaton applied to Total Synthesis

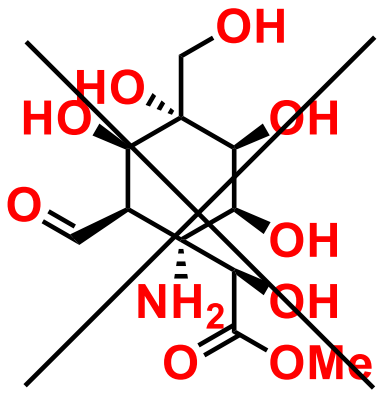
1. Low [O]-state
2. C(sp^2) rich
3. C-C Bond or Intramolecular C-X



Dragmadine D

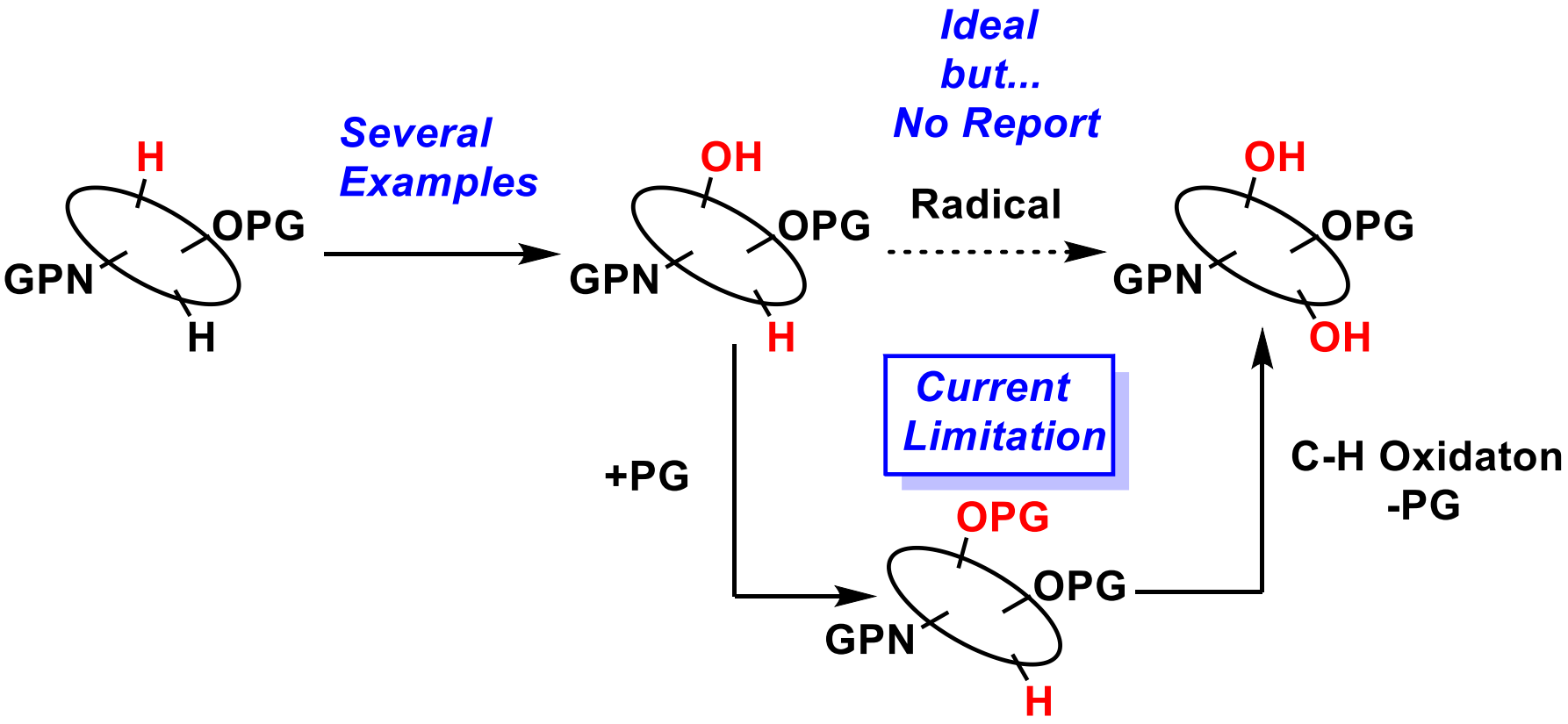


(+)-Epoxydictymene



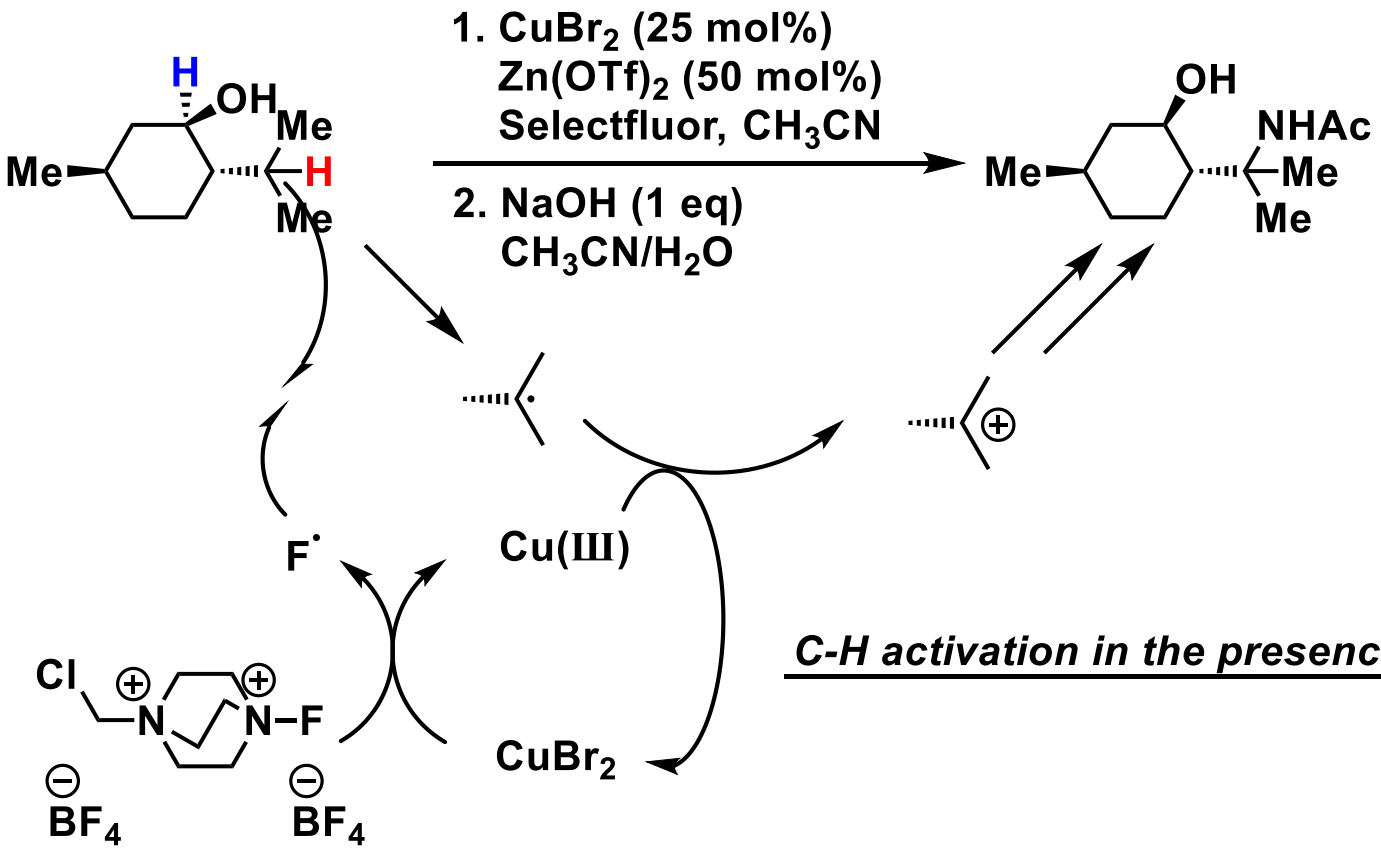
(-)-TTX without guanidine, orthoester

5) Summary



Protecting free C-H oxidation is required.

5) Summary



C-H activation in the presence of free -OH.

Baran *et. al. JACS.* 2012, 134, 2547

質問の回答

- ラジカル反応の利点は？

  極性反応とは異なる選択性が出せる可能性がある。極性反応は一番引き抜かれやすいプロトンが引き抜かれて反応するの対して、ラジカル反応では比較的ＢＤＥが低いＣ－Ｈ結合のうちどれかが切れる。反応するＣ－Ｈは両者で異なることがある。

  また混み合ったところも反応させられるというのも大きな利点であると思います。

質問の回答

- High[O]なN.P.もtwo-phase-likeにつくるのはいい方向なのか？

  私は今の時点では無理ではないかと思っていまして、それは後からヘテロ原子を入れていく戦略は位置選択性や保護、脱保護の問題を解決する必要があるからです。位置選択性はともかく保護脱保護は求電子ラジカルを使えばもしかしたら解決できるかもしれないというのが、最後のスライドの趣旨です。

質問の回答

- two-phase-like-synthesisは自然を模倣した合成だが、人間はそれを超えられるとおもうか？そのためにはどんな反応が必要か？
  自然界はイソプレンのようなヘテロ原子がないものを使っているのに対し、人間はヘテロ原子をもつ化合物を原料に使えるので、同じような
  two-phase-like-synthesisでも人間は自然界を超えられると思います。そのためにはまず炭素縮環構築段階を効率的にやる必要があって、そのための不飽和結合をもつ分子を金属触媒下効率よくつなげていける反応は非常に魅力的なのではないかと思いました。(不飽和結合は酸化段階の足がかりになるので)

質問の回答

- 全合成の技術はまだ発展する必要がありますか？

  天然物likeな化合物の方が医薬品のseedになる確率が有意に高いという論文（*J. Nat. Prod.* 2012, 75, 311−335）があって、それでもいまだにlarge-scaleで合成できる方法論が不足しているから、昨今医薬品の創出が難しくなっているとよくいわれています。

質問の回答

- Baranのingenolの合成でtotal-stepが劇的に減少している最大の要因は何か？

  不飽和結合をうまく使って適切な位置に酸素官能基を持つフラグメントをつなげて、酸化しなければいけない部分を極力減らしたtwo-phase-like-synthesisになっている点。 Wood(*J. Am. Chem. Soc.* 2004, 126, 16300-16301）の全合成もtwo-phase-like-synthesisといえるとは思うが、あまりにも酸化度の低いSMを使っているので、特に酸化段階がstep数が多い。

質問の回答

- C-H活性化でfragment coupling的にC-hetero結合をつくる反応をつくれば保護脱保護を回避できると思う。

  そういう解決もありだと思います。ありがとうございます。
- はじめから保護された酸素源を持つSMを使うのはだめなのか？

  ヘテロ原子の根元にアニオンを出すのは難しいので、はじめからヘテロ原子を持っているものをＳＭには使えないということがあります。