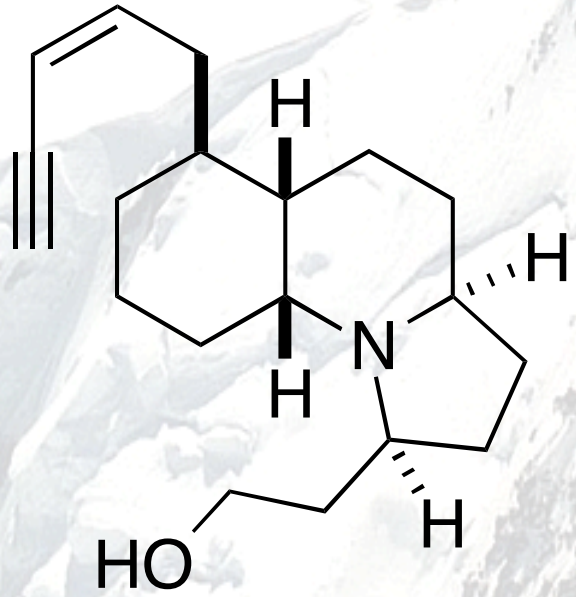
Total Synthesis of (±)-Gephyrotoxin by Amide-Selective Reductive Nucleophilic Addition



K. Shirokane, T. Wada, M. Yoritate, R. Minamikawa, N. Takayama, T. Sato, N. Chida*,
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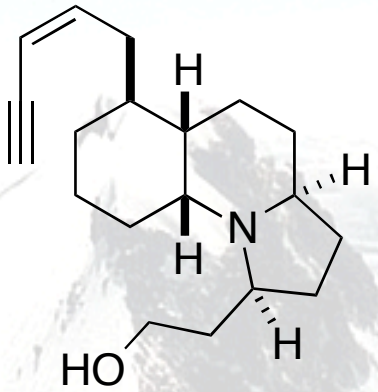
*Faculty of Science and Technology, Keio University (Japan)

Gephyrotoxin



- isolated 1977 from skin extracts of tropical dart frog (Dendrobates histrionicus)
- mild muscarinic antagonist
- array of neurological activities
- 3 total syntheses of (±)-Gephyrotoxin by Kishi 1980, Hart 1983 and Overman 1983
- 6 formal syntheses
- (+)-Gephyrotoxin by Kishi 1981
- (-)-Gephyrotoxin by Spino 2013

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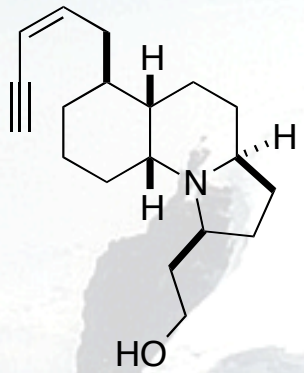
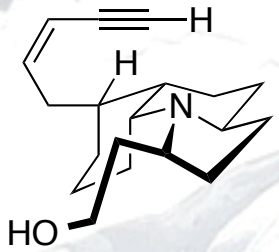
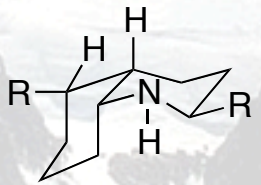
Total Synthesis of Overman

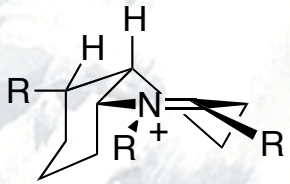




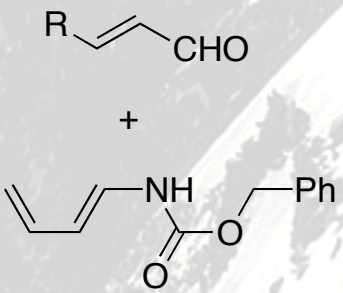
intramolecular
Michael approach



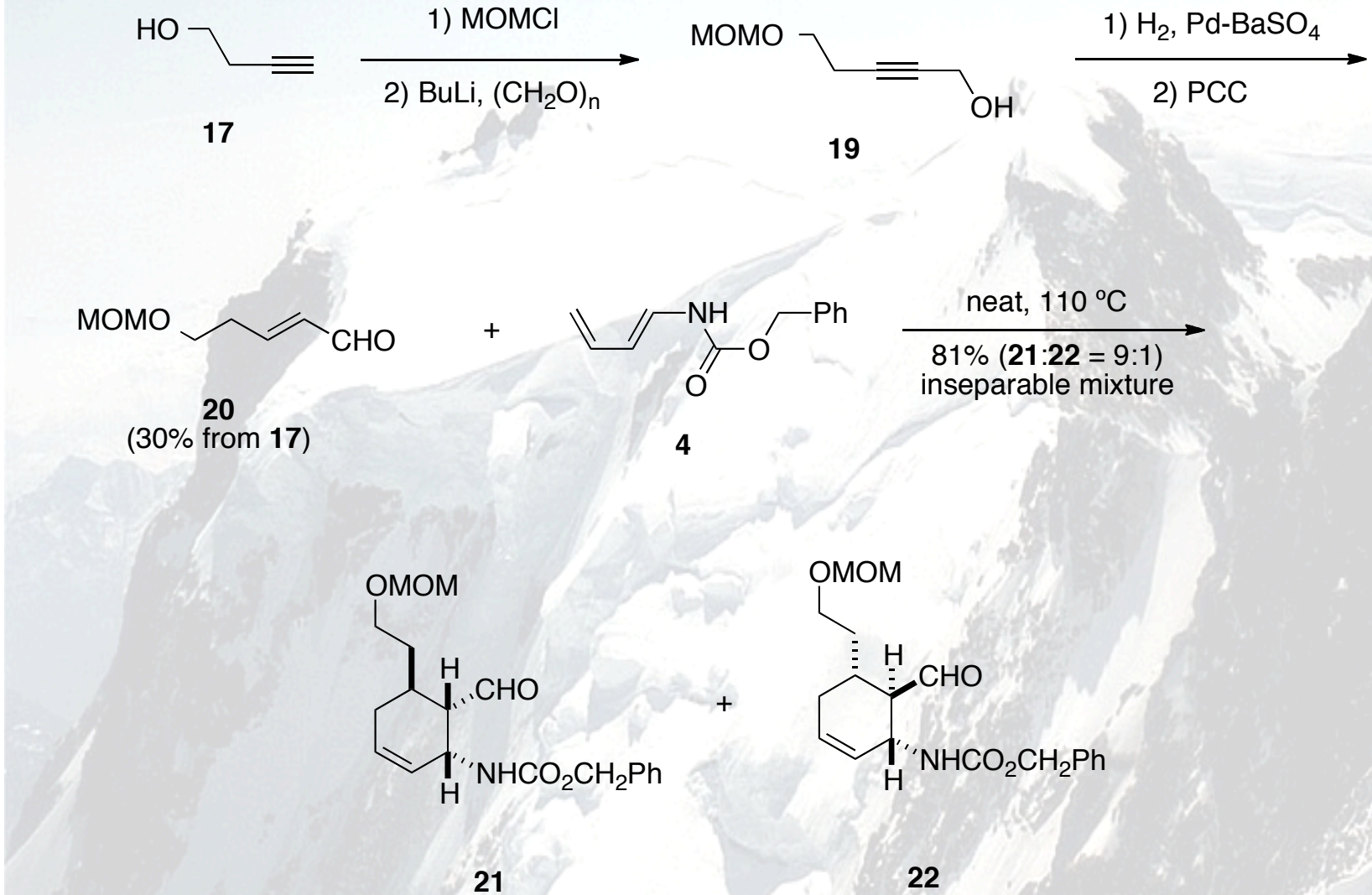
bicyclic iminium ion
reduction



dienamide
Diels-Alder
approach



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



17

19

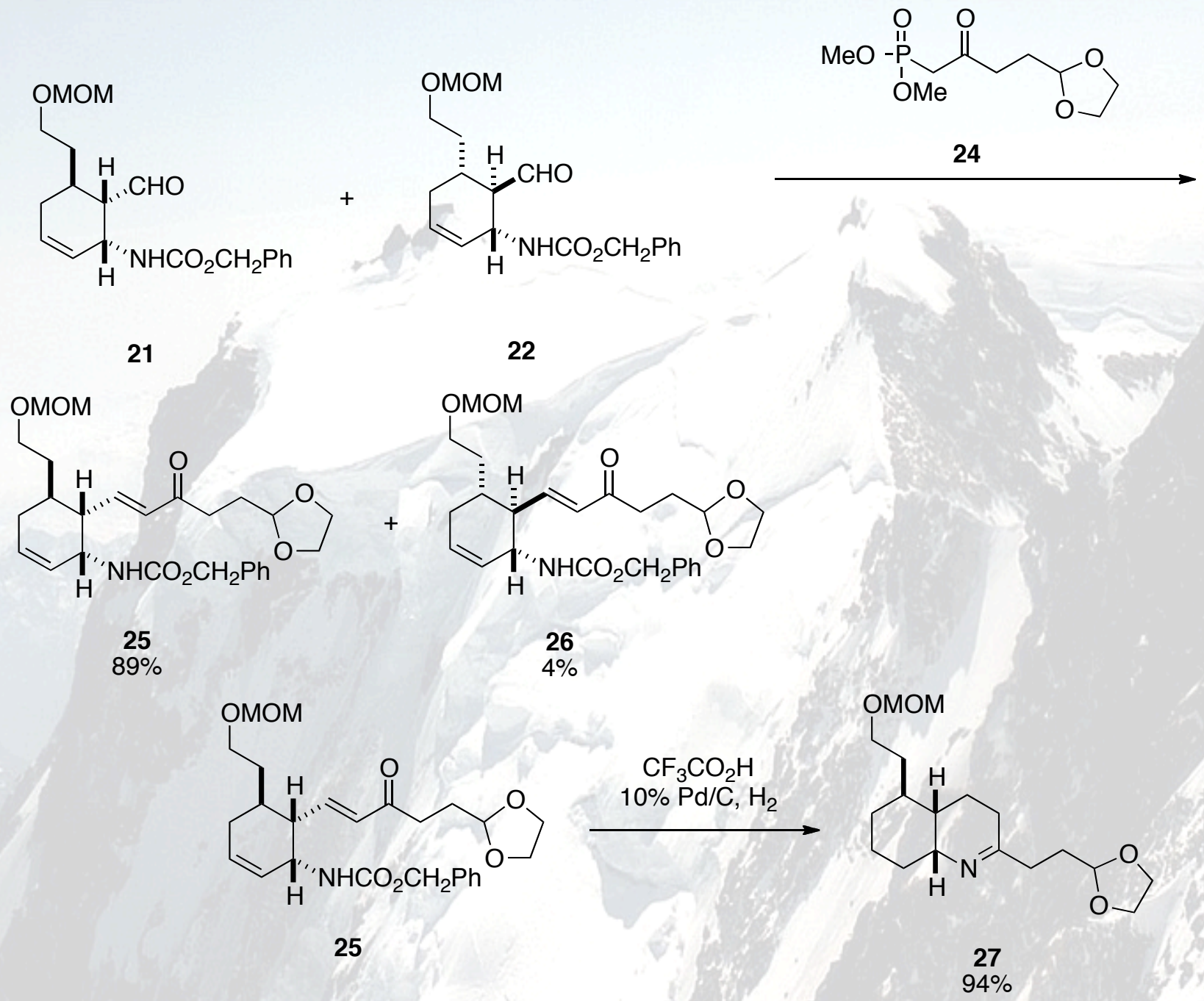
20
(30% from **17**)

4

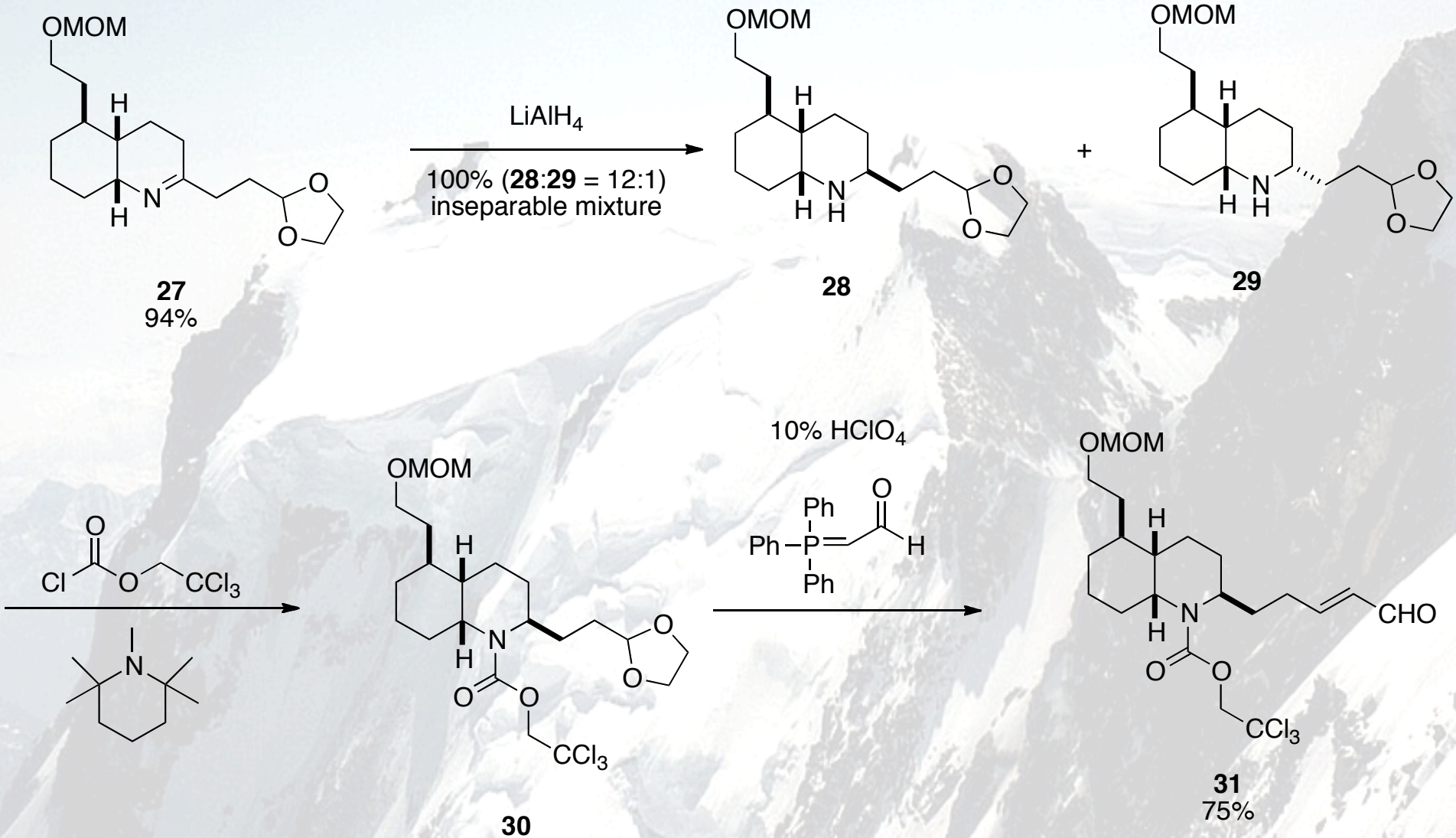
21

22

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



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



27
94%

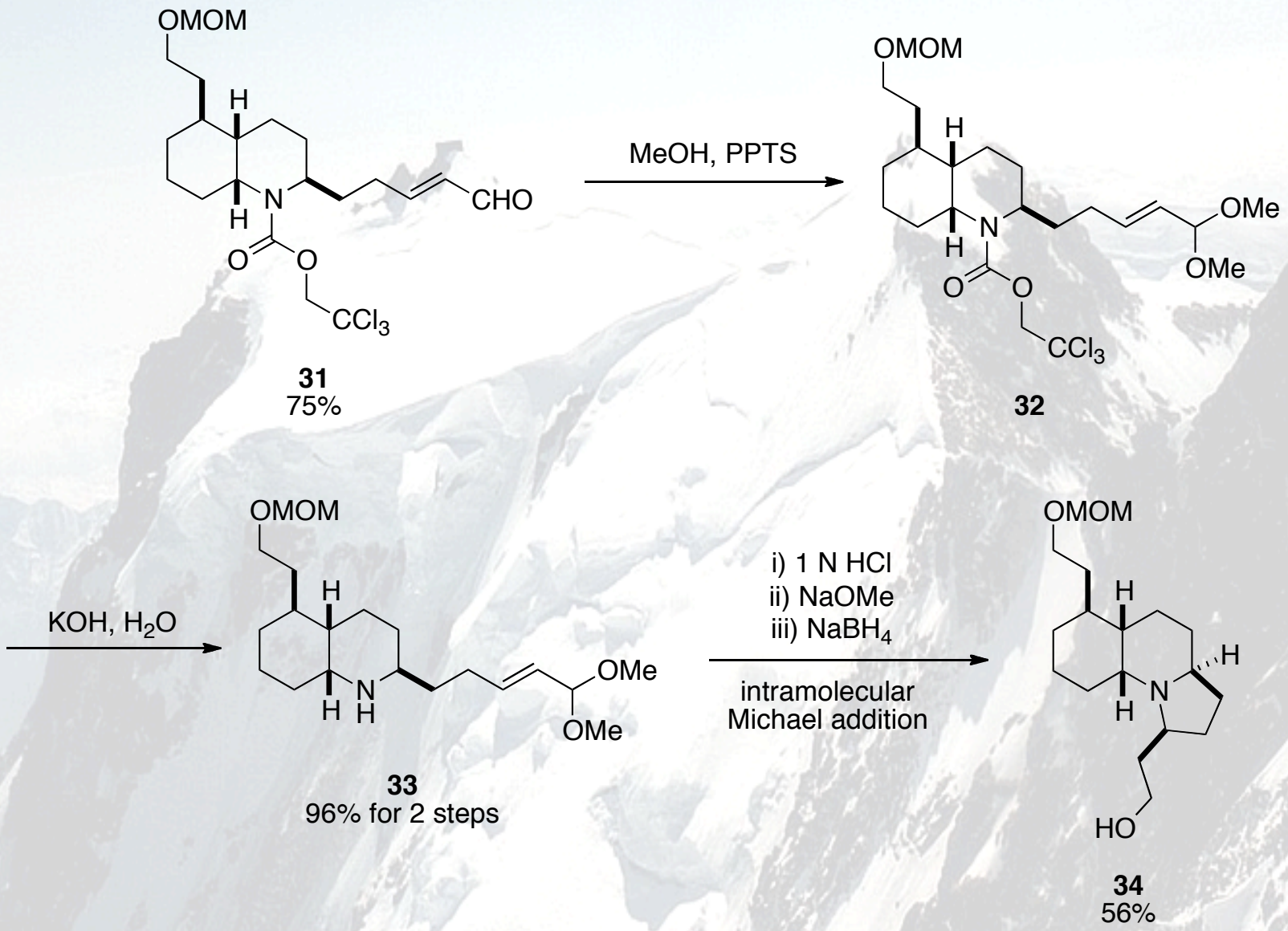
28

29

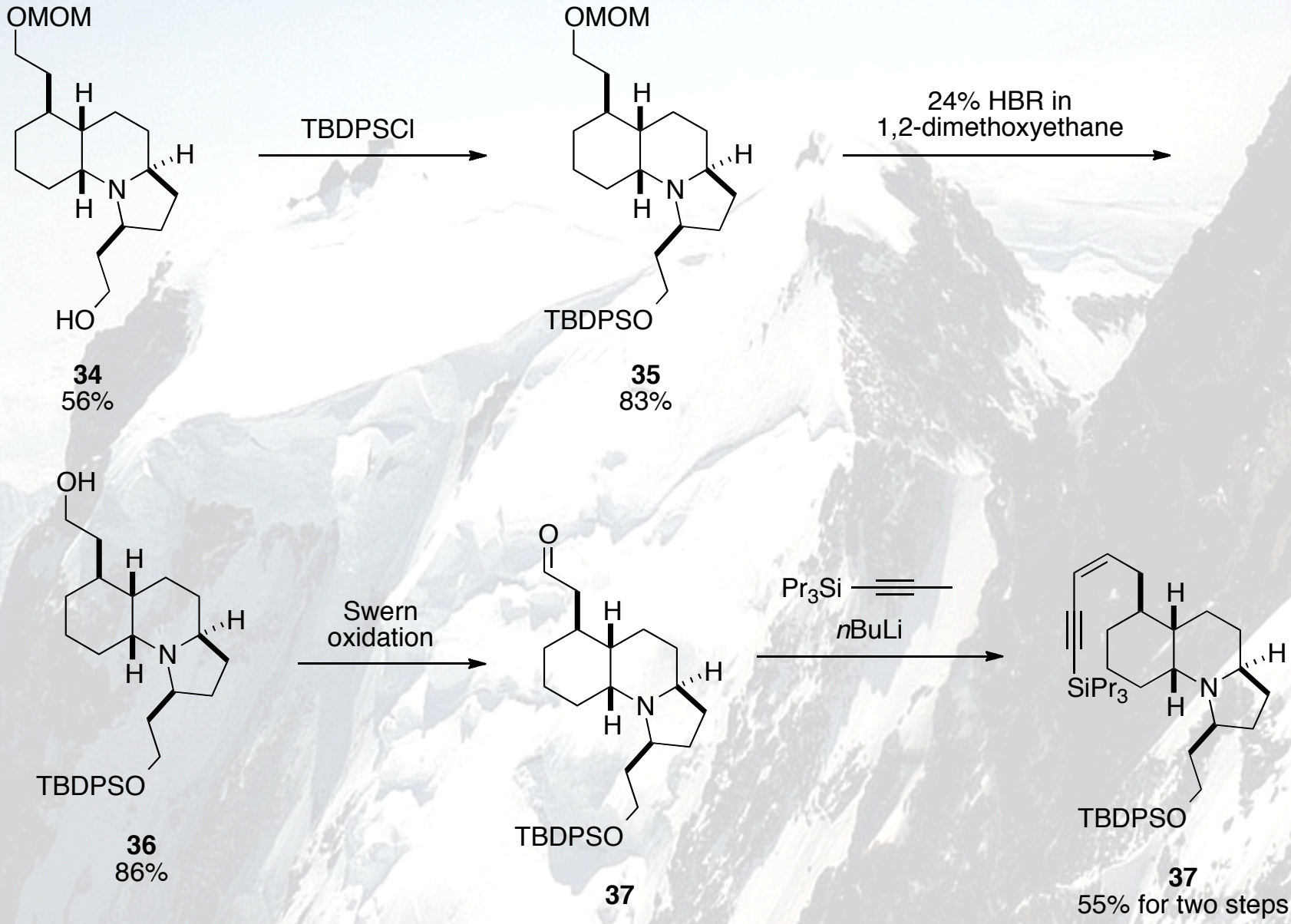
30
85%

31
75%

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



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



34
56%

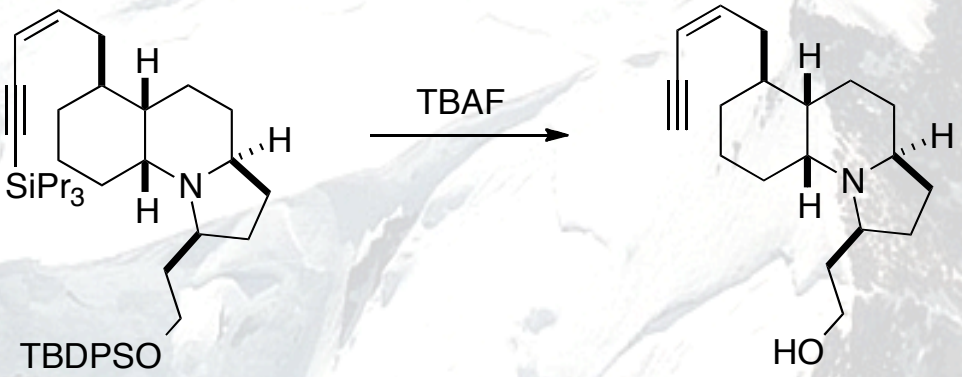
35
83%

36
86%

37

37
55% for two steps

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



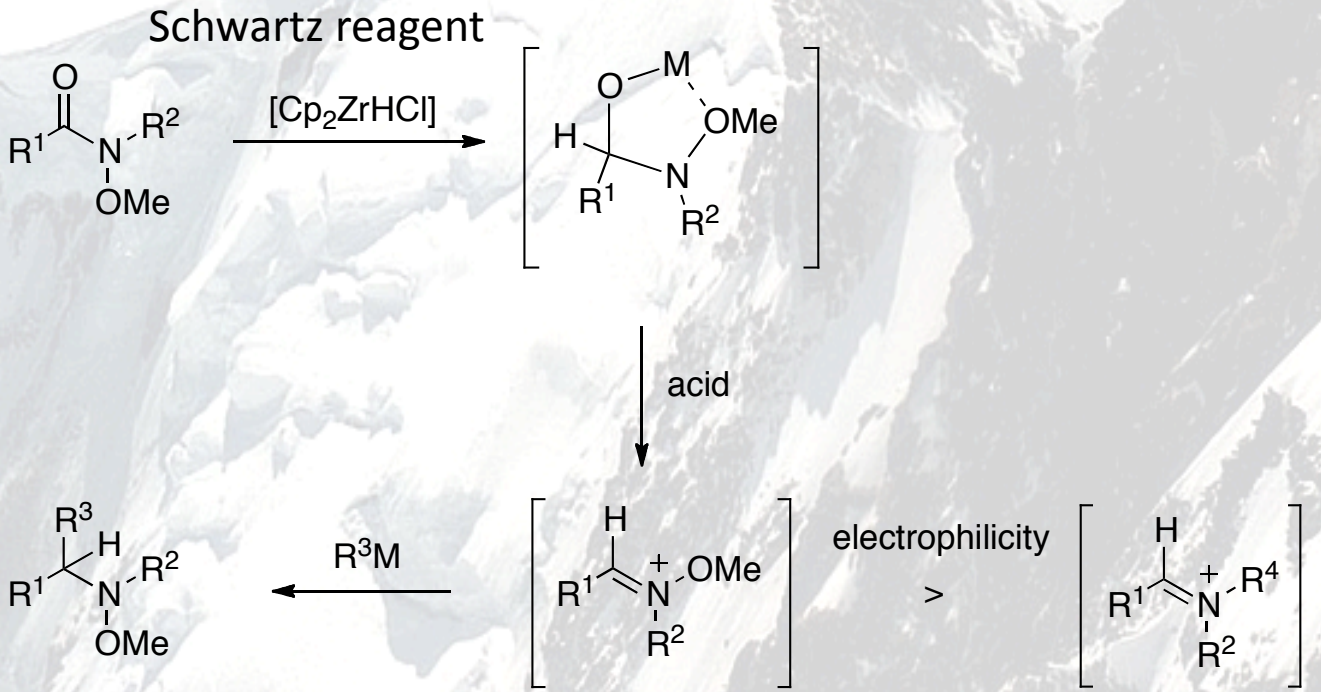
37
55% for two steps

(±)-Gephyrotoxin
58%

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

Approach of Chida:

Chemoselective reductive nucleophilic addition to *N*-methoxyamides



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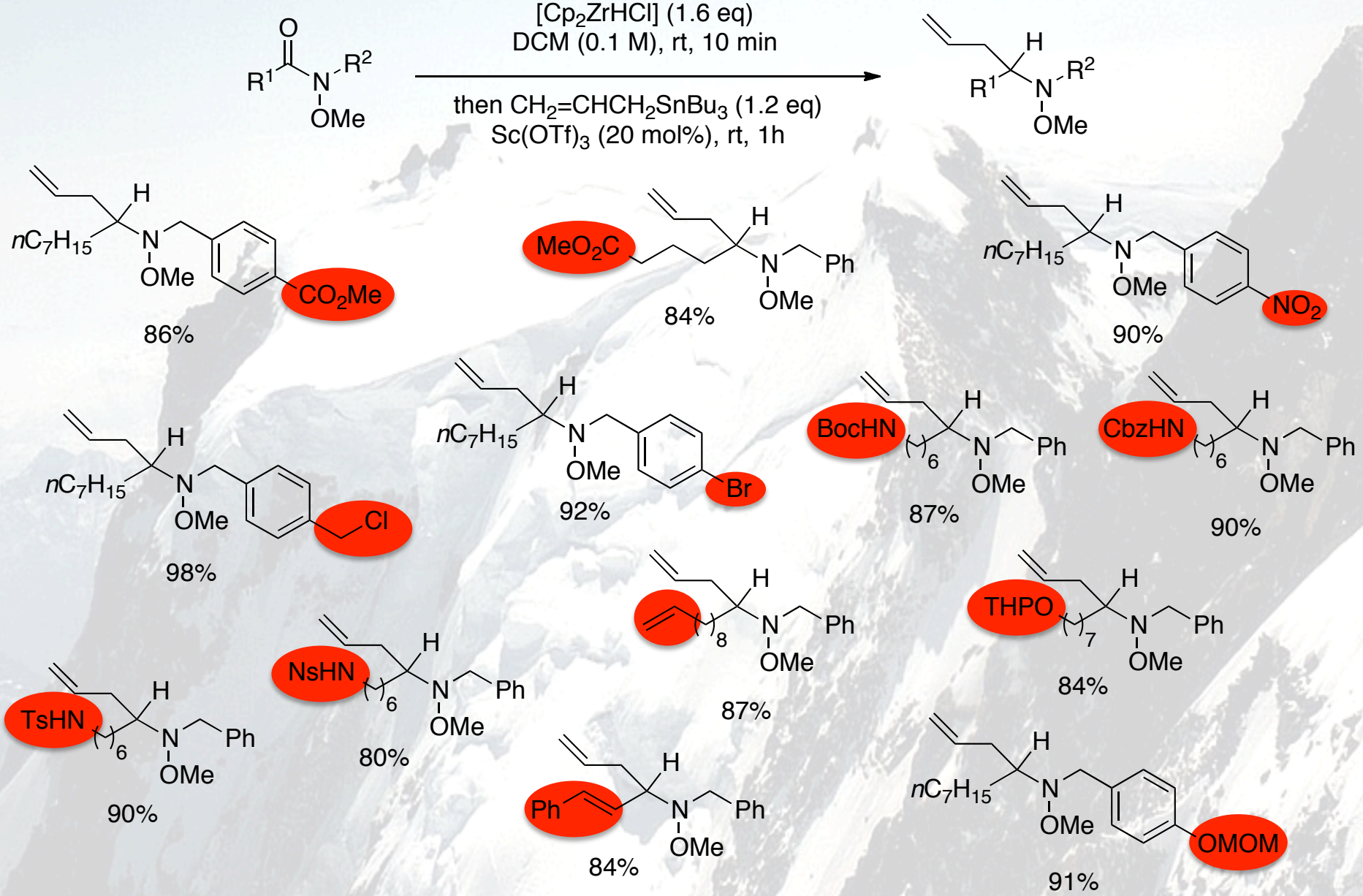
Scope of the chemoselective reductive allylation of N-methoxyamides:



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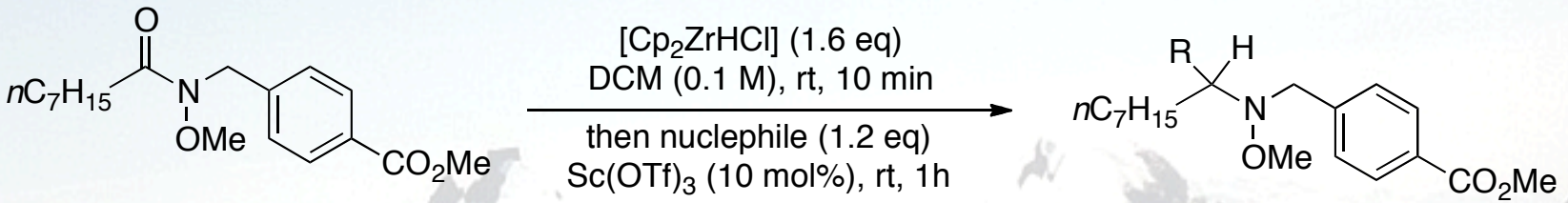
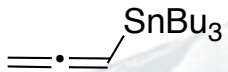
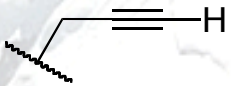
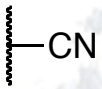
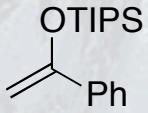
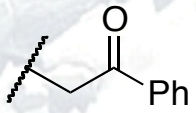
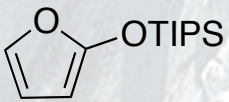
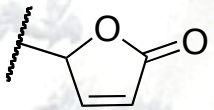
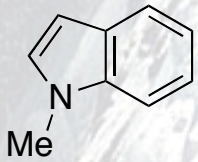
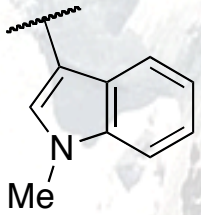
Variation of the nucleophile



nucleophile	product	yield
		71%
TMS-CN		81%
		74%
		78% (d.r. = 1.6:1)
		75%

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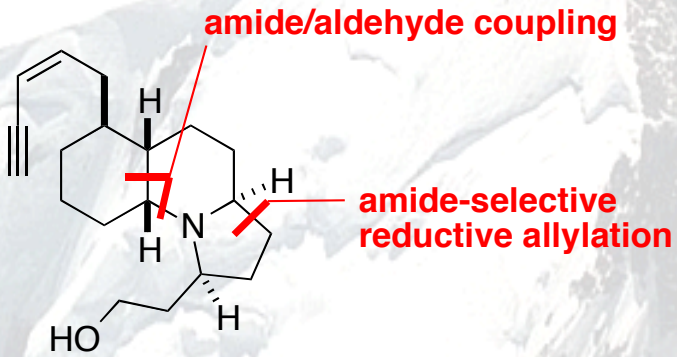
Application: Total Synthesis of (±)-Gephyrotoxin



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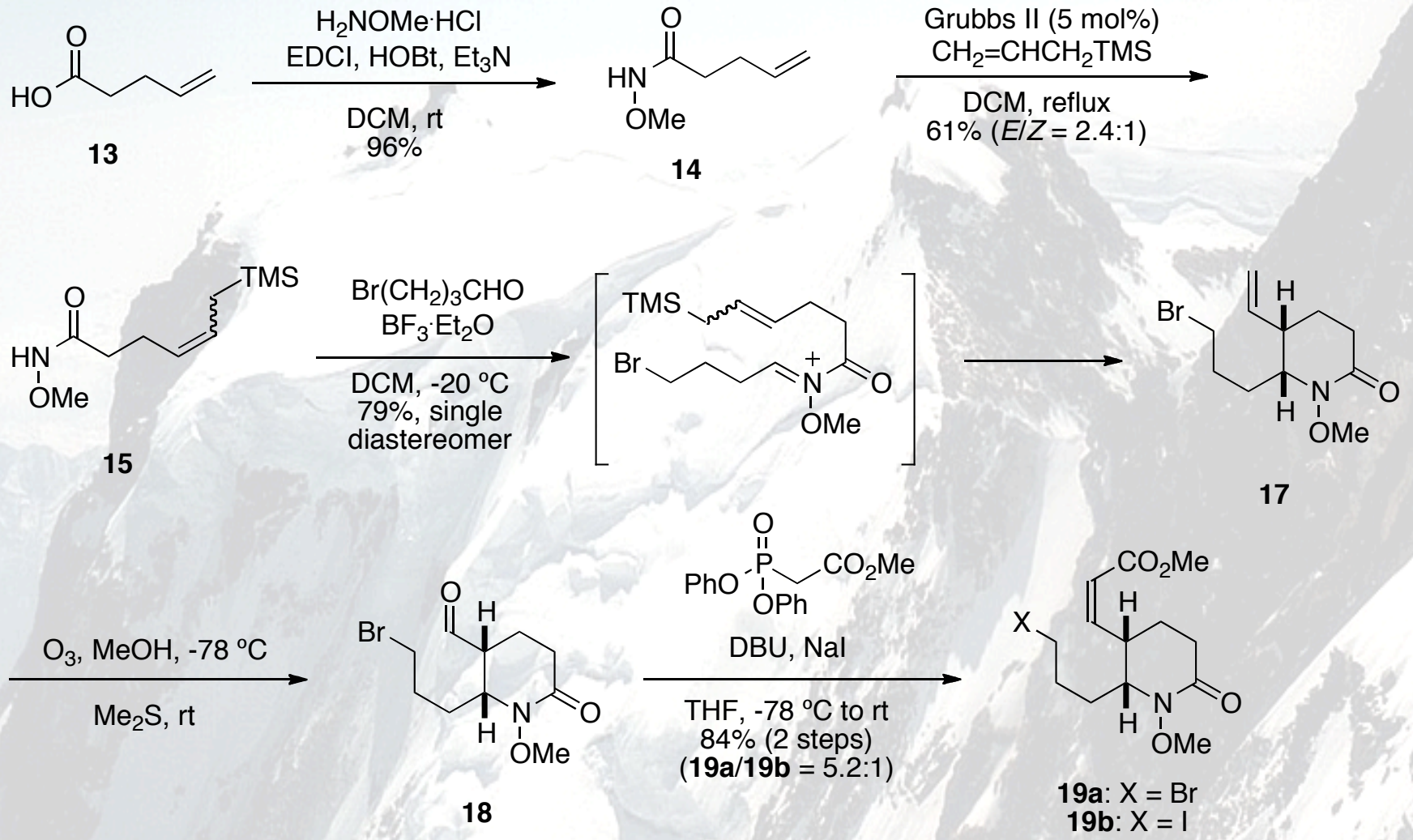

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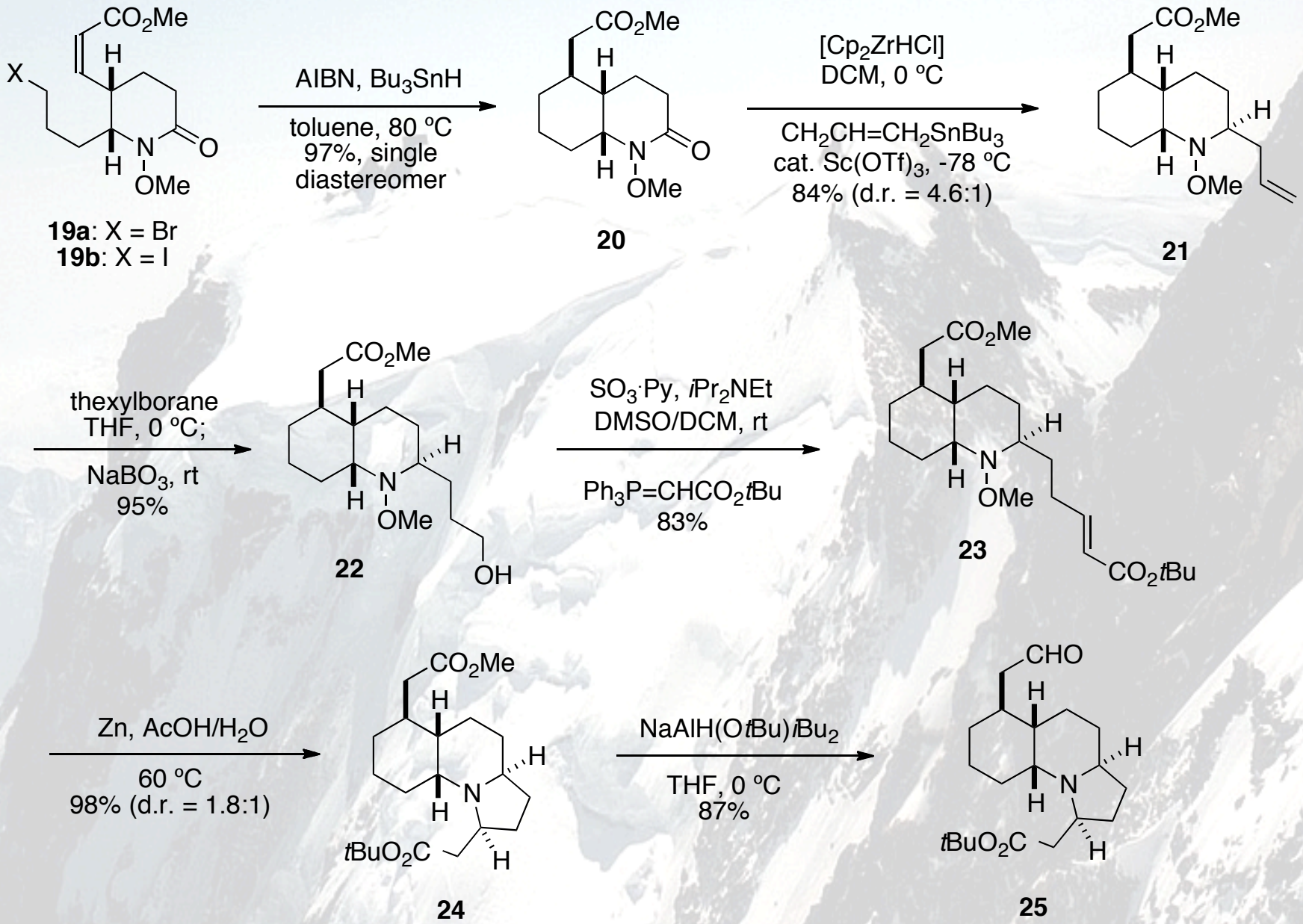

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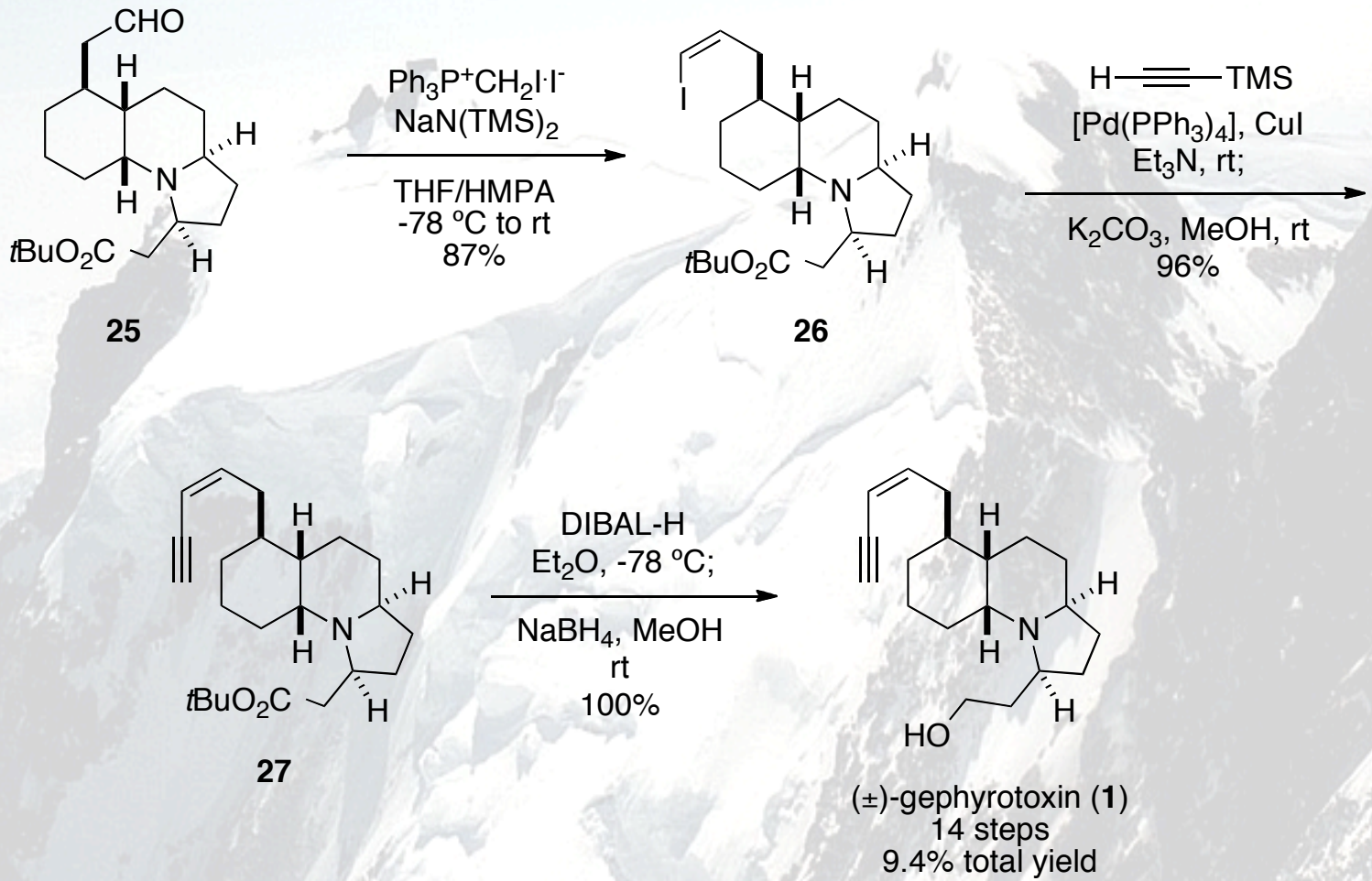

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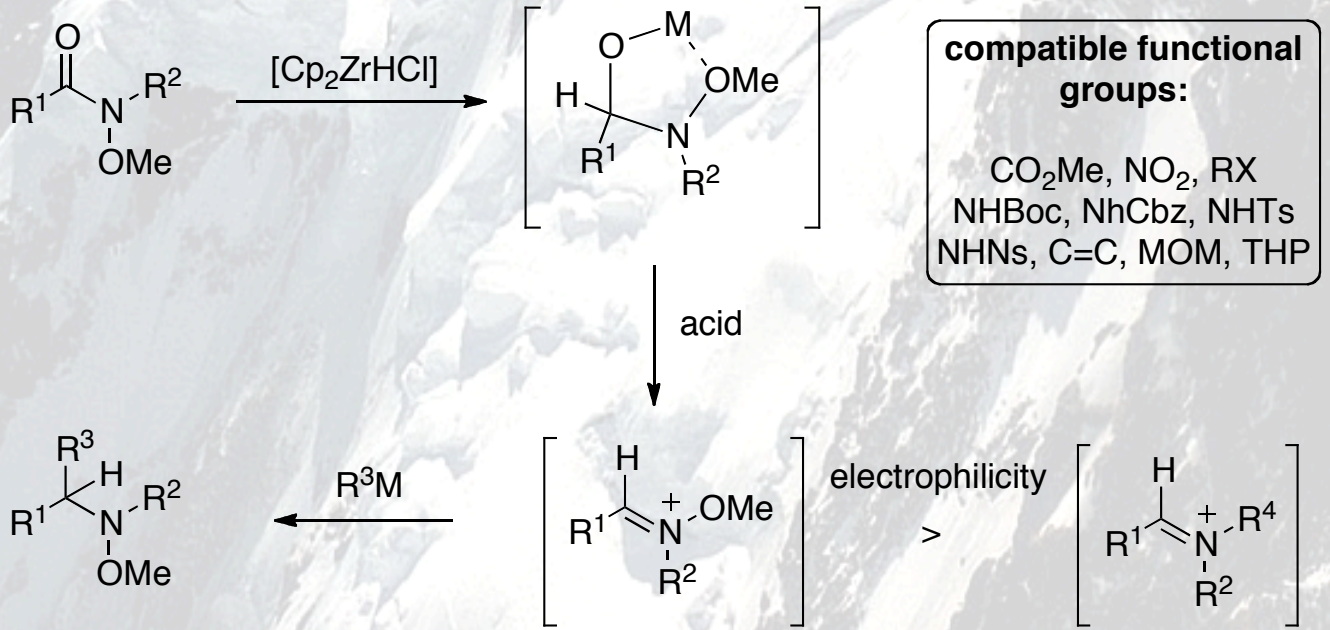
Conclusion:

- Quite efficient total synthesis
  - 14 steps form commercially available 4-pentenoic acid (Overman: 19 steps; Kishi: 24 steps; Hart: 21 steps)
  - 9.4% overall yield (Overman: 2.0%; Kishi: not reported; Hart: 1.0)

- Interesting key methodology: N-methoxy group as reactivity control element
  - minimization of the need of protecting groups
  - increased nucleophilicity of the iminium ion enable amide-selective nucleophile addition in presence of methyl ester



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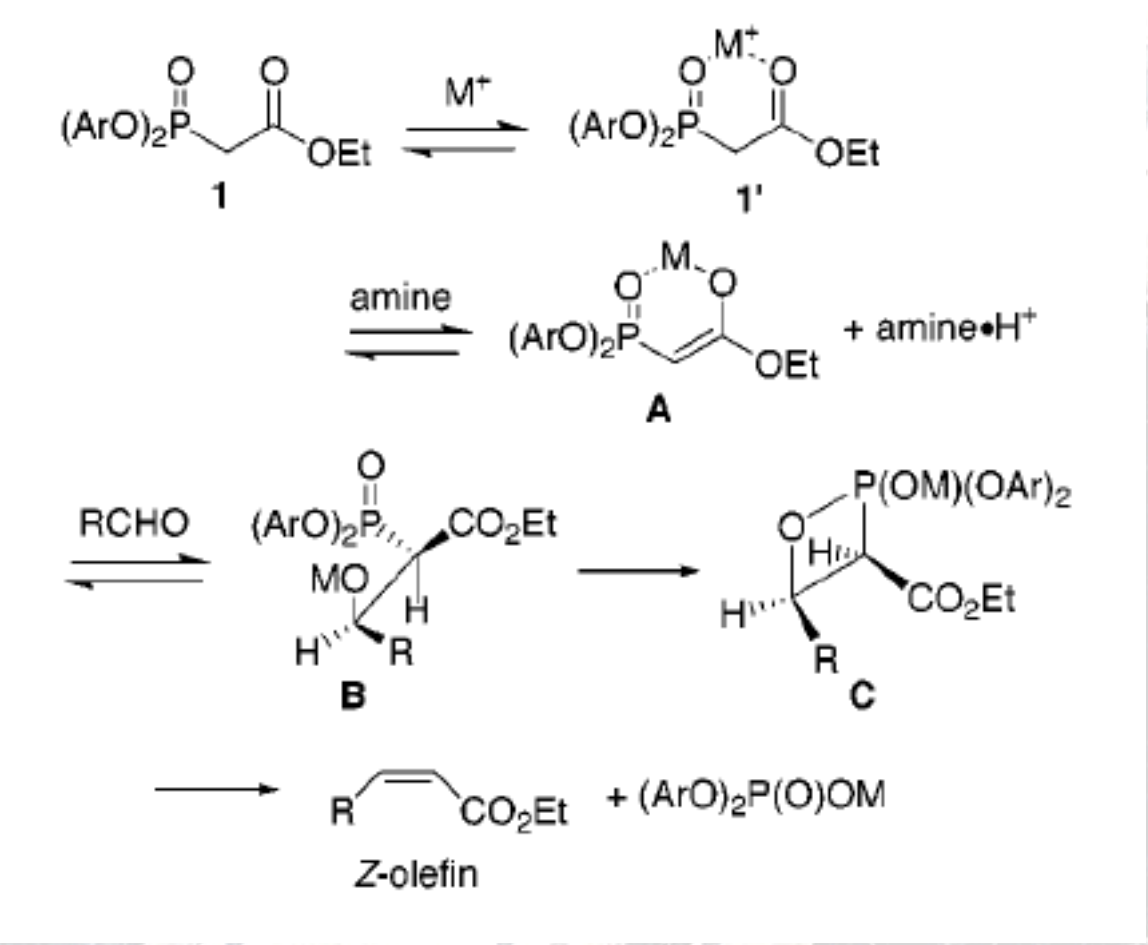
END

Z-Selective Horner-Wadsworth-Emmons Reaction of Ethyl (Diarylphosphono)acetates Using Sodium Iodide and DBU:



K. Ando, T. Oishi, M. Hirama, H. Ohno, T. Ibuka, *J. Org. Chem.* **2000**, *65*, 4745.