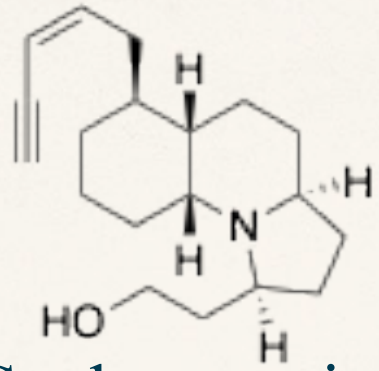


# Total Synthesis of Gephyrotoxin by Amide-Selective Reductive Nucleophilic Addition

Kenji Shirokane, Takamasa Wada, Makoto Yoritate, Ryo Minamikawa, Nobuaki Takayama, Takaaki Sato,* and Noritaka Chida*

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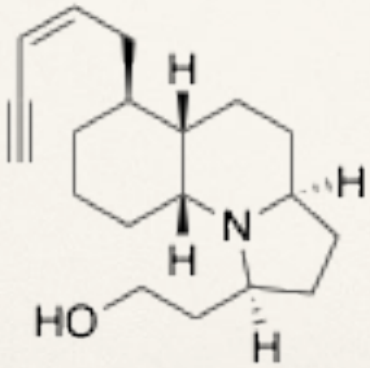
Yongzhao Yan
12-7-2013

Wipf group Current Literature

# Gephyrotoxin

- First isolated in 1977, from skin extracts of the Colombian frog (Dendrobates histrionicus).
- Structure was elucidated by crystallography.
- Possesses an array of neurological activities, including mild muscarinic activity.




Picture from http://en.wikipedia.org/wiki/Harlequin_poison_frog

J. W. Daly, B. Witkop, T. Tokuyama, T. Nishikawa, I. L. Karle, *Helv. Chim. Acta* **1977,** 60, 1128–1140

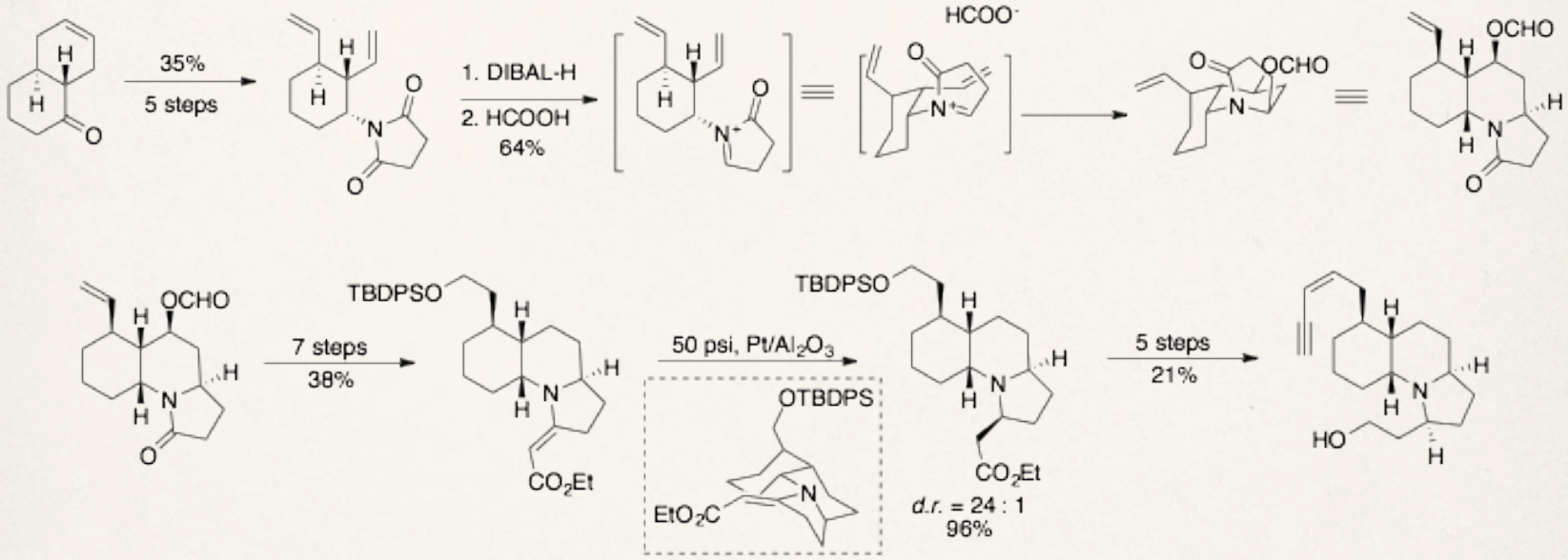
# Total Synthesis of Gephyrotoxin

- The groups of Kishi, Hart, and Overman reported the total synthesis of gephyrotoxin in 1980s.
- Many groups had also reported formal synthesis of gephyrotoxin. Most of these synthesis are based on Kishi's route.


1. R.Fujimoto, Y. Kishi, J. F. Blount, *J. Am. Chem. Soc.* **1980,** *102,* 7154 – 7156 ;
2. D. J. Hart, *J. Org. Chem.* **1981**, *46,* 3576 – 3578 ;
3. D. J. Hart, K. Kanai, *J. Am. Chem. Soc.* **1983**, *105*, 1255–1263;
4. L.E. Overman, D. Lesuisse, M. Hashimoto, *J. Am. Chem. Soc.* **1983**, *105,* 5373–5379;
5. R. Fujimoto, Y. Kishi, *Tetrahedron Lett.* **1981**, *22,* 4197 – 4198.
6. Y. Ito, E. Nakajo, M. Nakatsuka, T. Saegusa, *Tetrahedron Lett.* **1983**, *24*, 2881– 2884;
7. W. H. Pearson, W.-K. Fang, *J. Org. Chem.* **2000**, *65*, 7158–7174;
8. L.-L. Wei, R.P. Hsung, H.M. Sklenicka, A.I. Gerasyuto, *Angew. Chem. Int. Ed.* **2001**, *40*, 1516–1518;
9. M. Santarem, C. Vanucci- Bacque, G. Lhommet, *J. Org. Chem.* **2008**, *73*, 6466 – 6469

# Hart's Synthesis

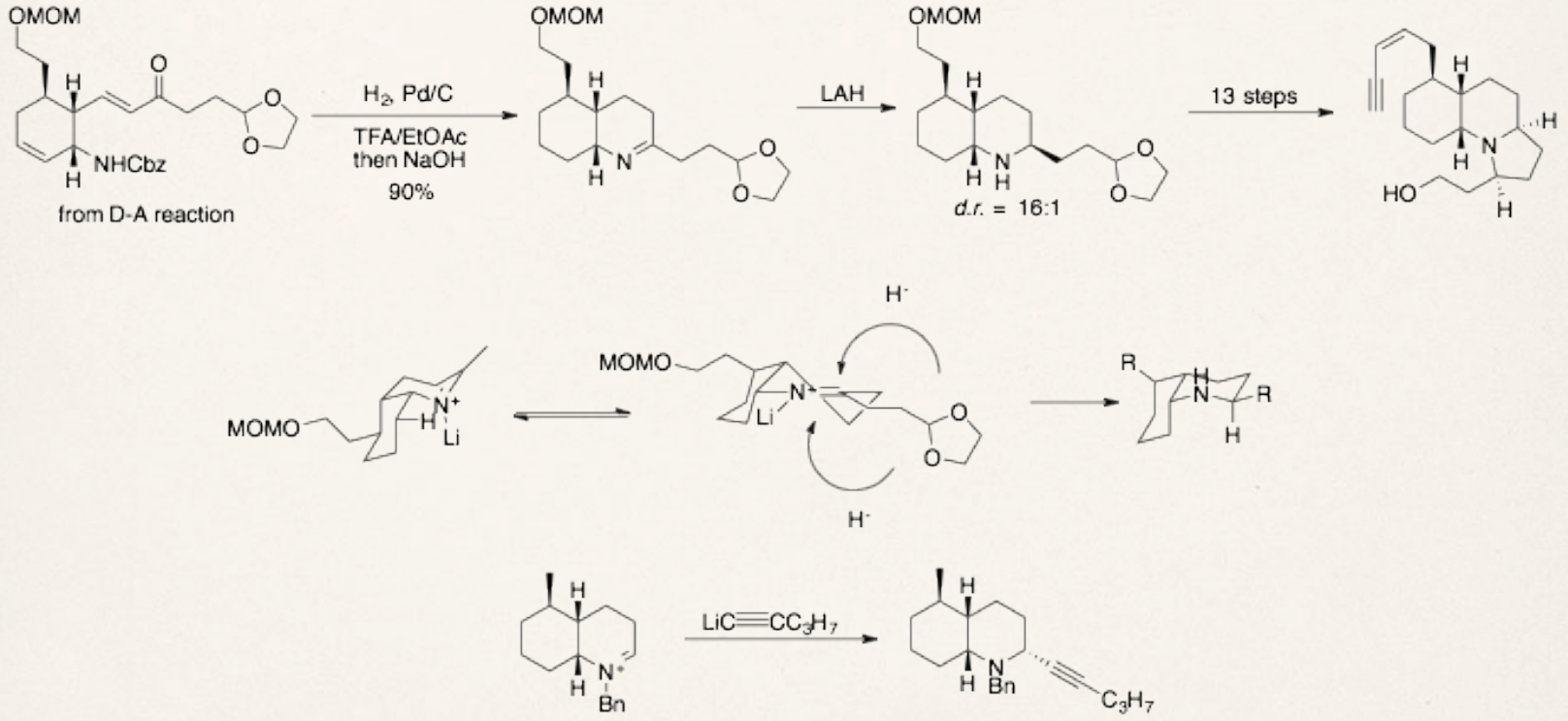
## Acyliminium Ion Cyclization :





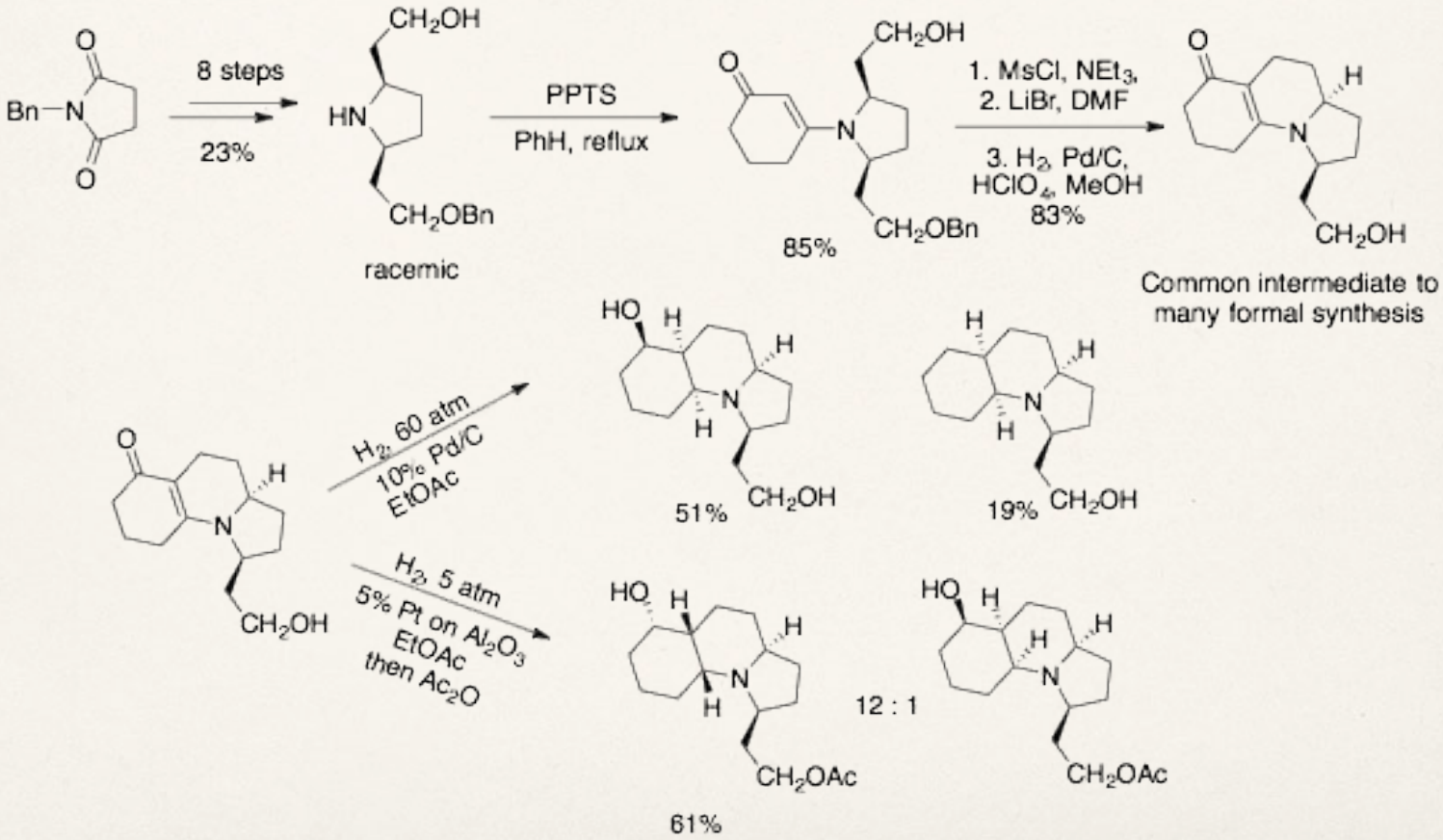
1. D. J. Hart, *J. Org. Chem.* **1981**, *46,* 3576 – 3578 ;
2. D. J. Hart, K. Kanai, *J. Am. Chem. Soc.* **1983**, *105*, 1255–1263;

# Overman's Synthesis



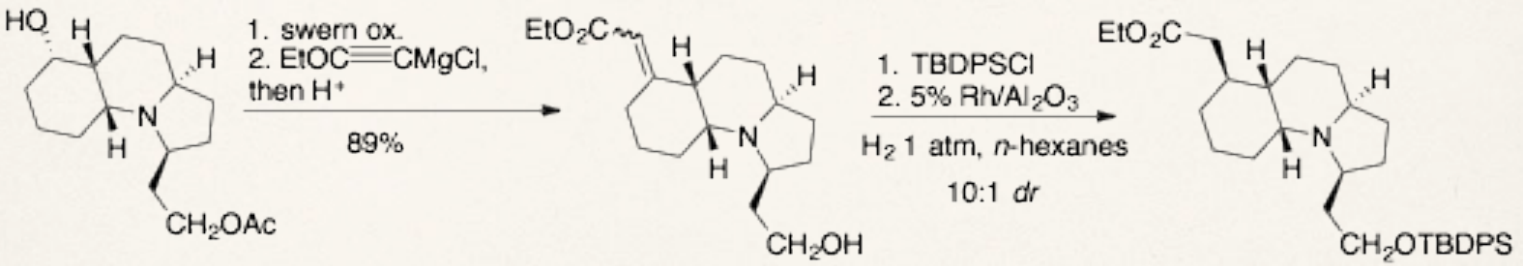

1. L.E. Overman, D. Lesuisse, M. Hashimoto, *J. Am. Chem. Soc.* **1983**, *105,* 5373–5379;

# Kishi's Synthesis

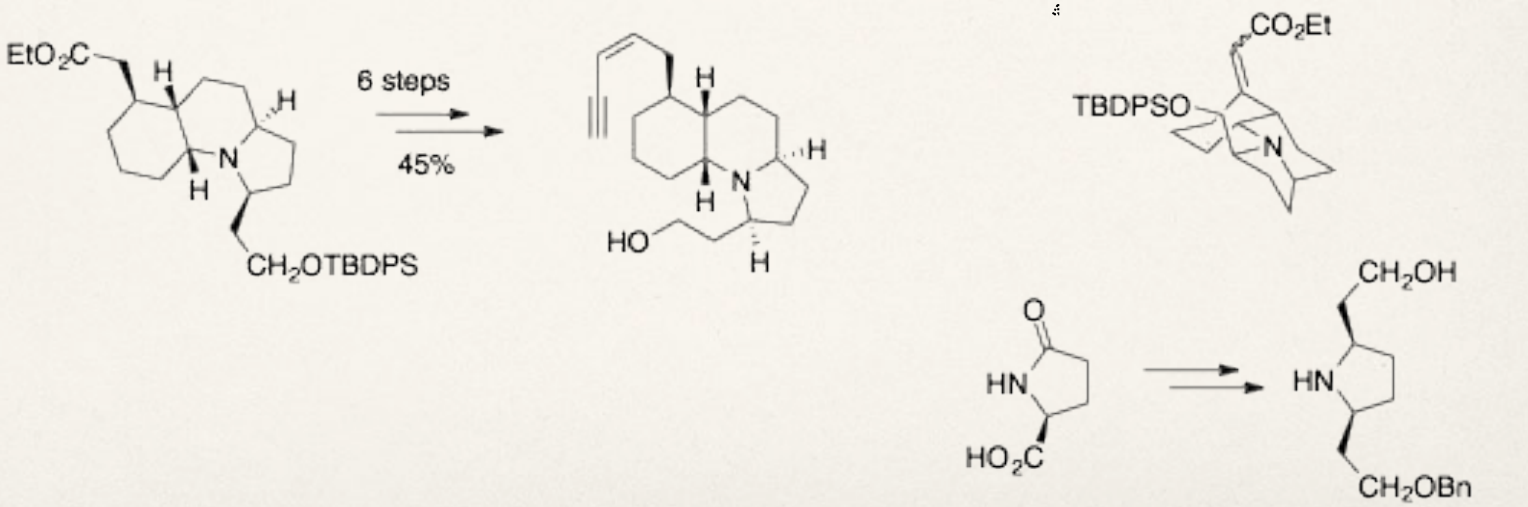



1. R.Fujimoto, Y. Kishi, J. F. Blount, *J. Am. Chem. Soc.* **1980,** *102,* 7154 – 7156 ;

# Kishi's Synthesis




compares to unprotected ester gave 1:1 *dr*

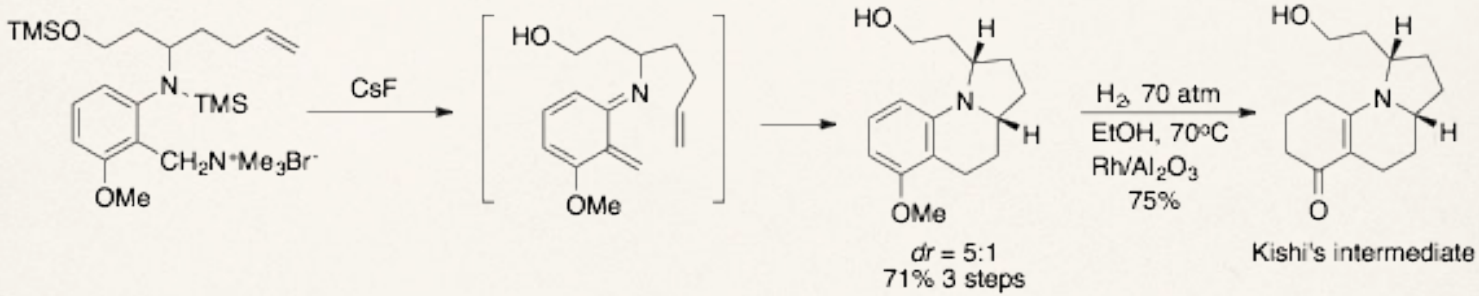



optically pure intermediate

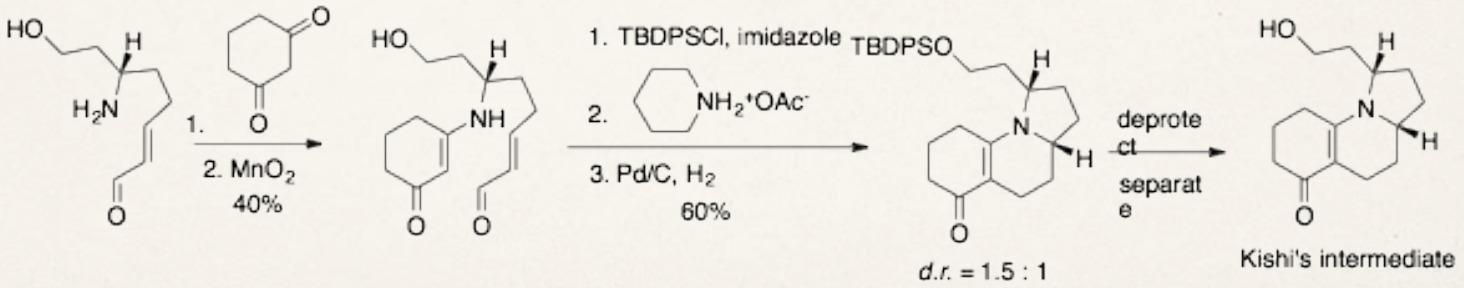

1. R.Fujimoto, Y. Kishi, J. F. Blount, *J. Am. Chem. Soc.* **1980,** *102,* 7154 – 7156;
2. R. Fujimoto, Y. Kishi, *Tetrahedron Lett.* **1981**, *22,* 4197 – 4198.

# Formal Synthesis Utilizing Kishi's Intermediate

## Ito and Saegusa's synthesis:




## Hsung's synthesis:

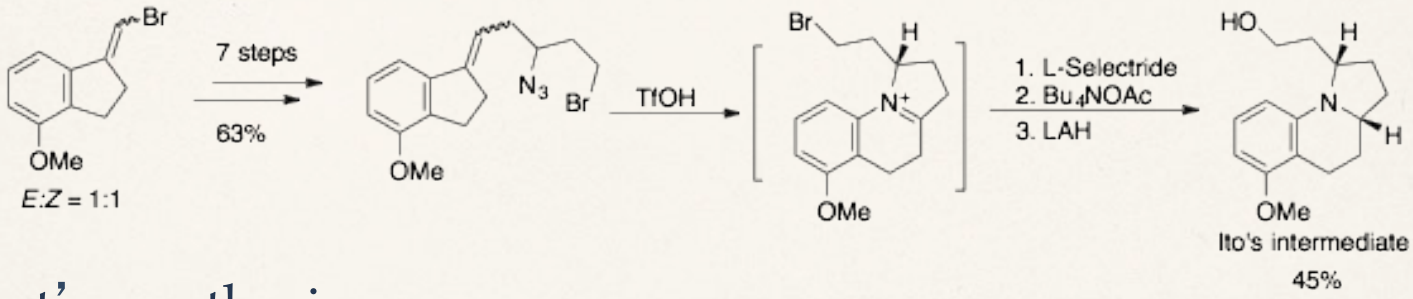




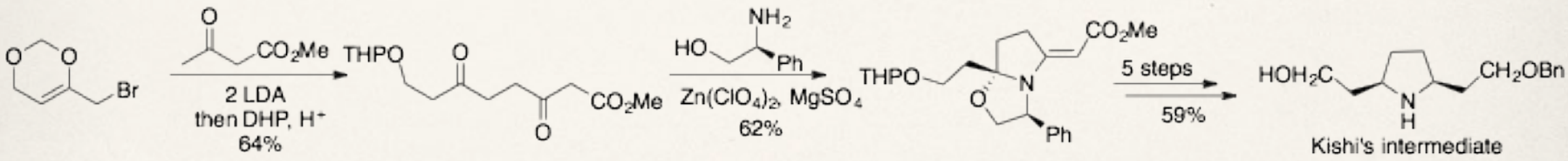
1. Y. Ito, E. Nakajo, M. Nakatsuka, T. Saegusa, *Tetrahedron Lett.* **1983**, *24*, 2881– 2884;
2. L.-L. Wei, R.P. Hsung, H.M. Sklenicka, A.I. Gerasyuto, *Angew. Chem. Int. Ed.* **2001**, *40*, 1516–1518;

# Formal Synthesis Utilizing Kishi's Intermediate

## Pearson's synthesis:




## Lhommet's synthesis:

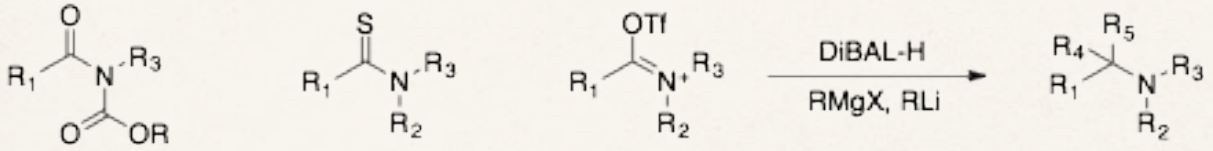




1. W. H. Pearson, W.-K. Fang, *J. Org. Chem.* **2000**, *65*, 7158–7174;
2. M. Santarem, C. Vanucci- Bacque, G. Lhommet, *J. Org. Chem.* **2008**, *73*, 6466 – 6469

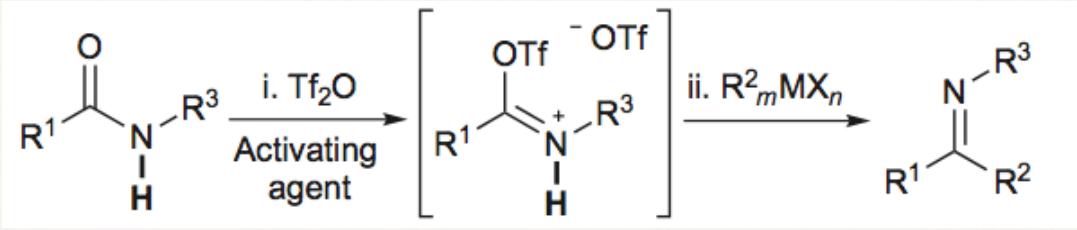
# Amide-Selective Reductive Nucleophilic Addition

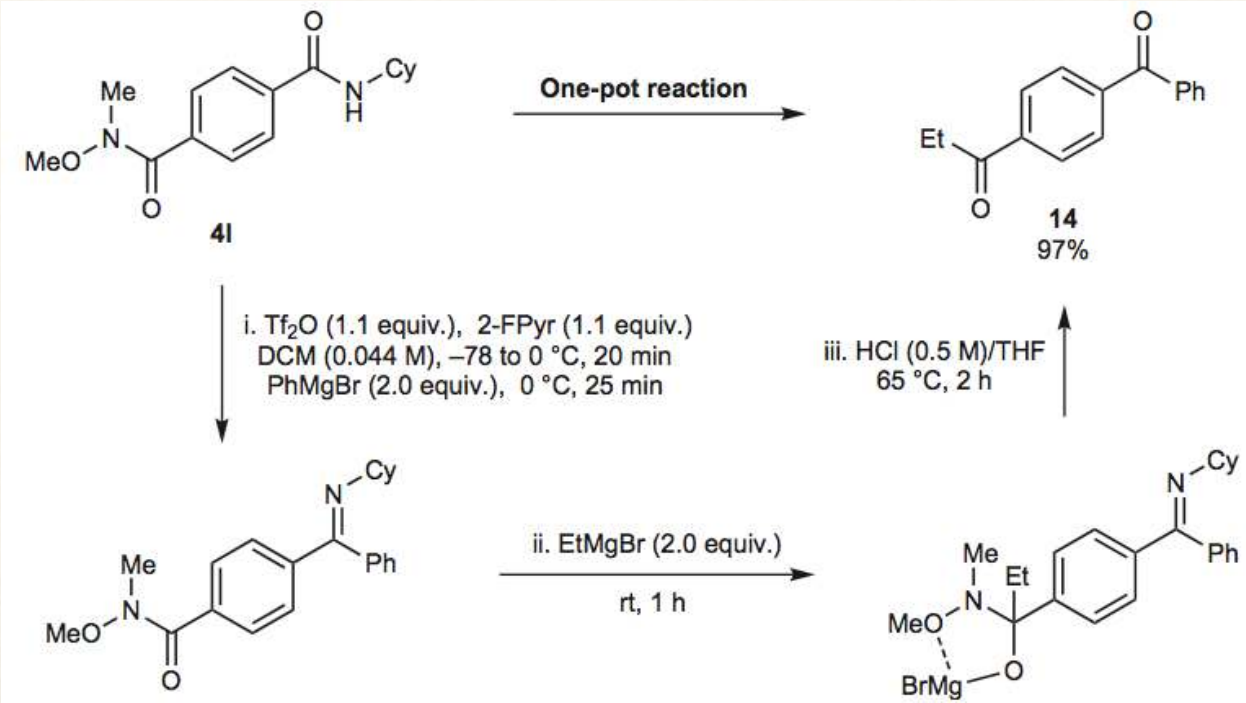
- General approaches to activate the amide group requires preactivation the carbonyl group and reactive reagents.




1. Y. Oda, T. Sato, N. Chida, *Org. Lett.* **2012,** *14*, 950 – 953

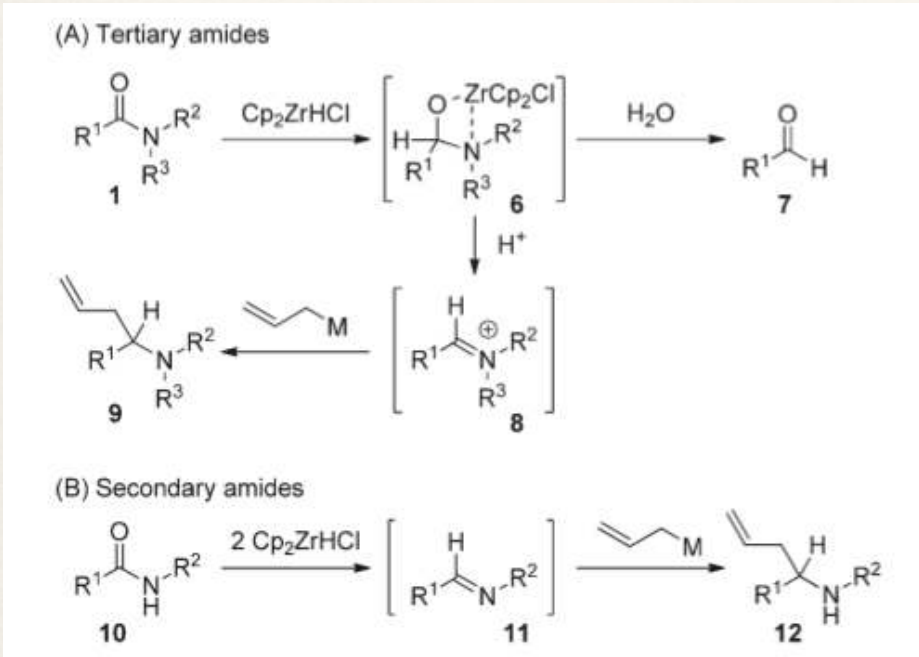
# Charette's Chemoselective Amide Transformations

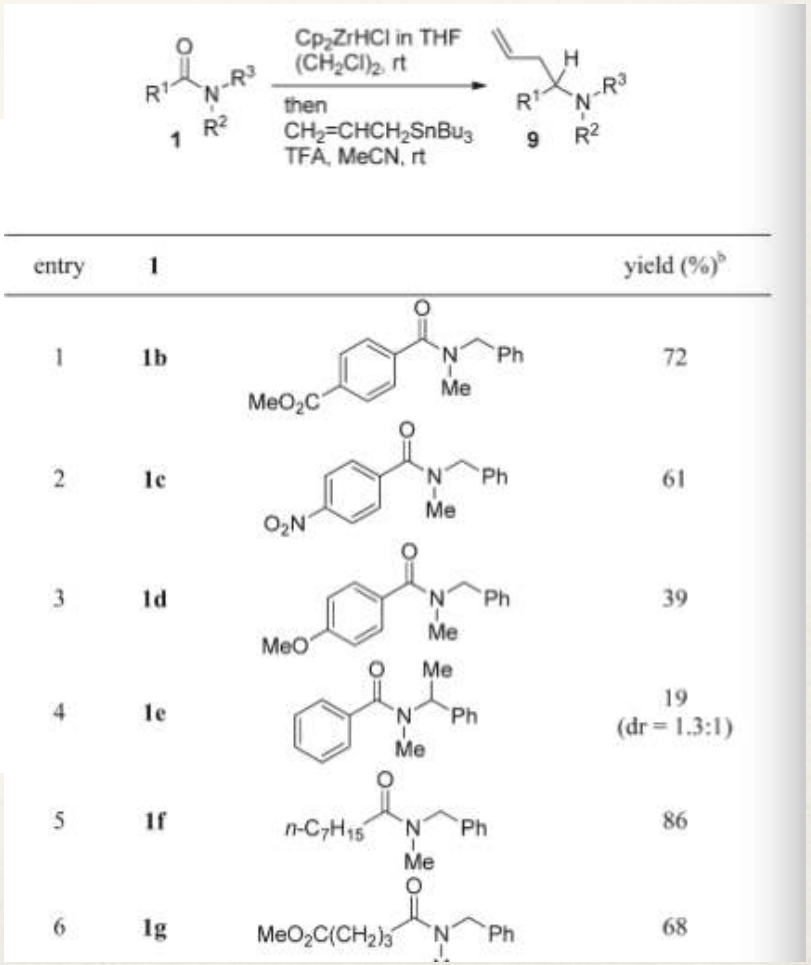



1. W. S. Bechara, G. Pelletier, A. B. Charette, *Nat. Chem.* **2012**, 4, 228 – 234

# Utilizing Schwartz's Reagent

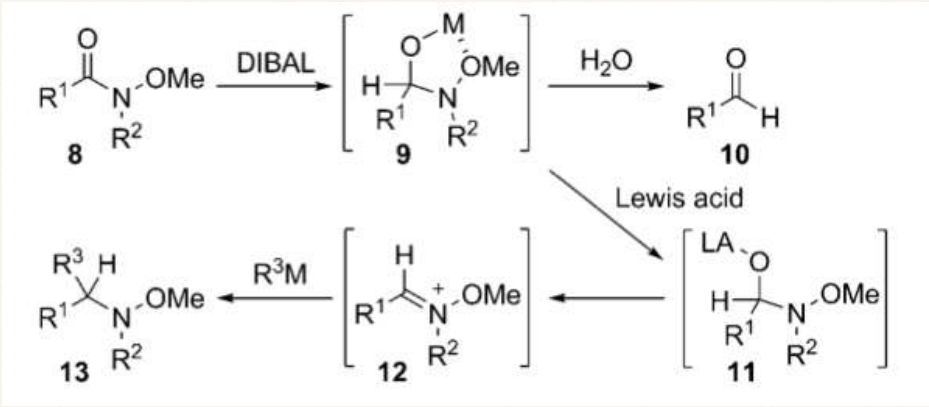


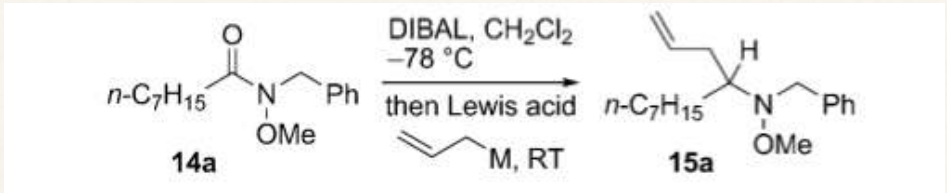




| entry | 1 | yield (%)[b] |
|---|---|---|
| 1 | 1b | 72 |
| 2 | 1c | 61 |
| 3 | 1d | 39 |
| 4 | 1e | 19 (dr = 1.3:1) |
| 5 | 1f | 86 |
| 6 | 1g | 68 |

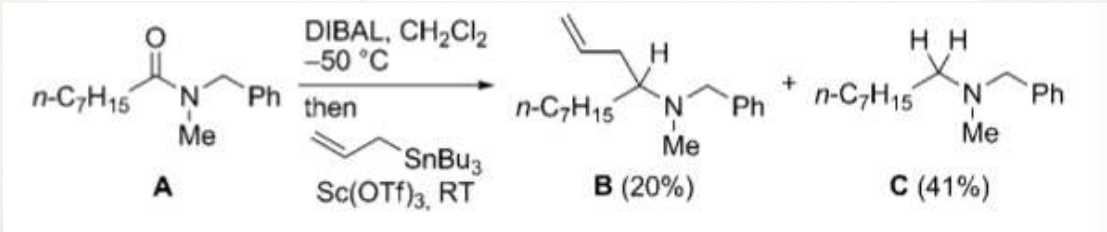
1. Y. Oda, T. Sato, N. Chida, *Org. Lett.* **2012,** *14*, 950 – 953

# N-Methoxyamides Transformation



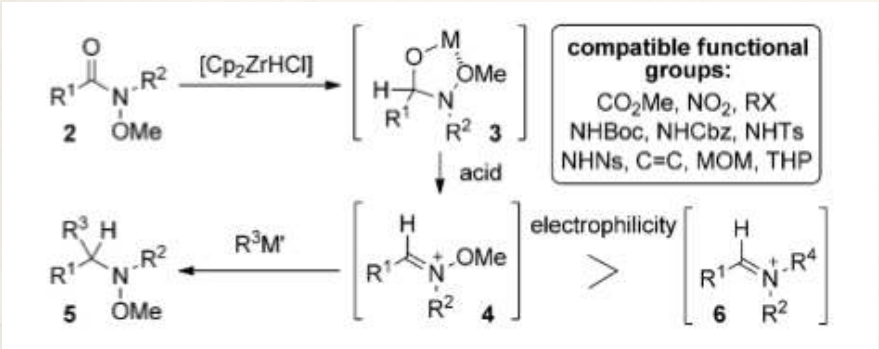



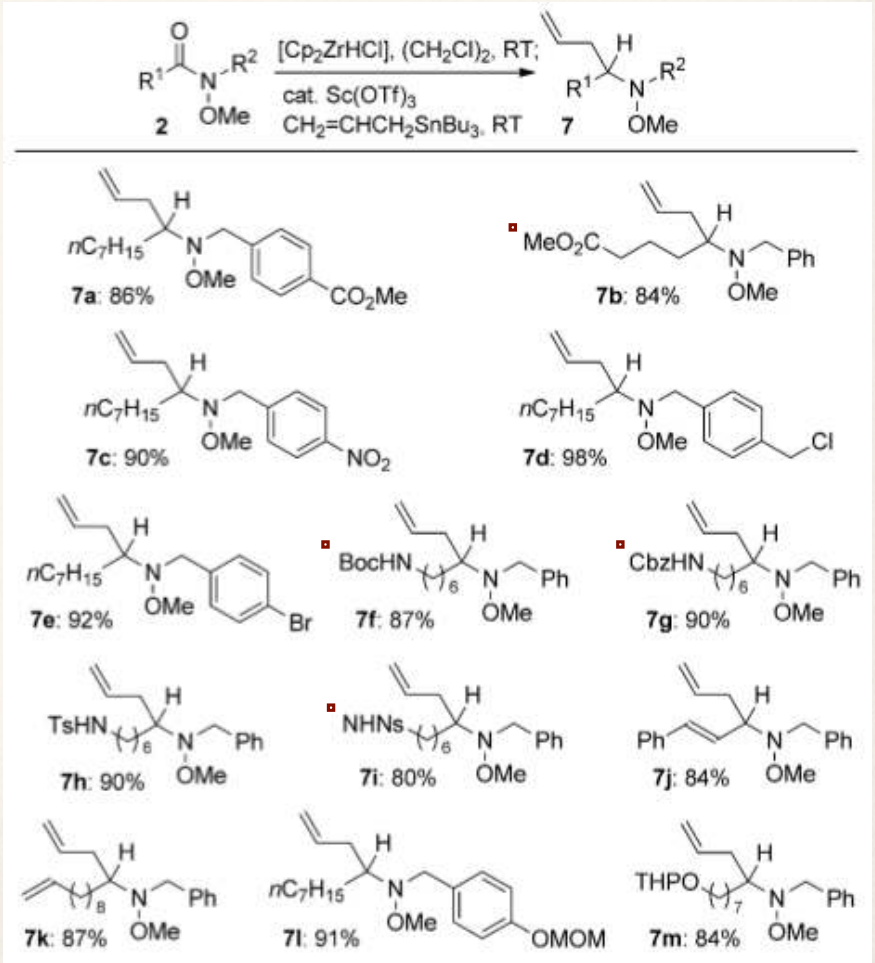

| Entry | Lewis acid | M | Yield [%] |
|---|---|---|---|
| 8 | $Sc(OTf)_3$ | $SnBu_3$ | 92 |




1. Shirokake, K.; Kurosaki, Y.; Sato, T.; Chida, N. Angew. *Chem. Int. Ed.,* **2010,** *49,* 6369–6372.

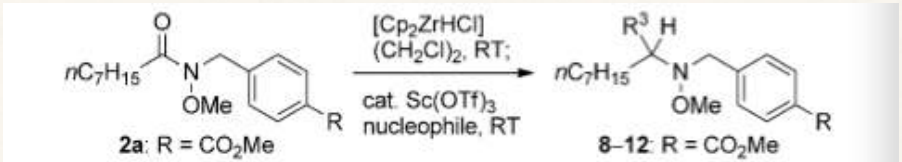
# Amide-Selective Reductive Nucleophilic Addition

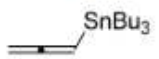
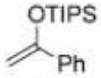
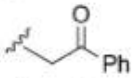
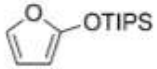
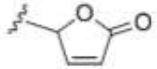
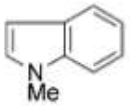
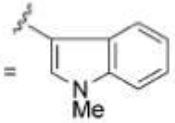



*Angew. Chem. Int. Ed.*. doi: 10.1002/anie.201308905

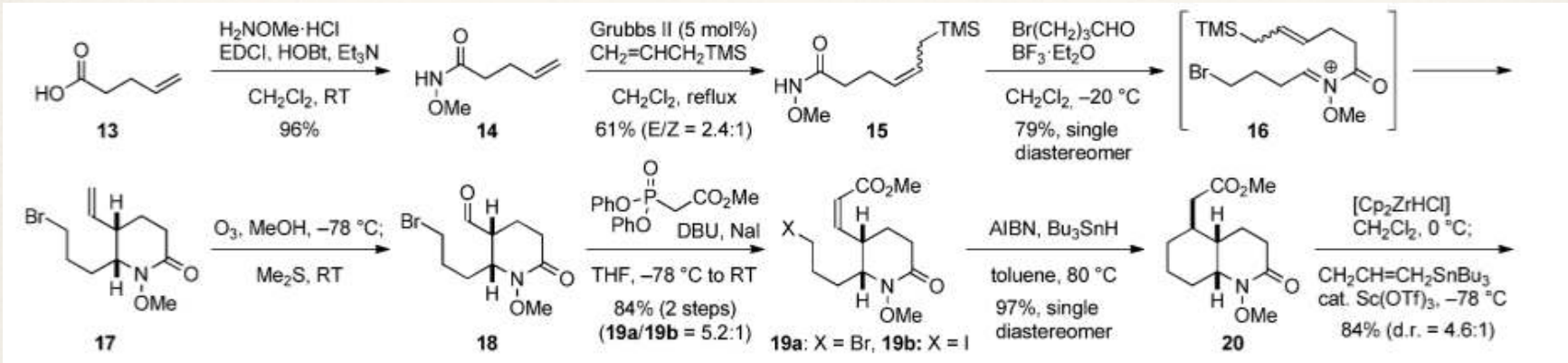
# Amide-Selective Reductive Nucleophilic Addition




| Entry | Nucleophile | Product | Yield[b] [%] |
|---|---|---|---|
| 1 |  |  | 71 |
| 2 | TMS-CN |  | 81 |
| 3 |  |  | 74 |
| 4 |  |  | 78 (d.r. = 1.6:1) |
| 5[c] |  |  | 75 |

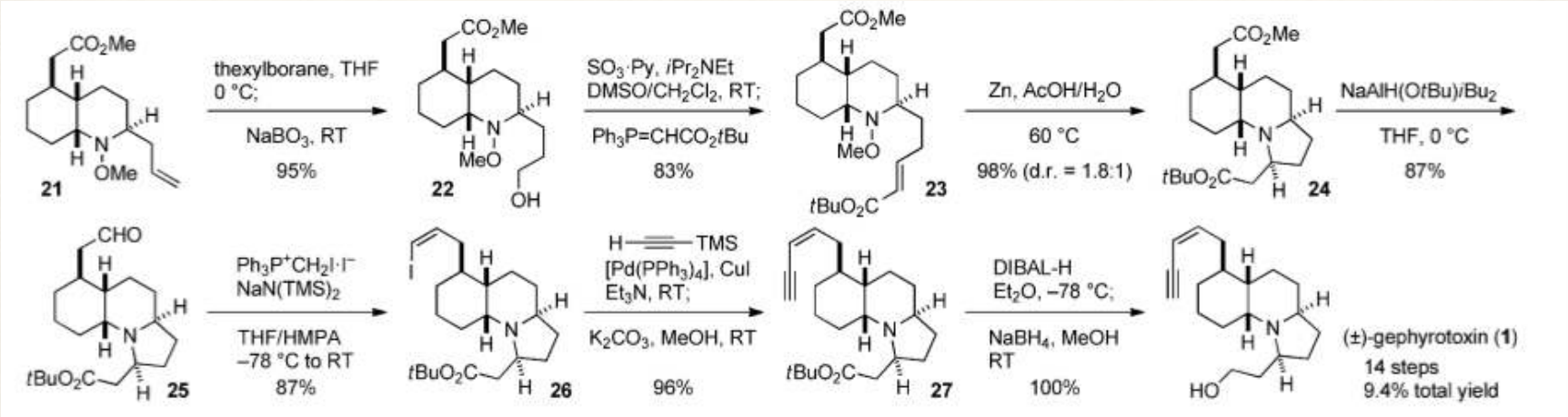
*Angew. Chem. Int. Ed.*. doi: 10.1002/anie.201308905

# Total Synthesis of Gephyrotoxin




*Angew. Chem. Int. Ed.*. doi: 10.1002/anie.201308905

# Total Synthesis of Gephyrotoxin




*Angew. Chem. Int. Ed.*. doi: 10.1002/anie.201308905

# Conclusion

- 14 steps synthesis of Gephyrotoxin, 9.4% yield from pentenioc acid.
- N-methoxy group served as an activating/protecting group.
- Chemoselective amide-reductive reaction allowed methyl ester survived without reduction and protection.