

Total Synthesis of Gephyrotoxin by Amide-Selective Reductive Nucleophilic Addition

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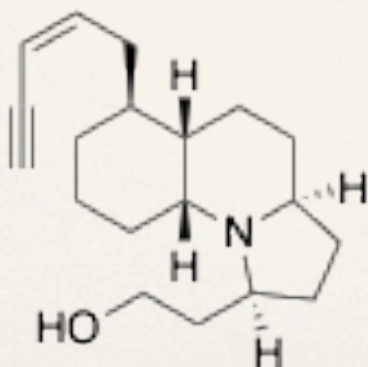
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Yongzhao Yan
12-7-2013

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

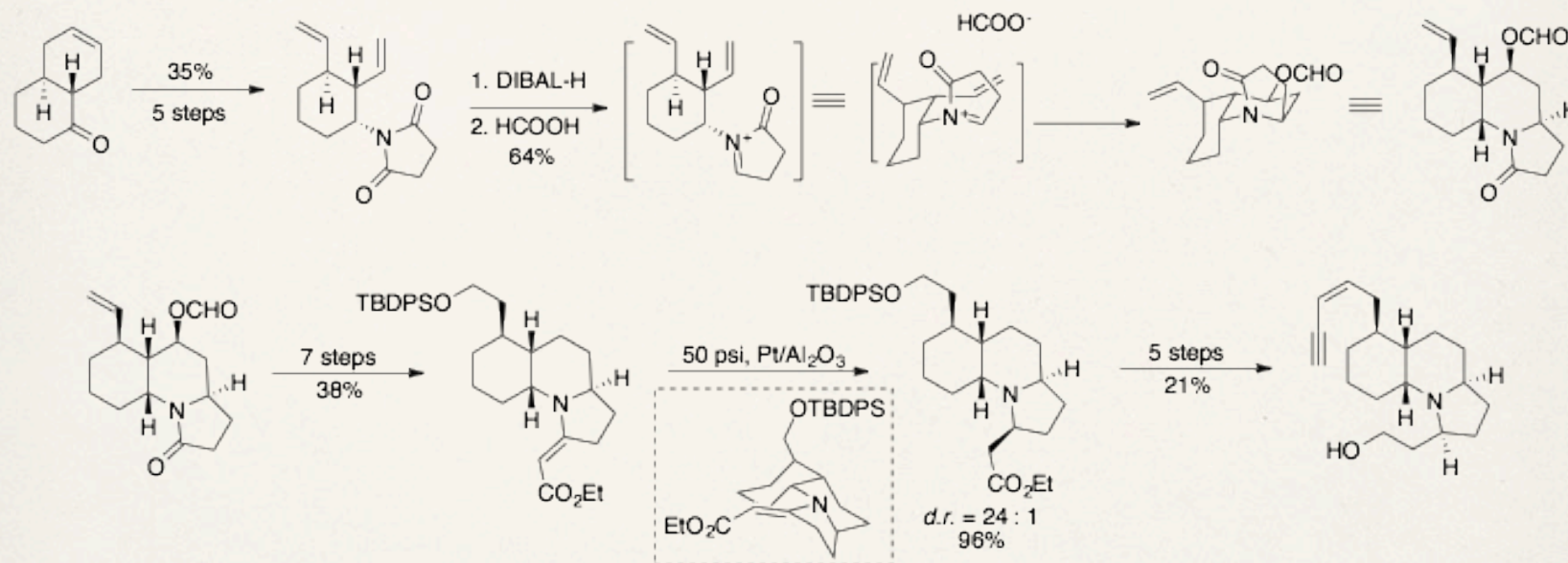
Total Synthesis of Gephyrotoxin

- ❖ 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. Gerasuto, *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

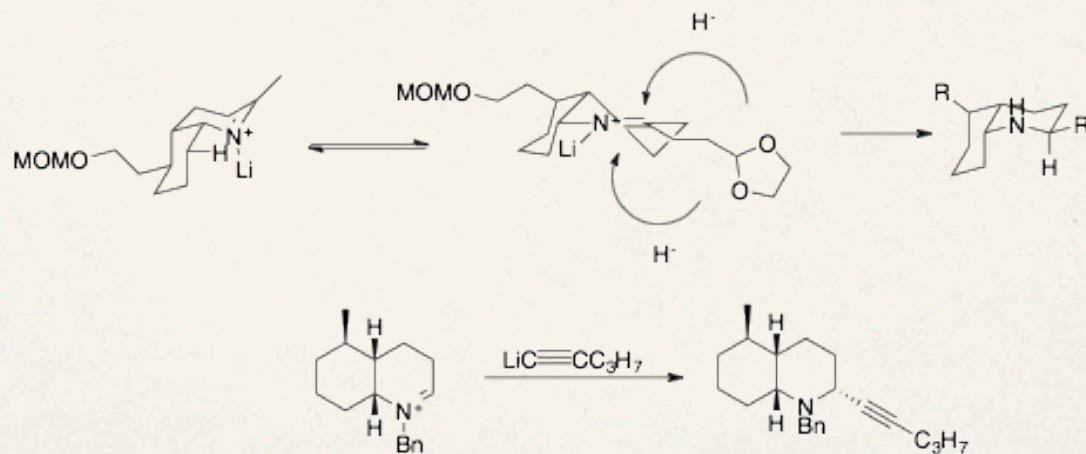
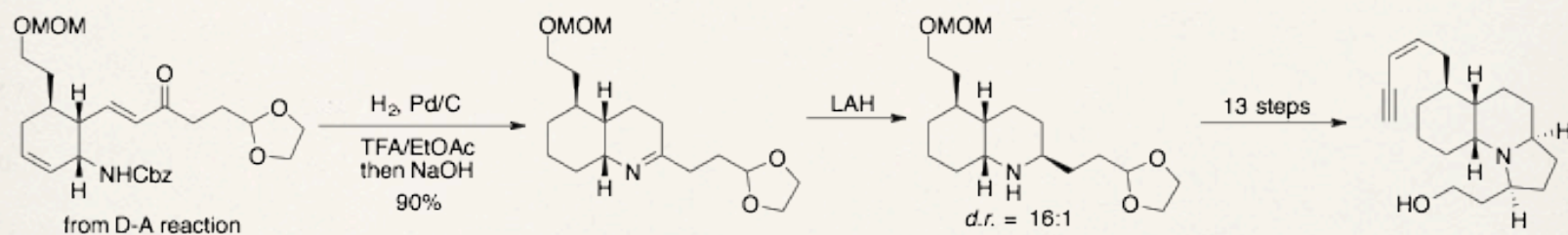
Acyliminium Ion Cyclization :



1. D. J. Hart, *J. Org. Chem.* **1981**, *46*, 3576 – 3578 ;

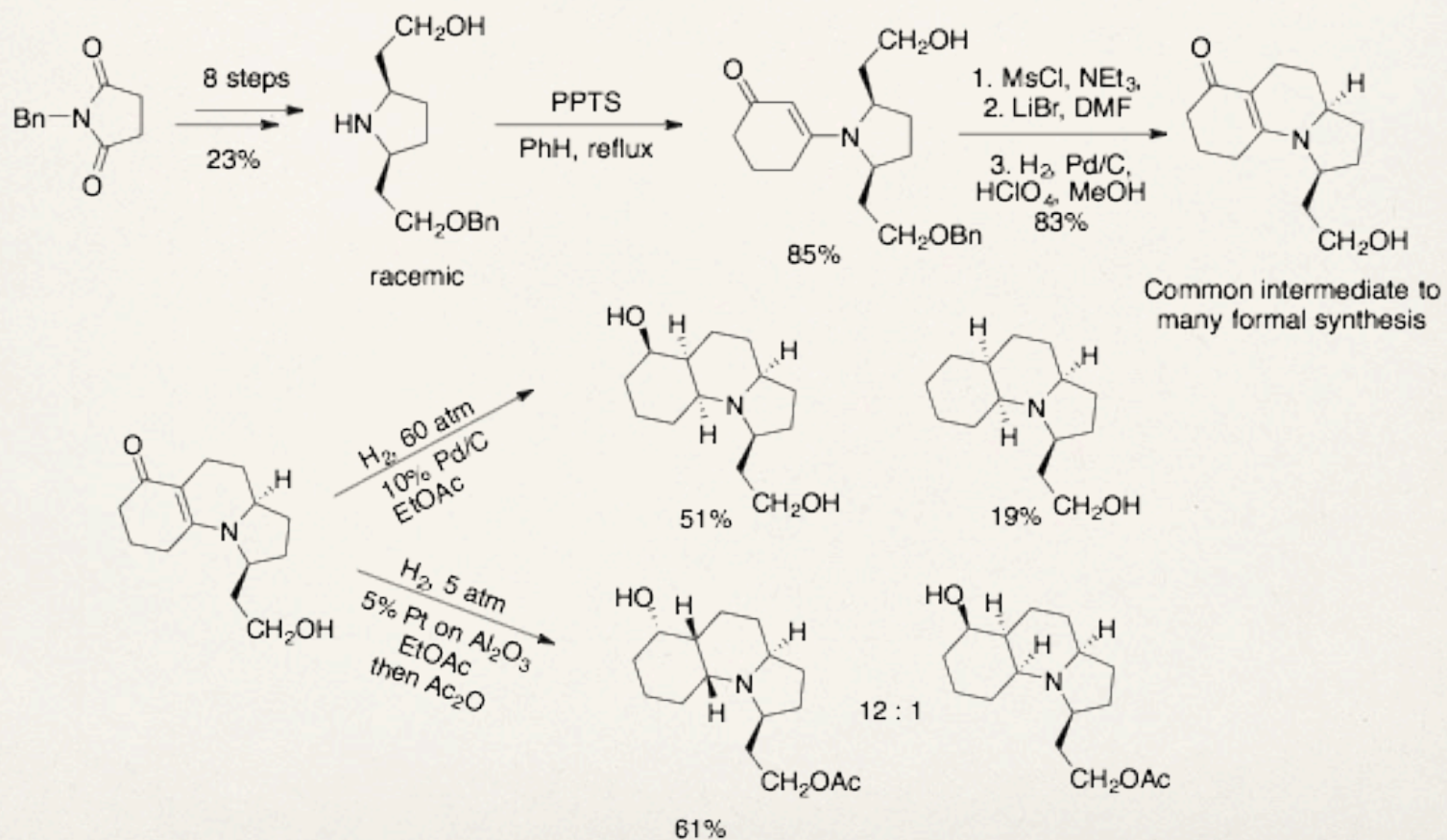
2. D. J. Hart, K. Kanai, *J. Am. Chem. Soc.* **1983**, *105*, 1255–1263;

Overman's Synthesis



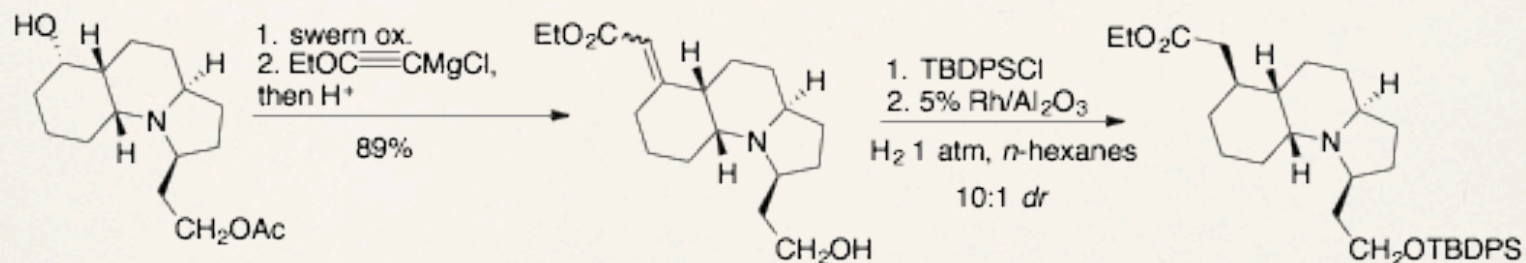
1. L.E. Overman, D. Lesuisse, M. Hashimoto, *J. Am. Chem. Soc.* **1983**, *105*, 5373–5379;

Kishi's Synthesis

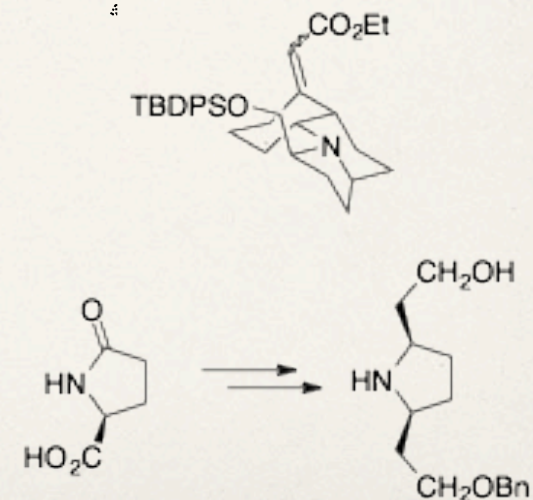
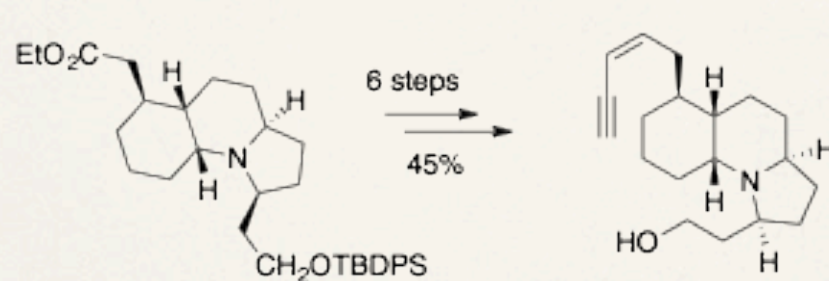


1. R. Fujimoto, Y. Kishi, J. F. Blount, *J. Am. Chem. Soc.* **1980**, *102*, 7154 – 7156 ;

Kishi's Synthesis



compares to unprotected ester gave 1:1 dr



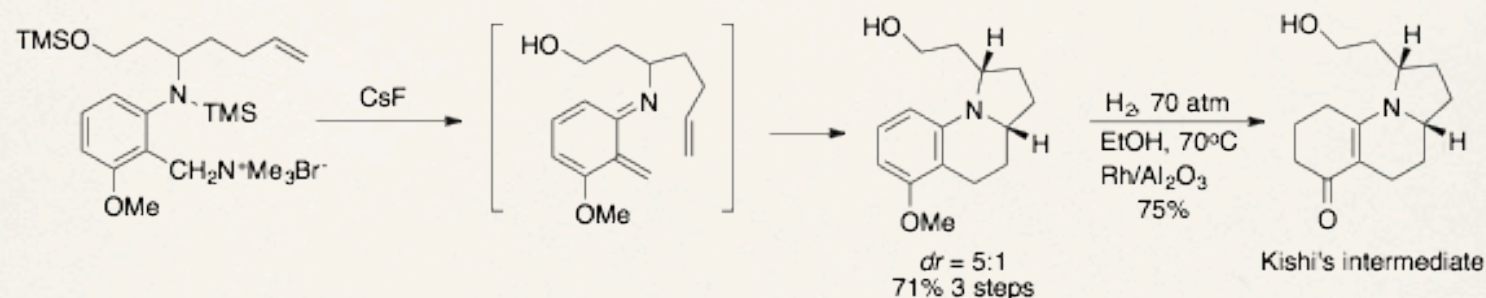
optically pure intermediate

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

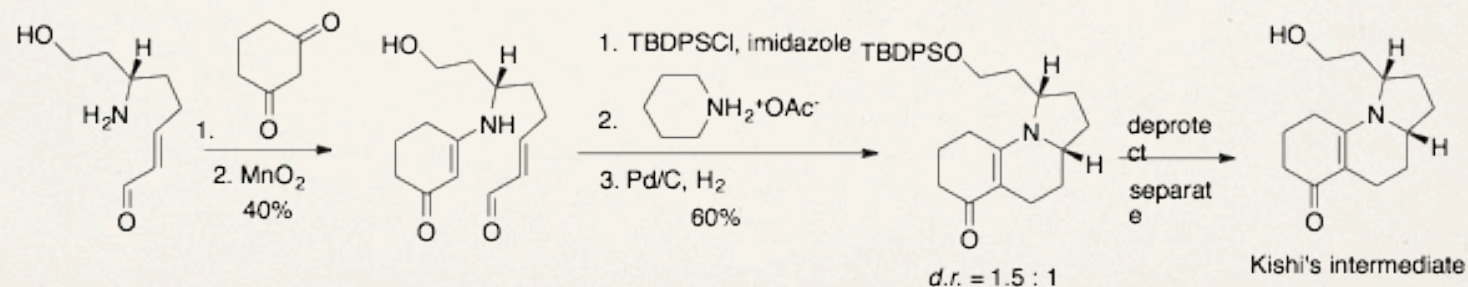
2. R. Fujimoto, Y. Kishi, *Tetrahedron Lett.* **1981**, *22*, 4197 – 4198.

Formal Synthesis Utilizing Kishi's Intermediate

Ito and Saegusa's synthesis:



Hsung's synthesis:

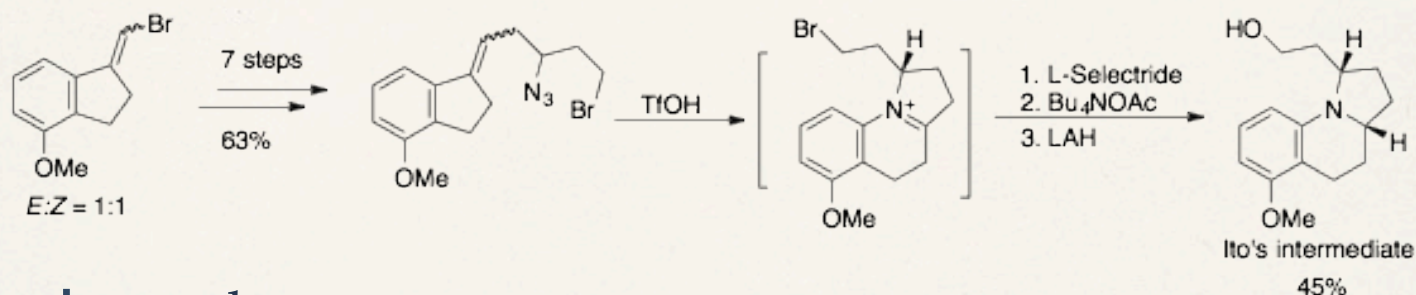


1. Y. Ito, E. Nakajo, M. Nakatsuka, T. Saegusa, *Tetrahedron Lett.* **1983**, *24*, 2881–2884;

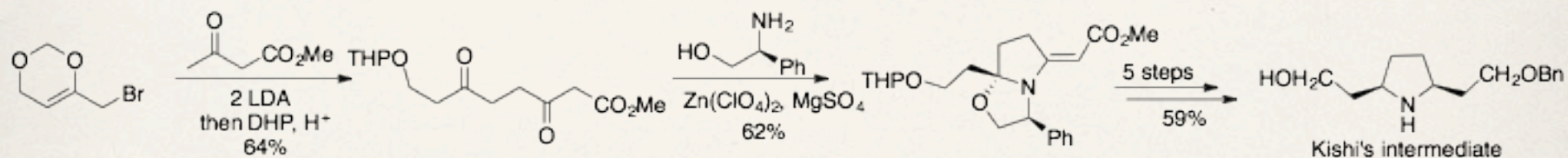
2. L.-L. Wei, R.P. Hsung, H.M. Sklenicka, A.I. Gerasyuto, *Angew. Chem. Int. Ed.* **2001**, *40*, 1516–1518;

Formal Synthesis Utilizing Kishi's Intermediate

Pearson's synthesis:



Lhommet's synthesis:



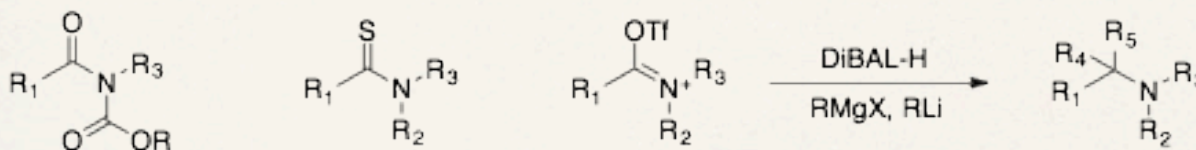
1. W. H. Pearson, W.-K. Fang, *J. Org. Chem.* **2000**, *65*, 7158–7174;

2. M. Santarem, C. Vanucci-Bacque, G. Lhommet, *J. Org. Chem.* **2008**, *73*, 6466 – 6469

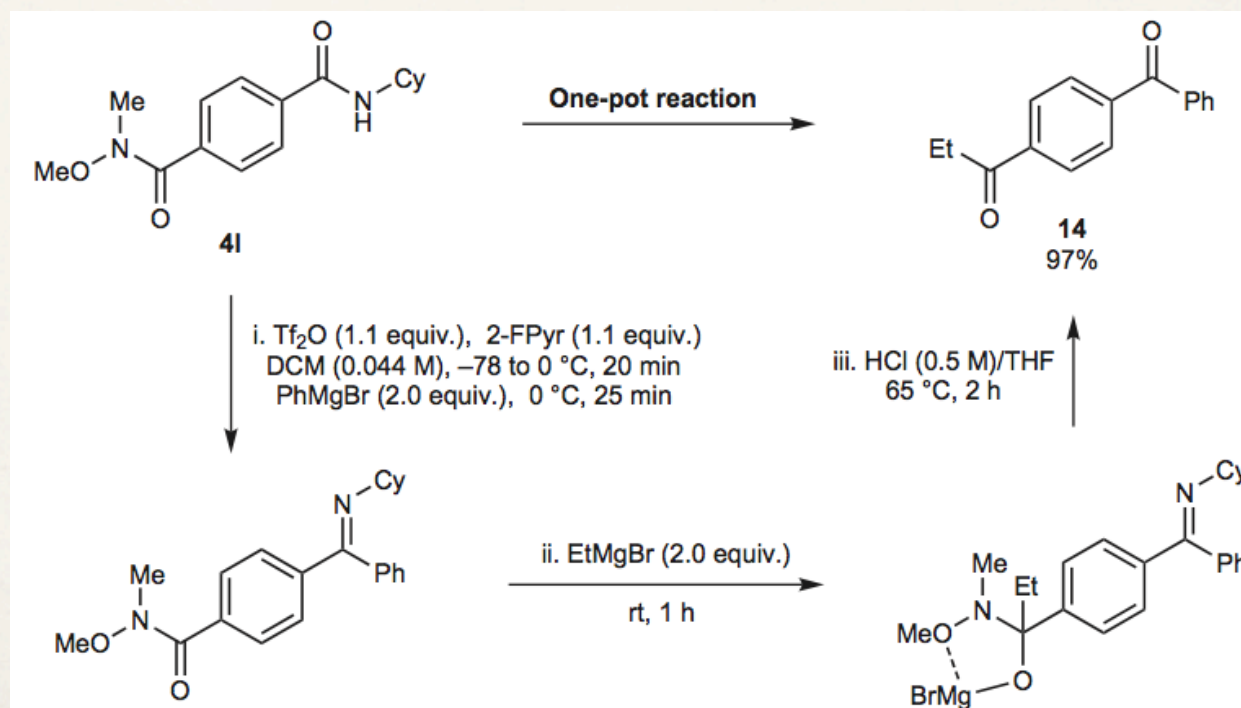
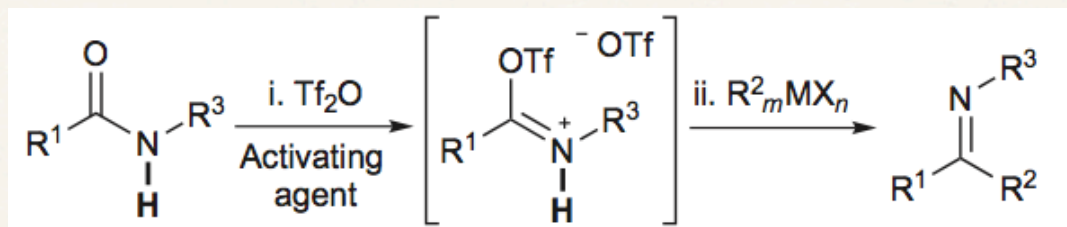
Amide-Selective Reductive Nucleophilic Addition



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



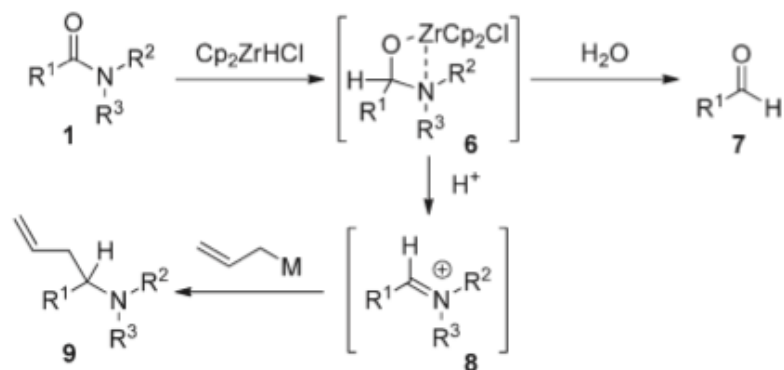
Charette's Chemoselective Amide Transformations



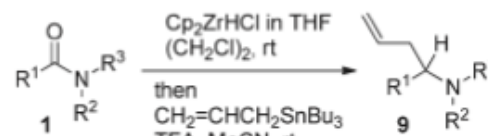
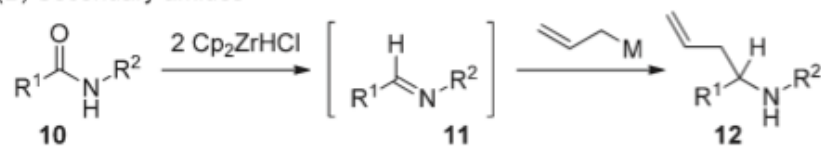
1. W. S. Bechara, G. Pelletier, A. B. Charette, *Nat. Chem.* 2012, 4, 228 – 234

Utilizing Schwartz's Reagent

(A) Tertiary amides



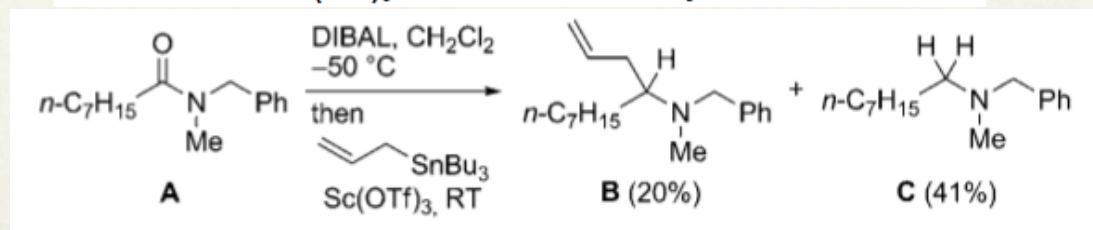
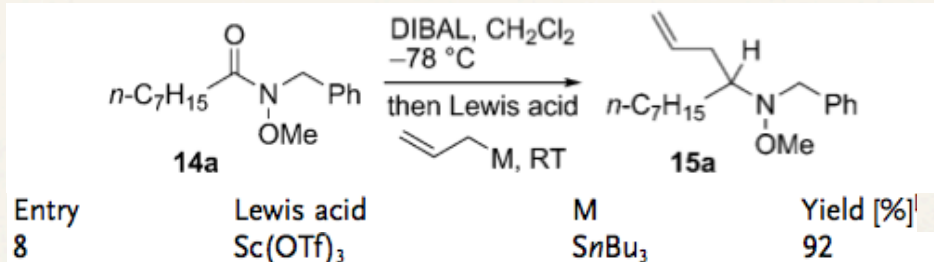
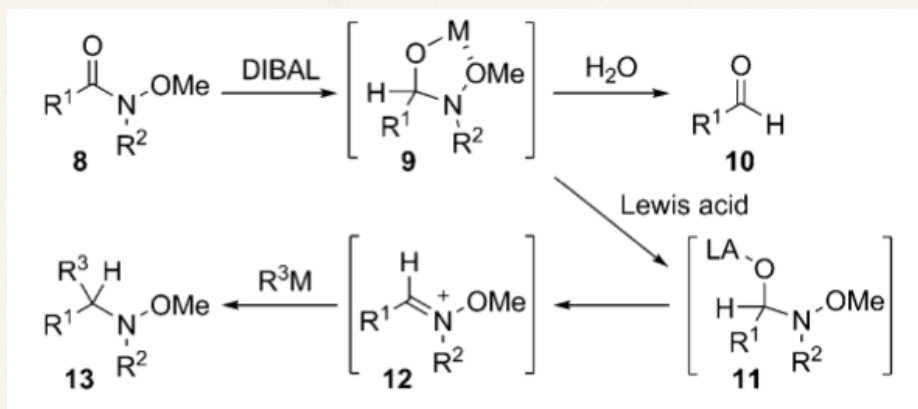
(B) Secondary amides



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

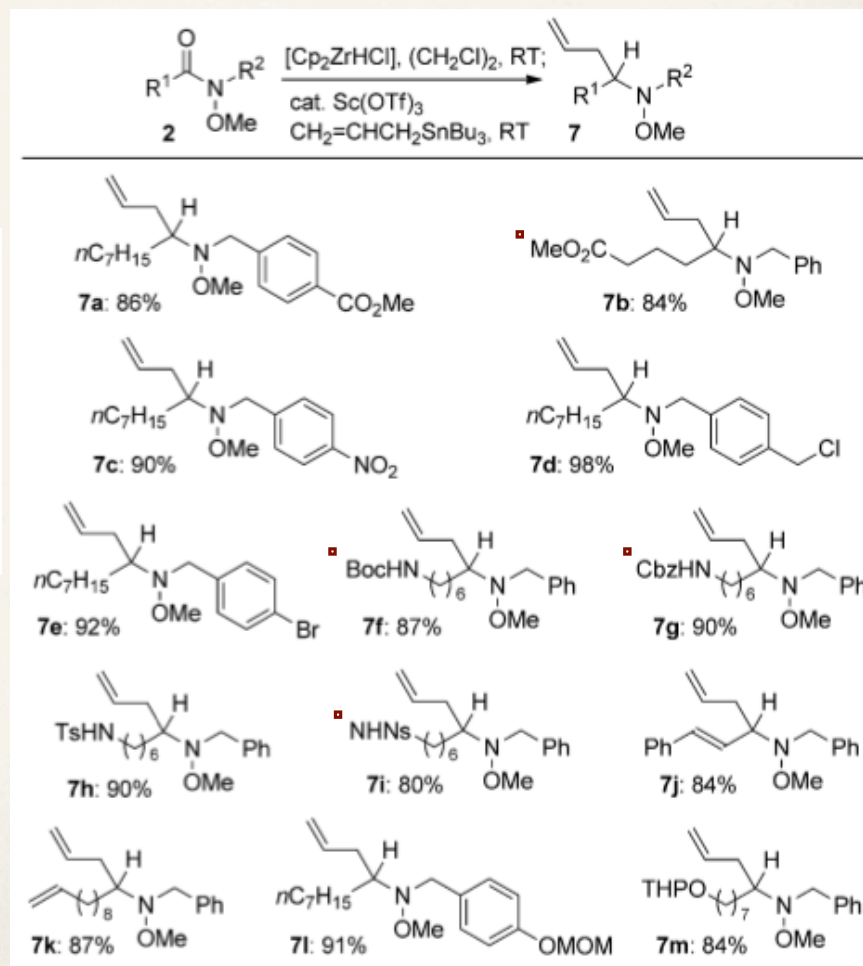
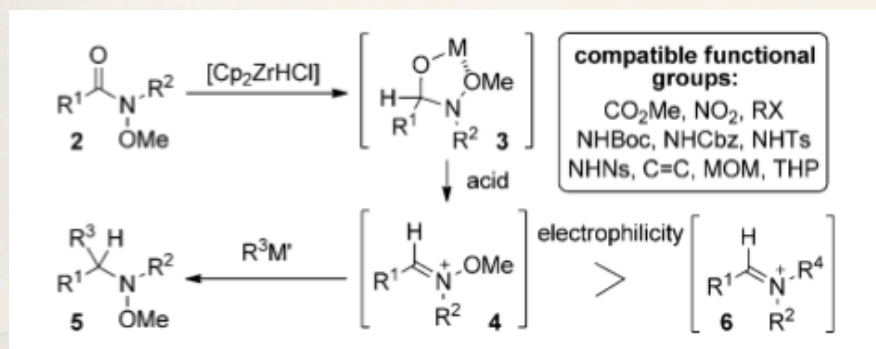
1. Y. Oda, T. Sato, N. Chida, *Org. Lett.* **2012**, *14*, 950 – 953

N-Methoxyamides Transformation



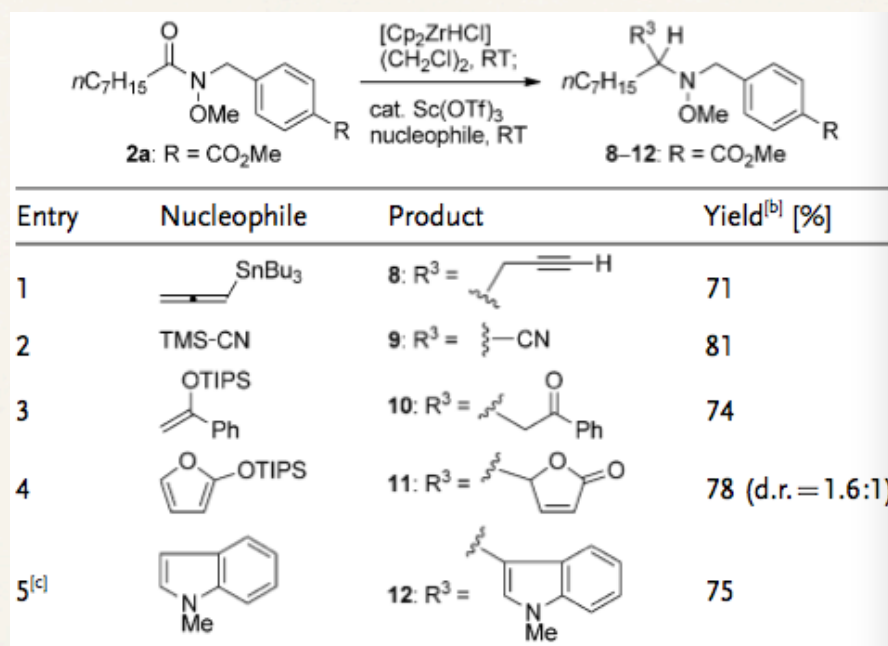
1. Shirokake, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.*, **2010**, *49*, 6369–6372.

Amide-Selective Reductive Nucleophilic Addition

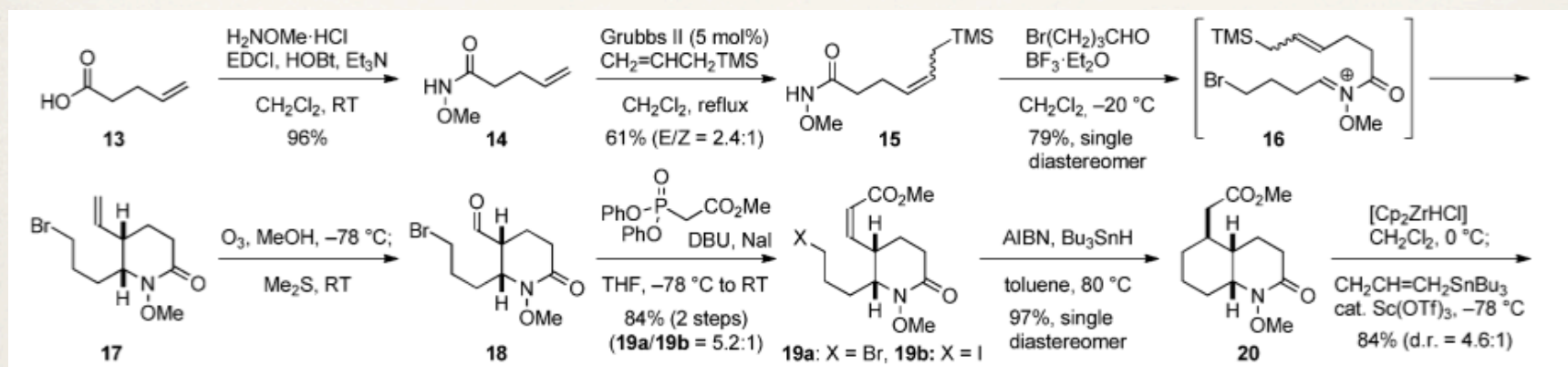


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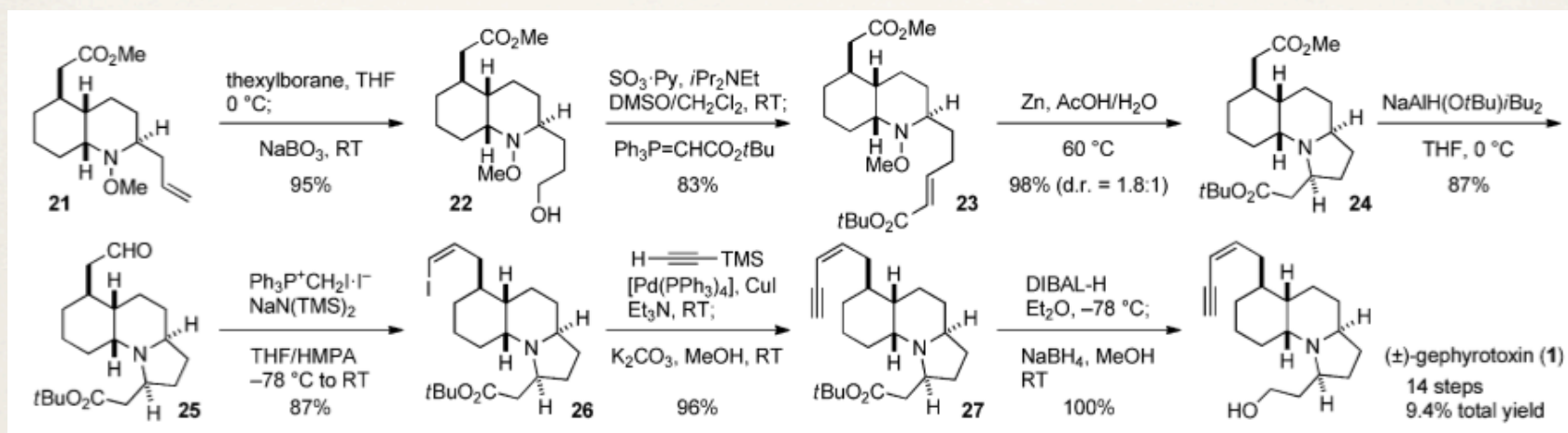
Amide-Selective Reductive Nucleophilic Addition



Total Synthesis of Gephyrotoxin



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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.