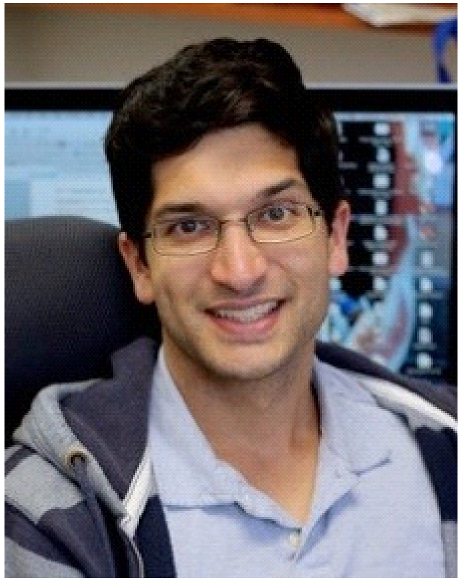
Stereoinversion of tertiary alcohols to tertiary-alkyl isonitriles and amines

2016. 4. 30.

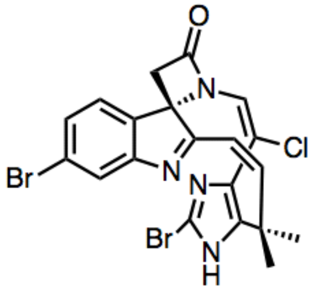
Kosuke Minagawa (D1)

Ryan A. Shenvi



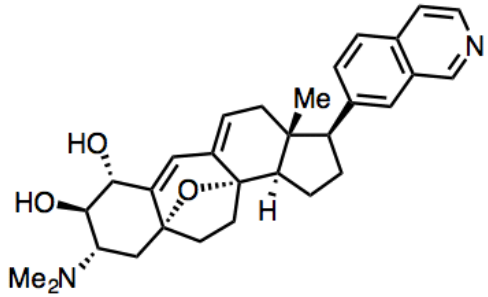
1999-2003: Pennsylvania State University (B.S., Prof. Raymond L. Funk)

2003-2008: The Scripps Research Institute (Ph.D., Prof. Phil S. Baran)



(±)–Chartelline C

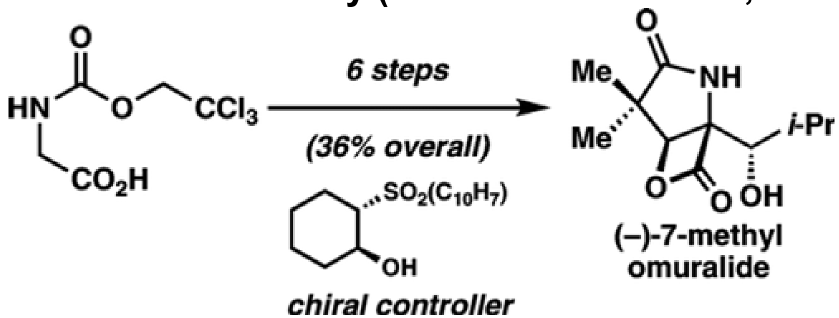
***JACS*. 2008, *130*, 7241.**



(+)–Cortistatin A

***JACS*. 2006, *128*, 14028.**

2008-2010: Harvard University (Postdoctoral Fellow, Prof. Elias J. Corey)



***JACS*. 2009, *131*, 5746.**

2010-: The Scripps Research Institute (Assistant Prof.)

2014-: The Scripps Research Institute (Associate Prof.)

Areas of interest

Neuroscience

synthesize important classes of CNS-active metabolites

. *JACS*, 2012
. *Org. Lett.*, 2015
. *Nature Chem.*, 2015
. *Nat. Prod. Rep.*, 2016

Unusual pharmacophores

asmarine alkaloids
the isocyanoterpenes

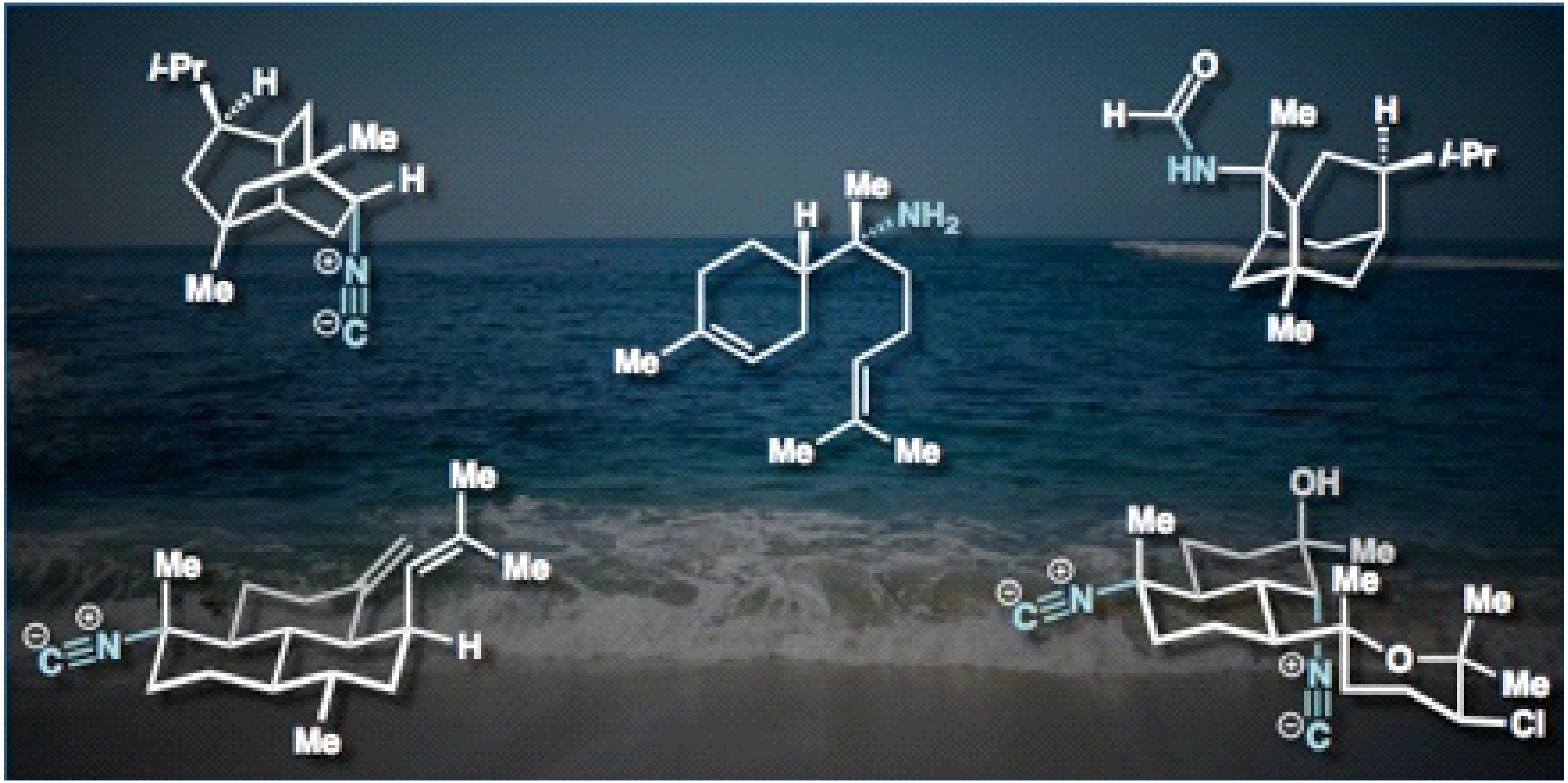
. *JACS*, 2012
. *JACS*, 2012
. *Nature*, 2013
. *ACIE*, 2015
. *Nat. Prod. Rep.*, 2015
. *Synlett*, 2016

Hydrogen Atom Transfer

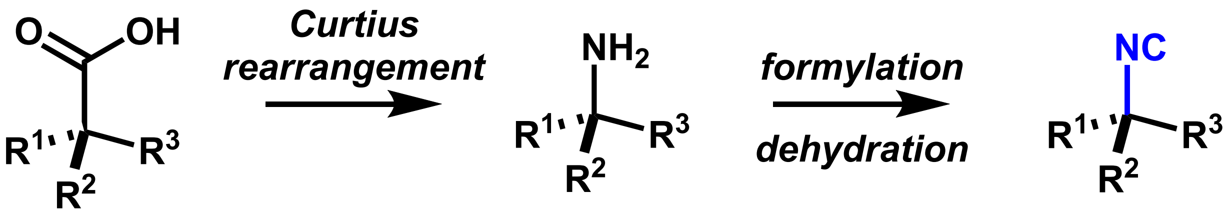
Co, Fe and Mn-catalyzed reactions
synthesis of inaccessible secondary metabolites

. *Nature Chem.*, 2012
. *JACS*, 2014
. *JACS*, 2014
. *JACS*, 2016

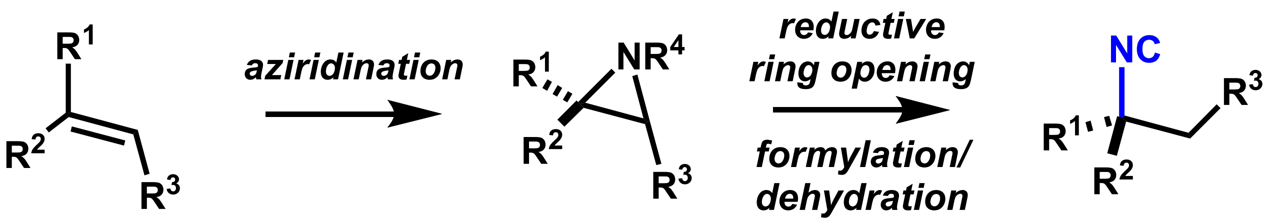
Nitrogenous terpenes isolated from marine organisms



Strategies to generate stereogenic tert-alkyl isonitriles (1)



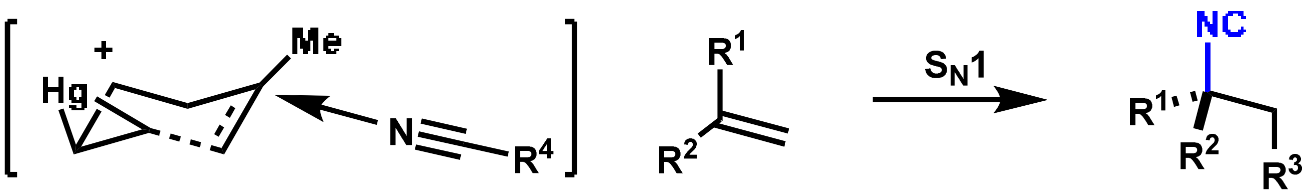
Piers (1989)[1], Asaoka (1995)[2], Yamada (2002)[3], Mander (2006)[4]



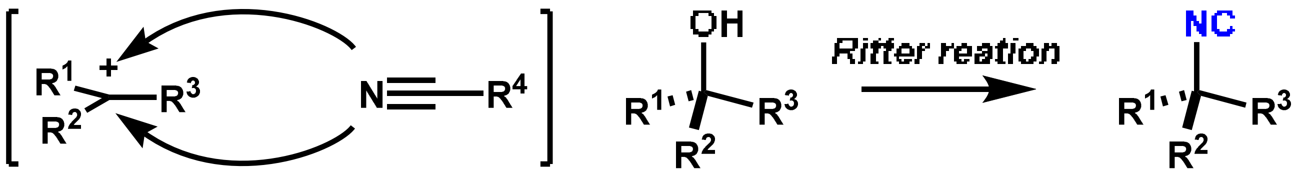
Wood (2004)[5]

1. Piers, E.; Llinas-Brunet, M. *J. Org. Chem.* **1989**, *54*, 1483.
2. Ohkuba, T.; Akino, H.; Asaoka, M.; Takei, H. *Tetrahedron Lett.* **1995**, *36*, 3365.
3. Miyaoka, H.; Shida, H.; Yamada, N.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.* **2002**, *43*, 2227
4. Fairweather, K. A.; Mander, L. N. *Org. Lett.* **2006**, *8*, 3395.
5. White, R. D.; Keaney, G. F.; Slown, C. D.; Wood, J. L. *Org. Lett.* **2004**, *6*, 1123.

Strategies to generate stereogenic tert-alkyl isonitriles (2)



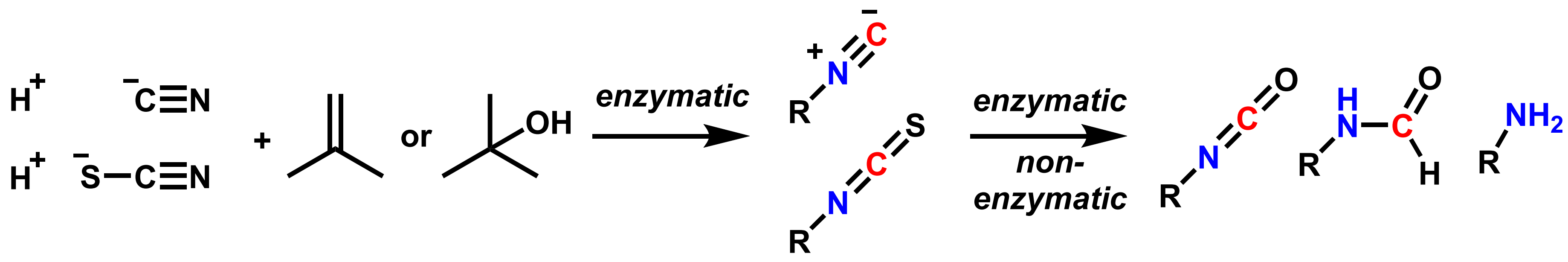
Albizati (1985)[1]



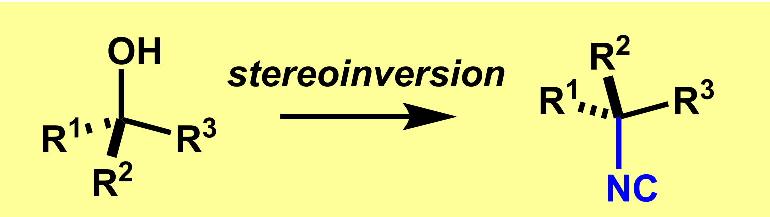
Corey (1987)[2], Jiménez (2007)[3], Srikrishna (2009)[4]

1. Stevens, R. V.; Albizati, K. F. *J. Org. Chem.* **1985**, *50*, 632.
2. Corey, E. J.; Magriotis, P. A. *J. Am. Chem. Soc.* **1987**, *109*, 287.
3. Castellanos, L.; Duque, C.; Rodríguez, J.; Jiménez, C. *Tetrahedron* **2007**, *63*, 1544.
4. Srikrishna, A.; Ravi, G.; Subbaiah, D. R. C. *Synlett* **2009**, *1*, 32.

General biosynthetic pathway



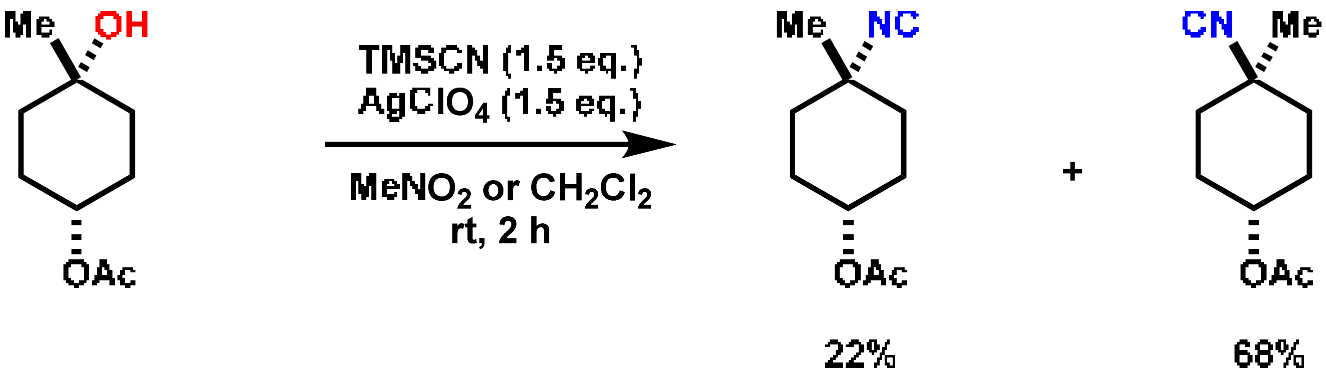
Simpson, J. S.: Garson, M.J. *Tetrahedron Lett.* **1998**, *39*, 5819.



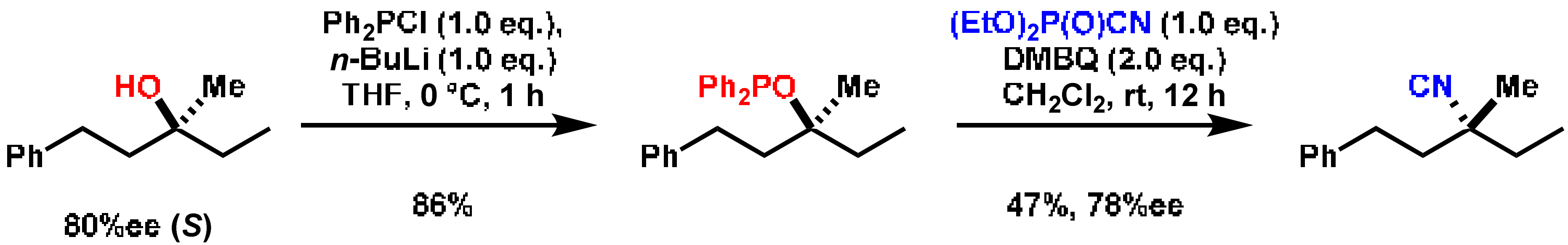
Sakaguchi (2002)[1], Mukaiyama (2006)[2], Shenvi (2013)[3]

1. Kitano, Y.; Ito, T.; Suzuki, T.; Sakaguchi, I. et *al. J. Chem. Soc., Perkin Trans. 1* **2002,** 2251.
2. Masutani, K.; Minowa, T.; Hagiwara, Y.; Mukaiyama, T. Bu*ll. Chem. Soc. Jpn.* **2006,** 79*,* 1106.
3. Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. Na*ture* **2013,** 50*1,* 195.

Tertiary alcohol displacement to form isonitrile



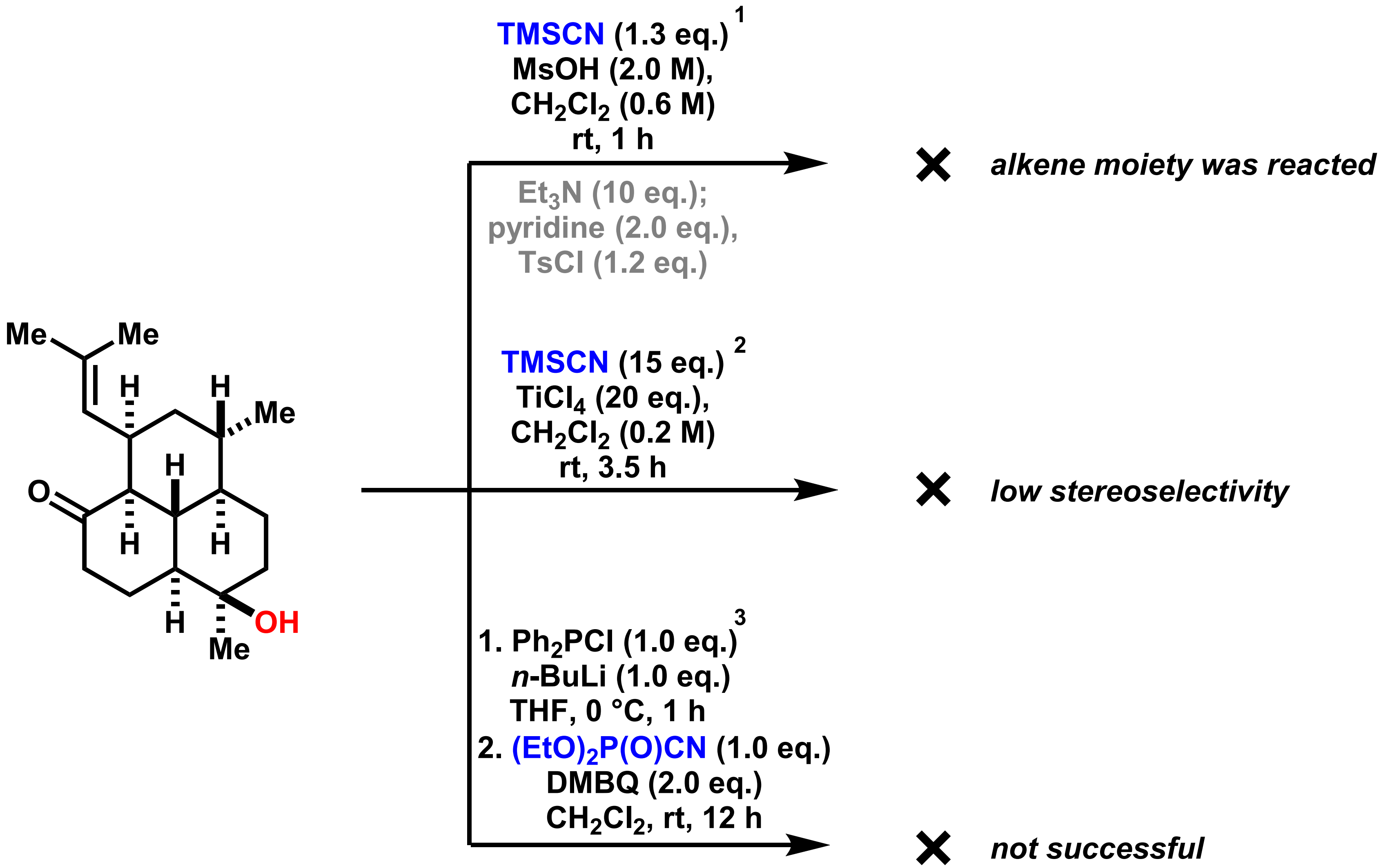
Kitano, Y.; Chiba, K.; Tada. M. *Synthesis* **2001**, *3*, 437.



DMBQ: 2,6-dimethoxy-1,4-benzoquinone

Masutani, K.; Minowa, T.; Hagiwara, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106.

Attempt for more complex compound



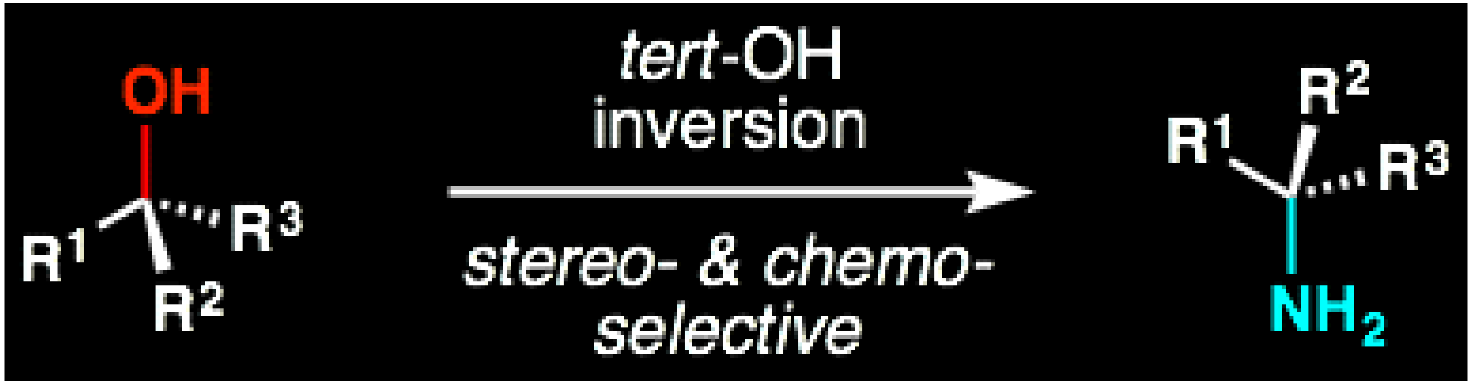
1. Okuda, I.; Kitano, Y. *Synthesis* **2011**, *24*, 3997.
2. Corey, E. J.; Magriotis, P. J. *J. Am. Chrm. Soc.* **1987**, *109*, 287,
3. Masutani, K.; Minowa, T.; Hagiwara, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106.

LETTER

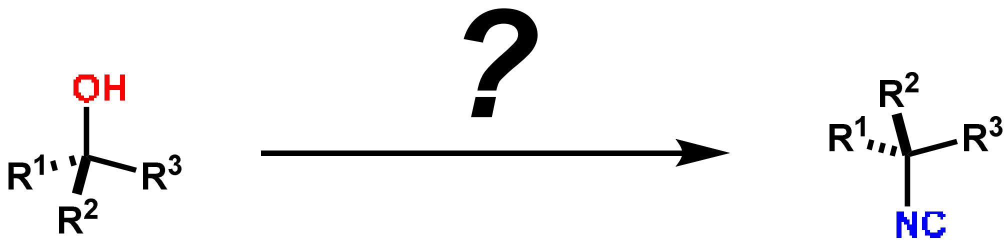
doi:10.1038/nature12472

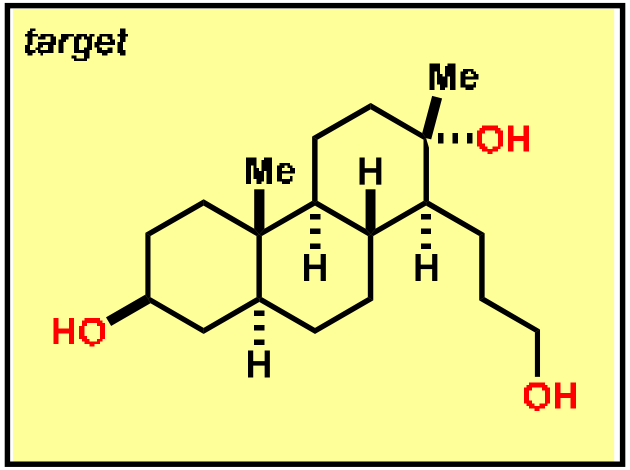
Stereoinversion of tertiary alcohols to tertiary-alkyl isonitriles and amines

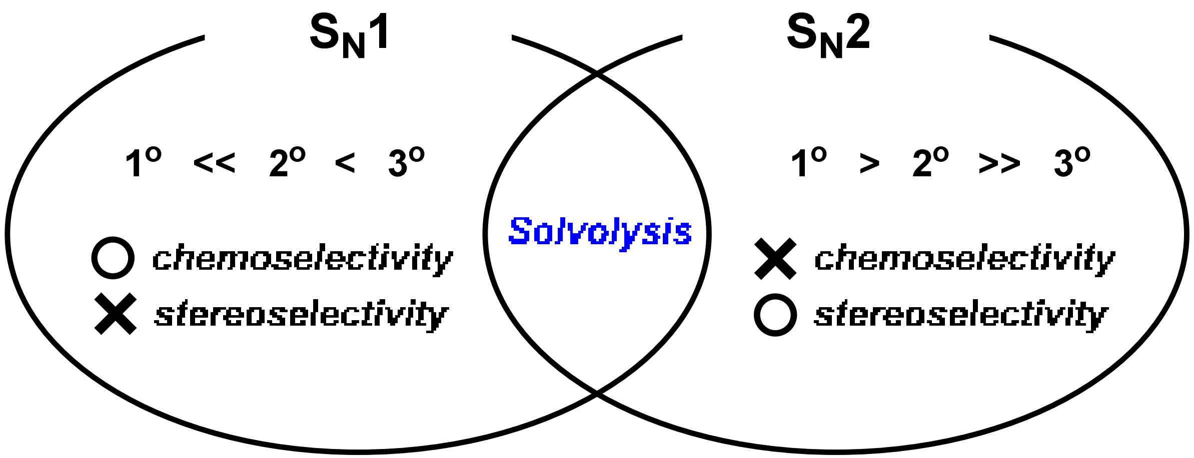
Sergey V. Pronin[1], Christopher A. Reiher[1] & Ryan A. Shenvi[1]



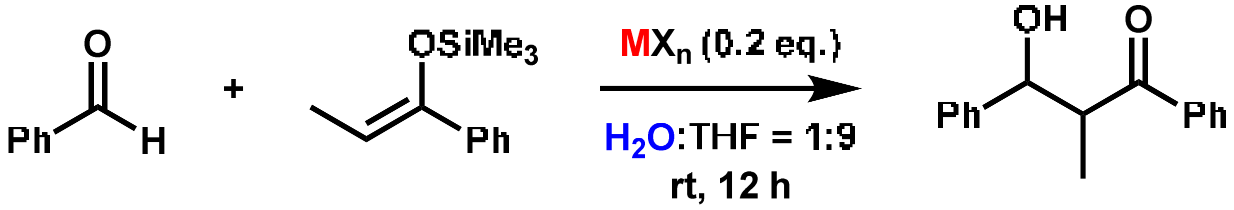
Strategy for stereoinversion



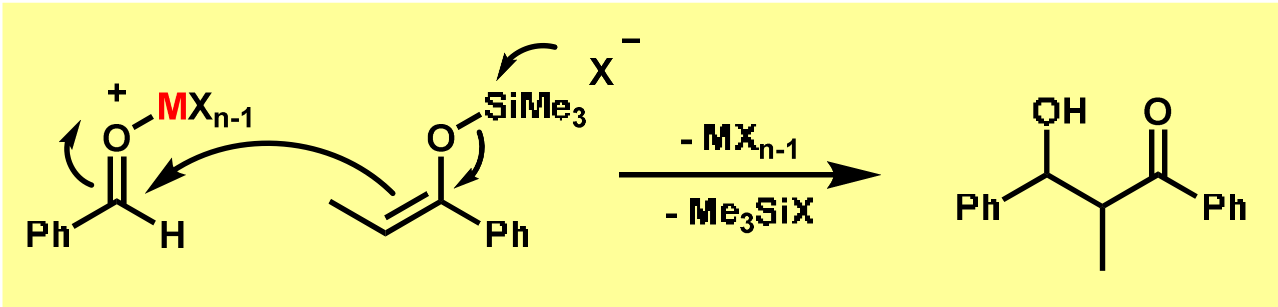


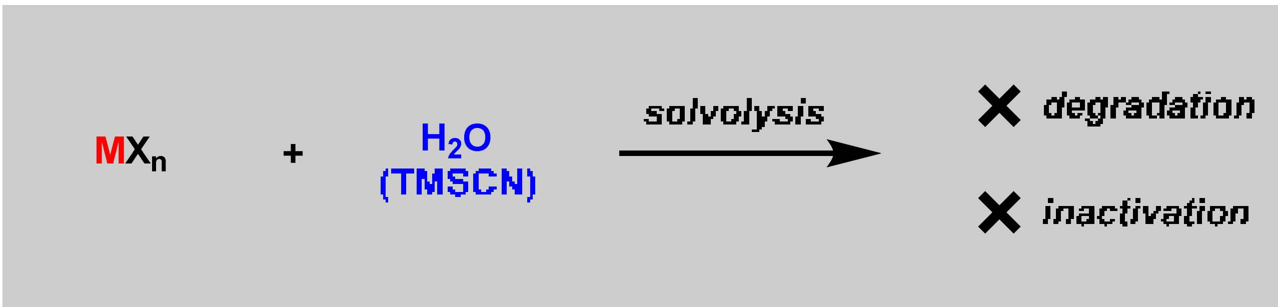


Kobayashi's work: Lewis acid catalysed solvolysis



Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.





pK_h and WERC (1)

· pK_h (K_h : hydrolysis constant, 加水分解定数),

$$x\,M^{Z+} + y\,H_2O \rightleftharpoons M_x(OH)_y^{(xz-y)+} + y\,H^+$$

$$v_1 = k_1[M^{z+}]^x \cdot [H_2O]^y$$
$$v_2 = k_2[M_x(OH)_y^{(xz-y)+}] \cdot [H^+]^y$$

Equilibrium state: $v_1 = v_2$

$$K = \frac{k_1}{k_2} = \frac{[M_x(OH)_y^{(xz-y)+}] \cdot [H^+]^y}{[M^{z+}]^x \cdot [H_2O]^y}$$

$[H_2O]^y$ is the constant at equilibrium state

$$K_{xy} = K \cdot [H_2O]^y = \frac{[M_x(OH)_y^{(xz-y)+}] \cdot [H^+]^y}{[M^{z+}]^x}$$

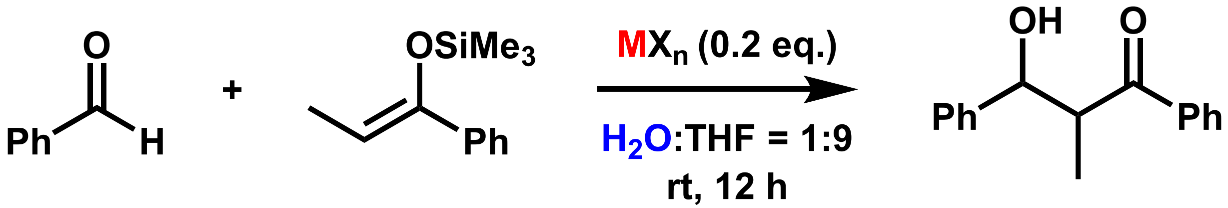
pK_h = -log(K_{xy}) (index of hydrolysis rate)

· WERC (water exchange rate constant, 水分子交換定数)

$$[MS_6]^{n+} + L \rightleftharpoons [MLS_5]^{n+} + S$$ (S: solvent, L: ligand)

WERC (index of ligand exchange rate)

pK_h and WERC (2)



(fast) $4.3 \leqq pK_h \leqq 10.1$ *(late)*
and
(fast) WERC $\geqq 3.2x10^{6}\ M^{-1}sec^{-1}$
gave more than 50% in the aldol reaction

Li $^{+1}$ 13.64 $4.7x10^{7}$	Be — —											B $^{+3}$ — —	C —	N — —
Na $^{+1}$ 14.18 $1.9x10^{8}$	Mg $^{+2}$ 11.44 $5.3x10^{5}$											Al $^{+3}$ 1.14 $1.6x10^{0}$	Si $^{+4}$ — —	P $^{+5}$ — —
K $^{+1}$ 14.46 $1.5x10^{8}$	Ca $^{+2}$ 12.85 $5x10^{7}$	Sc $^{+3}$ 4.3 $4.8x10^{7}$	Ti $^{+4}$ $\leq$2.3 —	V $^{+3}$ 2.26 $1x10^{3}$	Cr $^{+3}$ 4.0 $5.8x10^{-7}$	Mn $^{+2}$ 10.59 $3.1x10^{7}$	Fe $^{+2}$ 9.5 $3.2x10^{6}$	Co $^{+2}$ 9.65 $2x10^{5}$	Ni $^{+2}$ 9.86 $2.7x10^{4}$	Cu $^{+2}$ 7.53 $2x10^{8}$	Zn $^{+2}$ 8.96 $5x10^{8}$	Ga $^{+3}$ 2.6 $7.6x10^{2}$	Ge $^{+4}$ — —	As — —
Rb — —	Sr — —	Y $^{+3}$ 7.7 $1.3x10^{7}$	Zr $^{+4}$ 0.22 —	Nb $^{+5}$ (0.6) —	Mo $^{+5}$ — —	Tc — —	Ru $^{+3}$ — —	Rh $^{+3}$ 3.4 $3x10^{-8}$	Pd $^{+2}$ 2.3 —	Ag $^{+1}$ 12 $>5x10^{6}$	Cd $^{+2}$ 10.08 $>1x10^{8}$	In $^{+3}$ 4.00 $4.0x10^{4}$	Sn $^{+4}$ — —	Sb $^{+5}$ — —
Cs — —	Ba 13.47 $>6x10^{7}$	Ln $^{+3}$ 7.6-8.5 10^{6}-10^{8}	Hf $^{+4}$ 0.25 —	Ta $^{+5}$ (-1) —	W $^{+6}$ — —	Re $^{+5}$ — —	Os $^{+3}$ — —	Ir $^{+3}$ — —	Pt $^{+2}$ 4.8 —	Au $^{+1}$ — —	Hg $^{+2}$ 3.40 $2x10^{9}$	Tl $^{+3}$ 0.62 $7x10^{5}$	Pb $^{+2}$ 7.71 $7.5x10^{9}$	Bi $^{+3}$ 1.09 —

La $^{+3}$ 8.5 $2.1x10^{8}$	Ce $^{+3}$ 8.3 $2.7x10^{8}$	Pr $^{+3}$ 8.1 $3.1x10^{8}$	Nd $^{+3}$ 8.0 $3.9x10^{8}$	Pm — —	Sm $^{+3}$ 7.9 $5.9x10^{8}$	Eu $^{+3}$ 7.8 $6.5x10^{8}$	Gd $^{+3}$ 8.0 $6.3x10^{7}$	Tb $^{+3}$ 7.9 $7.8x10^{7}$	Dy $^{+3}$ 8.0 $6.3x10^{7}$	Ho $^{+3}$ 8.0 $6.1x10^{7}$	Er $^{+3}$ 7.9 $1.4x10^{8}$	Tm $^{+3}$ 7.7 $6.4x10^{6}$	Yb $^{+3}$ 7.7 $8x10^{7}$	Lu $^{+3}$ 7.6 $6x10^{7}$

pK_{hAl} << 4.3
$WERC_{Al}$ << $3.2x10^{6}$

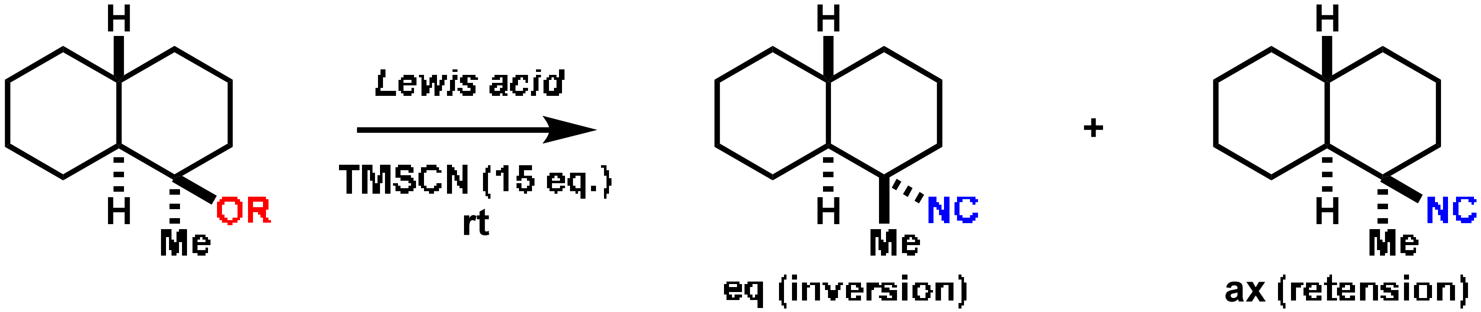
$$Al(OTf)_3 \xrightarrow{H_2O} Al^{3+} + 3\ ^{-}OTf \overset{H_2O}{\rightleftharpoons} [Al(H_2O)_6]^{3+} \overset{H_2O}{\rightleftharpoons} H_3O^{+}[Al(H_2O)_5(OH)]^{2+}$$

pK_{hNa} >> 4.3
$WERC_{Na}$ > $3.2x10^{6}$

$$NaOTf \xrightarrow{H_2O} Na^{+} + \ ^{-}OTf \overset{H_2O}{\rightleftharpoons} [Na(H_2O)_n]^{+} \overset{H_2O}{\not\rightarrow}$$

Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.

Optimization of Lewis acids and alcohol derivatives



entry	proportion (mol%)	*Lewis acid*	R	NC(%)	d.r. (eq : ax)
1	10	$ZnBr_2$	TFA	0	n/a
2	5	$Mg(OTf)_2$	TFA	0	n/a
3	5	$Bi(OTf)_3$	TFA	14	49 : 51
4	5	$Y(OTf)_3$	TFA	70	84 : 16
5	3	$Sc(OTf)_3$	TFA	86	88 : 12
6	3	$Sc(OTf)_3$	H	0	n/a
7	3	$Sc(OTf)_3$	Ac	75	76 : 24
8	3	$Sc(OTf)_3$	CHO	61	66 : 34
9	3	$Sc(OTf)_3$	$C(O)C_2F_5$	69	85 : 15
10	3	$Sc(OTf)_3$	$C(O)C_3F_7$	79	87 : 13

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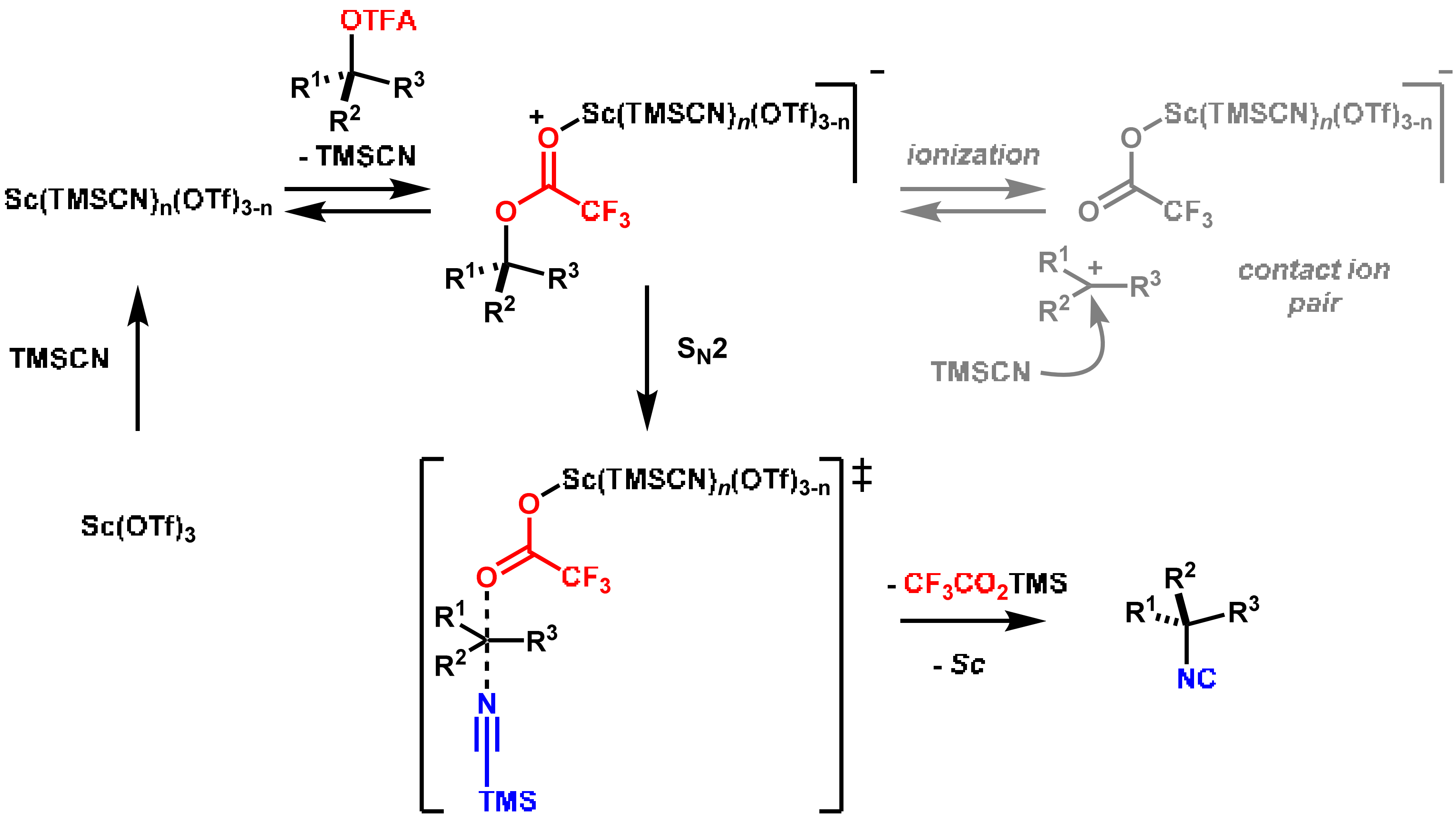
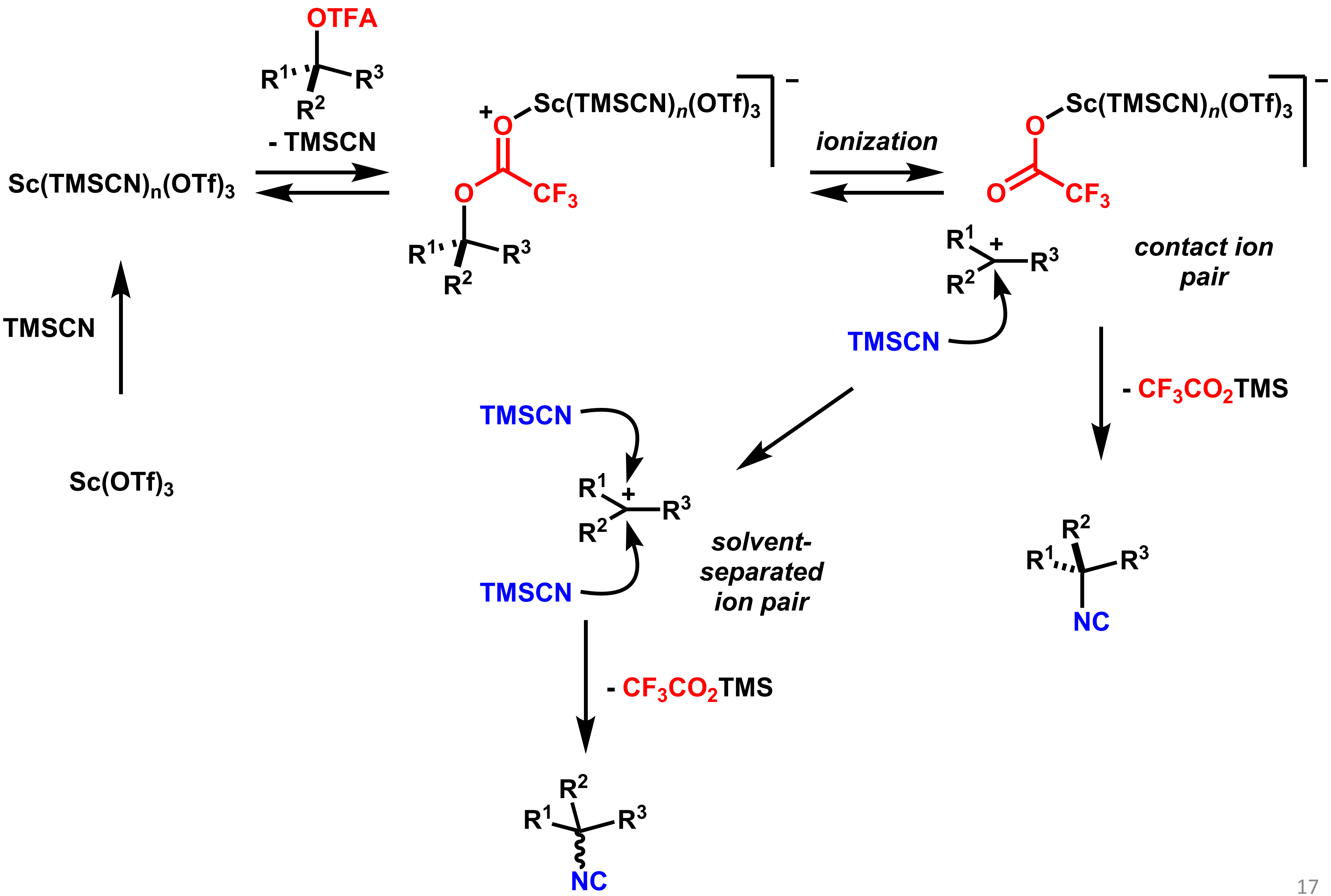
Proposed mechanism (1)

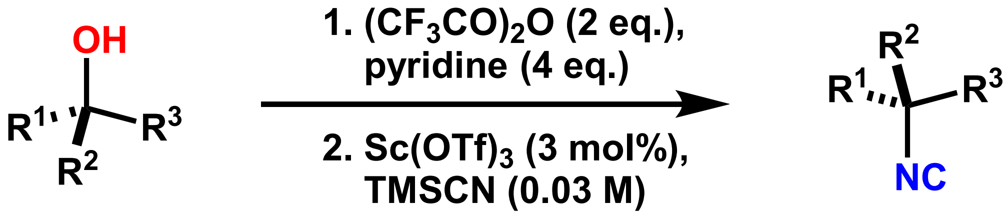


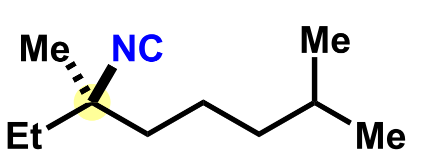
Pronin, S. V.; Reiher, C. A., Shenvi, R. A. *Nature* **2013**, *501*, 195.

Proposed mechanism

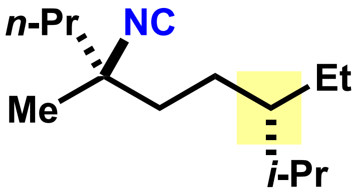


Substrate scope (solvolysis of TMSCN)

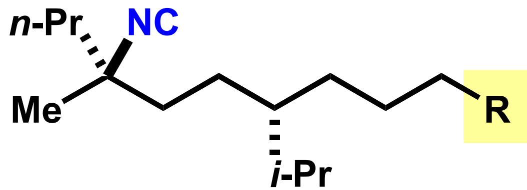




78%, 90%(inversion)
(e.r. = 84:16)



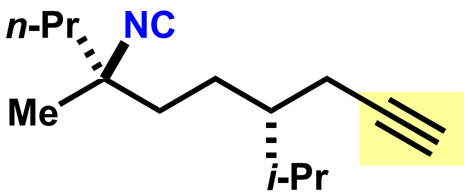
71% (d.r.=88:12)



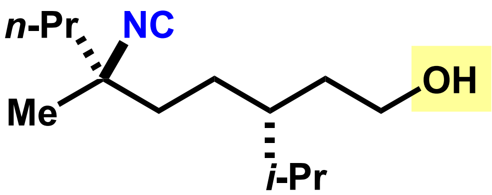
R = ⌇—CO_2Et :68% (d.r.=89:11)

R = ⌇—CN :67% (d.r.=86:14)

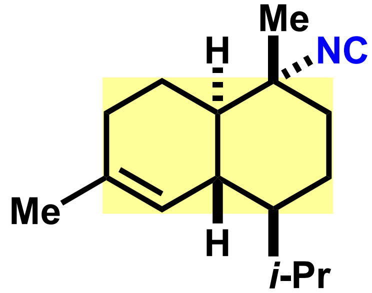
* Sc(OTf)$_3$ (6mol%)



74% (d.r.=88:12)



71% (d.r.=90:10)



59% (d.r.=91:9)

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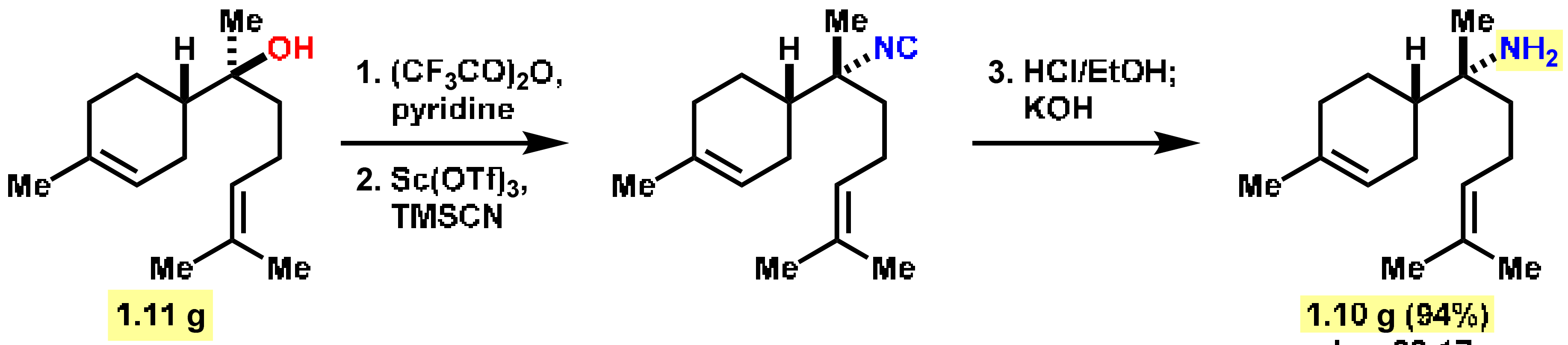
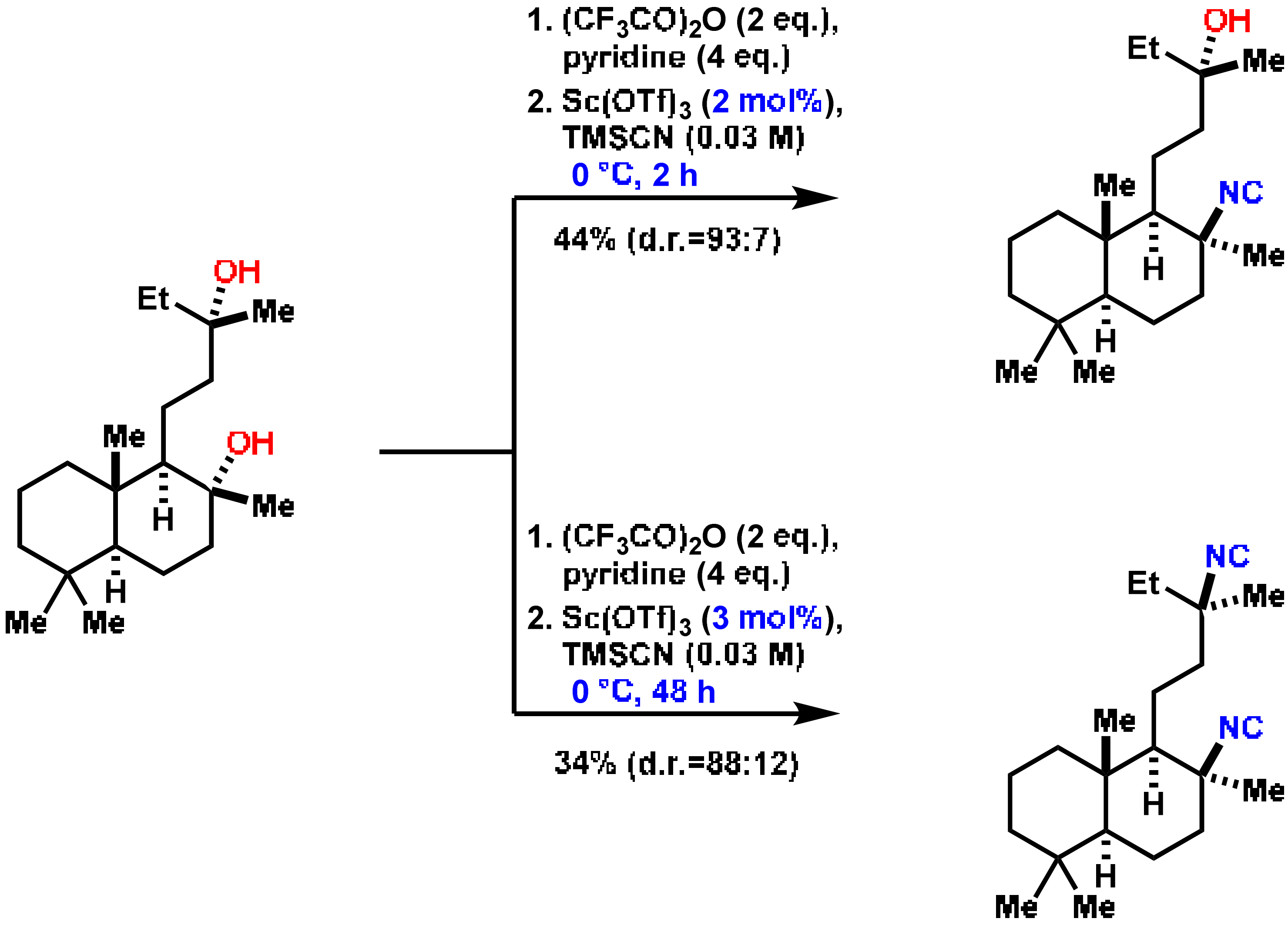
advantage of this isocyanation (1) (gram scale)



✓ *gram scale synthesis*

advantage of this isocyanation (2) (reaction order)



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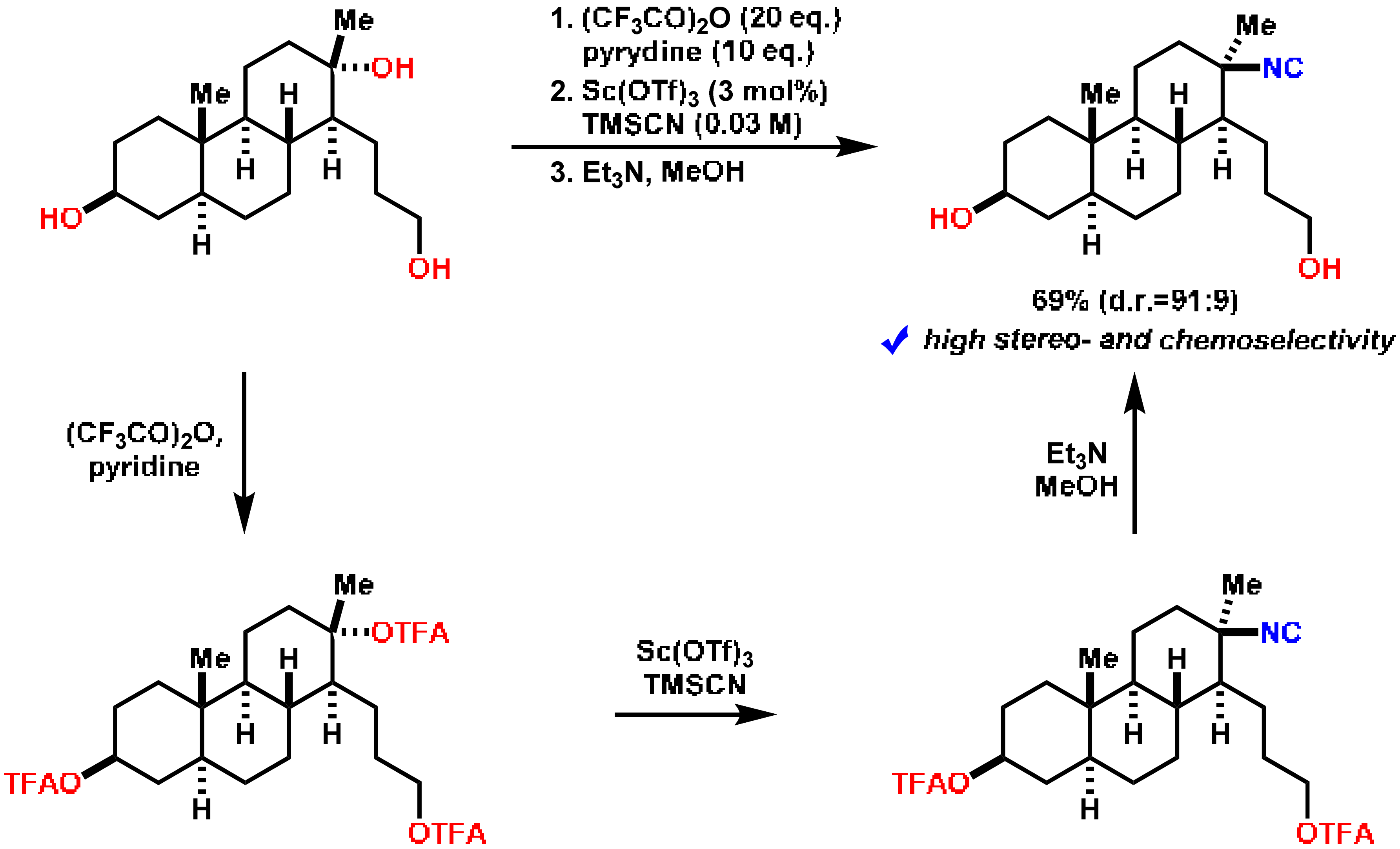
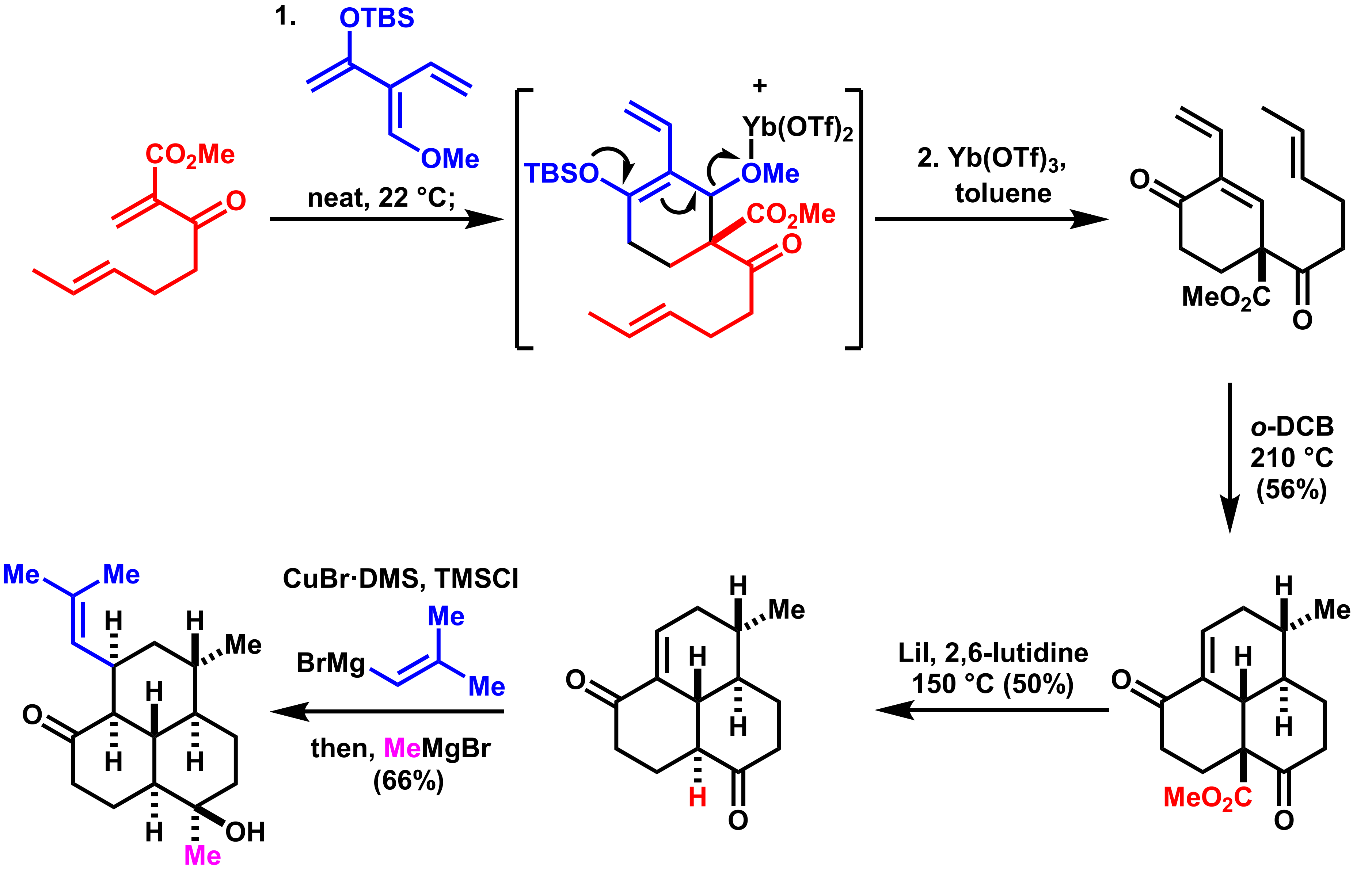
advantage of this isocyanation (3)
(stereo- and chemoselectivity)



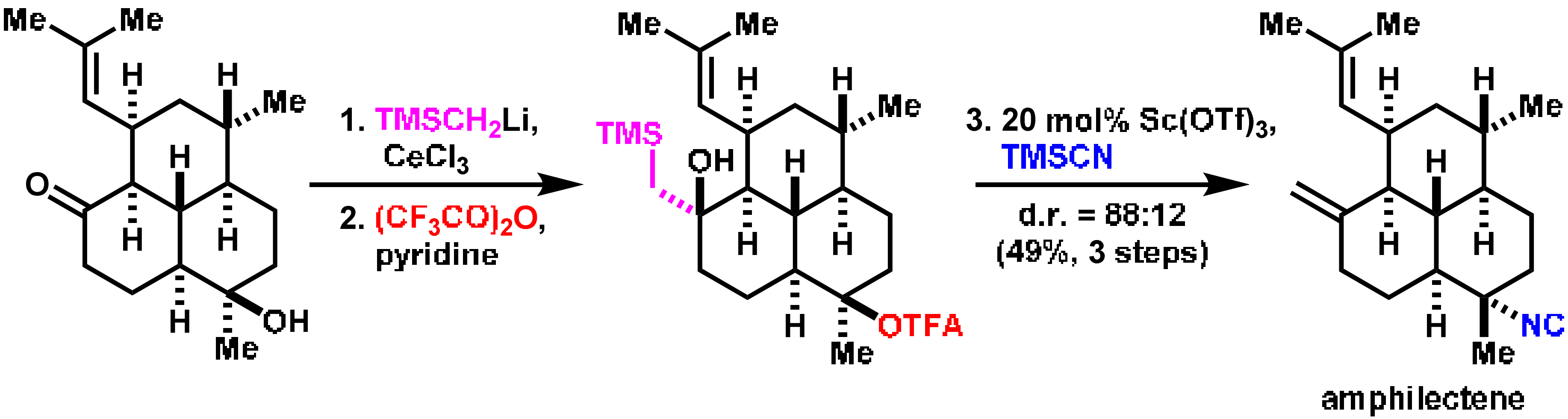
Pronin. S. V.; Reiher. C. A., Shenvi, R. A. *Nature* **2013**, *501*, 195.

Application to total synthesis of marine diterpene (1)



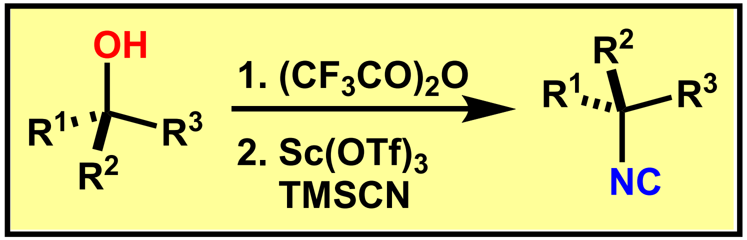
Pronin, S. V.; Shenvi, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 19604.

Application to total synthesis of marine diterpene (2)

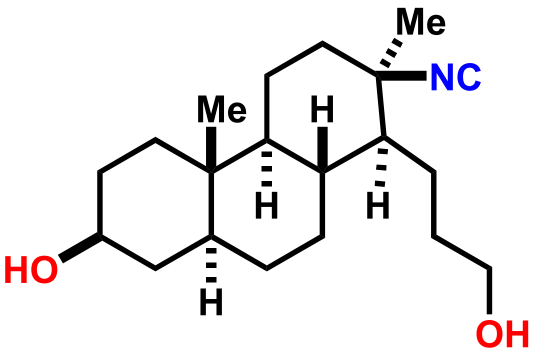


Pronin, S. V.; Shenvi, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 19604.

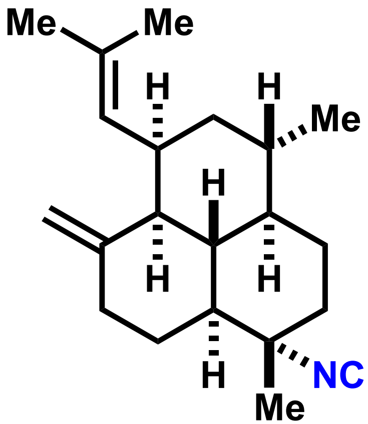
Summary



<stereoinversion of tertiary alcohols to tertiary-alkyl isonitriles>



stereo- and chemoselectivity

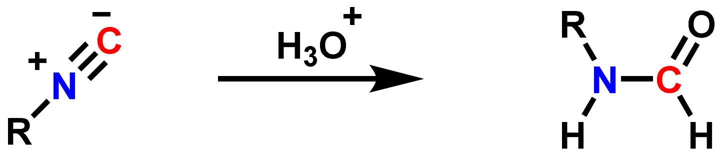


total synthesis of amphilectene

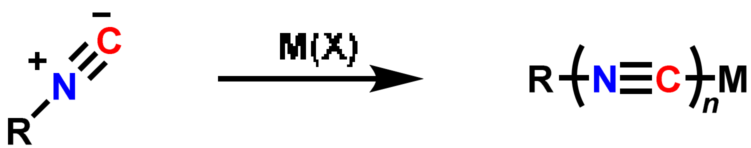
Appendix

Representative isonitrile reactivity

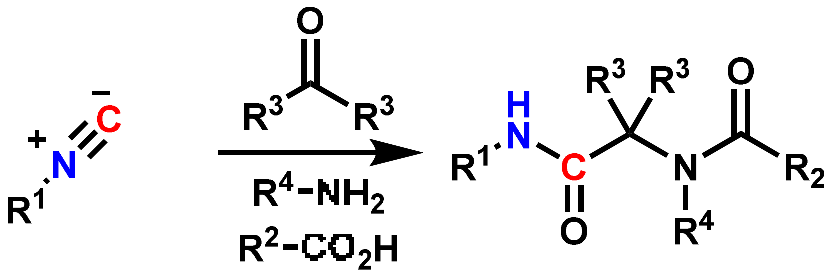
·Hydrolysis



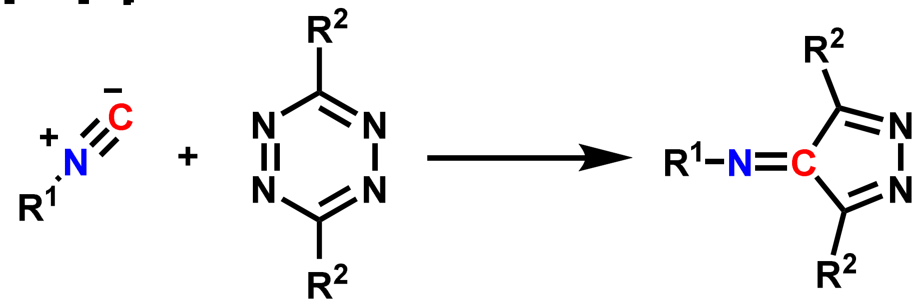
·Metal coordination



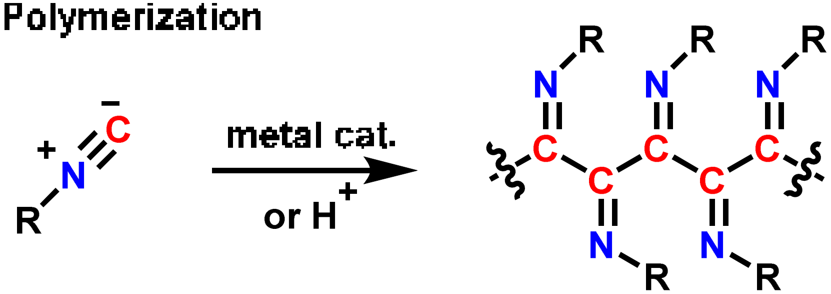
·Ugi reaction



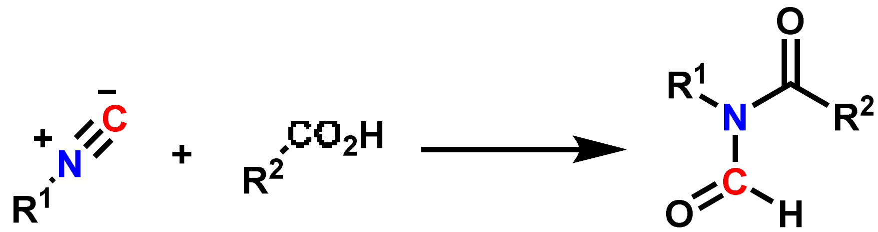
·[4+1] cycloaddition



·Polymerization

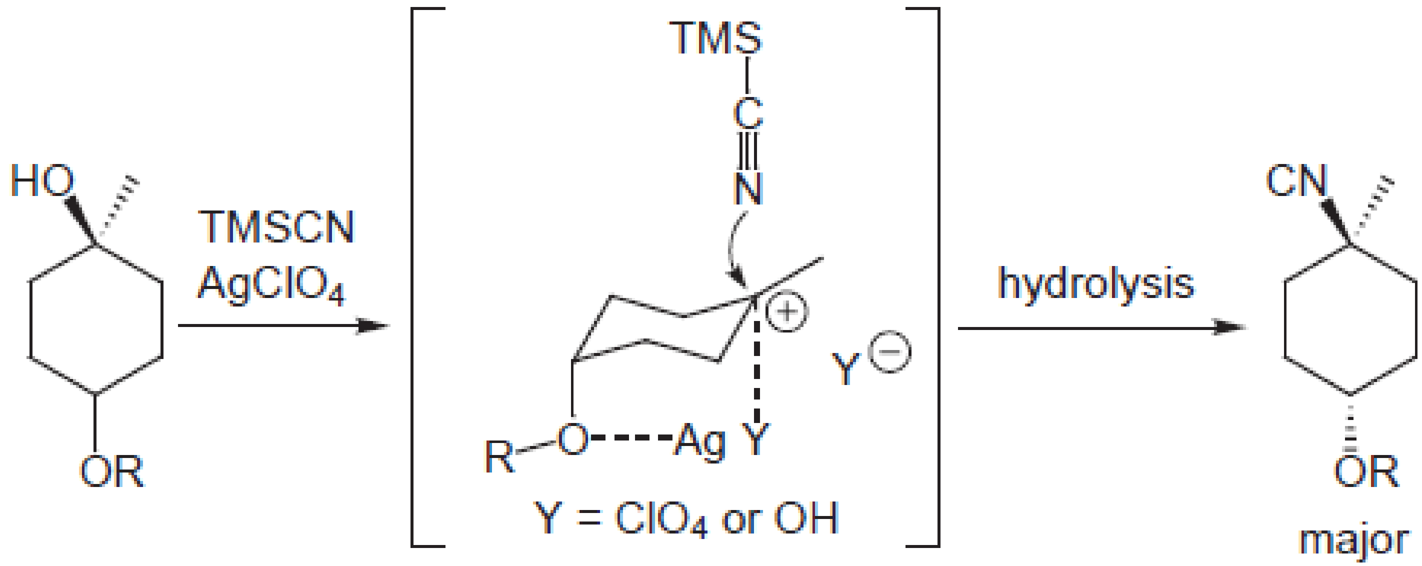


·N-Formyl amide formation

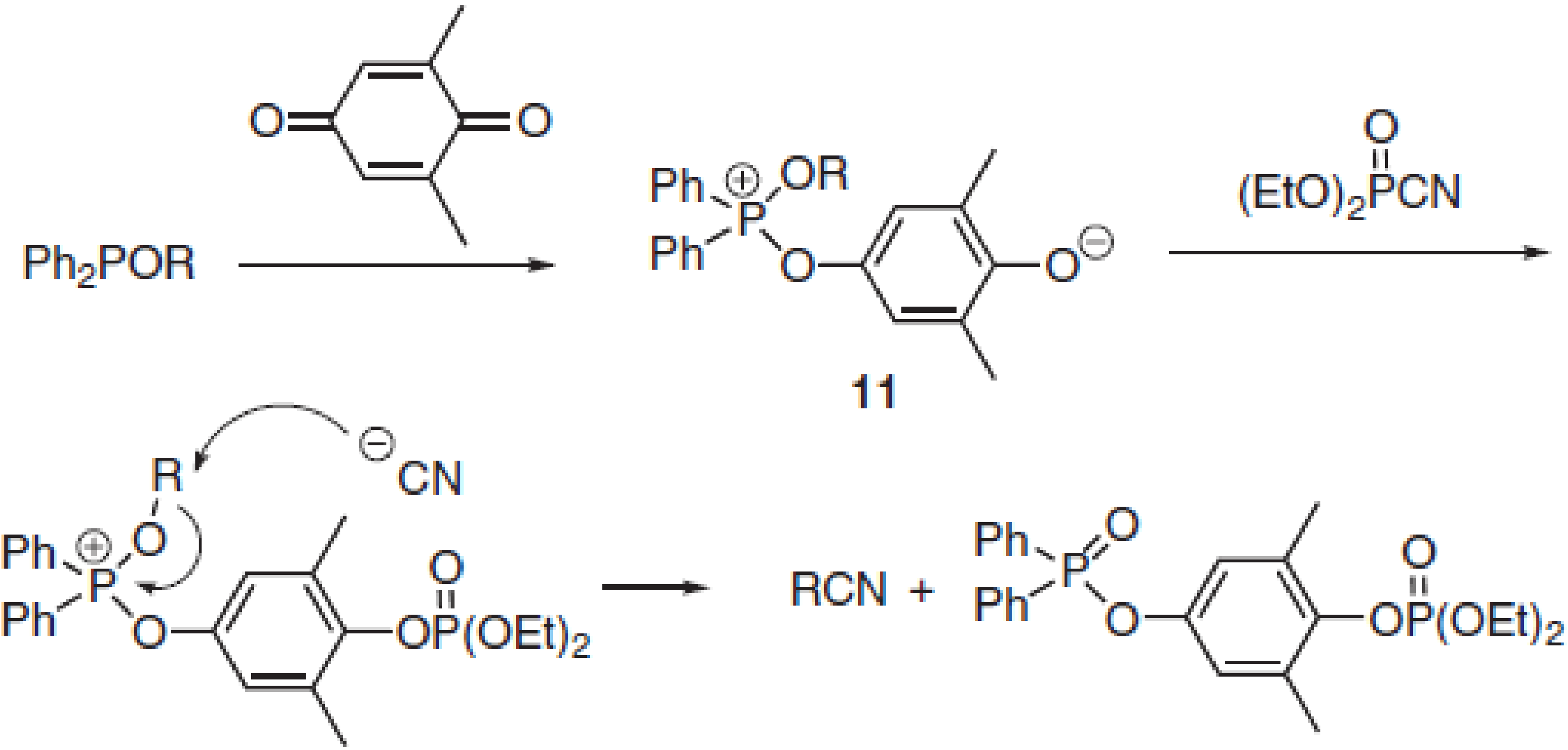


Schnermann, M. J.; Shenvi, R. A. *Nat. Prod. Rep.* **2015**, *32*, 543.

Stereoserectivity



Stereoserectivity

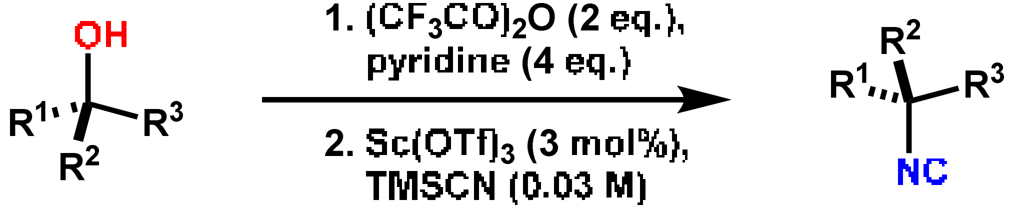


Complete list of Lewis acids screened

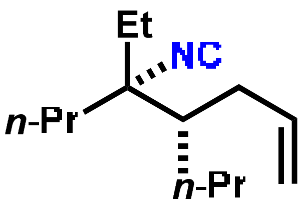
TMSOTf, $Ti(O\textit{i}\text{-}Pr)_4$, $ZnBr_2$, $Mg(OTf)_2$, $AgClO_4$, $Bi(OTf)_3$, $Yb(OTf)_3$,

$Er(OTf)_3$, $Sm(OTf)_3$, $La(OTf)_3$, $Y(OTf)_3$, $Sc(OTf)_3$.

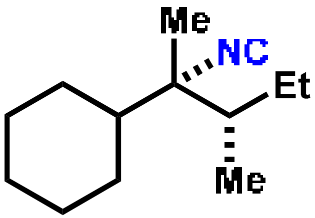
Limitation of this isocyanation



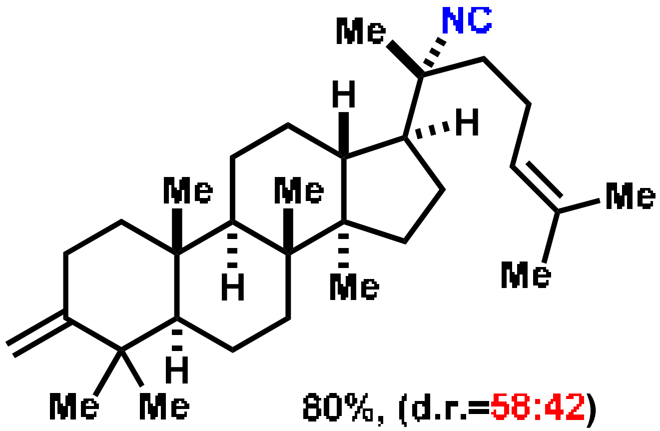
- Highly branched tertiary alcohols ✖ *poor diastereoselectivity*



58%, (d.r.=70:30)



78%, (d.r.=63:37)



80%, (d.r.=58:42)

Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. *Nature* **2013**, *501*, 195.

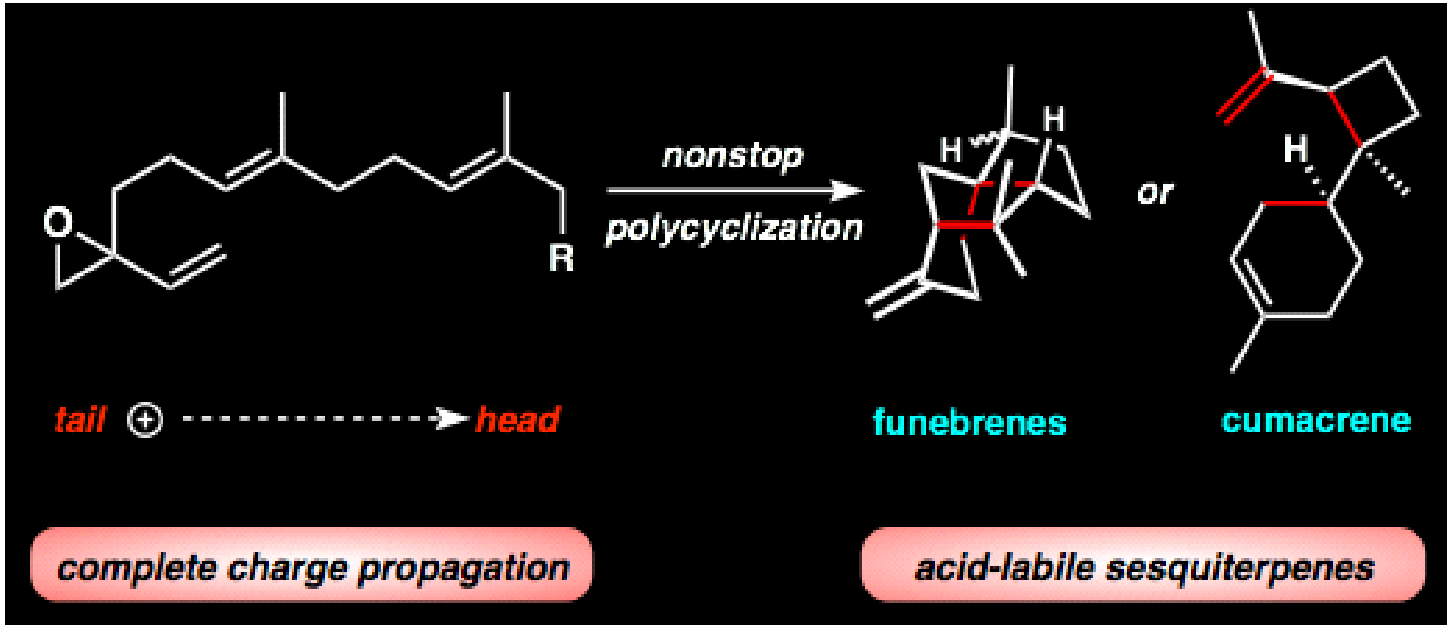
nature chemistry

ARTICLES

PUBLISHED ONLINE: 23 SEPTEMBER 2012 | DOI: 10.1038/NCHEM.1458

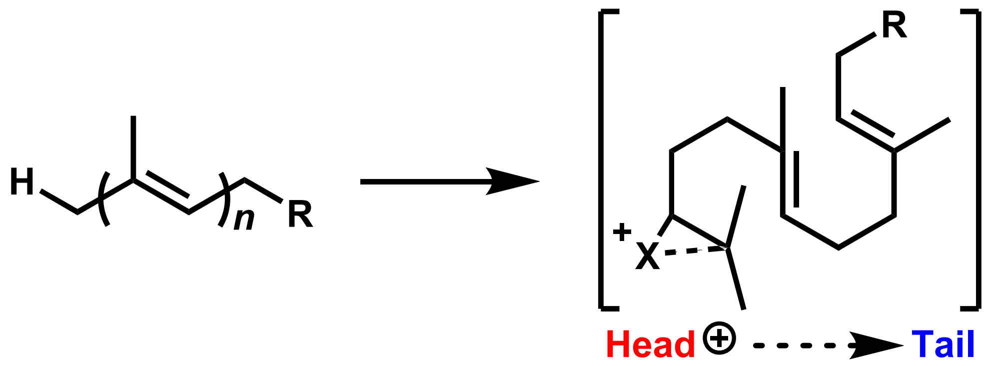
Synthesis of highly strained terpenes by non-stop tail-to-head polycyclization

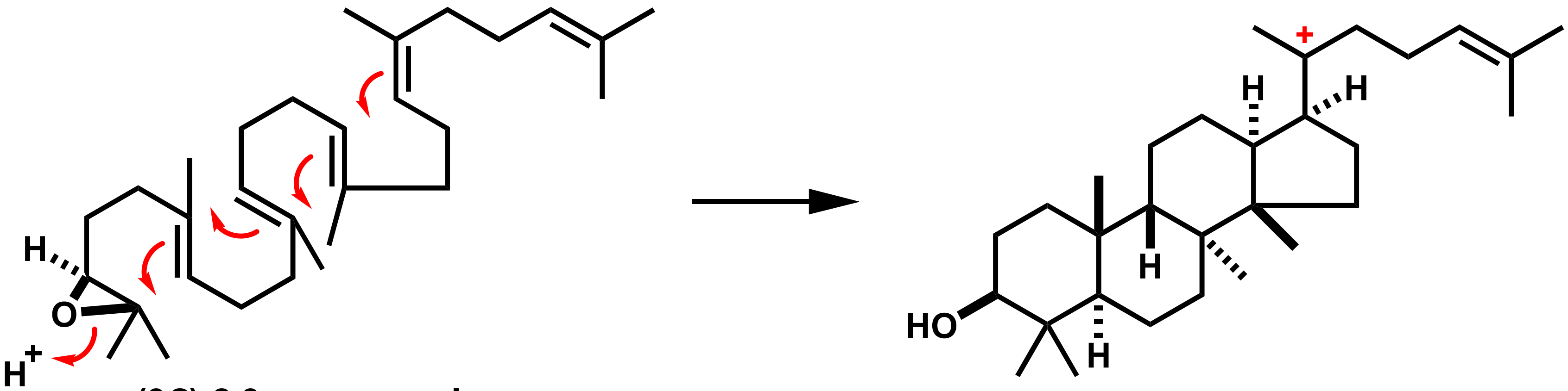
Sergey V. Pronin and Ryan A. Shenvi*



Pronin, S. V.; Shenvi, R. A. *Nature Chem.* **2012**, *4*, 915.

Head-to-Tail VS. Tail-to-Head

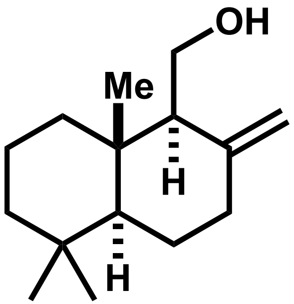




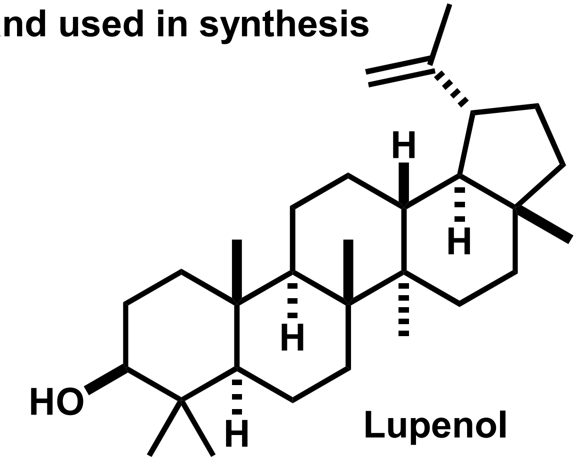
(3*S*)-2,3-epoxysqualene

protosterol intermediate

✓ extensively studied and used in synthesis

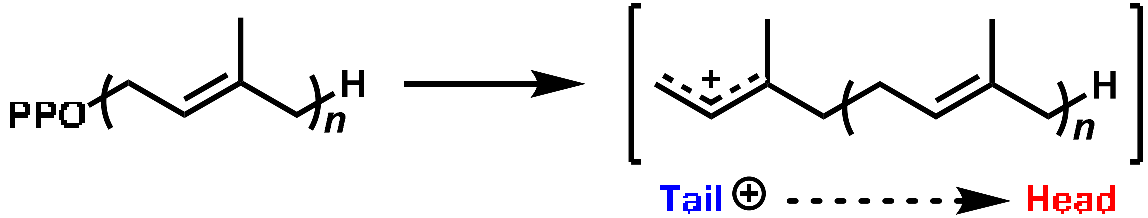


Albicanol

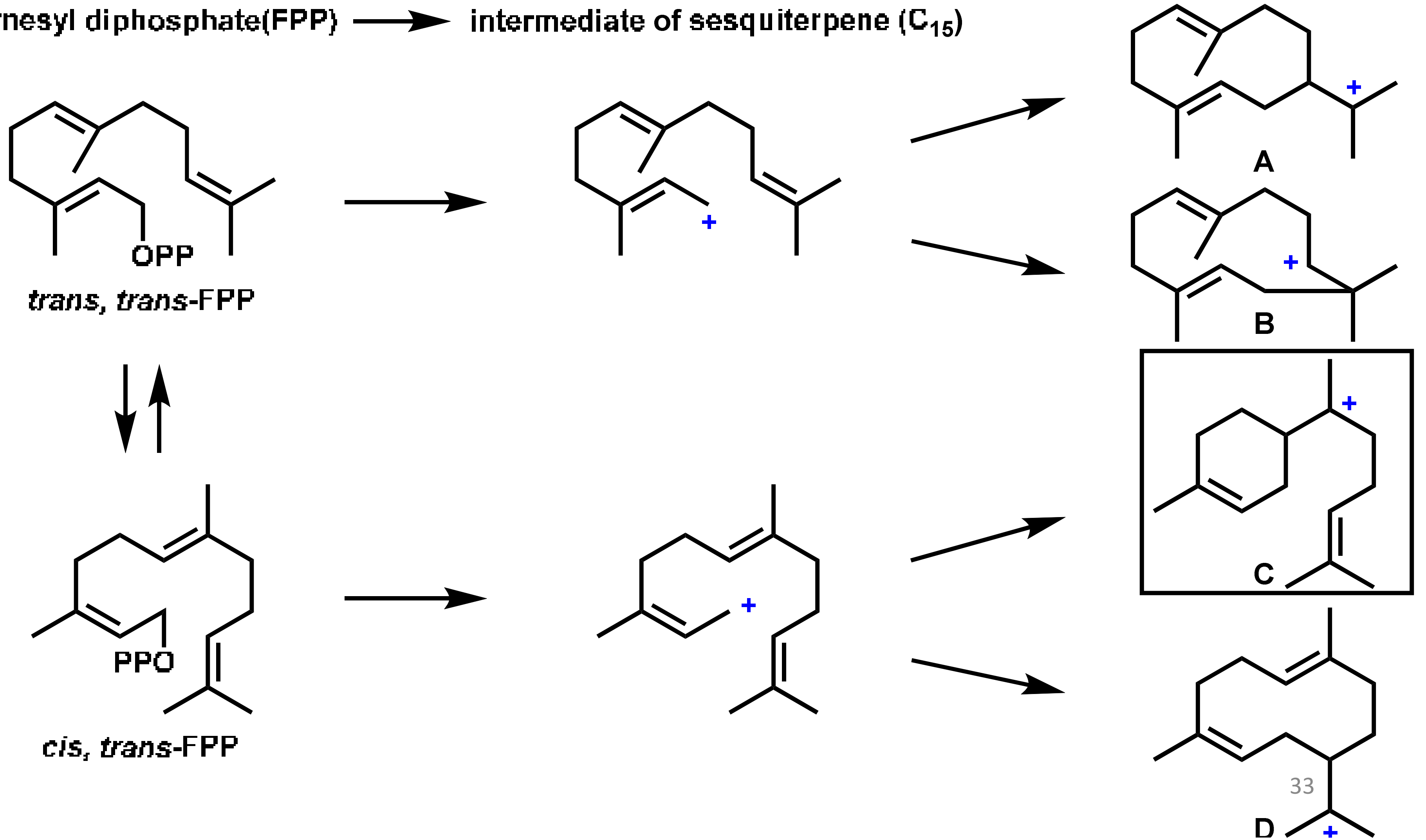


Lupenol

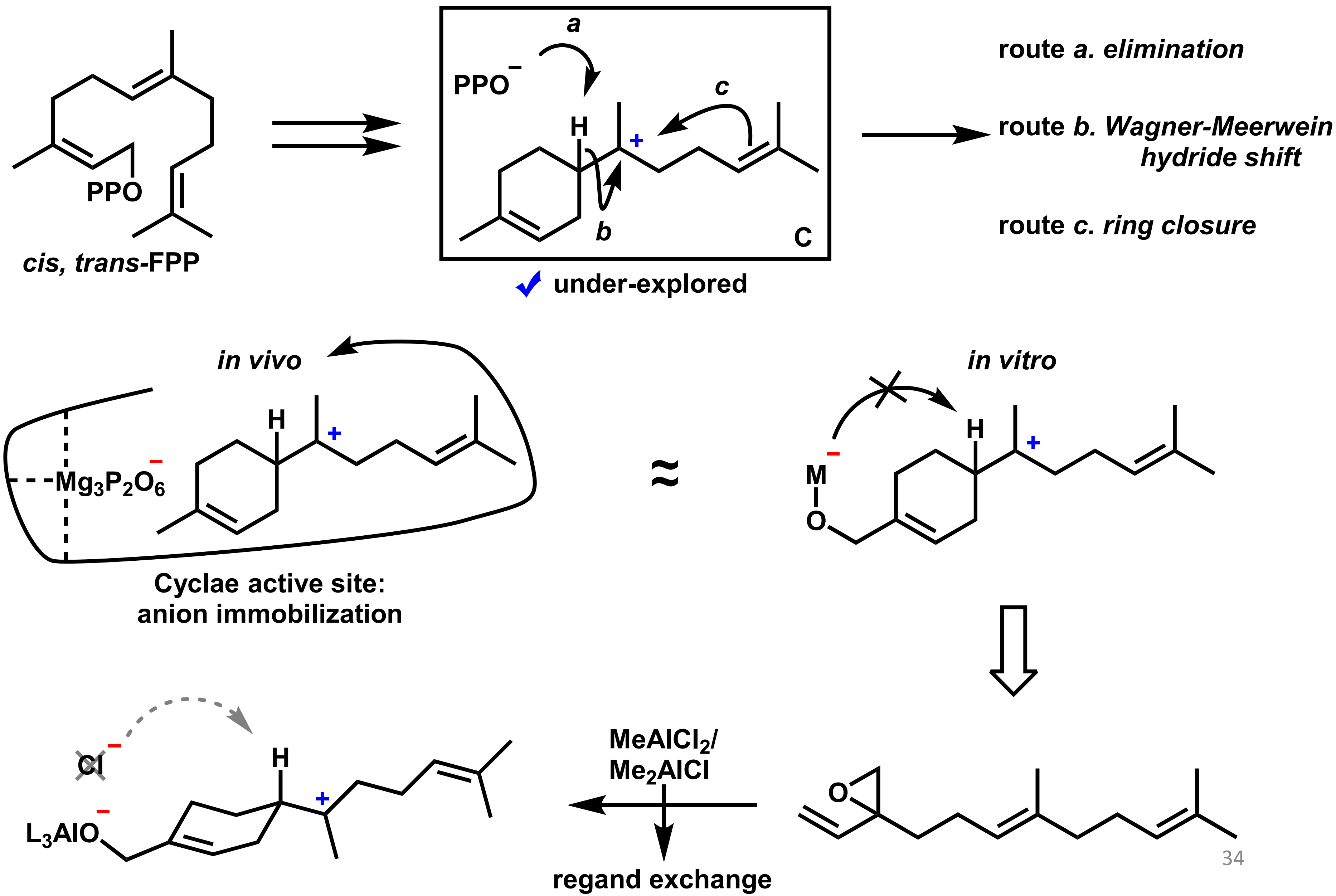
Head-to-Tail VS. Tail-to-Head



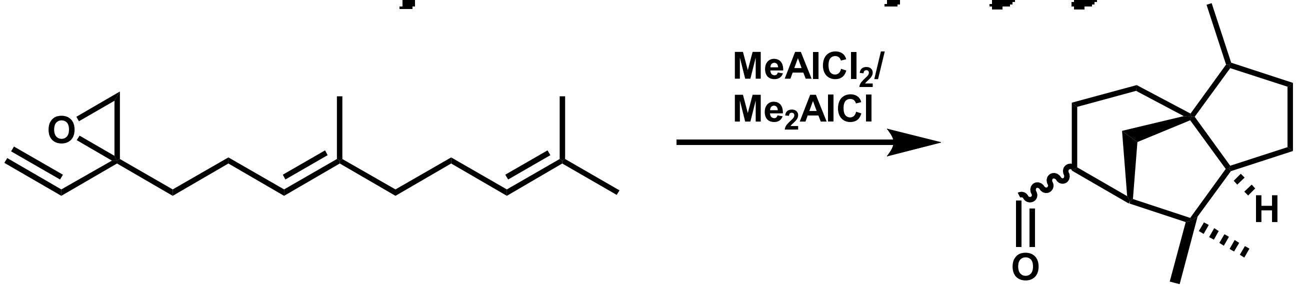
Farnesyl diphosphate(FPP) ⟶ intermediate of sesquiterpene (C_{15})



Non-stop tail to head polycyclization

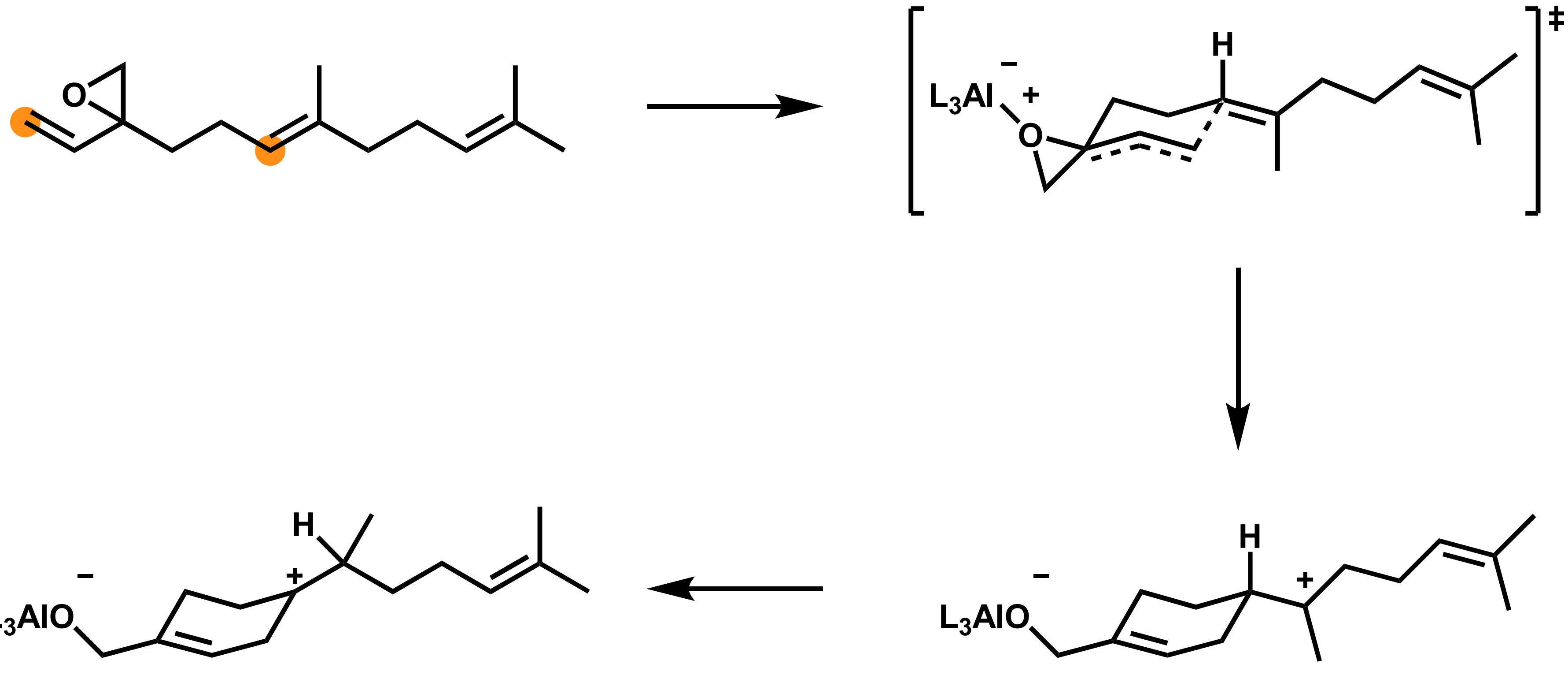


Non-stop tail to head polycyclization

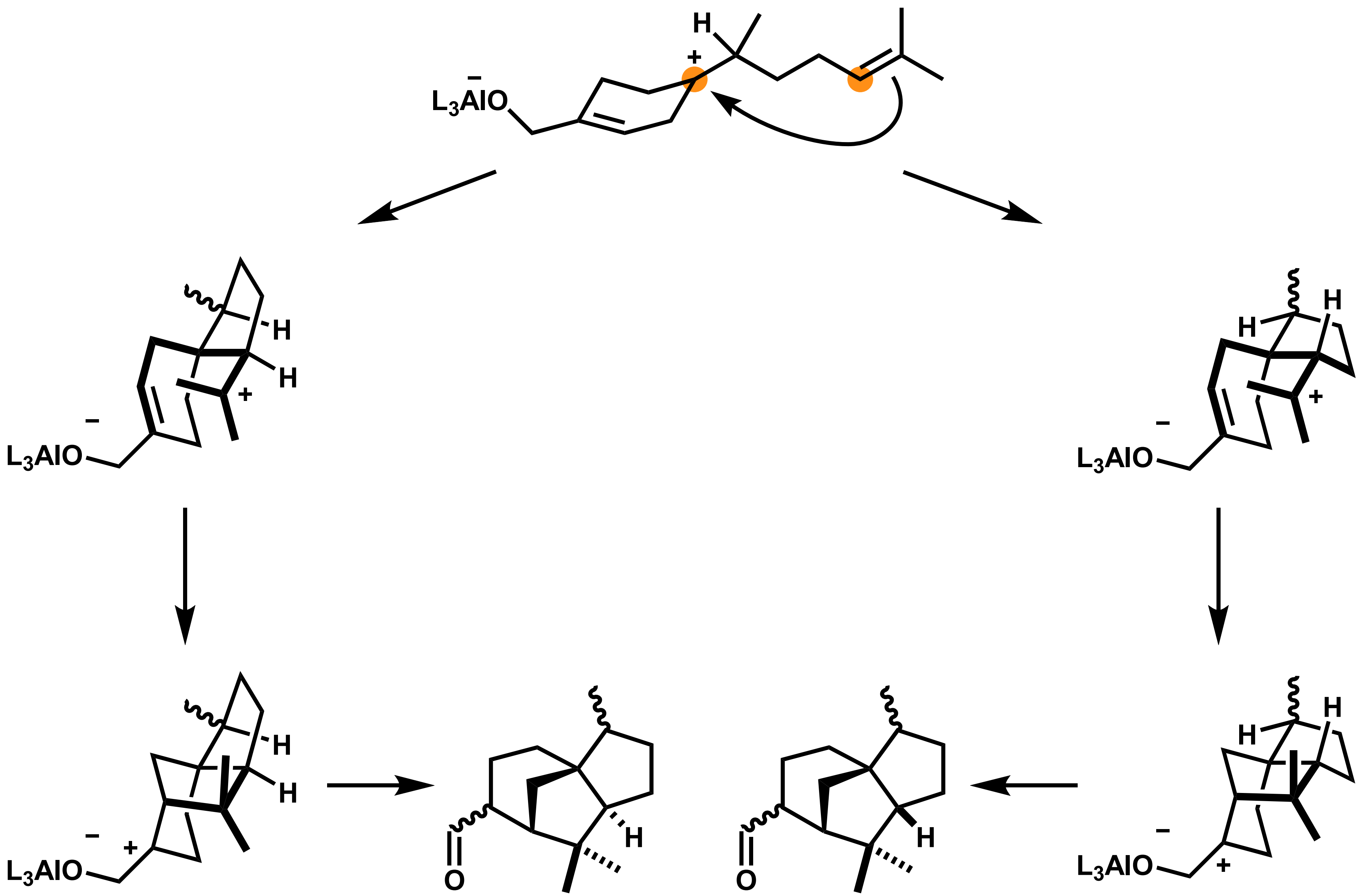


funebrene

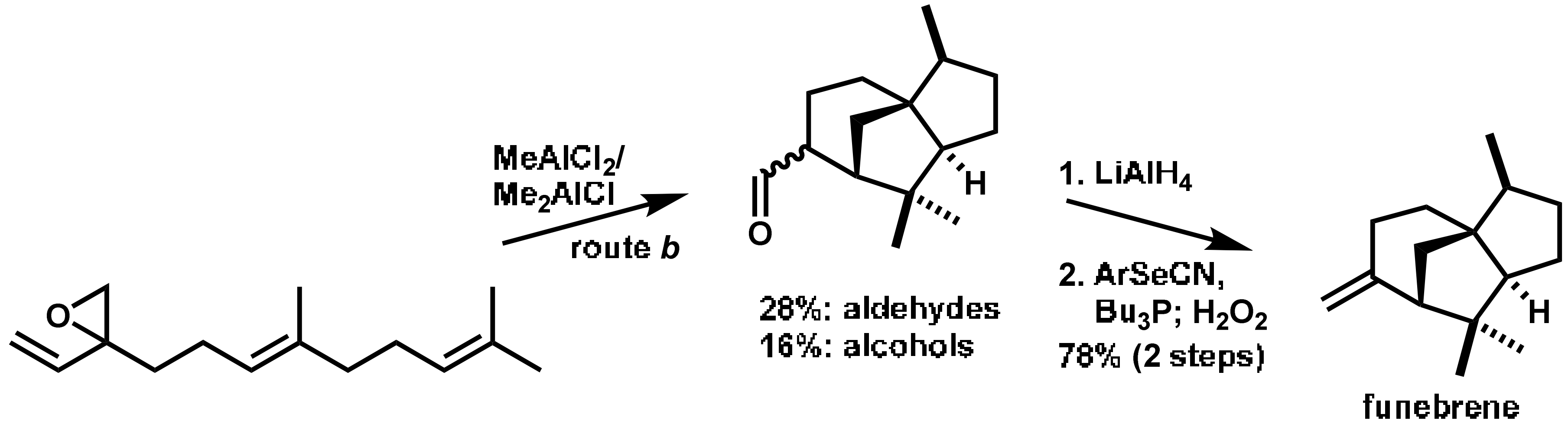
·proposed mechanism

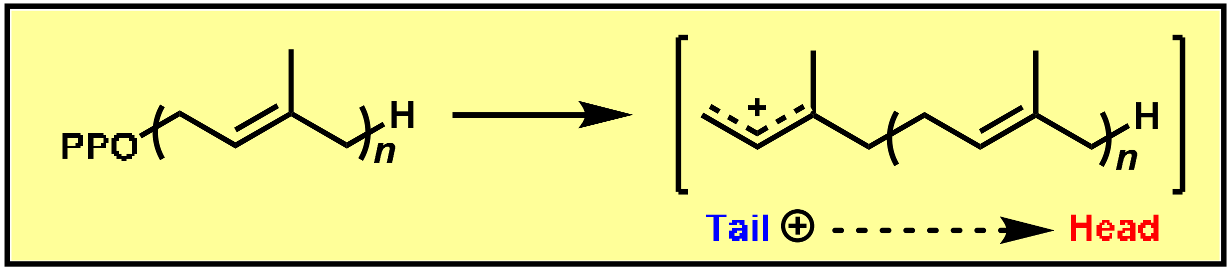


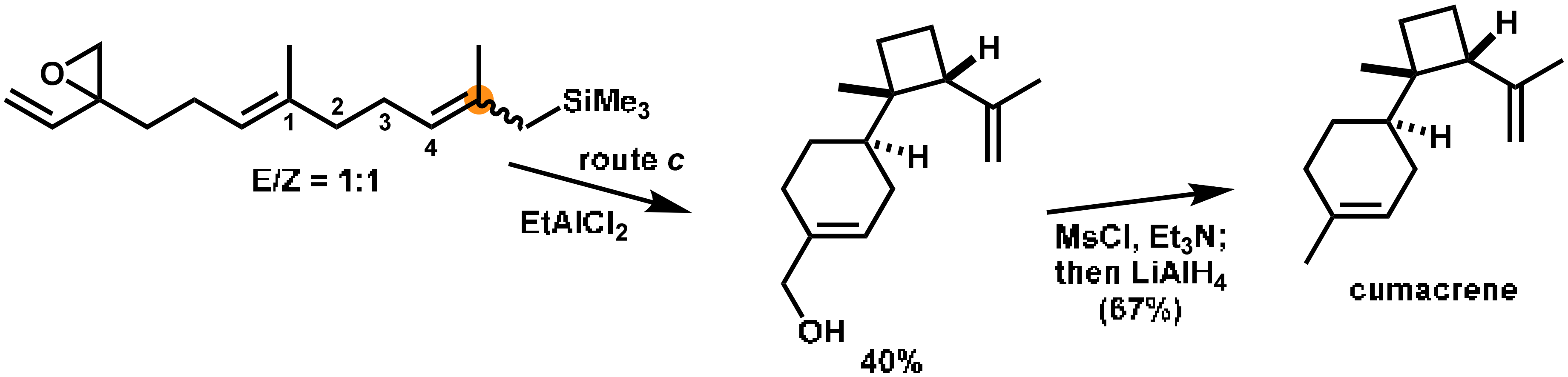
Non-stop tail to head polycyclization



Non-stop tail to head polycyclization







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Synthesis of (−)-Neothiobinupharidine

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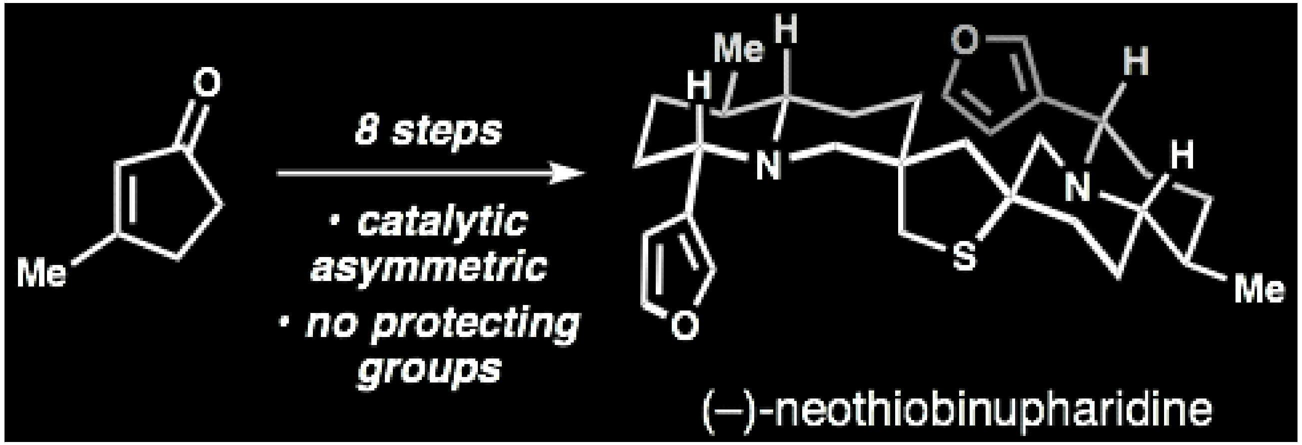
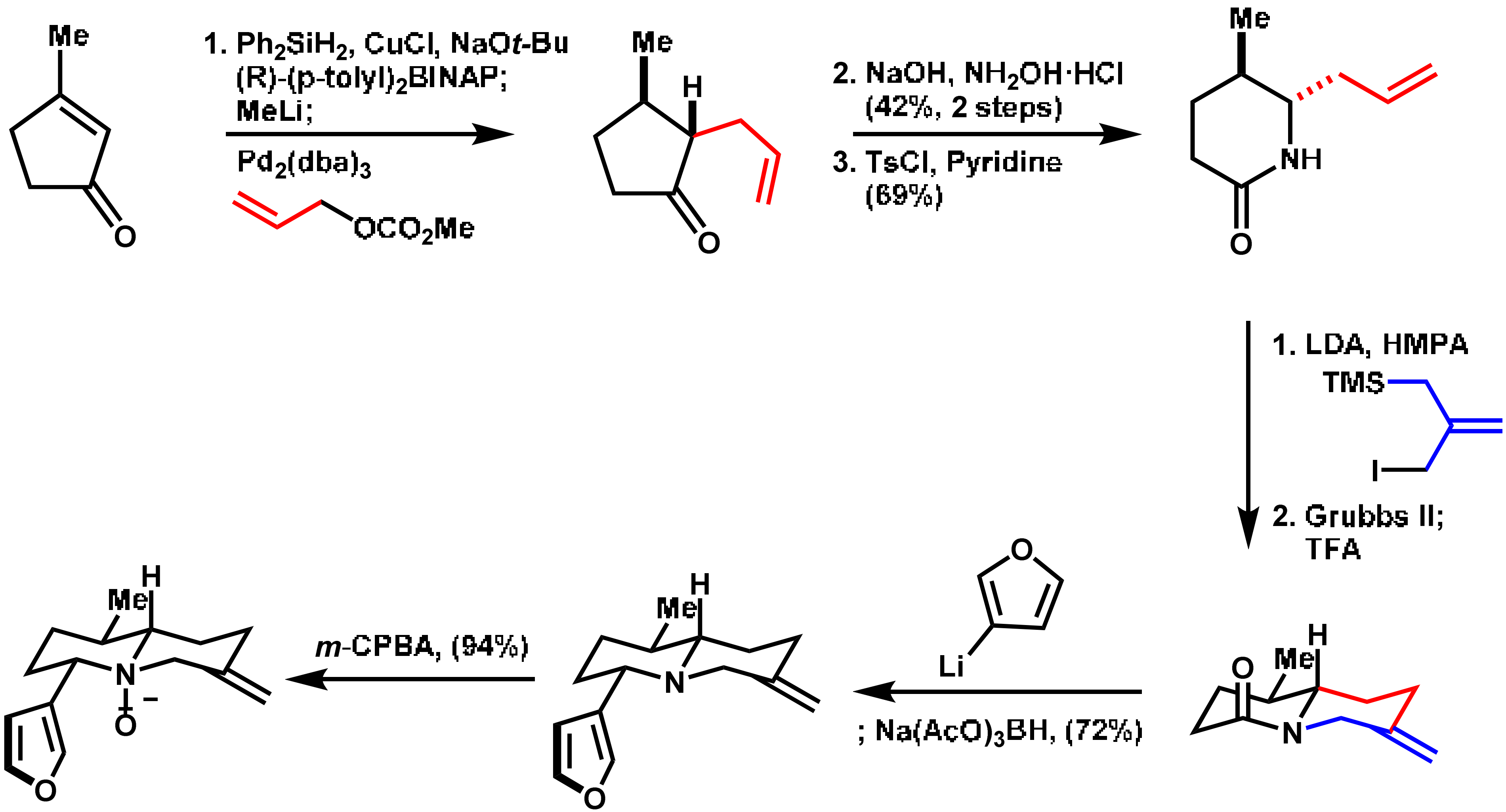
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States



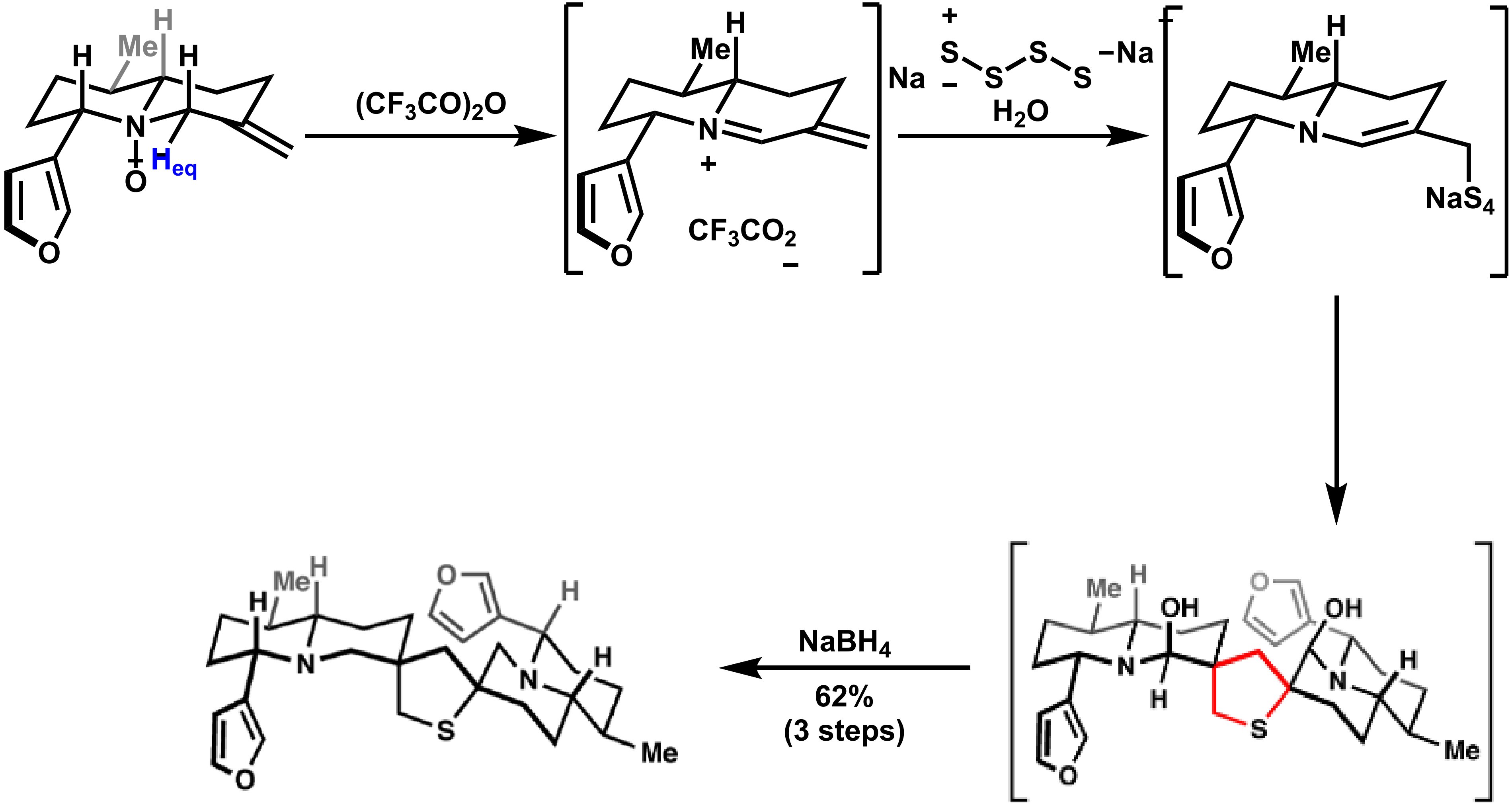
Jansen, D. J.; Shenvi, R. A. *J. Am. Chem. Soc.* **2013**, *135*, 1209.

Synthesis of (-)-neothiobinupharidine



Jansen, D. J.; Shenvi, R. A. *J. Am. Chem. Soc.* **2013**, *135*, 1209.

Synthesis of (-)-neothiobinupharidine



(-)-neothiobinupharidine

Jansen, D. J.; Shenvi, R. A. *J. Am. Chem. Soc.* **2013**, *135*, 1209.