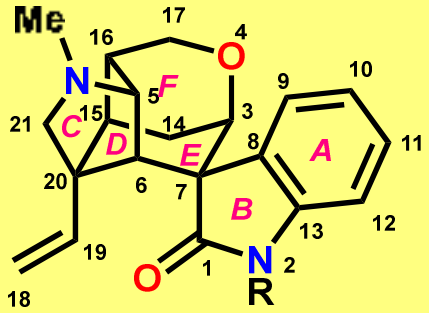
Total synthesis of (+)-gelsemine

Three approaches to synthesize gelsemine

Yuki Fujimoto 16/02/27

Introduction



R = H gelsemine
R = OMe gelsevirine

Isolation

gelsemium sempervirens, Carolina jasmine in English[1)]

Biological activity

an agonist for glycine receptor, which is stronger than glycine[2)]

Structural features

hexacyclic cage structure
seven contiguous chiral carbon center
(include two quaternary carbon, C7 &C20)
oxindole structure

Total syntheses (racemic)

- Johnson, A. P. *et al. J. Chem. Soc. Chem. Commun.* 1994, 763.
  Johnson, A. P. *et al. J. Chem. Soc. Chem. Commun.* 1994, 765.
- Speckamp, W. N. *et al. J. Chem. Soc. Chem. Commun.* 1994, 767.
- Fukuyama, T.; Liu. G. *J. Am. Chem. Soc.* 1996, *118*, 7426.
- Hart, D. J. *et. al. J. Am. Chem. Soc.* 1997, 119, 6226.
- Overman, L. E. *et. al. Angew. Chem. Int. Ed.* 1999, *38*, 2934.
- Ng, F. W.; Lin, H.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* 2002, *124*, 9812.

Total syntheses (asymmetric)

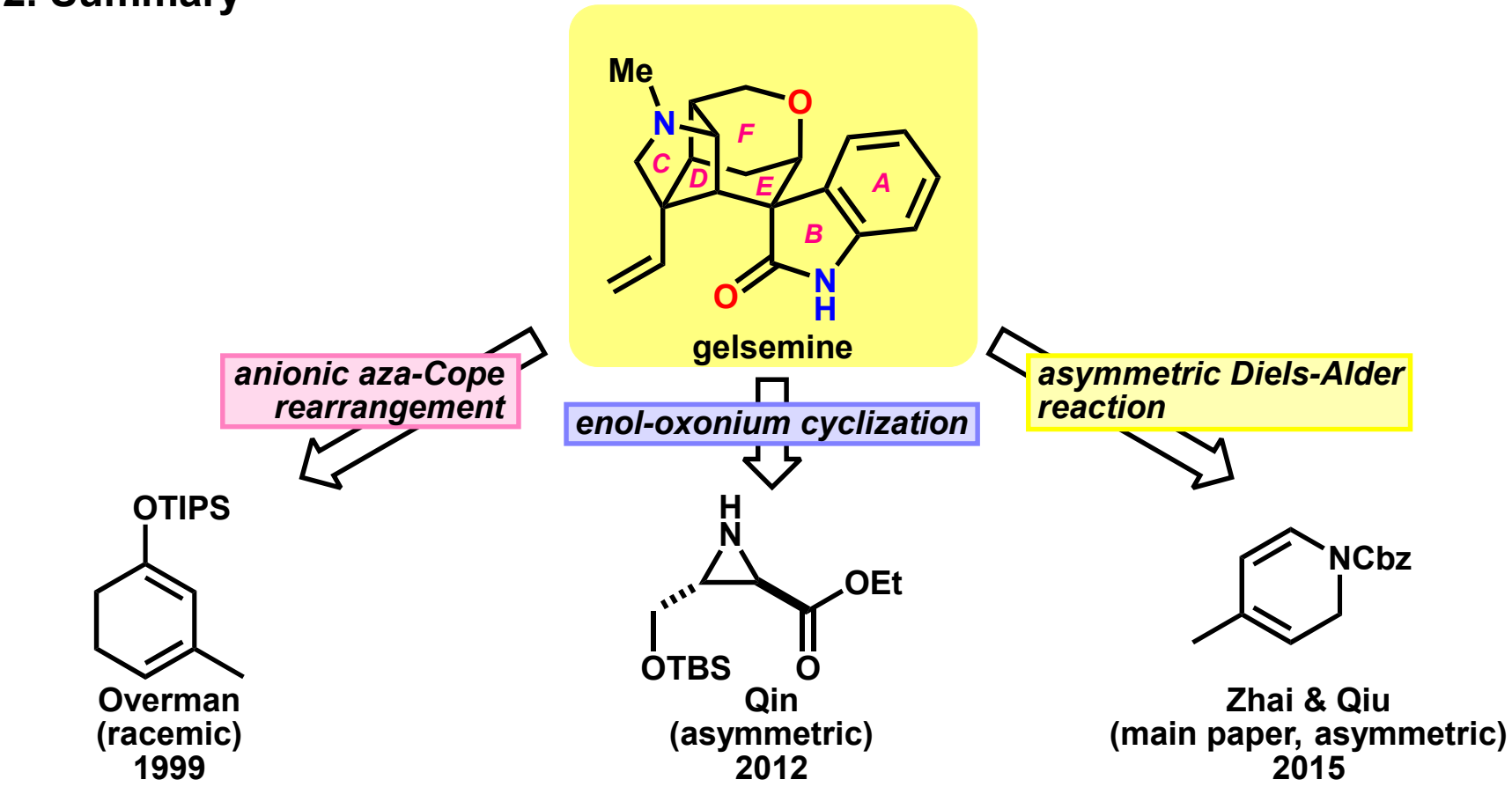
- Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem. Int. Ed.* 2000, *39*, 4073.
- Qin, Y. *et al. Angew. Chem. Int. Ed.* 2012, *51*, 4909.
- Qiu, F. G. *et al. Nature. Commun.* 2015, *6*, 7204.

1) Sonnenschein, F. L. *Ber. Dtsch. Chem. Ges*. **1876**, *9*, 1182.

2) Zhang, J. Y.; Gong, N.; Huang, J. L.; Guo, L. C.; Wang, Y. X. *Pain*. **2013**, *154*, 2452

Today's menu

1. Strategies of gelsemine synthesis
   1-1. Anionic aza-Cope rearrangement by Overman
   1-2. Enol-oxonium cyclization by Qin
   1-3. Asymmetric Diels-Alder by Zhai & Qiu
2. Summary



Overman's synthesis

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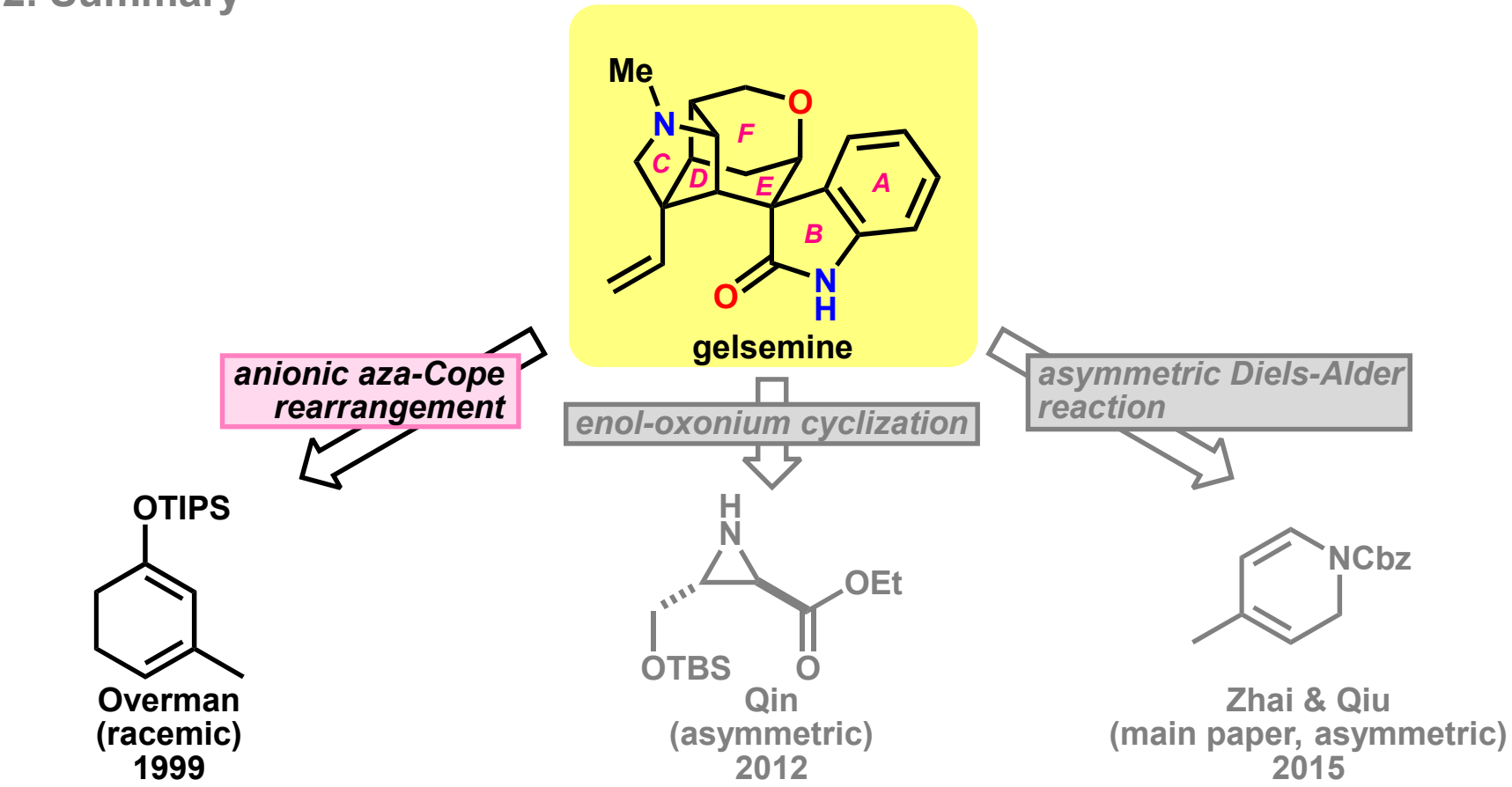
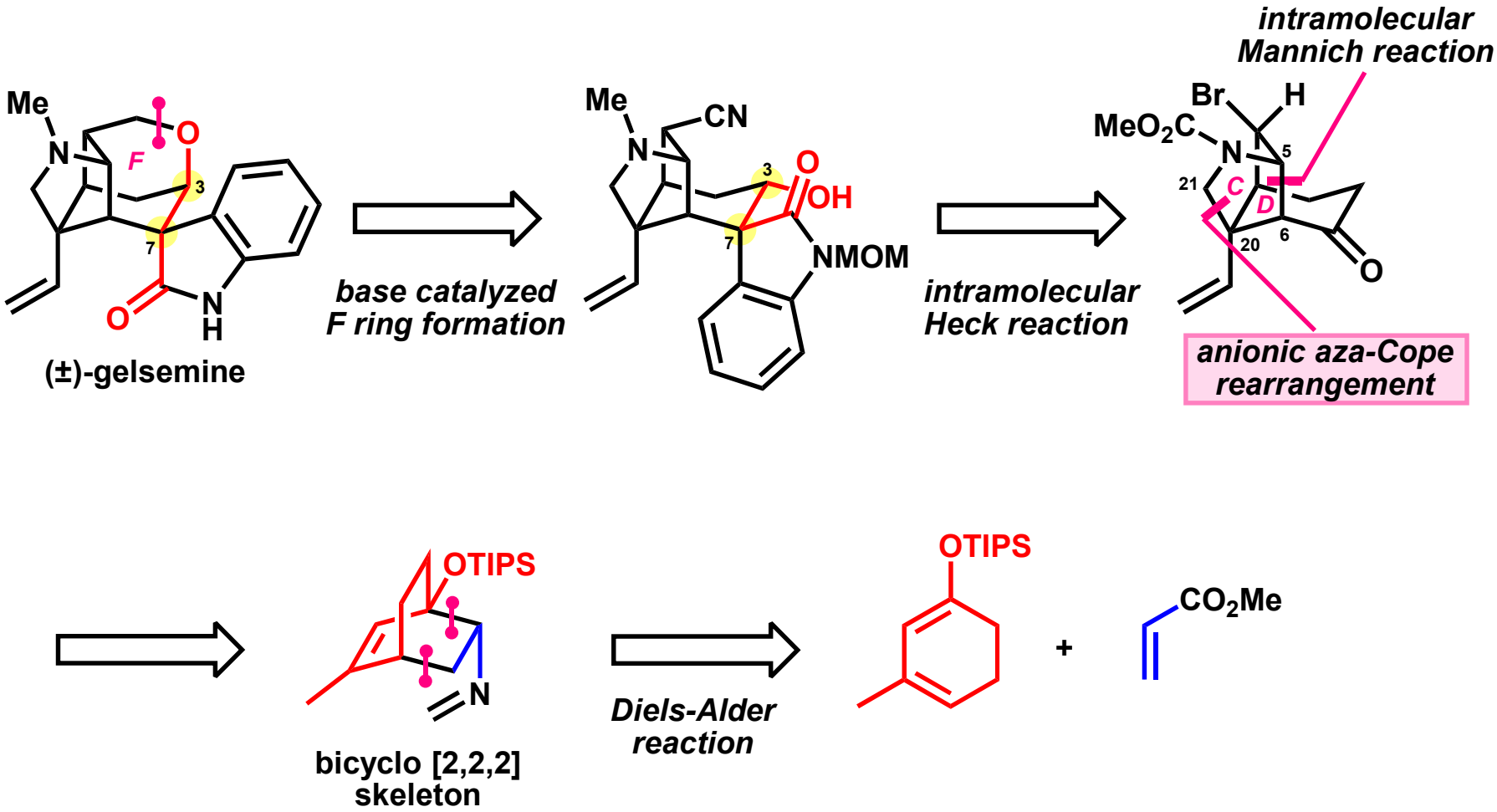
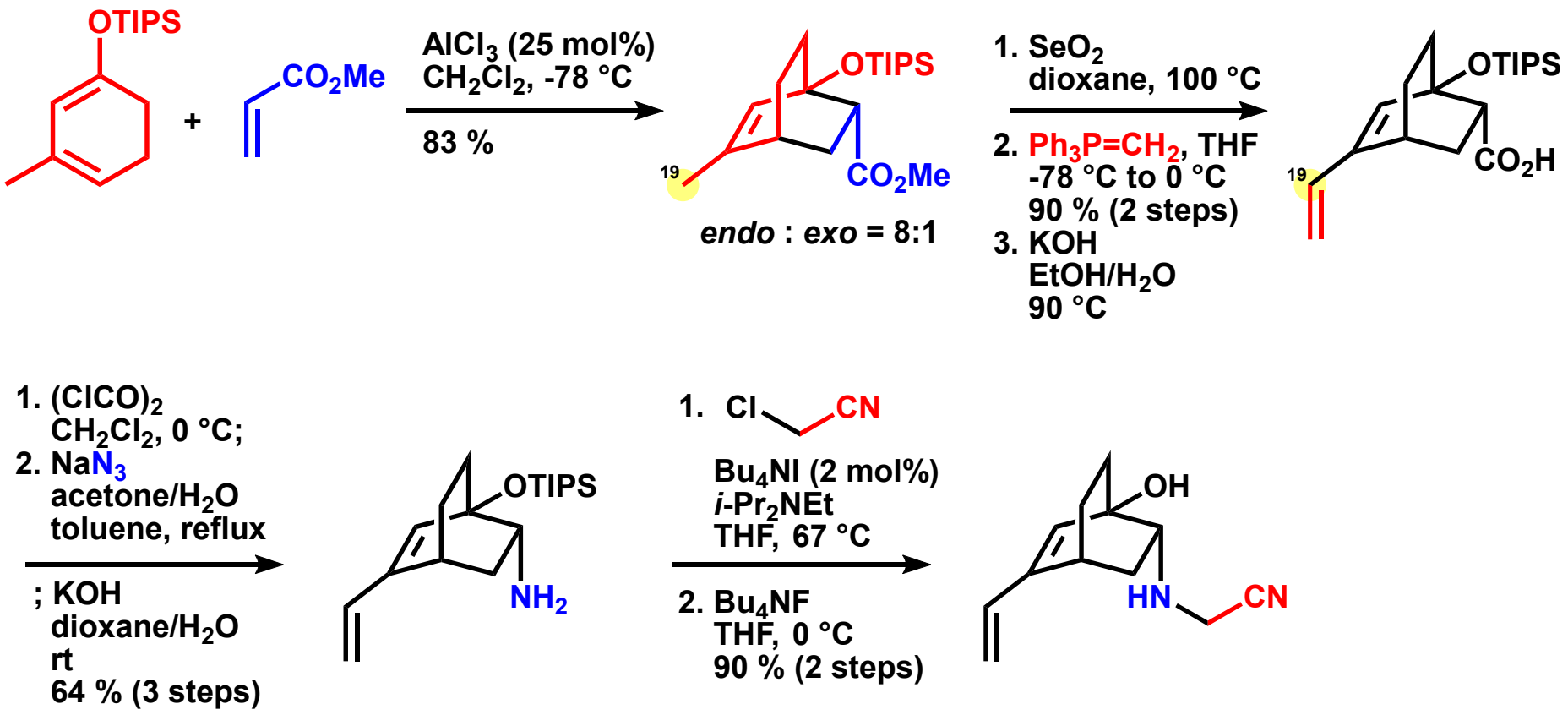


Retrosynthetic analysis



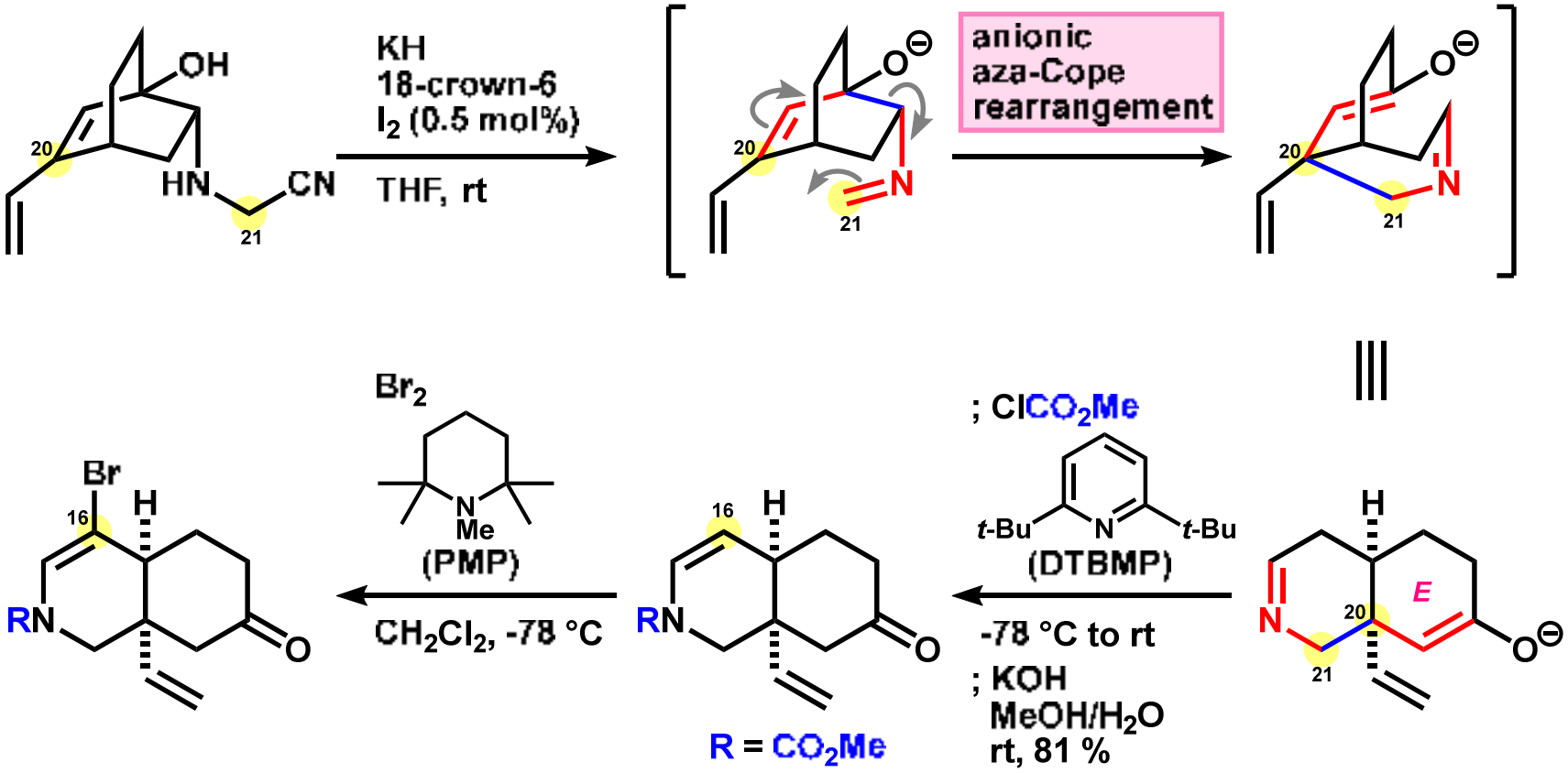
Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharpe, M. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934.

Construction of bicyclo [2,2,2] skeleton



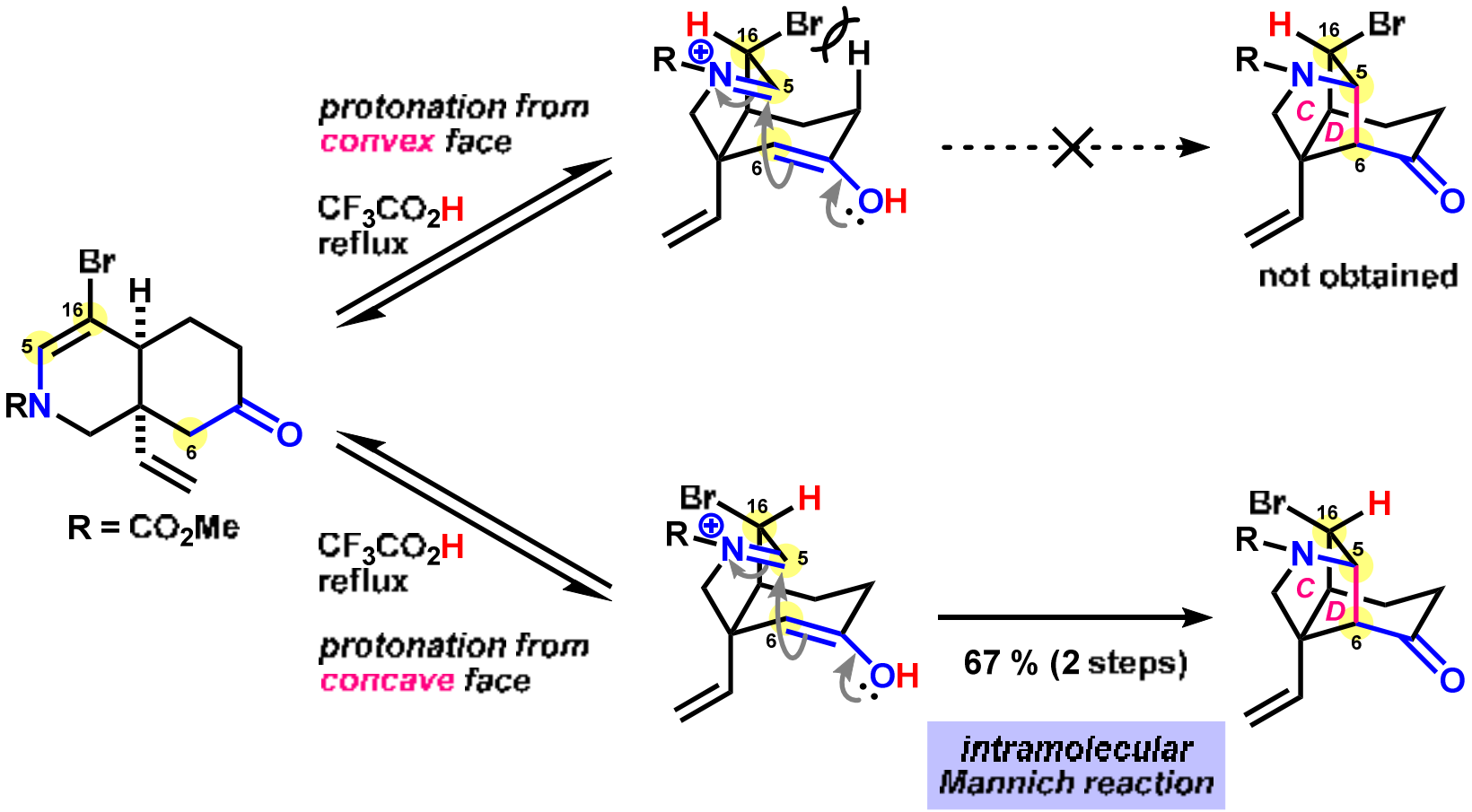
Earley, W. G.; Jacobsen, J.; Meier, P.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3781.

Anionic aza-Cope rearrangement



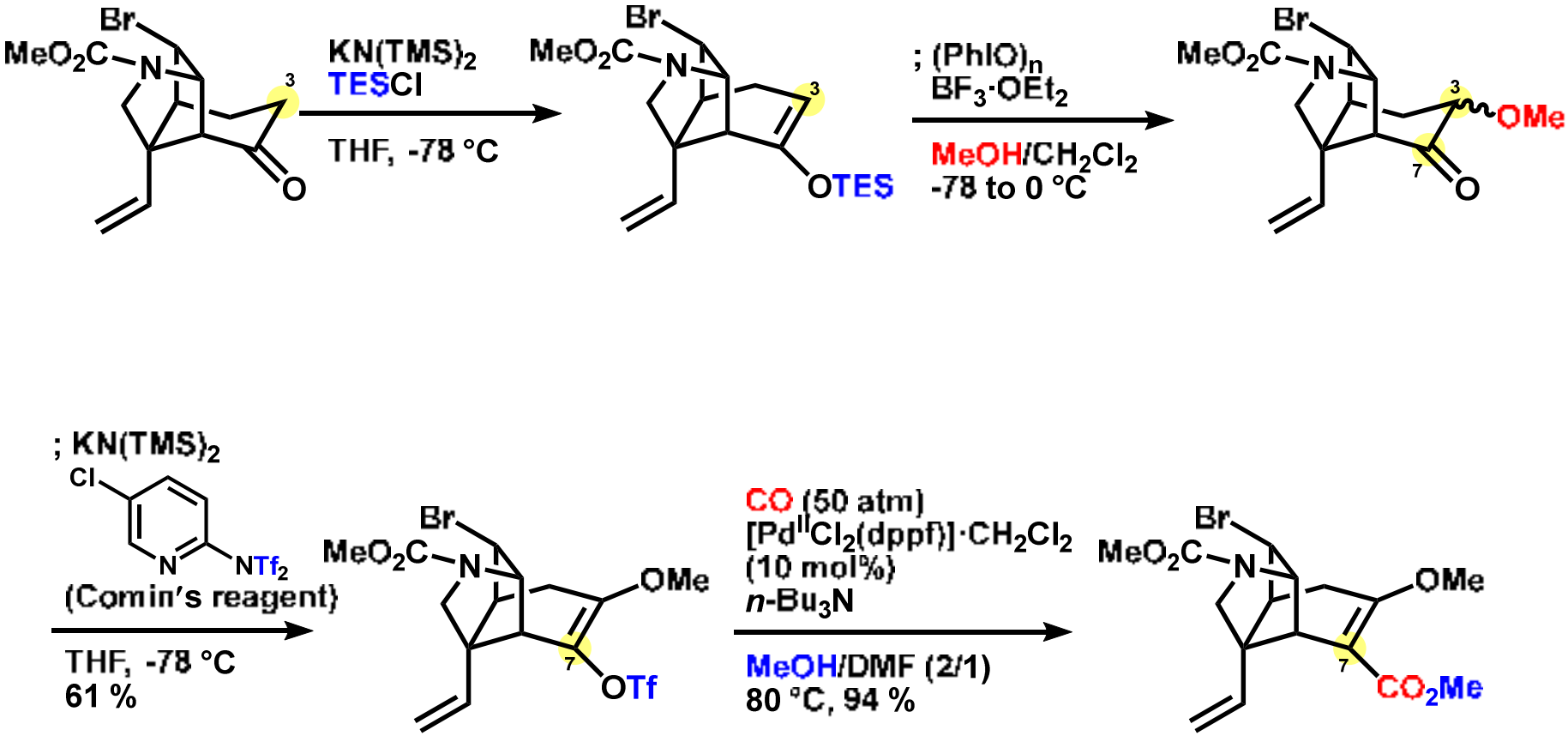
Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharpe, M. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934.

Intramolecular Mannich reaction



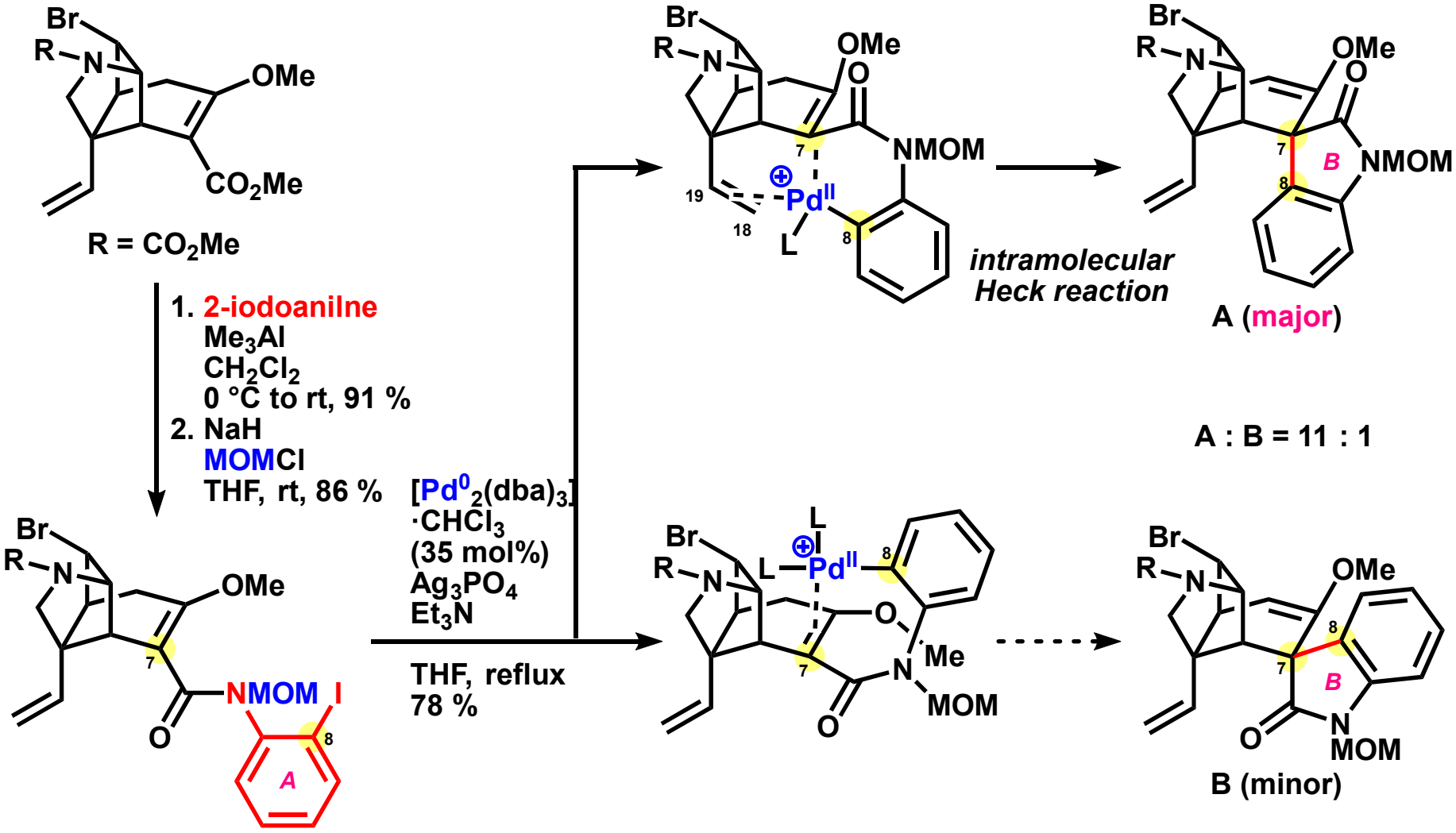
Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharpe, M. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934.

Functionalization at C3 & C7 position



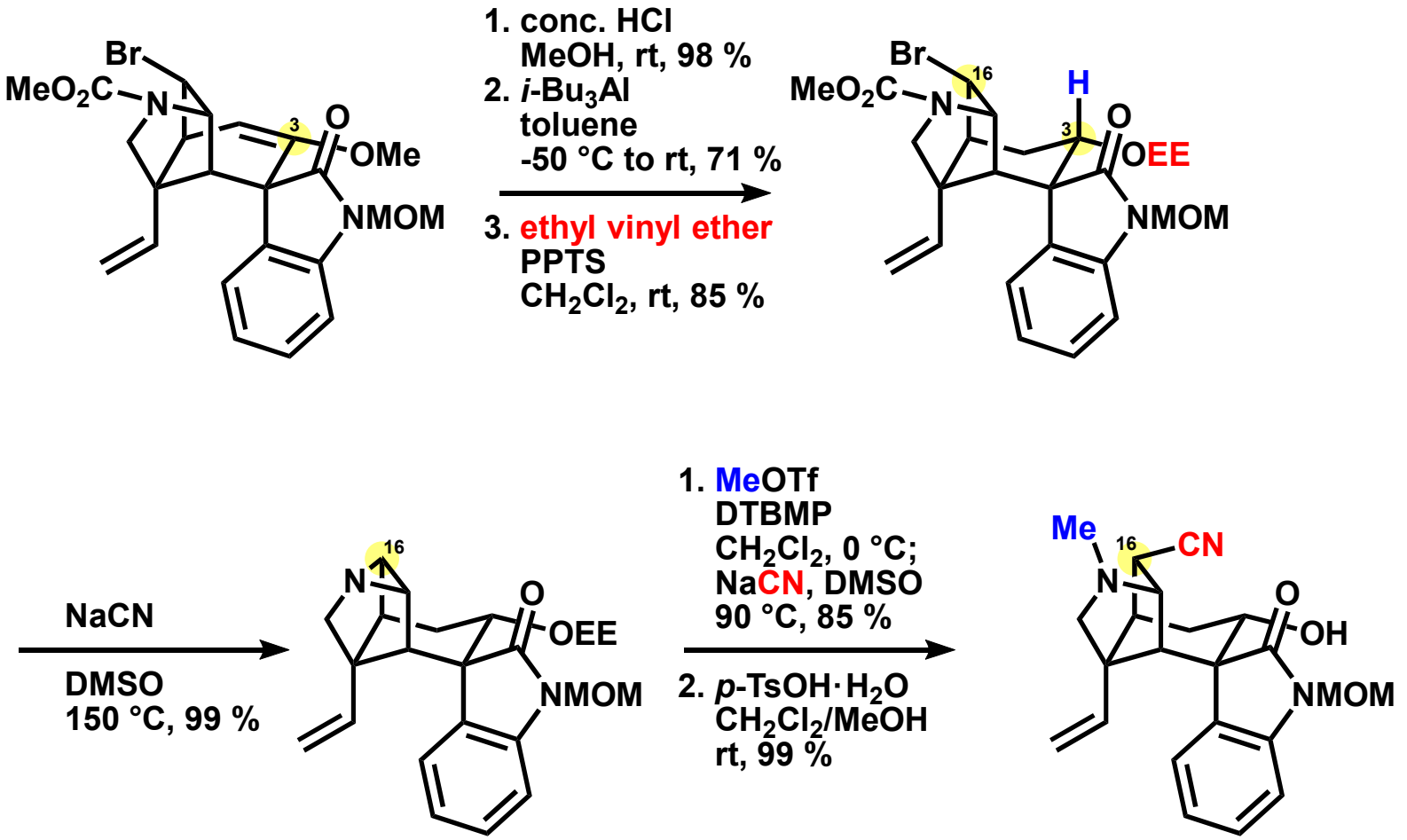
Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharpe, M. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934.

Intramolecular Heck reaction



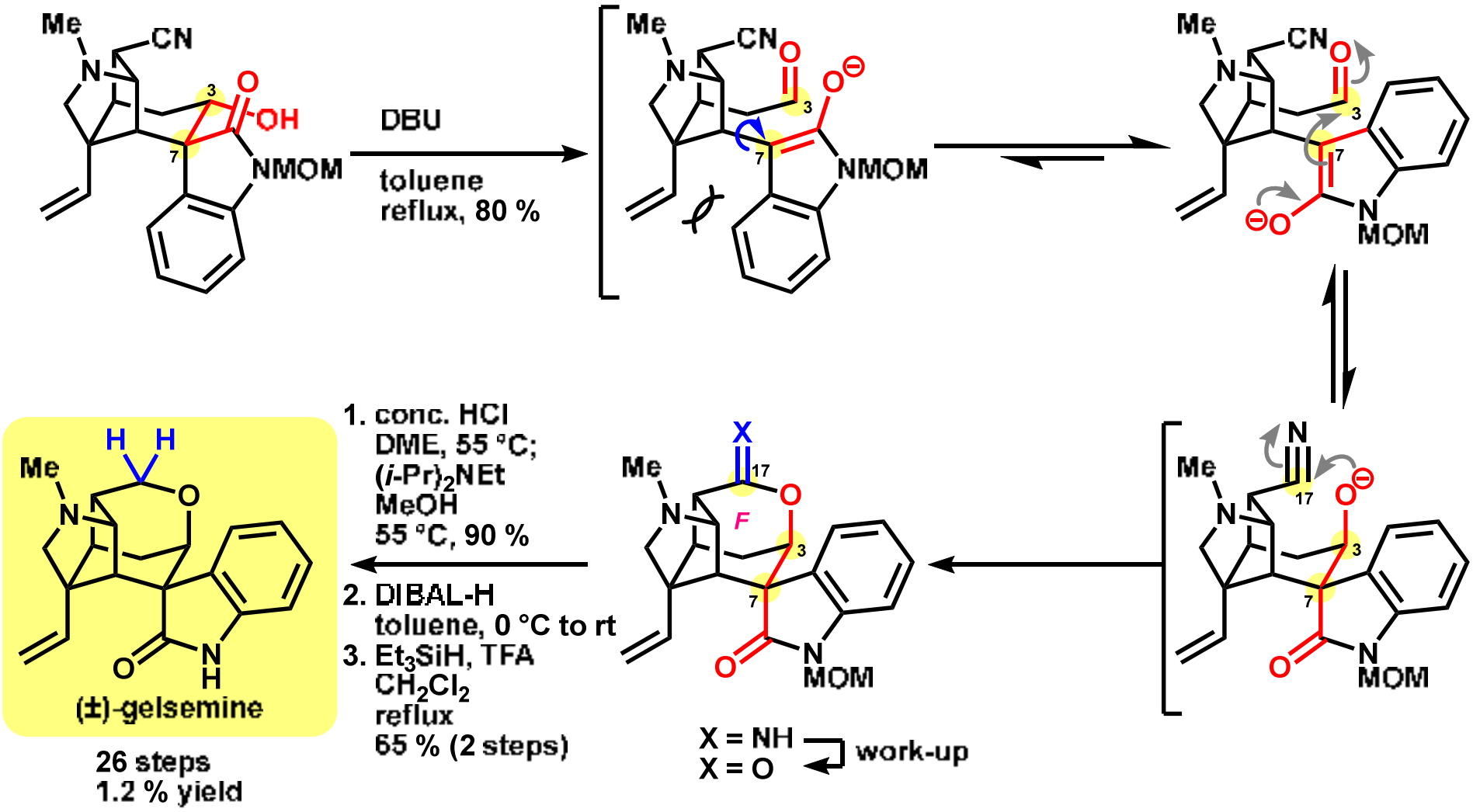
Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharpe, M. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934.

Functionalization at C3 & C16 position



Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharpe, M. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934.

Completion of total synthesis



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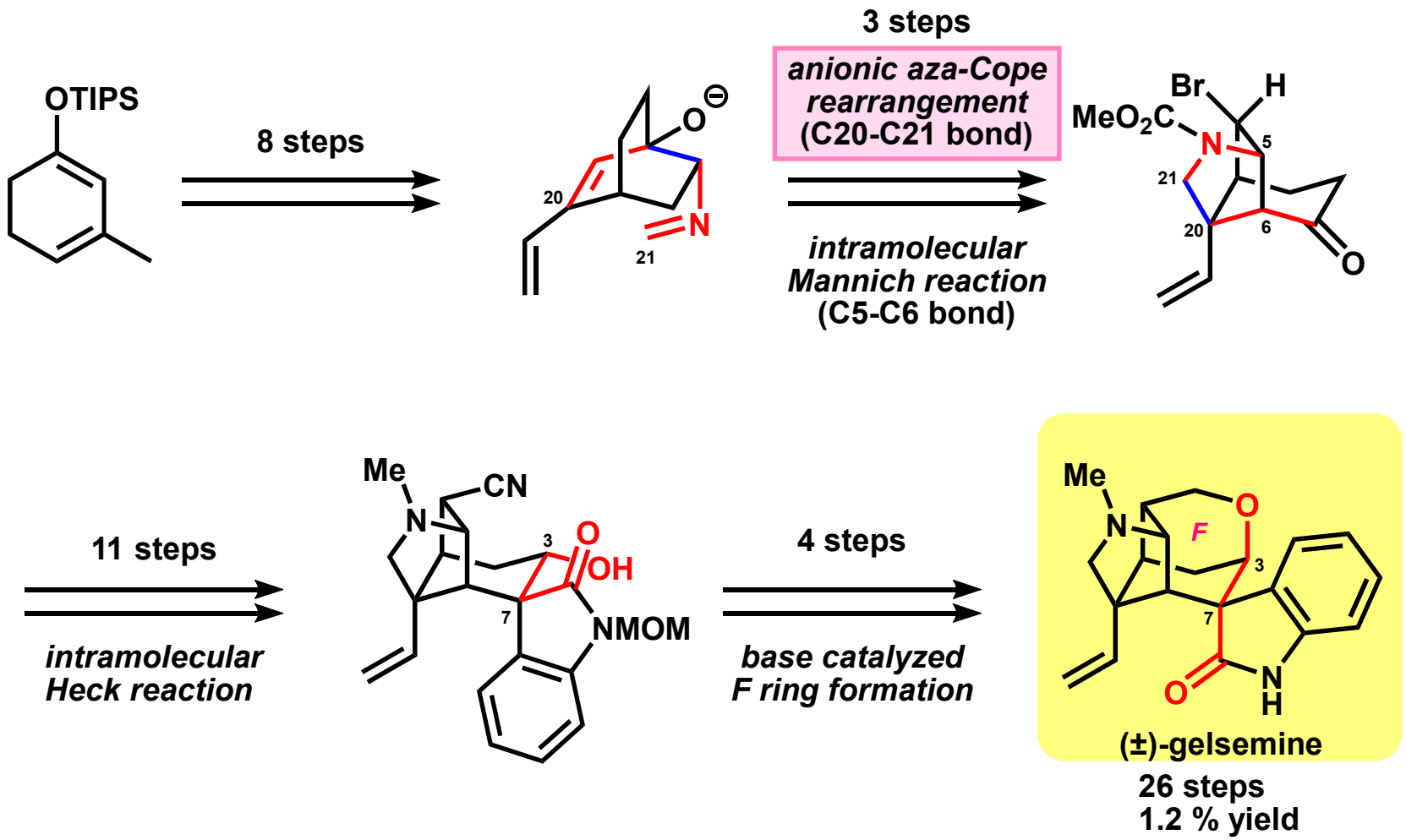
Summary of Overman's synthesis



Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharpe, M. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934.

Qin's synthesis

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1-3. Asymmetric Diels-Alder by Zhai & Qiu

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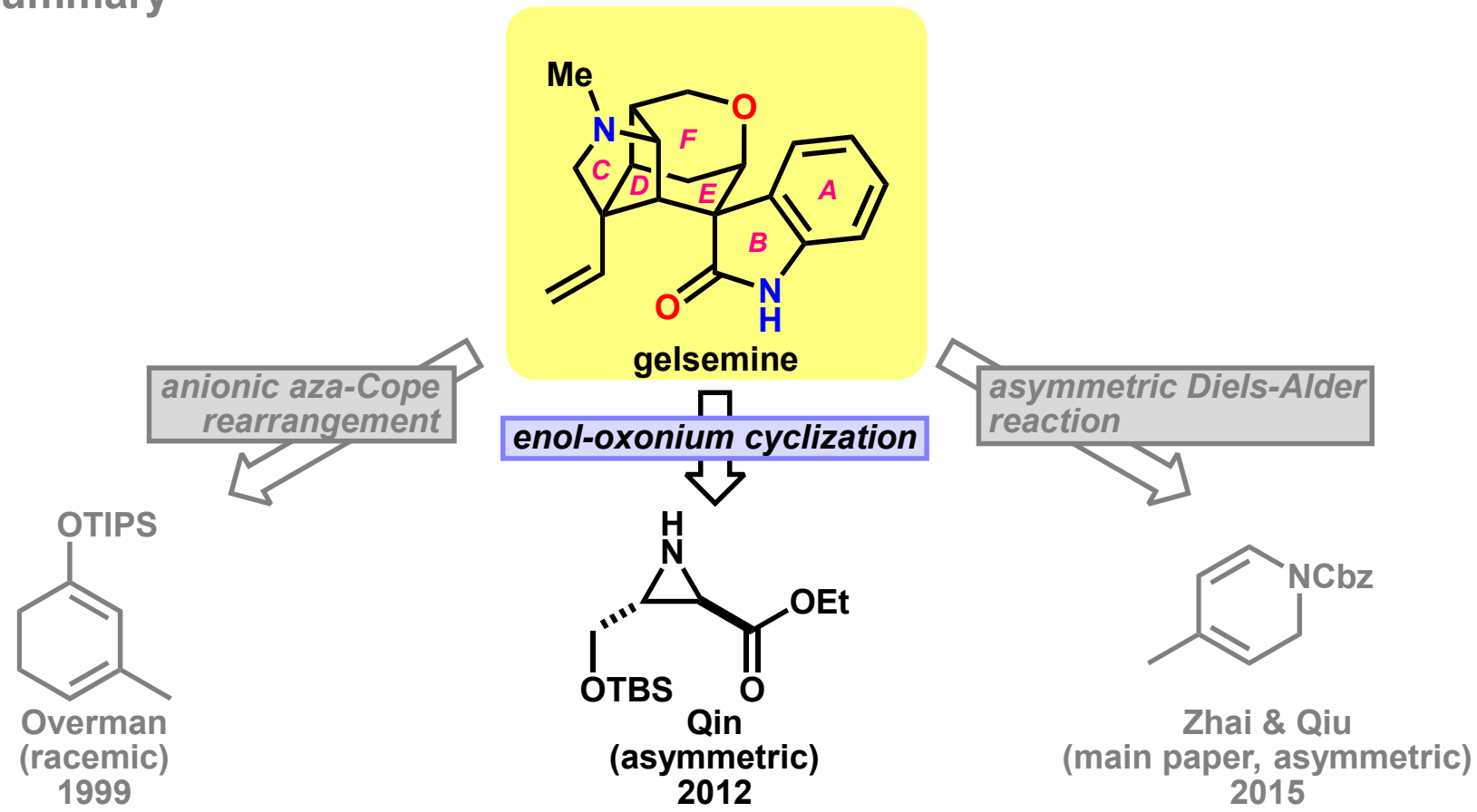
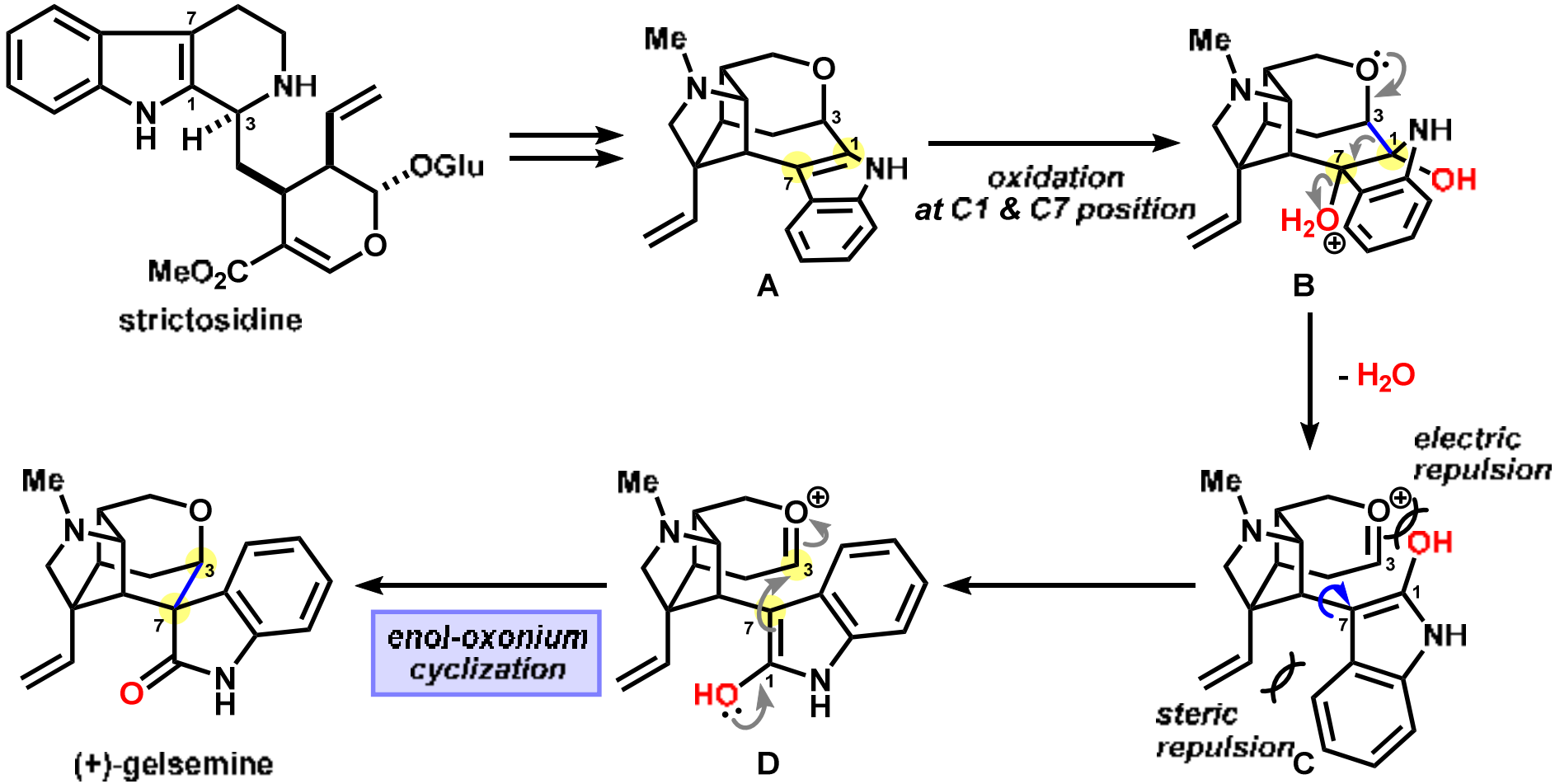
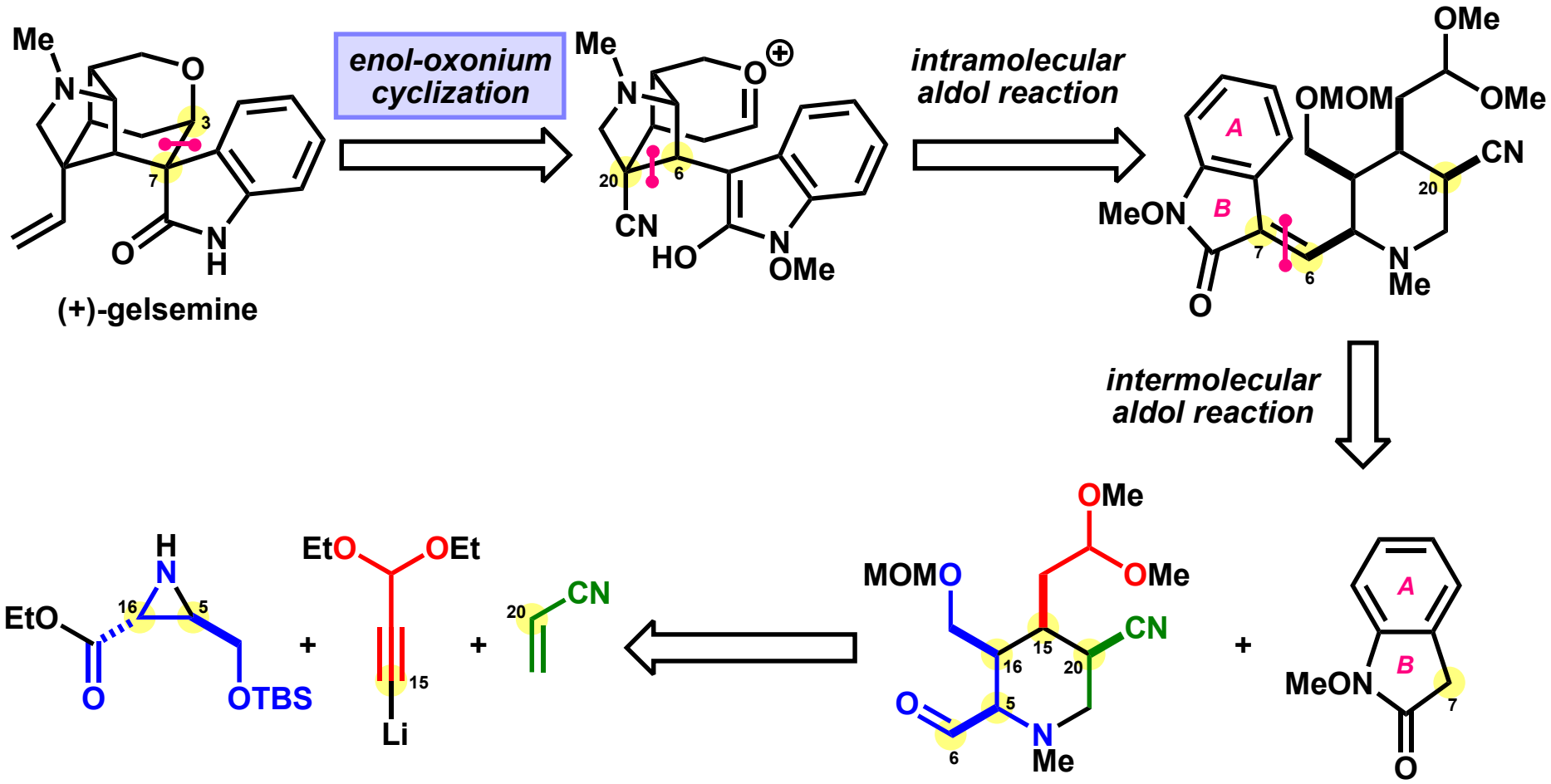


Proposed biosynthesis pathway



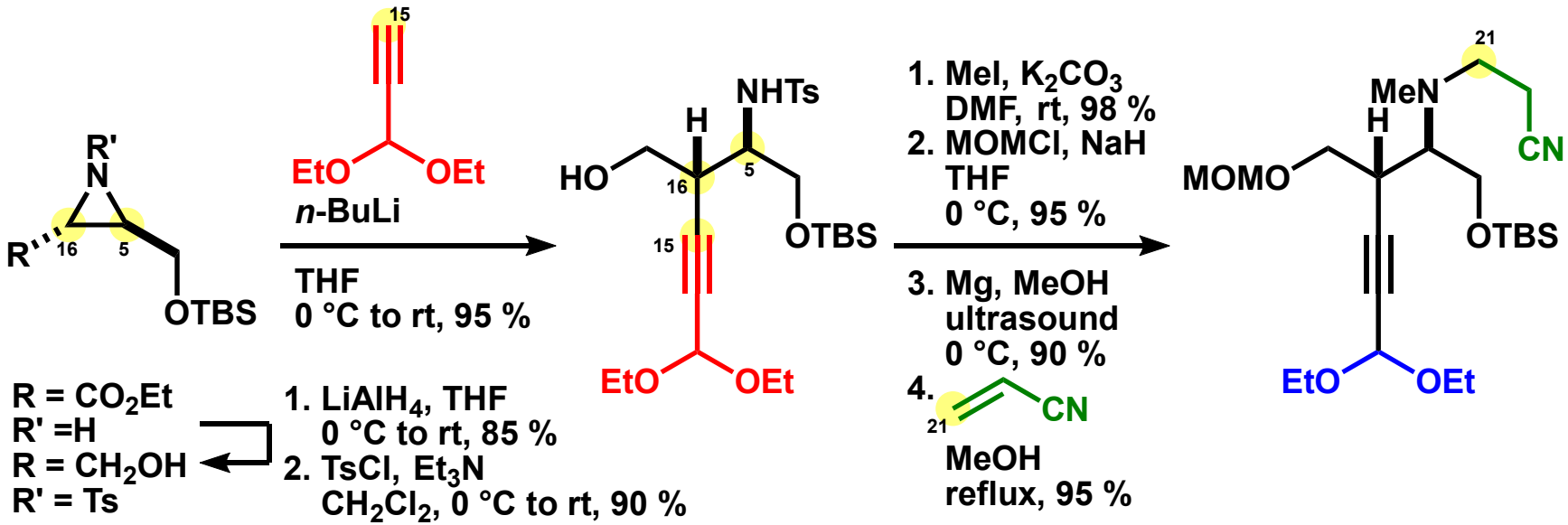
Ponglux, D. *et. al. Tetrahedron* **1988**, *44*, 5075.

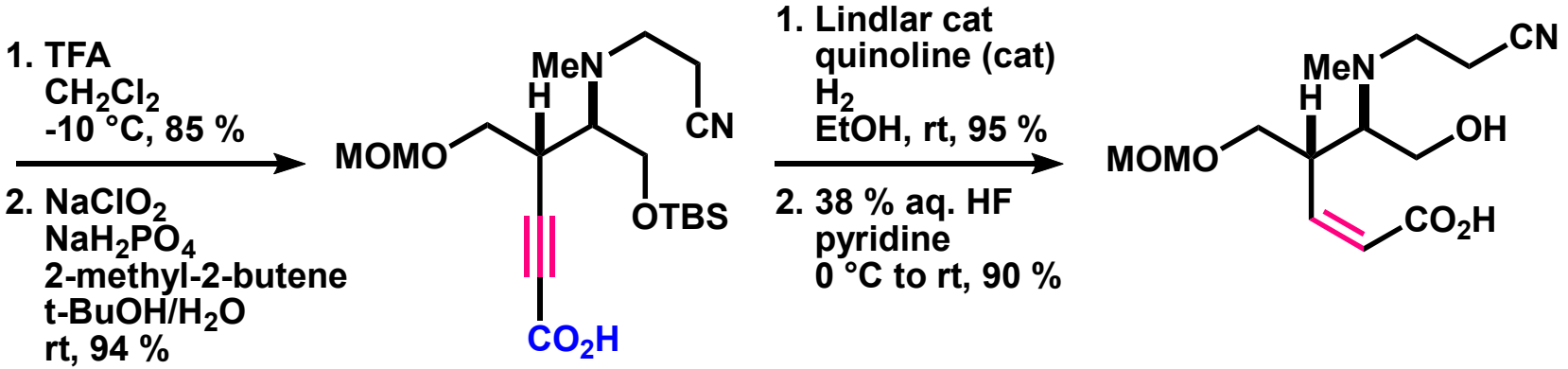
Retrosynthetic analysis



Zhou, X.; Xiao, T.; Iwama, Y.; Qin, Y. *Angew. Chem. Int. Ed*. **2012**, *51*, 4909.

Stereoselective synthesis of piperidine ring





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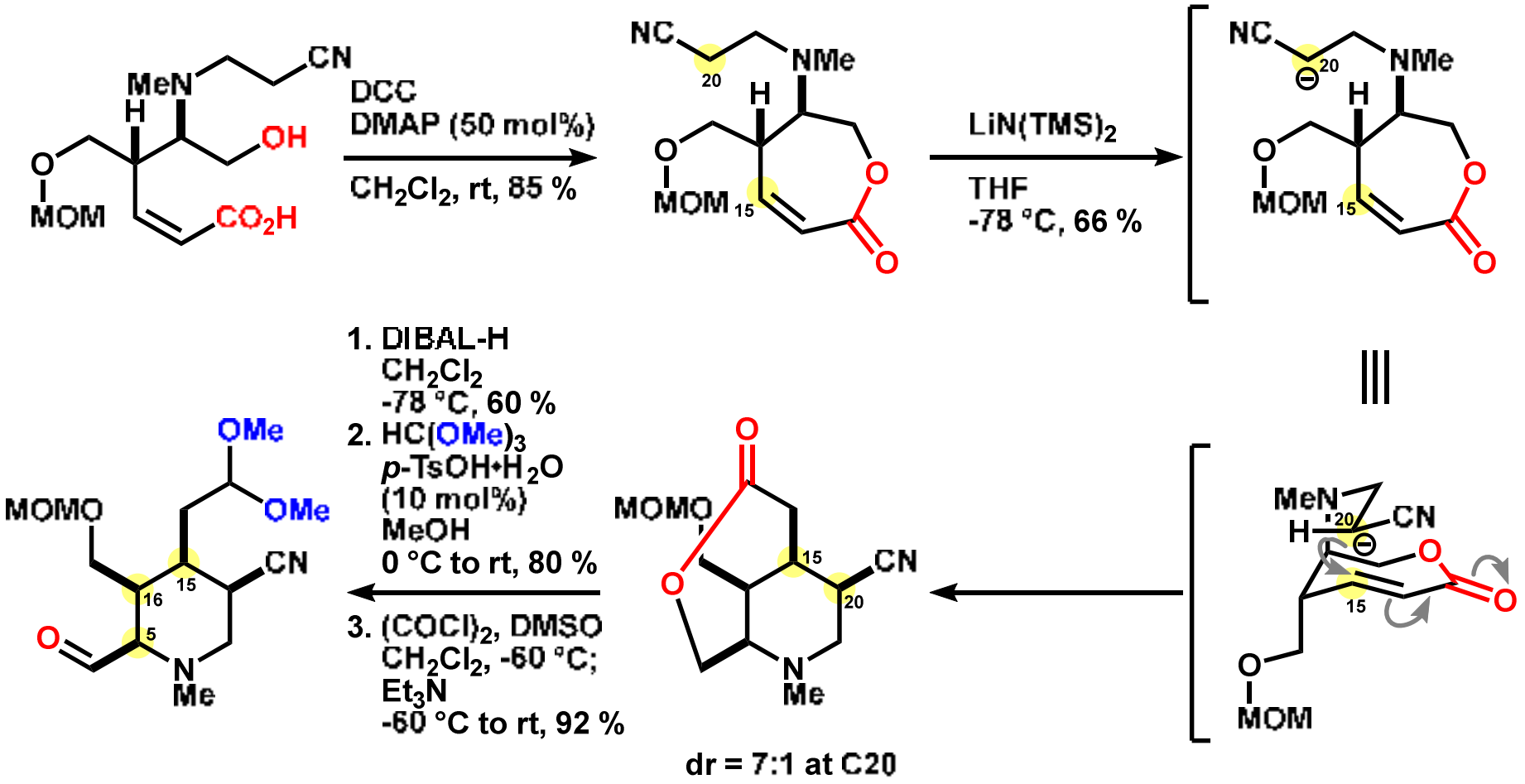

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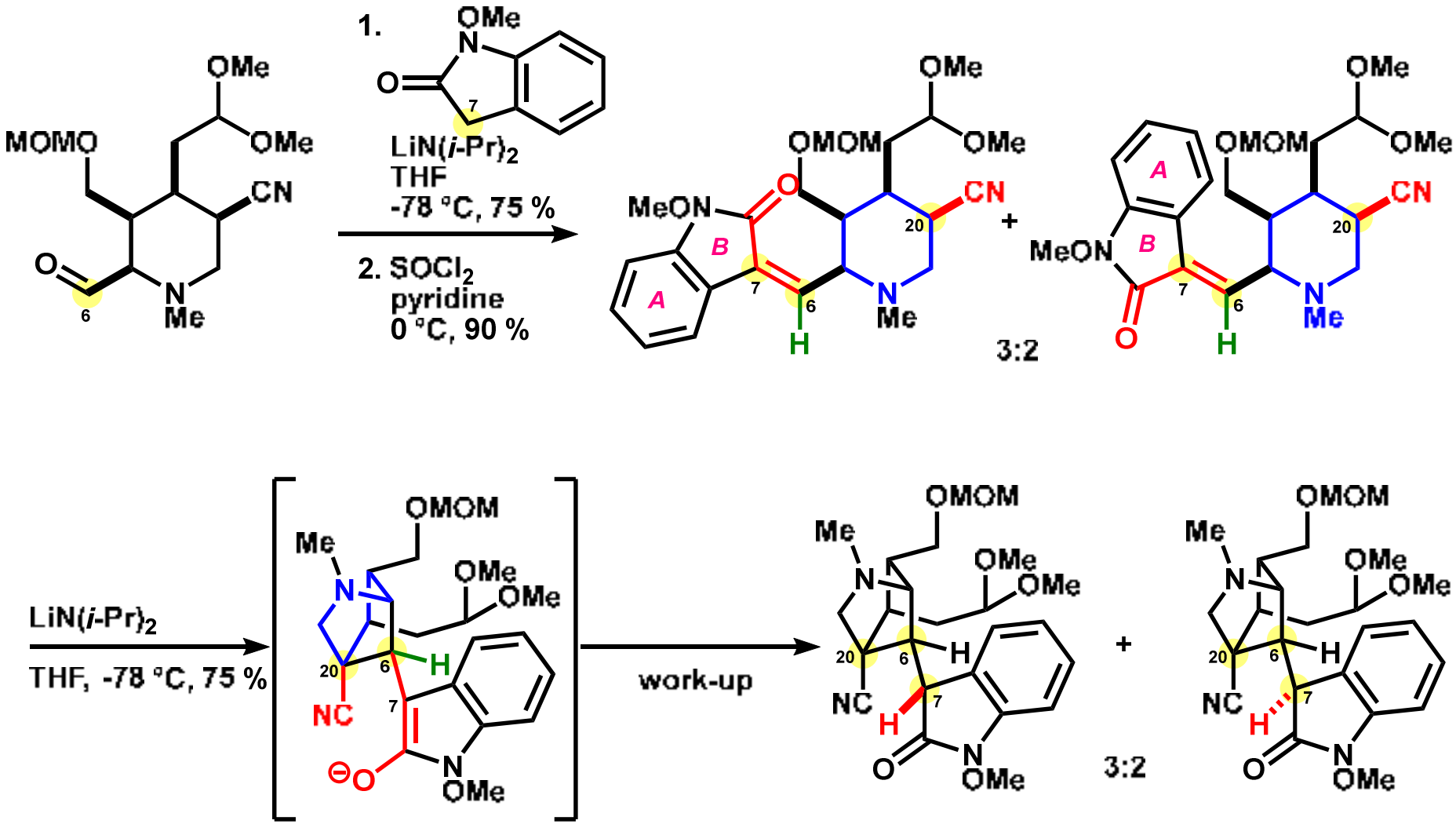
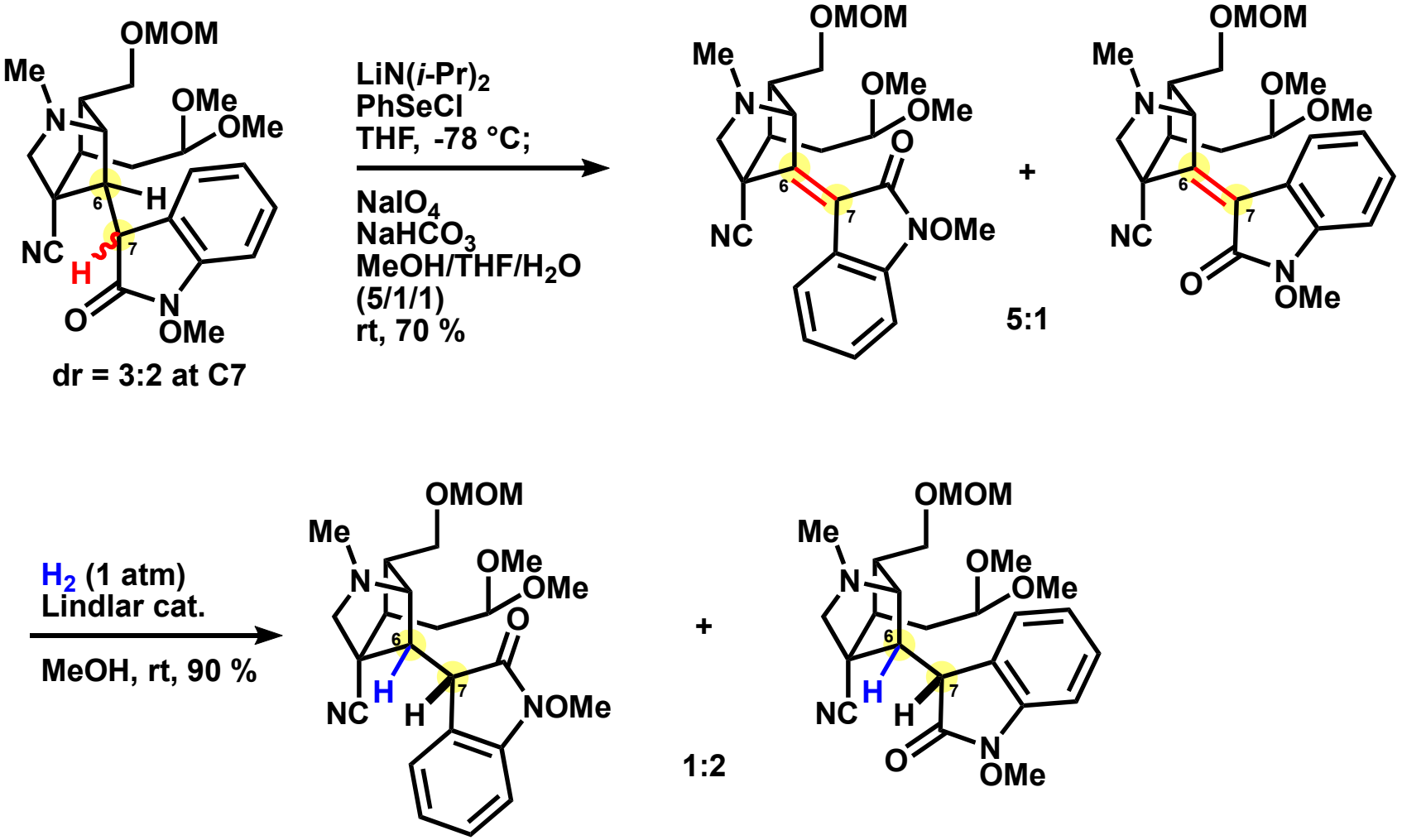
Intramolecular aldol reaction



Zhou, X.; Xiao, T.; Iwama, Y.; Qin, Y. *Angew. Chem. Int. Ed*. **2012**, *51*, 4909.

Inversion of C6 stereocenter



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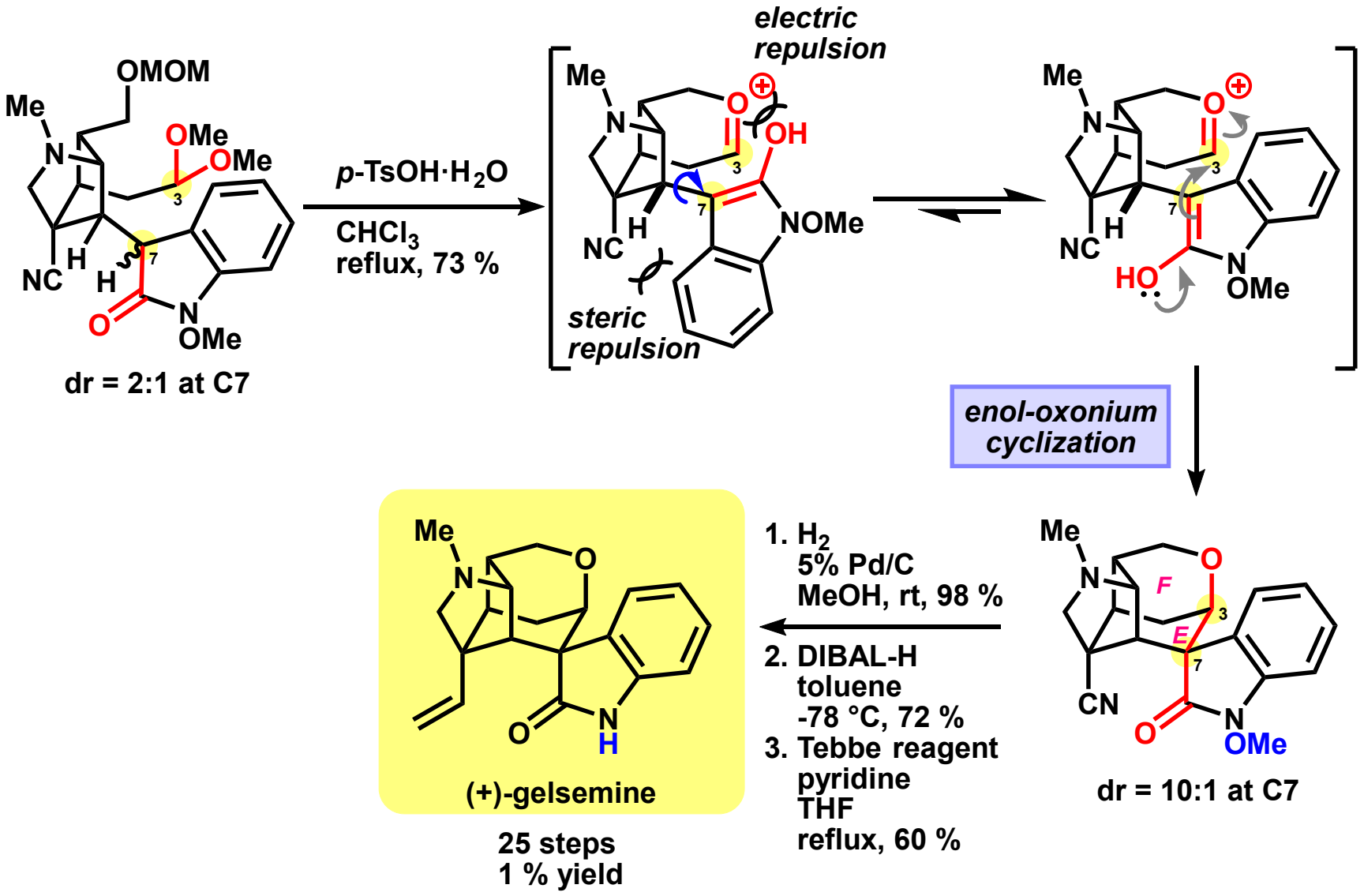
Completion of total synthesis



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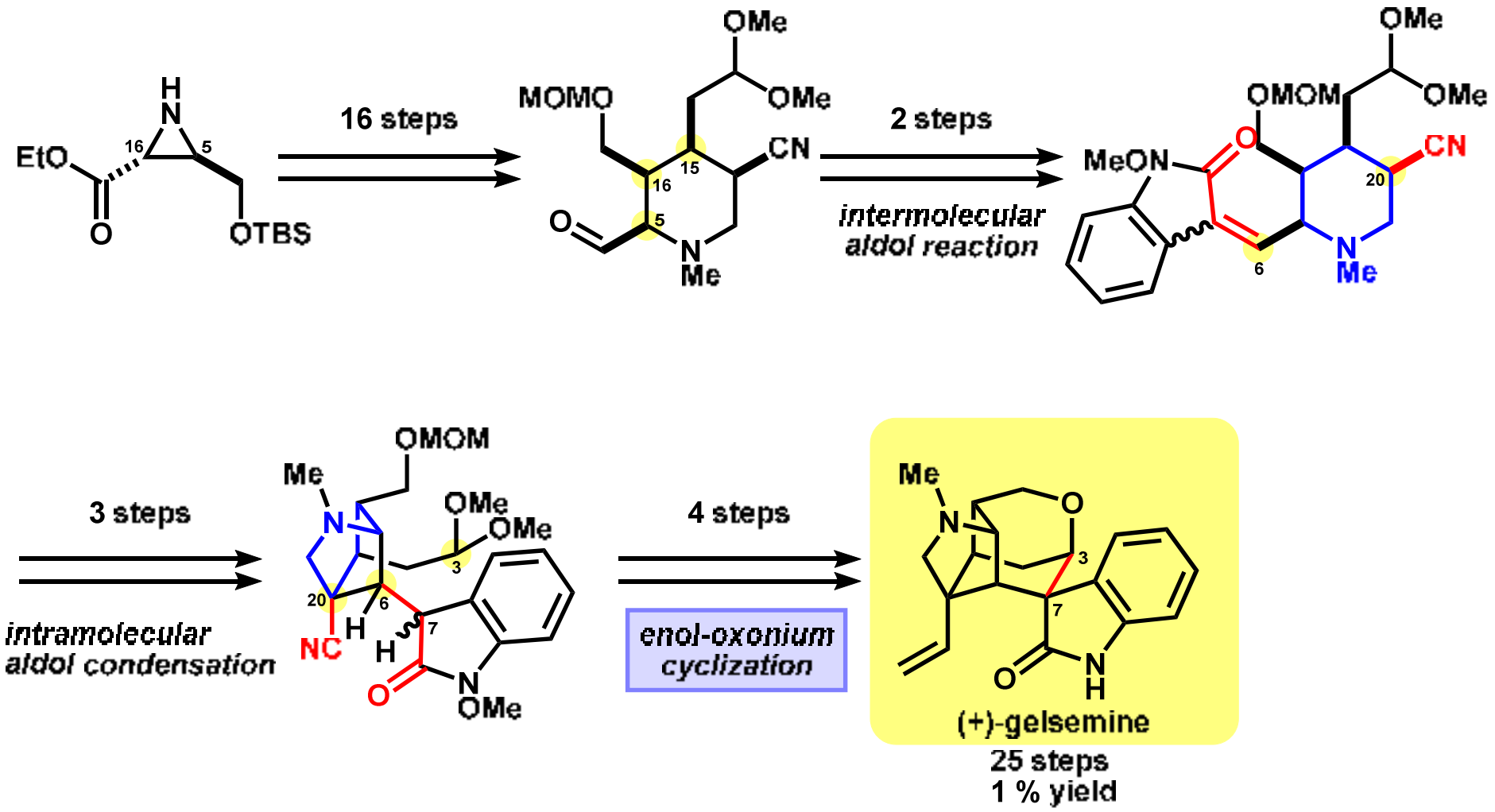
Summary of Qin's synthesis



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Qiu's synthesis

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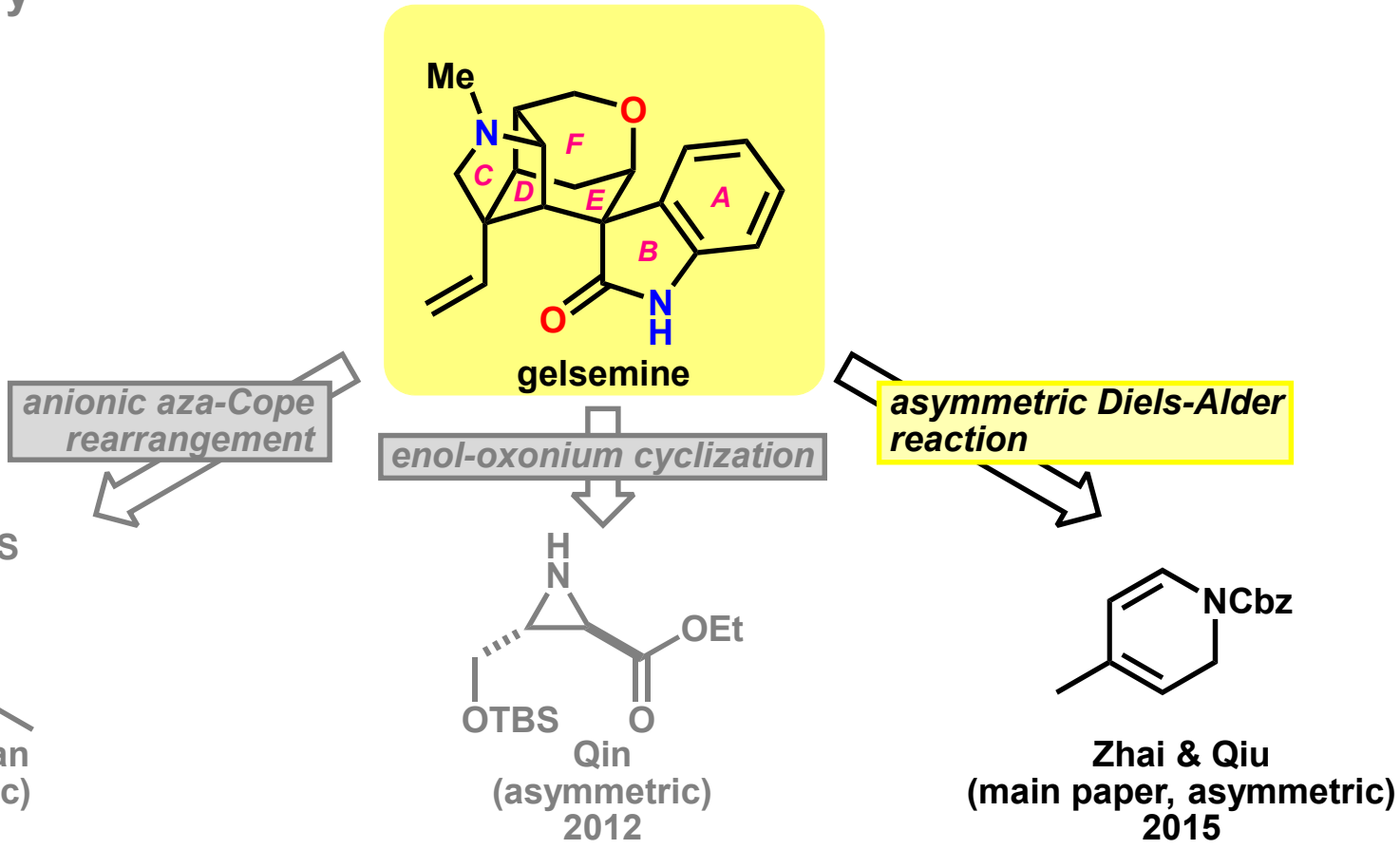
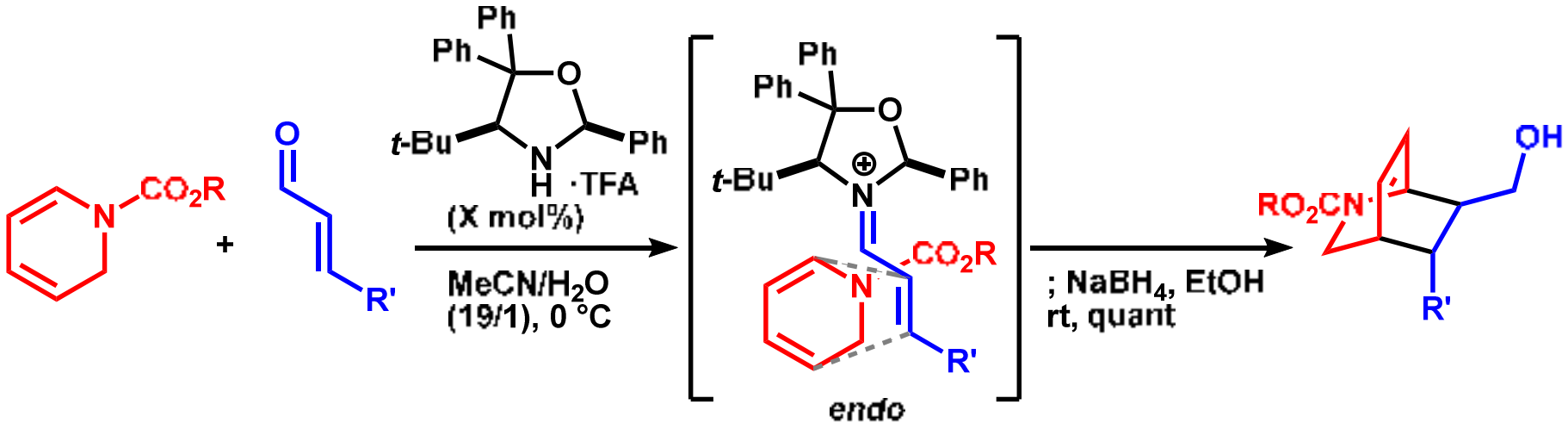


Oxazolidine catalyzed asymmetric Diels-Alder reaction

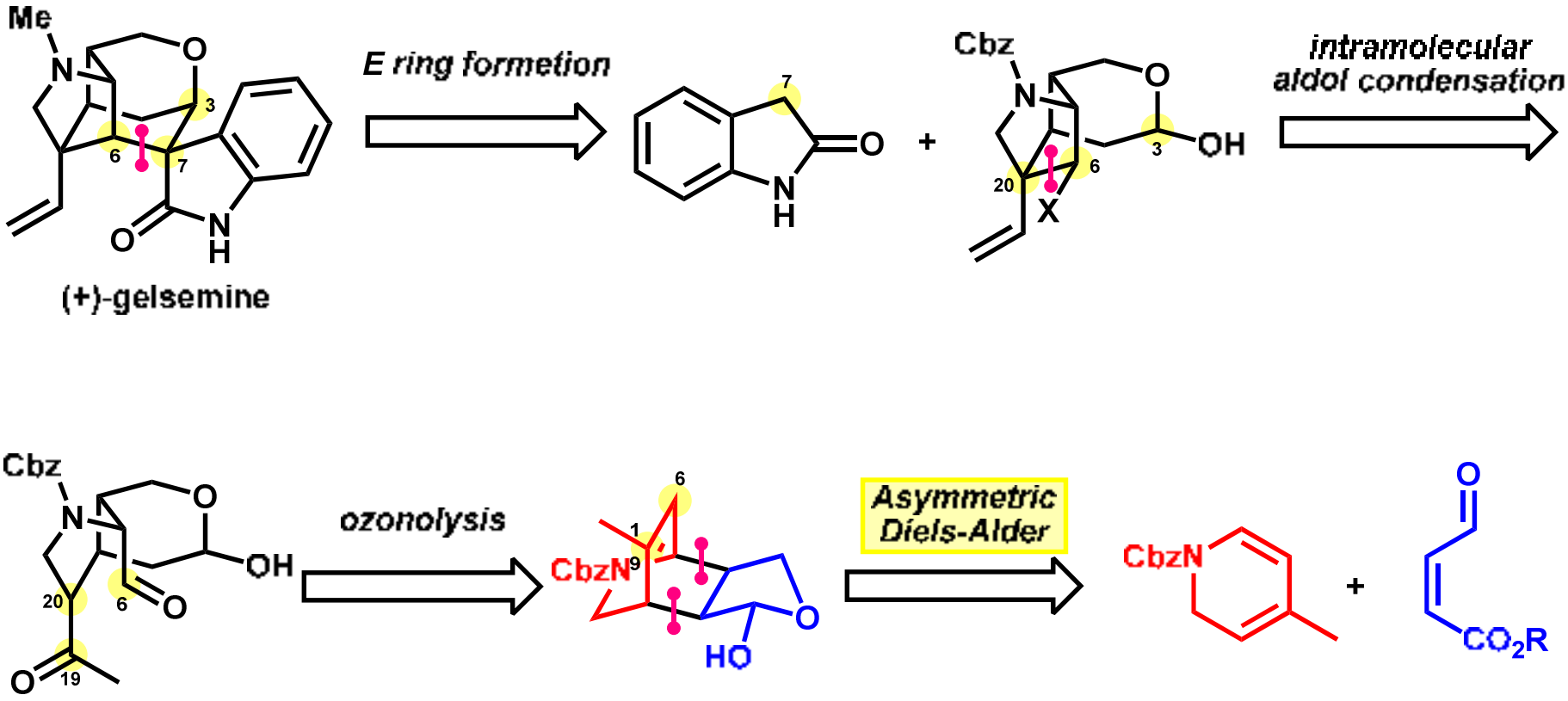


entry	X (mol%)	R	R'	yield	ee (*endo*)
1	10	Ph	H	71	>99
2	10	Bn	H	90	>99
3	5	Bn	H	61	97
4	2.5	Bn	H	44[a]	85
5	10	*t*-Bu	H	51	>99
6	10	Ph	CO_2Me	68	>99
7	10	Bn	CO_2Me	83	>99

[a] *endo* : *exo* = 2:1

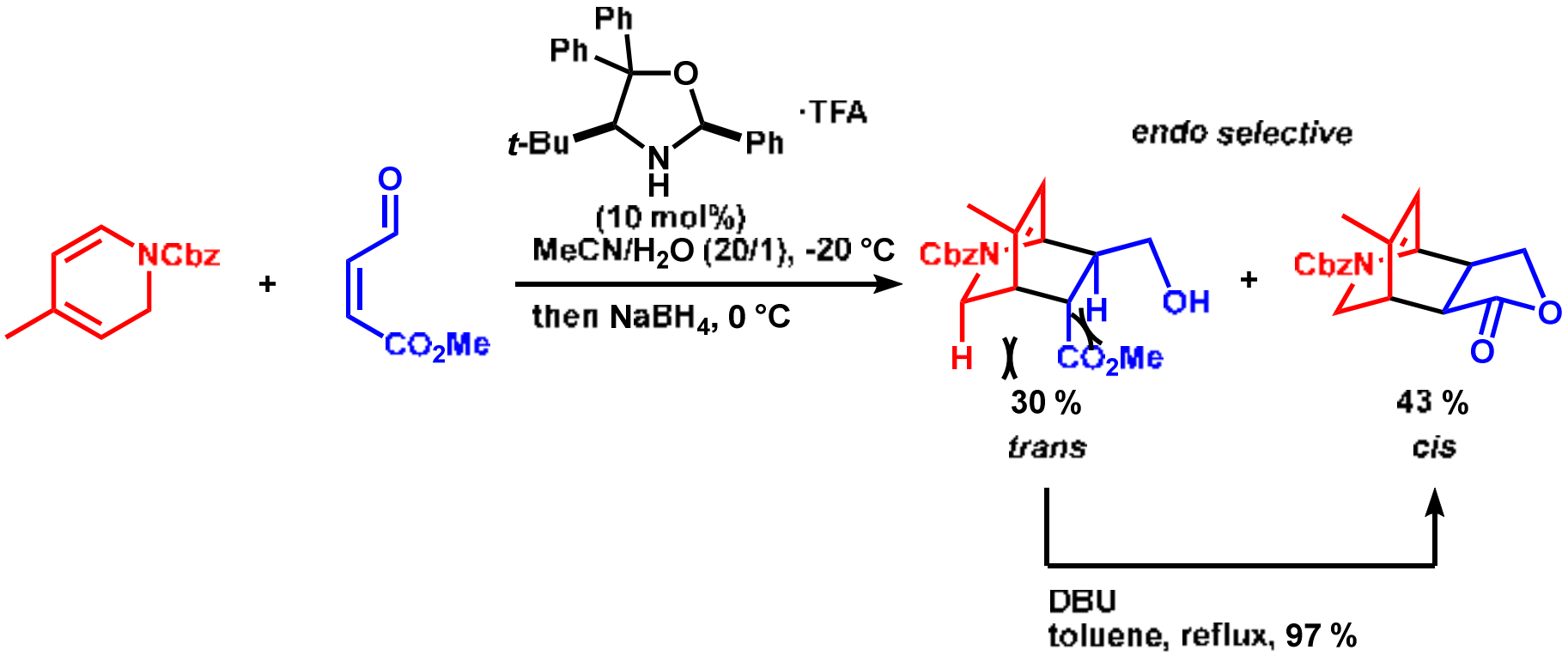
Nakano, H. *et al. Chem. Commun*. **2010**, *46*, 4827

Retrosynthetic analysis



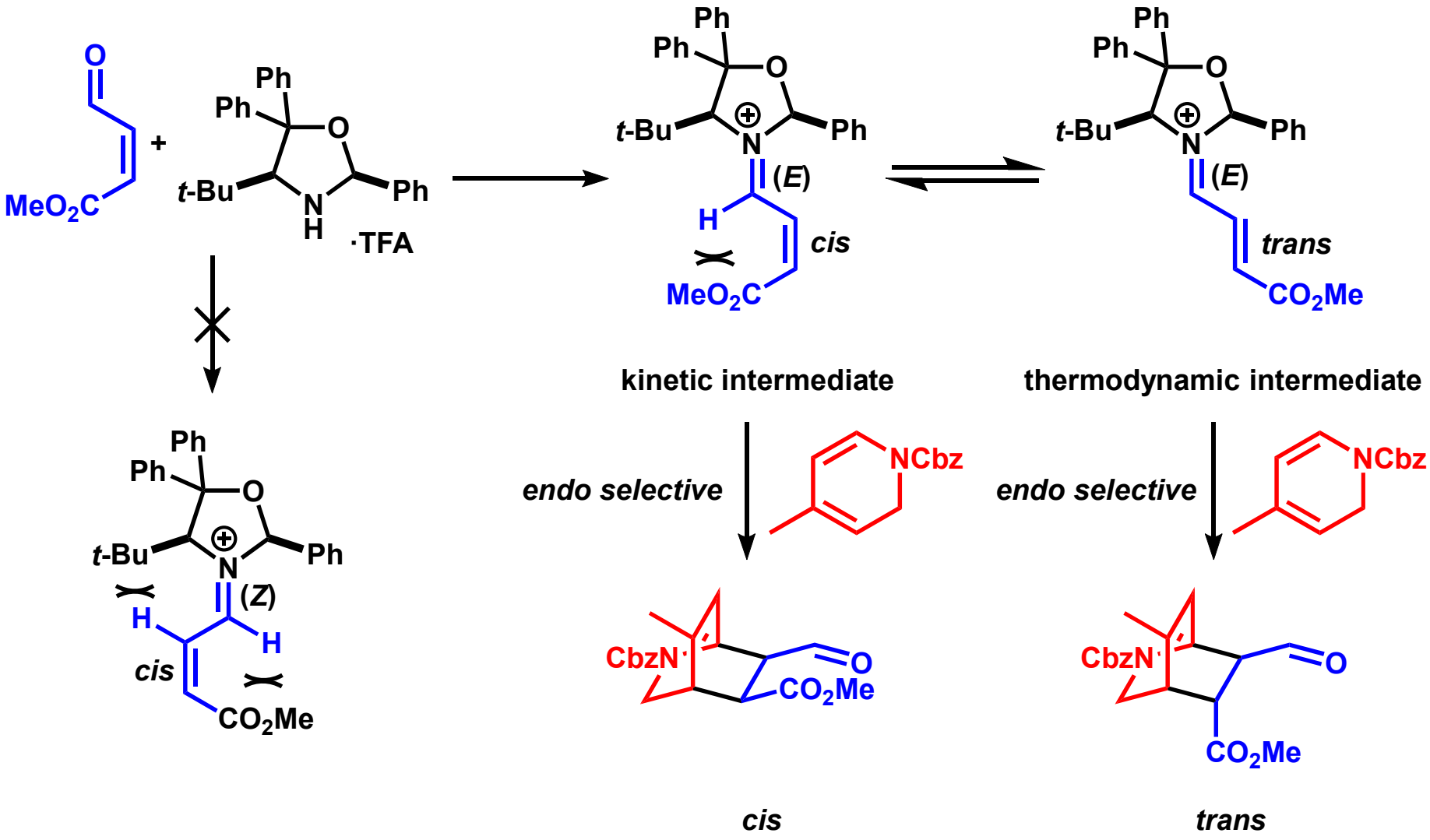
Chen, D.; Duan, S.; Tao, C.; Zhai, H.; Qui, F. G. *Nature. Commun.* **2015**, *6*, 7204.

Asymmetric Diels-Alder reaction



Chen, D.; Duan, S.; Tao, C.; Zhai, H.; Qui, F. G. *Nature. Commun.* **2015**, *6*, 7204.

Stereoselectivity of Diels-Alder reaction



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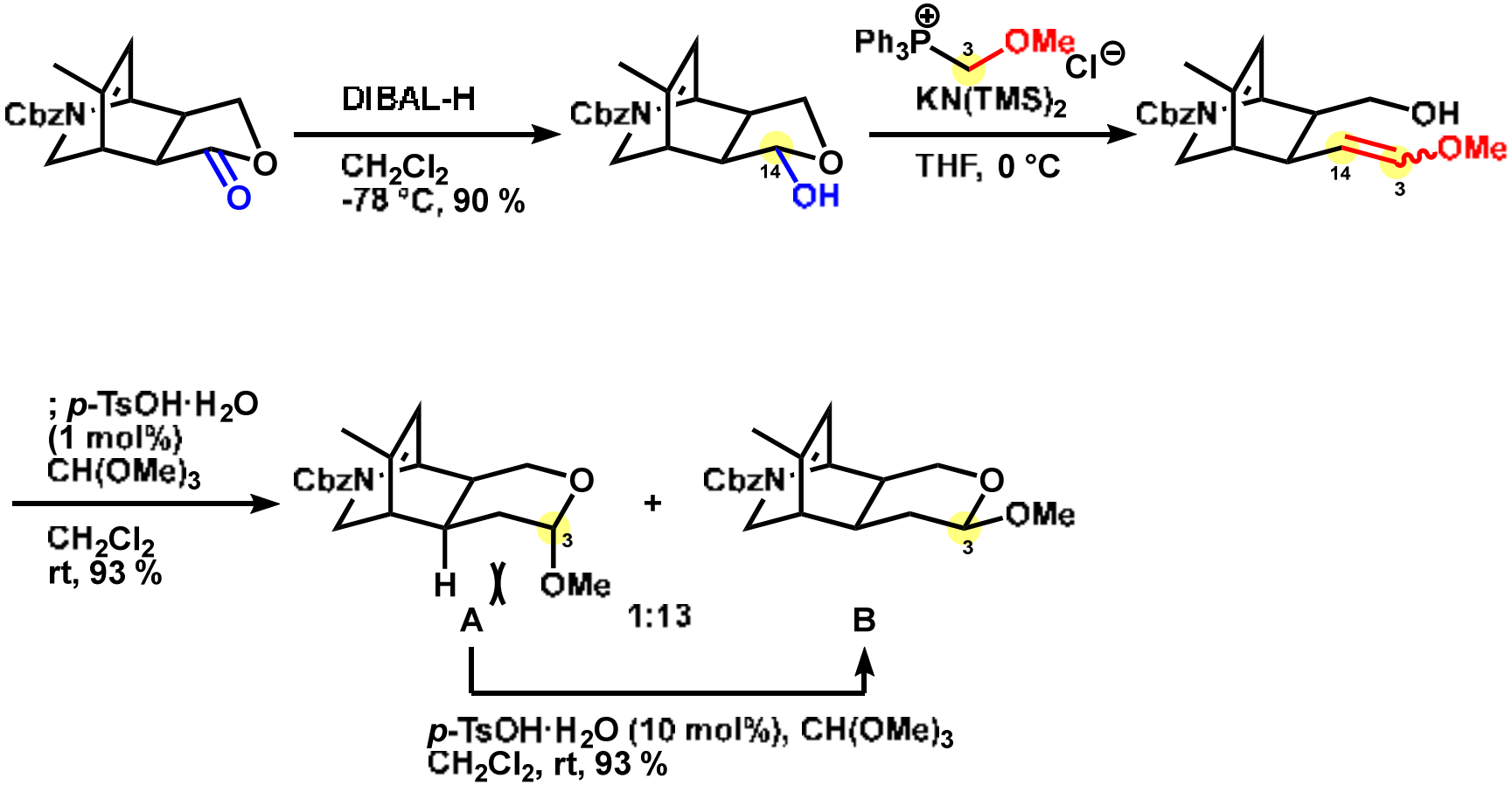
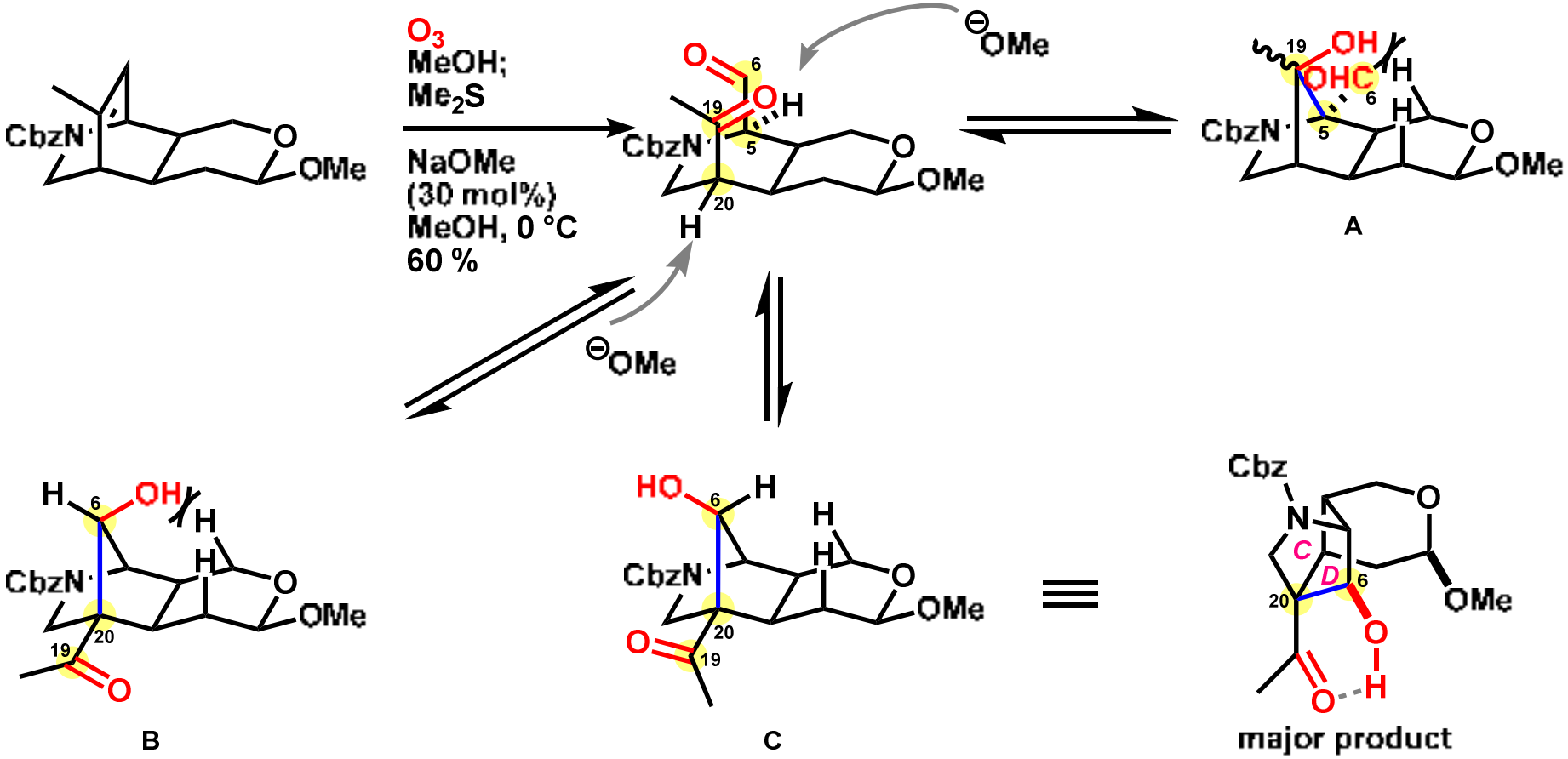
Construction of F ring

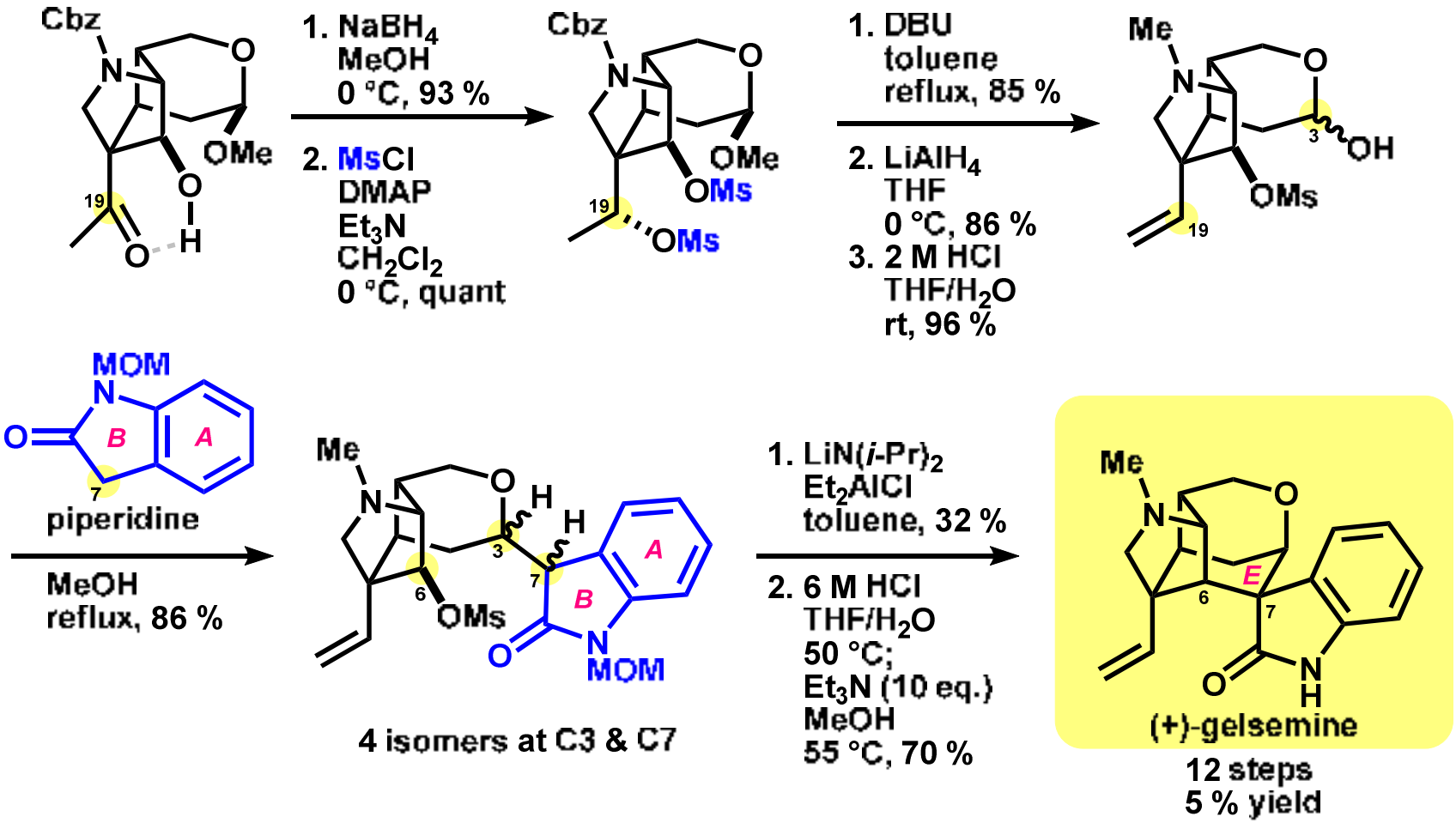


Chen, D.; Duan, S.; Tao, C.; Zhai, H.; Qui, F. G. *Nature. Commun.* **2015**, *6*, 7204.

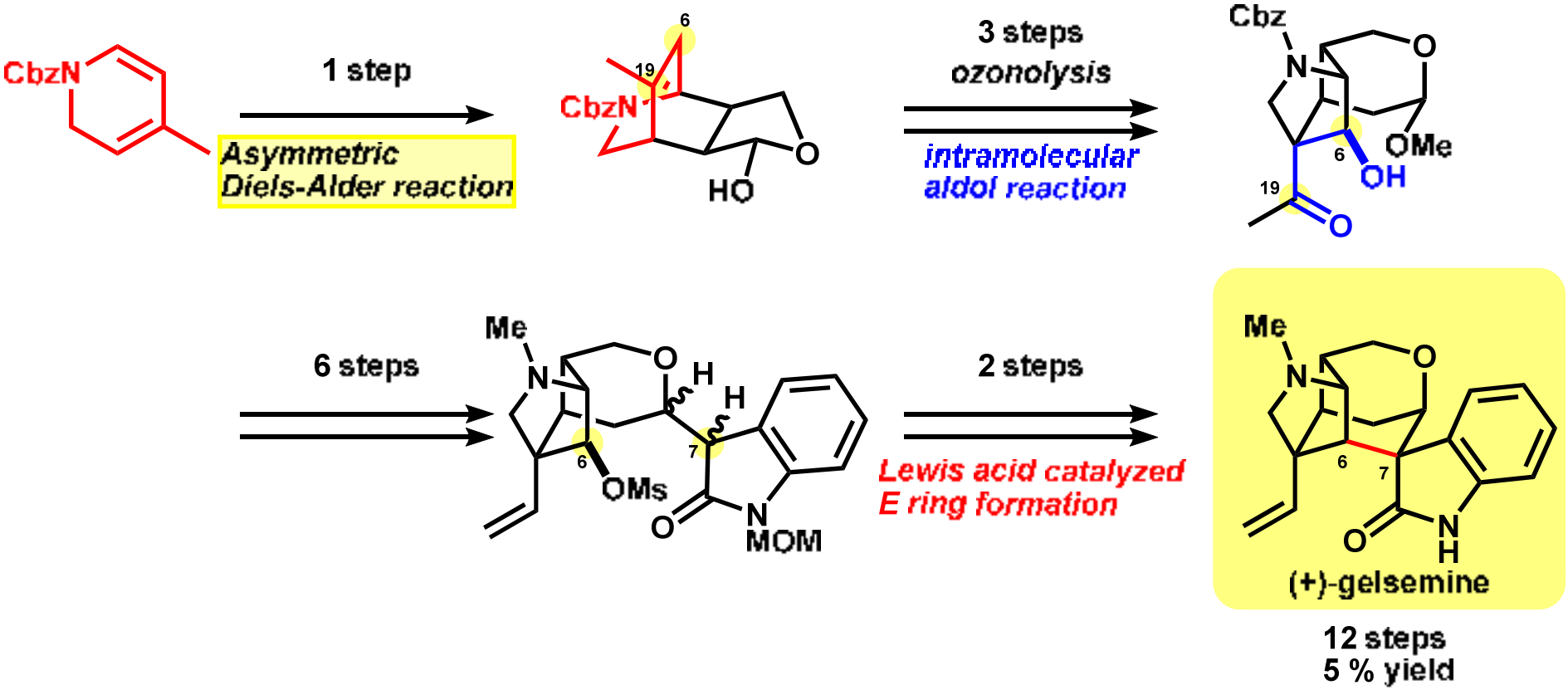
Ozonolysis & intramolecular aldol reaction



Completion of total synthesis



Summary of Qiu's synthesis



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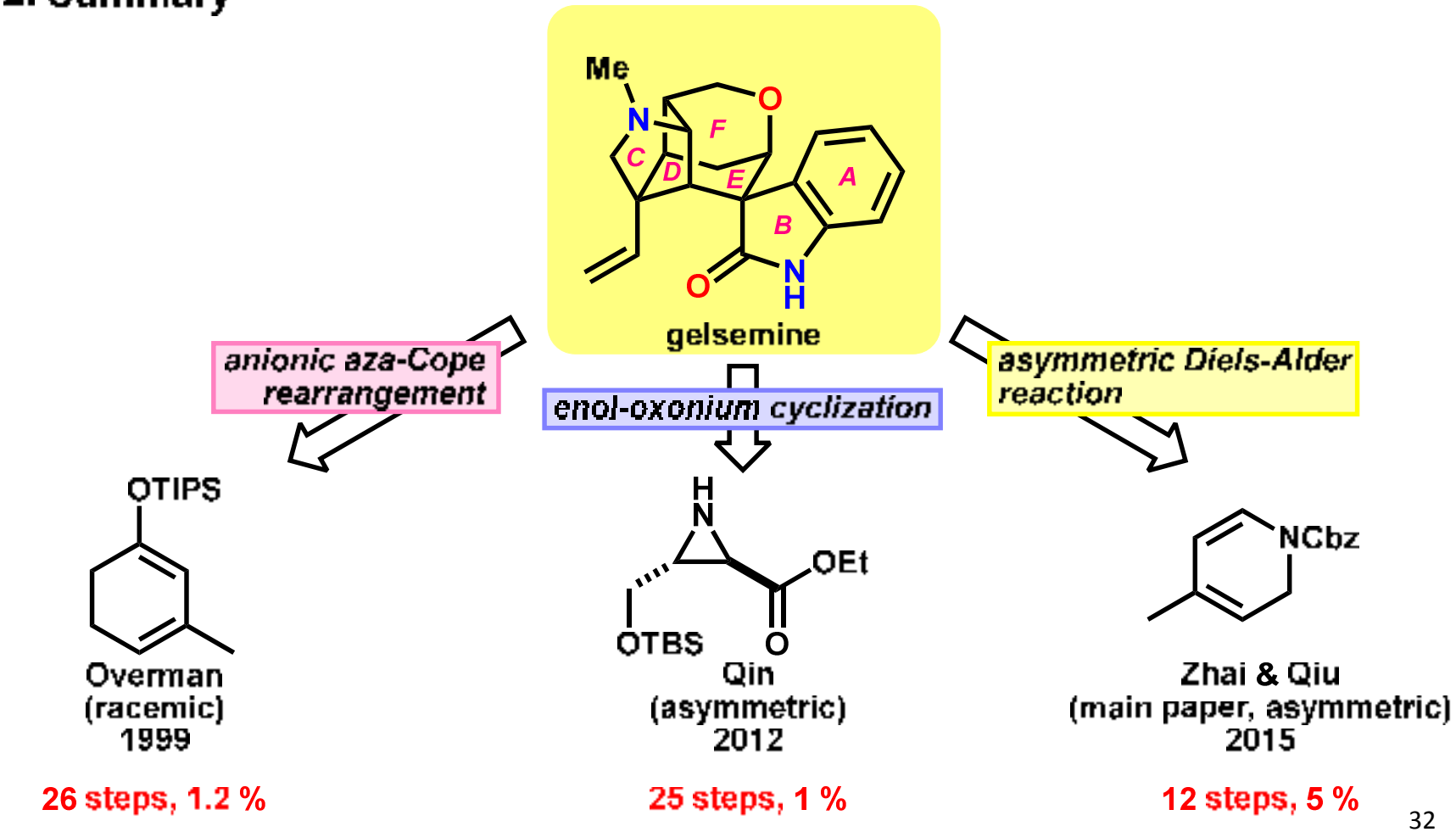
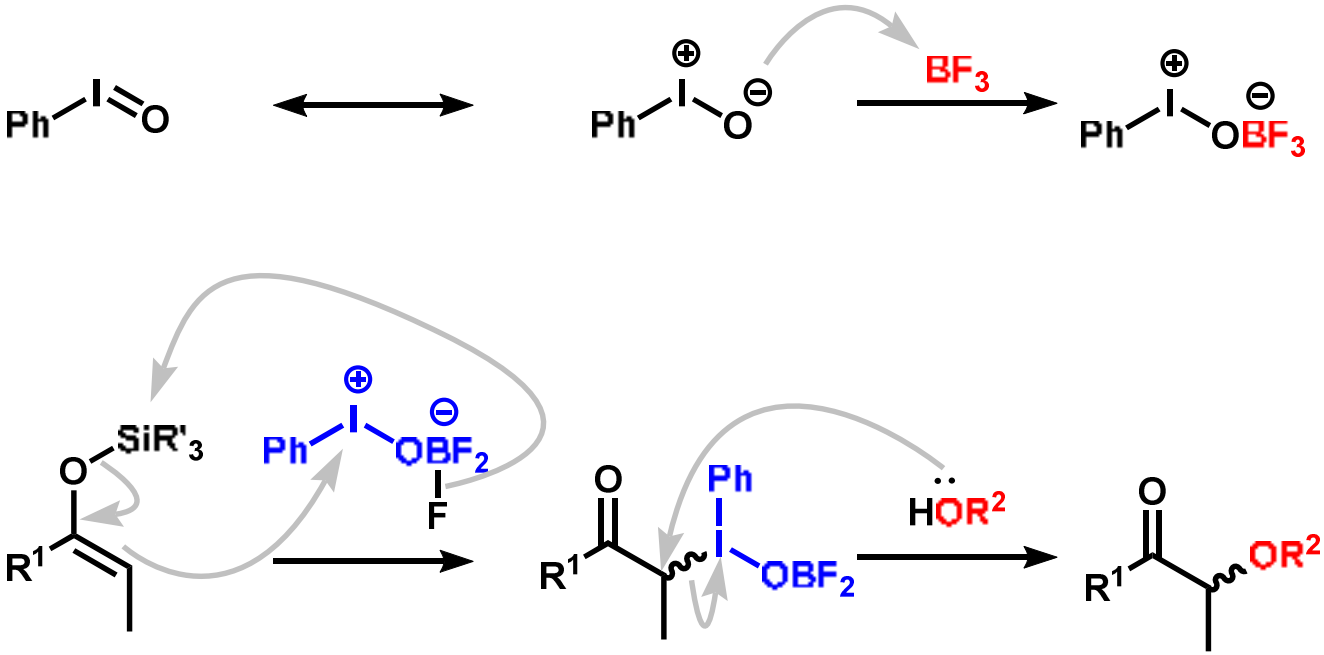


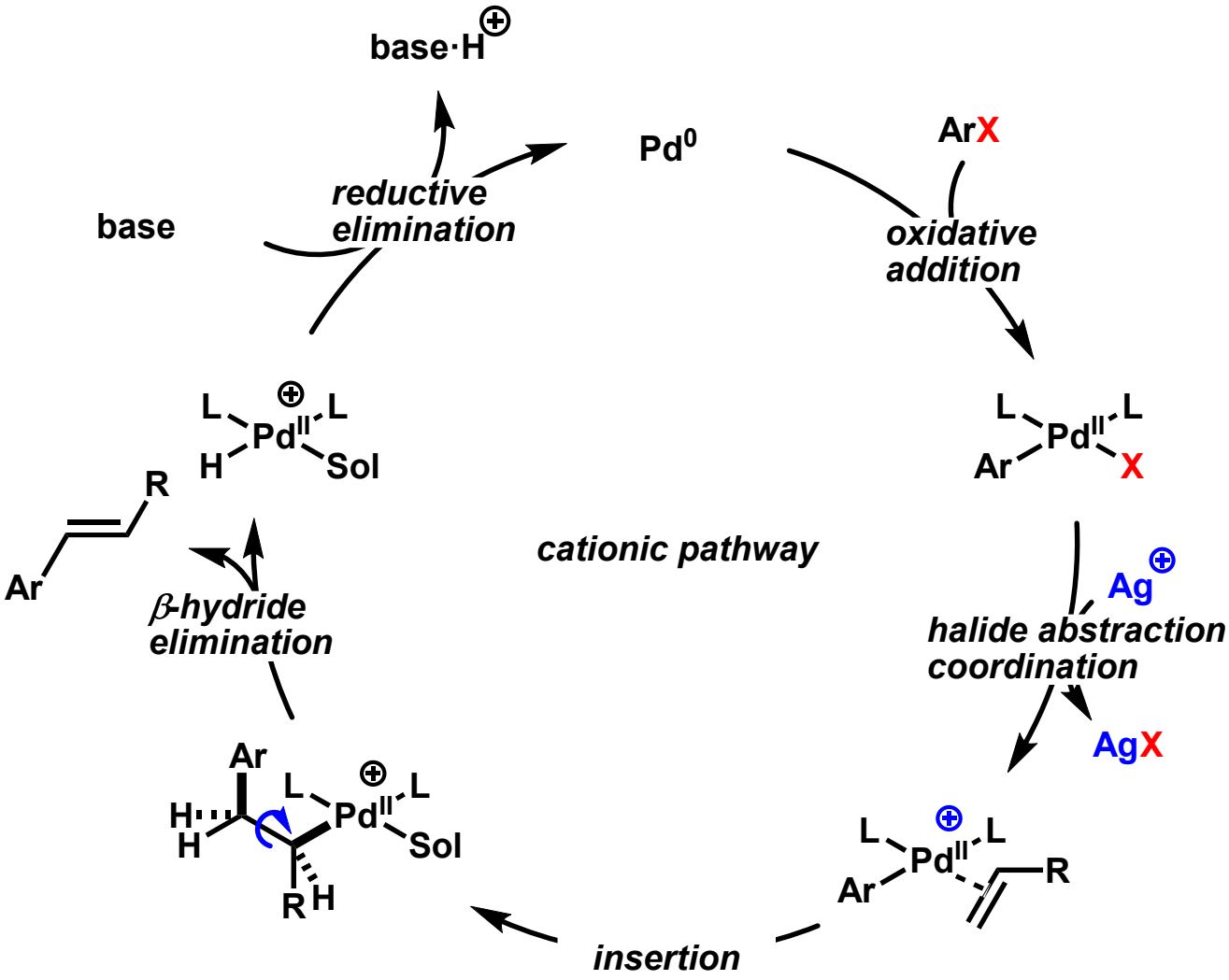
Appendix

Oxidation of silyl enol ether with iodosobenzene



Moriarty, R. M.; Prakash, O.; Duncan, M. P.; Vaid, R. K. *J. Org. Chem.* **1987**, *52*, 150

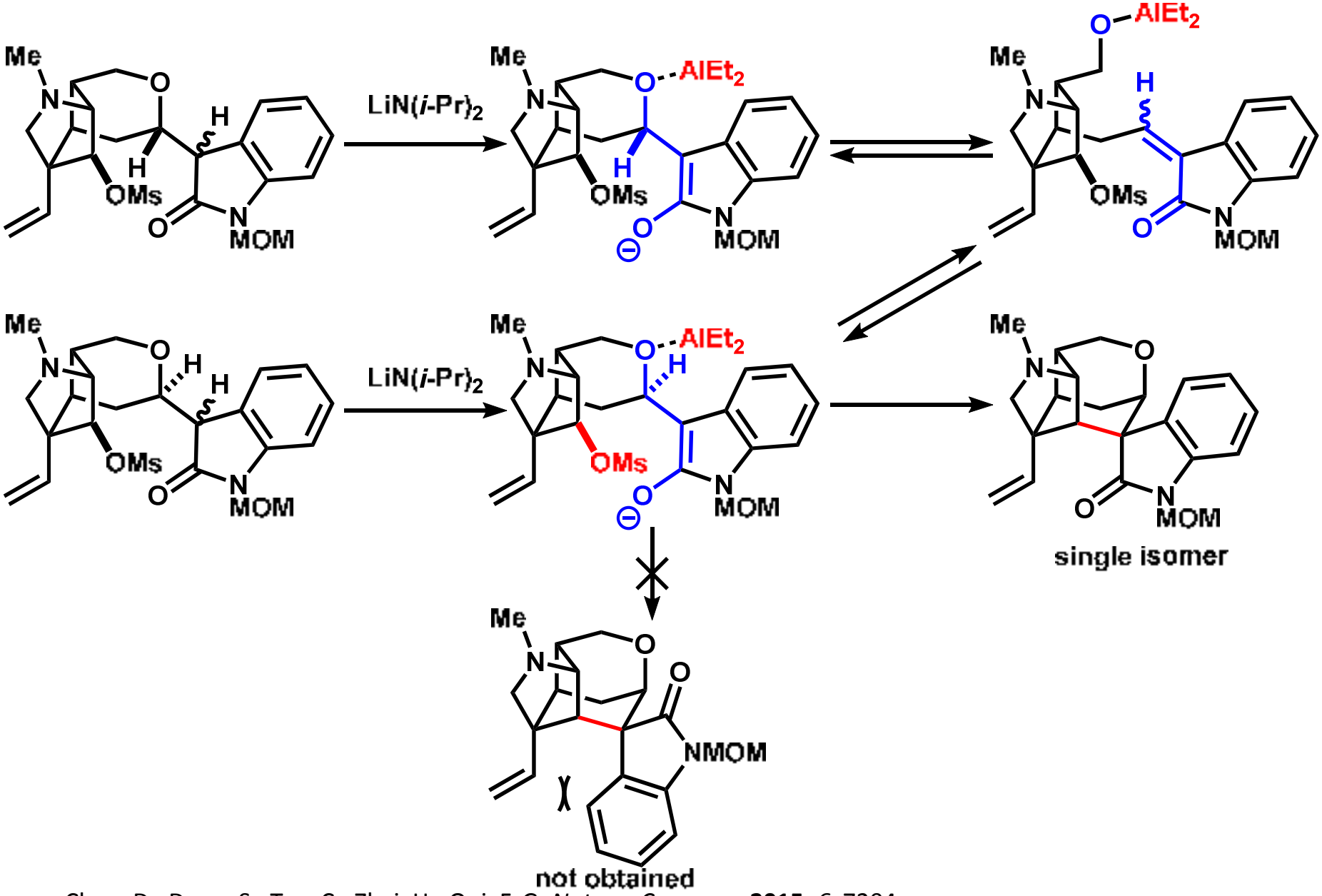
Heck reaction with silver salt



Cabri, W. *et al. J. Org. Chem*. **1991**, *56*, 5796

Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc*. **1991**, *113*, 1417

Lewis acid catalyzed SN2 substitution



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