

The application of [5+2] cycloadditions in natural product synthesis

Reporter: Baochao Yang

December 09, 2021

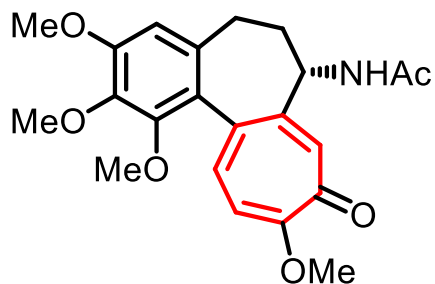
Index

- **Introduction**
- **Main Contents**
 - **Oxidopyrylium-mediated [5+2]cycloaddition**
 - **Pyridinium and quinolinium-mediated [5+2] cycloadditions**
 - **Perezzone-type [5+2] cycloadditions**
 - **[5+2] cycloadditions of vinyl cyclopropanes (VCPs)**
 - **[5+2] cycloadditions of five-carbon organometallic complexes**
- **Summary**

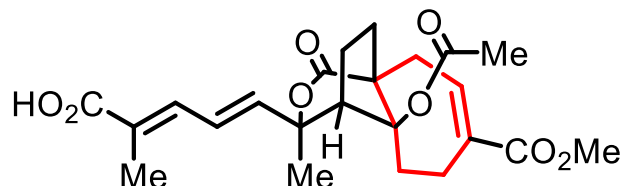
Index

- **Introduction**
- **Main Contents**
 - Oxidopyrylium-mediated [5+2]cycloaddition
 - Pyridinium and quinolinium-mediated [5+2] cycloadditions
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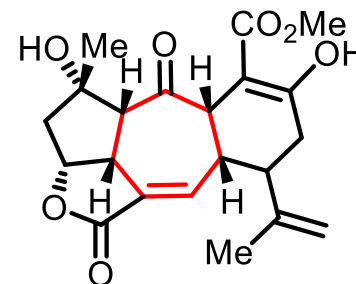
Selected natural products containing seven-membered ring skeleton



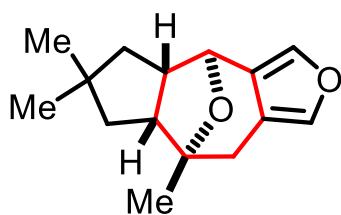
(-)-colchicine



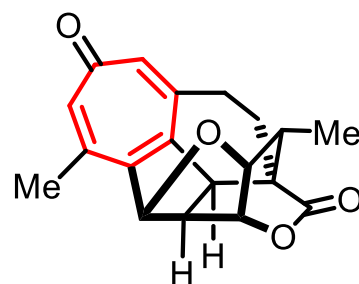
pseudolaric acid B



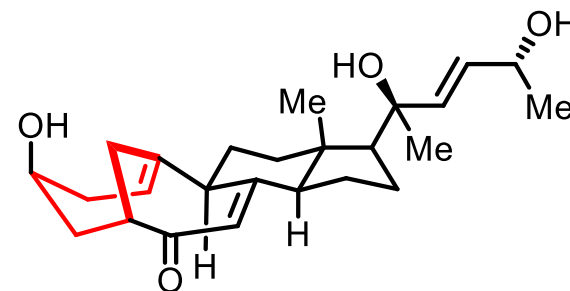
rameswaralide



furanether B



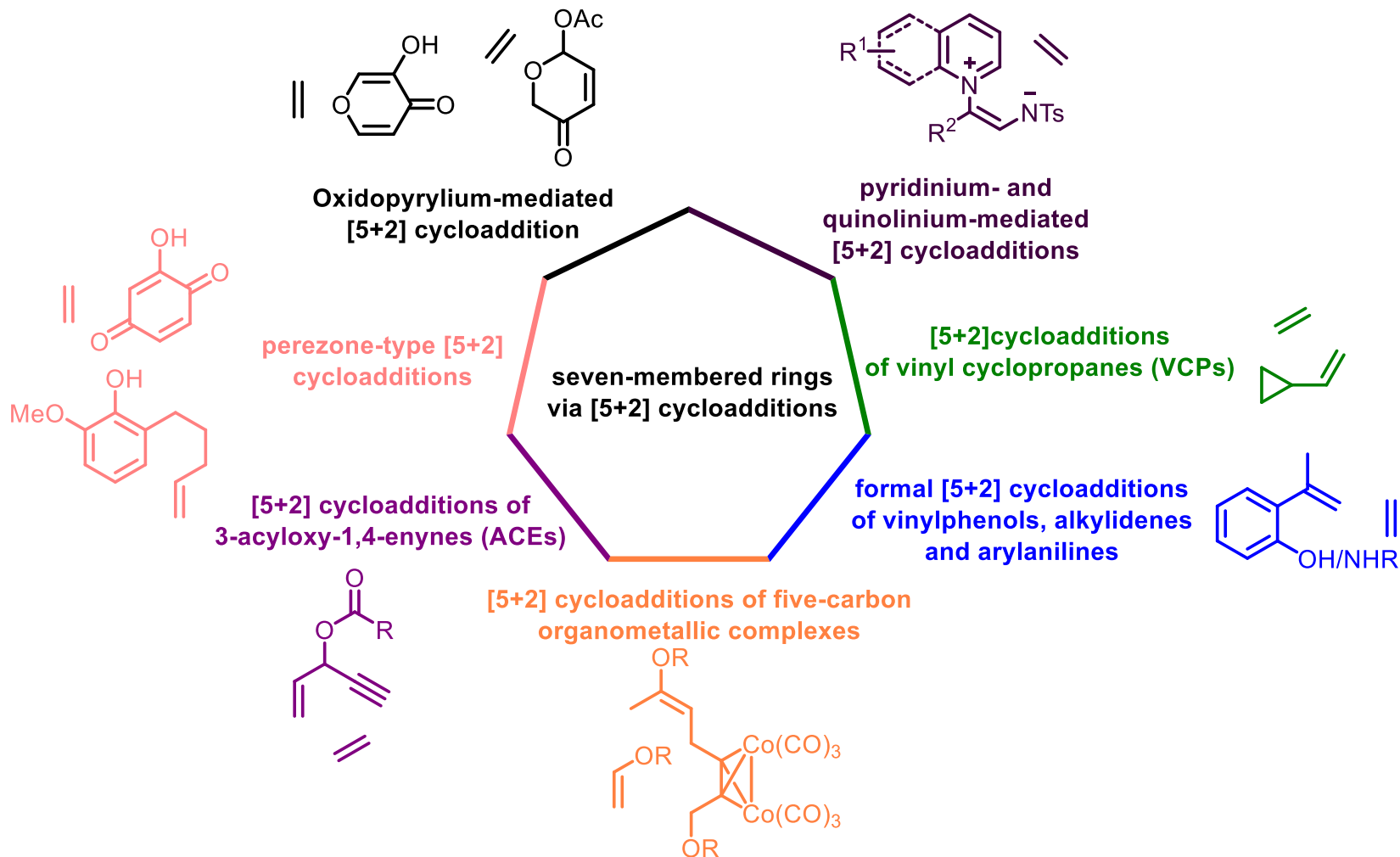
harringtonolide



cyclocitrinol

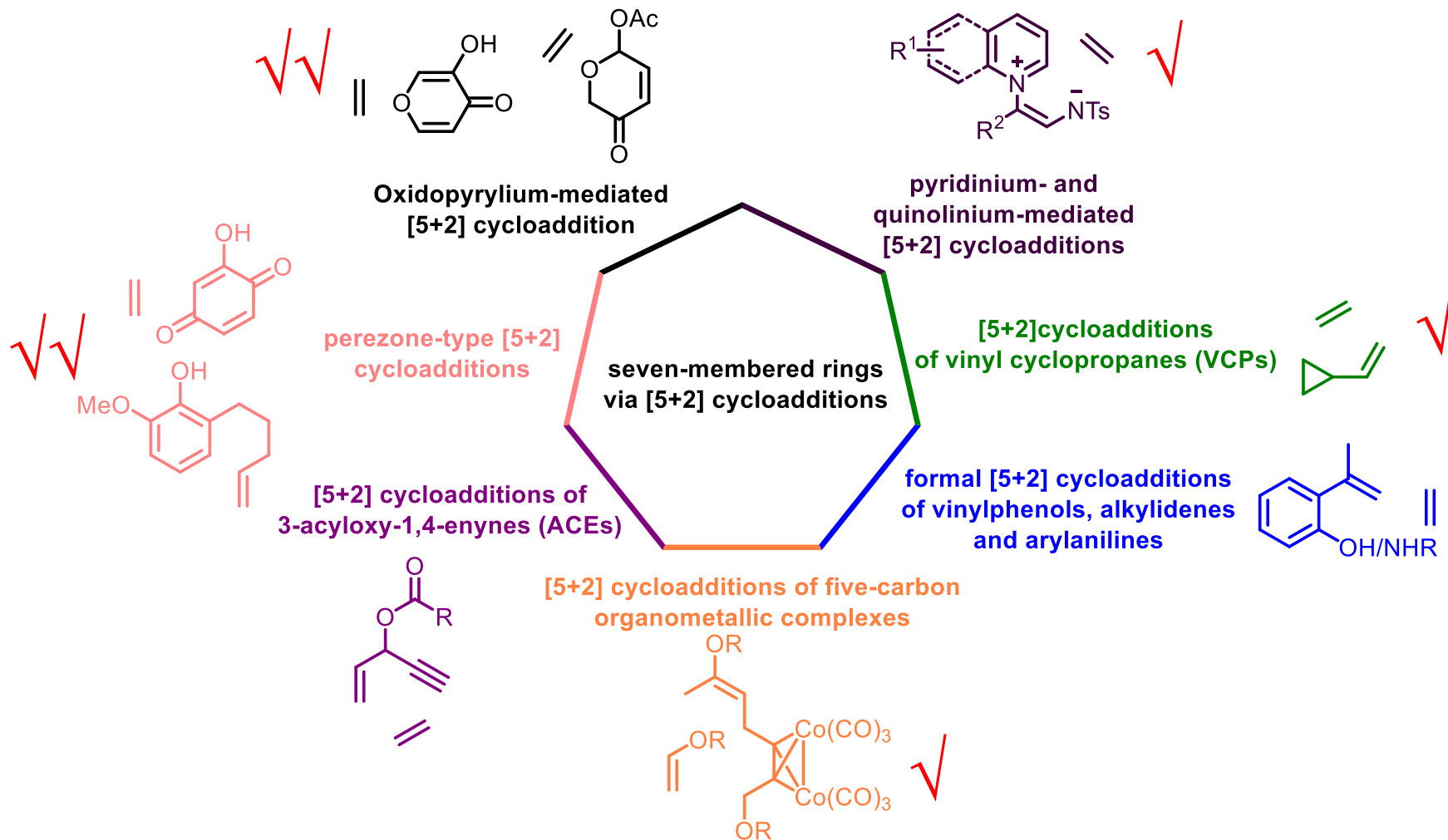
Among them, the most famous molecule is Colchicine, which is a commonly used drug in the treatment of gout.

Main type of intermediates involved in [5+2] cycloadditions



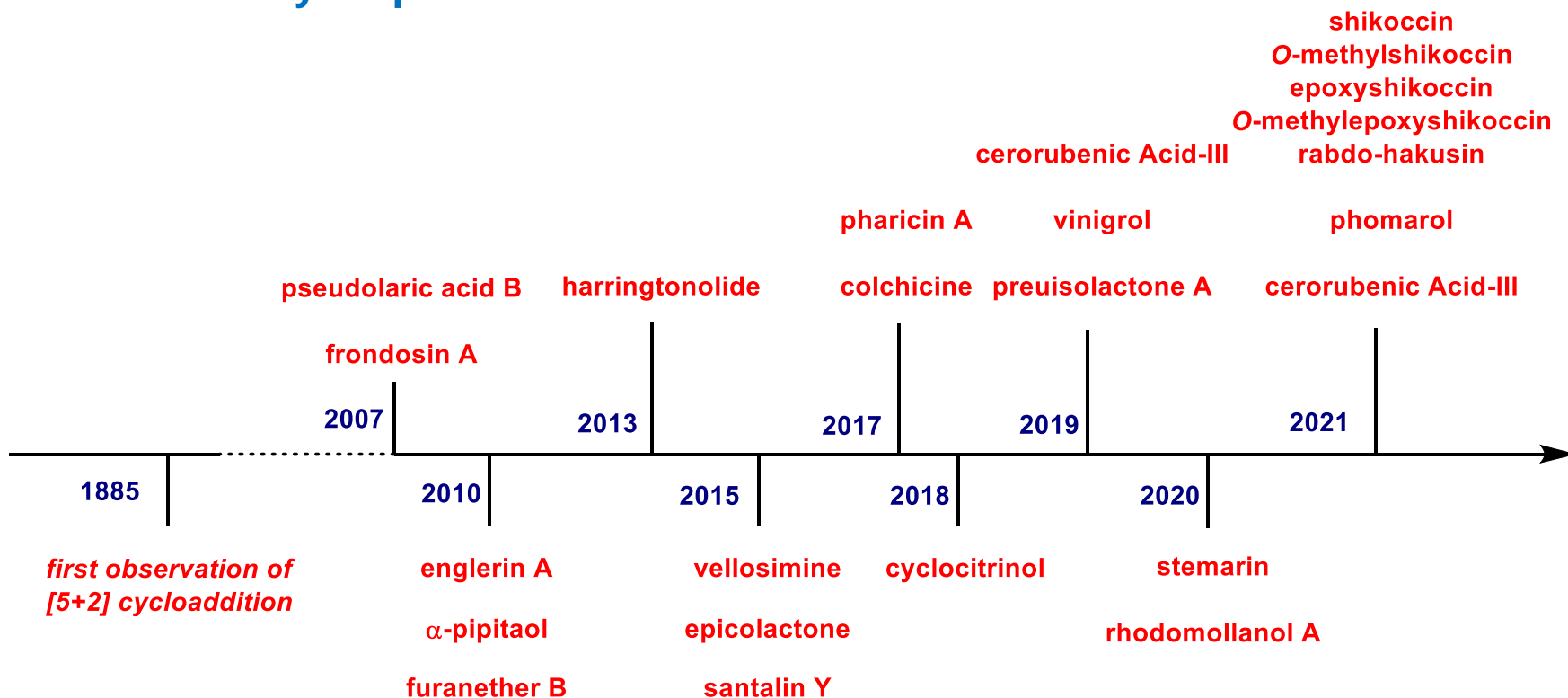
(a) H. Pellissier, *Adv. Synth. Catal.* **2018**, *360*, 1551. (b) K. E. O. Ylijoki, J. M. Stryker, *Chem. Rev.* **2013**, *113*, 2244. (c) K. Gao, Y.-G. Zhang, Z. Wang, H. Ding, *Chem. Commun.* **2019**, *55*, 1859. (d) L. Min, X. Liu, C.-C. Li, *Acc. Chem. Res.* **2020**, *53*, 703. (e) X. Liu, Y.-J. Hu, J.-H. Fan, J. Zhao, S. Li, C.-C. Li, *Org. Chem. Front.* **2018**, *5*, 1217.

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(a) H. Pellissier, *Adv. Synth. Catal.* **2018**, *360*, 1551. (b) K. E. O. Ylijoki, J. M. Stryker, *Chem. Rev.* **2013**, *113*, 2244. (c) K. Gao, Y.-G. Zhang, Z. Wang, H. Ding, *Chem. Commun.* **2019**, *55*, 1859. (d) L. Min, X. Liu, C.-C. Li, *Acc. Chem. Res.* **2020**, *53*, 703. (e) X. Liu, Y.-J. Hu, J.-H. Fan, J. Zhao, S. Li, C.-C. Li, *Org. Chem. Front.* **2018**, *5*, 1217.

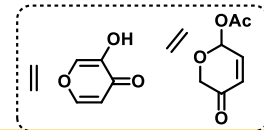
From 2008 to 2021, Natural products were synthesized by [5+2] cycloaddition reaction as a key step



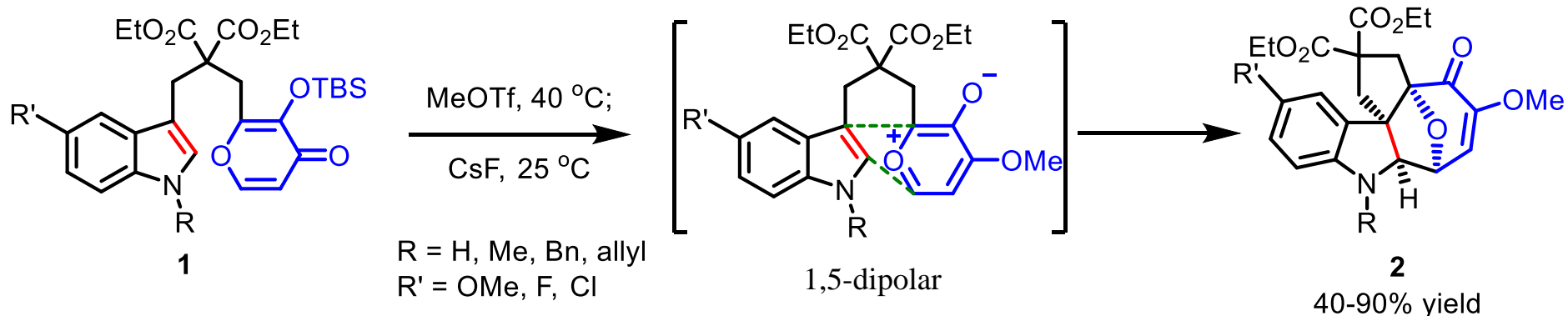
For reviews, see: (a) K. E. O. Ylijoki, J. M. Stryker, *Chem. Rev.* **2013**, *113*, 2244. (b) L. Min, X. Liu, C.-C. Li, *Acc. Chem. Res.* **2020**, *53*, 703. (c) X. Liu, Y.-J. Hu, J.-H. Fan, J. Zhao, S. Li, C.-C. Li, *Org. Chem. Front.* **2018**, *5*, 1217. (d) L. Min, Y.-J. Hu, J.-H. Fan, W. Zhang, C.-C. Li, *Chem. Soc. Rev.* **2020**, *49*, 7015. (e) K. Gao, Y.-G. Zhang, Z. Wang, H. Ding, *Chem. Commun.* **2019**, *55*, 1859. For selected examples, see: (f) J. Hu, Z. Jia, K. Xu, H. Ding, *Org. Lett.* **2020**, *22*, 1426. (g) B. Wang, Z. Liu, Z. Tong, B. Gao, H. Ding, *Angew. Chem. Int. Ed.* **2021**, *60*, 14892. (h) J. Gao, P. Rao, K. Xu, S. Wang, Y. Wu, C. He, H. Ding, *J. Am. Chem. Soc.* **2020**, *142*, 4592. (i) X. Liu, J. Liu, J. Wu, G. Huang, R. Liang, L. Wa. Chung, C.-C. Li, *J. Am. Chem. Soc.* **2019**, *141*, 2872. (j) L. Min, X. Lin, C.-C. Li, *J. Am. Chem. Soc.* **2019**, *141*, 15773. (k) J.-H. Fan, J.-J. Wang, F. Li, G. Wang, Q. Guo, L. W. Chung, C.-C. Li, *CCS Chem.* **2021**, *3*, 348. (l) X. Liu, J. Liu, J. Wu, C.-C. Li, *J. Org. Chem.* **2021**, *86*, 11125. (m) A. J. E. Novak, C. E. Grigglesstone, D. Trauner, *J. Am. Chem. Soc.* **2019**, *141*, 15515. (n) B. M. Trost, Y. Hu, D. B. Horne, *J. Am. Chem. Soc.* **2007**, *129*, 11781. (o) B. M. Trost, J. Waser, A. Meyer, *J. Am. Chem. Soc.* **2007**, *129*, 14556.

Index

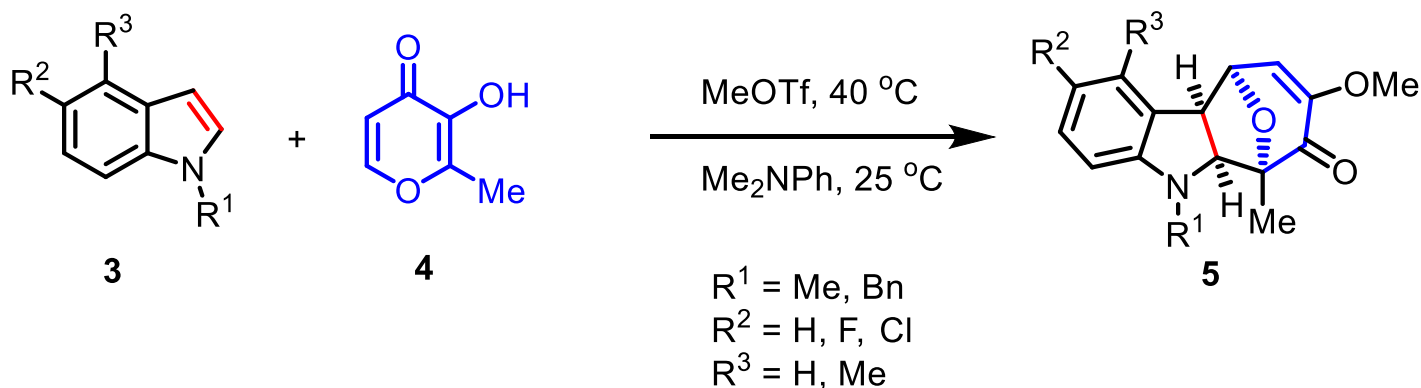
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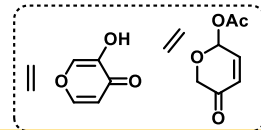
Intramolecular [5+2] cycloaddition



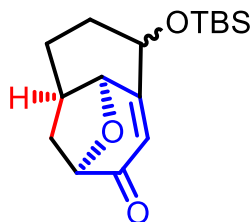
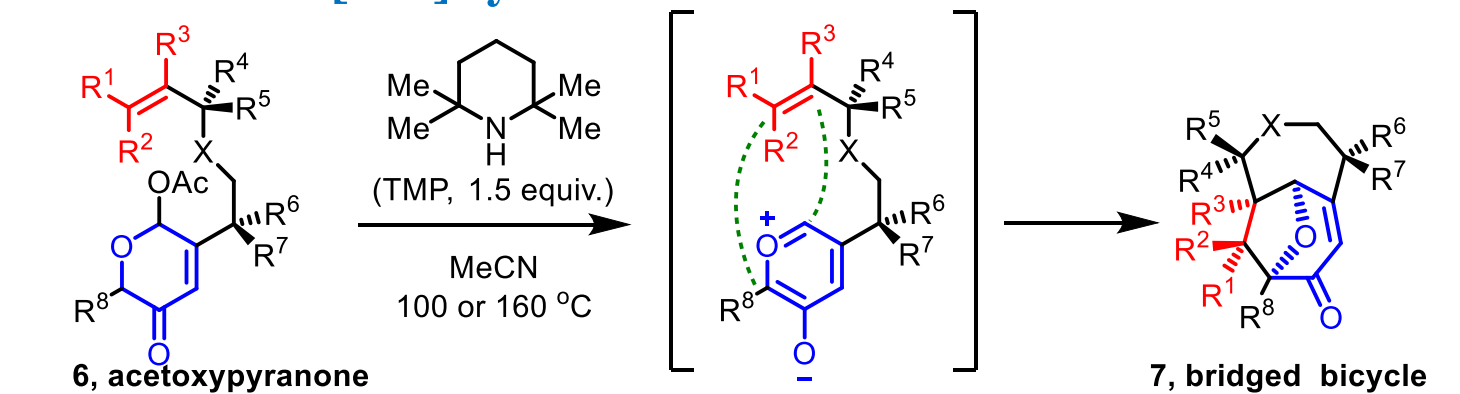
Intermolecular [5+2] cycloaddition



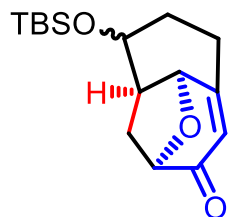
This is the first dearomative indole [5+2] cycloaddition with an oxidopyrylium ylide



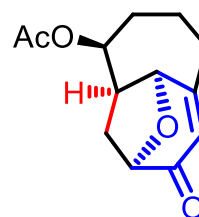
Type II intramolecular [5+2] cycloaddition



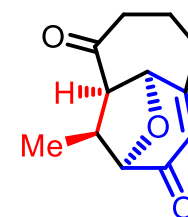
7a, 90%
dr = 1.6:1



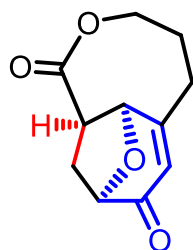
7b, 88%
dr = 1.3:1



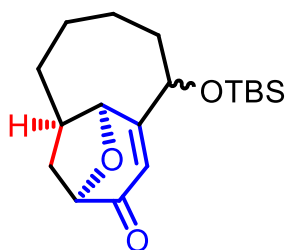
7c, 92%
dr > 20:1



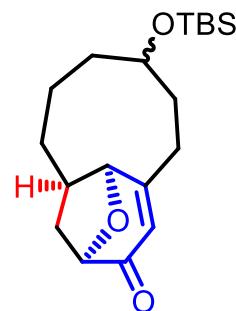
7d, 92%
dr > 20:1



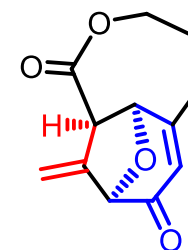
7e, 90%



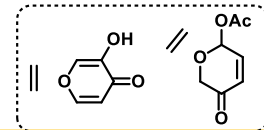
7f, 91%
dr = 1.3:1



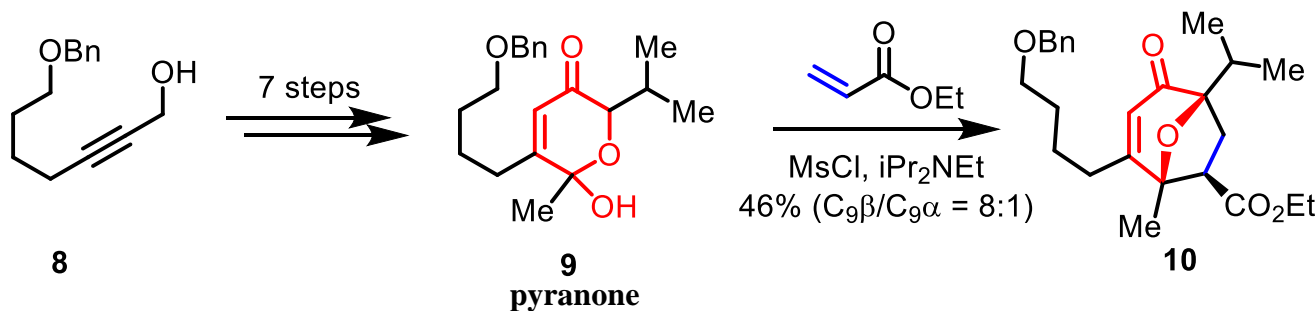
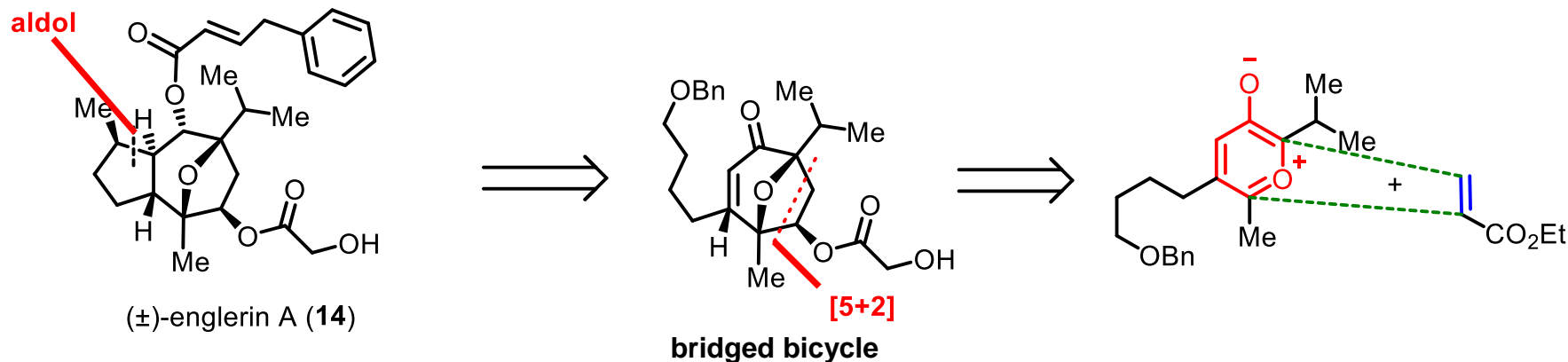
7g, 61%
dr = 1.7:1

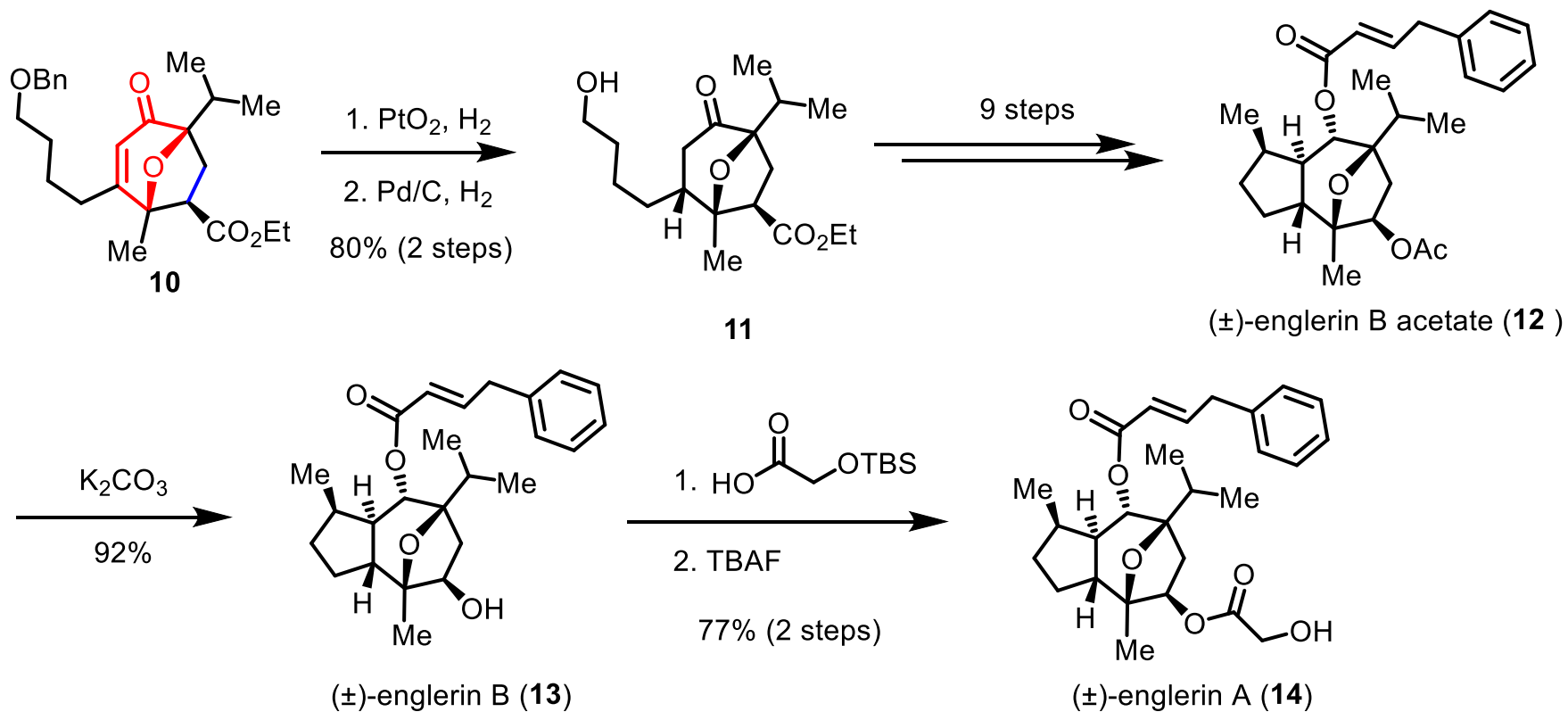
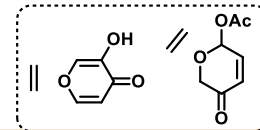


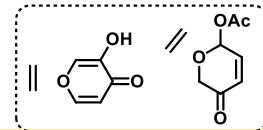
7h, 94%



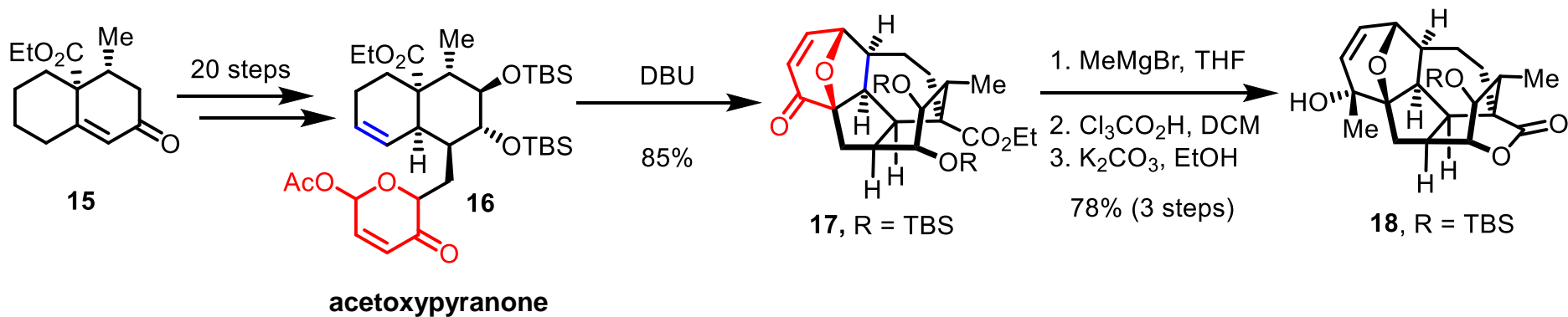
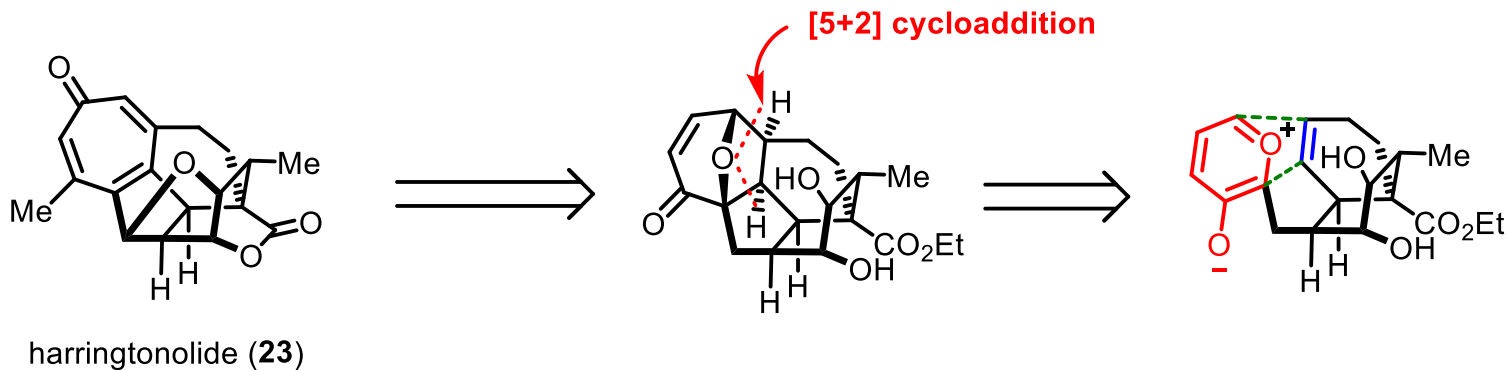
Total synthesis of (±)-englerin

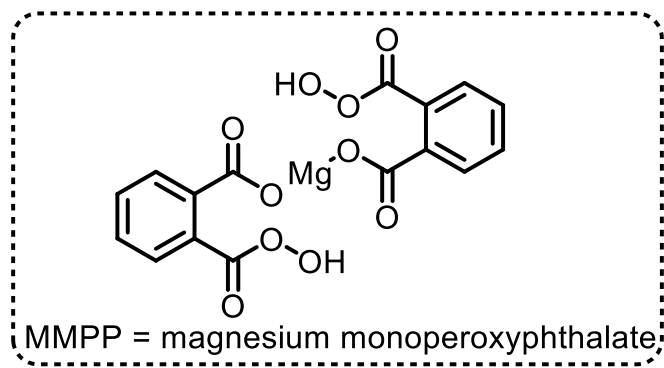
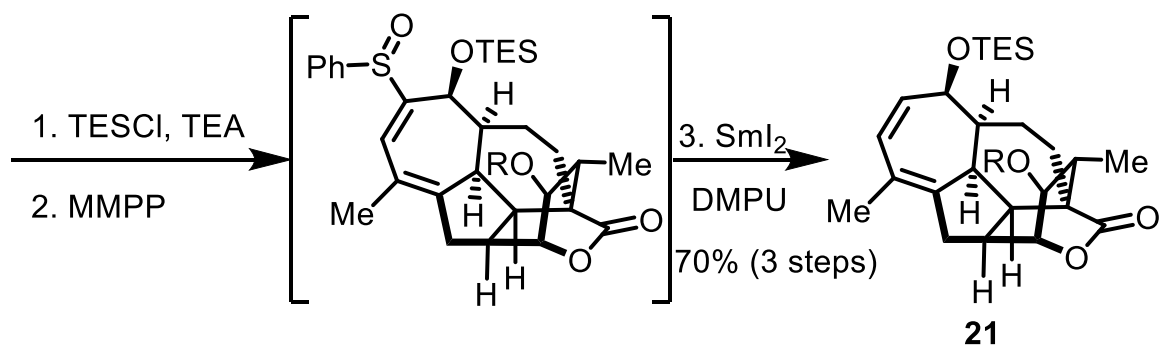
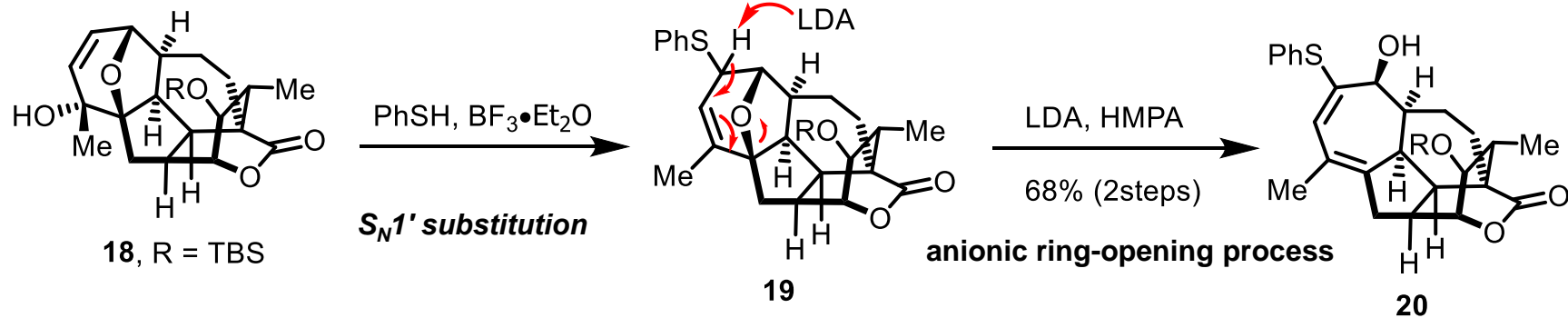
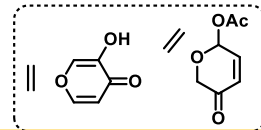


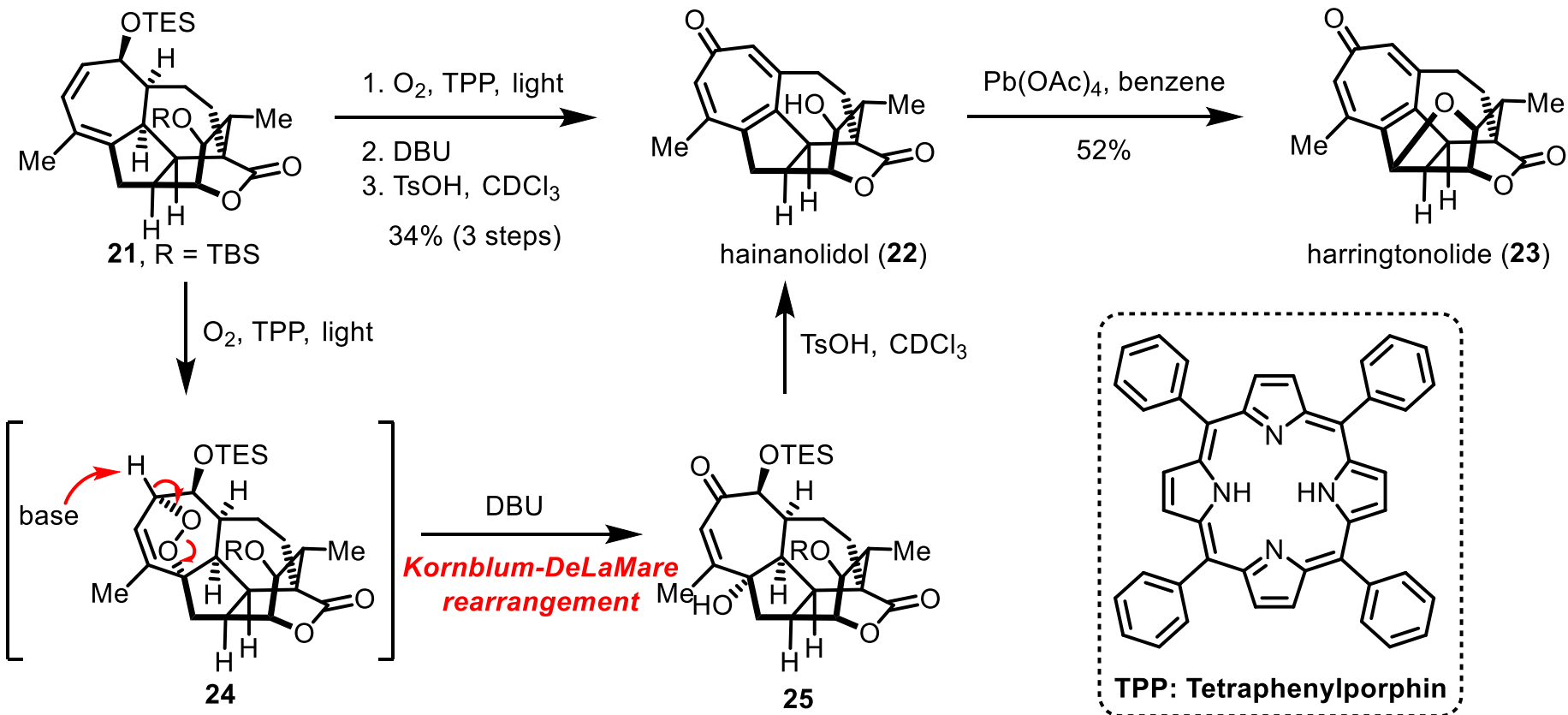
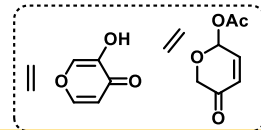




Total synthesis of harringtonolide

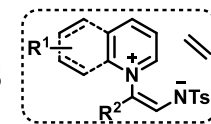




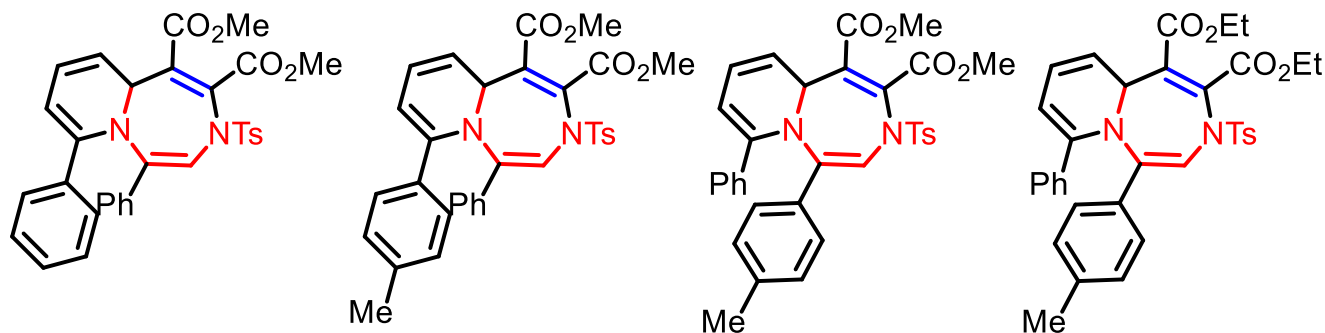
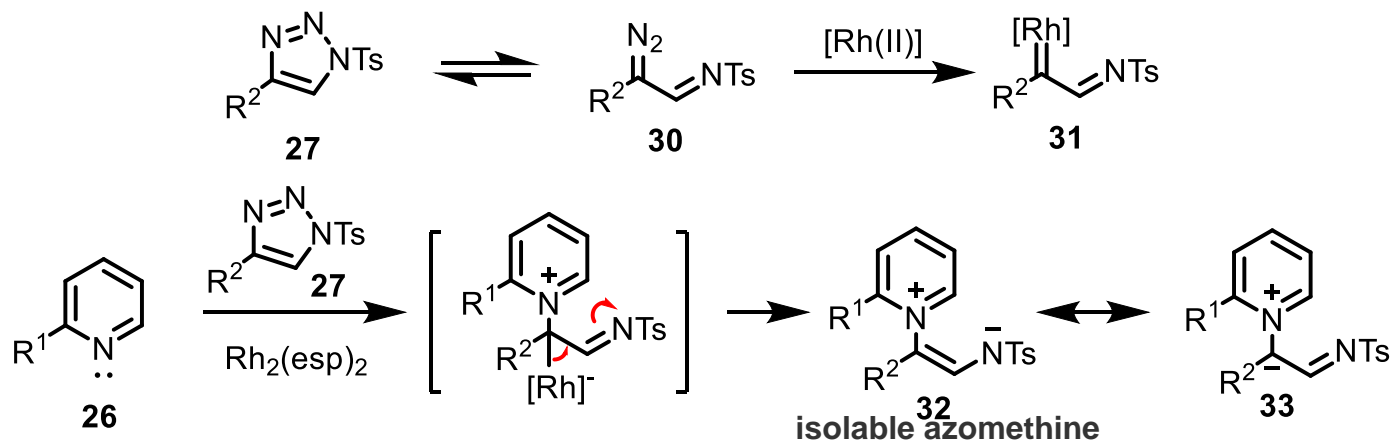
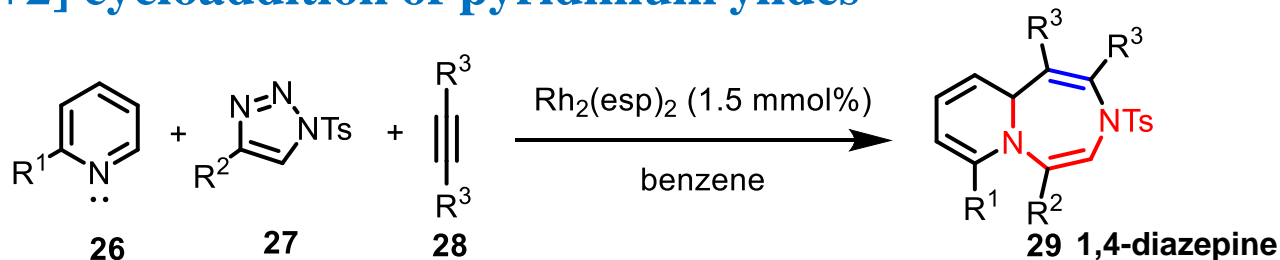


Index

- Introduction
- Main Contents
 - Oxidopyrylium-mediated [5+2]cycloaddition
 - **Pyridinium and quinolinium-mediated [5+2] cycloadditions**
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Rh-catalyzed [5+2] cycloaddition of pyridinium ylides



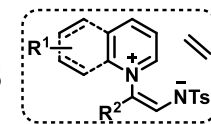
29a, 82%

29b, 80%

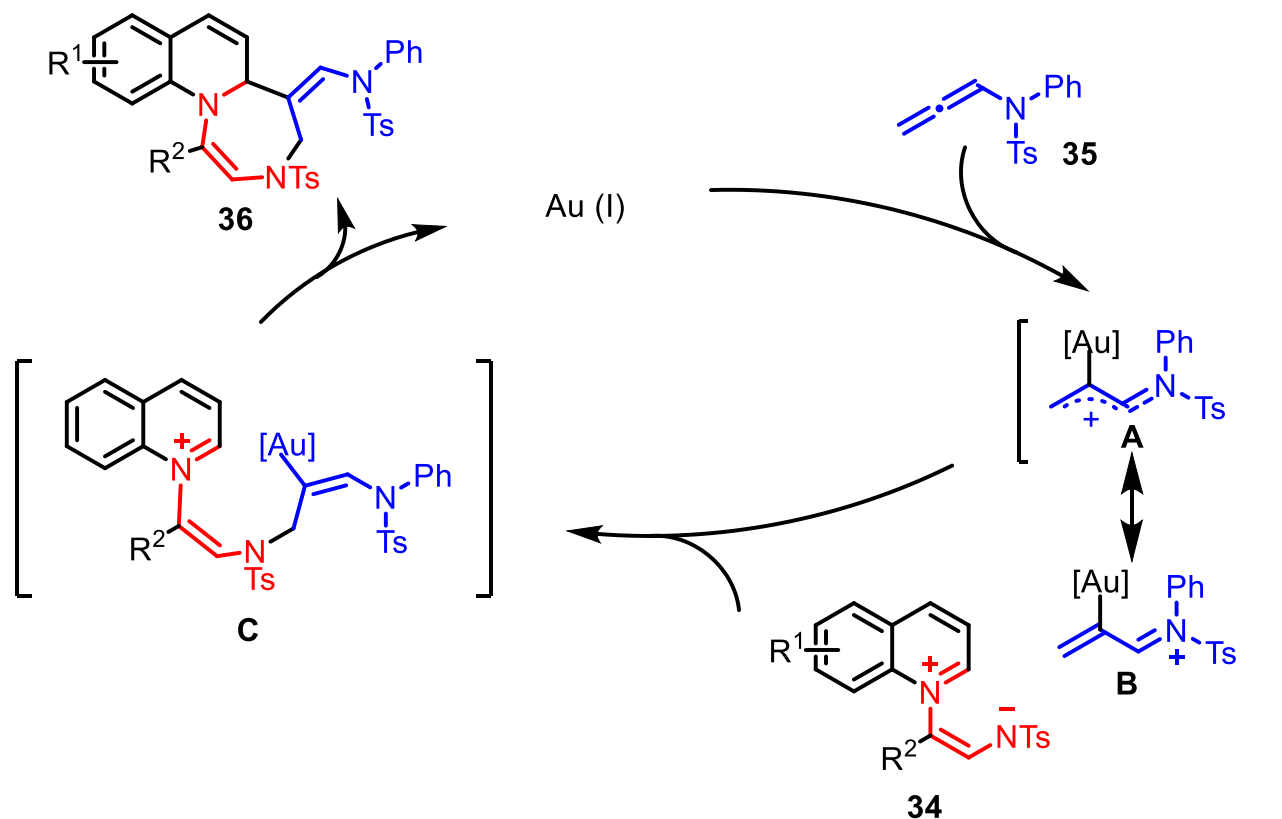
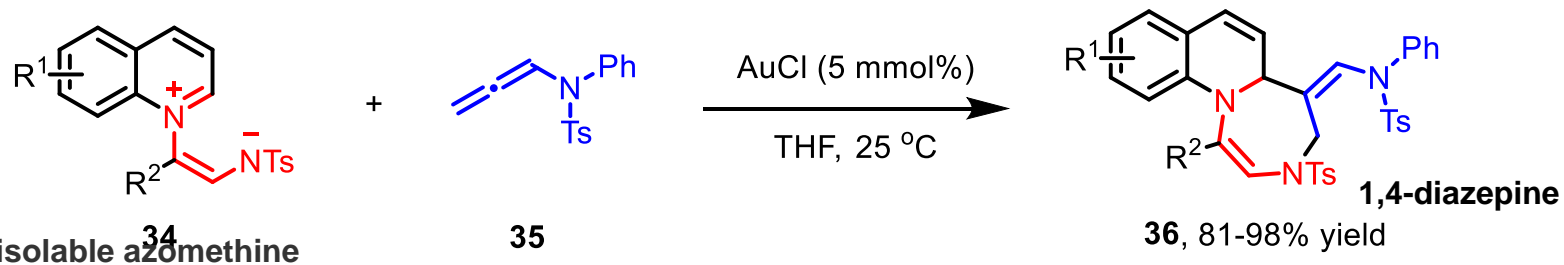
29c, 88%

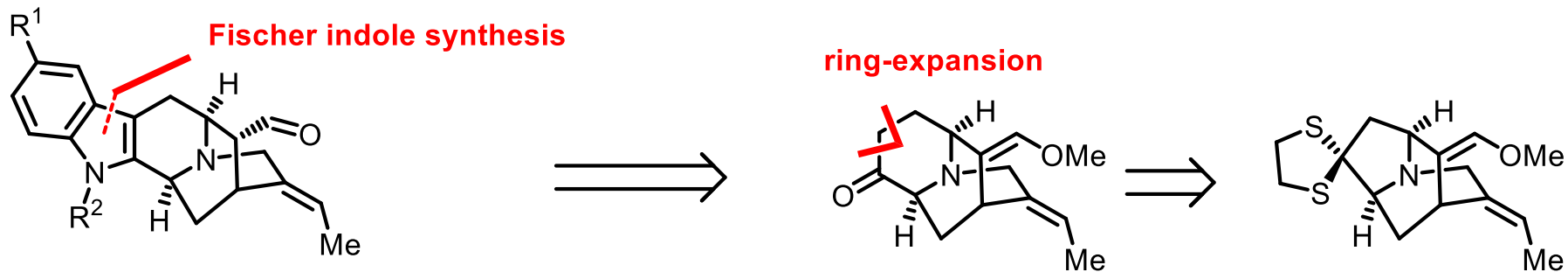
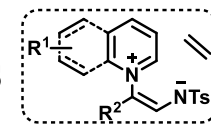
29d, 83%

D. J. Lee, H. S. Han, J. Shin and E. J. Yoo, *J. Am. Chem. Soc.* **2014**, *136*, 11606.



Gold-catalyzed [5+2] cycloaddition of quinolinium ylide

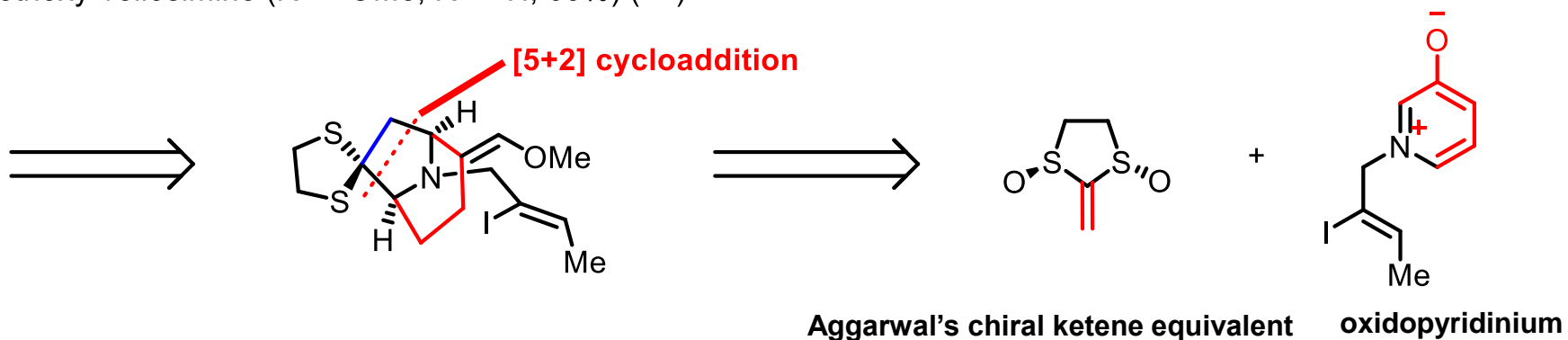


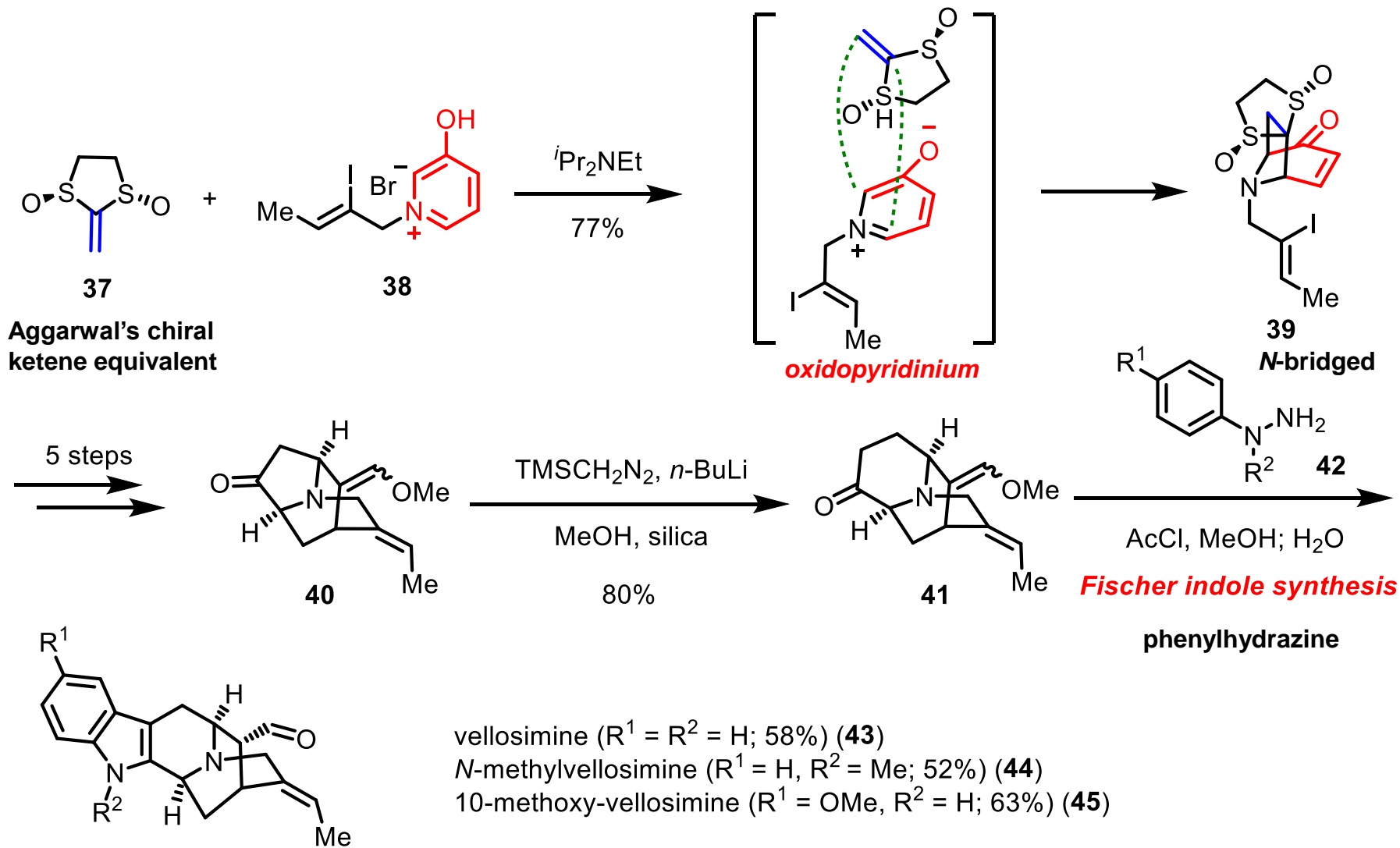
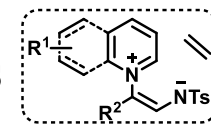


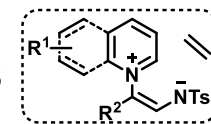
vellosimine ($R^1 = R^2 = H$; 58%) (**43**)

N-methylvellosimine ($R^1 = H$, $R^2 = Me$; 52%) (**44**)

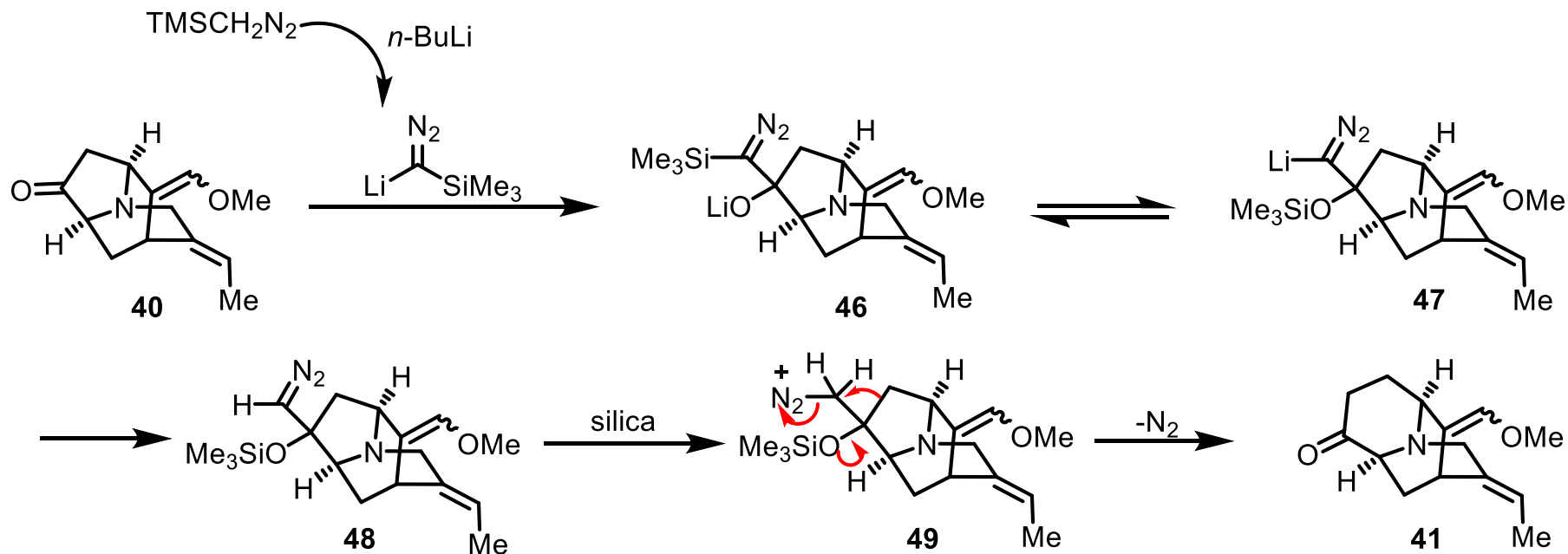
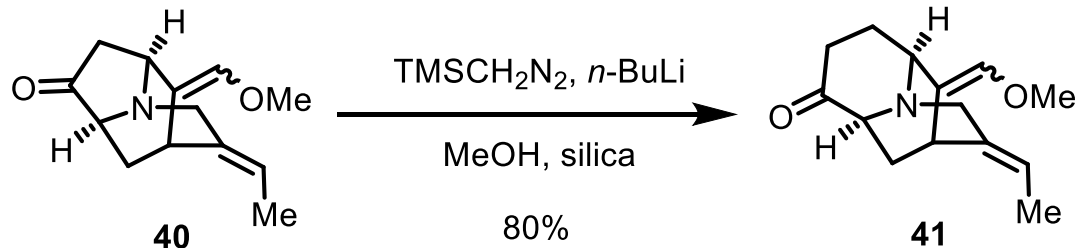
10-methoxy-vellosimine ($R^1 = OMe$, $R^2 = H$; 63%) (**45**)





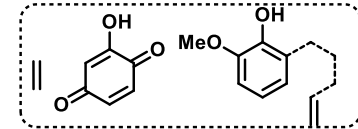


Ring expansion

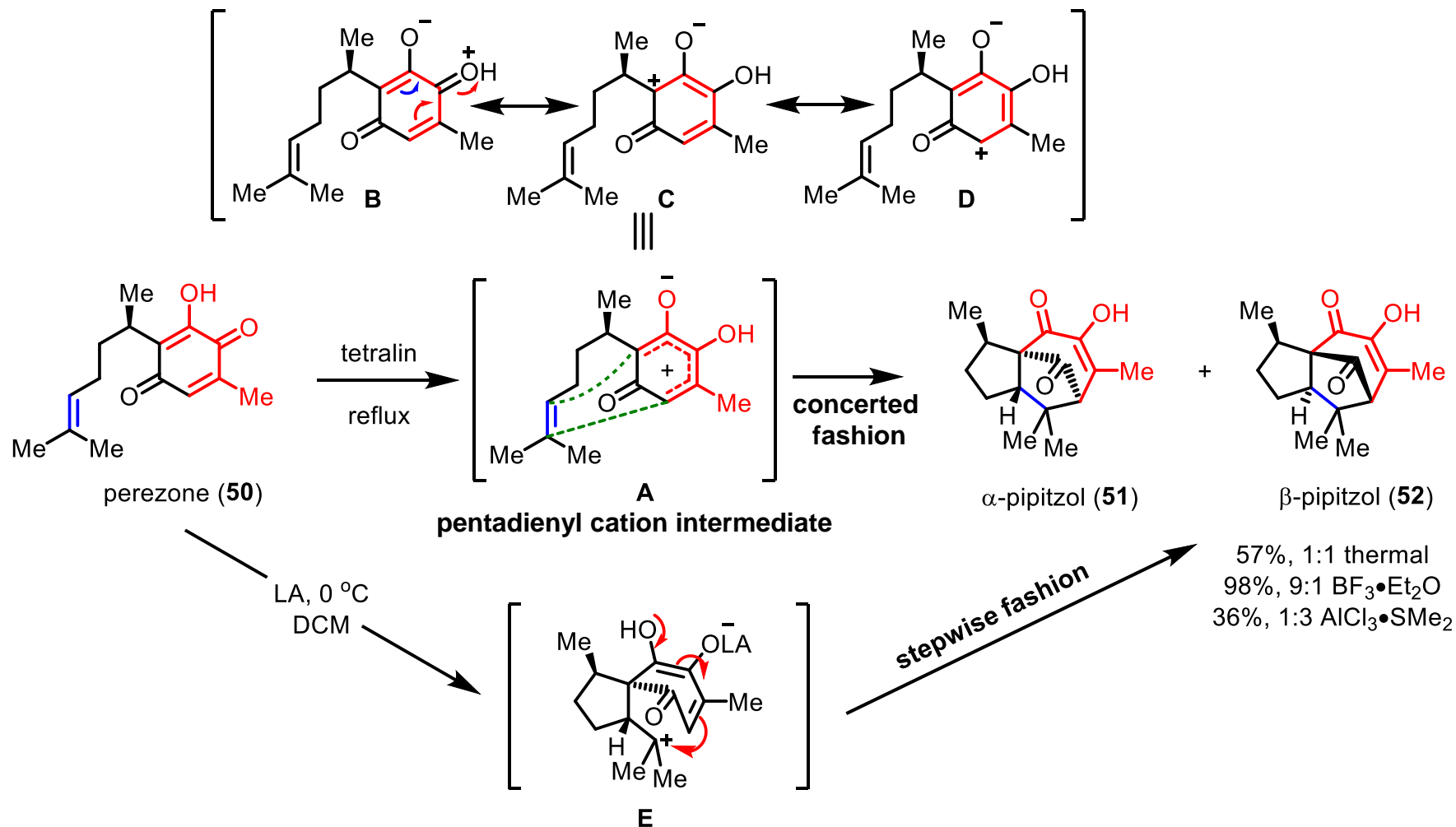


Index

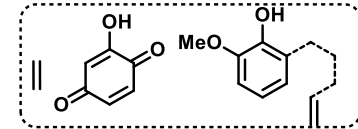
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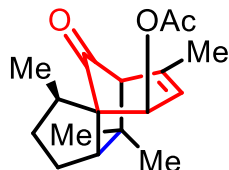
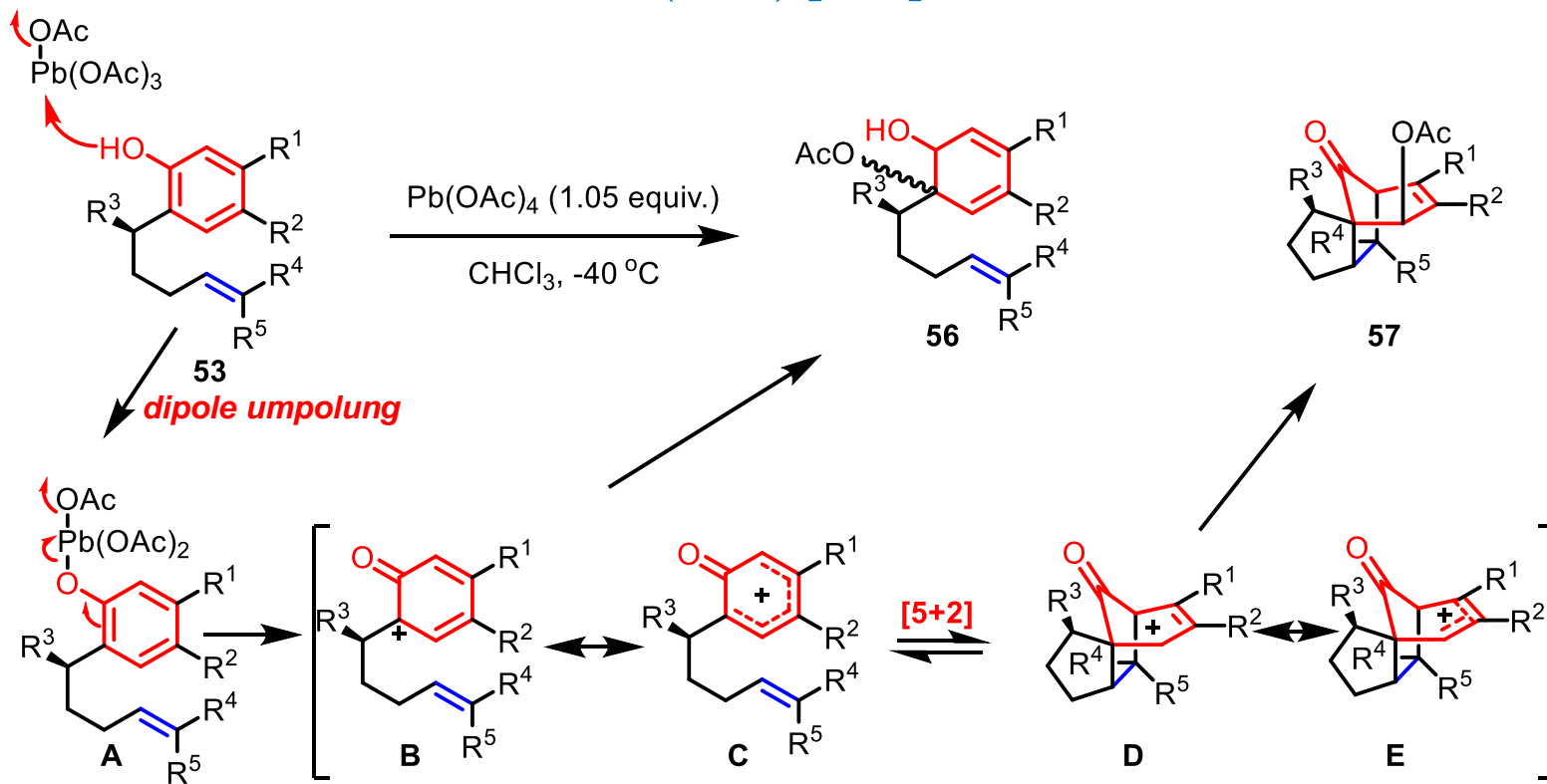
Perezone to Pipitzol Transformation



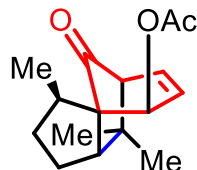
(a) J. M. Sanders, *Proc. Chem. Soc.* **1906**, 22, 134. (b) F. G. P. J. Remfry, *Chem. Soc.* **1913**, 103, 1076. (c) F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, J. Romo, *Tetrahedron Lett.* **1965**, 21, 1577. (d) F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, *Tetrahedron* **1966**, 22, 2387.



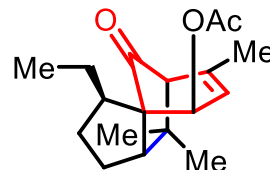
Oxidative dearomatization-induced (ODI) [5+2] cascade reaction



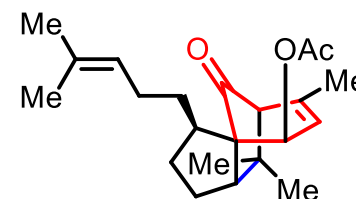
57a, 61%



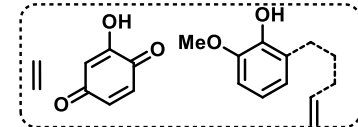
57b, 54%



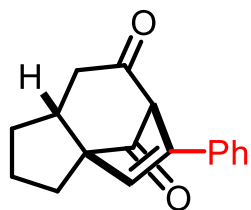
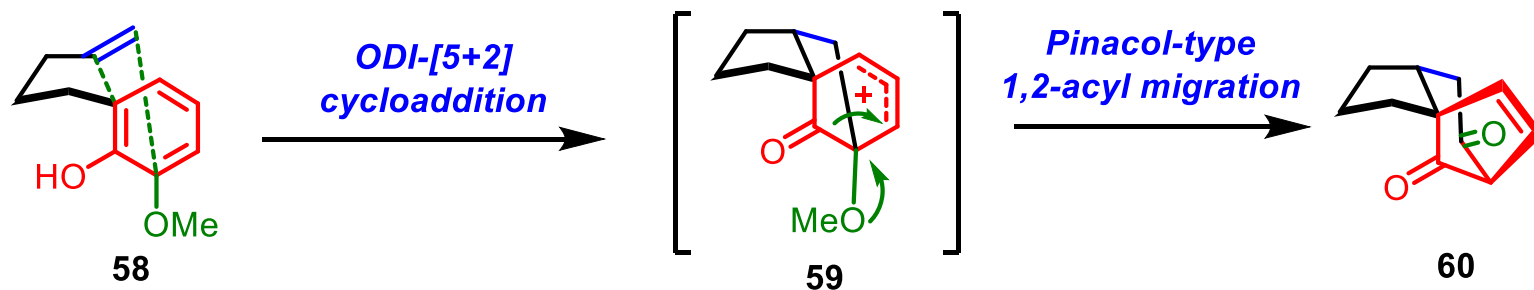
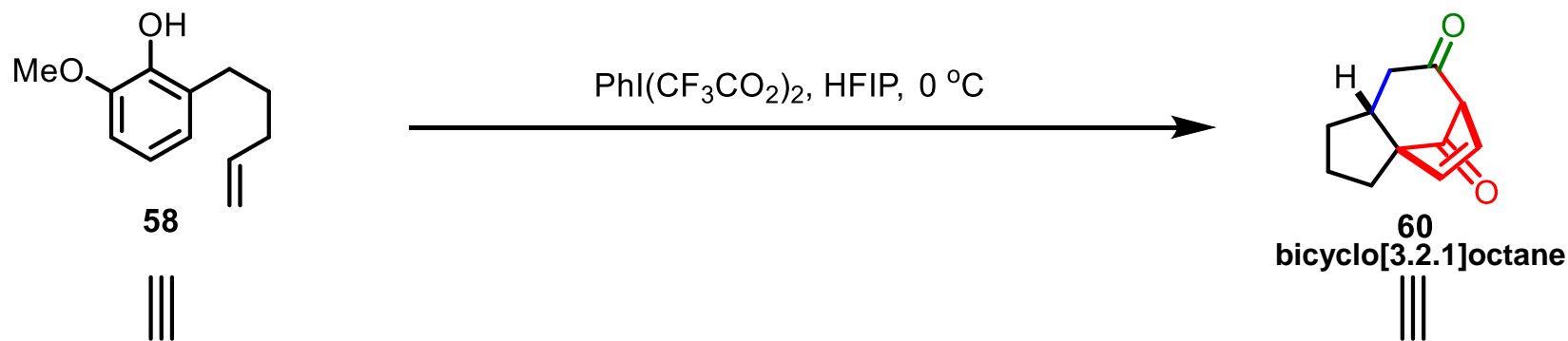
57c, 52%



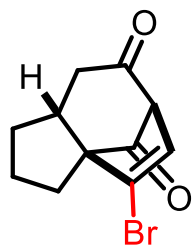
57d, 65%



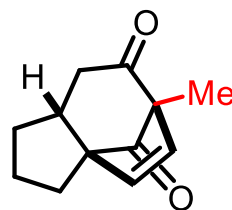
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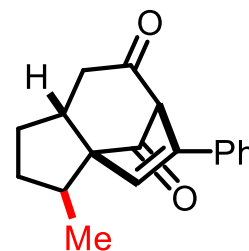
60a, 85%



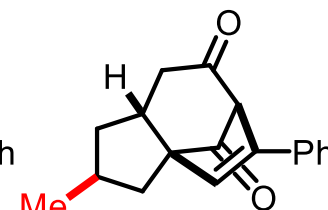
60b, 67%



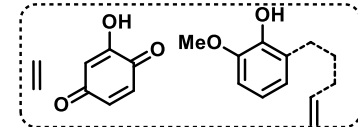
60c, 63%



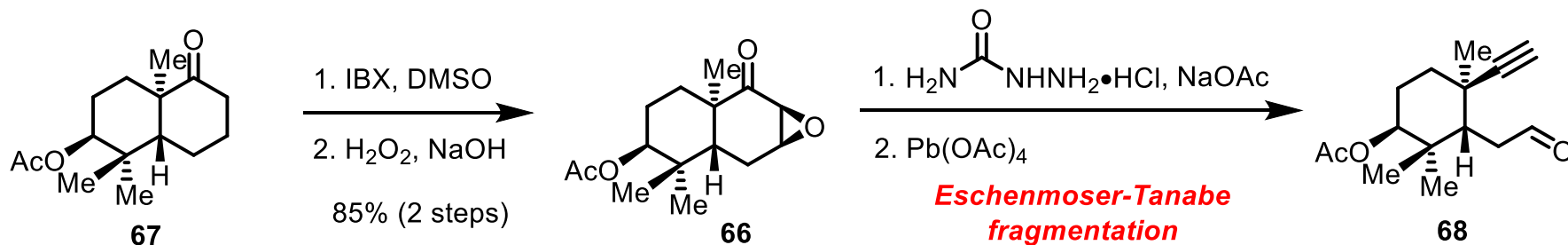
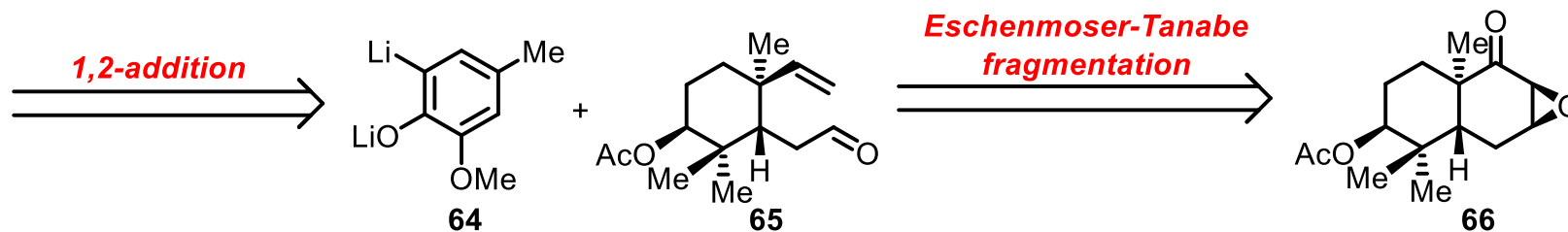
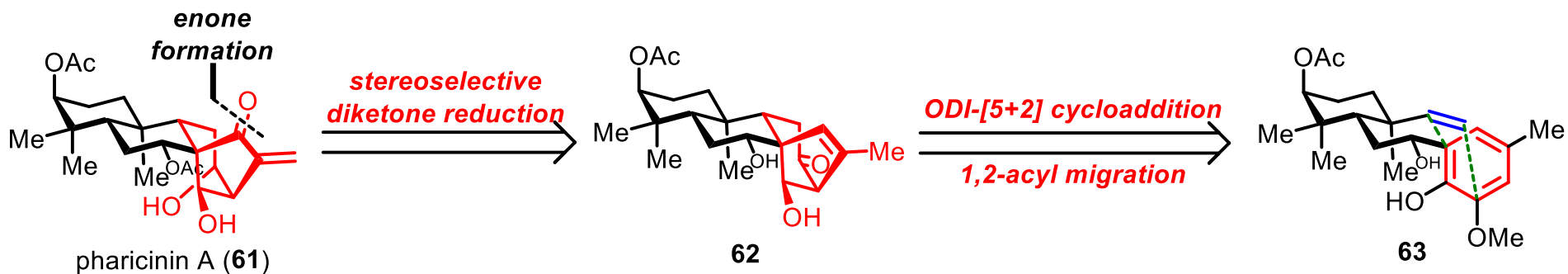
60d, 82% (20:1 dr)

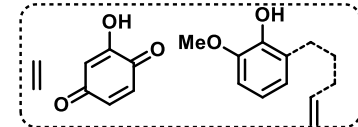


60e, 76% (10:1 dr)

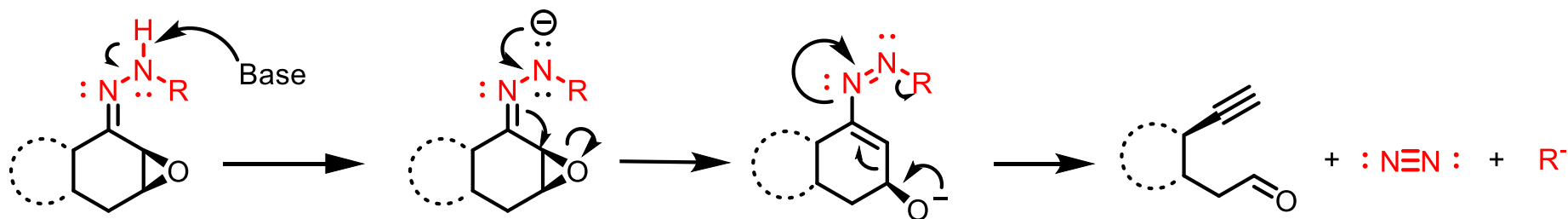
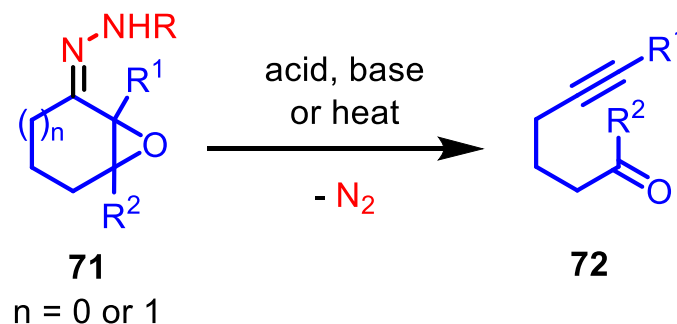
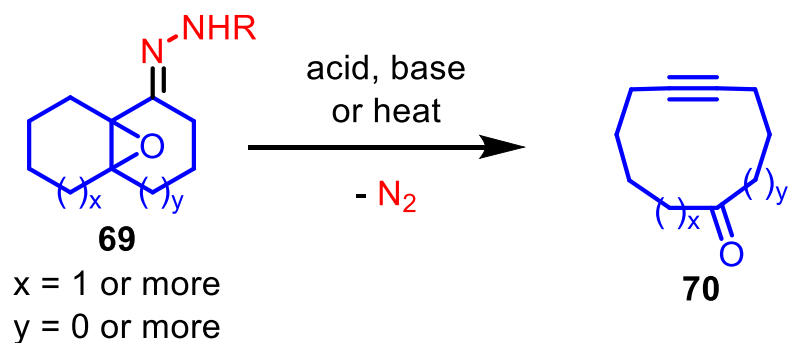
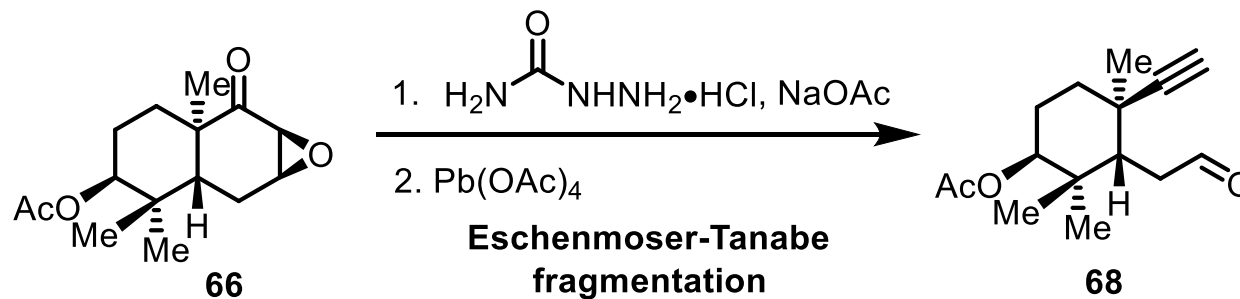


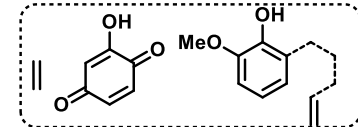
Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylpsurata C, and Psurata C



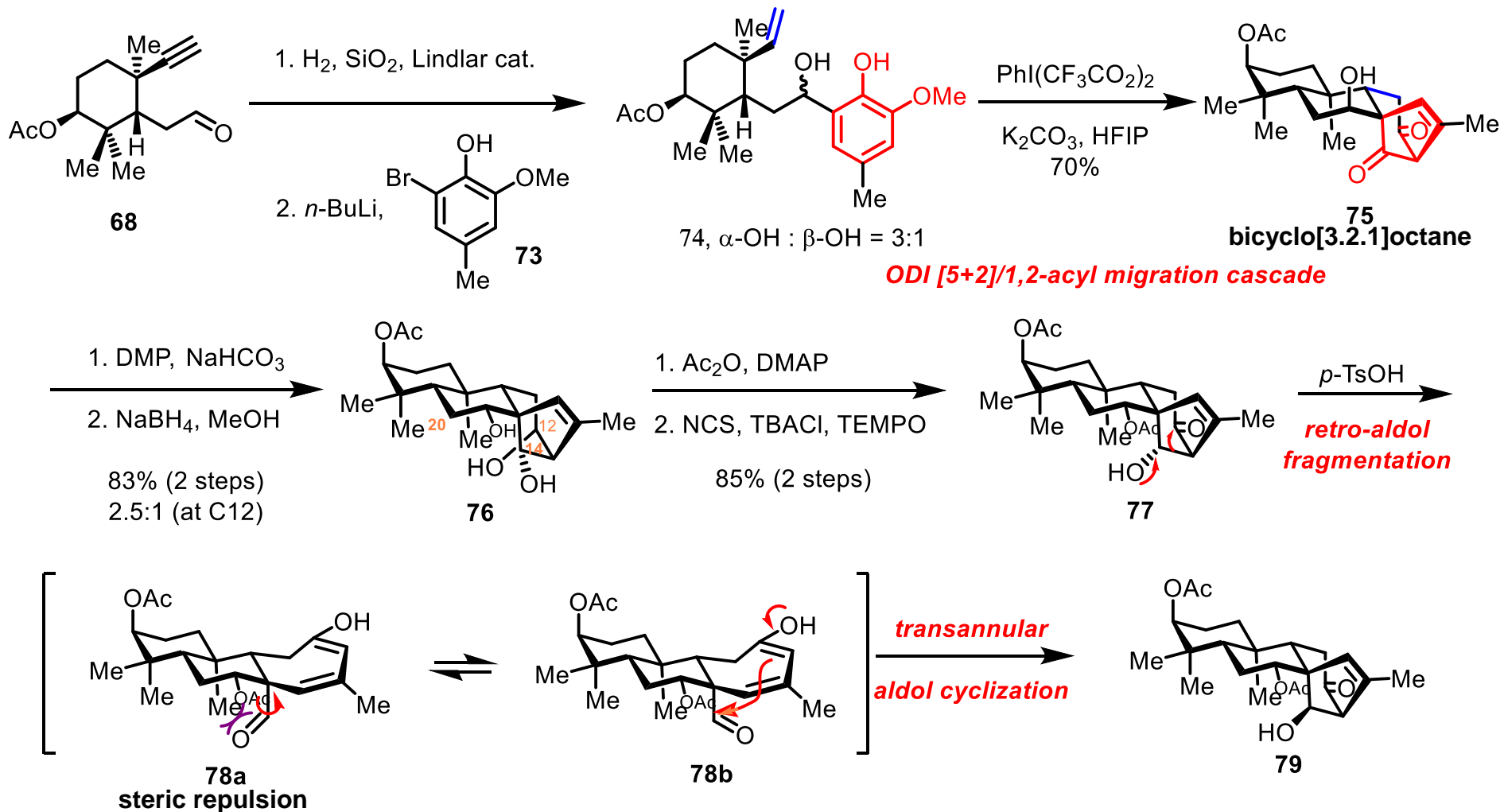


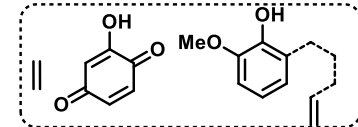
Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylpsaurata C, and Psaurata C



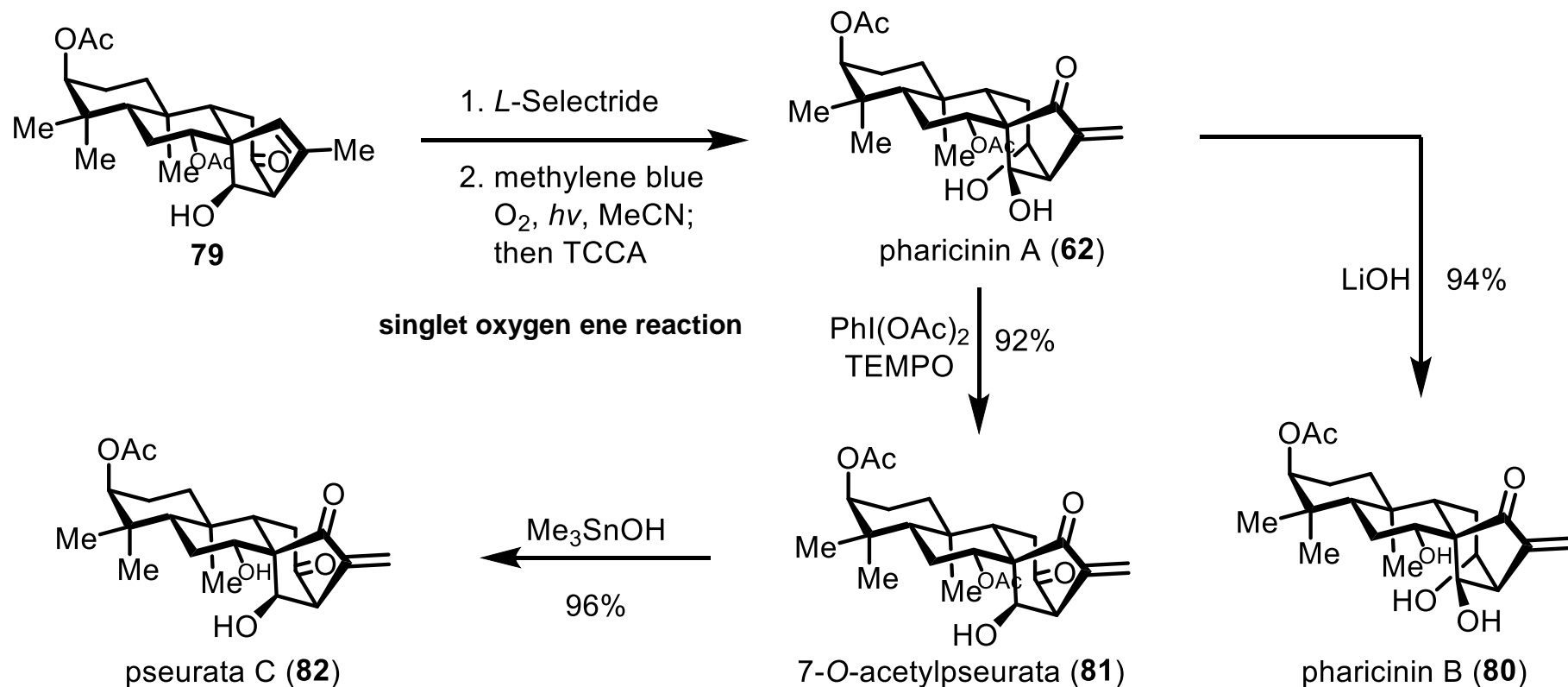


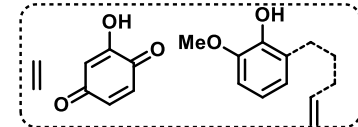
Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylpsaurata C, and Psaurata C



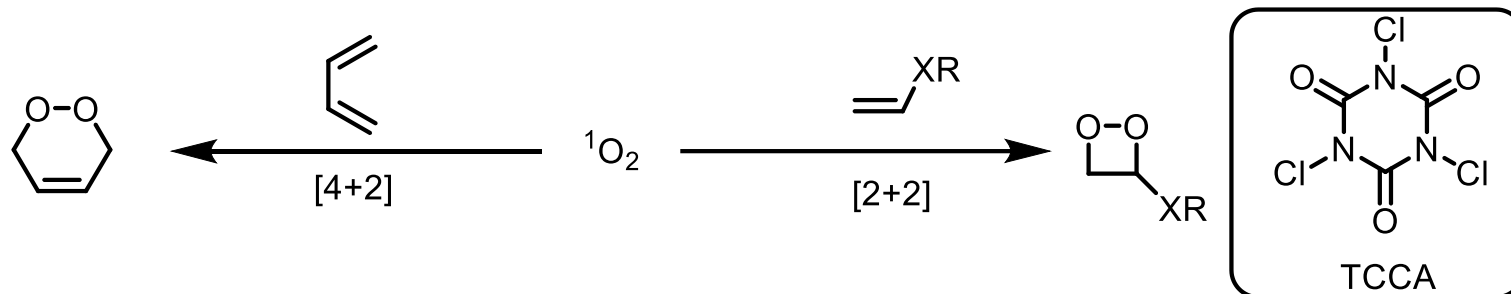
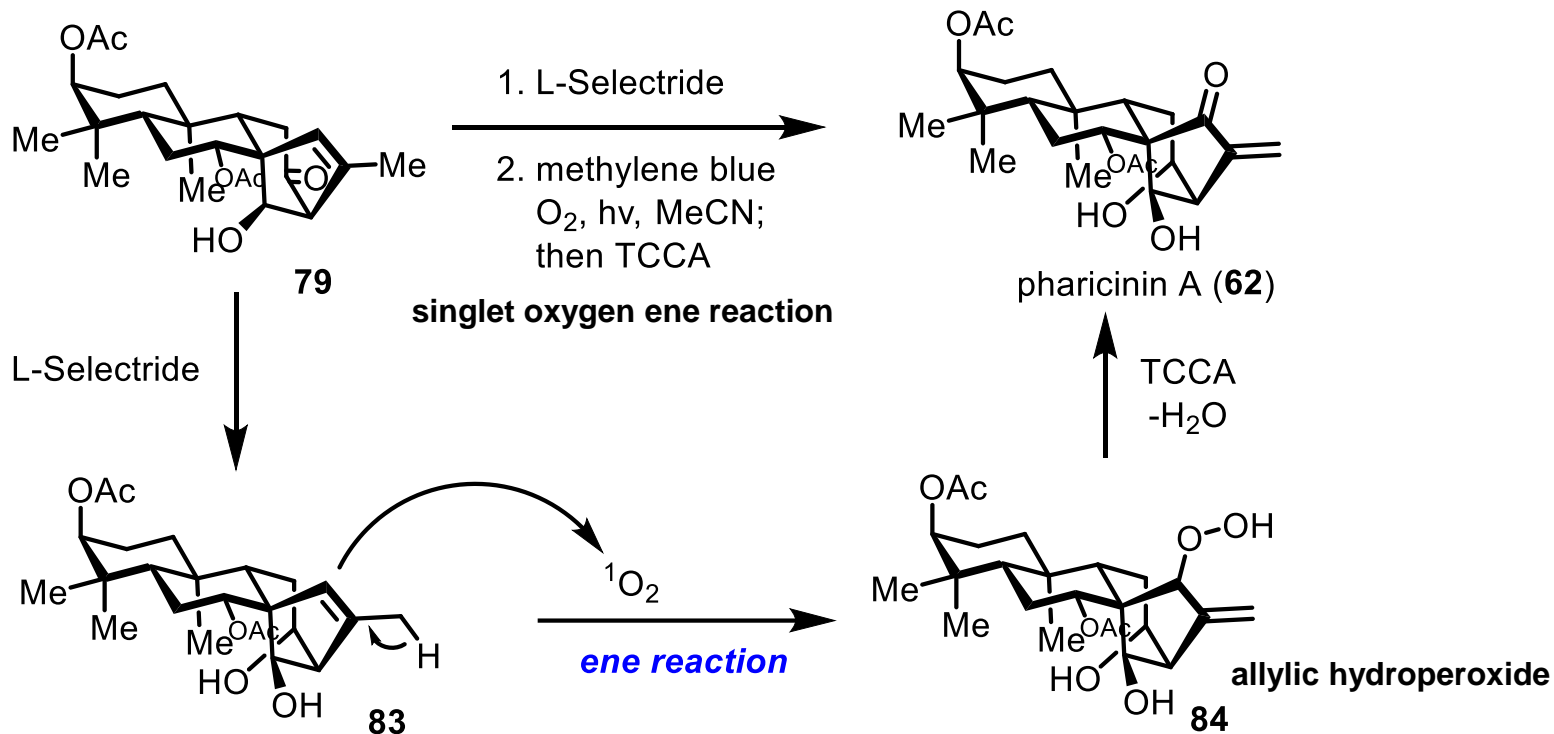


Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylpsaurata C, and Psaurata C





Total Syntheses of Pharicinin A, Pharicinin B, 7-O-Acetylpseurata C, and Pseurata C



M. Prein, W. Adam, *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 477.

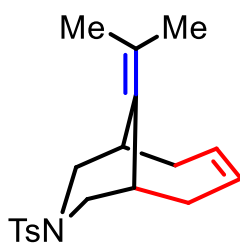
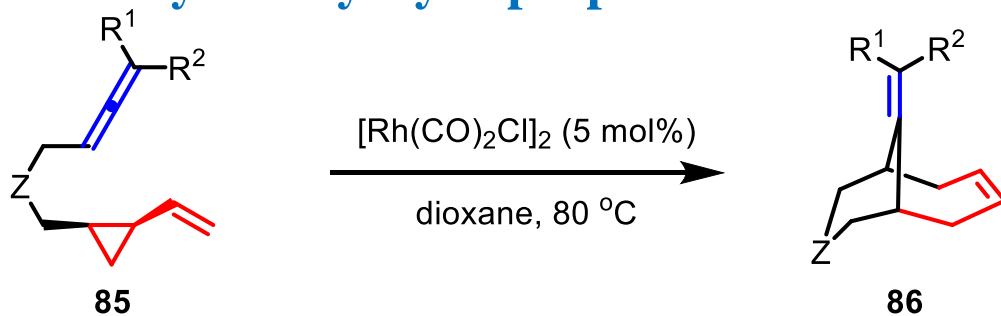
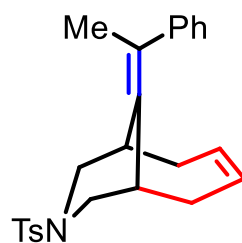
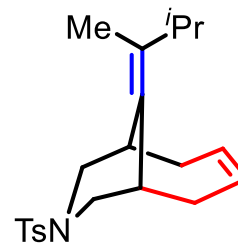
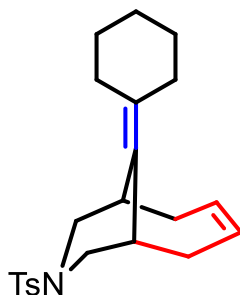
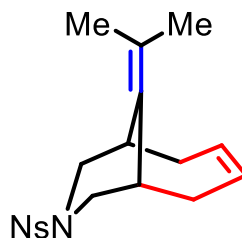
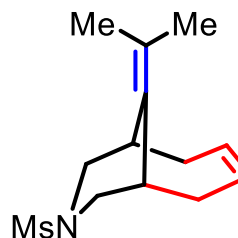
Fisher, T. J.; Dussault, P. H. *Tetrahedron Lett.* **2010**, 51, 5615.

Index

- Introduction
- Main Contents
 - Oxidopyrylium-mediated [5+2]cycloaddition
 - Pyridinium and quinolinium-mediated [5+2] cycloadditions
 - Perezzone-type [5+2] cycloadditions
 - **[5+2] cycloadditions of vinyl cyclopropanes (VCPs)**
 - [5+2] cycloadditions of five-carbon organometallic complexes
- Summary



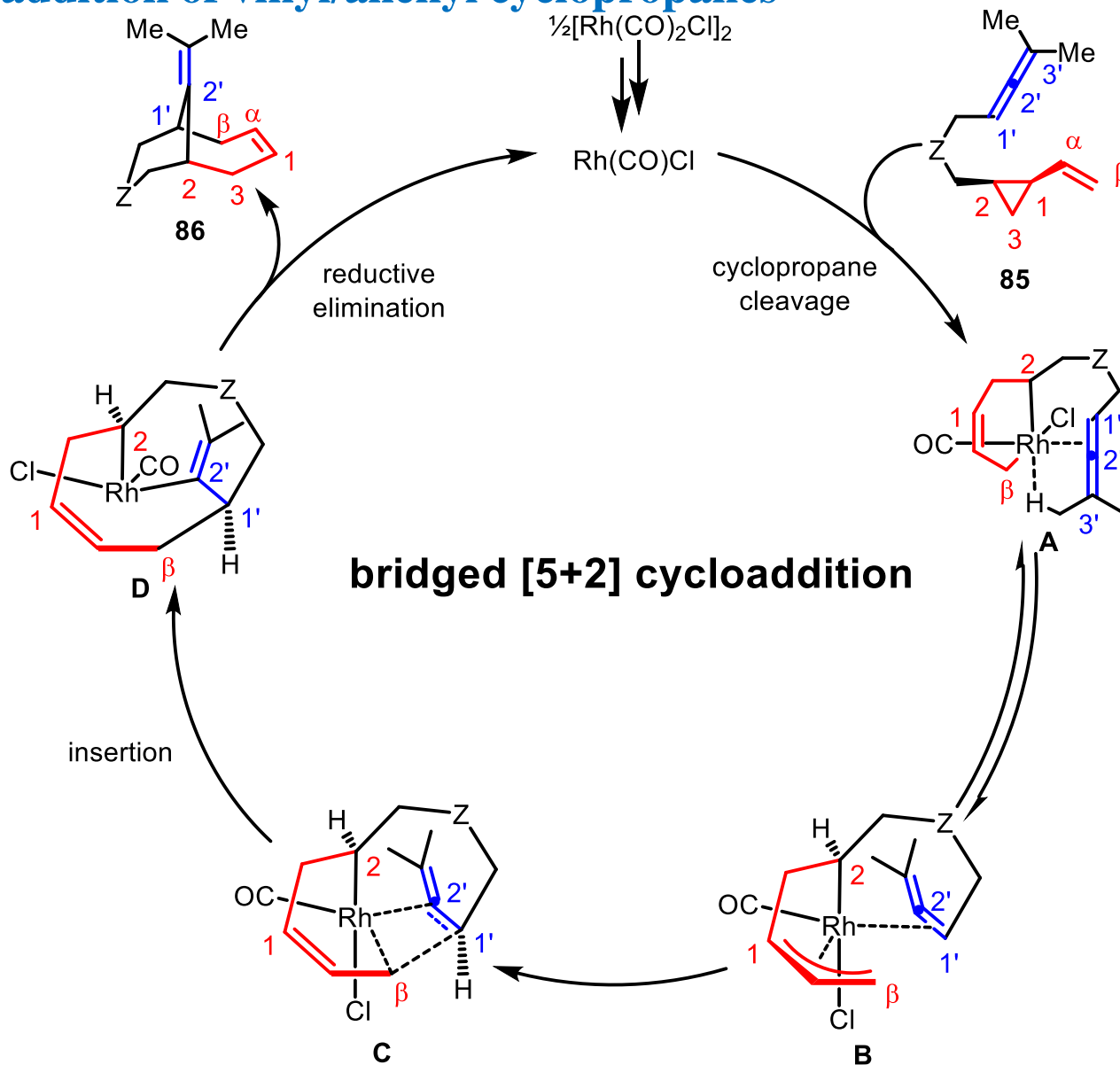
[5+2] cycloaddition of vinyl/allenyl cyclopropanes

**86a**, 80%**86b**, 62%**86c**, 78%**86d**, 73%**86e**, 78%**86f**, 75%

In 2017, Yu group discovered that vinylcyclopropane can react with allene by rhodium(I)-catalyzed intramolecular [5+2] cycloaddition to synthesize the challenging bicyclo[4.3.1]decane skeleton

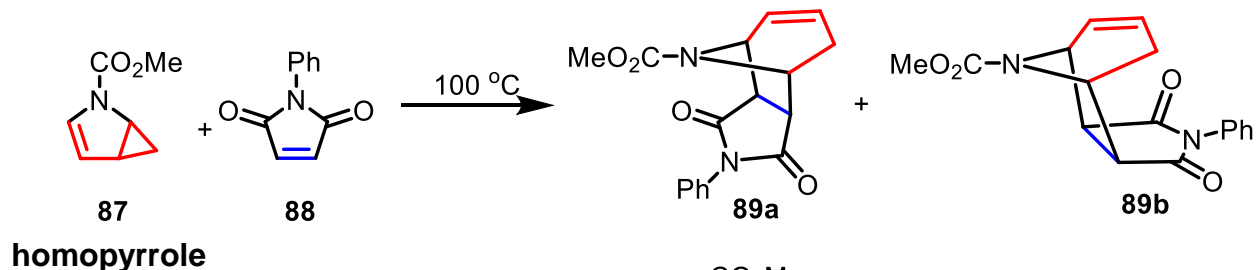


[5+2] cycloaddition of vinyl/allenyl cyclopropanes

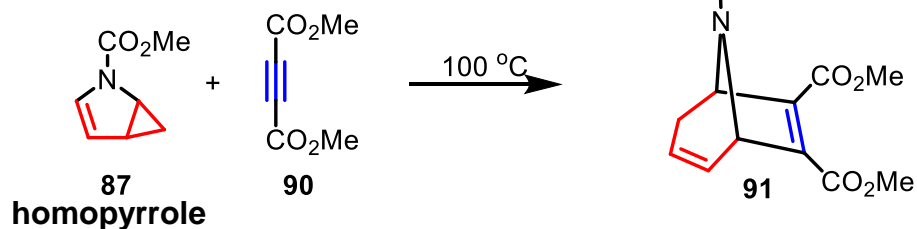




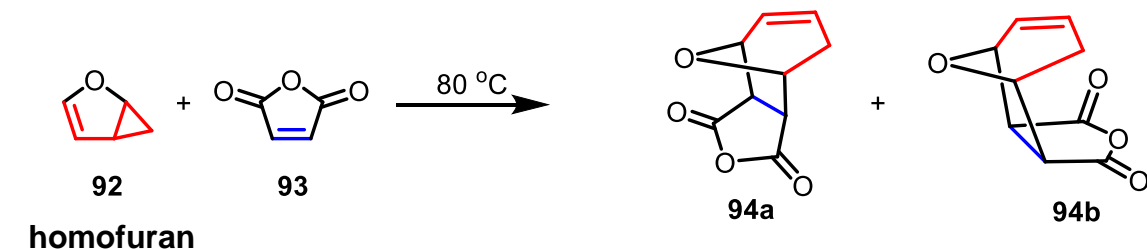
[5+2] cycloaddition of vinyl/allenyl cyclopropanes



homopyrrole

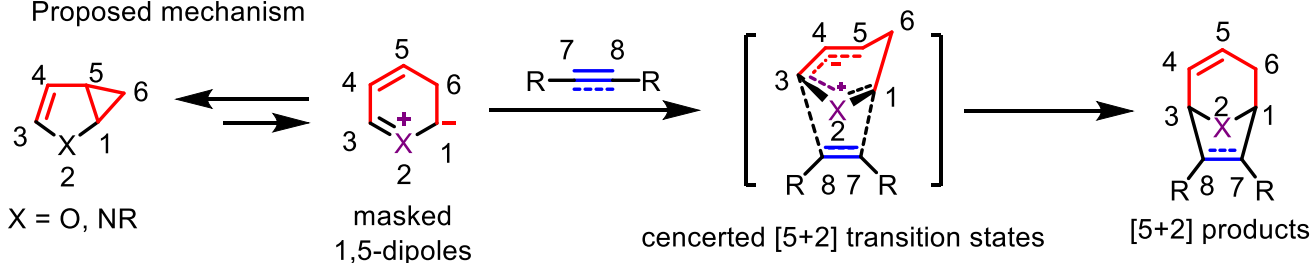


homopyrrole



homofuran

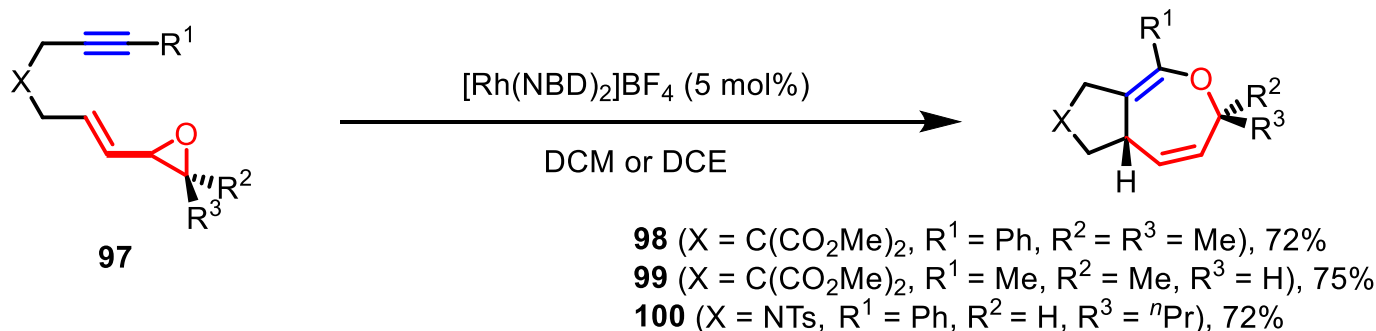
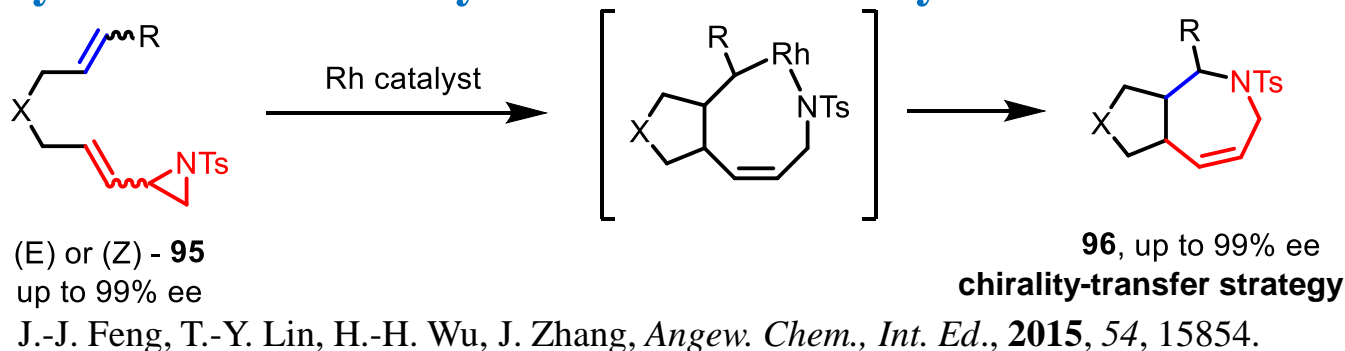
Proposed mechanism



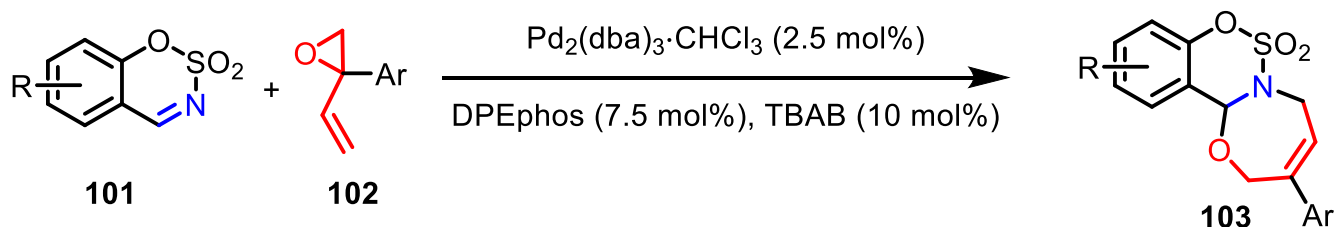
- (a) F. W. Fowler, *Angew. Chem., Int. Ed.* **1971**, *10*, 135; (b) R. Herges, I. Ugi, *Angew. Chem., Int. Ed.* **1985**, *24*, 594.
 (c) P.-J. Cai, F.-Q. Shi, Y. Wang, X. Li, Z.-X. Yu, *Tetrahedron* **2013**, *69*, 7854



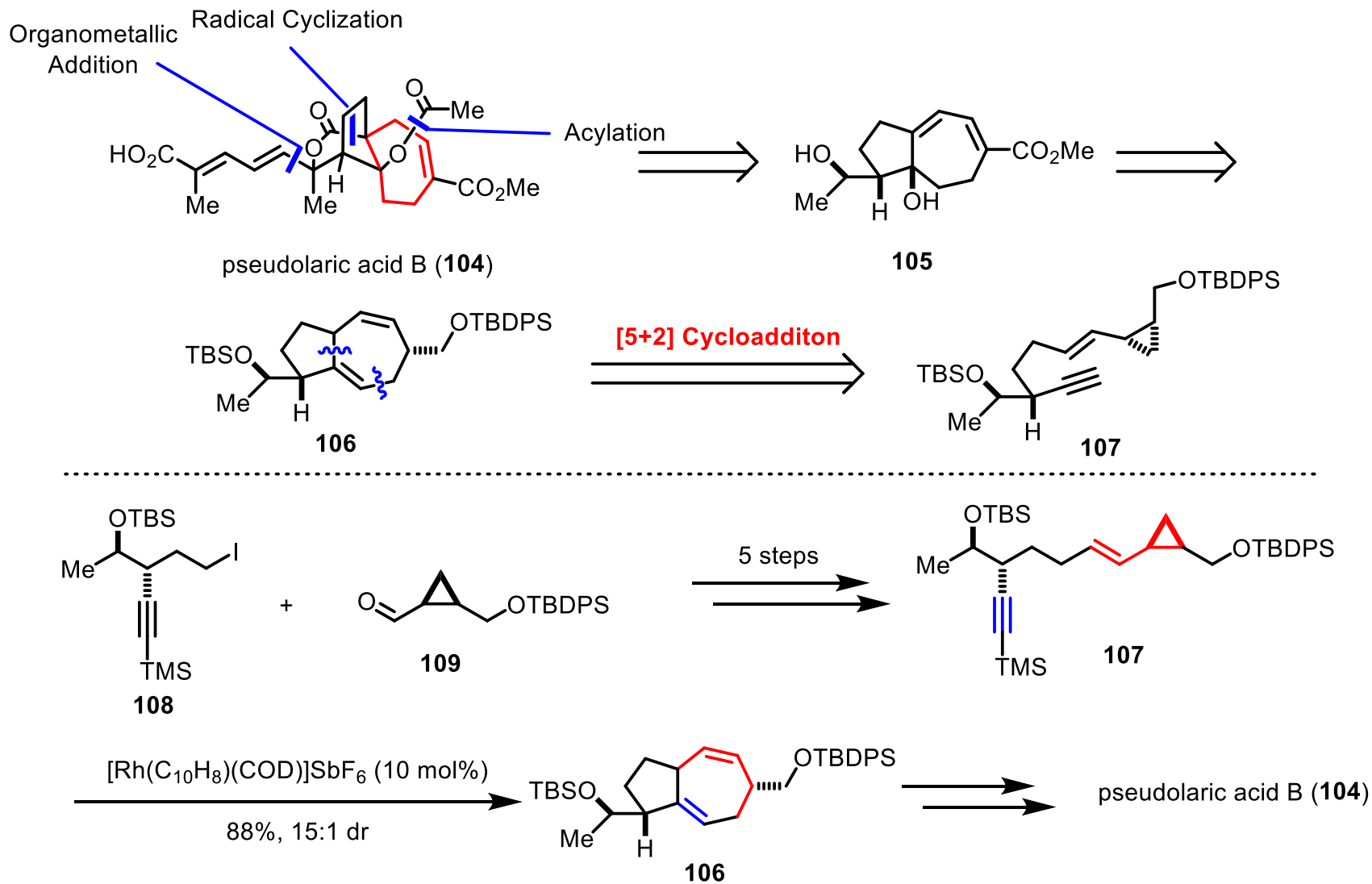
Hetero-[5+2] cycloaddition of vinyl aziridines and vinyl oxiranes



J.-J. Feng, J. Zhang, *ACS Catal.*, **2017**, *7*, 1533.

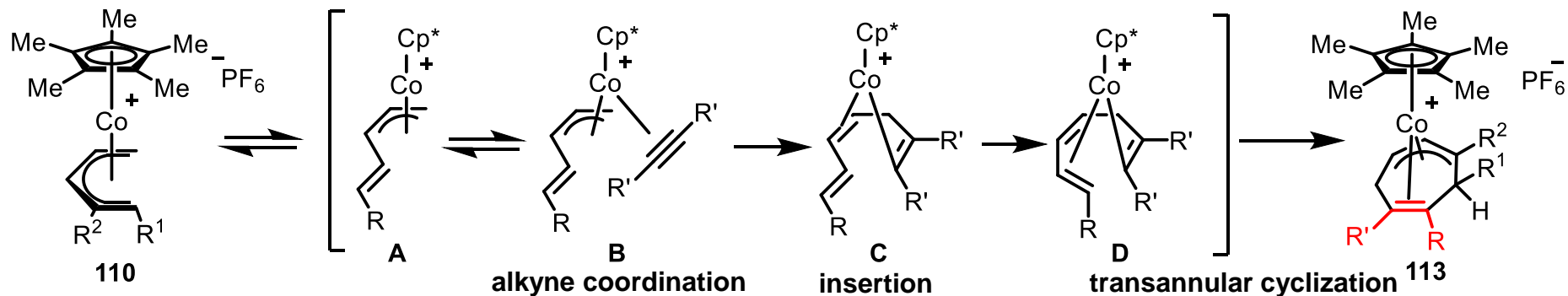
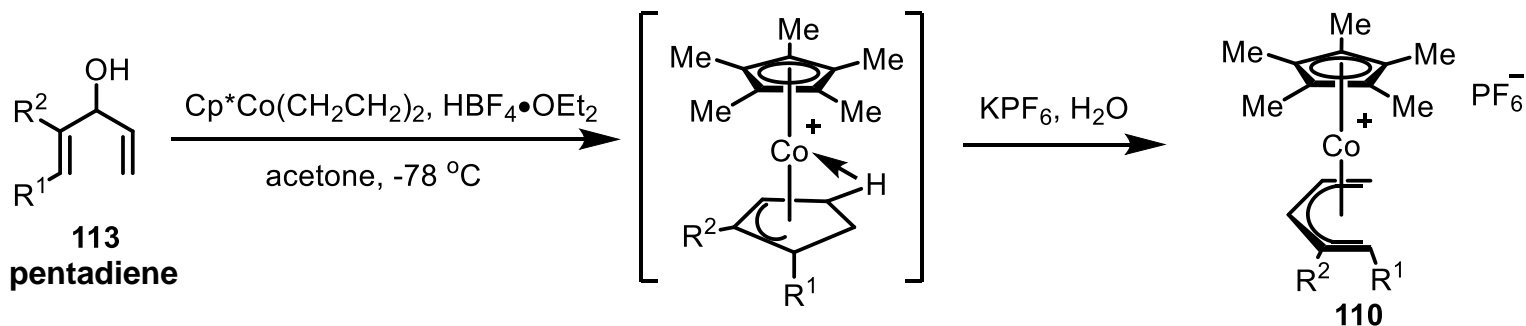
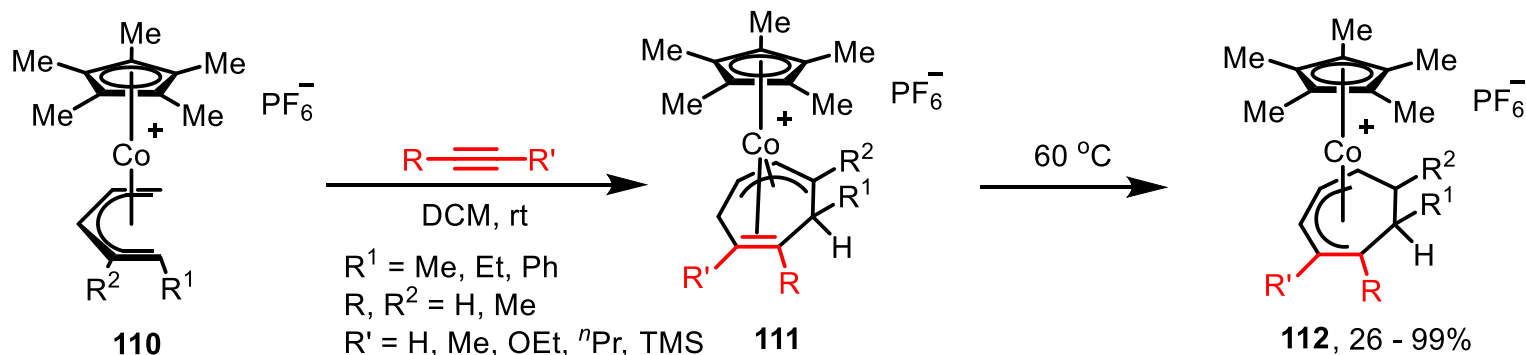
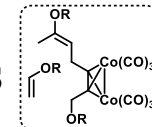


Y. Wu, C. Yuan, C. Wang, B. Mao, H. Jia, X. Gao, J. Lia, F. Jiang, L. Zhou, Q. Wang, H. Guo, *Org. Lett.* **2017**, *19*, 6268.

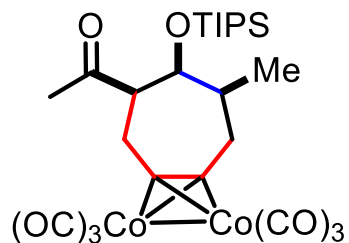
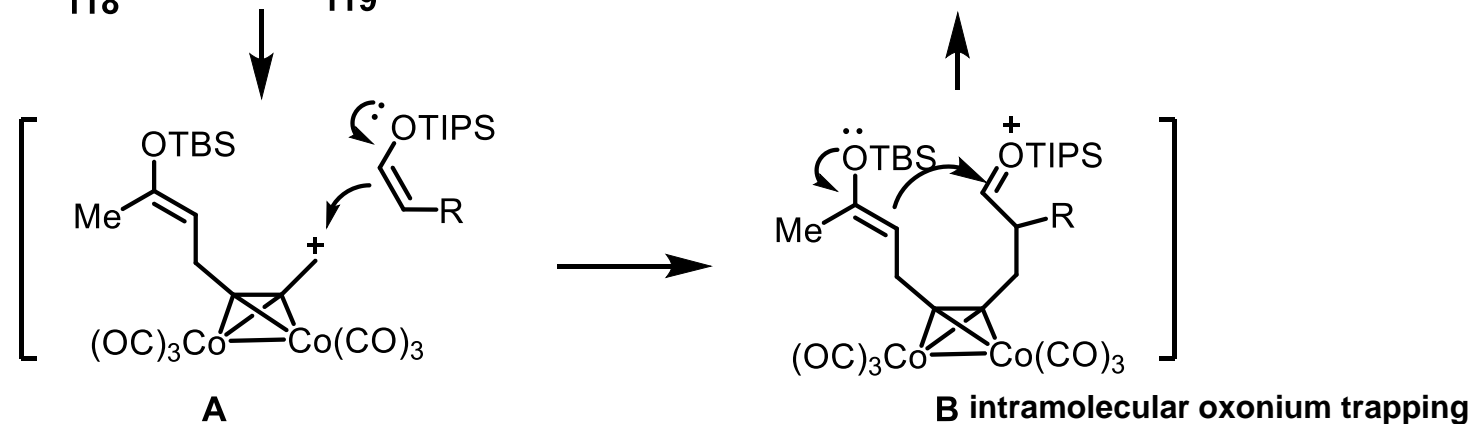
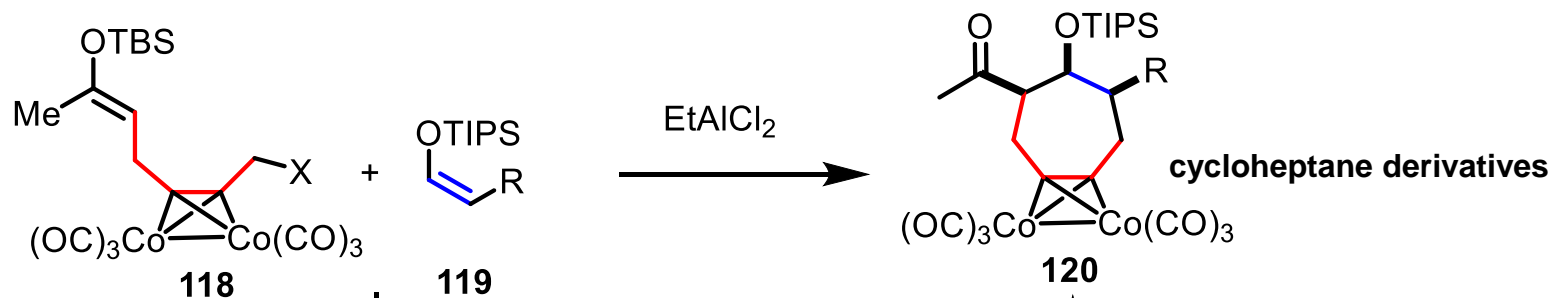
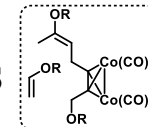


Index

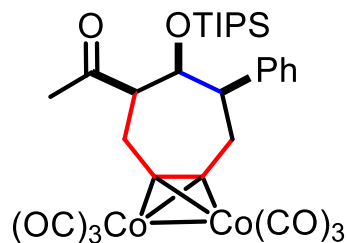
- Introduction
- Main Contents
 - Oxidopyrylium-mediated [5+2]cycloaddition
 - Pyridinium and quinolinium-mediated [5+2] cycloadditions
 - Perylene-type [5+2] cycloadditions
 - [5+2] cycloadditions of vinyl cyclopropanes (VCPs)
 - **[5+2] cycloadditions of five-carbon organometallic complexes**
- Summary



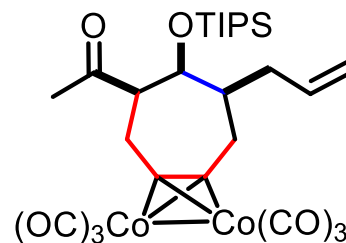
This process can be considered as a novel "interrupted Nazarov" cyclization, in which the cationic intermediate is intercepted prior to the electrocyclization.



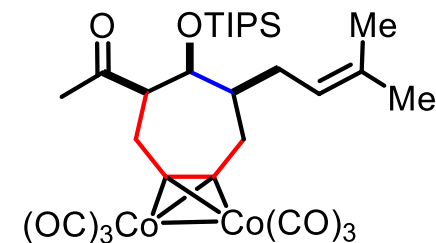
120a, 69%



120b, 77%

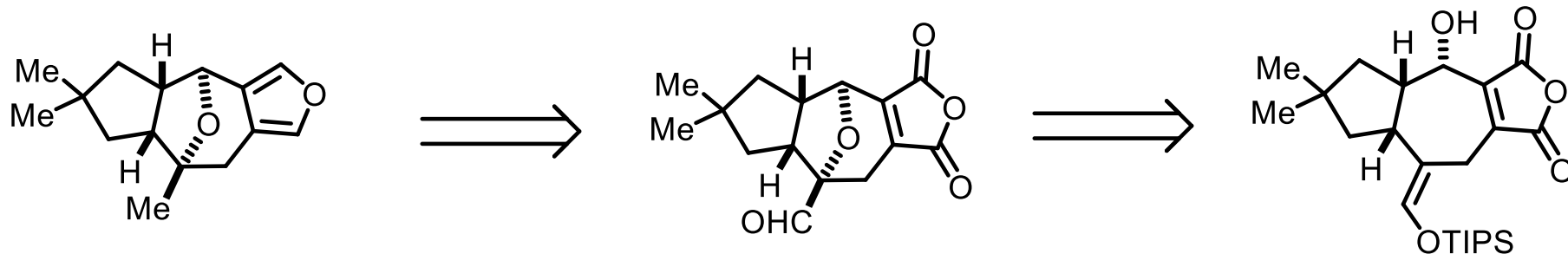
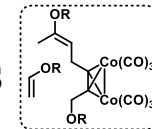


120c, 76%

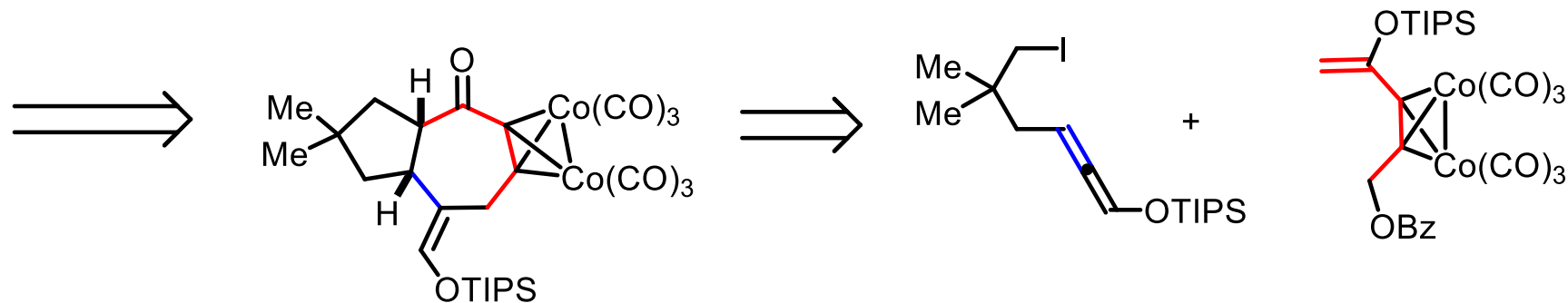


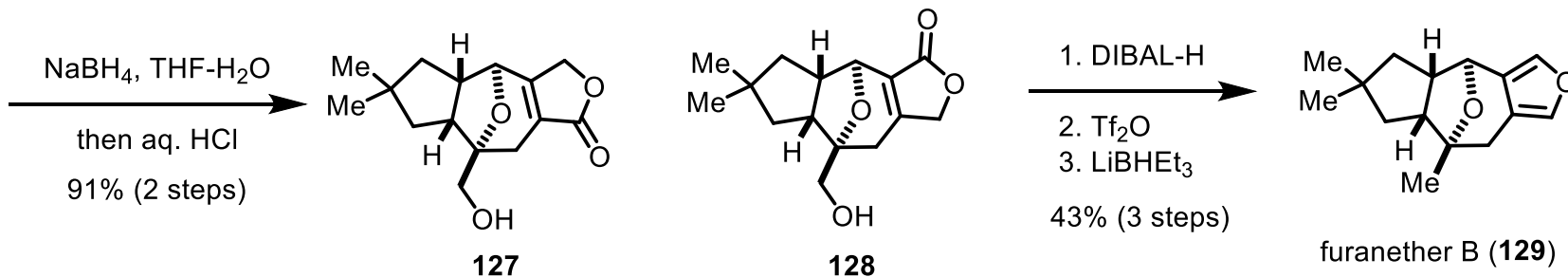
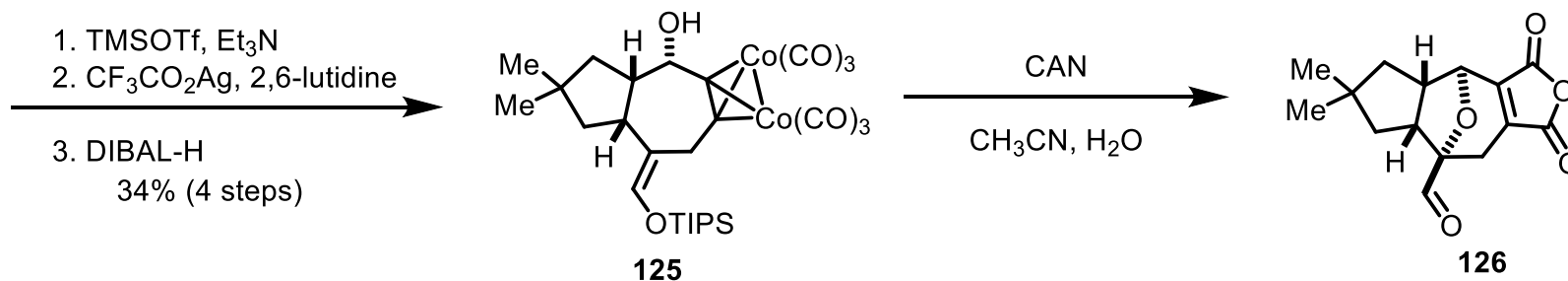
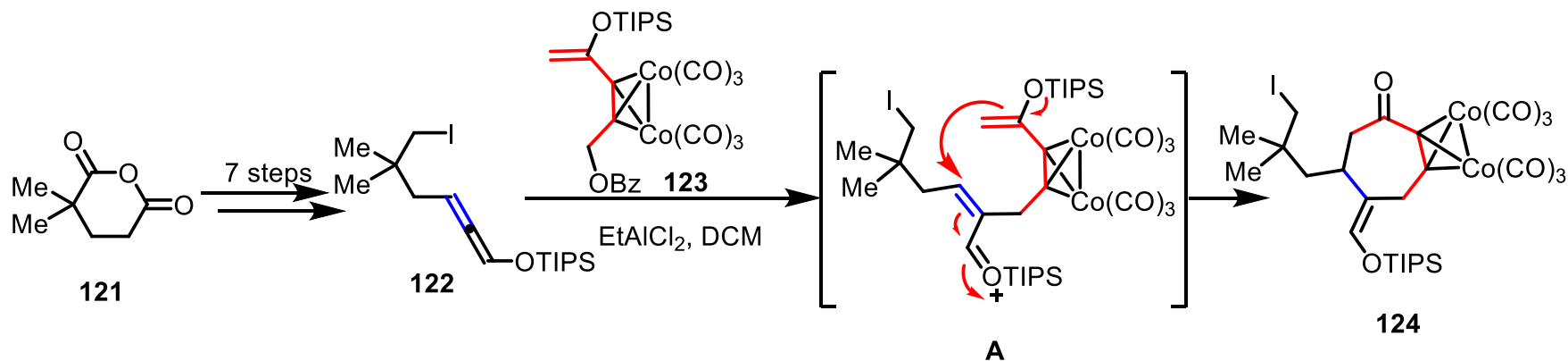
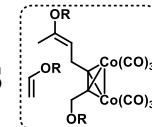
120d, 86%

M. Kudo, F. Kondo, H. Maekawa, T. Shimizu, M. Miyashita, K. Tanino, *Tetrahedron Lett.* **2014**, 55, 1192.



furanether B (129)

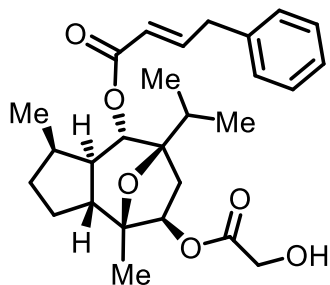
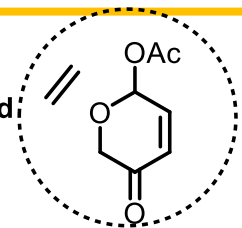




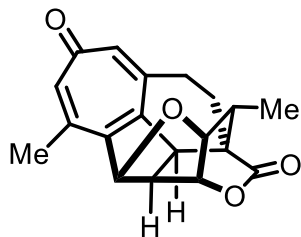
Index

- Introduction
- Main Contents
 - Oxidopyrylium-mediated [5+2]cycloaddition
 - Pyridinium and quinolinium-mediated [5+2] cycloadditions
 - Perezone-type [5+2] cycloadditions
 - [5+2] cycloadditions of vinyl cyclopropanes (VCPs)
 - [5+2] cycloadditions of five-carbon organometallic complexes
- Summary

Oxidopyrylium-mediated
[5+2] cycloaddition

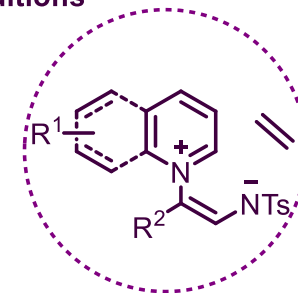
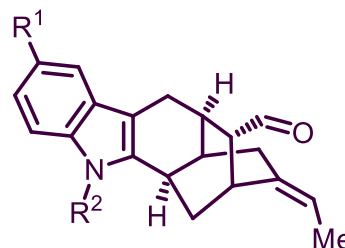


(±)-englerin A (**14**)



harringtonolide (**23**)

Pyridinium- and quinolinium-mediated
[5+2] cycloadditions

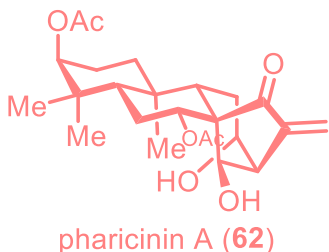
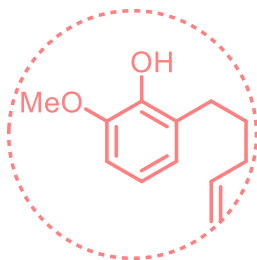


vellosimine ($R^1 = R^2 = H$; 58%) (**43**)

N-methylvellosimine ($R^1 = H, R^2 = Me$; 52%) (**44**)

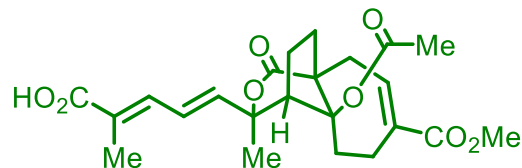
10-methoxy-vellosimine ($R^1 = OMe, R^2 = H$; 63%) (**45**)

Perezone-type [5+2]
cycloadditions



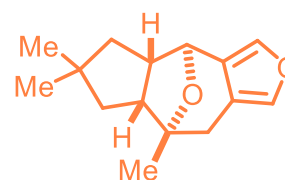
pharicin A (**62**)

[5+2] cycloadditions
of vinyl cyclopropanes (VCPs)

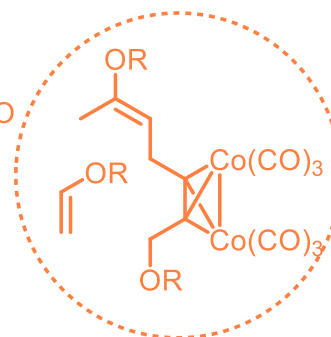


pseudolaric acid B (**104**)

[5+2] cycloadditions of five-carbon
organometallic complexes



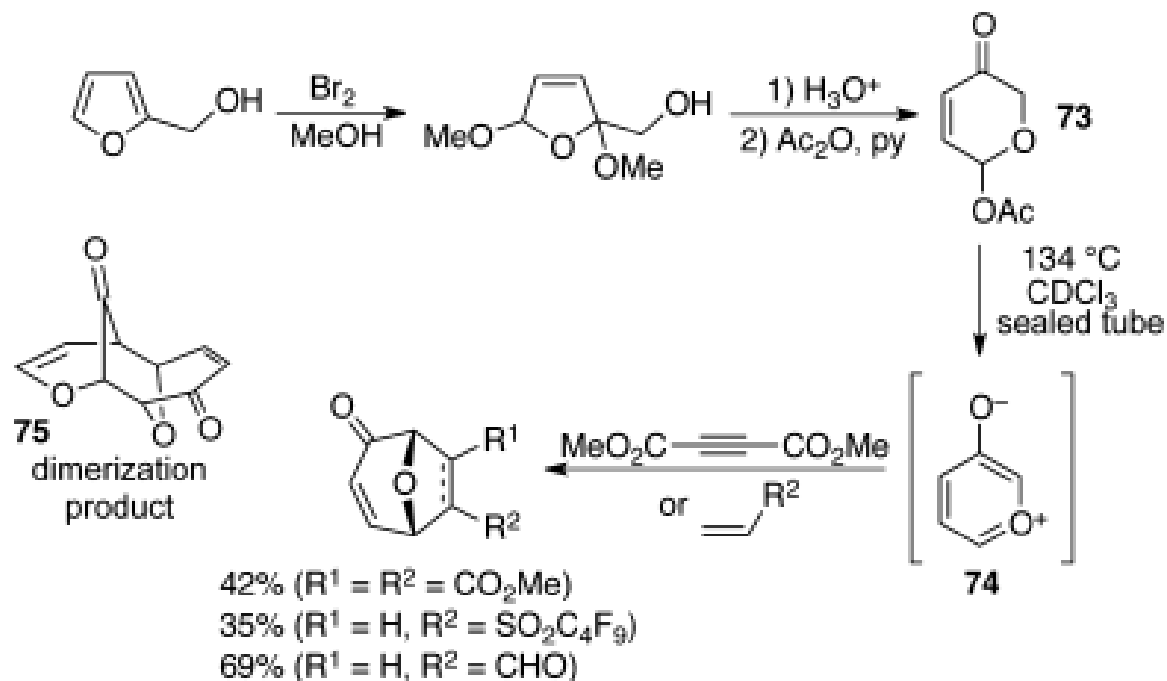
furanether B (**129**)



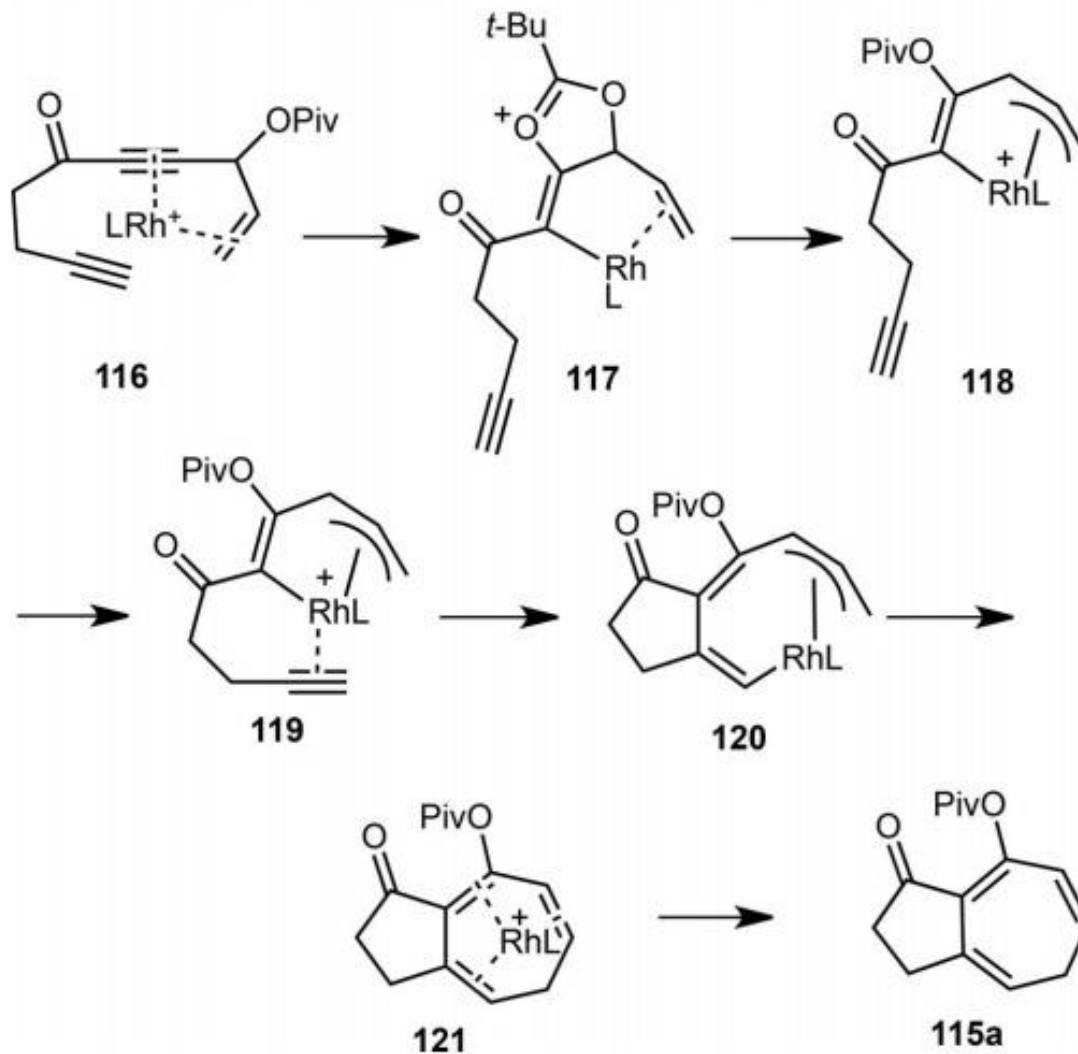
This seminar mainly introduce five kinds of strategies to synthesize 7-membered ring and its application in natural product. As you can see, every strategy has unique feature, but these two strategies are most commonly used in total synthesis.

Thank you !

Scheme 23. [5 + 2] Cycloaddition via Group Elimination

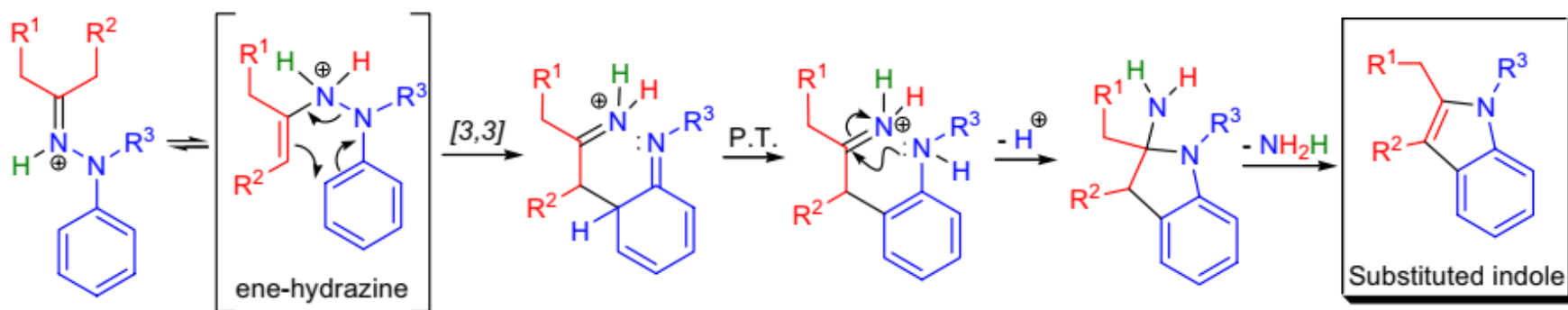
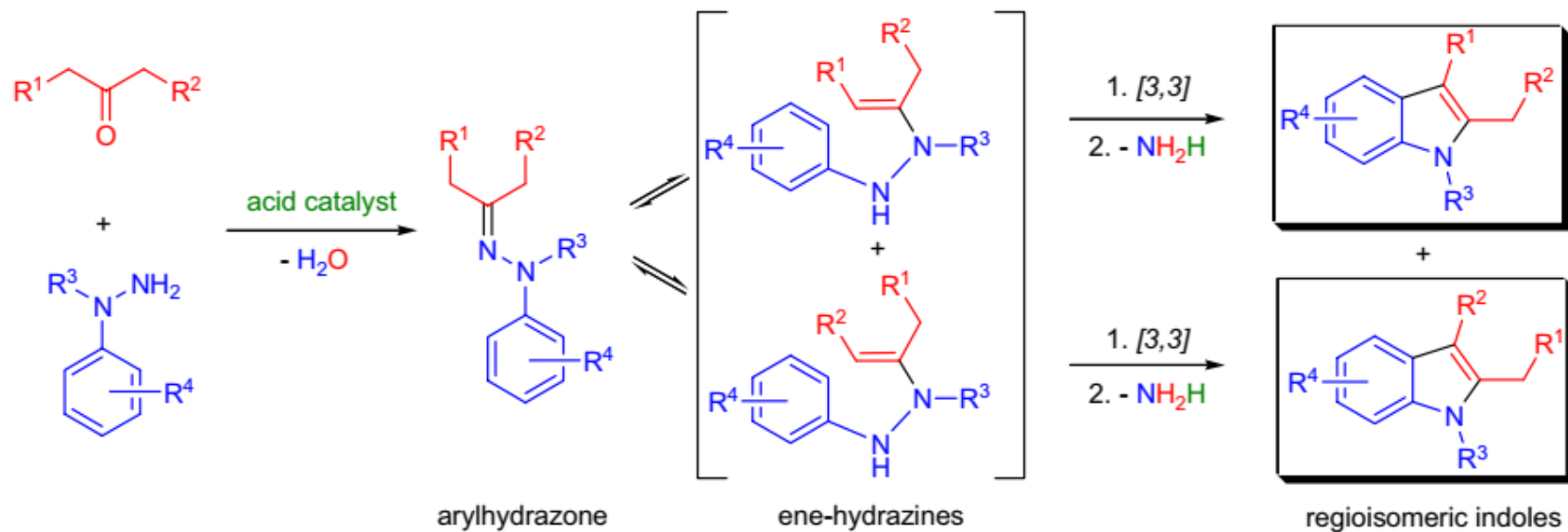


proposed mechanism (with $R^1 = R^2 = R^4 = R^5 = R^6 = H$, $R^3 = \text{Piv}$):



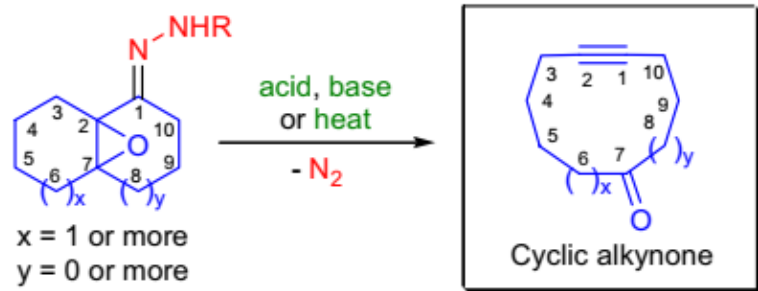
Scheme 36. Intramolecular [5+2] cycloaddition of inverted 3-acyloxy-1,4-enynes and alkynes.

Fischer indole synthesis

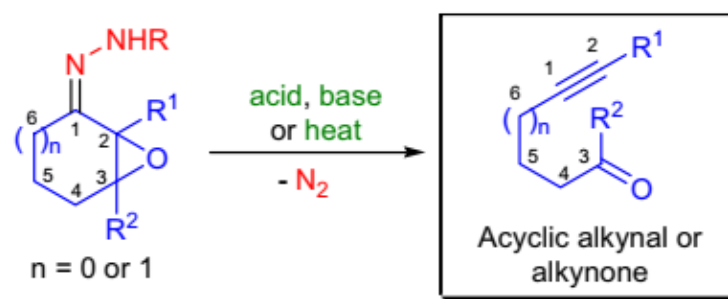


Eschenmoser-Tanabe fragmentation

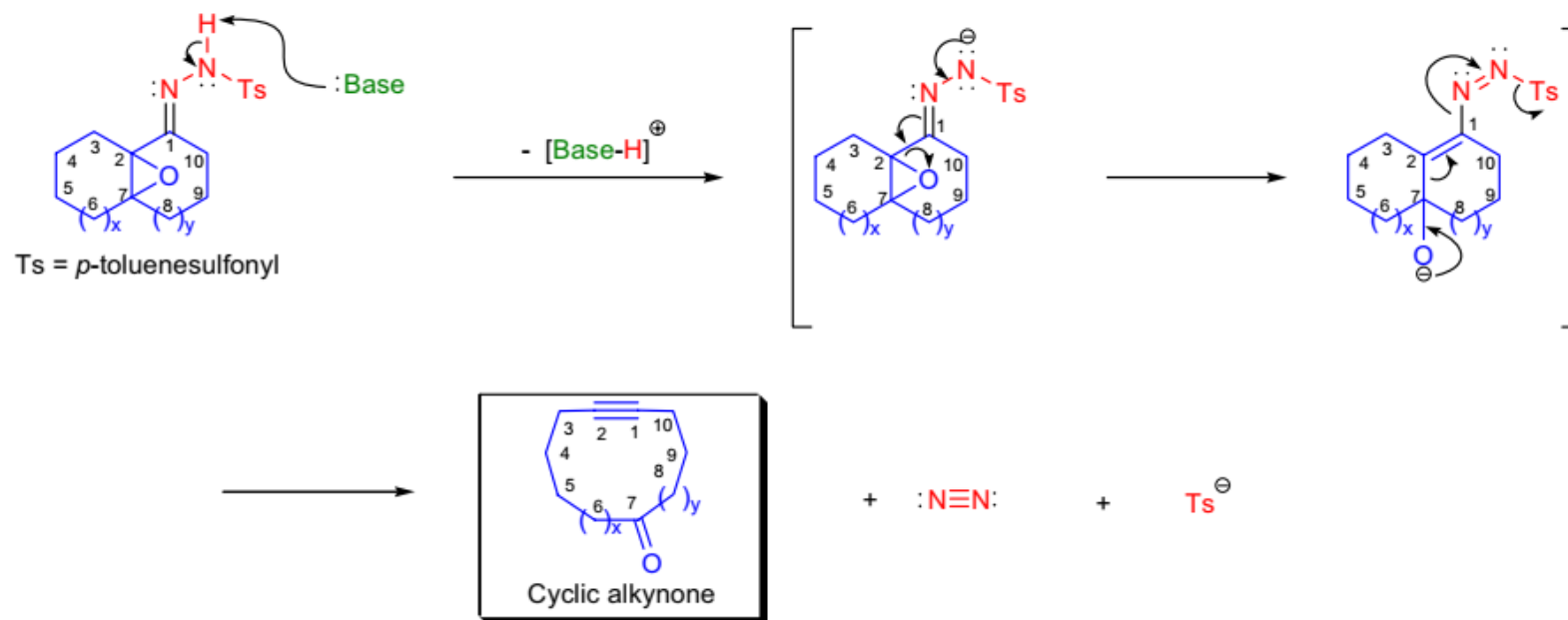
Synthesis of cyclic alkynes:



Synthesis of acyclic alkynes and alkynals:



R = tosyl, 2,4-dinitrophenyl; R¹⁻² = H, alkyl; when R² = H, then the product is an alkynal, and when R² = alkyl, then it is an alkyne



Eschenmoser-Tanabe fragmentation

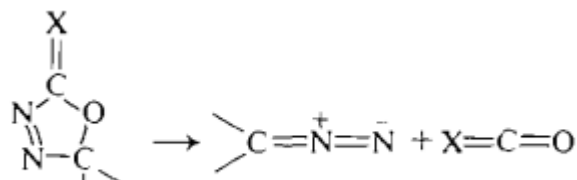
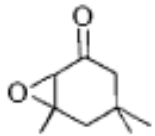
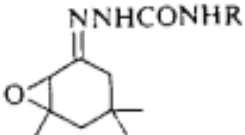
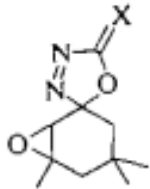

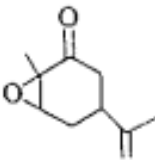
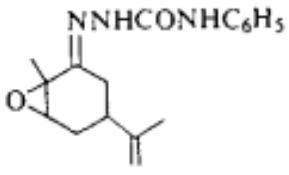
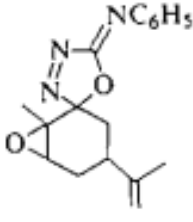
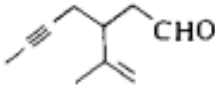
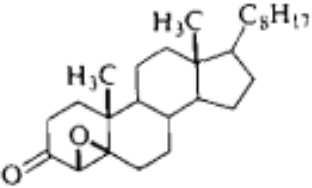
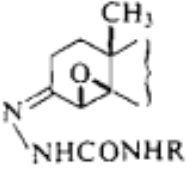
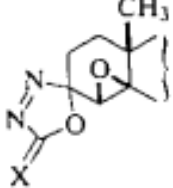
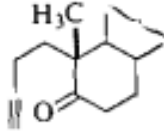
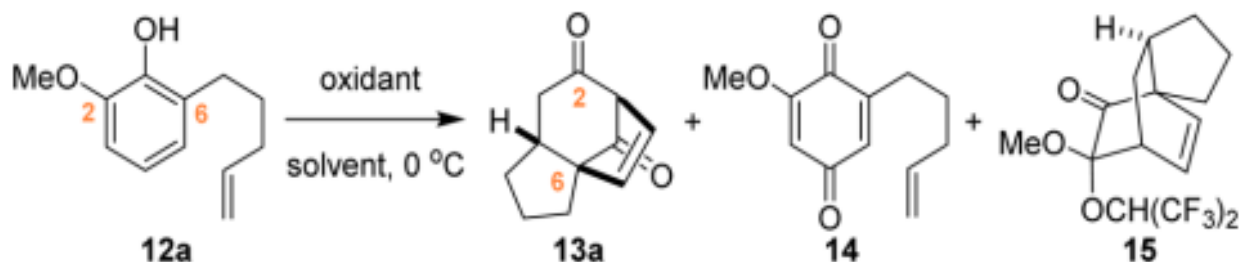


TABLE 1. α,β -Epoxyketone derivatives and thermolysis products

α,β -Epoxyketone	Semi-carbazone	Oxadiazoline	Acetylenic carbonyl	Isolated yield (%)
 1	 6 R = H 7 R = C ₆ H ₅	 13 X = O 14 X = NC ₆ H ₅	 20	44 ^a , 71 ^b
 2	 8	 15	 21	53 ^b
 3	 9 R = H 10 R = C ₆ H ₅	 16 X = NH 17 X = NC ₆ H ₅	 22	38 ^a , 64 ^b

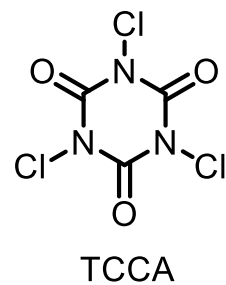
**Table 1. Optimization of the ODI-[5+2] Cycloaddition/
Pinacol-Type 1,2-Acyl Migration Cascade^a**



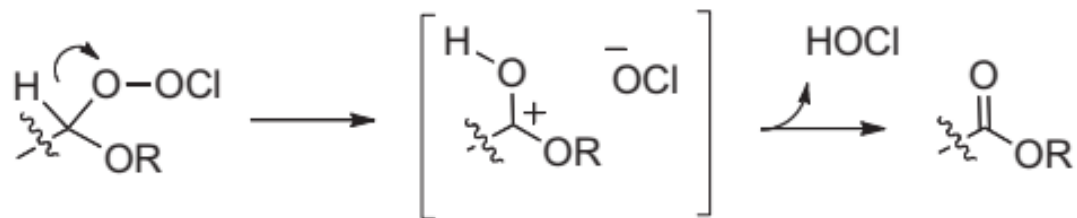
entry	oxidant	solvent	yield (%) ^b		
			13a	14	15
1	Pb(OAc) ₄ ^c	CHCl ₃	7	15	
2	PhI(OAc) ₂	CHCl ₃	16	30	
3	PhI(OAc) ₂	TFE	42	23	
4	PhI(OAc) ₂	HFIP	63	<5	18
5	PhI(CF ₃ CO ₂) ₂	HFIP	78	<5	<5

^aUnless stated otherwise, the reactions were performed with **12a** (0.2 mmol) and oxidant (1.1 equiv) in solvent (4 mL) at 0 °C for 20 min.

^bIsolated yields. ^cRun at -40 °C for 10 min. TFE = 2,2,2-trifluoroethanol, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.



Heterolytic fragmentation



Scheme 4. Mechanistic possibilities.