Total synthesis of (±)-Cephanolides

2021.06.19 Literature Seminar
M1 Kyohei Oga

contents

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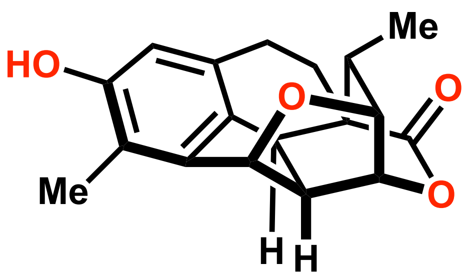
Total Synthesis of the *Cephalotaxus* Norditerpenoids (±)-Cephanolides A–D

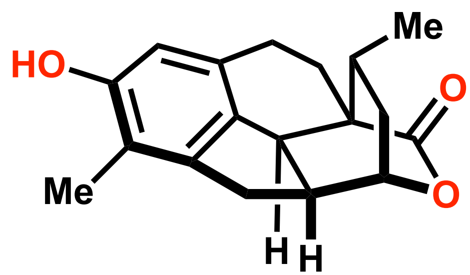
Maximilian Haider,[§] Goh Sennari,[§] Alina Eggert, and Richmond Sarpong*

contents

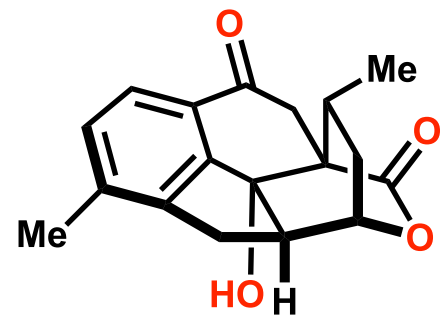
Cephanolide C18 dinorditerpenoids



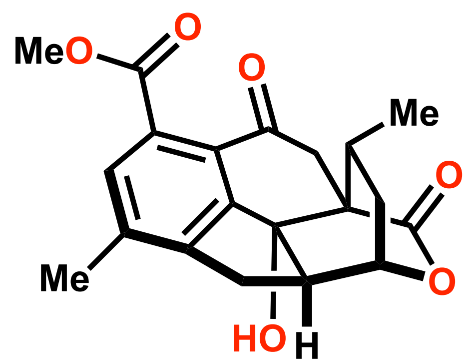
cephanolide A



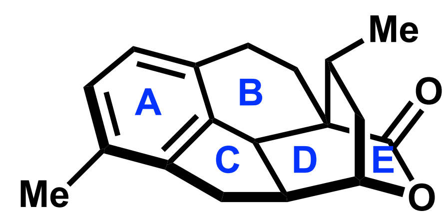
cephanolide B



cephanolide C



cephanolide D

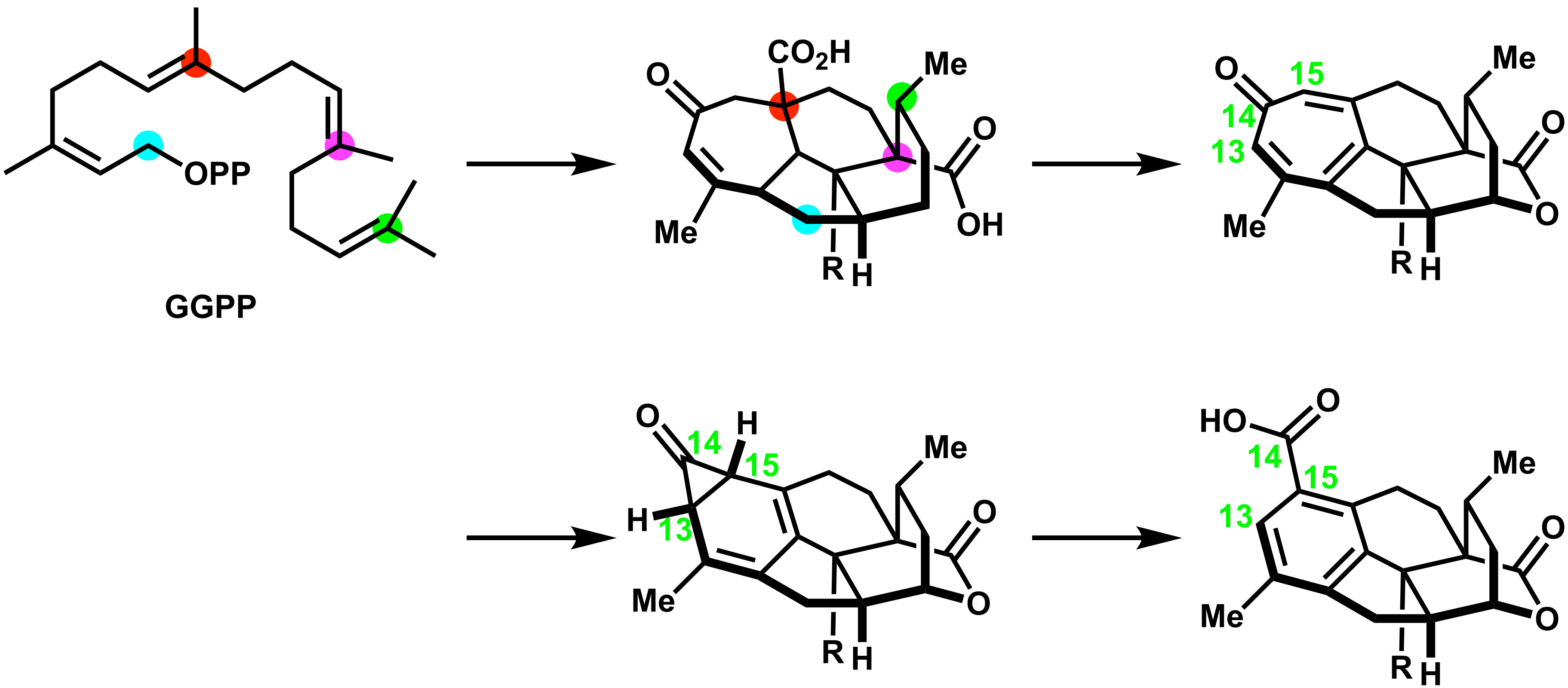


common framework

- **isolation : the seeds of *cephalotaxus harringtonia***
- **biological activity : plant growth inhibition, antineoplastic, antiviral, antitumor**
- **structure features : five ring system (A,B,C,D,E)**
- **total synthesis : two papers**

1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc.* **2021**, *143*, 2710 2) Xu, L.; Wang, C.; Gao, Z.; Zhao, Y. *J. Am. Chem. Soc.* **2018**, *143*, 7
3) Zhang, H.; He, H.; Gao, S. *Angew. Chem., Int. Ed.* **2020**, *59*, 20417

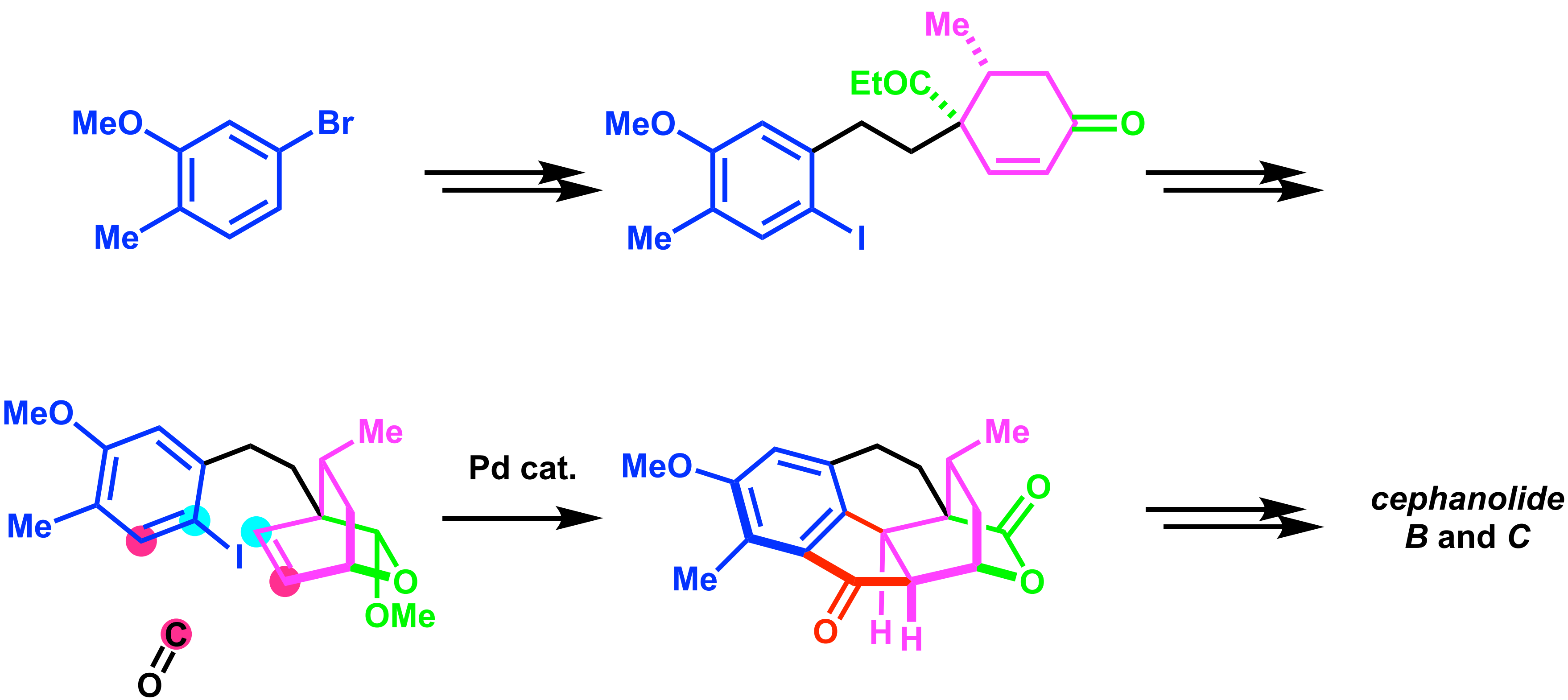
Biosynthesis of Cephanolides



Cephanolide group

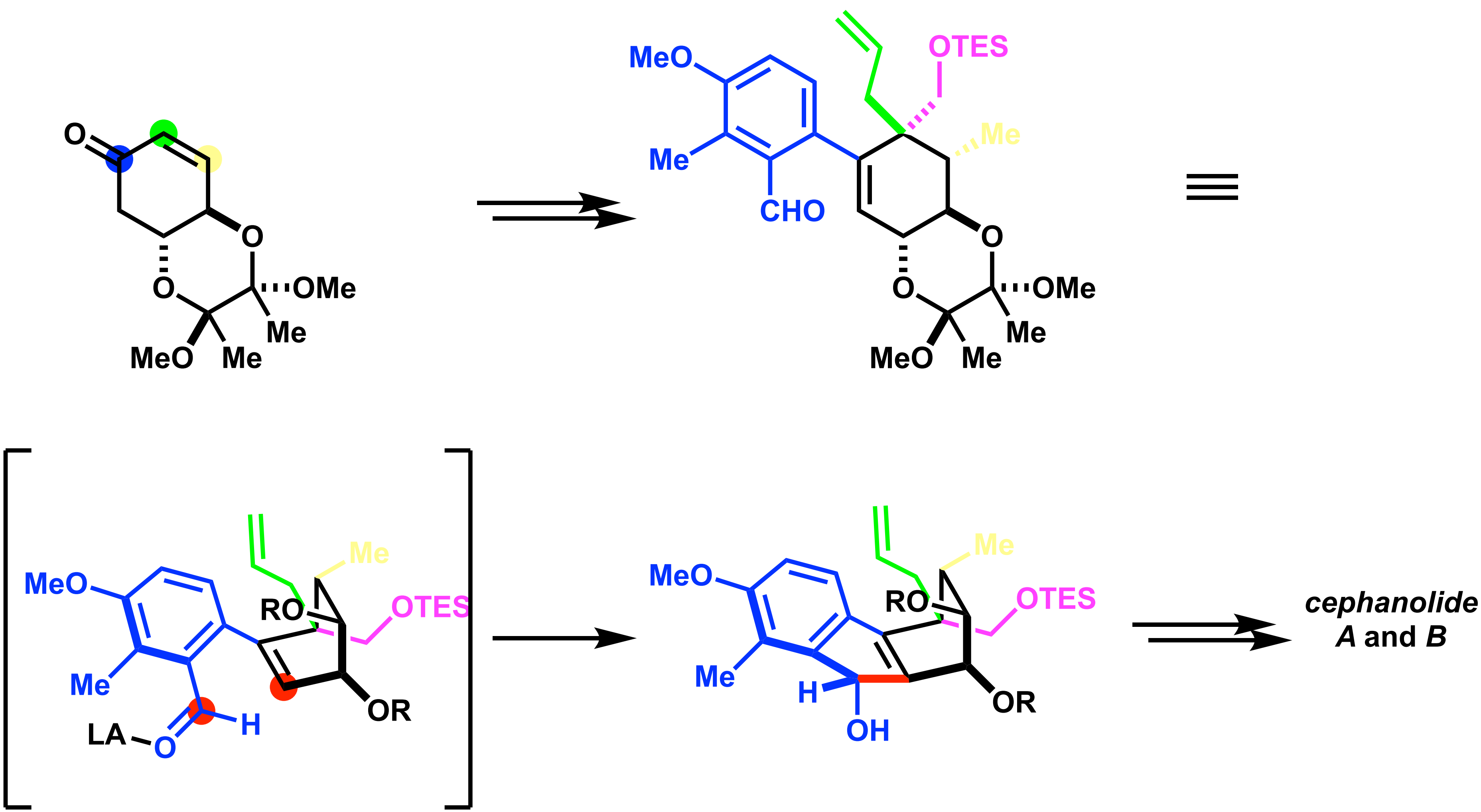
1) Gang, N.; Jian-Min, Y. *Org. Lett*. **2016**, *18*, 1880 2) Yao-Yue, F.; Jian-Min, Y. *J. Nat. Prod*. **2017**, *80*, 3159

Zhao's total synthesis



1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc.* **2021**, *143*, 2710 2) Xu, L.; Wang, C.; Gao, Z.; Zhao, Y. *J. Am. Chem. Soc.* **2018**, *143*, 7
3) Zhang, H.; He, H.; Gao, S. *Angew. Chem., Int. Ed.* **2020**, *59*, 20417

Gao's total synthesis



1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc.* **2021**, *143*, 2710 2) Xu, L.; Wang, C.; Gao, Z.; Zhao, Y. *J. Am. Chem. Soc.* **2018**, *143*, 7
3) Zhang, H.; He, H.; Gao, S. *Angew. Chem., Int. Ed.* **2020**, *59*, 20417

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Communication

Total Synthesis of the *Cephalotaxus* Norditerpenoids (±)-Cephanolides A–D

Maximilian Haider,[§] Goh Sennari,[§] Alina Eggert, and Richmond Sarpong*

Richmond Sarpong

Education and academic career:

Richmond Sarpong
-1995, B,S., Macalester College (Prof. Rebecca C. Hoye)
-2001, Ph.D., Princeton University (Prof. Martin F. Semmelhack)
-2004, Postdoctoral Fellow, Caltech (Prof. Brian M. Stoltz)
-2010, Assistant Professor, UCB
-2014, Associate Professor
-Present Full Professor, Executive Associate Dean (Chemistry)

Research topics

1. Total synthesis of natural products

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Bioinspired Diversification Approach Toward the Total Synthesis of Lycodine-Type Alkaloids
Hannah M. S. Haley,[⊥] Stefan E. Payer,[⊥] Sven M. Papidocha, Simon Clemens, Jonathan Nyenhuis, and Richmond Sarpong*

JACS
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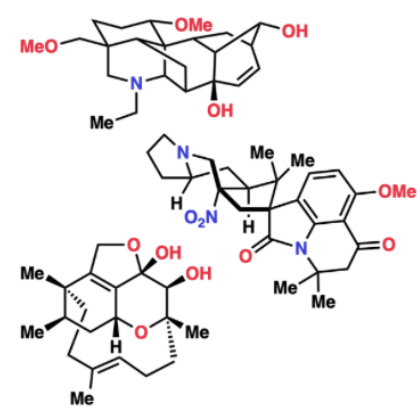
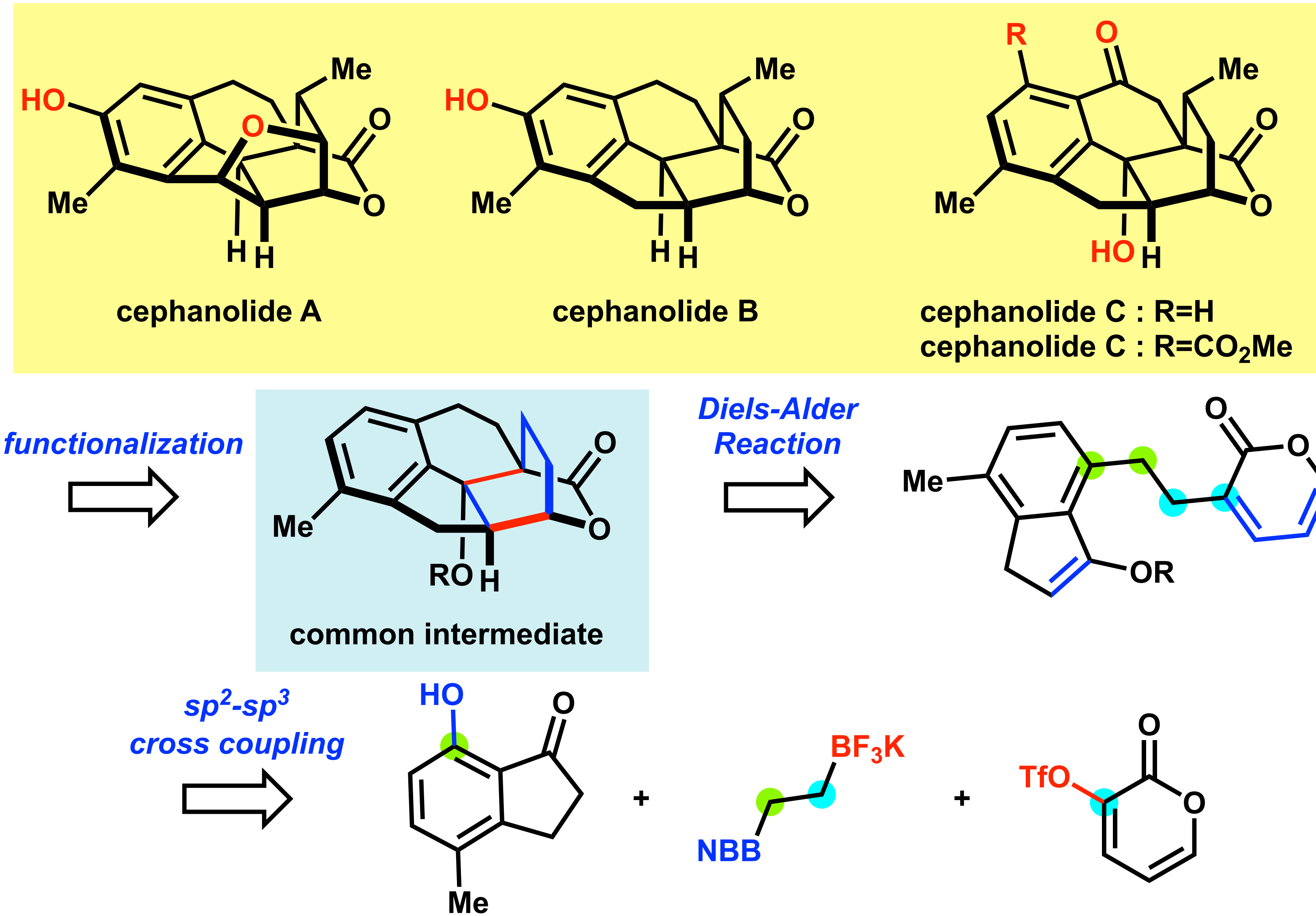
pubs.acs.org/JACS Article

C–C Bond Cleavage Approach to Complex Terpenoids: Development of a Unified Total Synthesis of the Phomactins
Paul R. Leger, Yusuke Kuroda, Stanley Chang, Justin Jurczyk, and Richmond Sarpong*

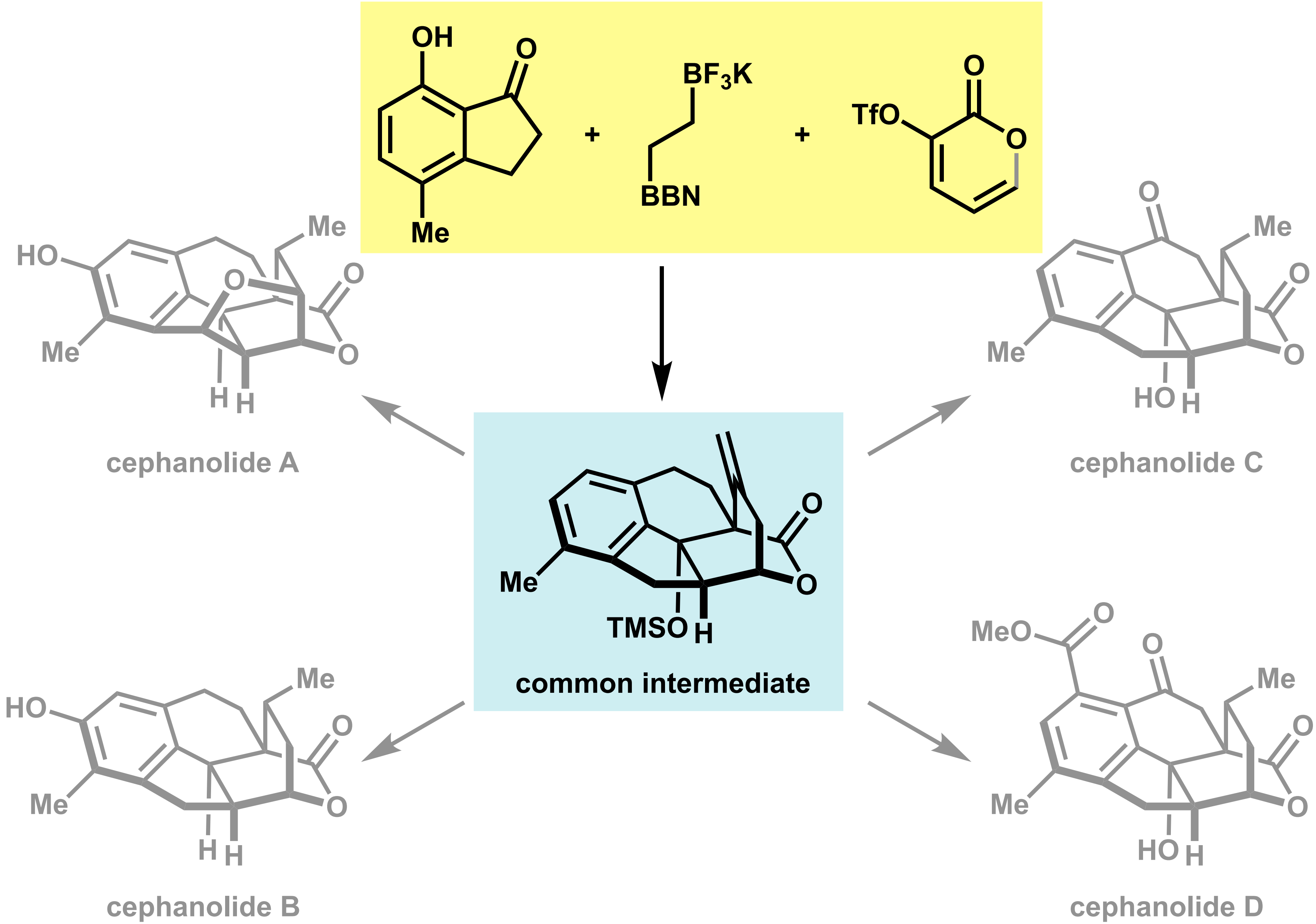


2. Development of synthesis method (C–H activation and C–C cleavage)

Sarpong's strategies and retrosynthesis

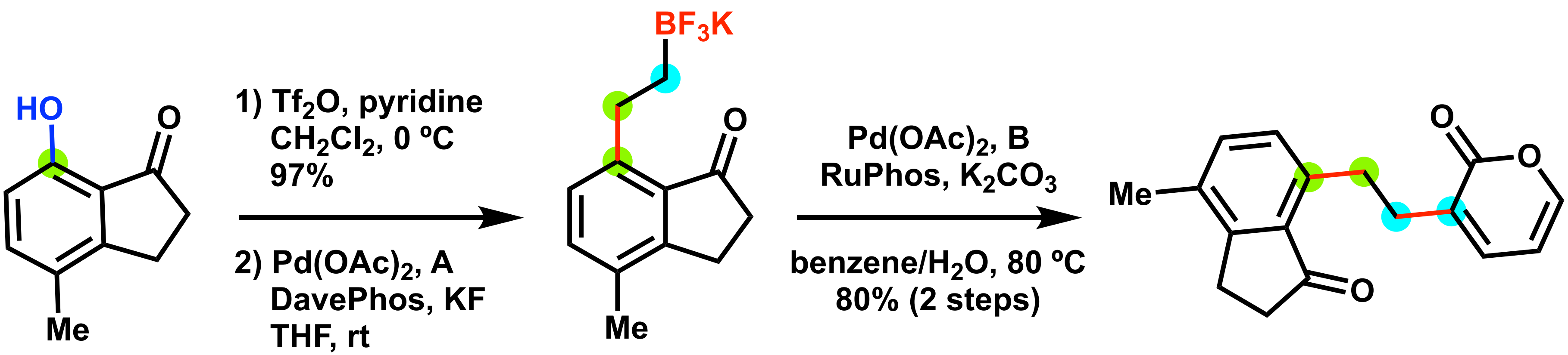


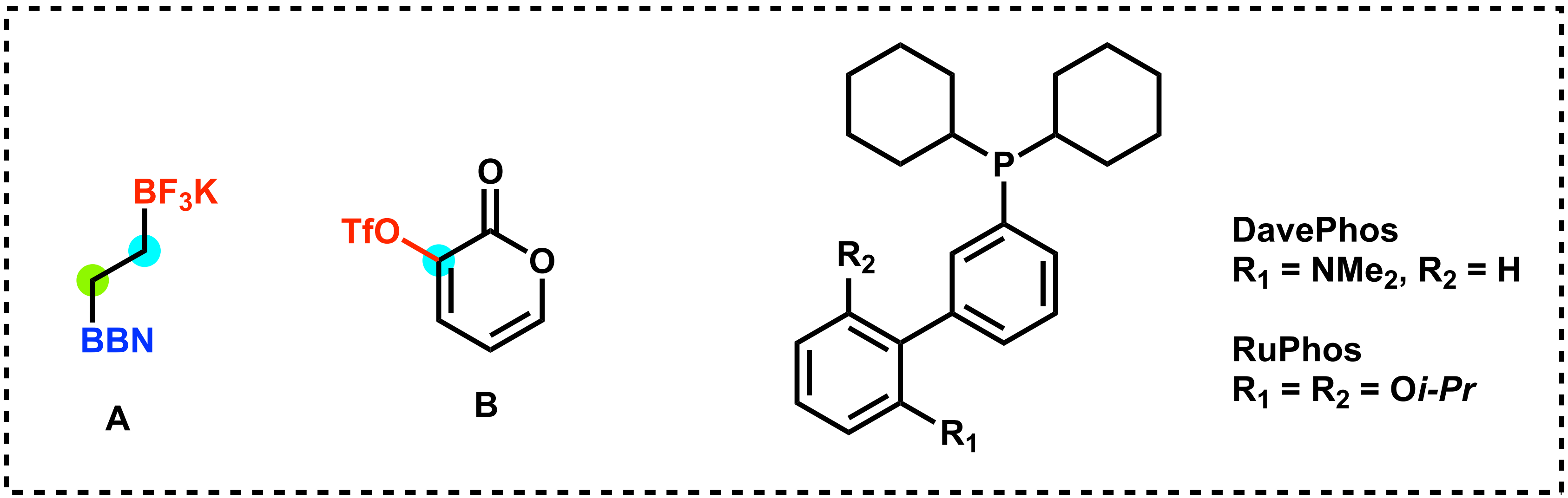
Synthesis of common intermediate



1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc.* **2021**, *143*, 2710

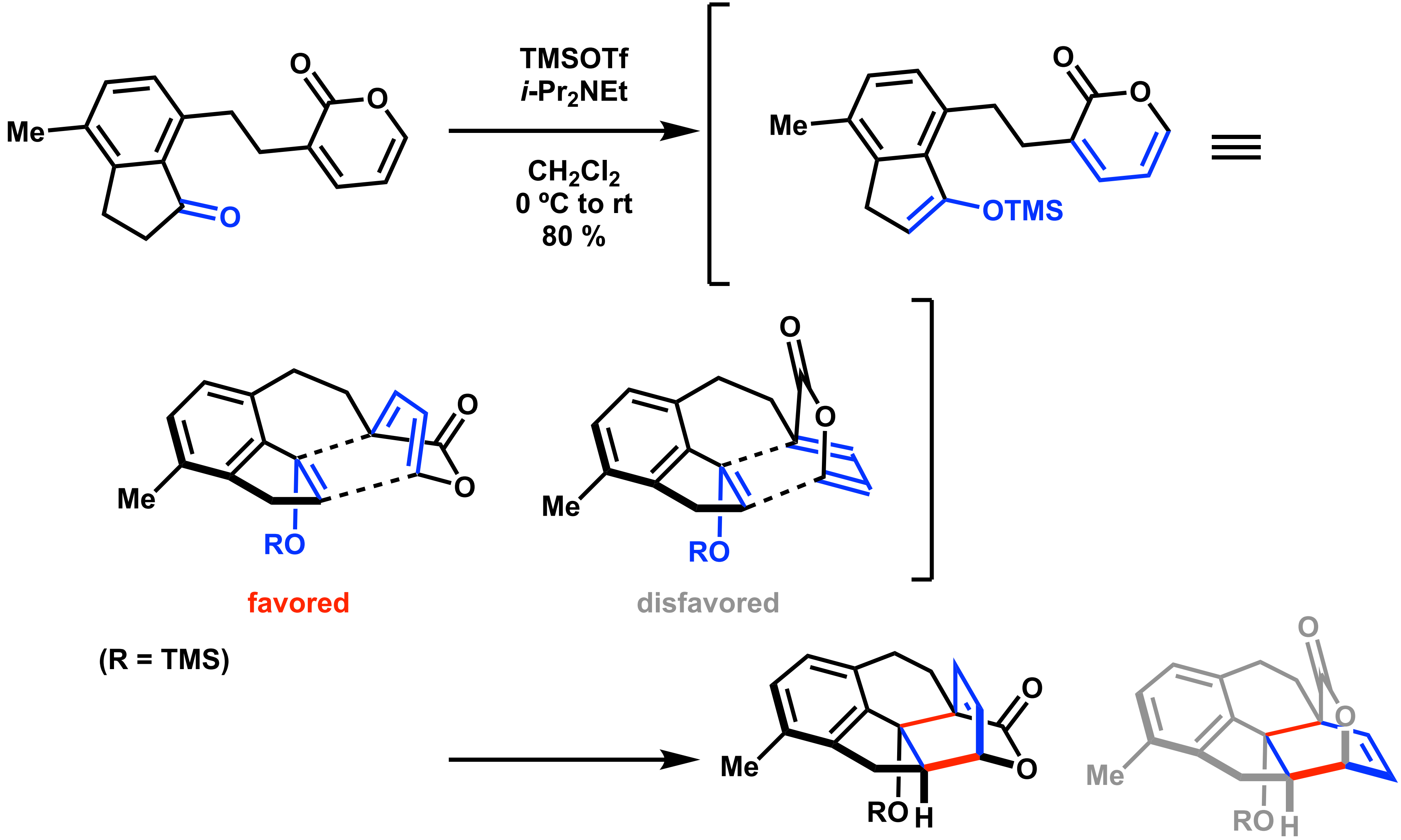
Selective *Suzuki* cross-coupling





1) Molander, G.; Sandrock, D. *J. Am. Chem. Soc.* **2008**, *130*, 15792 2) Molander, G.; Sandrock, D. *Org. Lett.* **2009**, *11*, 2369
3) Dreher, S.; Lim, S.; Sandrock, D.; Molander, G. *J. Org. Chem.* **2009**, *74*, 3626

Diels-Alder reaction

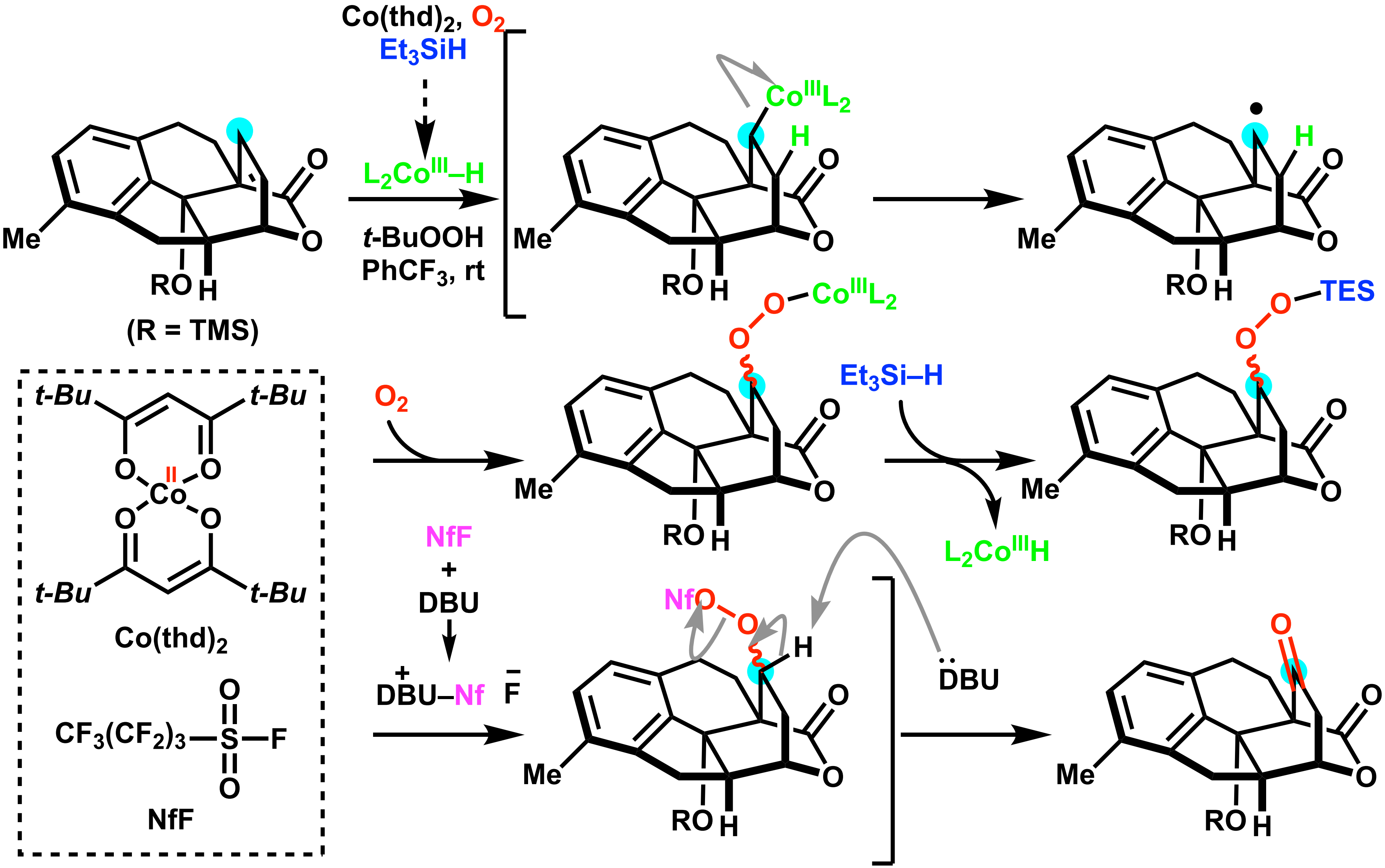


(*endo*)-adduct
(single diastereomer)

(*exo*)-adduct

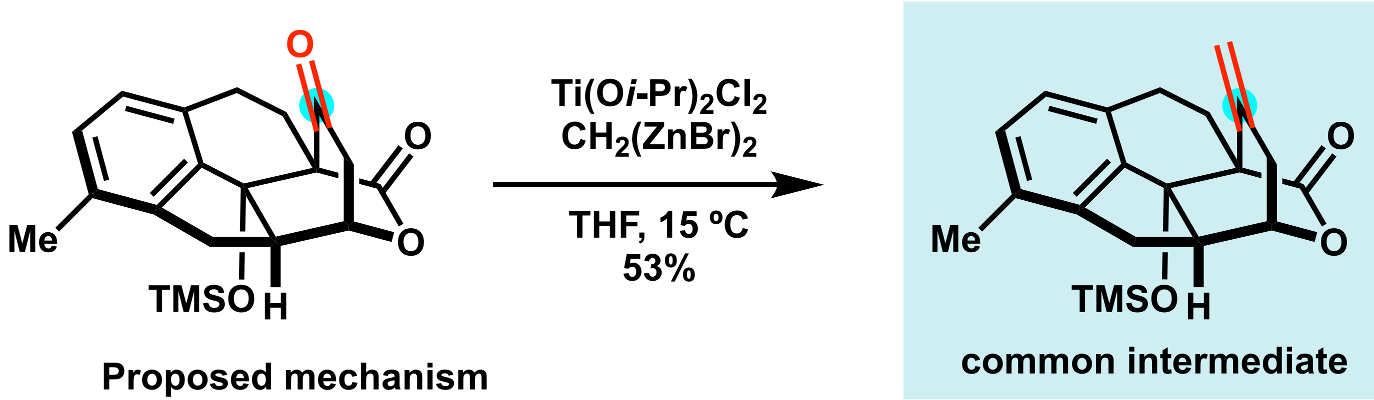
1) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc*. **1980**, *102*, 3248 2) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron*. **1988**, *44*, 4259

Isayama-Mukaiyama hydration

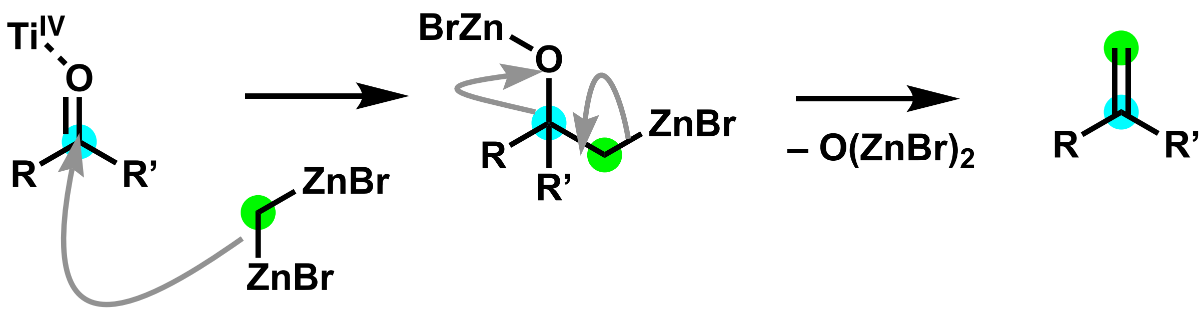


1) Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, *136*, 5916
2) Nagatomo, M.; Hagiwara, K.; Masuda, K.; Koshimizu, M.; Kawamata, T.; Matsui, Y.; Urabe, D.; Inoue, M. *Chem. – Eur. J.* **2016**, *22*, 222
3) Crossley, S.; Obradors, C.; Martinez, R.; Shenvi, R. *Chem. Rev.* **2016**, *116*, 8912

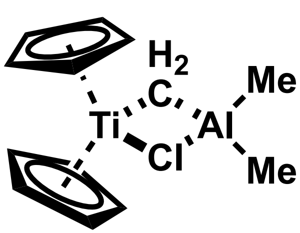
Olefination



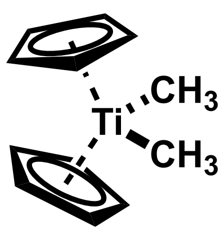
Proposed mechanism



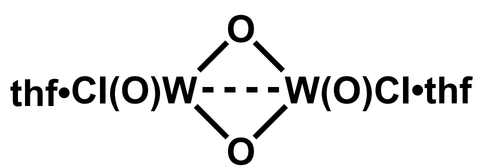
First of all, they attempted *Wittig* olefination but failled resulting from basicity of phosphorus ylides. Therefore, they focus on olefination reagents which are known to be less basic such as Tebbe, Petasis, Johnson-Peterson, Kauffmann, Nystedt and Lombardo olefinations.
Only the highlighted reagents delivered trace amounts of common intermediate.



Tebbe reagent



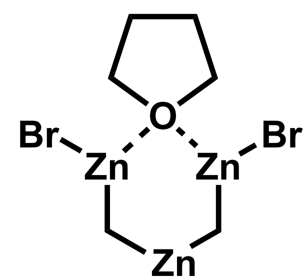
Petasis reagent



Kauffmann reagent

$CH_2I_2 + Zn + TiCl_4$

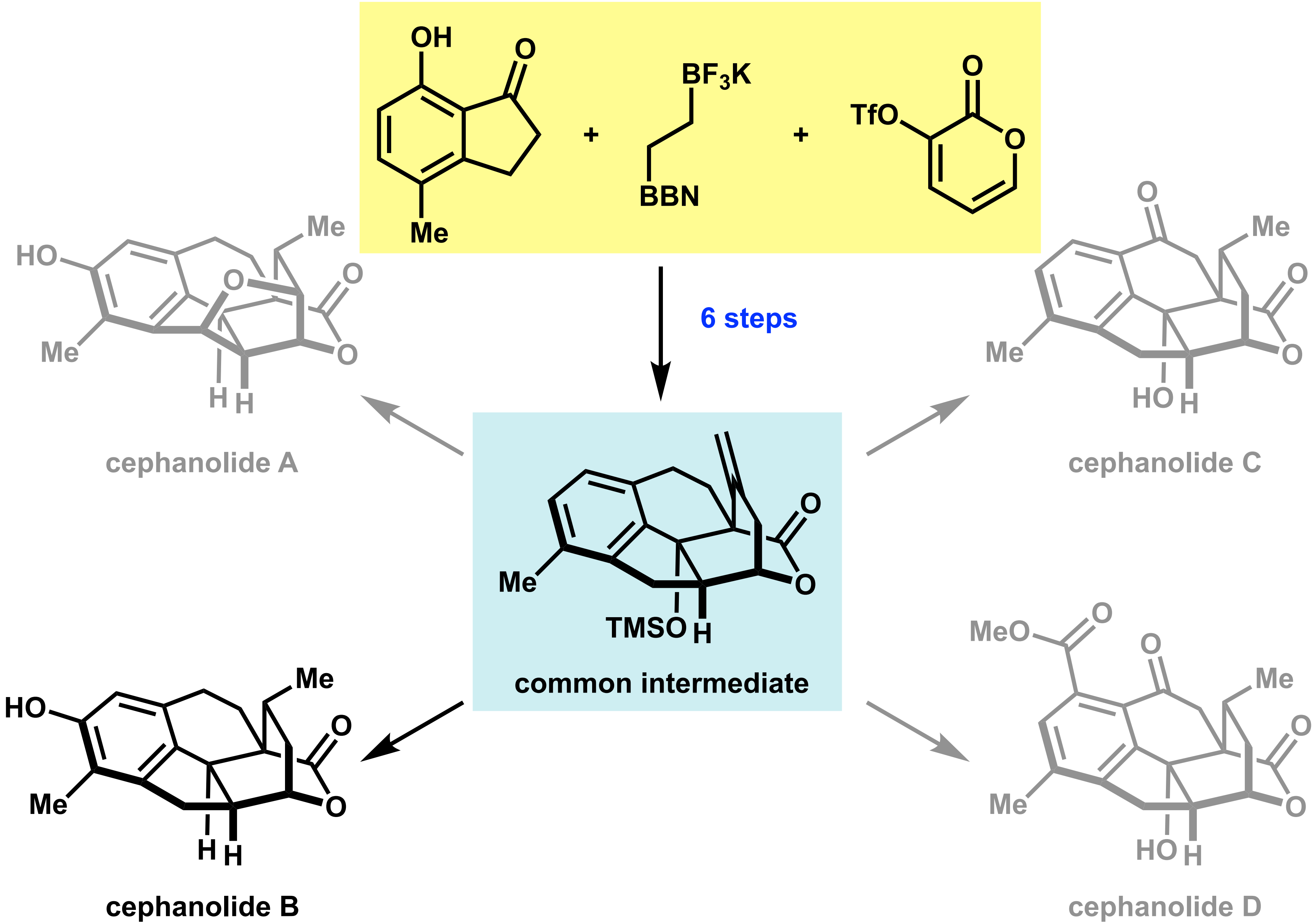
Lomberdo's reagent



Nysted reagent

1) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem*. **1994**, *59*, 2668 2) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett*. **1998**, *1998*, 313
3) Barnych, B.; Vatele, J. *Synlett*. **2011**, *13*, 1912 4) Chand, H. *Synlett*. **2009**, *15*, 2545
5) Okazoe, T.; Hibino, J.; Takai, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*, 45

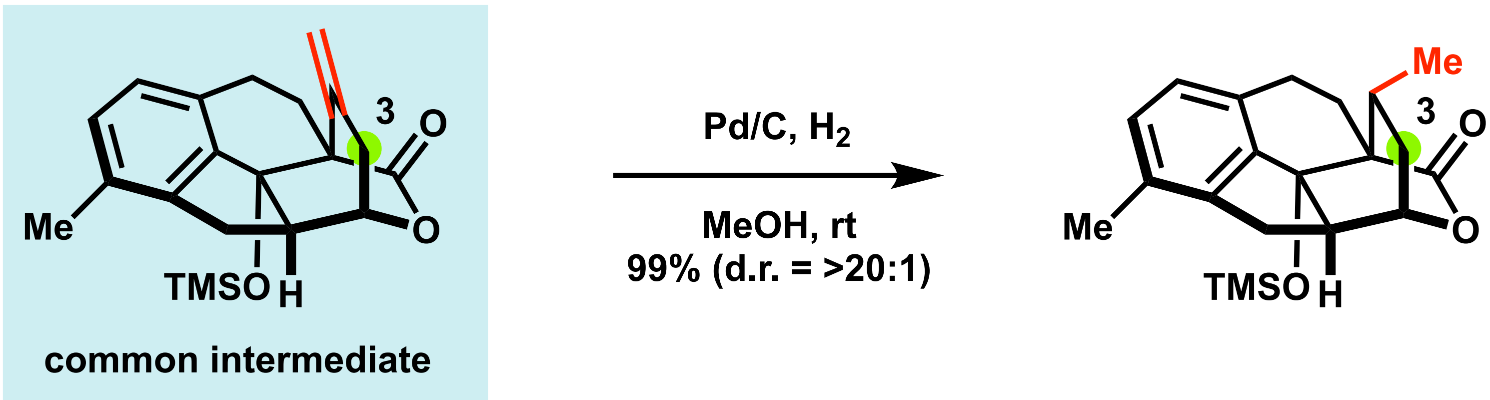
Total synthesis of Cephanolide B



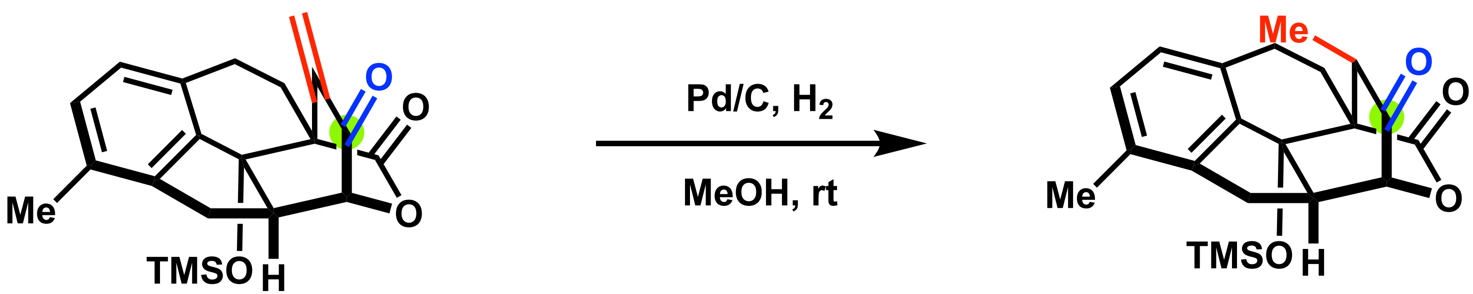
1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc*. **2021**, *143*, 2710

Heterogeneous Hydrogenation (1)

Total synthesis of Cephanolide B,C,D



Total synthesis of Cephanolide A

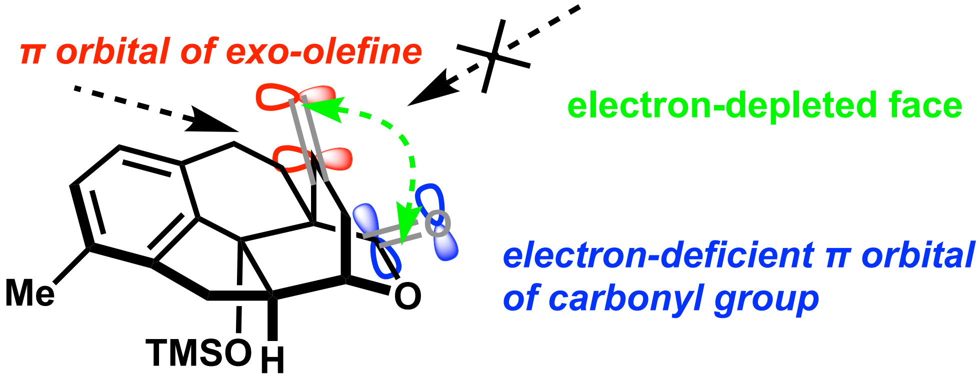


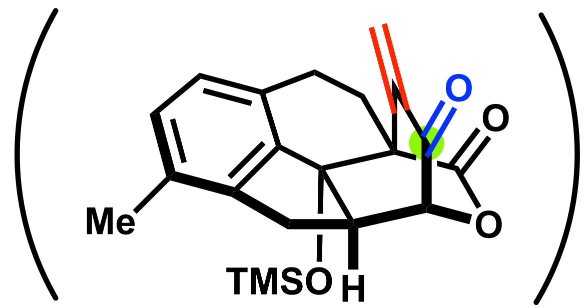
1) Woodward, R.; Bader, F.; Bickel, H.; Frey, A. *Tetrahedron* **1958**, *2*, 1 2) Pearlman, B. *J. Am. Chem. Soc*. **1979**, *101*, 6404
3) Hamlin, A.; Lapointe, D.; Owens, K.; Sarpong, R. *J. Org. Chem*. **2014**, *79*, 6783

Heterogeneous Hydrogenation (2)

Propasal 1

This face is not reactive because of electron-depleted by orbital interaction between *exo-olefine π orbital* and *carbonyl π* one*. Therefore, hydrolation occurred in opposite side.

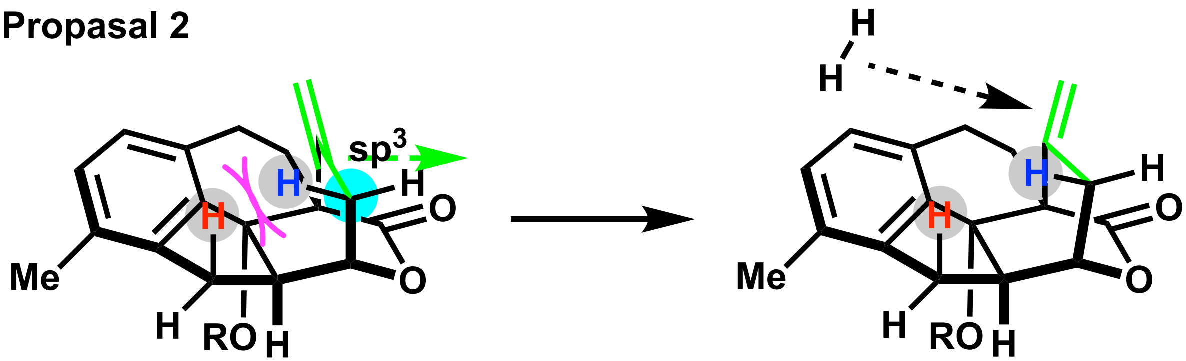




These effects were proposed by *Woodward* but was not still clear.

***HOMO* energy of enone decreased than exo-olefine, so these effects was weak and hydrolation occured from unhindered face.**

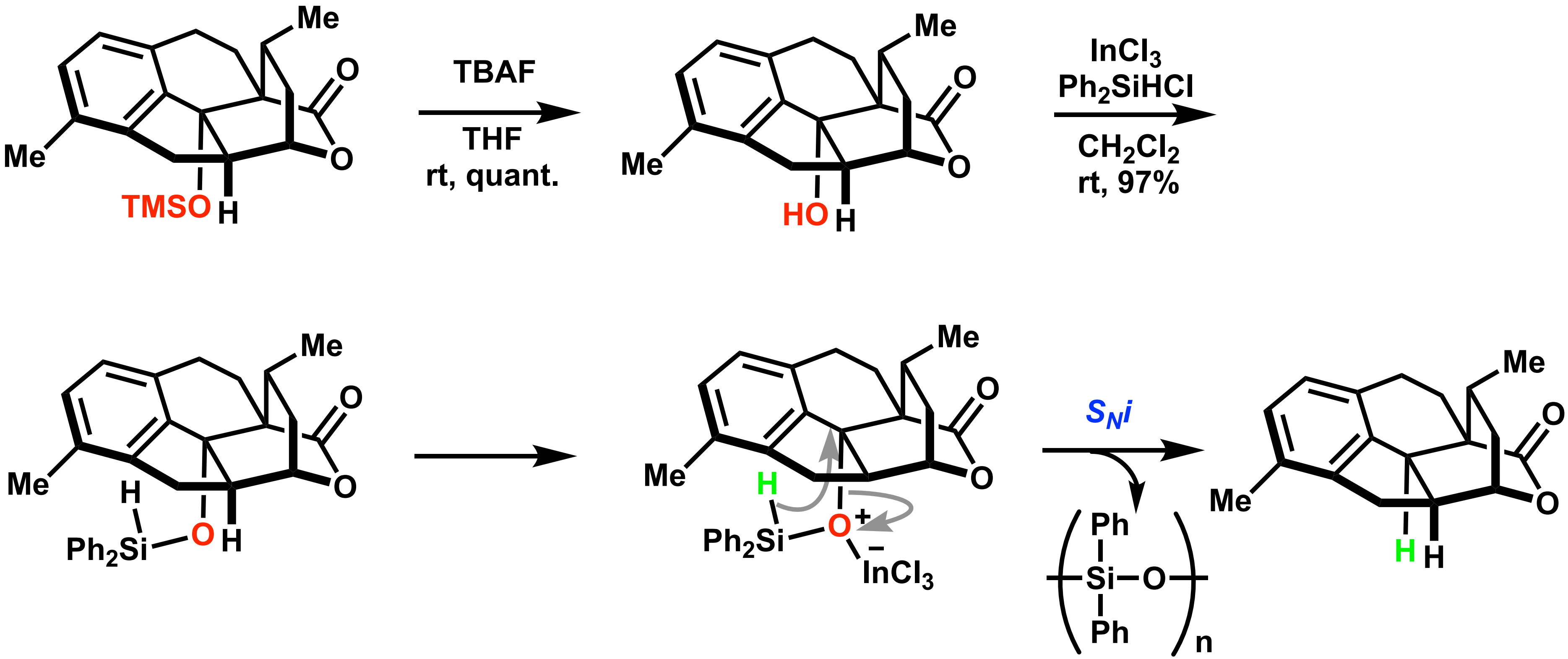
Propasal 2



A little conformation change occurred because of avoiding from 1,3-allylic strain

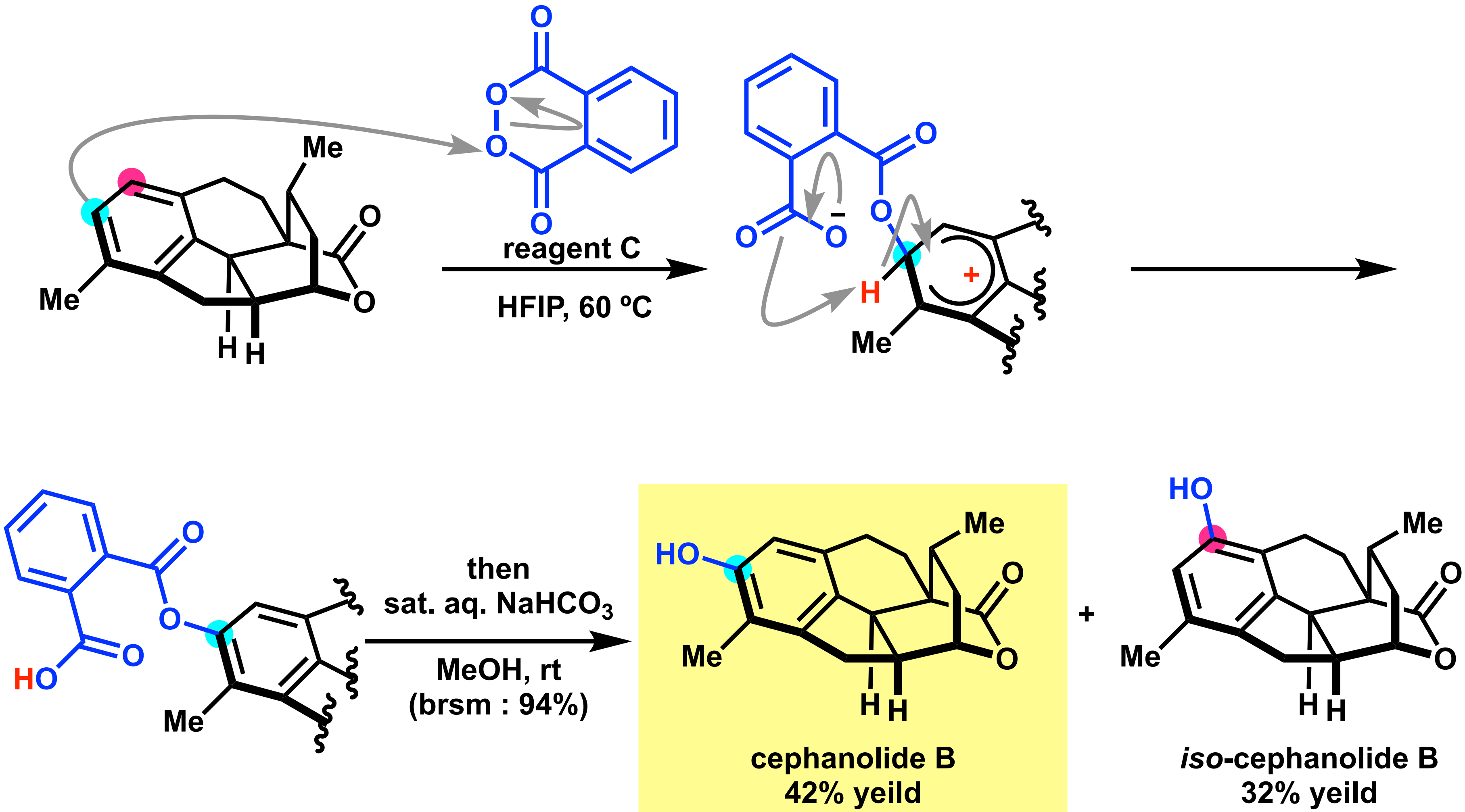
1) Woodward, R.; Bader, F.; Bickel, H.; Frey, A. *Tetrahedron* **1958**, *2*, 1 2) Pearlman, B. *J. Am. Chem. Soc.* **1979**, *101*, 6404
3) Hamlin, A.; Lapointe, D.; Owens, K.; Sarpong, R. *J. Org. Chem.* **2014**, *79*, 6783

Total synthesis of cephanolide B and *iso*-cephanolide B (1)



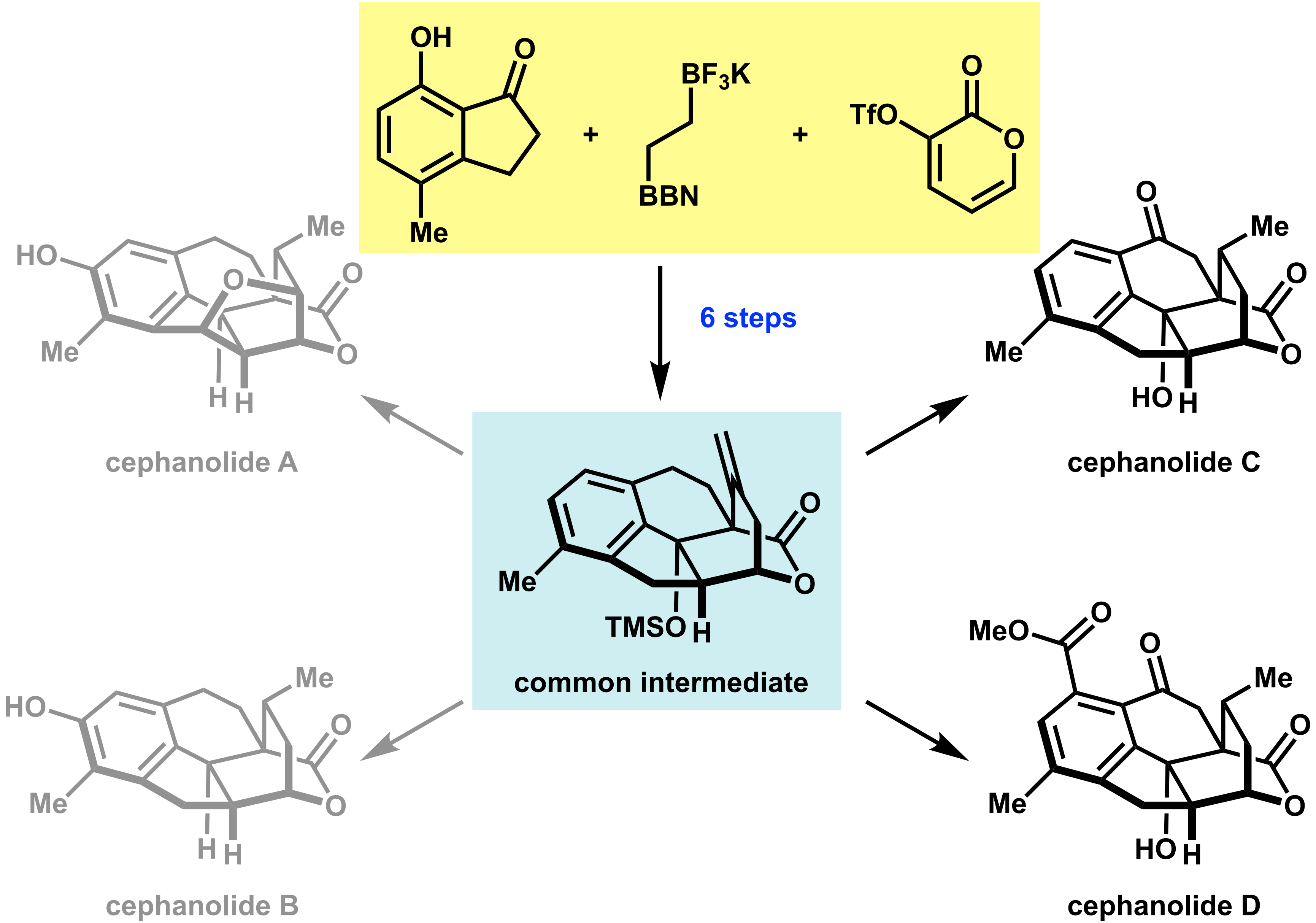
1) Miyai, T.; Ueba, M.; Baba, A. Synlett 1999, 1999, 182 2) Yasuda, M.; Onishi, Y.; Ueba, M.; Baba, A. *J. Org. Chem*. **2001**, *66*, 7741

Total synthesis of cephanolide B and *iso*-cephanolide B (2)



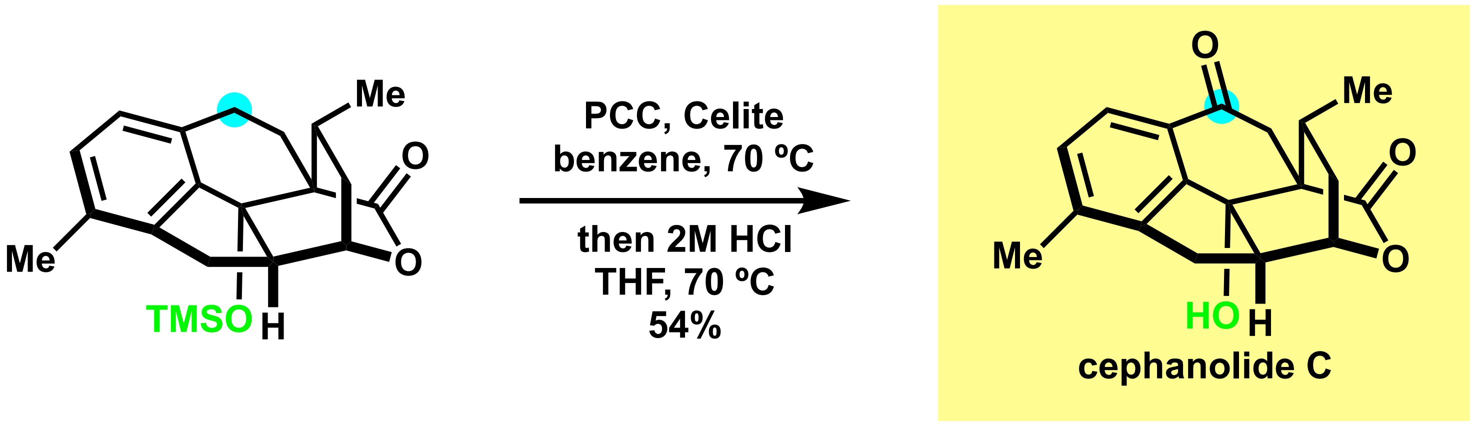
1)Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K.; Siegel, D. *Nature* **2013**, *499*, 192

Total synthesis of cephanolide C and D



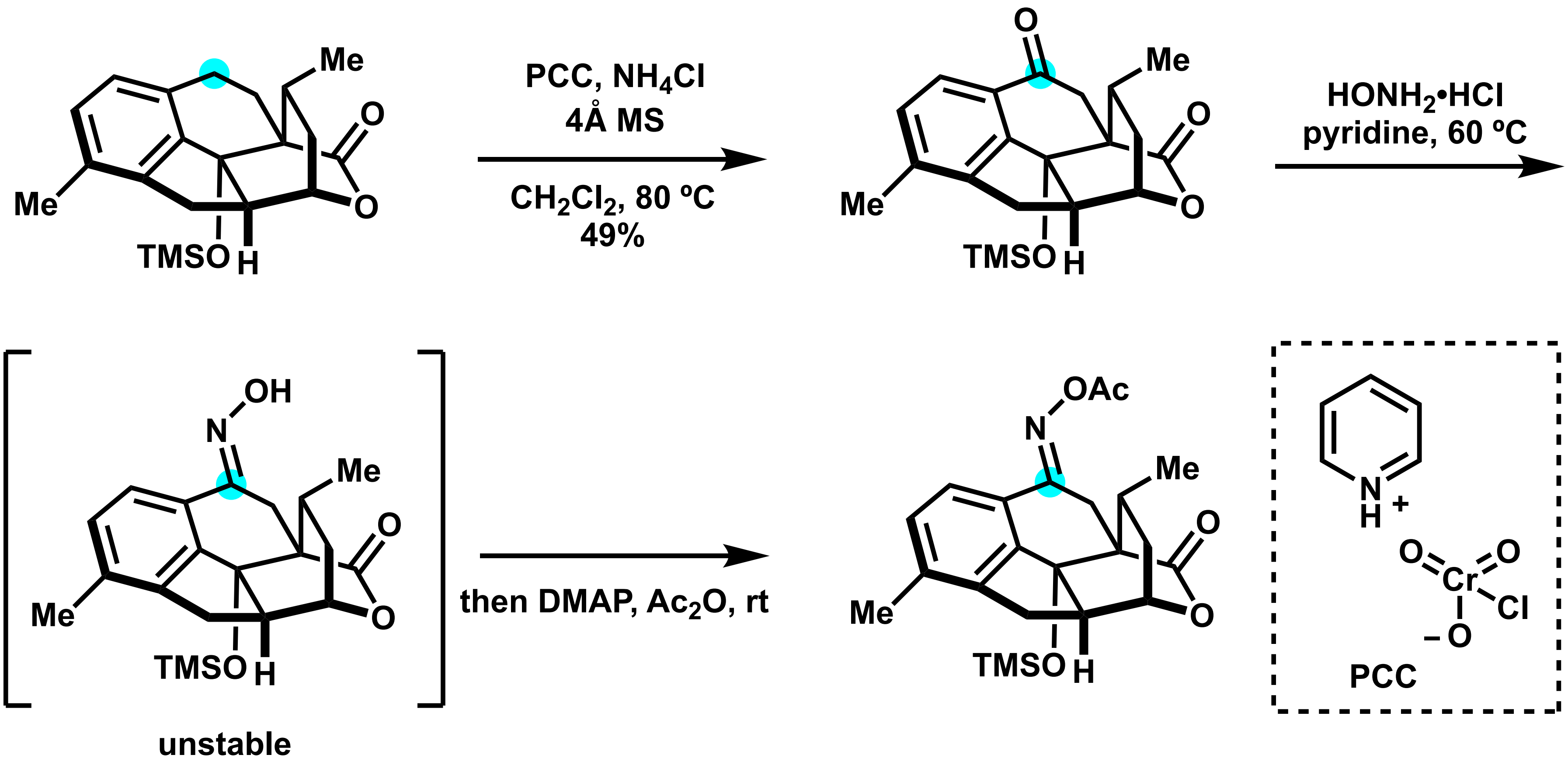
1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc*. **2021**, *143*, 2710

Total synthesis of cephanolide C



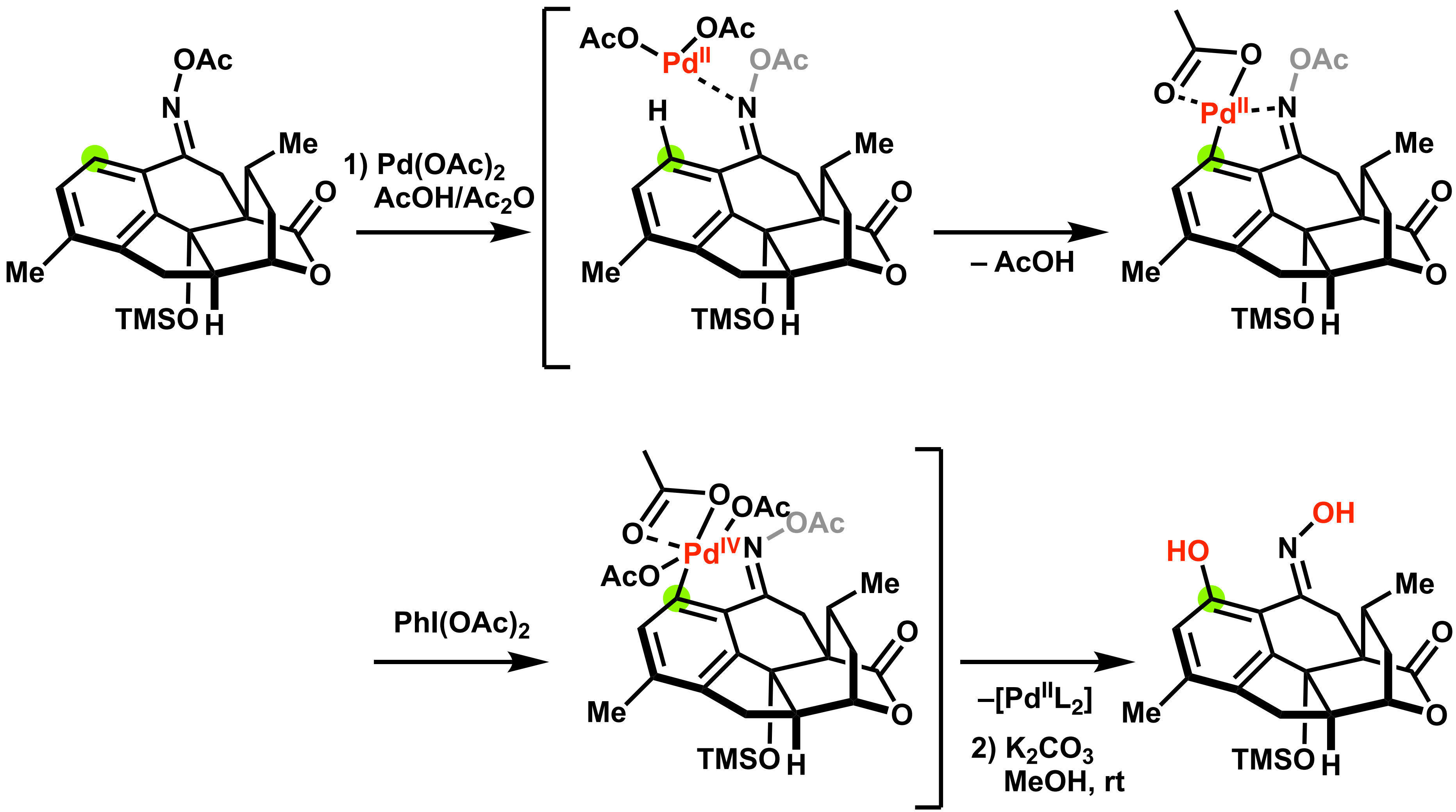
1) Xu, L.; Wang, C.; Gao, Z.; Zhao, Y. *J. Am. Chem. Soc*. **2018**, *140*, 5653

Total synthesis of cephanolide D (1)



1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc*. **2021**, *143*, 2710

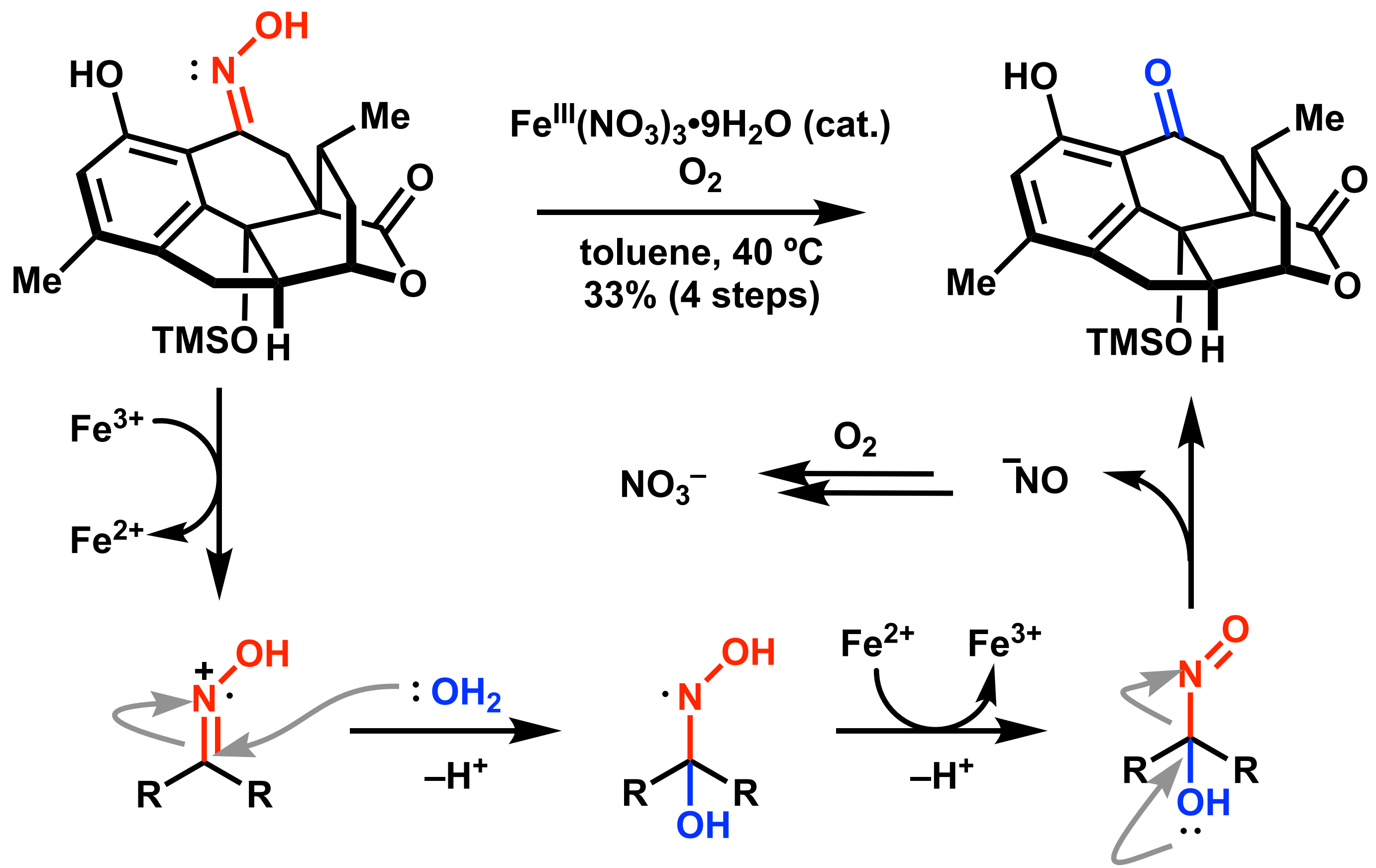
Total synthesis of cephanolide D (2)



1) Neufeldt, S.; Sanford, M. *Org. Lett.* **2010**, *12*, 532

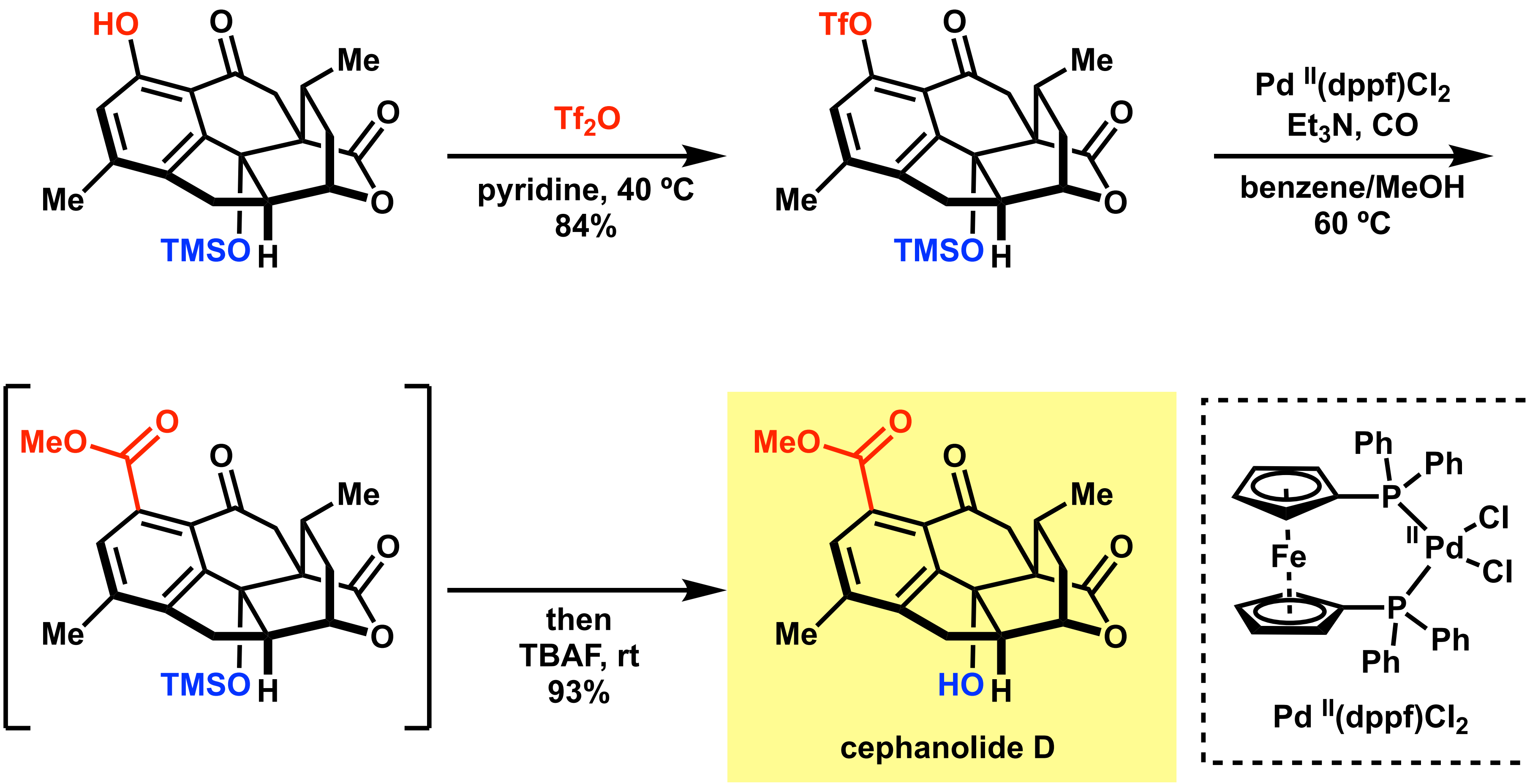
Total synthesis of cephanolide D (3)

Proposed mechanism



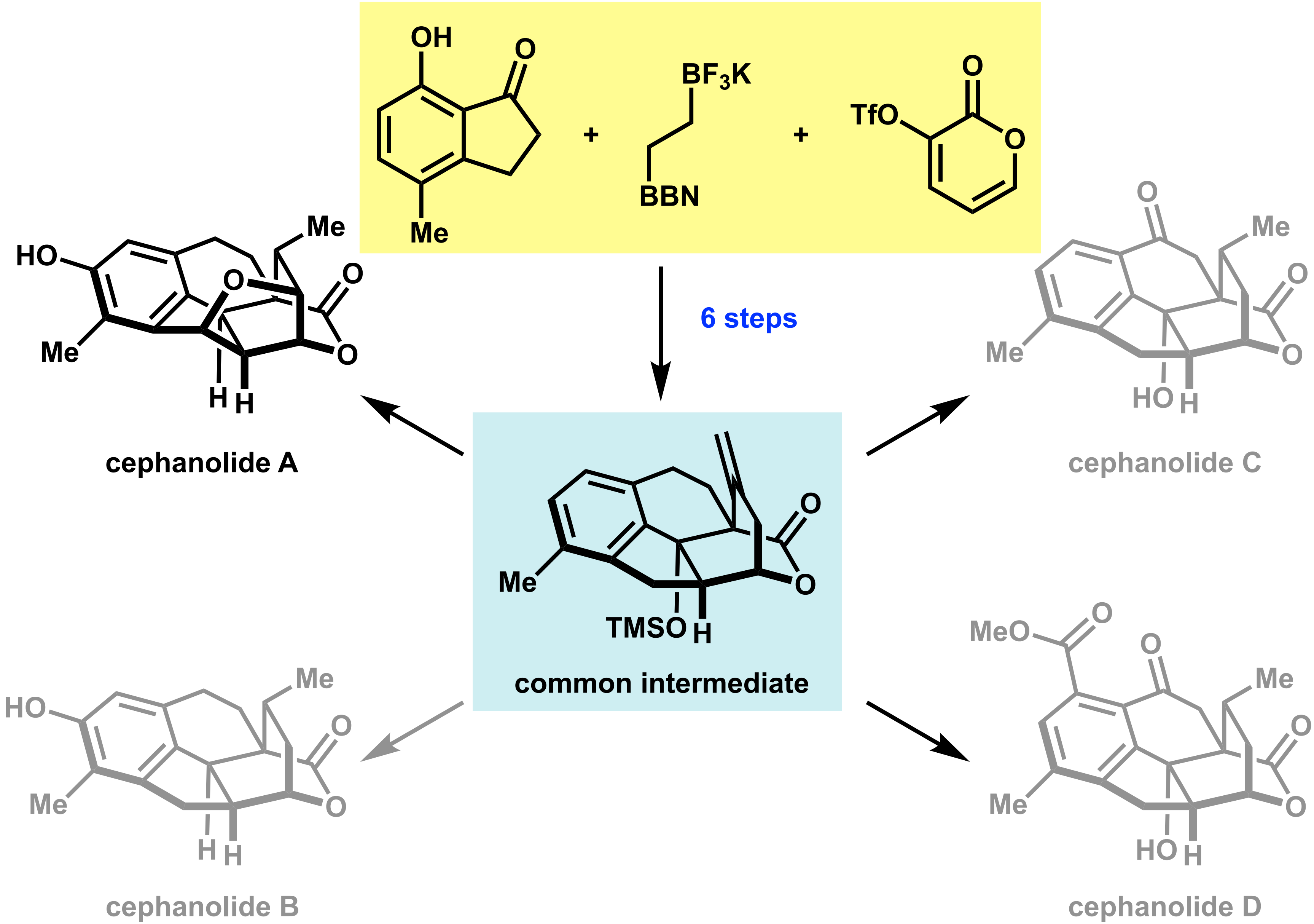
1) Li, Y.; Xu, N.; Mei, G.; Zhao, Y.; Zhao, Y.; Lyu, J.; Zhang, G.; Ding, C. *Can. J. Chem*. **2018**, *96*, 810
2) Zhang, G.; Mo, W.; Ding, C. *J. Org. Chem*. **2011**, *76*, 4665

Total synthesis of cephanolide D (4)



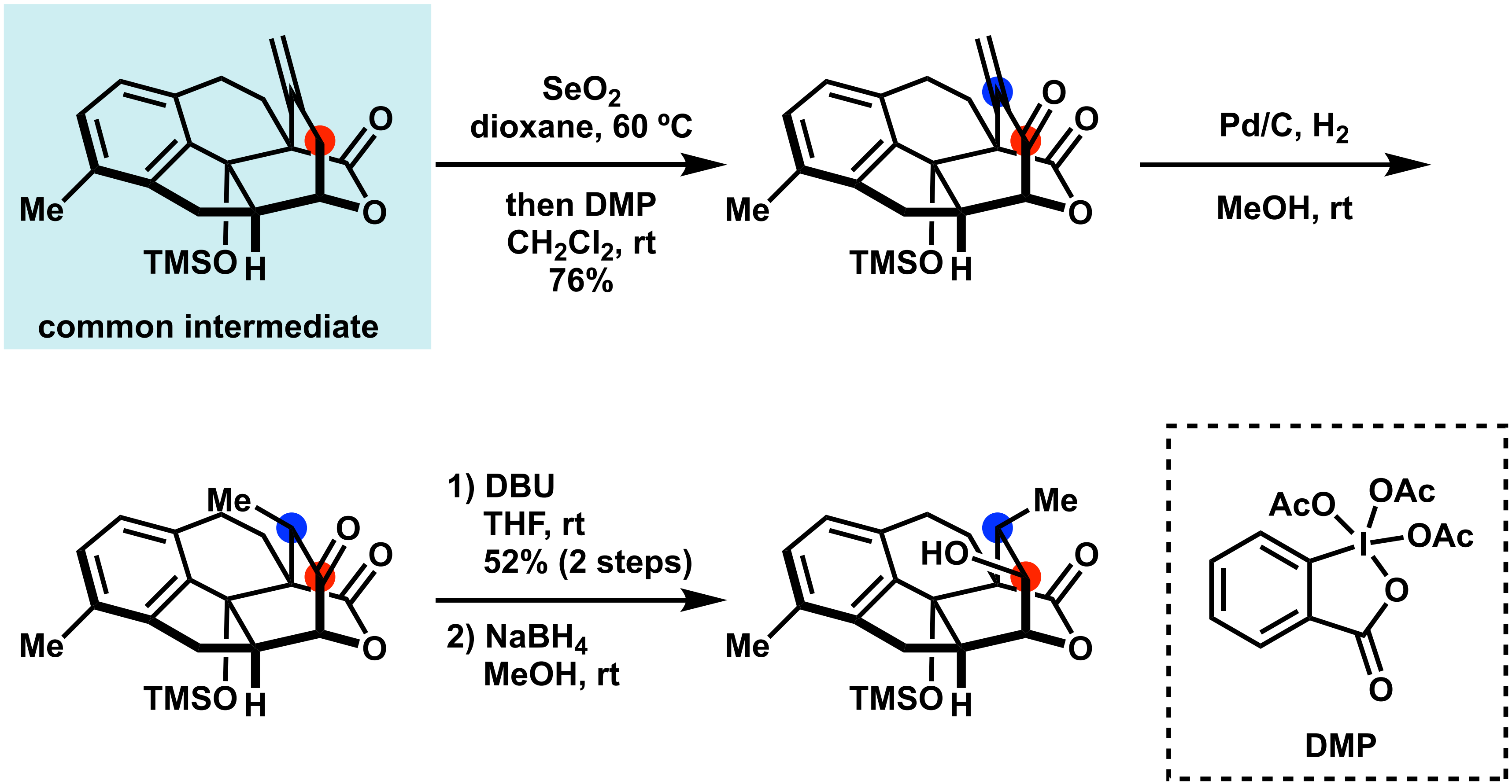
1) Rachel, M.; Joseph, M.; Buchwald, S.; *J. Am. Chem. Soc.* **2008**, *130*, 2754

Total synthesis of cephanolide A



1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc*. **2021**, *143*, 2710

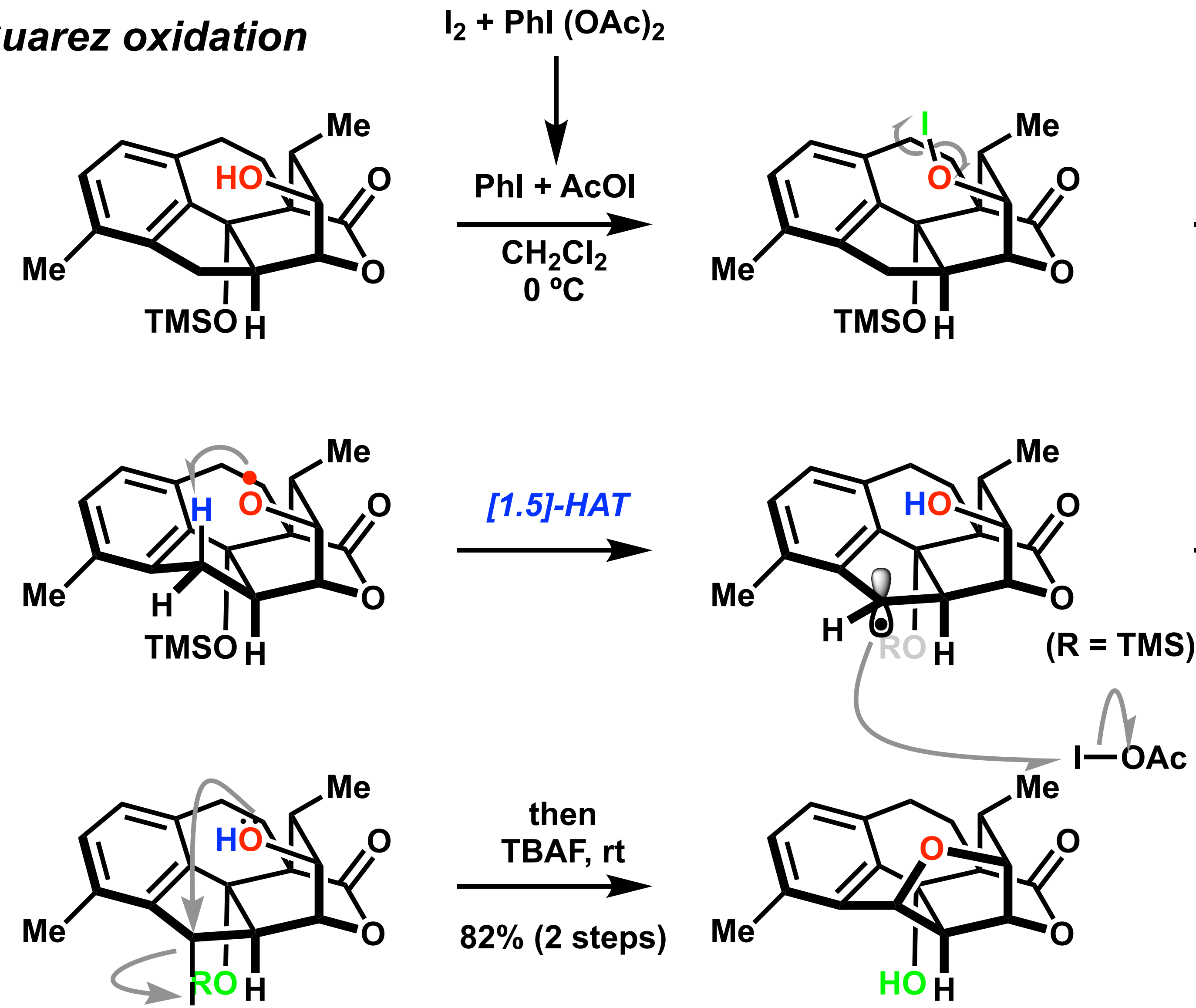
Total synthesis of cephanolide A (1)



1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc.* **2021**, *143*, 2710

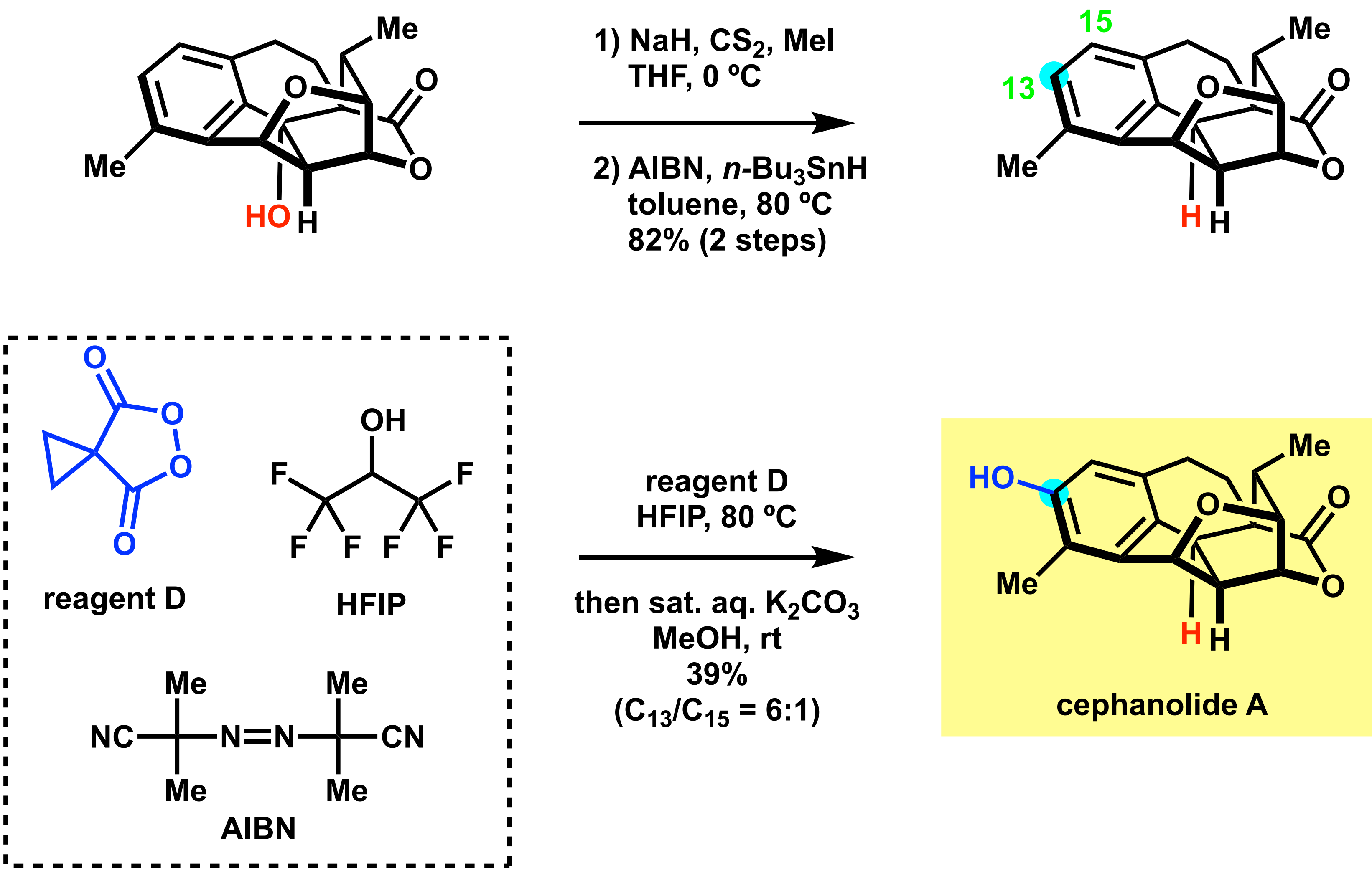
Total synthesis of cephanolide A (2)

Suarez oxidation



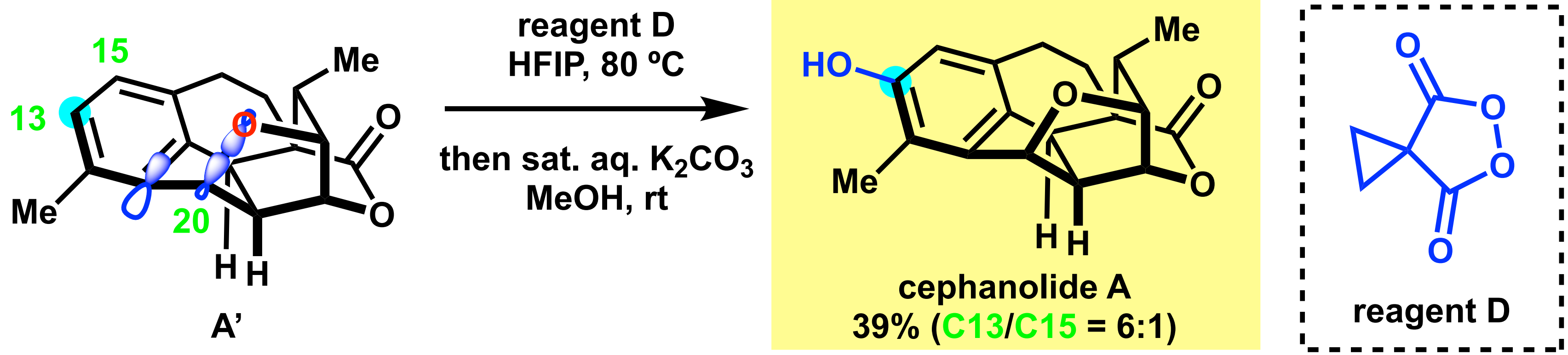
1) de Armas, P.; Carrau, R.; Concepcion, J.; Francisco, C.; Hernandez, R.; Suarez, E. *Tetrahedron Lett*. **1985**, *26*, 2493

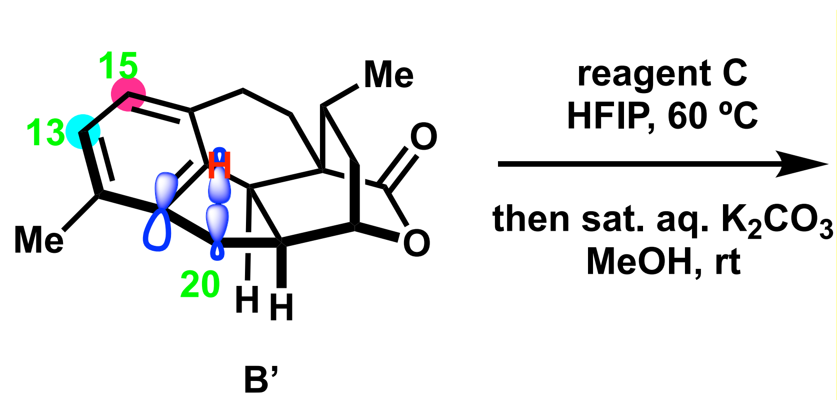
Total synthesis of cephanolide A (3)

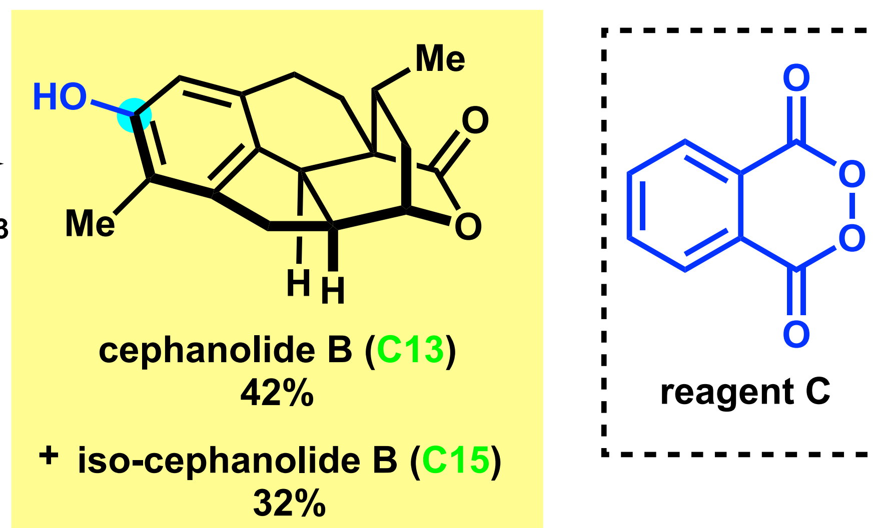


1) Dragan, A.; Kubczyk, T.; Rowley, J.; Sproules, S.; Tomkinson, N. *Org. Lett.* **2015**, *17*, 2618 2) Picon, S.; Tomkinson, N. *Org. Lett.* **2012**, *14*, 6250

Regioselectivity of oxidation



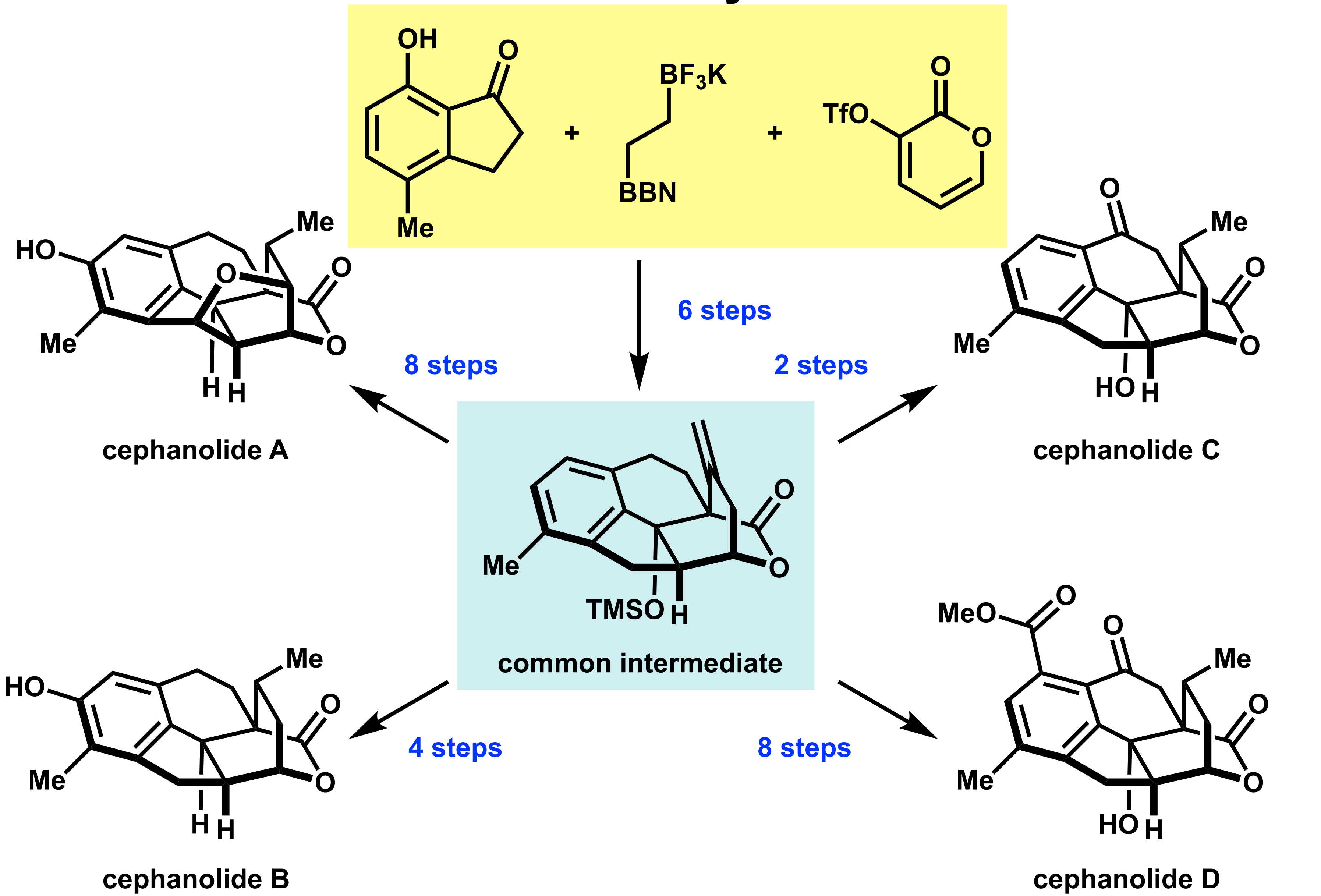




Electron-donacity: C–H > C–O
Nucleophilicity at C15: B' > A'

1) Dragan, A.; Tomkinson, N. *Org. Lett.* **2015**, *17*, 2618 2) Picon, S.; Tomkinson, N. *Org. Lett.* **2012**, *14*, 6250
3) Yuan, C.; Houk, K.; Siegel, D. *Nature* **2013**, *499*, 192

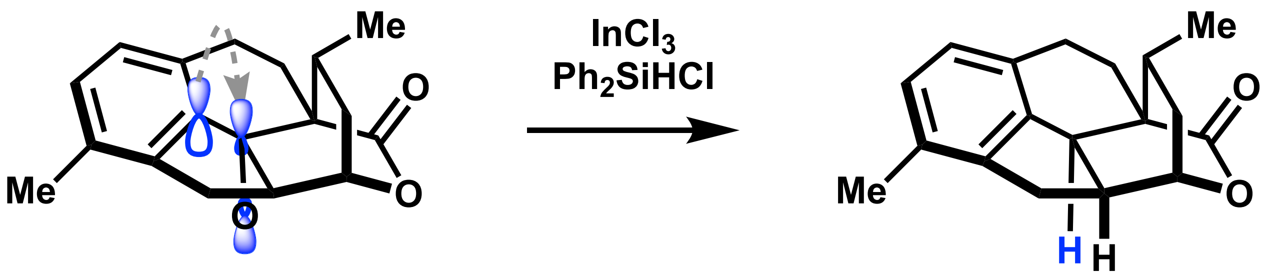
Summary



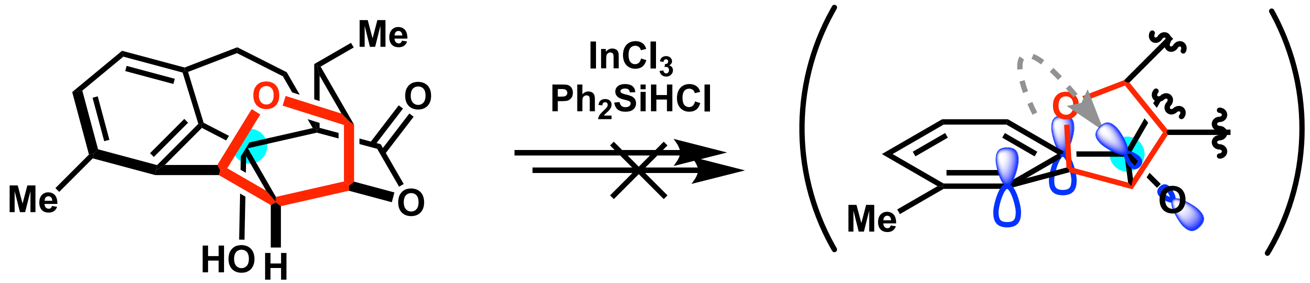
1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc.* **2021**, *143*, 2710

Appx. Conformation change

my proposal



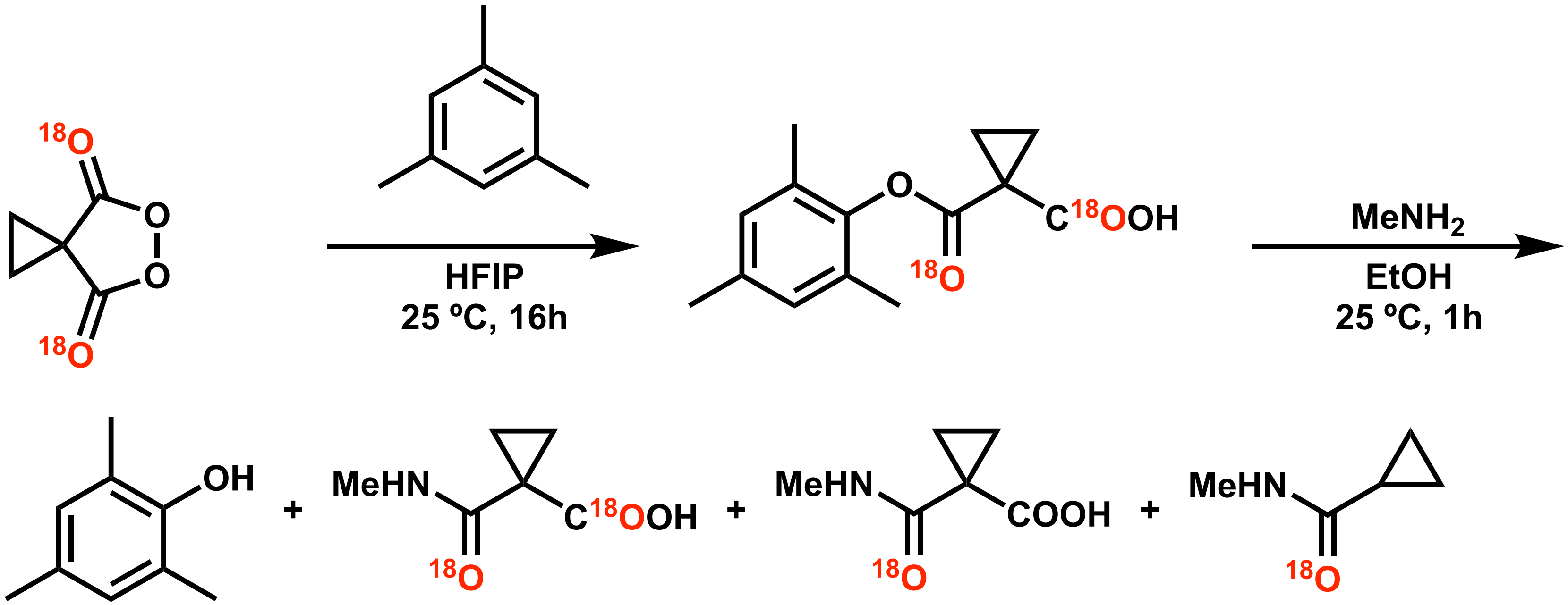
This conformation has good overlap between C-O σ* orbital and π orbital of aromatic ring, so deoxydation of Sn1-like is occured.

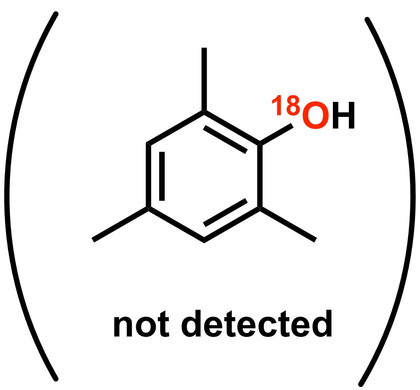


not good overlap

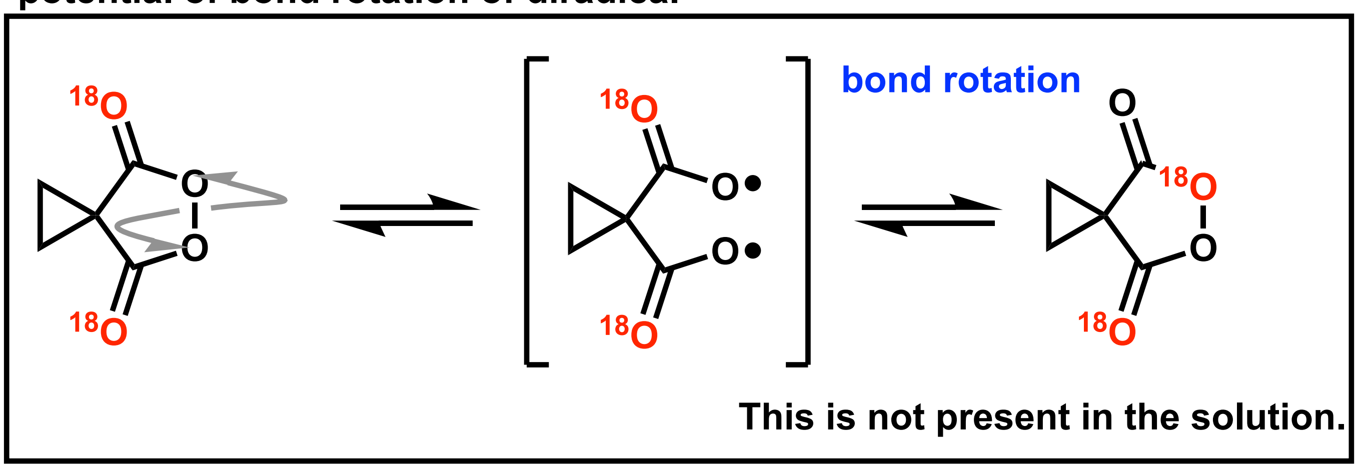
1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc.* **2021**, *143*, 2710

Appx. Radical pathway





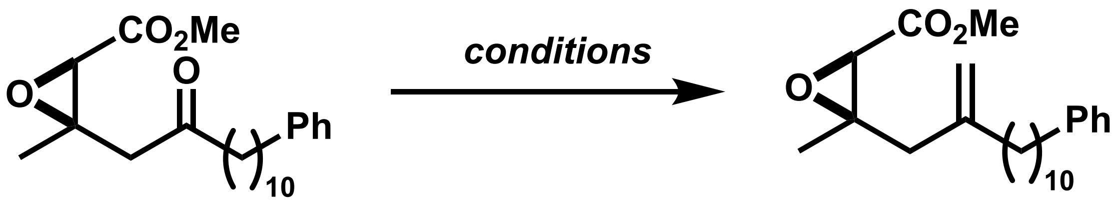
potential of bond rotation of diradical



1) Dragan, A.; Tomkinson, N. *Org. Lett*. **2015**, *17*, 2618

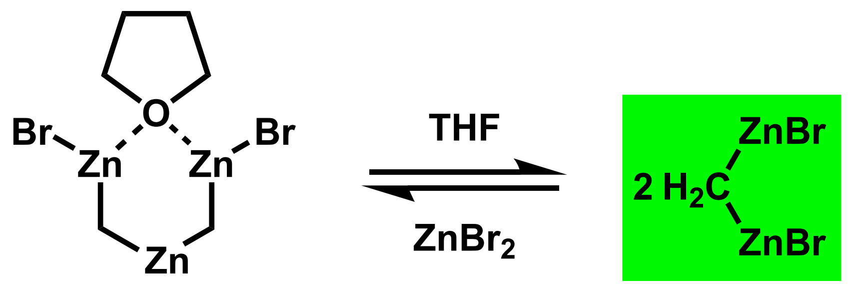
Appx. Zn + Ti (1)

1. Lewis Acid-type (no Zn(0))



entry	reagents	temp. (ºC)	yield
1	Zn, CH_2Br_2, $TiCl_4$	0 to rt	decomp.
2	$TiCl_4$, Nysted reagent	0 to 15	35
3	Ti(O*i*-Pr)$_2$Cl$_2$, Nysted reagent	0 to 15	70

Lewis acidity: $TiCl_4$ > Ti(O*i*-Pr)$_2$Cl$_2$ > Ti(O*i*-Pr)$_4$



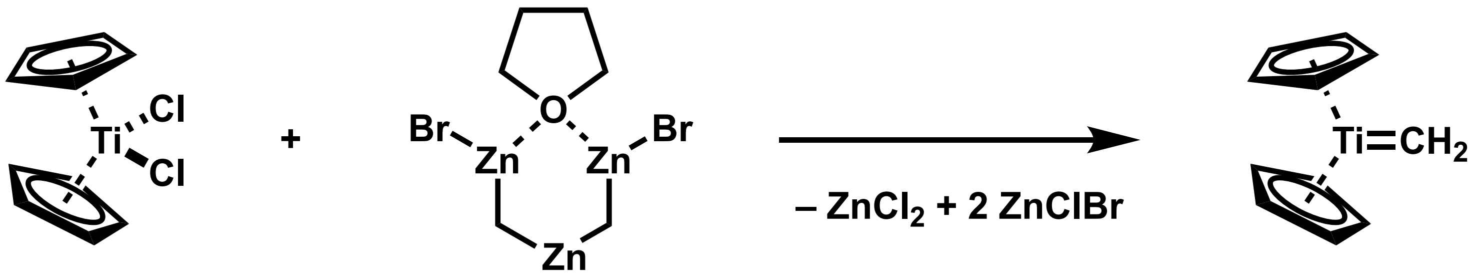
Nysted reagent

active species ?

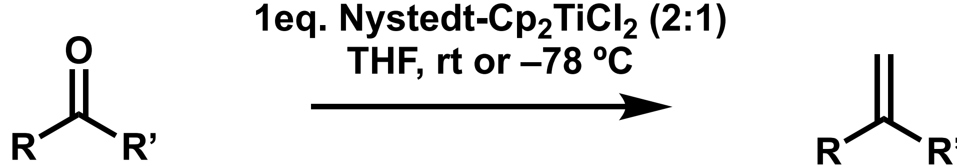
1) Barnych, B.; Vatele, J. *Synlett*. **2011**, *13*, 1912

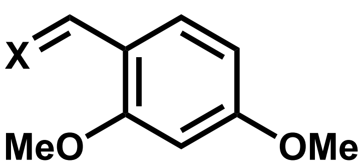
Appx. Zn + Ti (2)

2. Tebbe-type

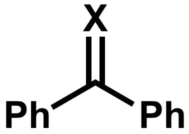


(2 eq.) Nystedt reagent (1 eq.) (2 eq.) proposed

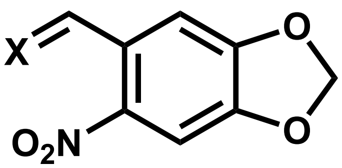




63%
rt, 2h



59%
–78 ºC, 20min



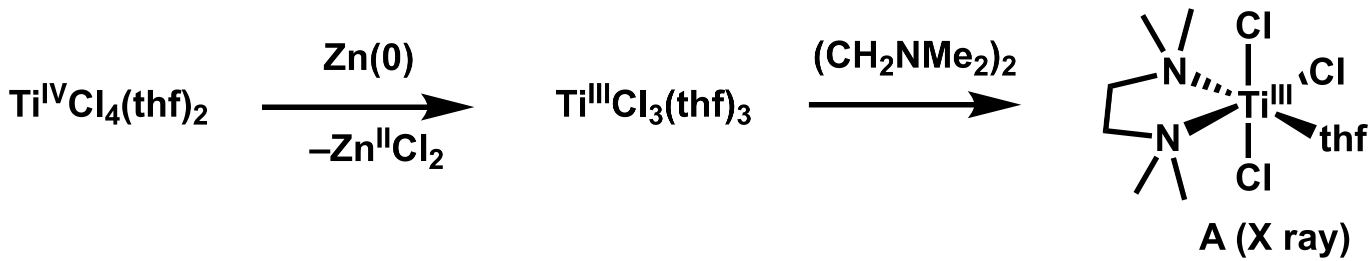
76%
–78 ºC, 20min

1) Haahr, A.; Rankovic, Z.; Hartley, C. *Tetrahedron Lett*. **2011**, *52*, 3020

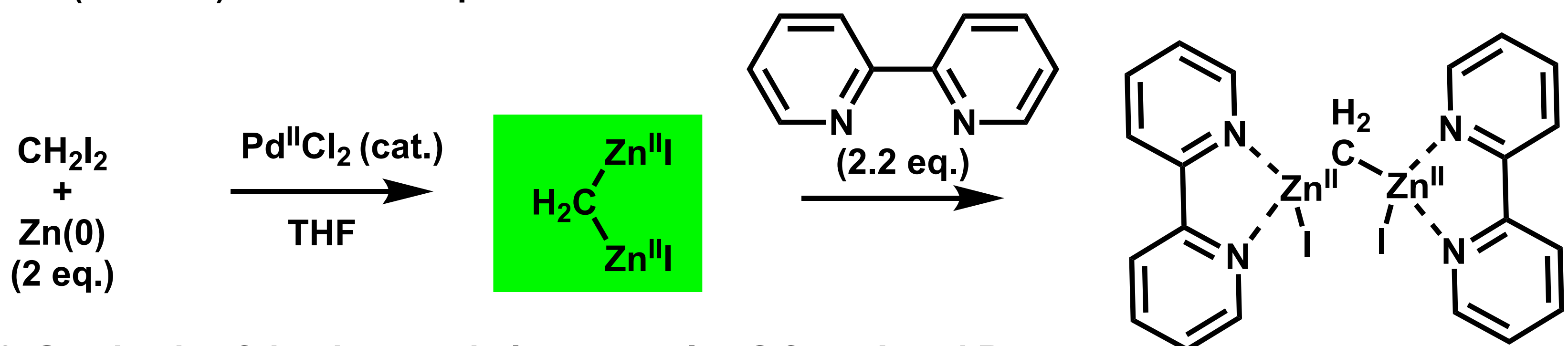
Appx. Zn + Ti (3)

3. Lombardo-type

3-1. Reduction of Ti(IV) to Ti(III) occurred by Zn(0)

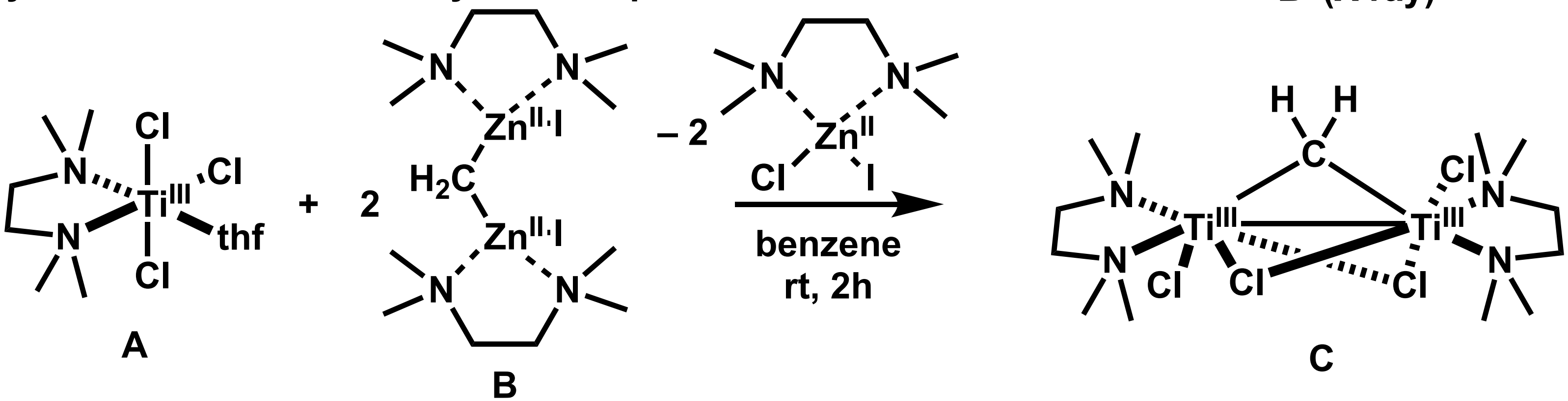


3-2. Di(idozinic)methane complexes



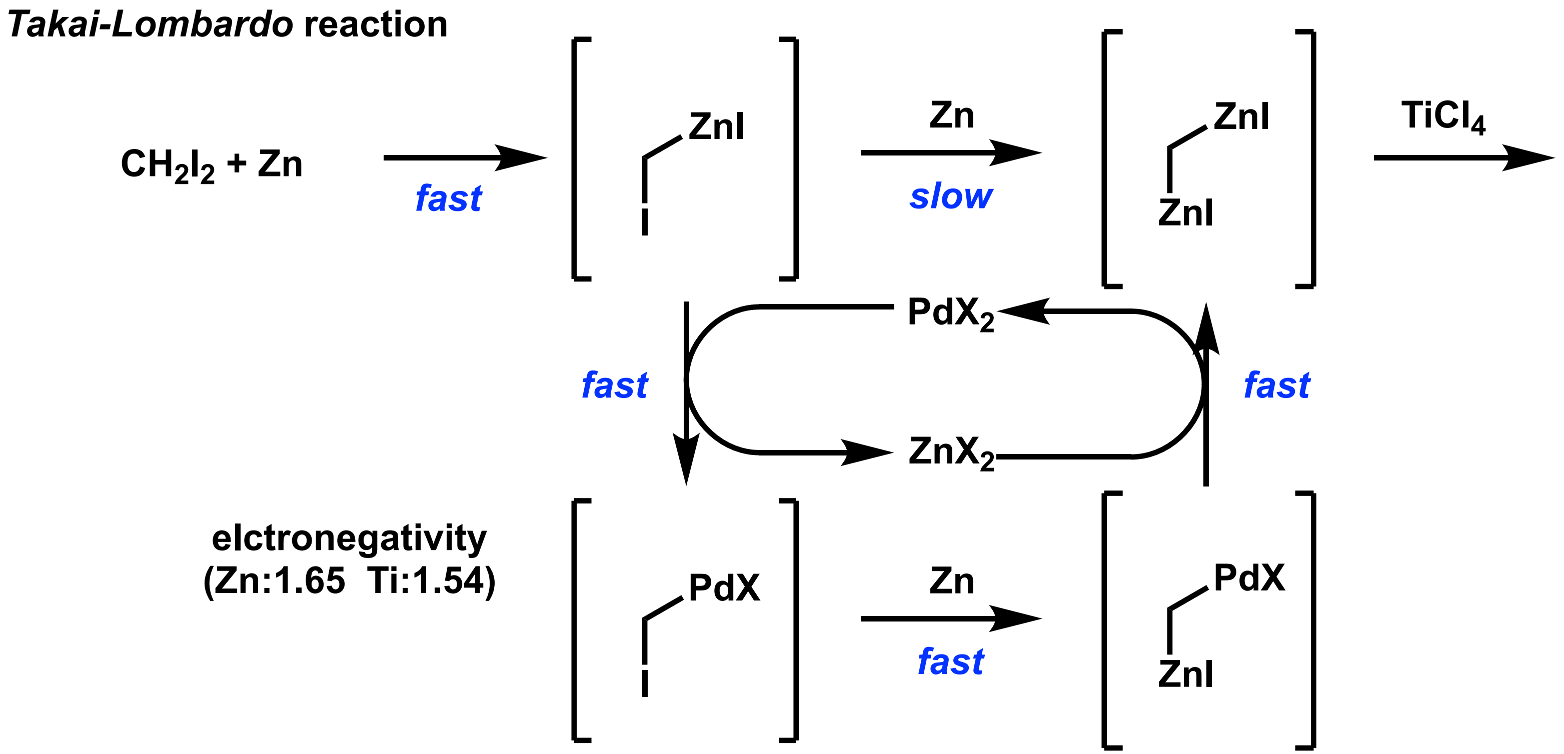
B' (X ray)

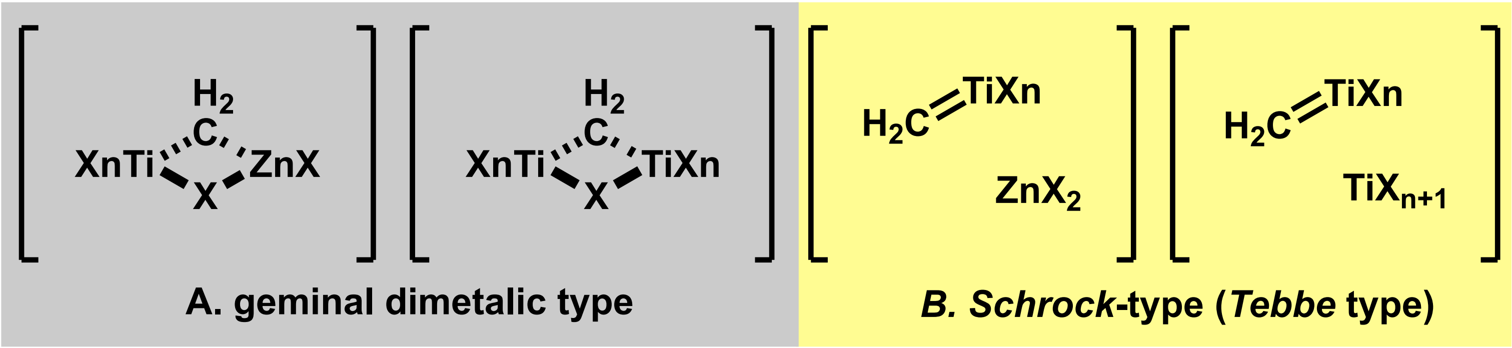
3-3. Synthesis of titanium methylene complex C from A and B



1) Kurogi, T.; Kuroki, K.; Moritani, S.; Takai, K. *Chem. Sci*. **2021**, *12*, 3509
2) Oshiki, T.; Kiriyama, T.; Tsuchida, K.; Takai, K. *Chem. Lett*. **2000**, *29*, 334
3) Nichida, Y.; Hosokawa, N.; Murai, M.; Takai, K. *J. Am. Chem. Soc*. **2015**, *137*, 114

Appx. Zn + Ti (4)

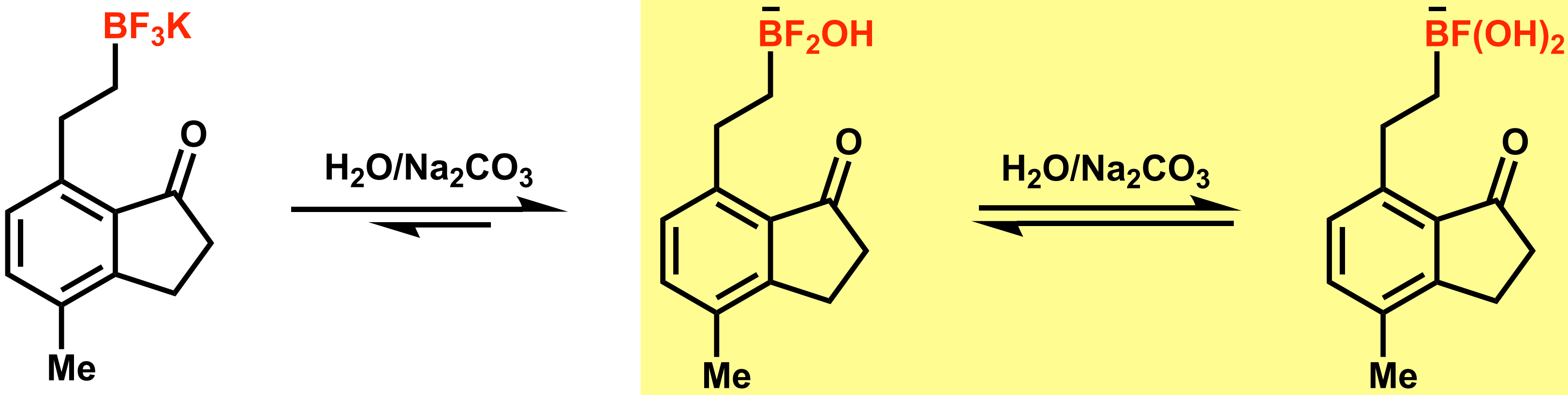




1) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem*. **1994**, *59*, 2668

Appx. Hydrous condition

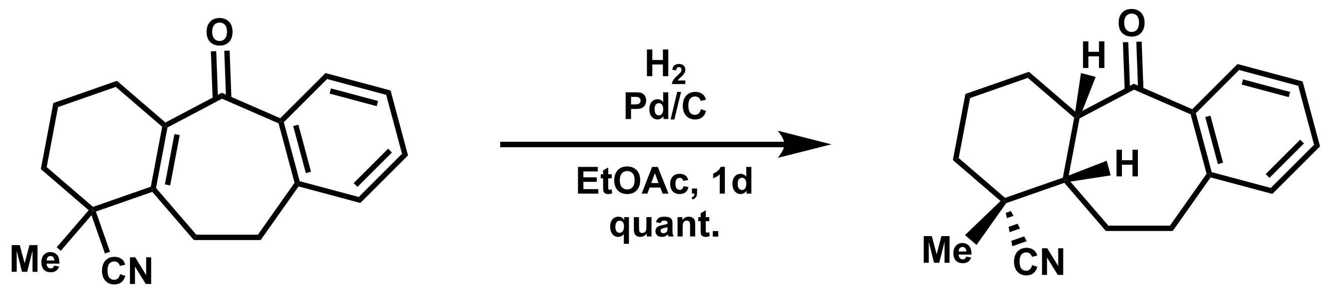
Unhydrous conditions **Hydrous conditions**



unreactive reactive

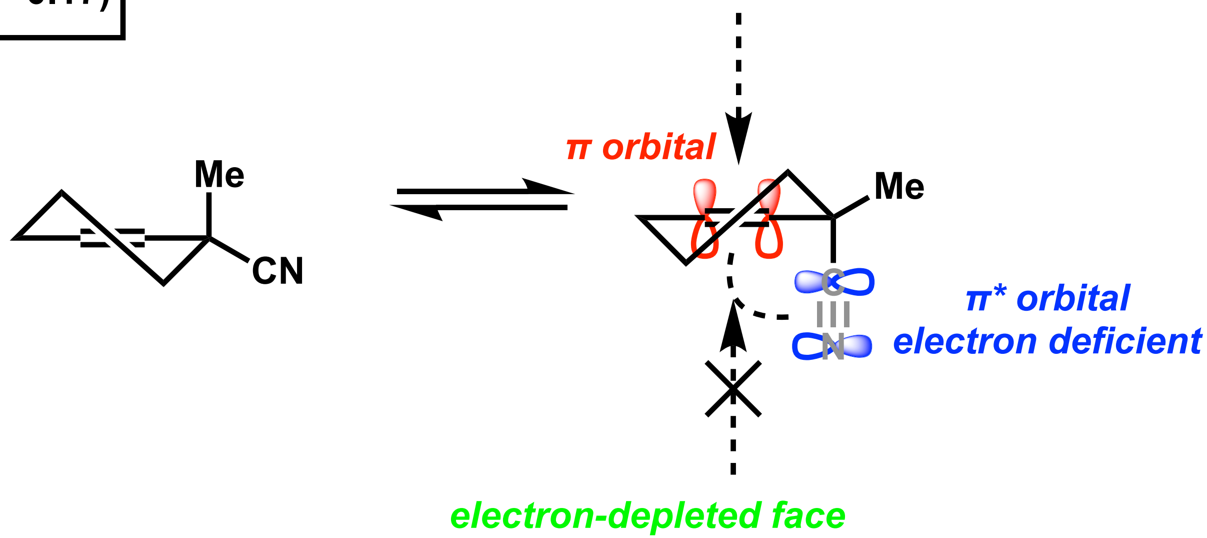
1) Haider, M.; Sennari, G.; Sarpong, R. *J. Am. Chem. Soc*. **2021**, *143*, 2710 2) Molander, G.; Canturk, B. *Angew. Chem. Int. Ed*. **2009**, *48*, 9240

Appx. Stereoelectonic orbital interaction



Me group (*A* = 1.7)
Cyano group (*A* = 0.17)

The reaction was occured in electron-rich face.

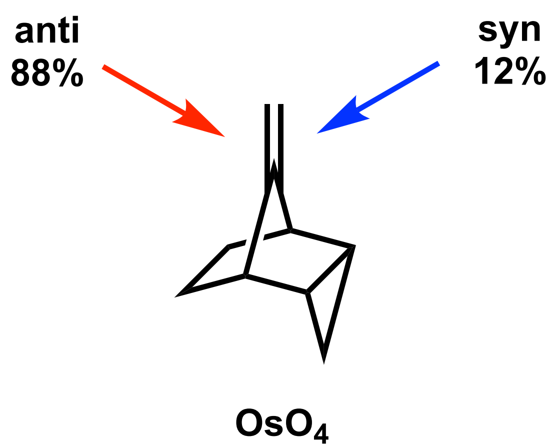


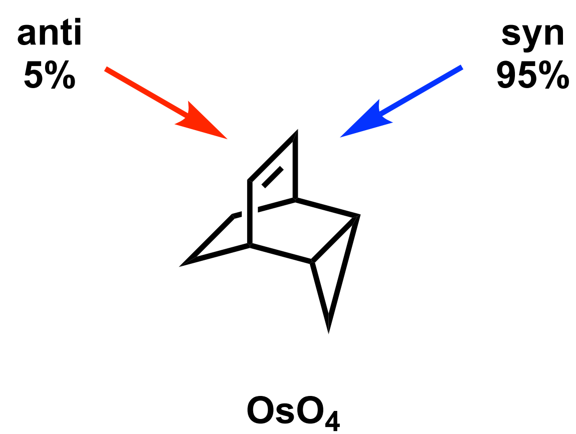
1) Hamlin, A.; Lapointe, D.; Owens, K.; Sarpong, R. *J. Org. Chem*. **2014**, *79*, 6783

Appx. π-facial selectivity (1)

π-facial selectivity
- **1. Steric factor**
- **2. Orbital phase factor**

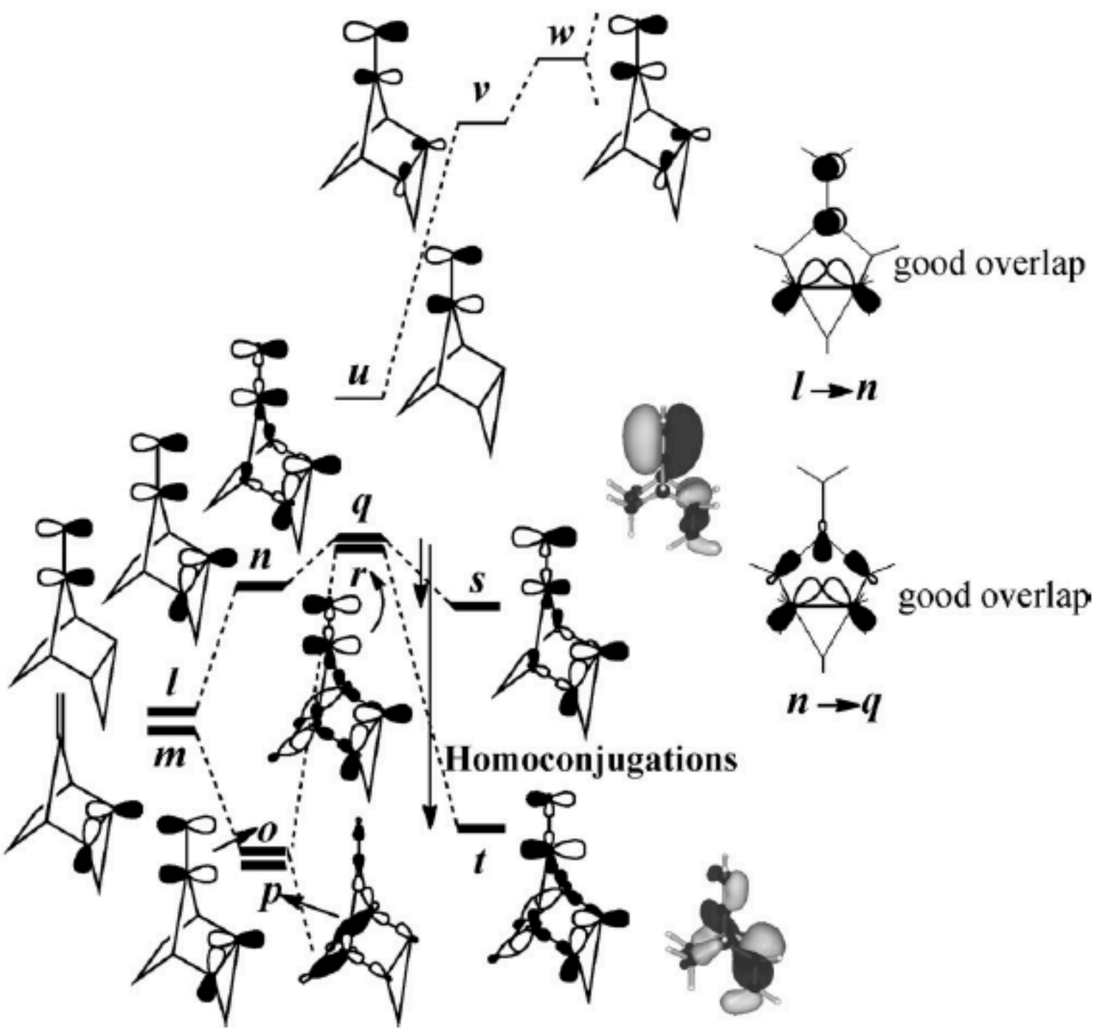
ex) dihydroxylation of tricyclic olefins with OsO_4

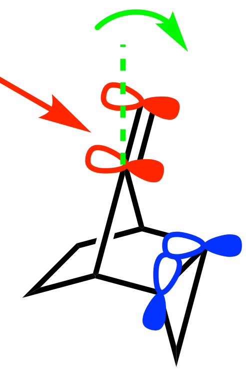




1) Tsuji, M. *Asian. J. Org. Chem*. **2015**, *4*, 659

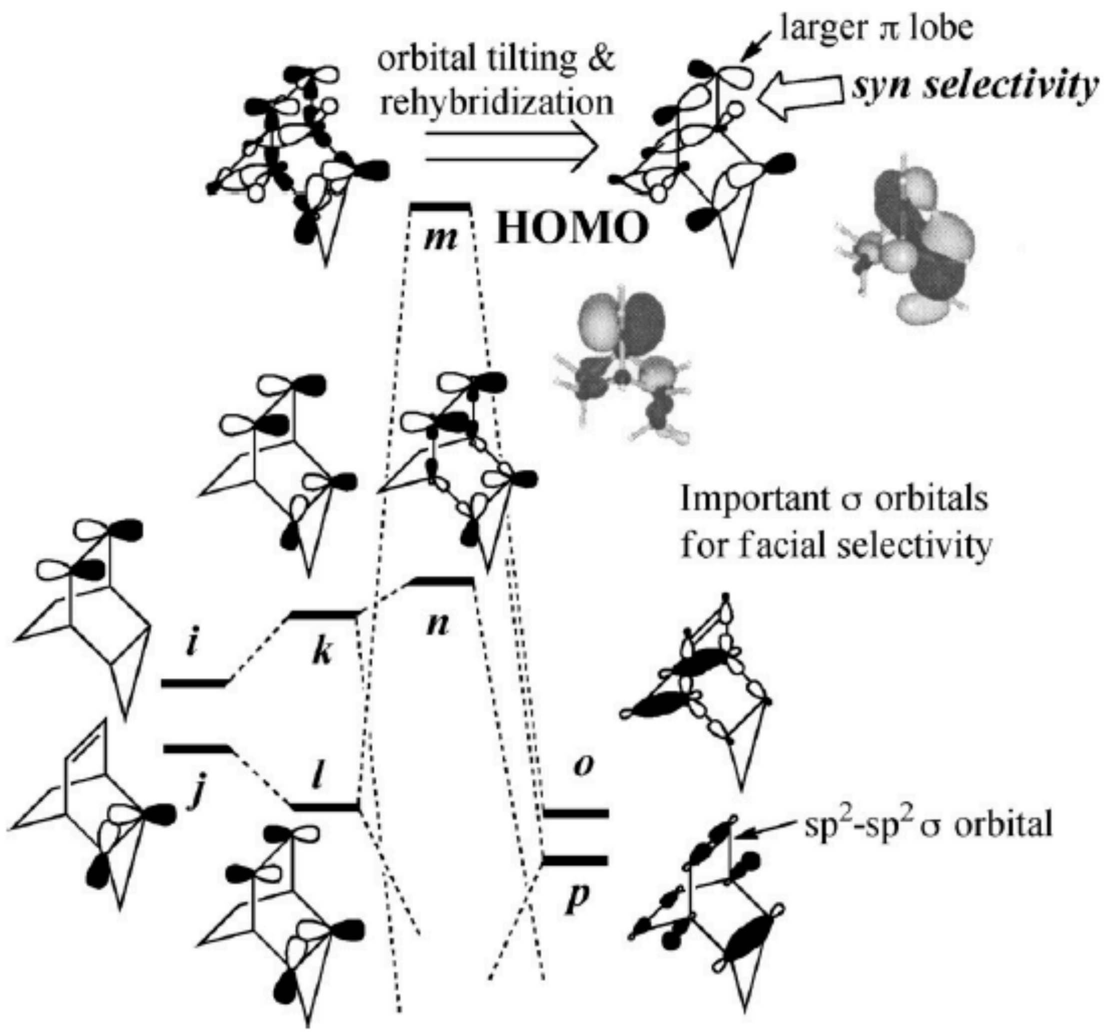
Appx. π-facial selectivity (2)





1) Tsuji, M. *Asian. J. Org. Chem*. **2015**, *4*, 659

Appx. π-facial selectivity (3)



1) Tsuji, M. *Asian. J. Org. Chem*. **2015**, *4*, 659