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Asymmetric Total Synthesis of Commiphoranes A and B

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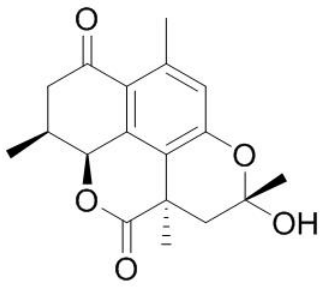
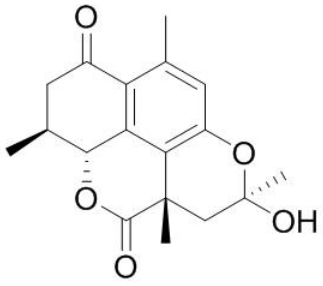
Petasis Research Group, Loker Hydrocarbon Research Institute
September 20, 2017



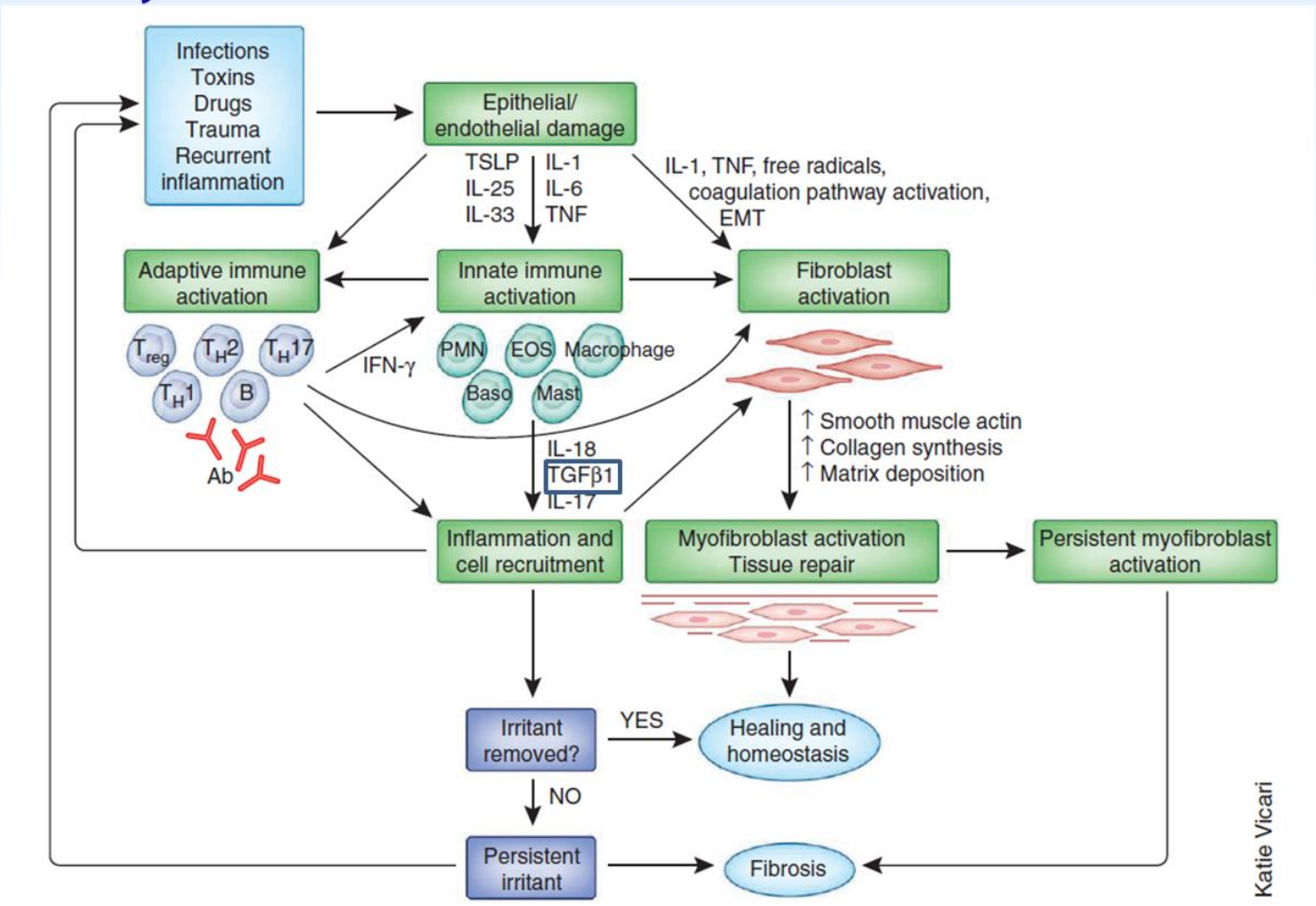
Commiphorane A



Commiphorane B

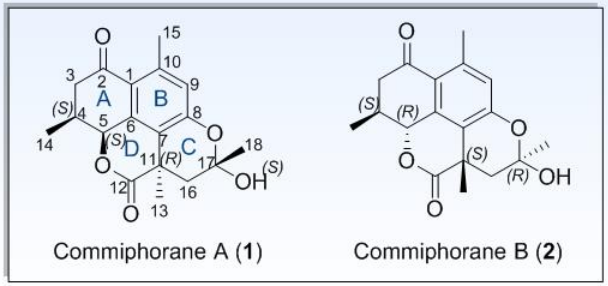
Fibrosis overview

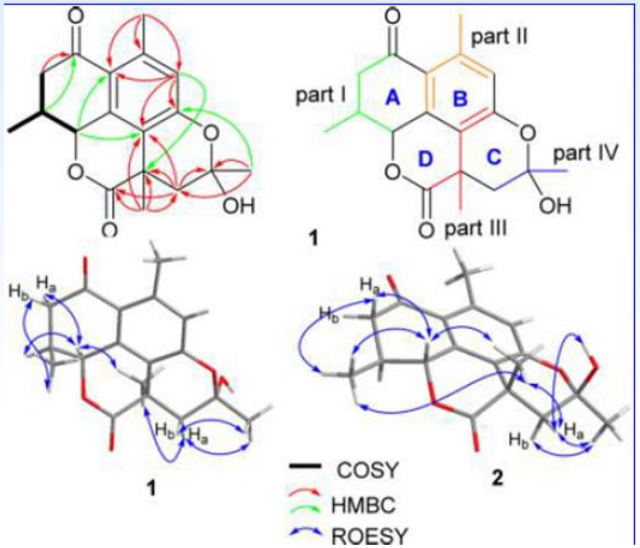
- Primary cause - Chronic inflammation



Wynn, T. A., et al., *Nat Med* **2012,** *18* (7), 1028-1040.

Newly isolated commiphoranes





Dong, L., et al., *Organic Letters* **2017,** *19* (1), 286-289.

Commiphoranes originates from Myrrh

dōTERRA wellness advocate

Myrrh

Commiphora myrrha

Plant Part: Resin
Extraction Method: Steam distillation
Aromatic Description: Hot, smoky, herbaceous, woody, dry

KEY BENEFITS

- Powerful cleansing properties, especially for the mouth and throat
- Soothing to the skin; promotes a smooth, youthful-looking complexion
- Promotes emotional balance and well-being

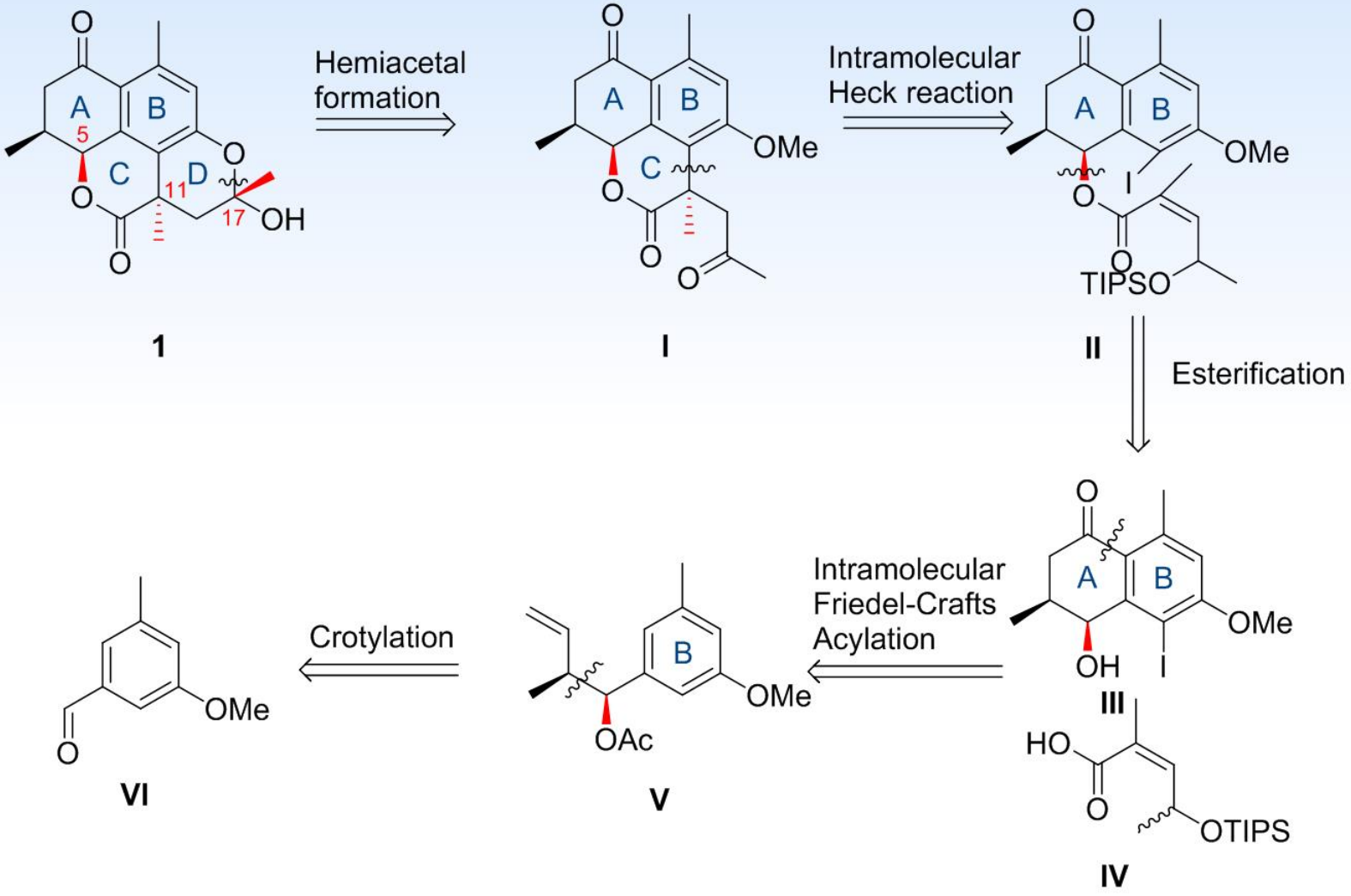
A Aromatic T Topical I Internal
N Neat–Can be used topically with no dilution

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

For more details, visit:
http://doterra.com/US/en/blog/diy-cuticle-cream

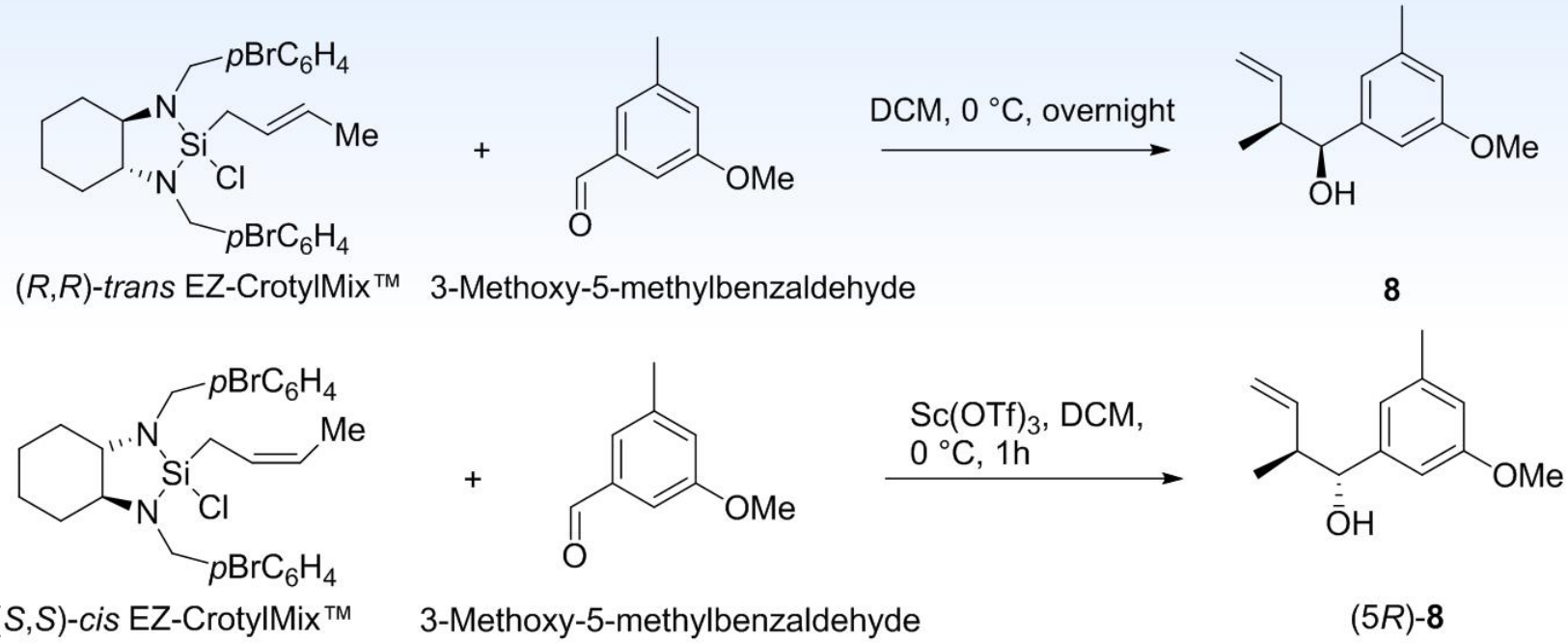
http://media.doterra.com/us/en/presentations/wa-myrrh.jpg

Retrosynthetic analysis



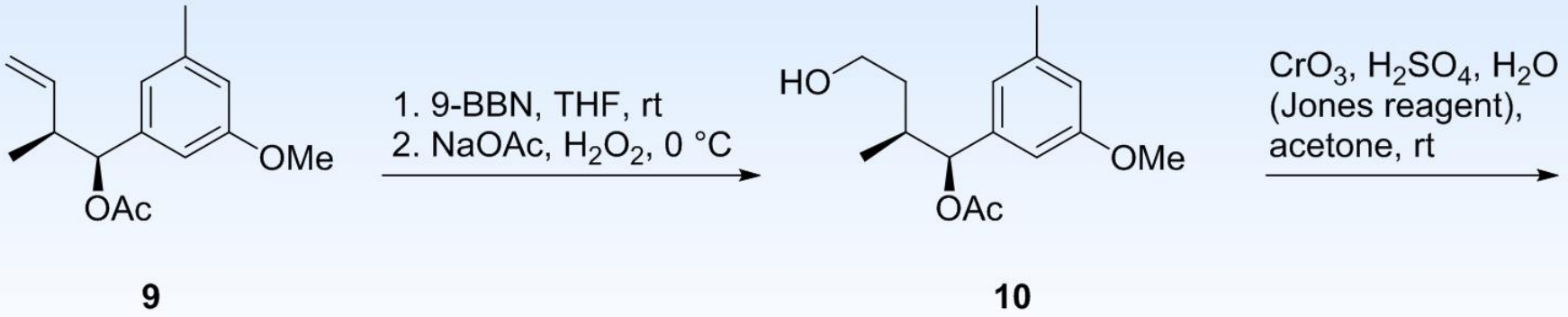
Enantioselective crotylation

- Stereochemistries are controlled by chiral reagents

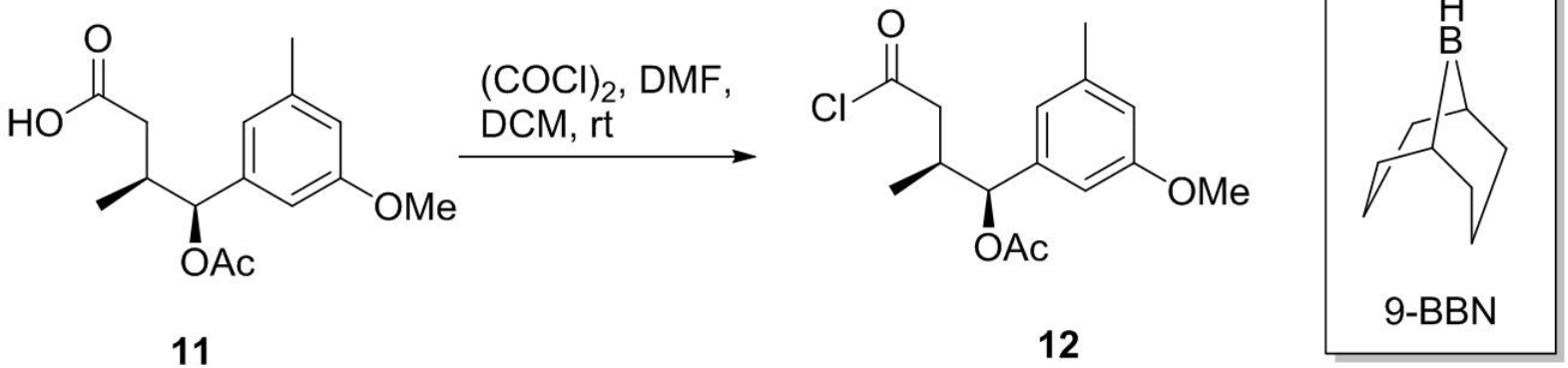


Kim, H., et al., *Journal of the American Chemical Society* **2011,** *133* (17), 6517-6520.
Hackman, B. M., et al., *Organic Letters* **2004,** *6* (23), 4375-4377.
Kubota, K., et al., *Angewandte Chemie* **2003,** *115* (8), 976-978.

Acyl chloride formation



9 **10**

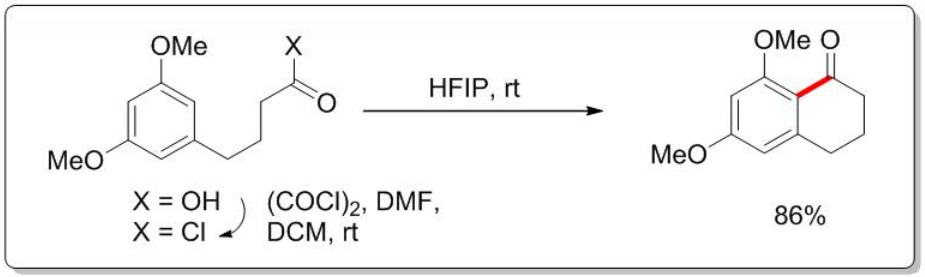


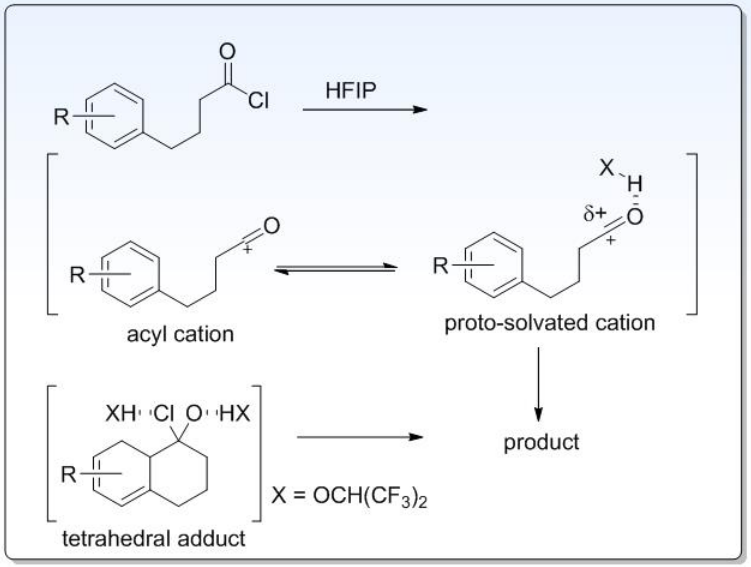
11 **12**

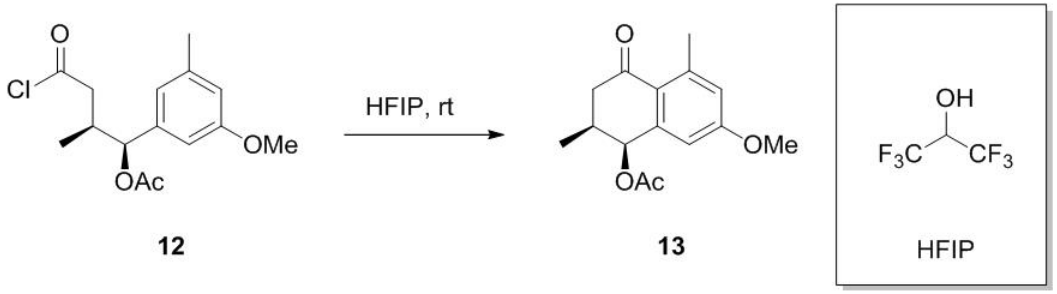
Boschi, D., et al., *Journal of Medicinal Chemistry* **2006,** *49* (10), 2886-2897.
Nagy, E., et al., *Journal of Medicinal Chemistry* **2017,** *60* (5), 1860-1875.
Ríos-Lombardía, N., et al., *The Journal of Organic Chemistry* **2011,** *76* (3), 811-819.

Intramolecular Friedel-Crafts promoted by HFIP

- Requires no reagent
- HFIP stabilizes transition state
- Works for sterically hindered substrates

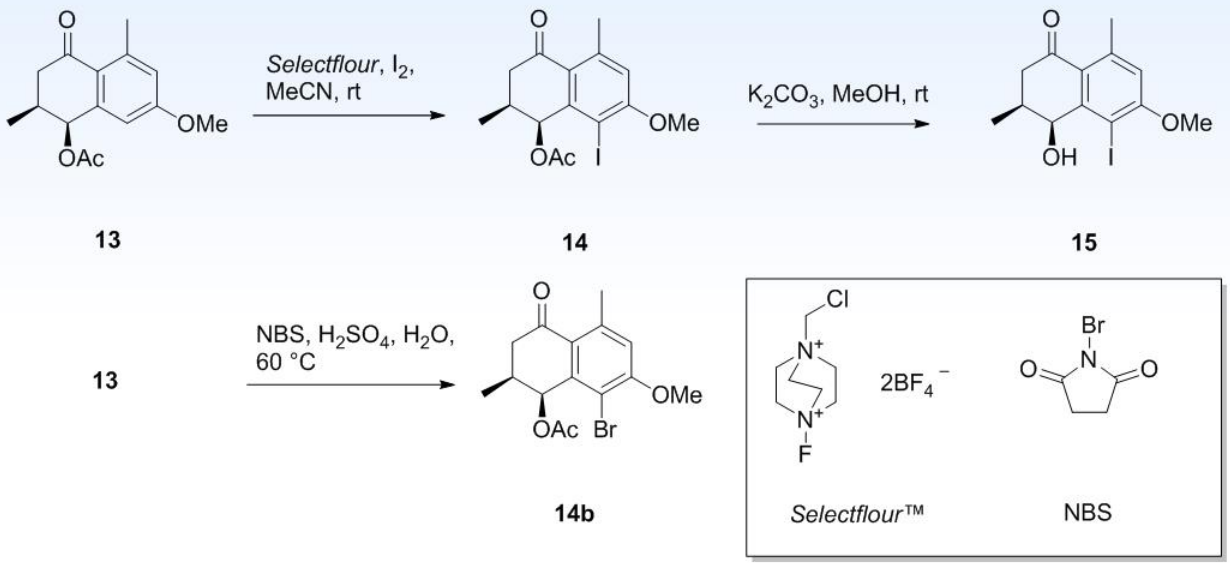






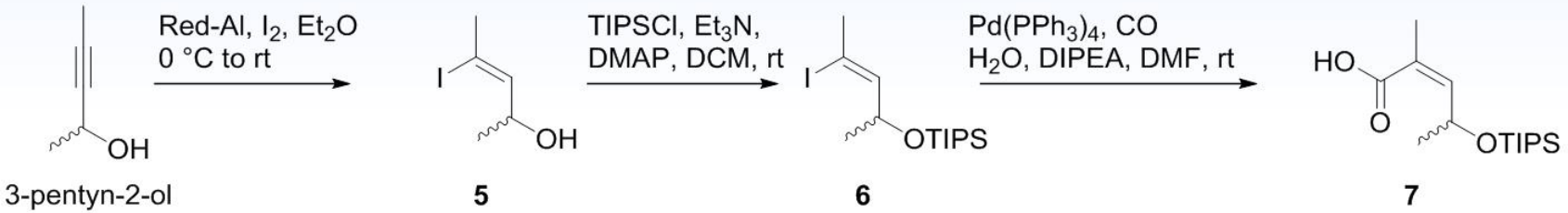
Motiwala, H. F., et al., *Organic Letters* **2015,** *17* (21), 5484-5487.

Regioselective halogenation



Boursalian, G. B., et al., *Nat Chem* **2016,** *8* (8), 810-815.
Kamal, A., et al., *Tetrahedron: Asymmetry* **2003,** *14* (24), 3861-3866.
Pravst, I., et al., *Tetrahedron Letters* **2006,** *47* (27), 4707-4710.
Stavber, S., et al., *Chemical Communications* **2002,** (5), 488-489.

Synthesis of fragment **7**

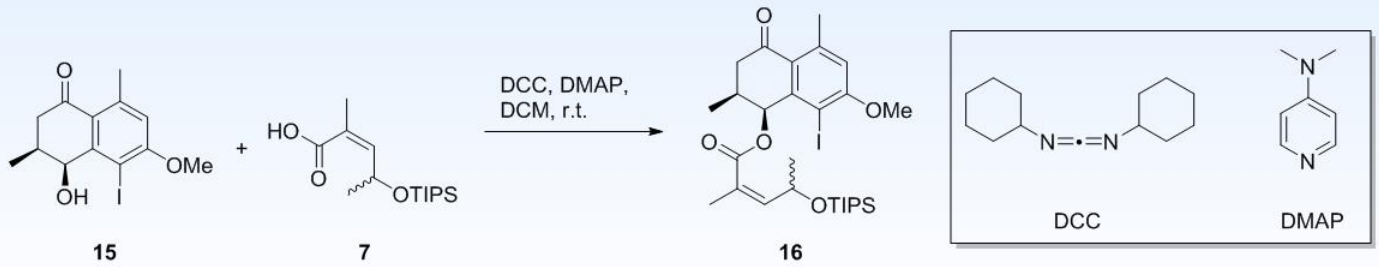


3-pentyn-2-ol **5** **6** **7**

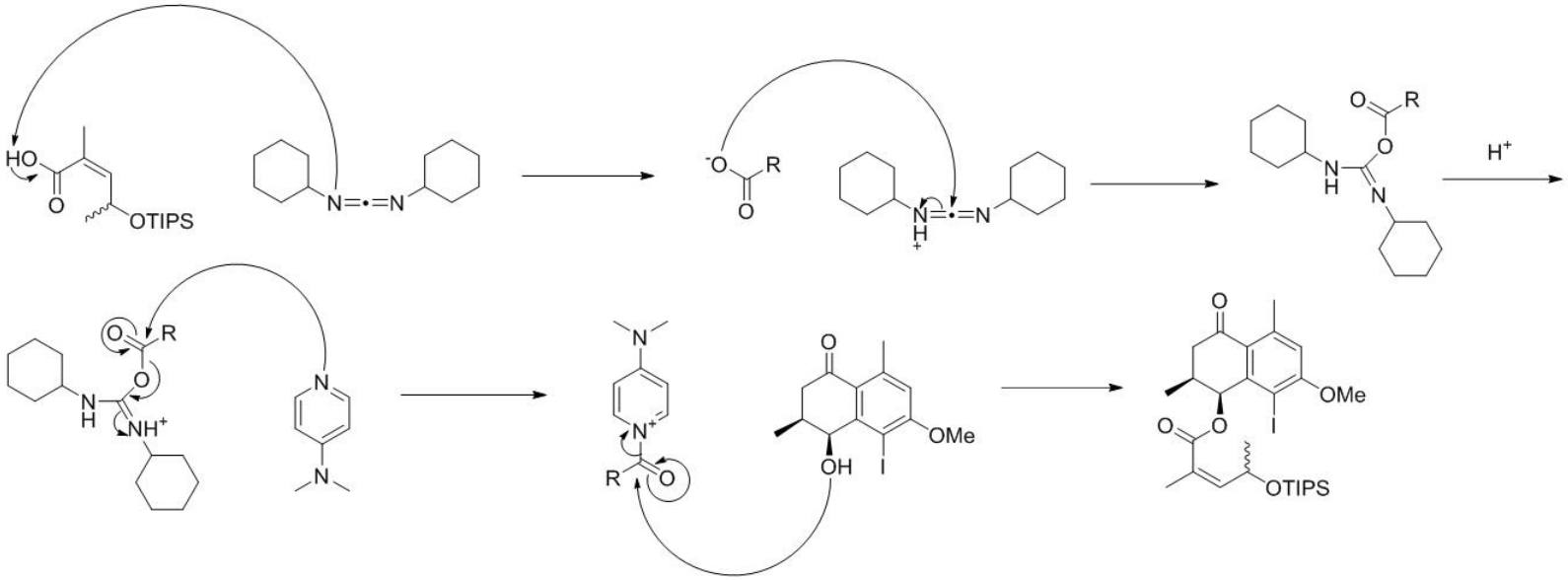
Lowe, J.T., et al., *Organic Letters* **2005,** *7* (8), 1529-1532.
Ashimori, A., et al., *Journal of the American Chemical Society* **1998,** *120* (26), 6488-6499.
Matsuura, T., et al., *Journal of the American Chemical Society* **1998,** *120* (26), 6500-6503.
Schoenberg, A., et al., *The Journal of Organic Chemistry* **1974,** *39* (23), 3318-3326.

DCC-mediated esterification

- Connects both halves of the compound



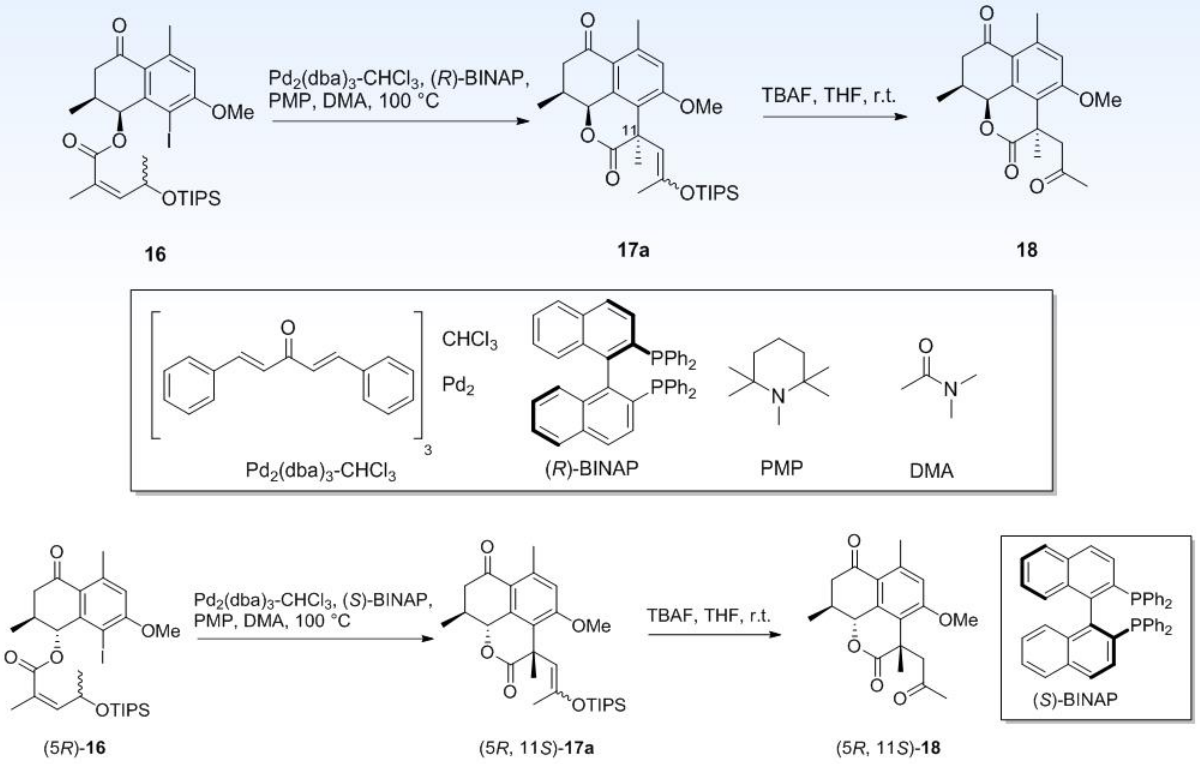
15 7 16



Shi, H., et al., *Journal of the American Chemical Society* **2015,** *137* (11), 3775-3778.
http://www.organic-chemistry.org/namedreactions/steglich-esterification.shtm

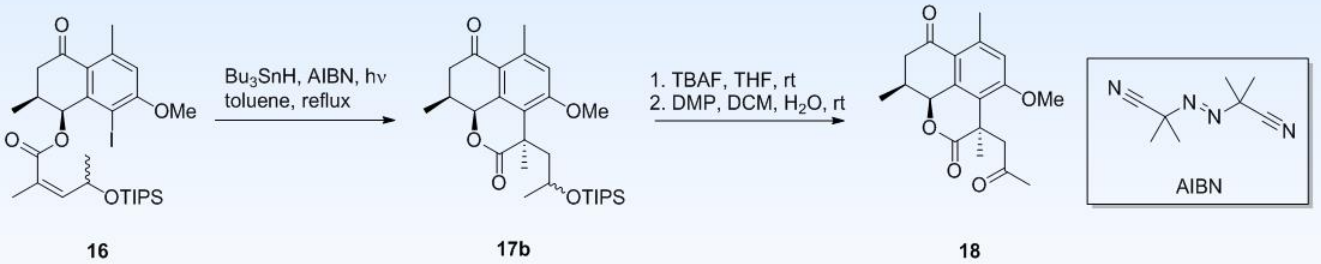
Intramolecular Heck reaction

- Chiral BINAP ligand controls stereoselectivity

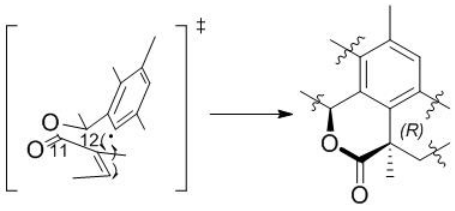


Dounay, A. B., et al., *Chemical Reviews* **2003,** *103* (8), 2945-2964.
Ohshima, T., et al., *Journal of the American Chemical Society* **1996,** *118* (30), 7108-7116.
DiLauro, A. M., et al., *The Journal of Organic Chemistry* **2011,** *76* (18), 7352-7358.

Radical cyclization – An alternative to Heck reaction



16 17b 18



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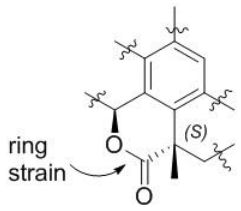

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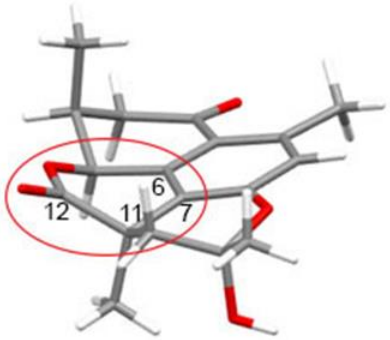
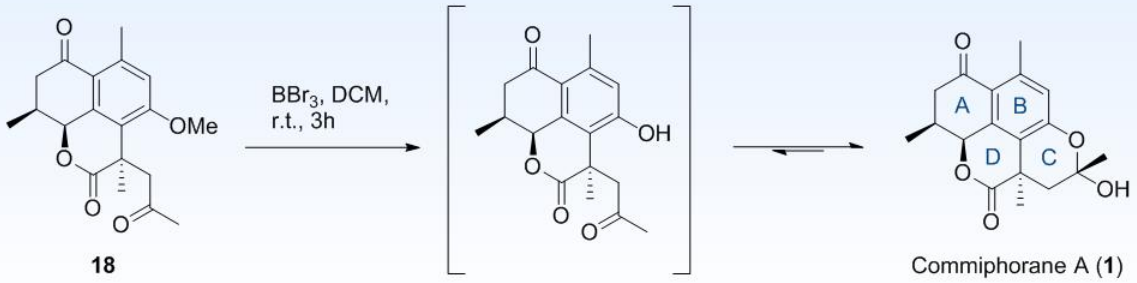
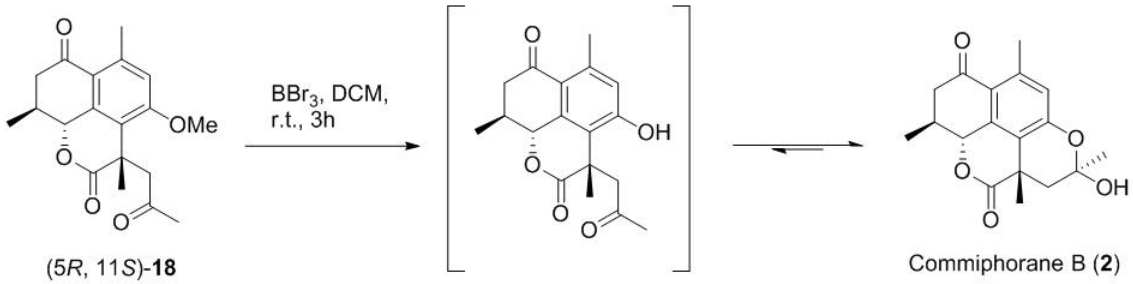


Gowrisankar, S., et al., *B Korean Chem Soc* **2007,** *28* (12), 2501-2504.
Stork, G., et al., *Journal of the American Chemical Society* **1982,** *104* (8), 2321-2323.

Intramolecular hemiacetal formation



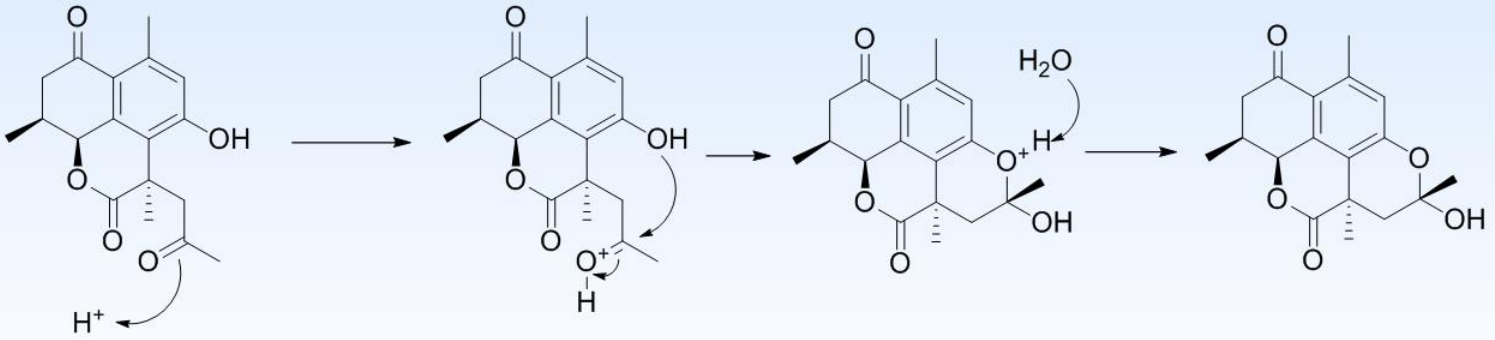
18 Commiphorane A (**1**)

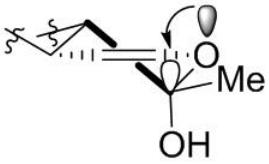


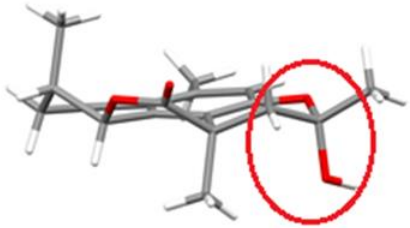
(5*R*, 11*S*)-**18** Commiphorane B (**2**)

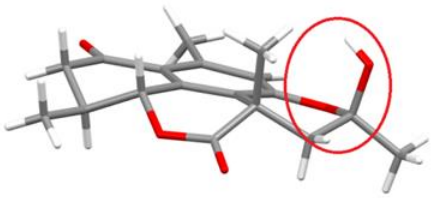
Krohn, K., et al., *European Journal of Organic Chemistry* **2004,** *2004* (1), 209-219.
Rao, Y., et al., *Organic & Biomolecular Chemistry* **2013,** *11* (36), 6029-6035.

Intramolecular hemiacetal formation



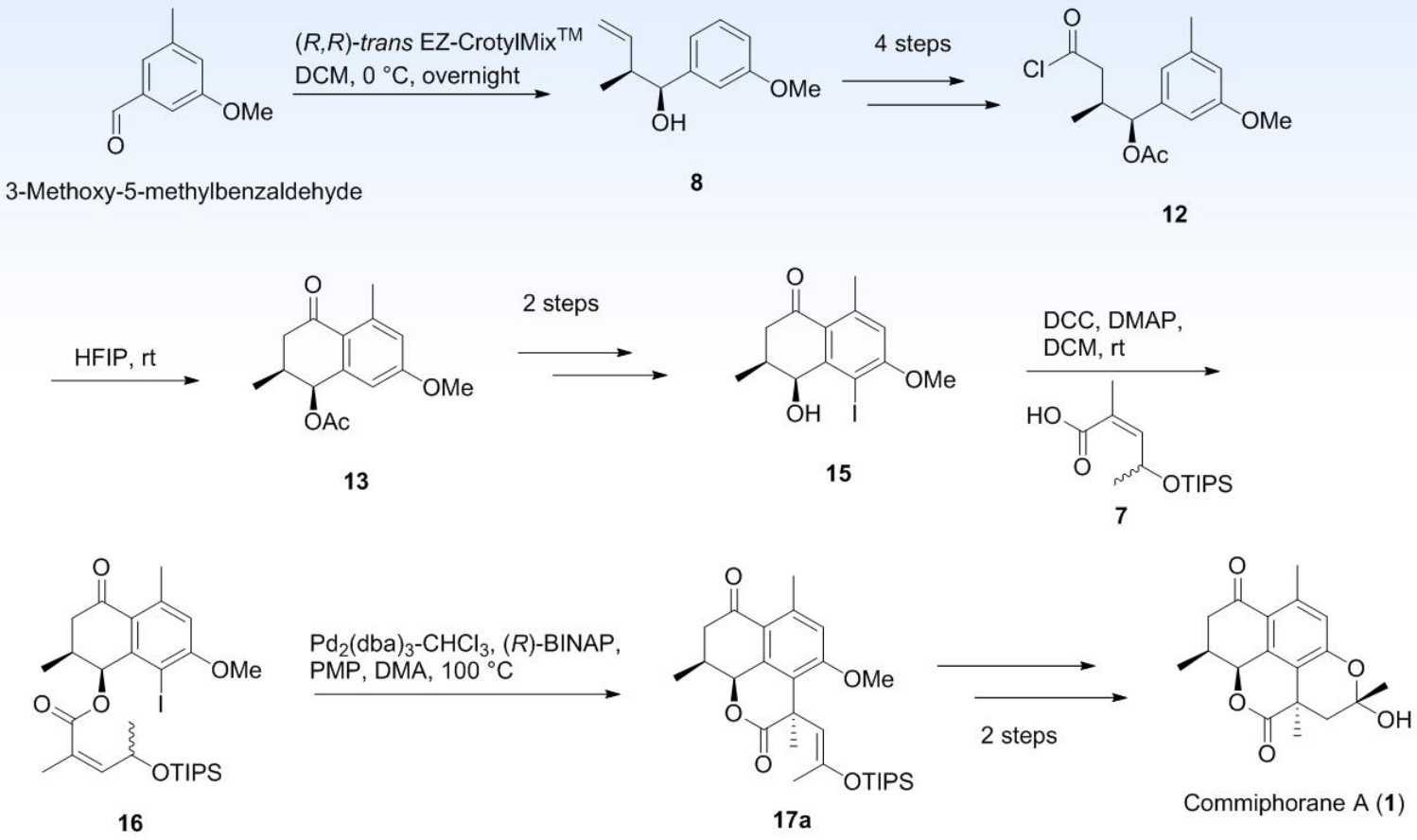




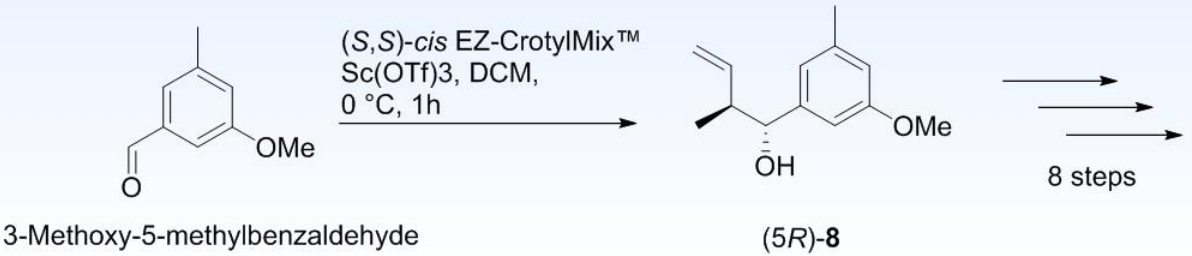


Juaristi, E., et al., *Tetrahedron* **1992,** *48* (24), 5019-5087.
Dong, L., et al., *Organic Letters* **2017,** *19* (1), 286-289.

Summary

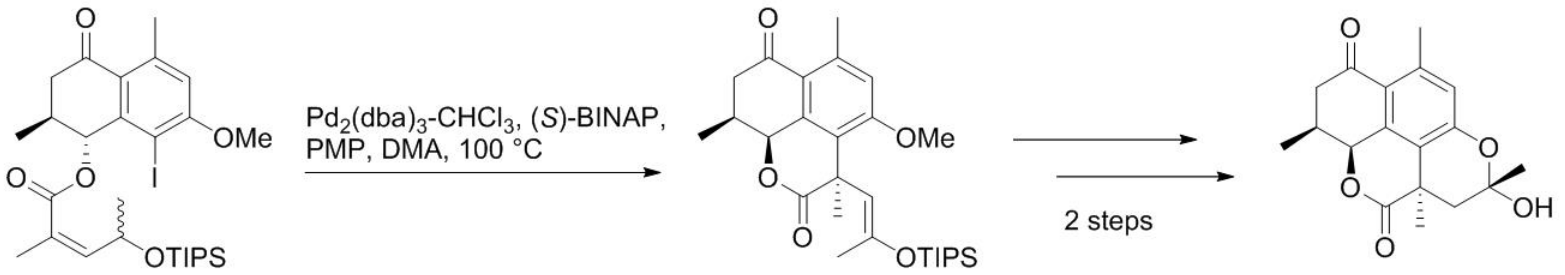

OMe
O
(R,R)-trans EZ-CrotylMix™
DCM, 0 °C, overnight
OMe
OH
4 steps
Cl
O
OMe
OAc
3-Methoxy-5-methylbenzaldehyde
8
12
HFIP, rt
O
OMe
OAc
2 steps
O
OMe
OH
I
DCC, DMAP,
DCM, rt
HO
O
OTIPS
13
15
7
O
OMe
O
O
I
OTIPS
Pd2(dba)3-CHCl3, (R)-BINAP,
PMP, DMA, 100 °C
O
OMe
O
O
OTIPS
2 steps
O
O
O
OH
O
16
17a
Commiphorane A (1)

Summary (2)



3-Methoxy-5-methylbenzaldehyde

(5*R*)-**8**



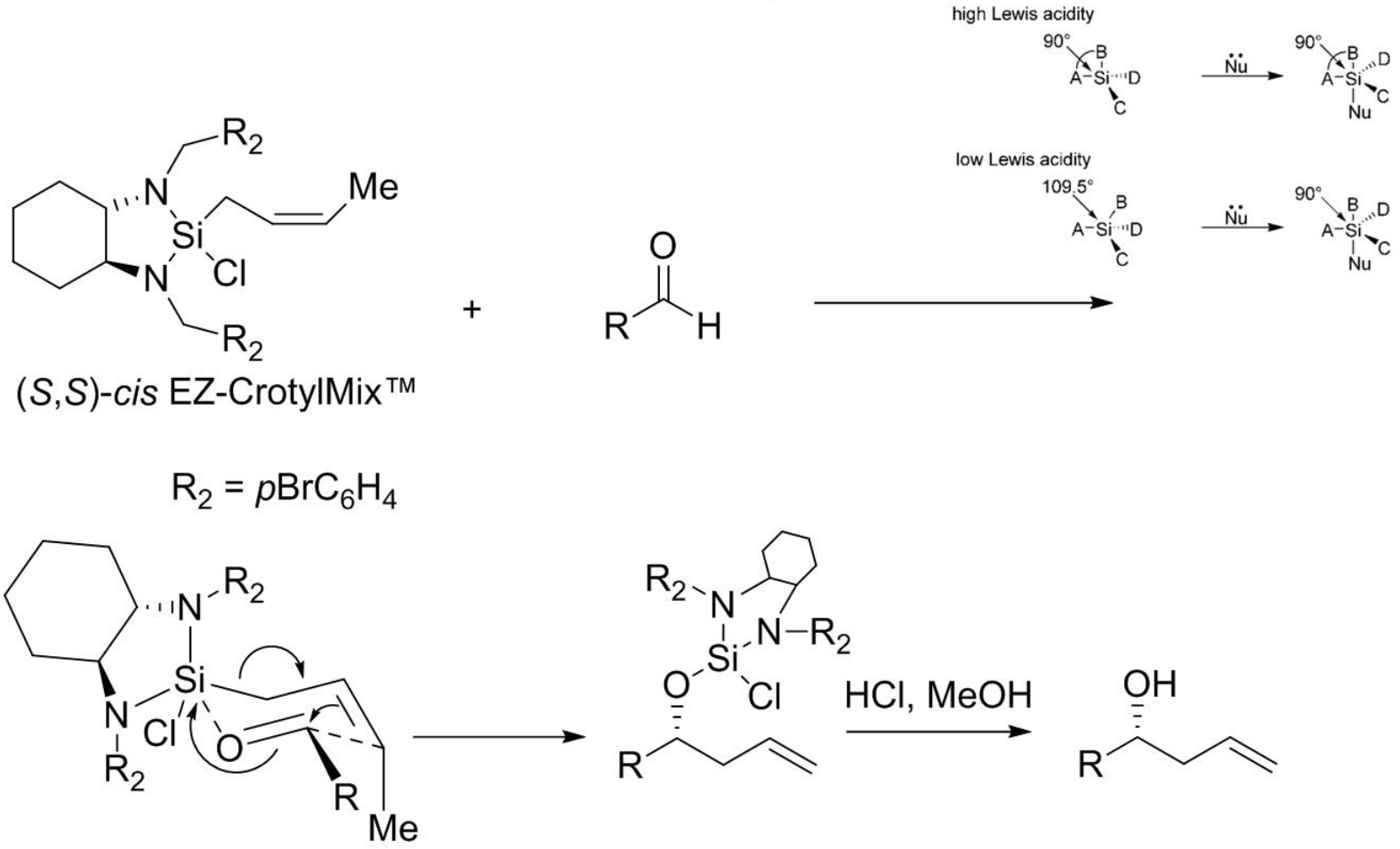
(5*R*)-**16**

(5*R*, 11*S*)-**17**

Commiphorane B (**2**)

Crotylation Mechanism

- Strain-release Lewis acidity of silane

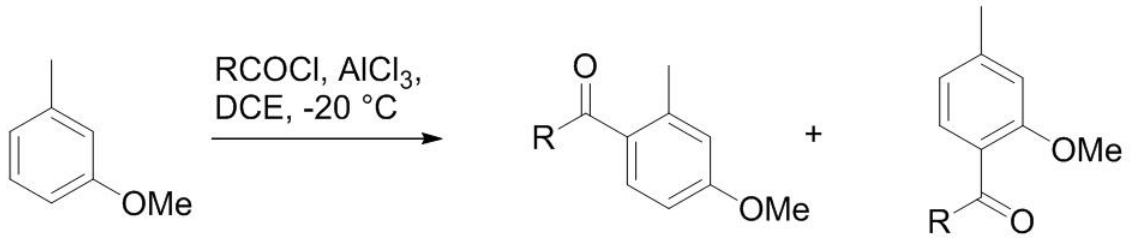


SUPPLEMENTAL INFORMATION

Zhang, X., et al., *Angewandte Chemie* **2005,** *117* (6), 960-963.
Matsumoto, K., et al., *The Journal of Organic Chemistry* **1994,** *59* (23), 7152-7155.

FC regioselectivity

- *Para* position is most electron rich
- Poor selectivity for reactive $MeCO^+$

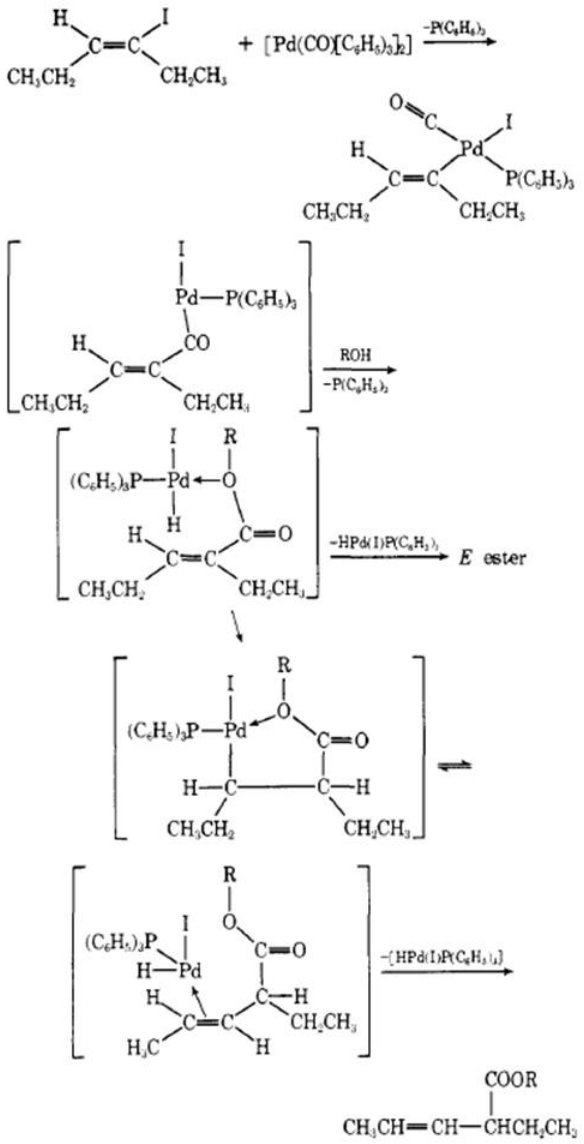


	para		*ortho*
R = Me:	6	:	4
R = Et:	10	:	1

SUPPLEMENTAL INFORMATION

Zhang, H., et al., *ACS Catalysis* **2016,** *6* (10), 6596-6600.

Carbonylation mechanism



SUPPLEMENTAL INFORMATION

Schoenberg, A., et al., *The Journal of Organic Chemistry* **1974,** *39* (23), 3318-3326.