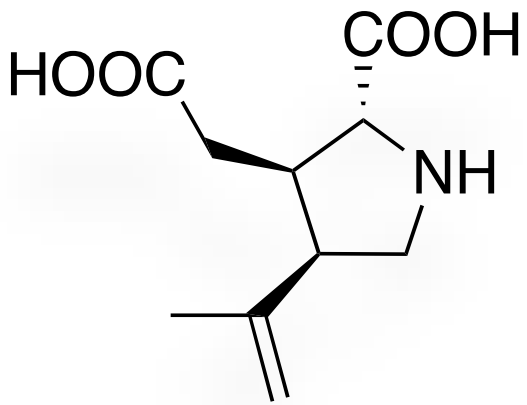


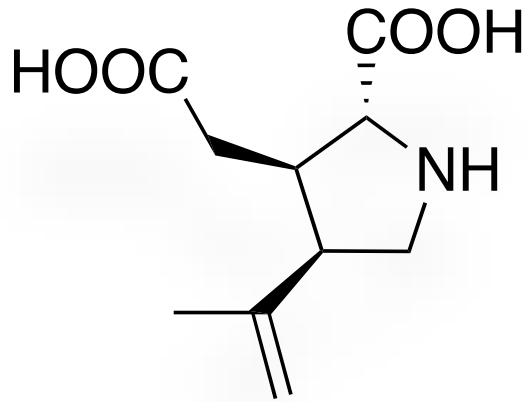
Kainic Acid



Reporters: **Yijun Wu** **Xiaoyun Liao** **Mingze Yang**

Supervisors: ***Prof.*** **Tao Ye,** ***Dr.*** **Yian Guo**

Classical Synthesis of Kainic Acid



- **Reporter: Yijun Wu**
- **Supervisors: *Prof.* Tao Ye, *Dr.* Yian Guo**
- **October 5th, 2020**

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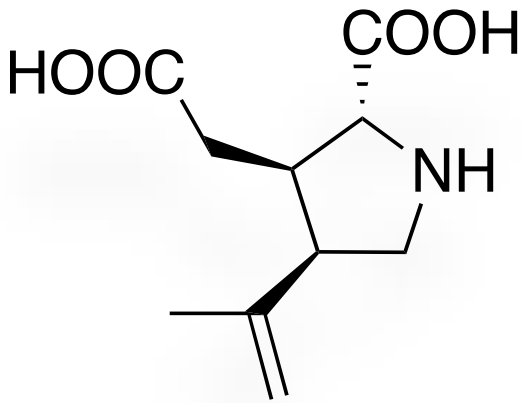
Background Information about Kainic Acid

Introduction

Introduction

Kainic Acid (KA) , or kainate, is an acid that naturally occurs in some seaweed. Kainic acid is a potent neuroexcitatory amino acid agonist that acts by activating receptors for glutamate, the principal excitatory neurotransmitter in the central nervous system.



Introduction

Kainic acid is a direct agonist of the glutamic kainate receptors and large doses of concentrated solutions produce immediate neuronal death by overstimulating neurons to death. Such damage and death of neurons is referred to as an excitotoxic lesion. Thus, in large, concentrated doses kainic acid can be considered a neurotoxin, and in small doses of dilute solution kainic acid will chemically stimulate neurons.

Total Synthesis of Kainic Acid

Total Synthesis of Kainic Acid

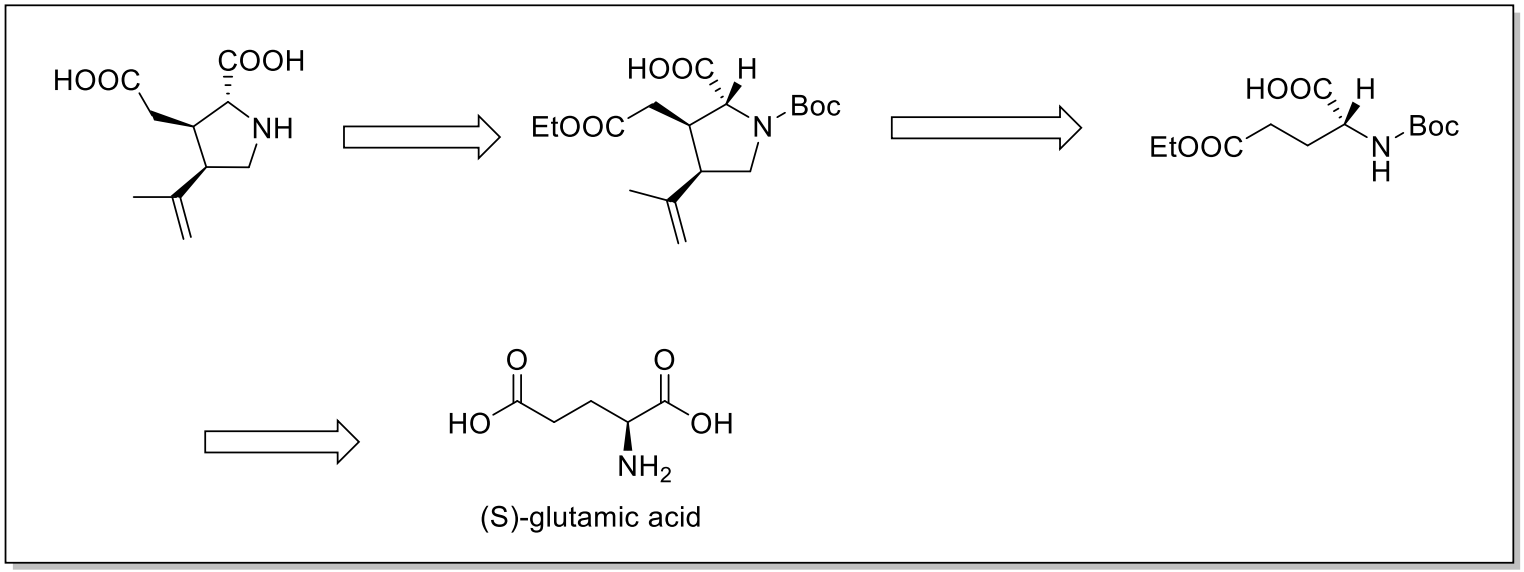
Approach for Stereocenters

- Chain Synthesis
  - Oppolzer, W.; Thirring, K., Enantioselective synthesis and absolute configuration of (-)-.alpha.-kainic acid. Journal of the American Chemical Society **1982**, 104 (18), 4978-4979.
  - hevliakov, M. V.; Montgomery, J., A Stereodivergent Approach to (−)-α-Kainic Acid and (+)-α-Allokainic Acid Utilizing the Complementarity of Alkyne and Allene Cyclizations. Journal of the American Chemical Society **1999**, 121 (48), 11139-11143.
- Ring Cut Down
  - Hanessian, S.; Ninkovic, S., Stereoselective Synthesis of (−)-α-Kainic Acid and (+)-α-Allokainic Acid via Trimethylstannyl-Mediated Radical Carbocyclization and Oxidative Destannylation. The Journal of Organic Chemistry **1996**, 61 (16), 5418-5424.
  - Nakagawa, H.; Sugahara, T.; Ogasawara, K., A concise route to (-)-kainic acid. Org Lett **2000**, 2 (20), 3181-3.
- Direct entry

Total Synthesis of Kainic Acid

Approach for Stereocenters

- Chain Synthesis

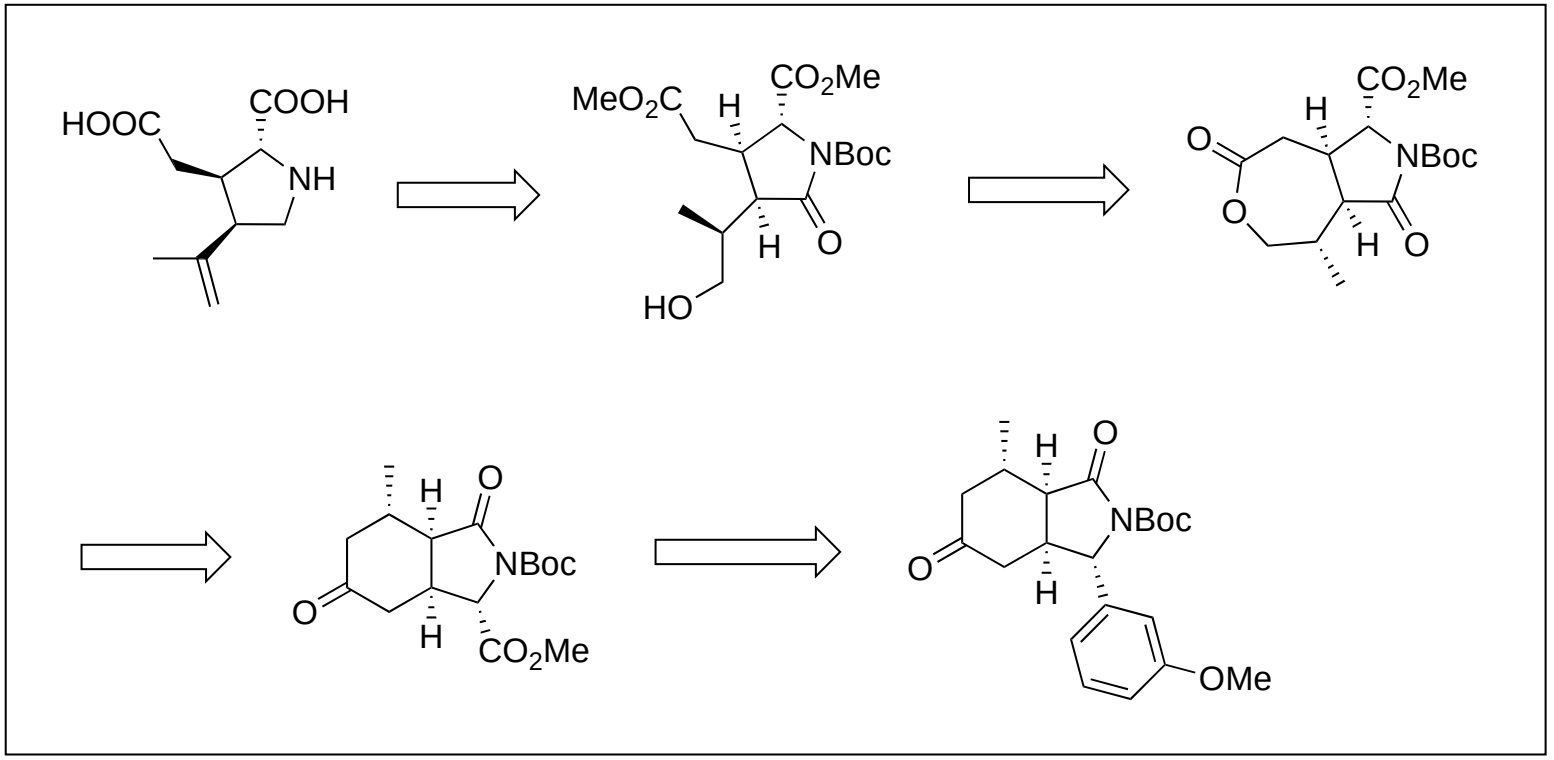


Clayden, J.; Menet, C. J.; Tchabanenko, K., *Tetrahedron* **2002,** *58* (23), 4727-4733.

Total Synthesis of Kainic Acid

Approach for Stereocenters

- Ring Cut Down

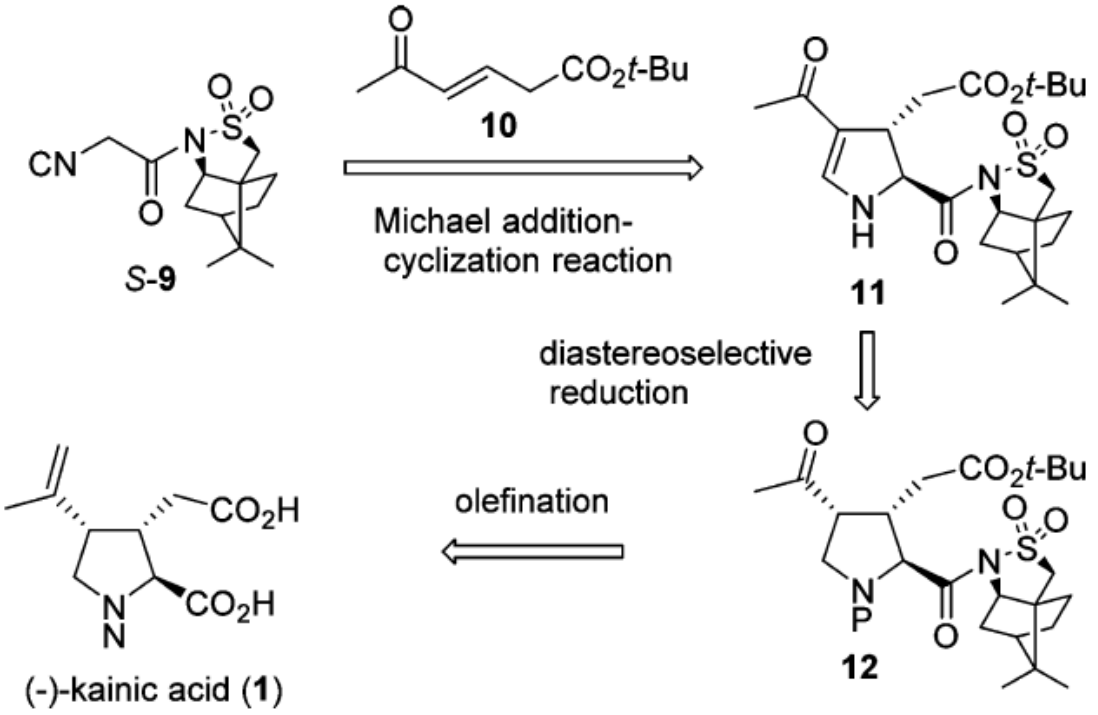


Clayden, J.; Menet, C. J.; Tchabanenko, K., *Tetrahedron* **2002,** *58* (23), 4727-4733.

Total Synthesis of Kainic Acid

Approach for Stereocenters

- Direct entry



Oe, K.; Ohfune, Y.; Shinada, T., *Org Lett* **2014,** *16* (9), 2550-3.

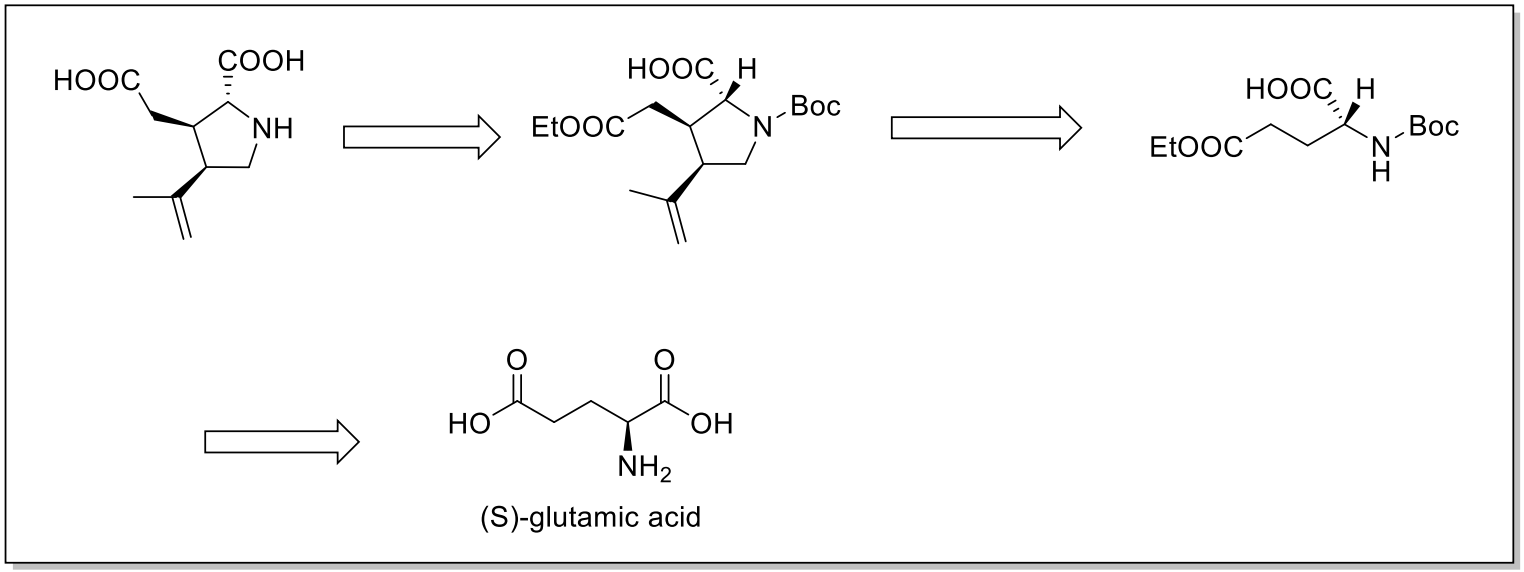
Wolfgang Oppolzer, Chemischer Informationsdienst 1982

Total Synthesis of Kainic Acid

Total Synthesis of Kainic Acid

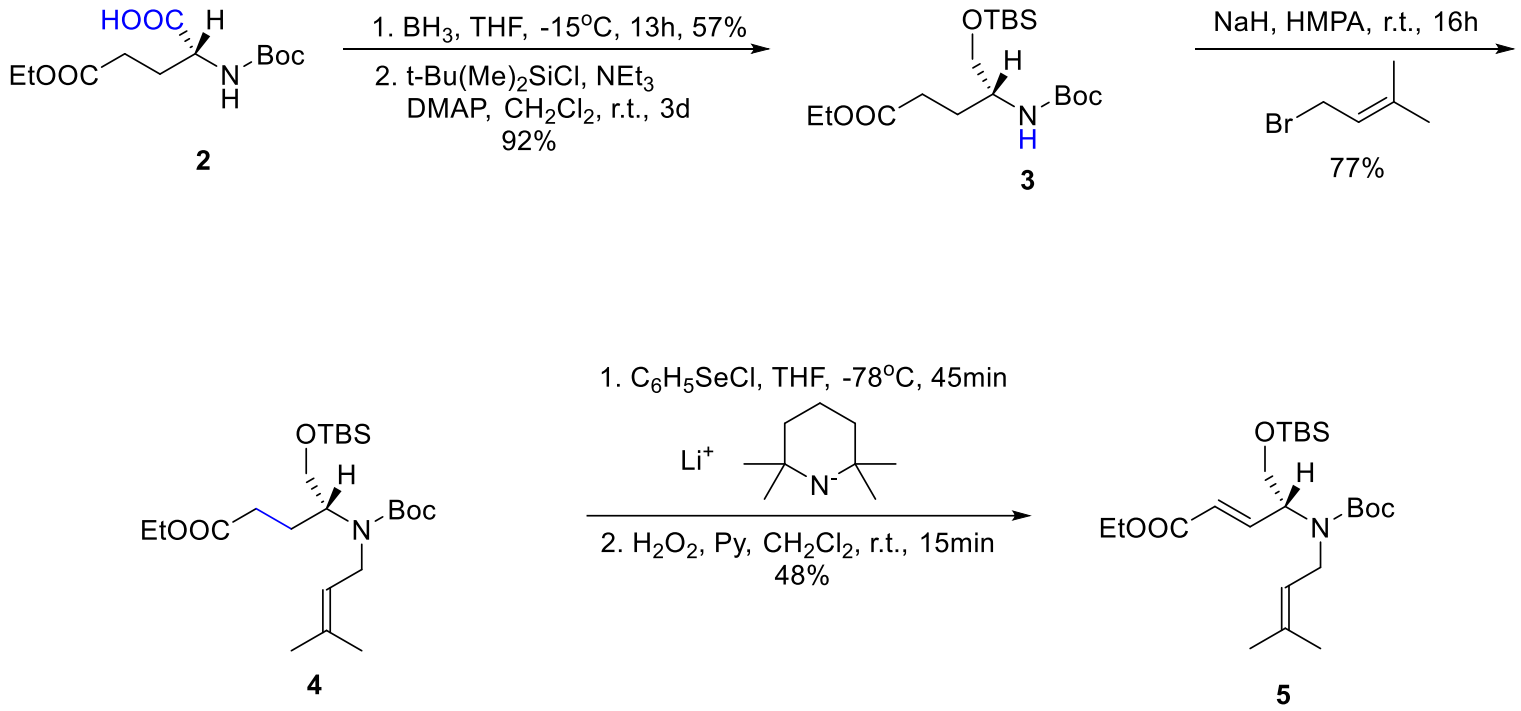
Synthesis Route

- Retrosynthesis



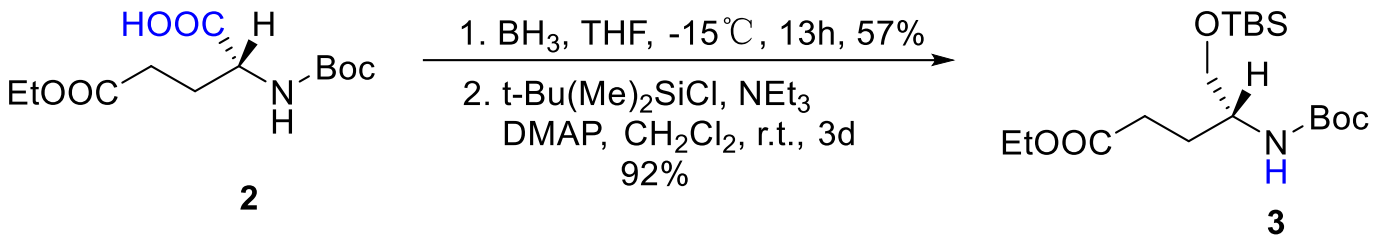
Total Synthesis of Kainic Acid

Synthesis Route

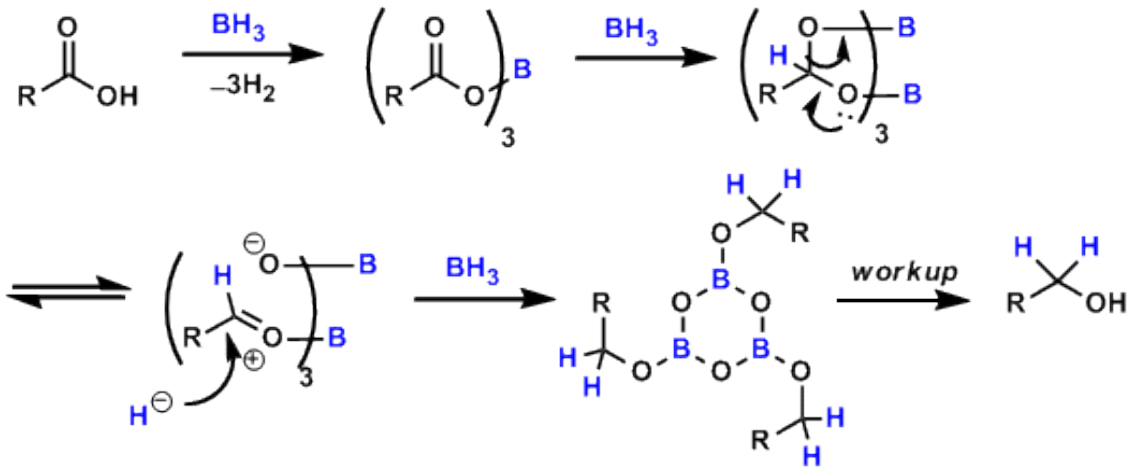


Total Synthesis of Kainic Acid

Reduction & Protection

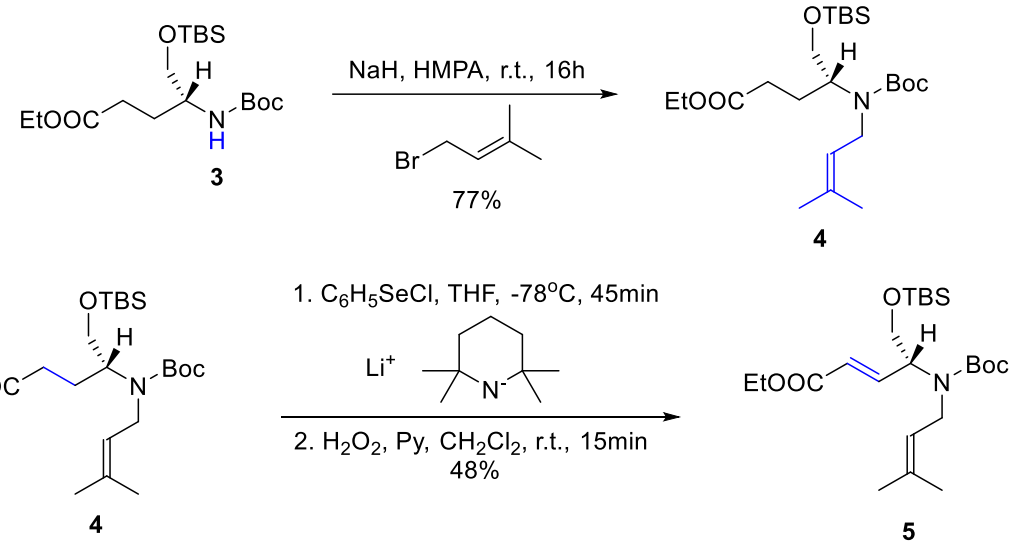


Mechanism

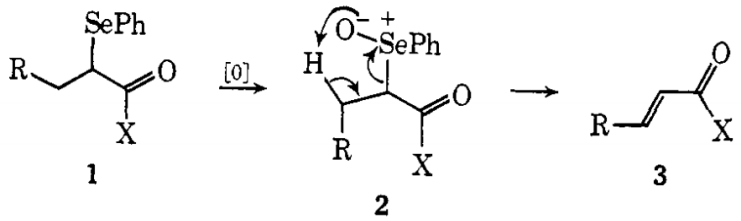


Total Synthesis of Kainic Acid

Alkenylation



Mechanism



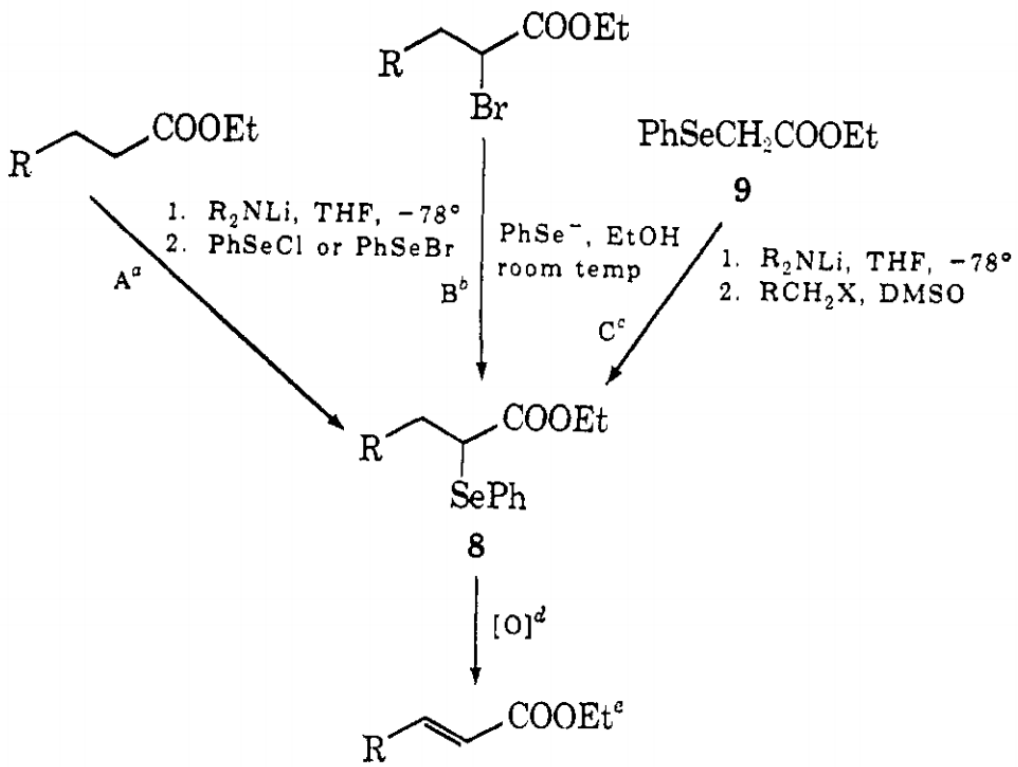
X can be hydrogen, alkyl, or alkoxy

Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y., *Journal of the American Chemical Society* **1973,** *95* (18), 6137-6139.

Total Synthesis of Kainic Acid

Alkenylation

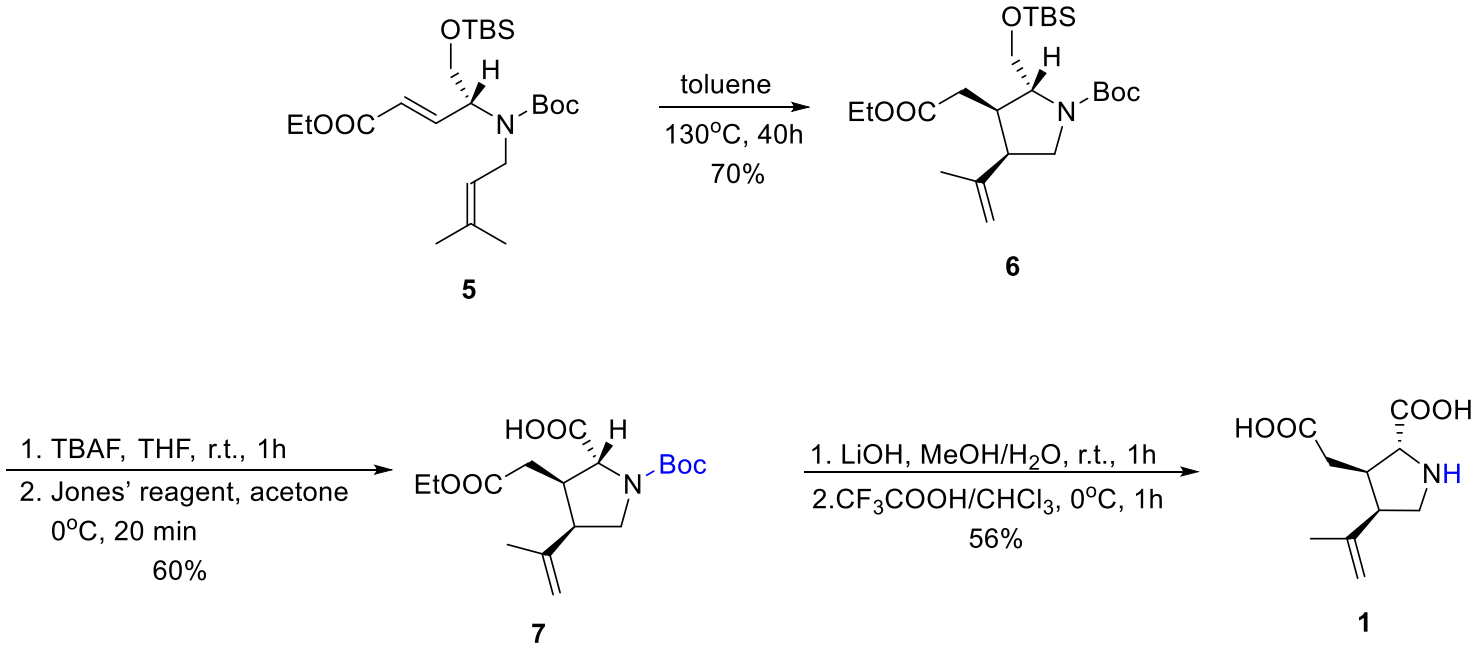
Mechanism



Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y., *Journal of the American Chemical Society* **1973,** *95* (18), 6137-6139.

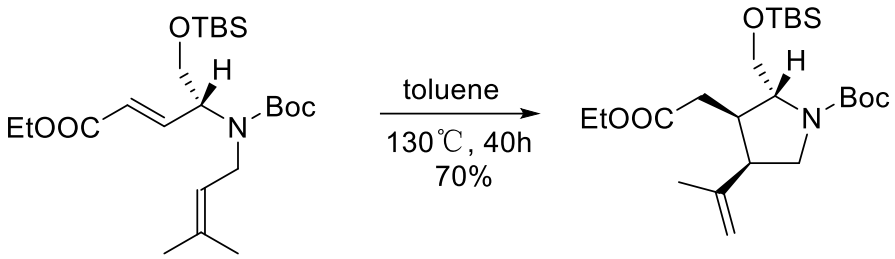
Total Synthesis of Kainic Acid

Synthesis Route

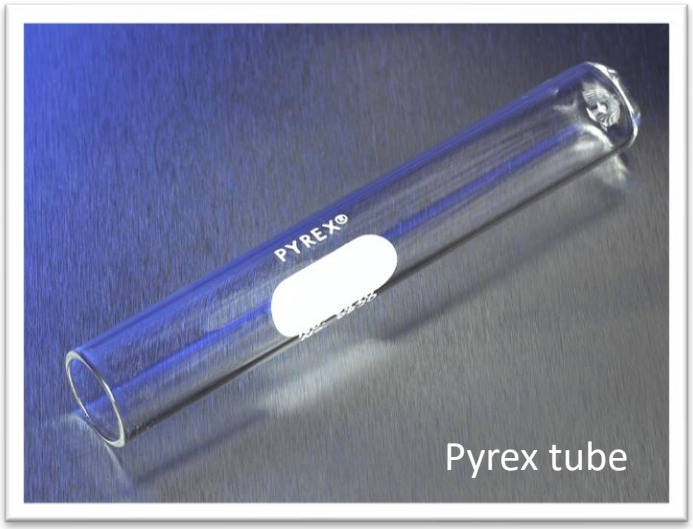


Total Synthesis of Kainic Acid

Cyclization

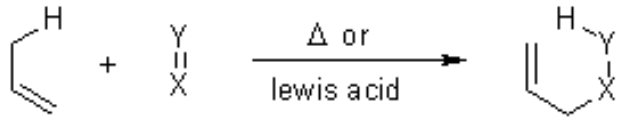


5 **6**



Mechanism

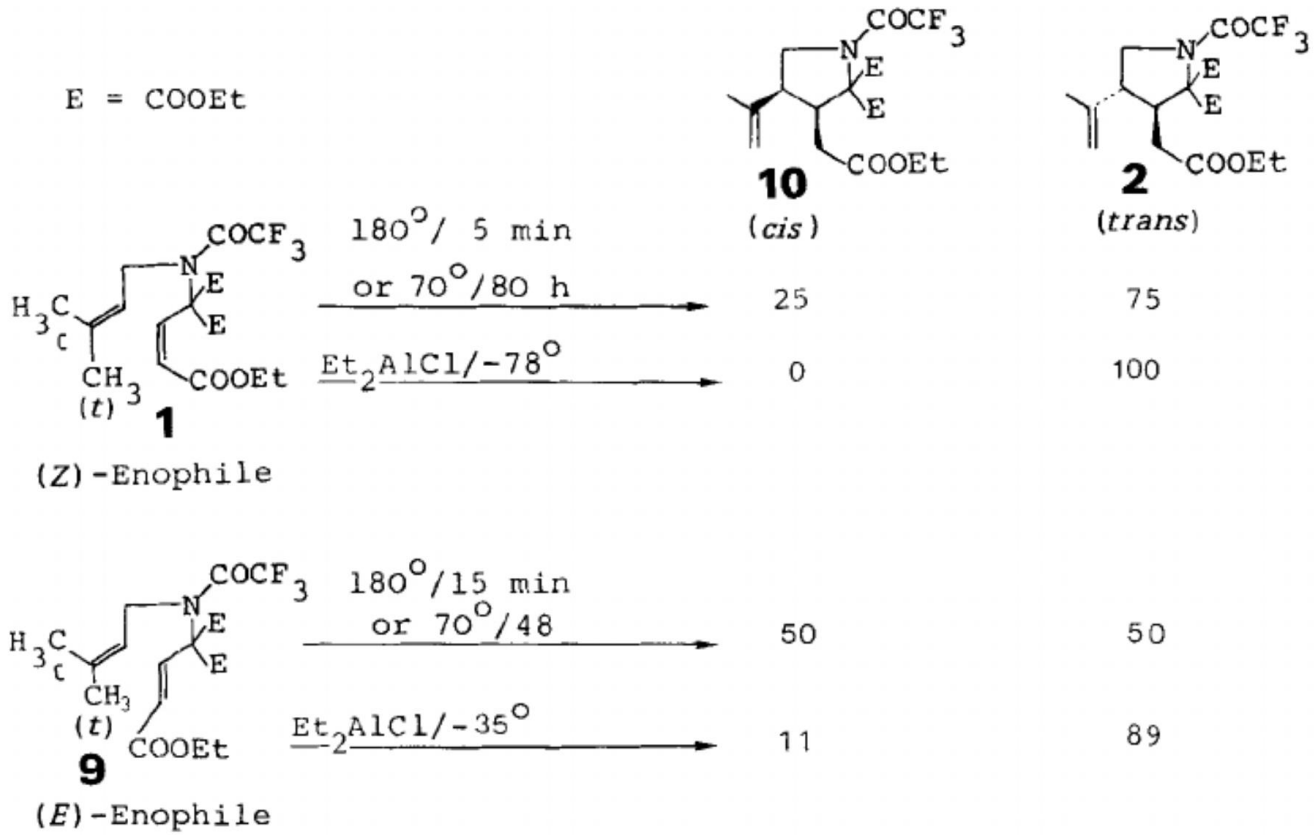
Ene Reaction



Total Synthesis of Kainic Acid

Cyclization

Mechanism

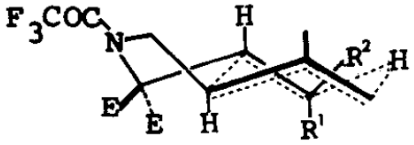


Oppolzer, W.; Robbiani, C., Helvetica Chimica Acta **1980**, 63 (7), 2010-2014.

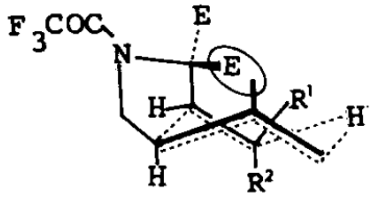
Total Synthesis of Kainic Acid

Cyclization

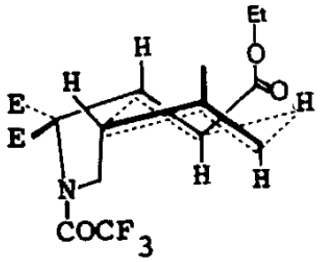
Mechanism



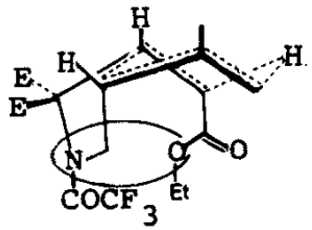
t-Ene → **2** *(trans)*
A (*Z*)-Enophile (R^1 = COOEt)
B (*E*)-Enophile (R^2 = COOEt)



t-Ene → **10** *(cis)*
C (*Z*)-Enophile (R^1 = COOEt)
D (*E*)-Enophile (R^2 = COOEt)
strong repulsion



c-Ene → **10** *(cis)*
F (*E*)-Enophile

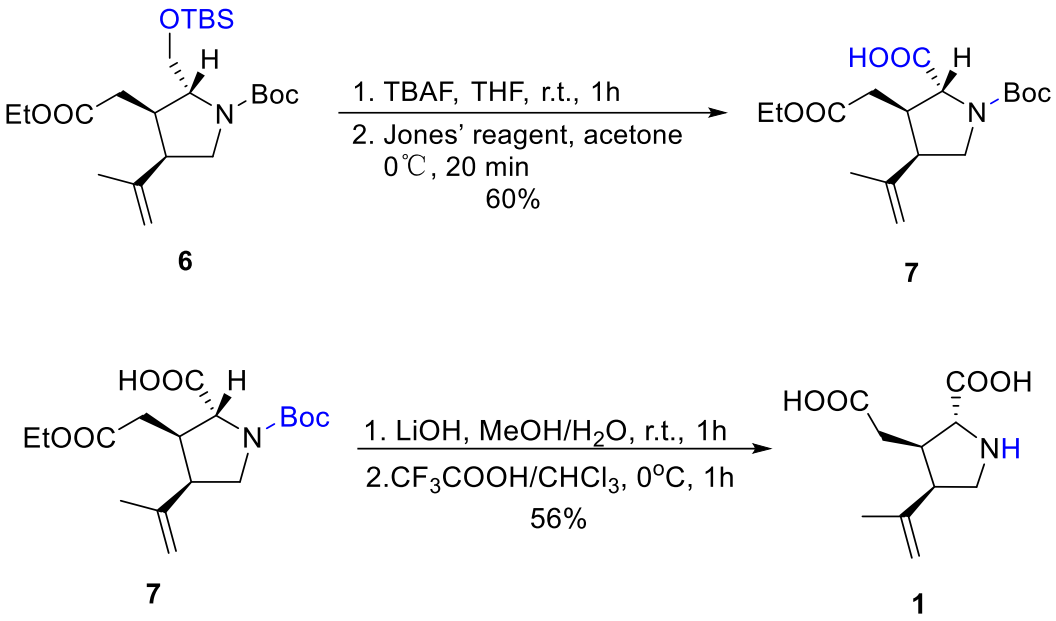


c-Ene → **10** *(cis)*
E (*Z*)-Enophile
moderate repulsion

Oppolzer, W.; Robbiani, C., Helvetica Chimica Acta **1980**, 63 (7), 2010-2014.

Total Synthesis of Kainic Acid

Deprotection & Oxidation



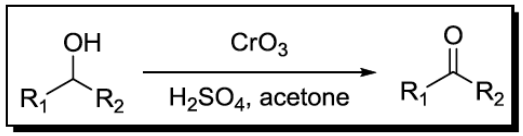
Q: What is the mechanism of Jones' Oxidation?

Total Synthesis of Kainic Acid

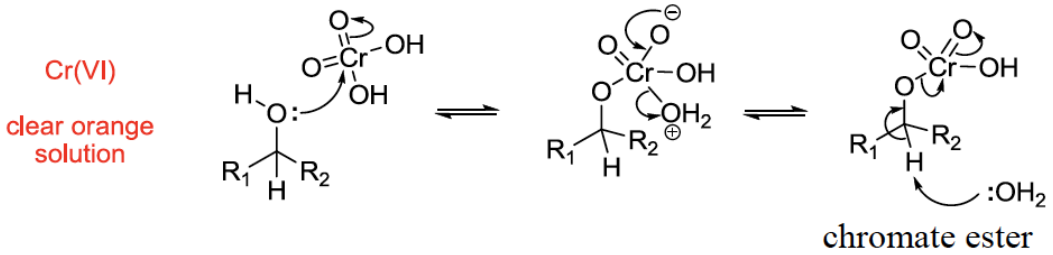
Hydrolysis & Deprotection

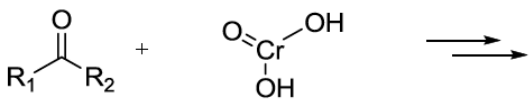
Mechanism

Jones' Oxidation



$CrO_3 + H_2O \longrightarrow H_2CrO_4$



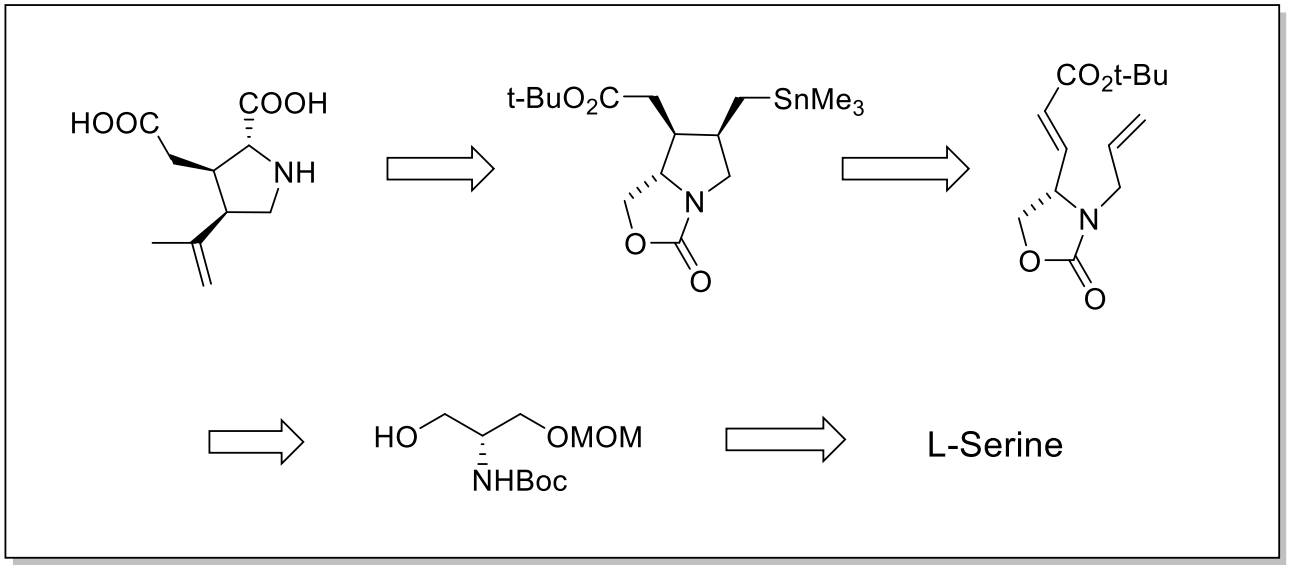


Stephen Hanessian, The Journal of Organic Chemistry 1996.

Total Synthesis of Kainic Acid

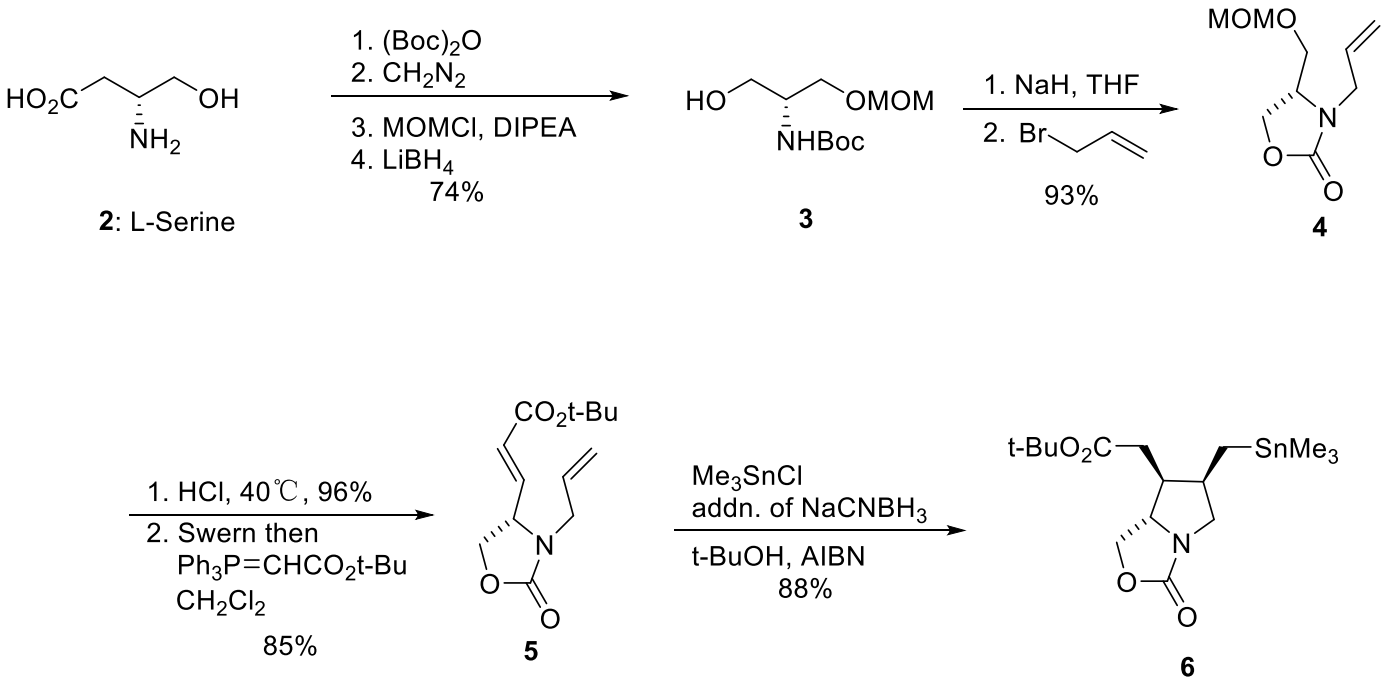
Total Synthesis of Kainic Acid

Retrosynthesis



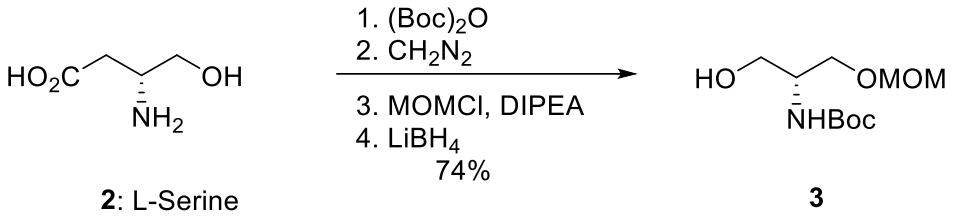
Total Synthesis of Kainic Acid

Synthesis route



Total Synthesis of Kainic Acid

Protection & Reduction

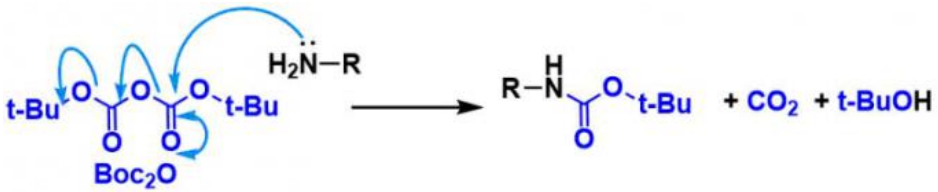


2: L-Serine

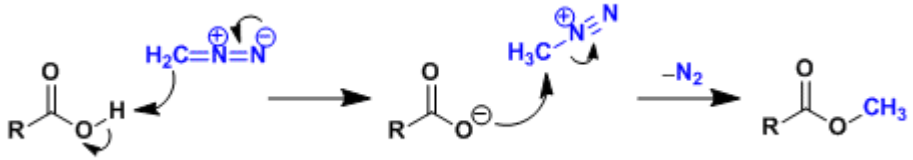
3

Mechanism

Boc Protection

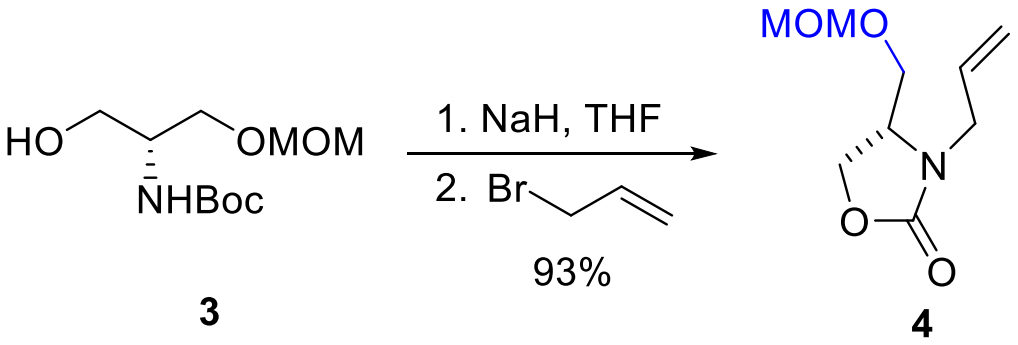


Methylation



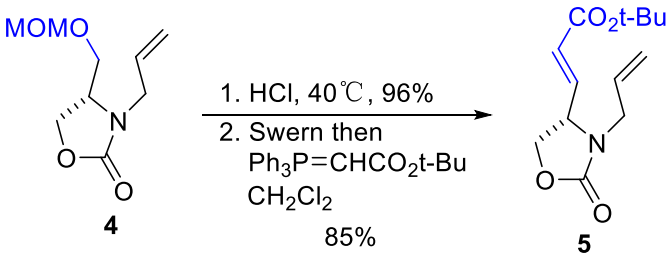
Total Synthesis of Kainic Acid

Alkylation



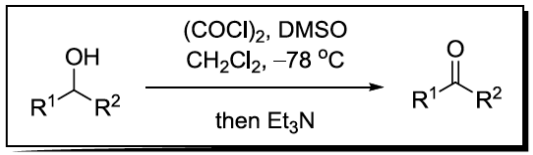
Total Synthesis of Kainic Acid

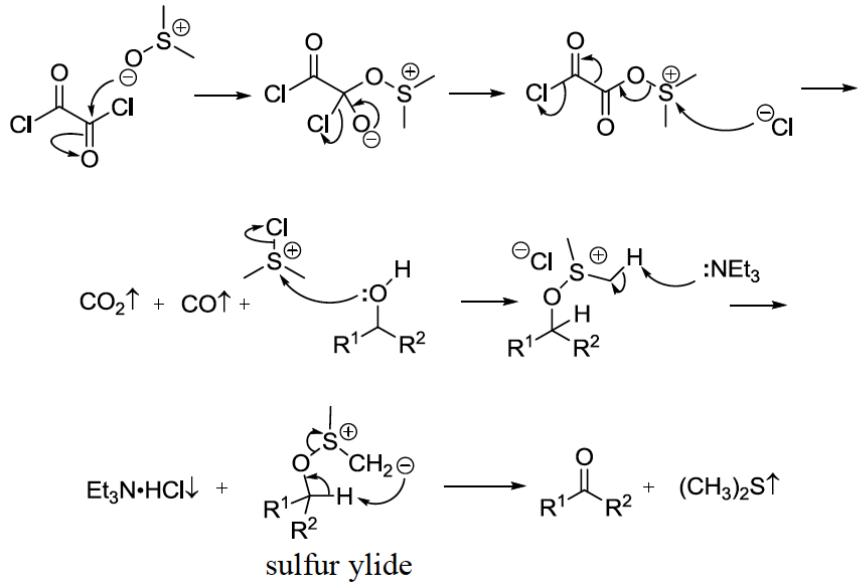
Deprotection, Oxidation & Olefination



Mechanism

Swern Oxidation



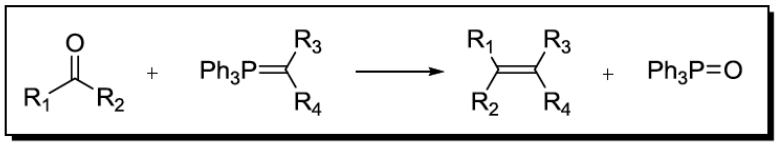


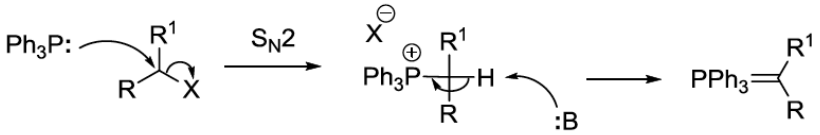
Total Synthesis of Kainic Acid

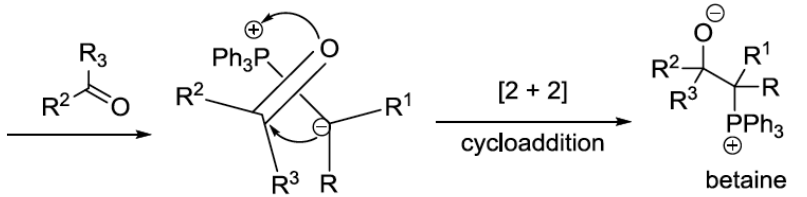
Deprotection, Oxidation & Olefination

Mechanism

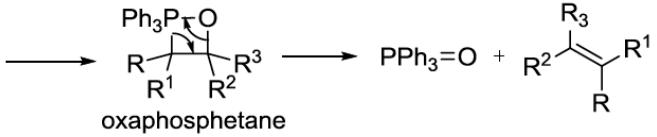
Wittig Reaction





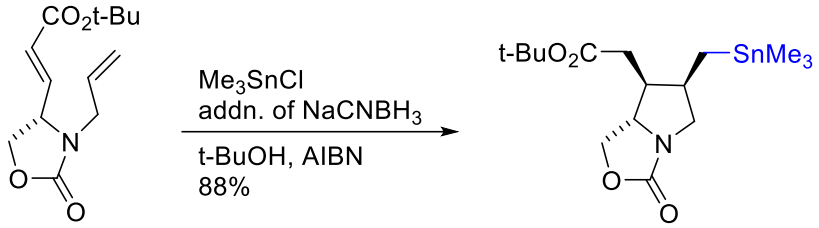


The "puckered" transition state, irreversible and concerted



Total Synthesis of Kainic Acid

Cyclization



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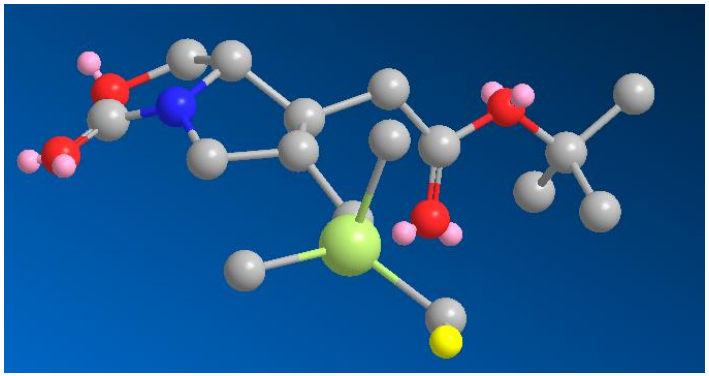
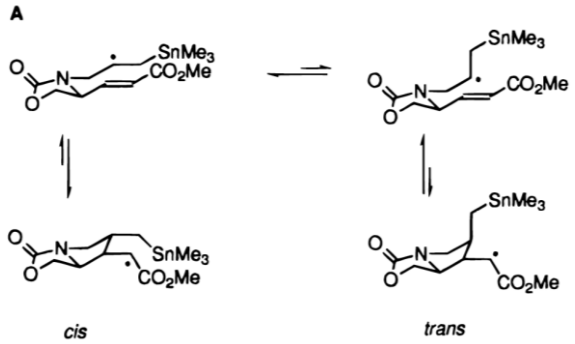
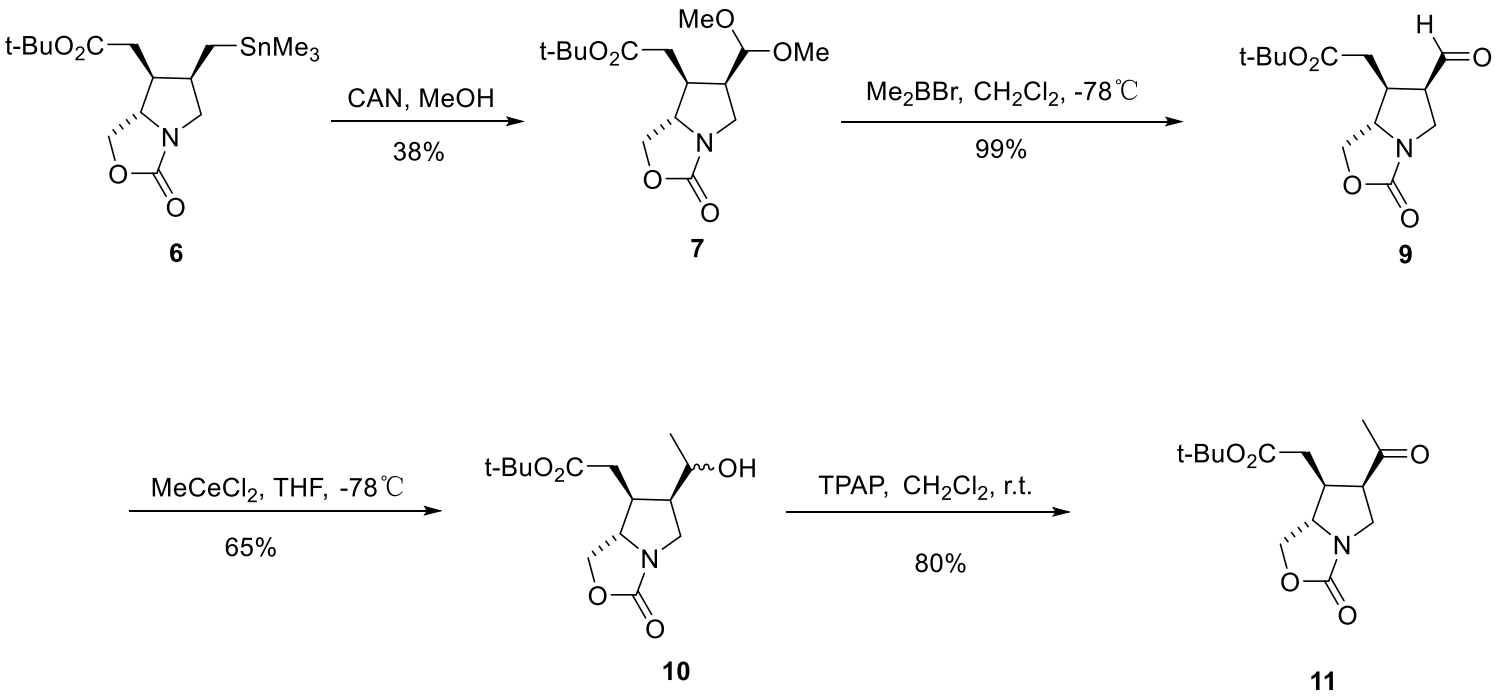
Mechanism





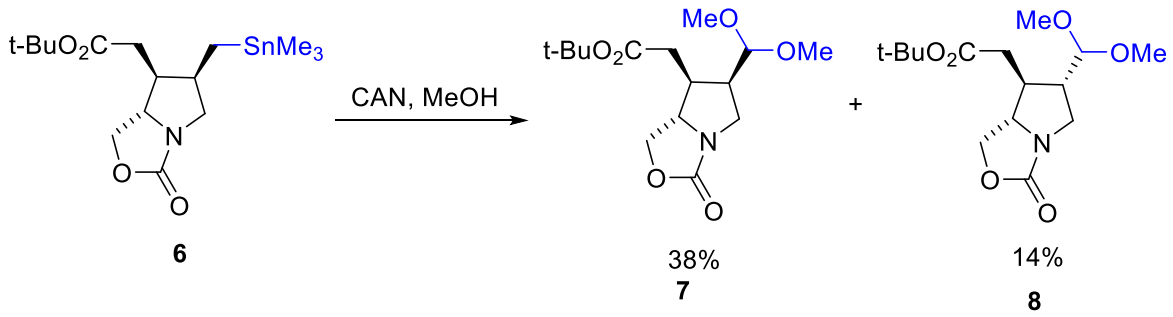
Total Synthesis of Kainic Acid

Synthesis route

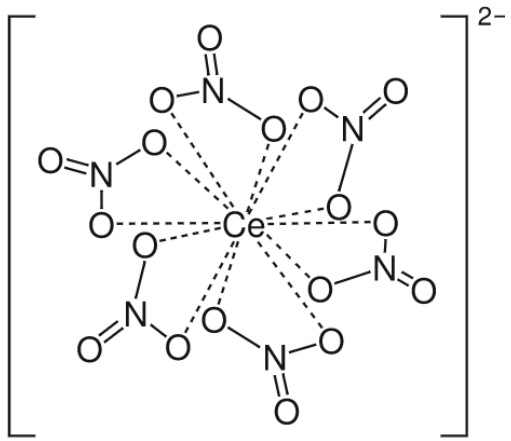


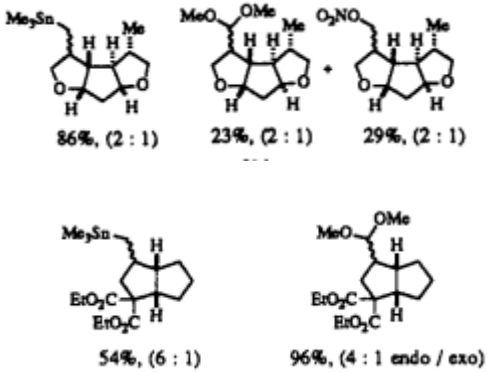
Total Synthesis of Kainic Acid

Oxidation



Mechanism

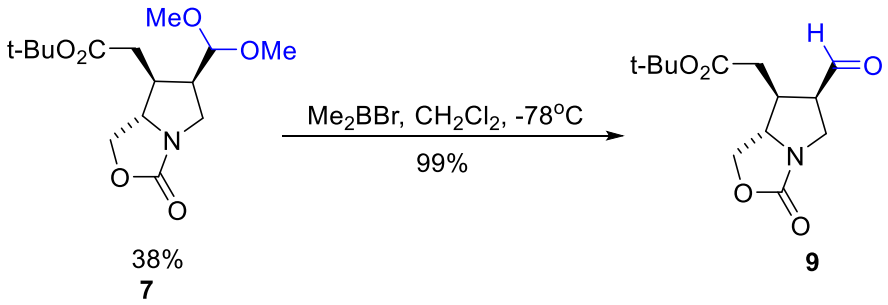




Hanessian, S.; Leger, R., Journal of the American Chemical Society **1992**, 114 (8), 3115-3117.

Total Synthesis of Kainic Acid

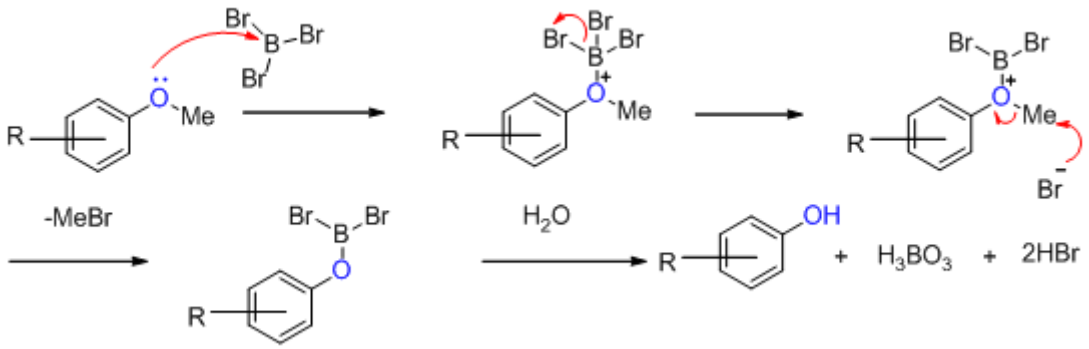
Demethylation



38%
7

9

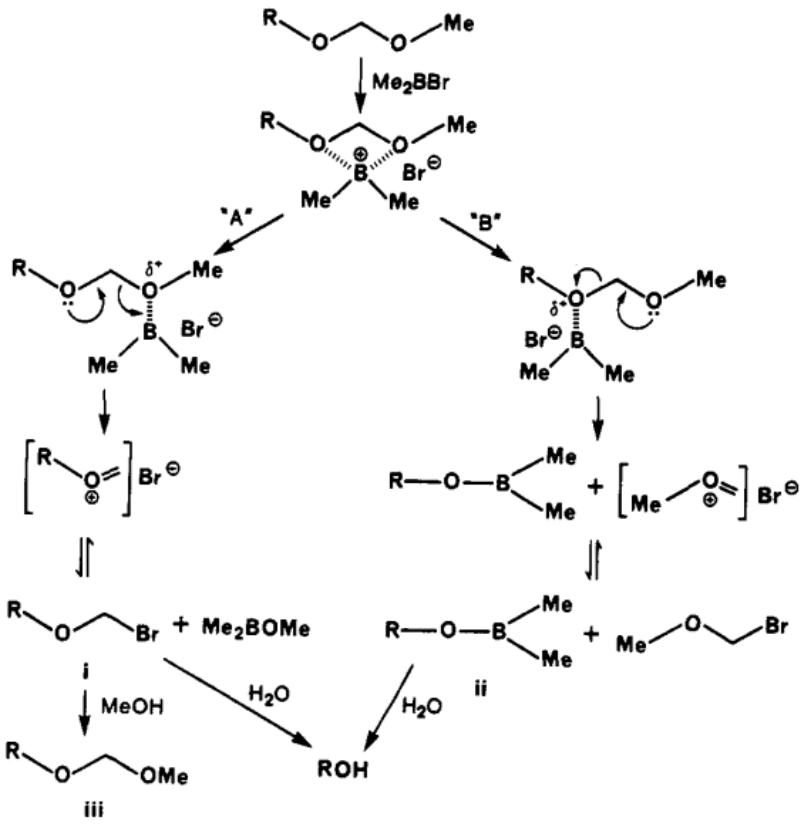
Mechanism



Total Synthesis of Kainic Acid

Demethylation

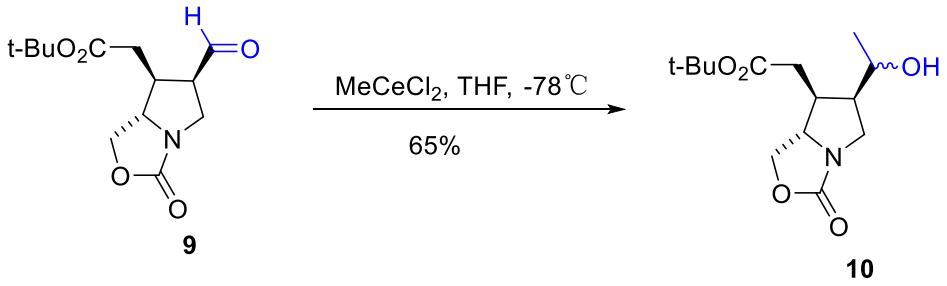
Mechanism



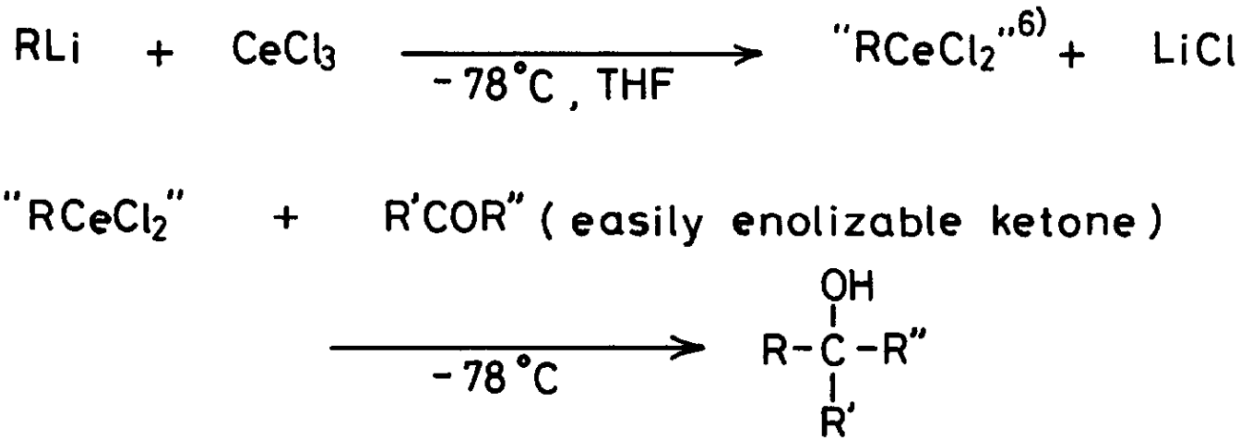
Guindon, Y.; Yoakim, C.; Morton, H. E., The Journal of Organic Chemistry **1984**, 49 (21), 3912-3920.

Total Synthesis of Kainic Acid

Nucleophilic Addition



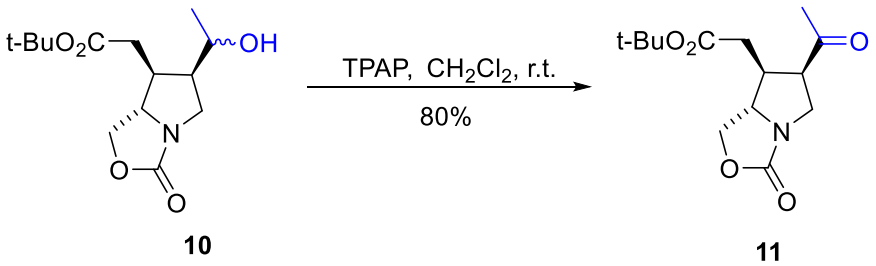
Mechanism



Imamoto, T.; Sugiura, Y.; Takiyama, N., Tetrahedron Letters **1984**, 25 (38), 4233-4236.

Total Synthesis of Kainic Acid

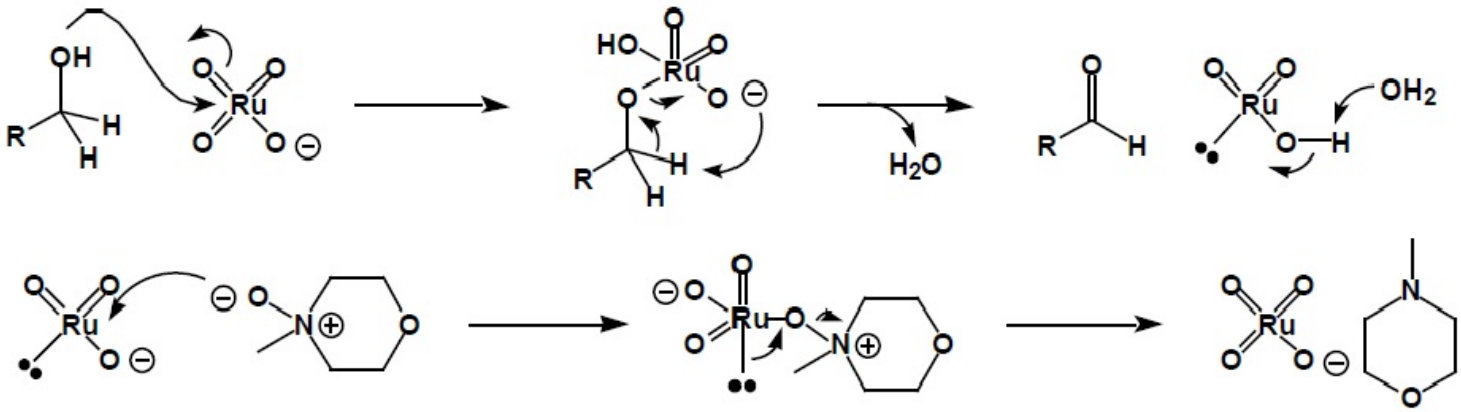
Oxidation



10 11

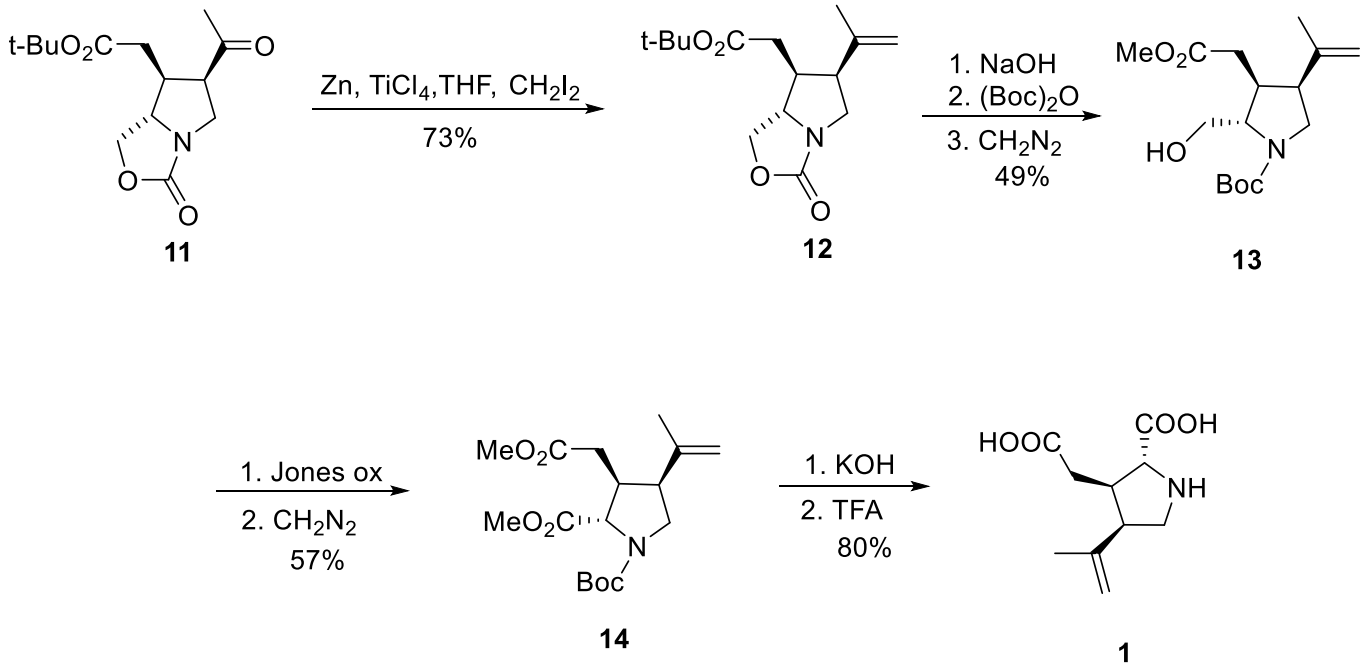
Mechanism

TPAP Oxidation, Ley-Griffith Oxidation



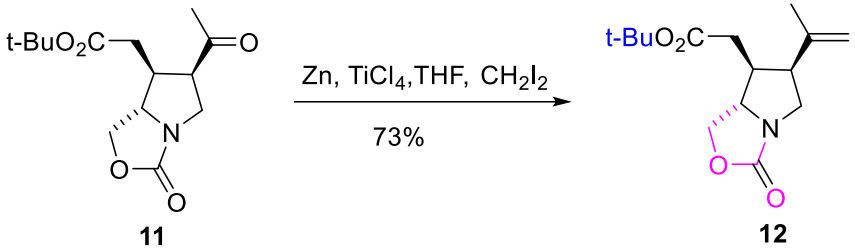
Total Synthesis of Kainic Acid

Synthesis route



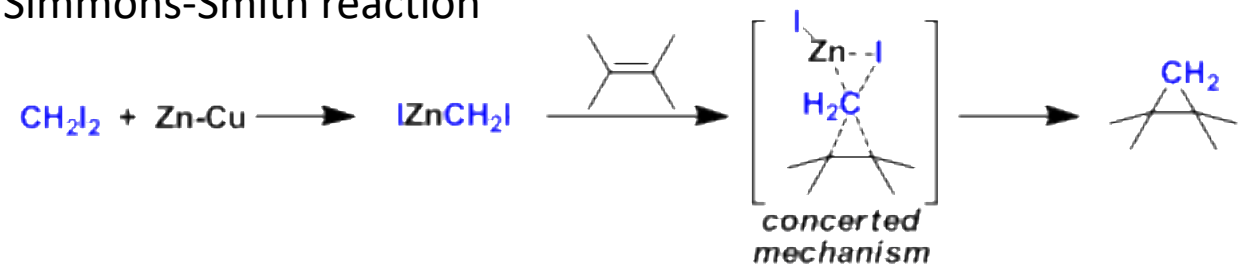
Total Synthesis of Kainic Acid

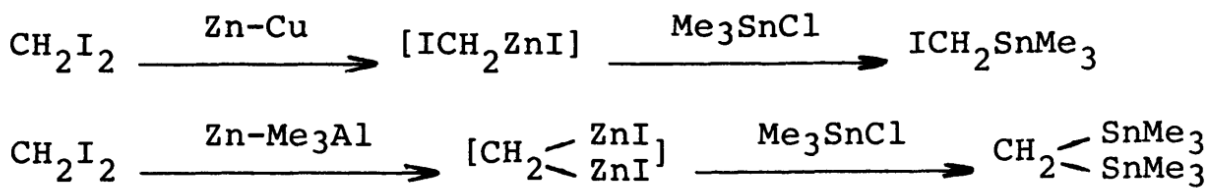
Nozaki Condition



Mechanism

Simmons-Smith reaction

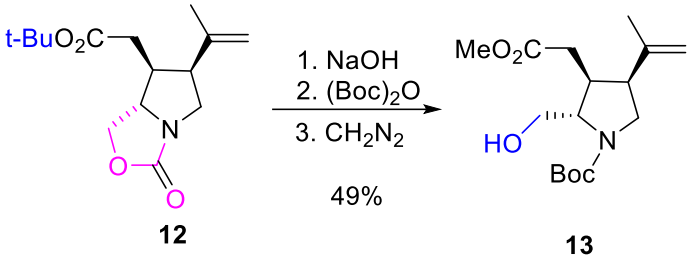




Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H., Tetrahedron Letters **1978**, 19 (27), 2417-2420.

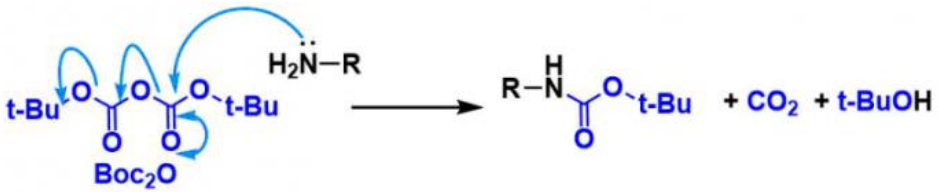
Total Synthesis of Kainic Acid

Deprotection, Hydrolysis & Protection

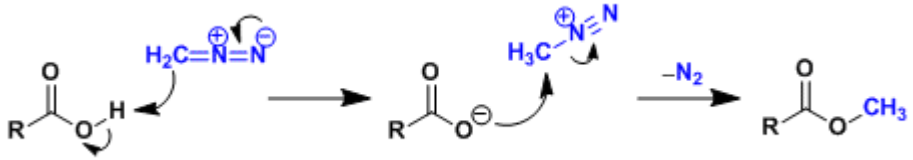


Mechanism

Boc Protection

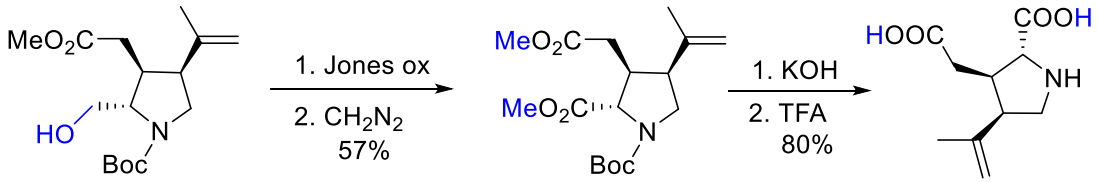


Methylation



Total Synthesis of Kainic Acid

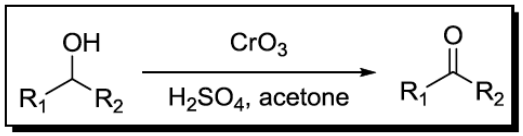
Oxidation



13 **14** **1**

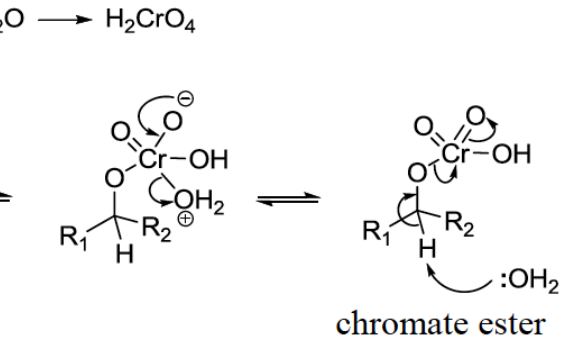
Mechanism

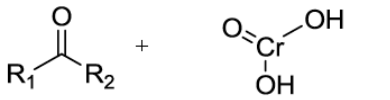
Jones' Oxidation



Cr(VI)

clear orange solution





Cr(III)

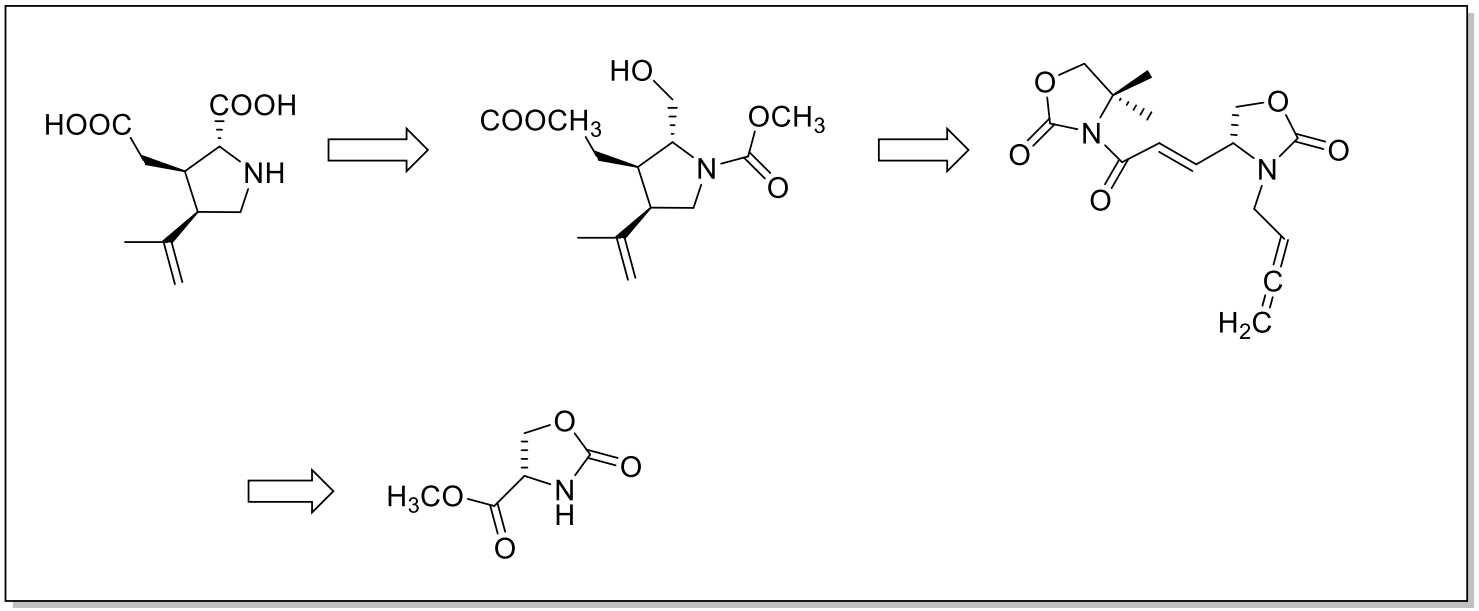
green

John Montgomery, Journal of the American Chemical Society 1999.

Total Synthesis of Kainic Acid

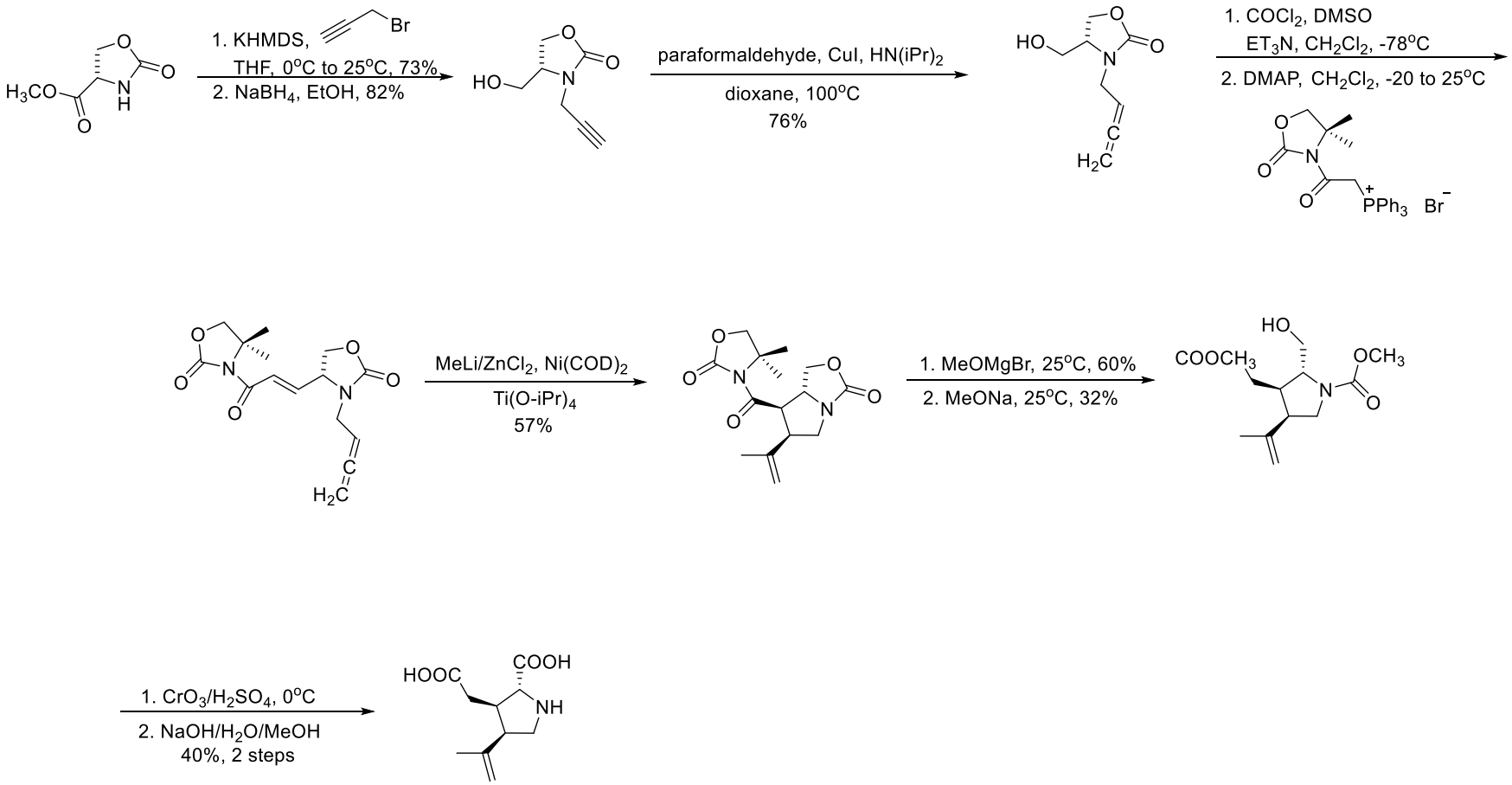
Total Synthesis of Kainic Acid

Retrosynthesis



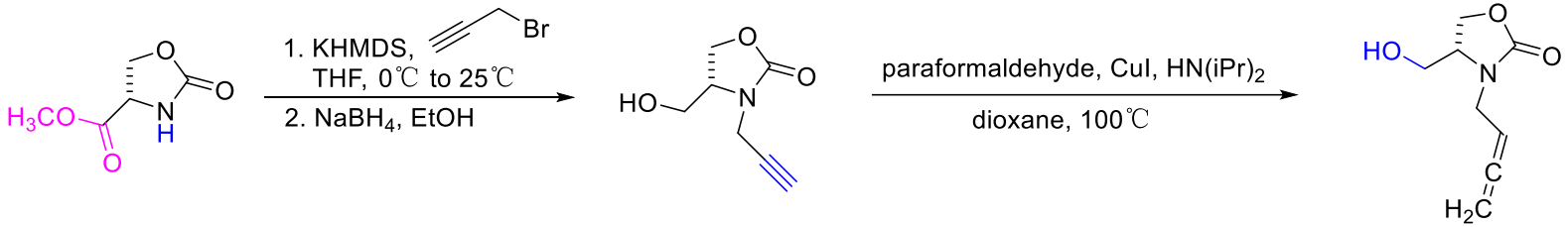
Total Synthesis of Kainic Acid

Synthesis Route

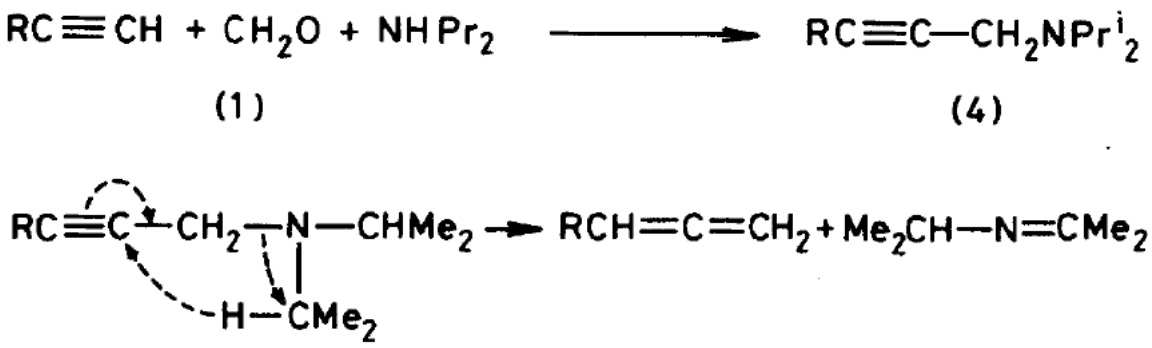


Total Synthesis of Kainic Acid

Alkylation



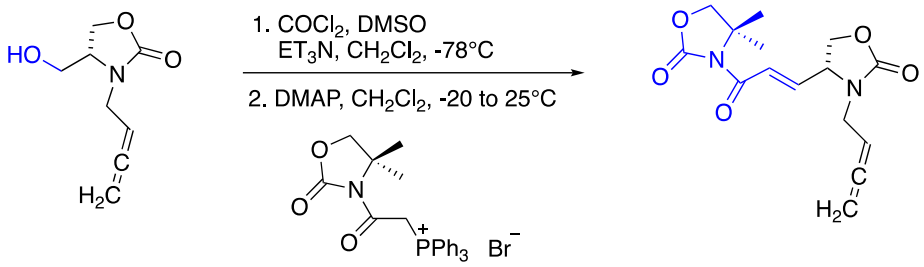
Mechanism



Takano, S.; Iwabuchi, Y.; Ogasawara, K., J. Chem. Soc., Chem. Commun. **1988**, (17), 1204-1206.

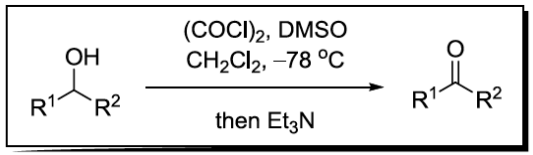
Total Synthesis of Kainic Acid

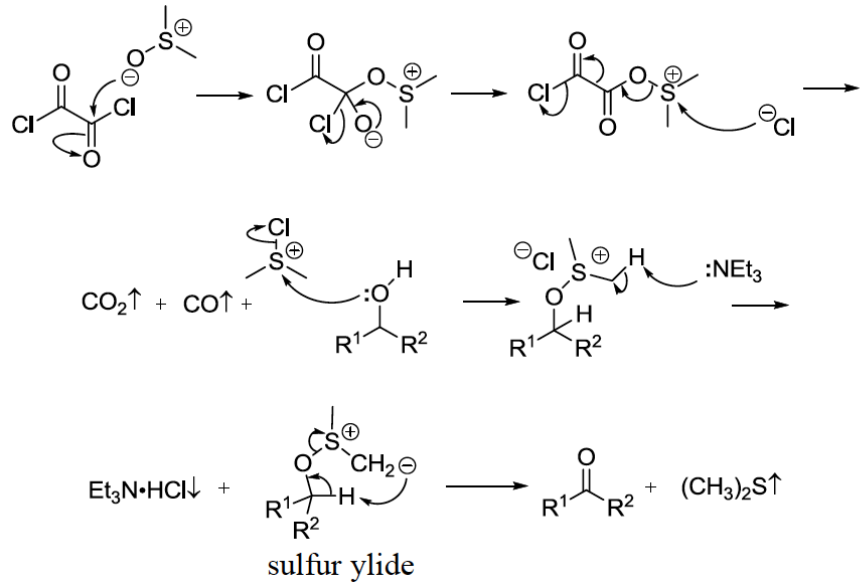
Swern Oxidation



Mechanism

Swern Oxidation



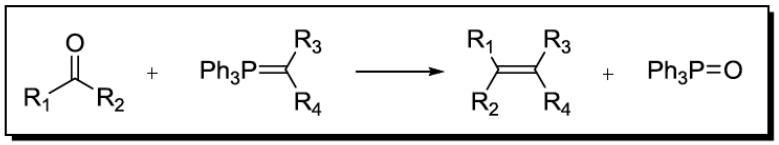


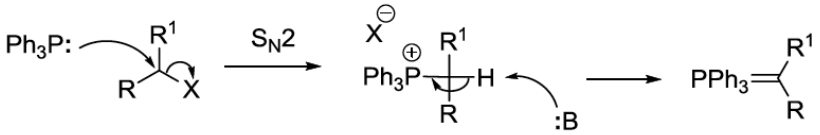
Total Synthesis of Kainic Acid

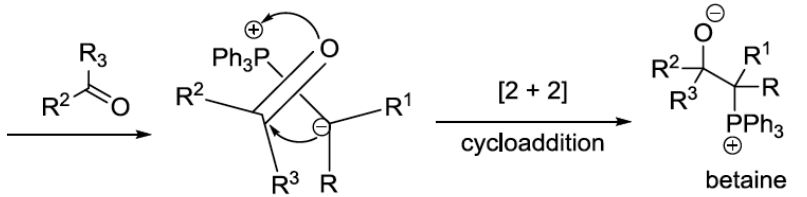
Wittig Reaction

Mechanism

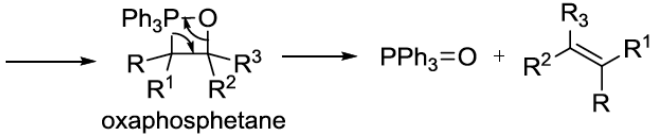
Wittig Reaction





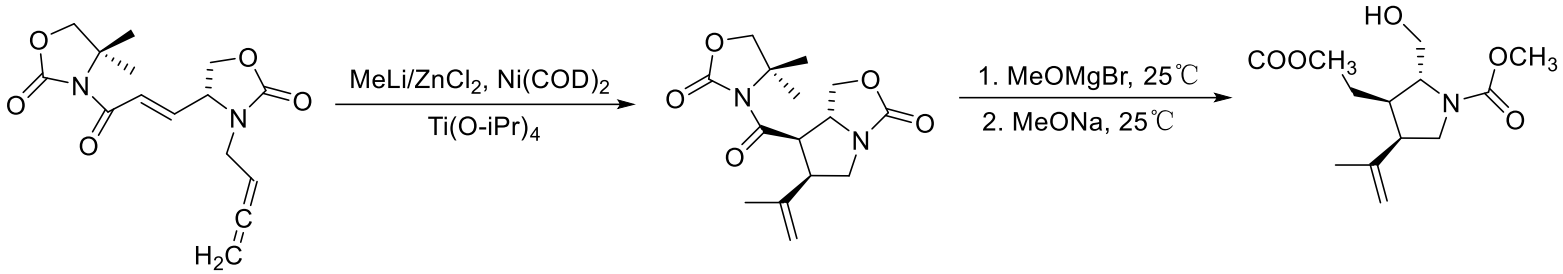


The "puckered" transition state, irreversible and concerted

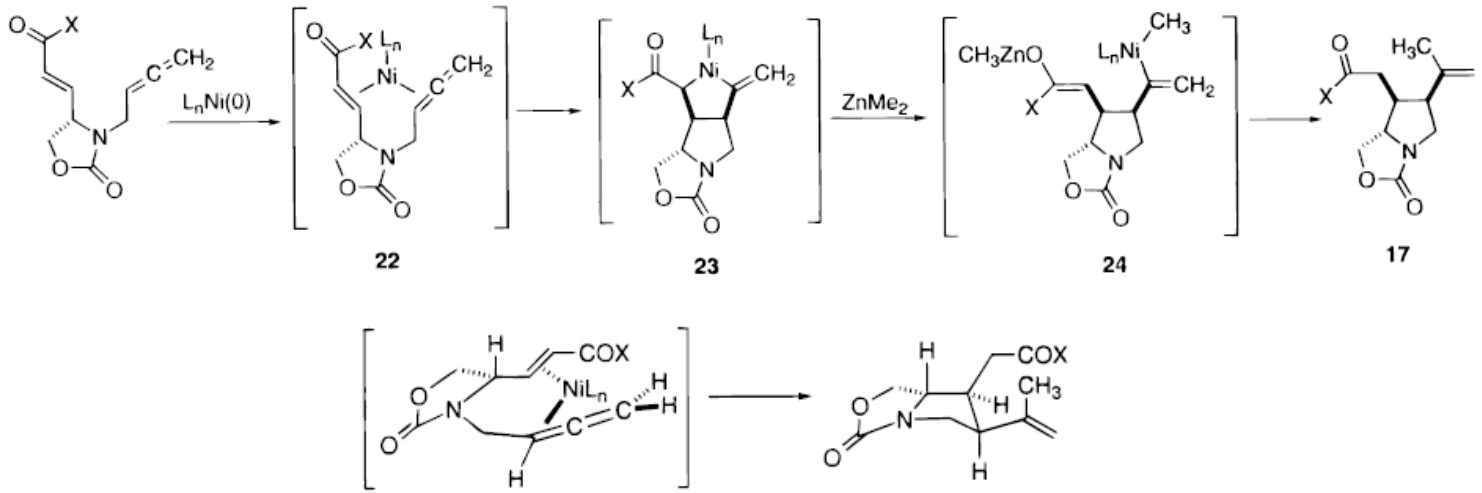


Total Synthesis of Kainic Acid

Reduction & Elimination

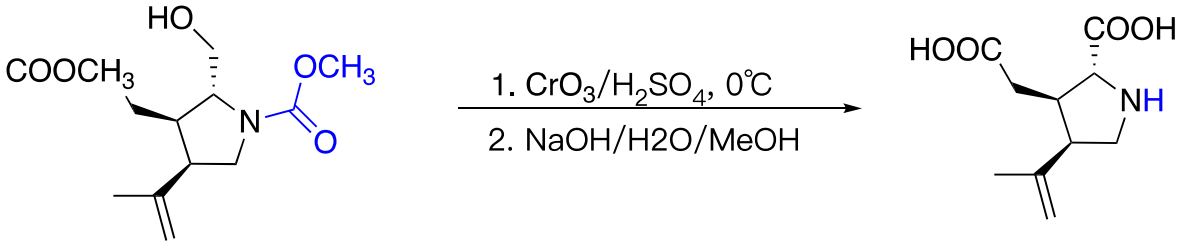


Mechanism



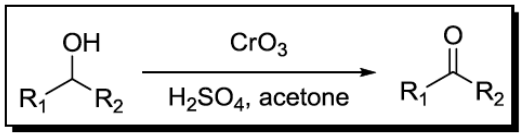
Total Synthesis of Kainic Acid

Oxidation



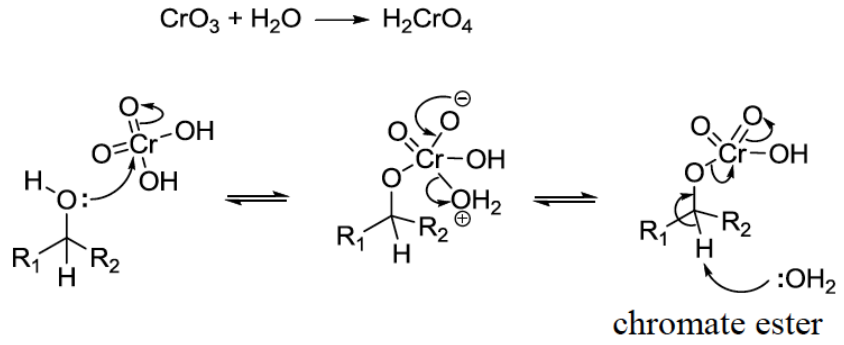
Mechanism

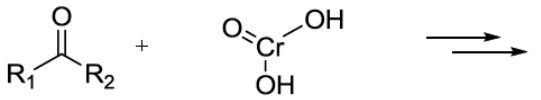
Jones' Oxidation



Cr(VI)

clear orange solution





Cr(III)

green

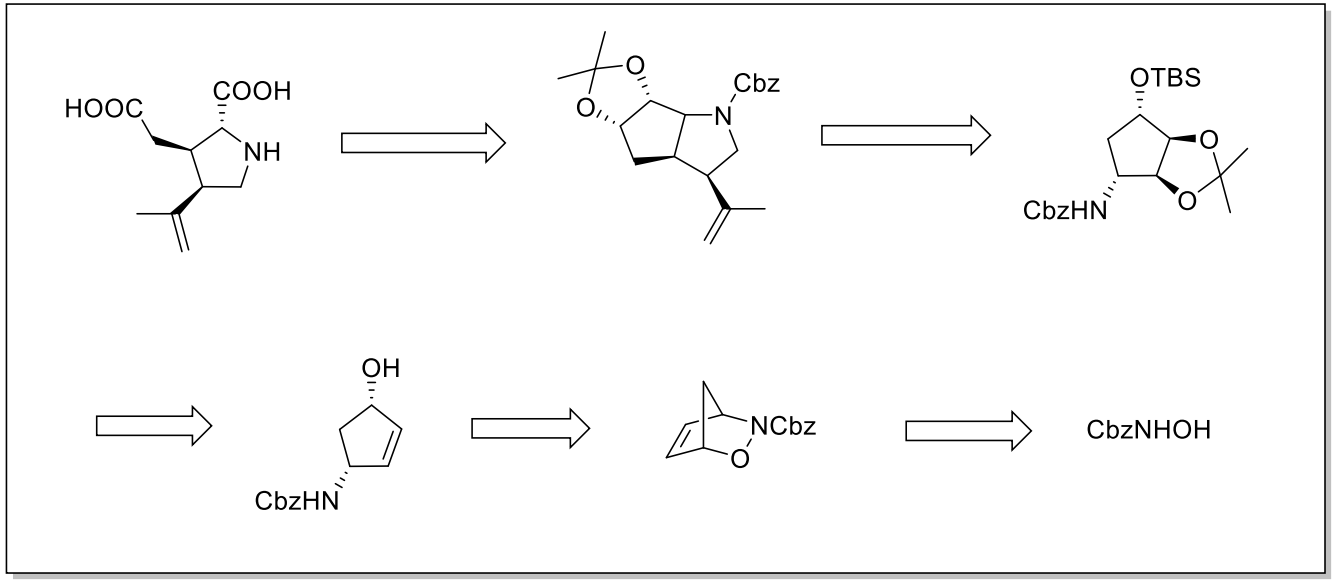
Kunio Ogasawara, Org Lett 2000.

Total Synthesis of Kainic Acid

Total Synthesis of Kainic Acid

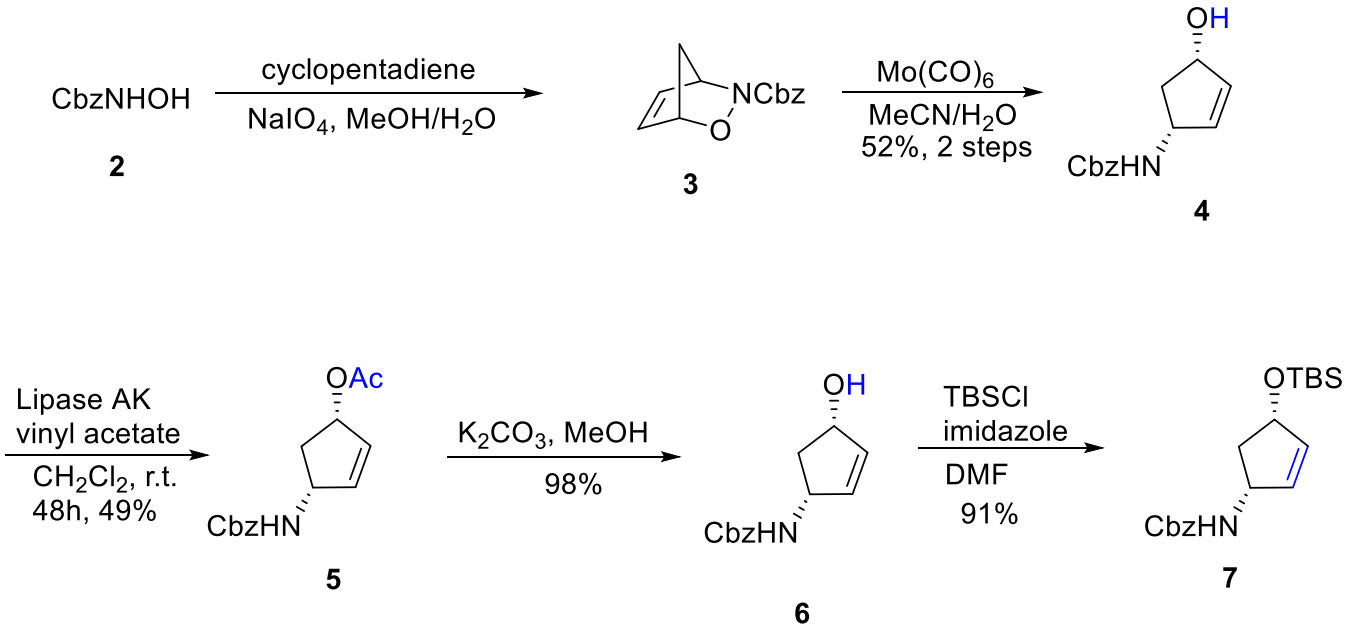
Kunio Ogasawara, Org Lett 2000.

- Retrosynthesis



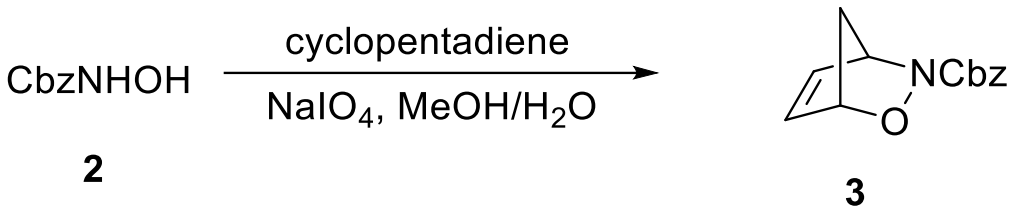
Total Synthesis of Kainic Acid

Synthesis Route



Total Synthesis of Kainic Acid

Diels-Alder Reaction



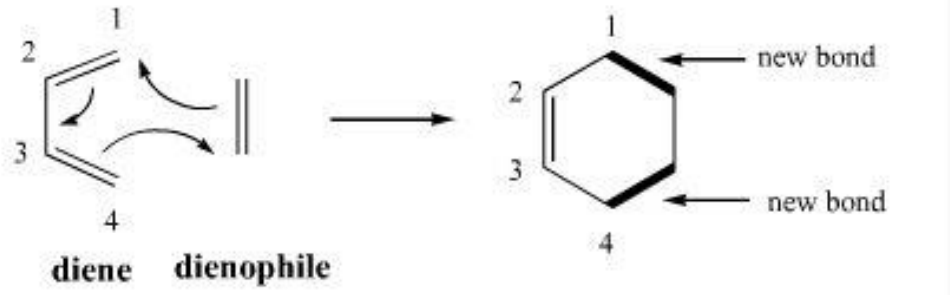
2 **3**

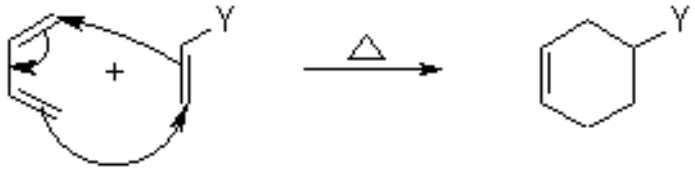
Q: What is the mechanism of this reaction?

Total Synthesis of Kainic Acid

Diels-Alder Reaction

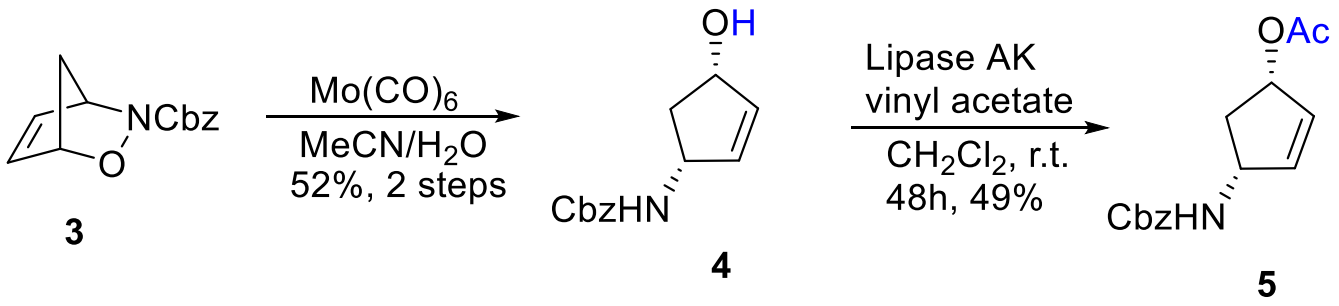
Mechanism





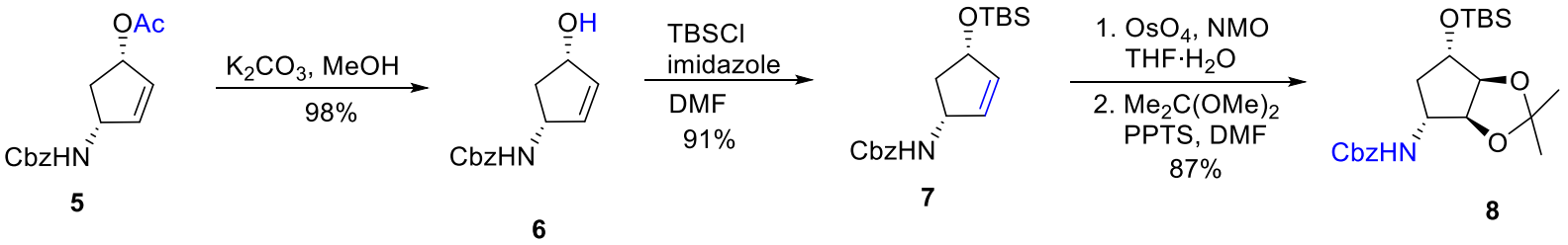
Total Synthesis of Kainic Acid

Substitution

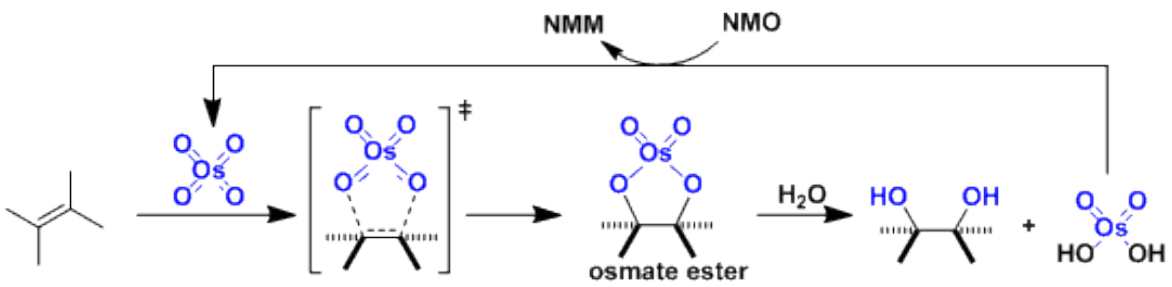


Total Synthesis of Kainic Acid

Hydrolysis & Protection

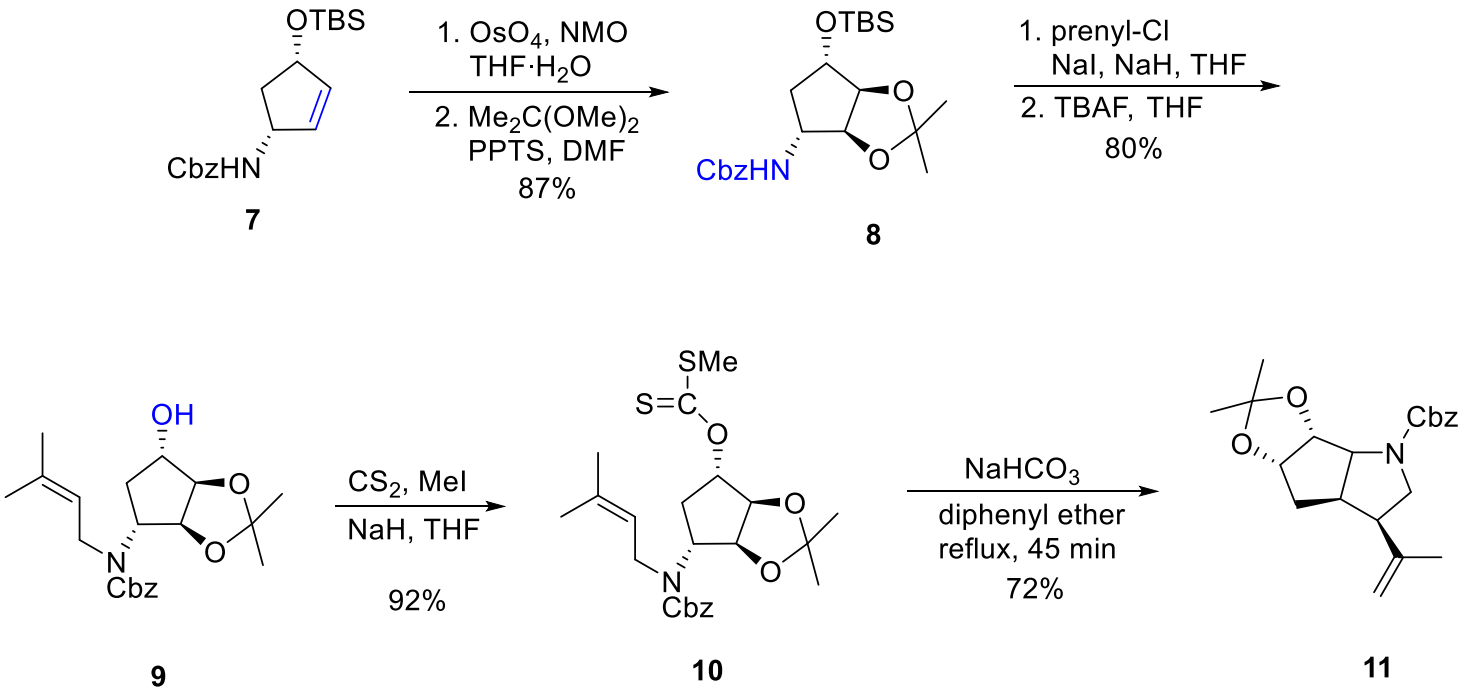


Mechanism



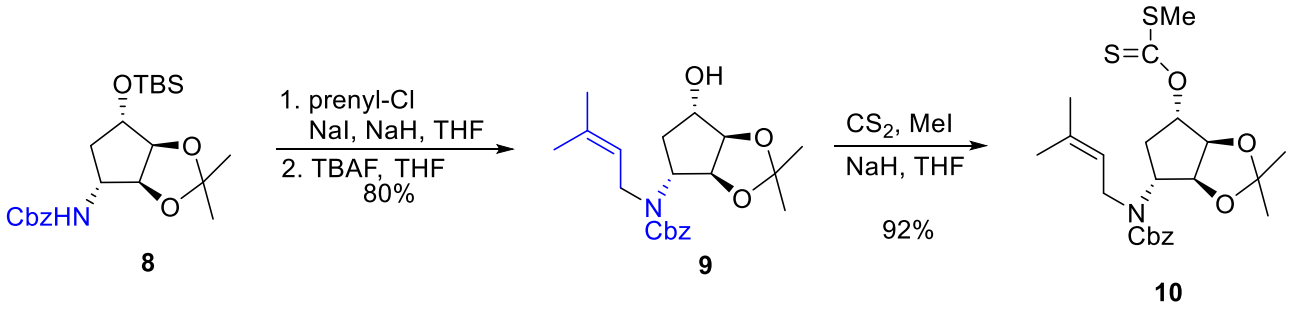
Total Synthesis of Kainic Acid

Synthesis Route



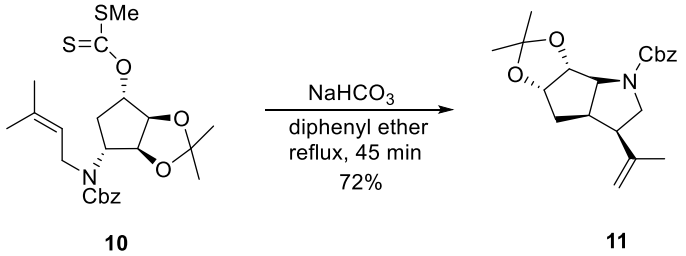
Total Synthesis of Kainic Acid

Alkylation & Desilylation



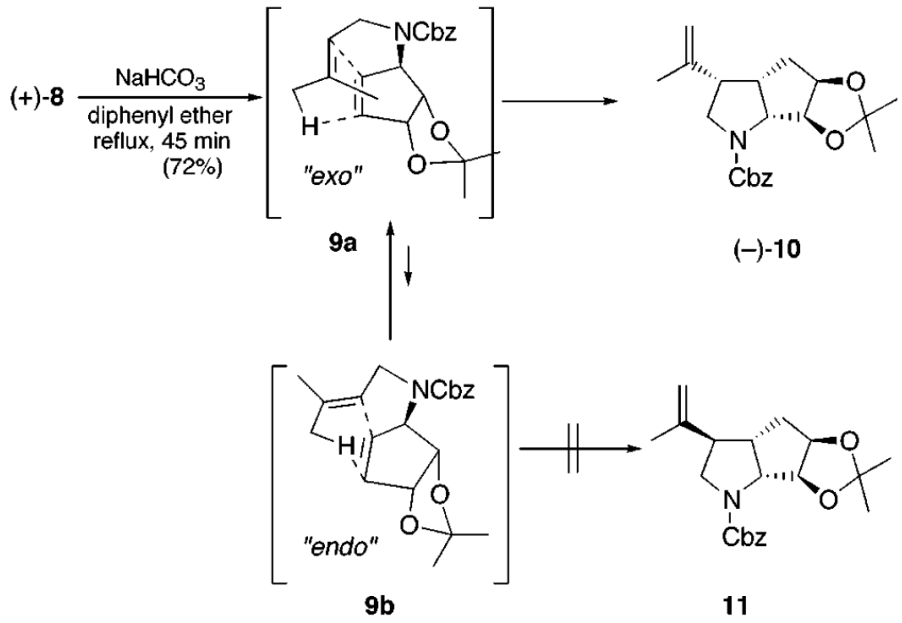
Total Synthesis of Kainic Acid

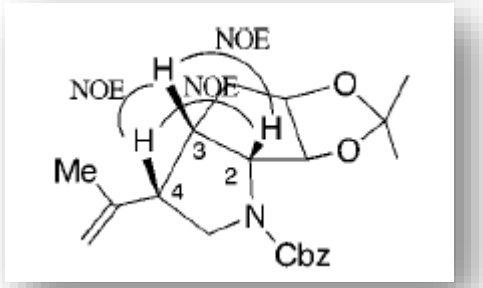
Elimination



10 11

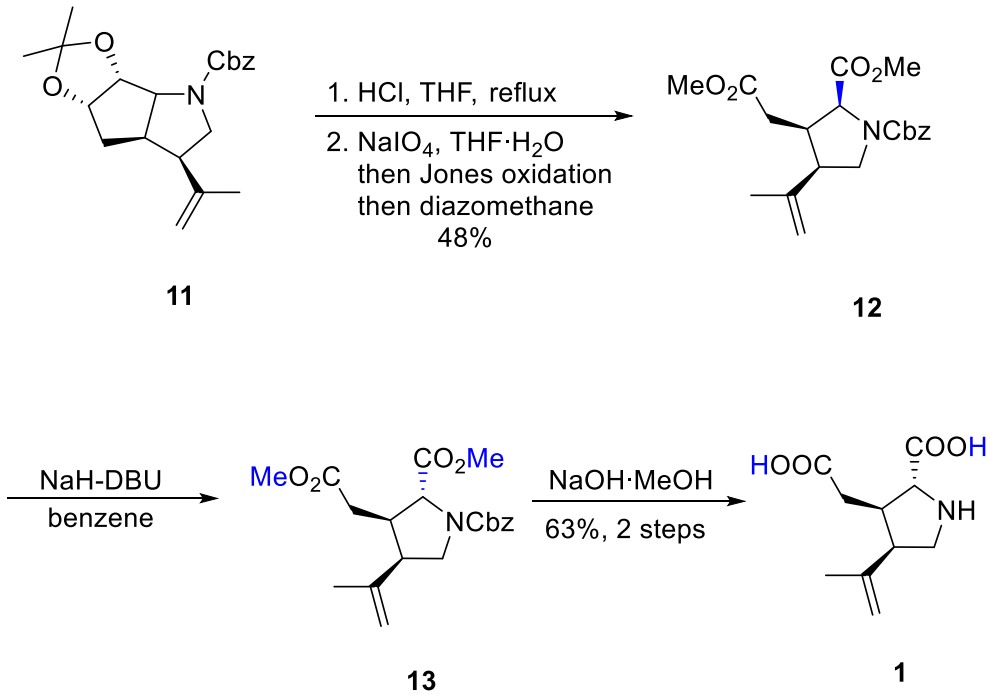
Mechanism





Total Synthesis of Kainic Acid

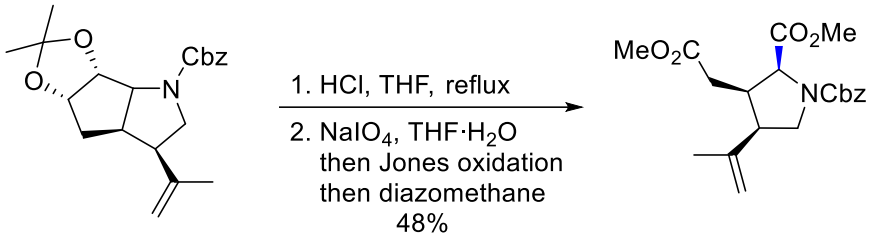
Synthesis Route



11 **12** **13** **1**

Total Synthesis of Kainic Acid

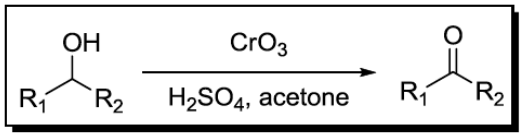
Oxidation



11 **12**

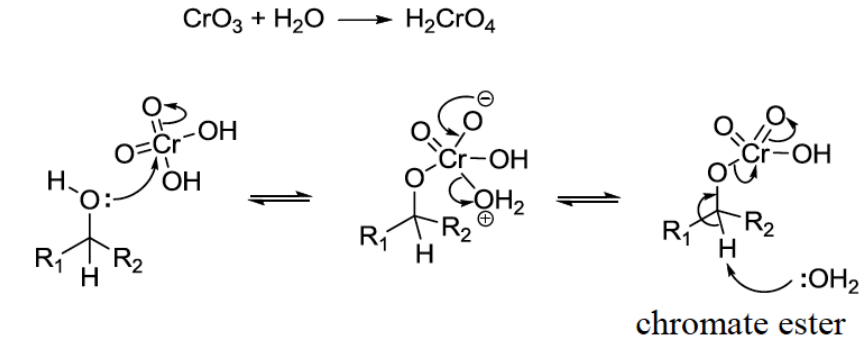
Mechanism

Jones' Oxidation



Cr(VI)

clear orange solution

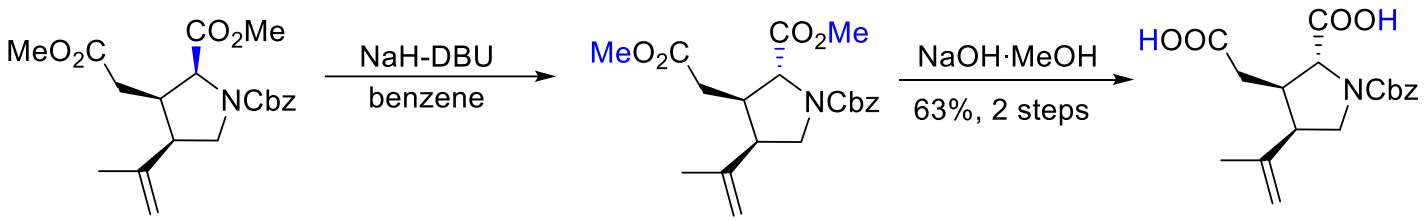


Cr(III)

green

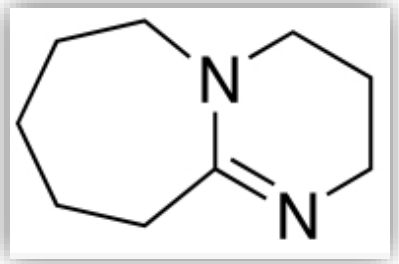
Total Synthesis of Kainic Acid

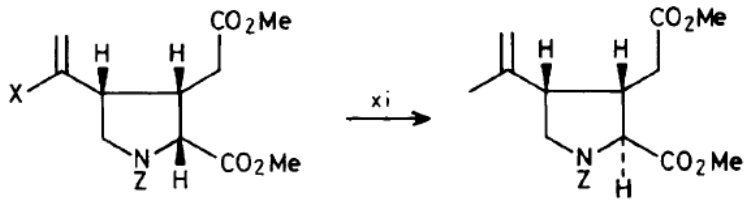
Conformational Transition



12 **13** **1**

Mechanism



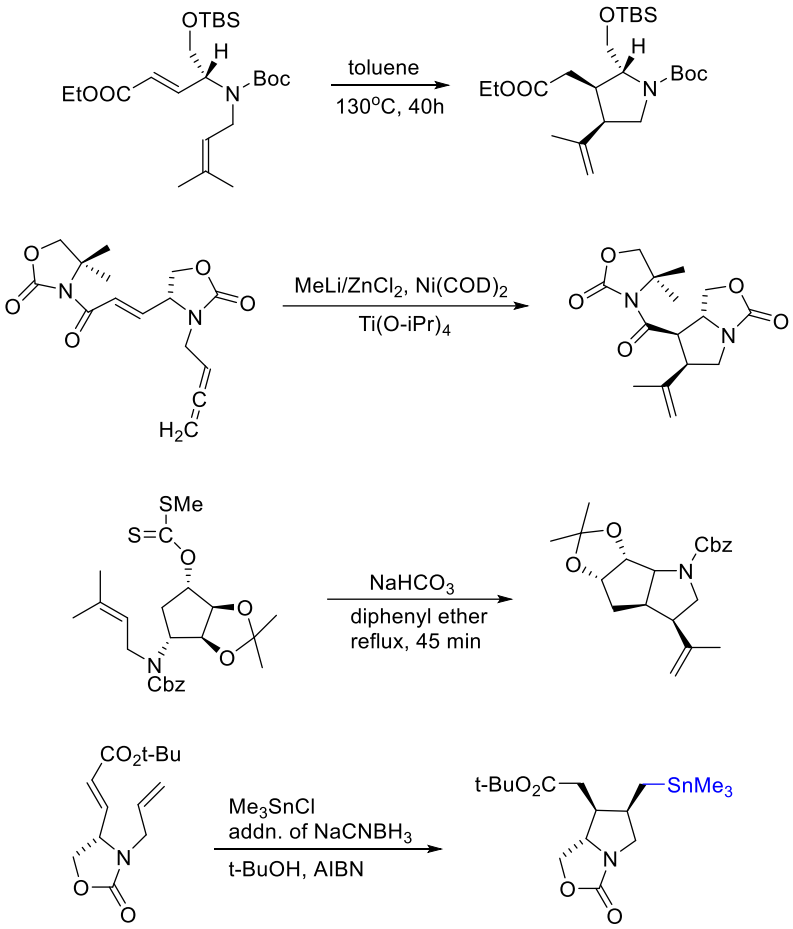


Takano, S.; Iwabuchi, Y.; Ogasawara, K., J. Chem. Soc., Chem. Commun. **1988**, (17), 1204-1206.

Summary

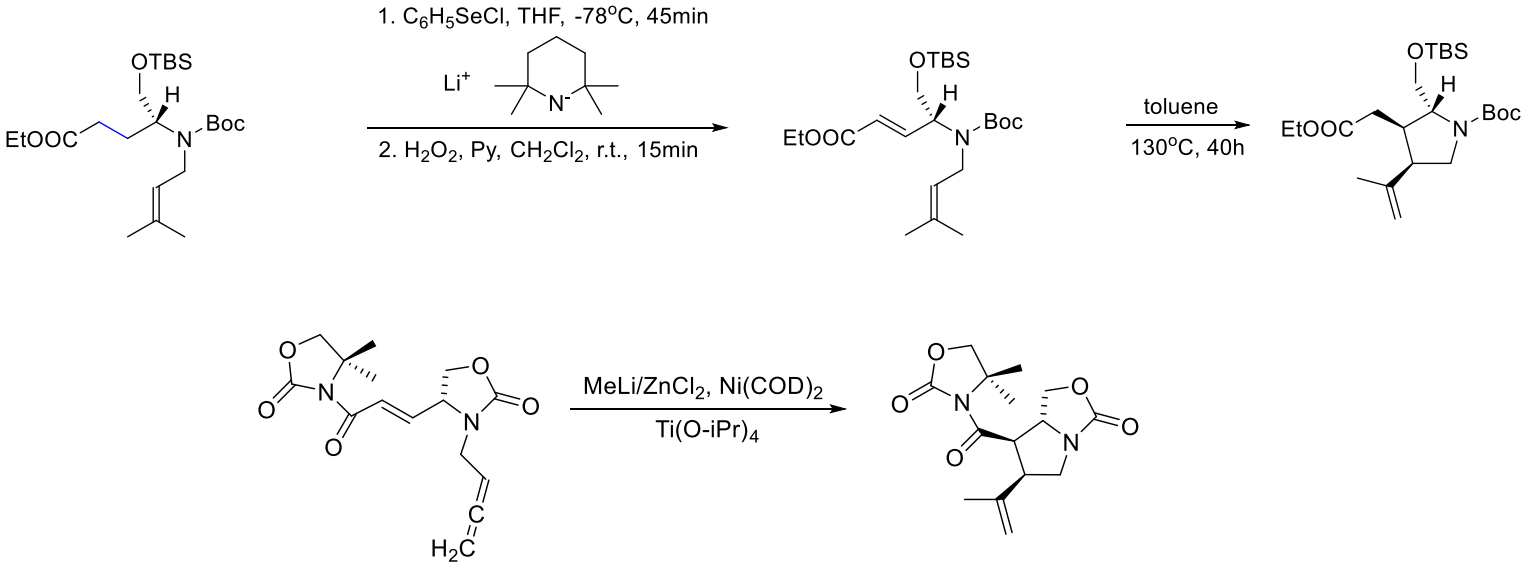
Total Synthesis of Kainic Acid

Ene Reaction



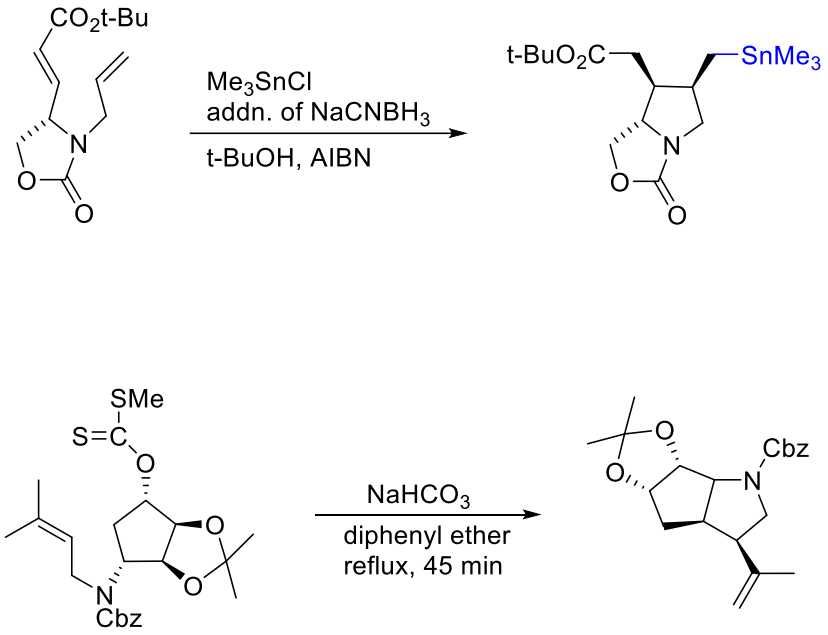
Total Synthesis of Kainic Acid

Approach for Stereocenters

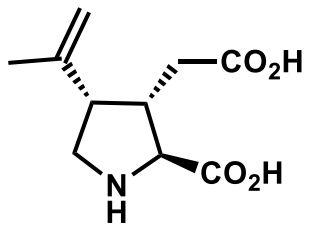


Total Synthesis of Kainic Acid

Approach for Stereocenters



Total Synthesis of (–)-α-Kainic Acid (2000-2010)



(-)-kainic acid (1)

Reporter: Xiaoyun Liao

Supervisors: *Prof.* Tao Ye

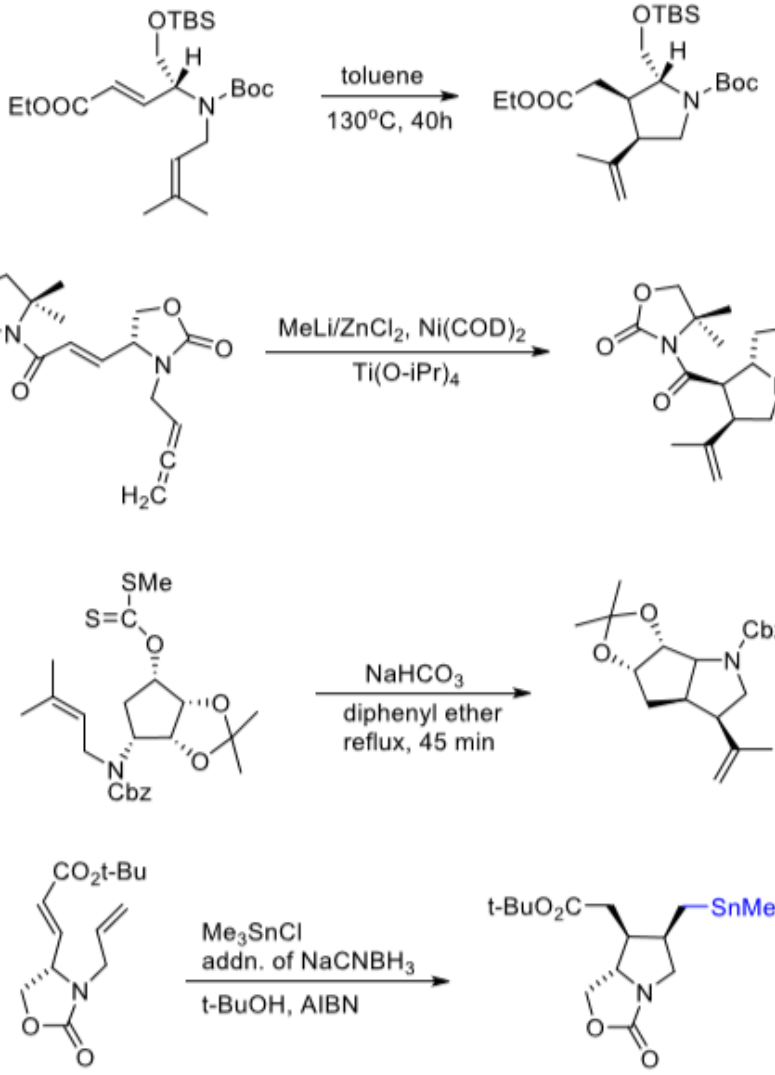
***Dr.* Yian Guo**

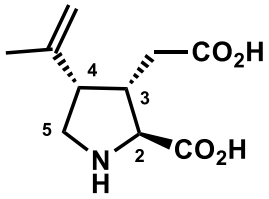
October 12th, 2020

Review

C^3–C^4 Bond Formation Pathways

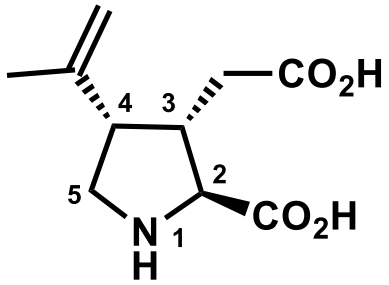
Ene reaction





(-)-kainic acid (1)

Contents

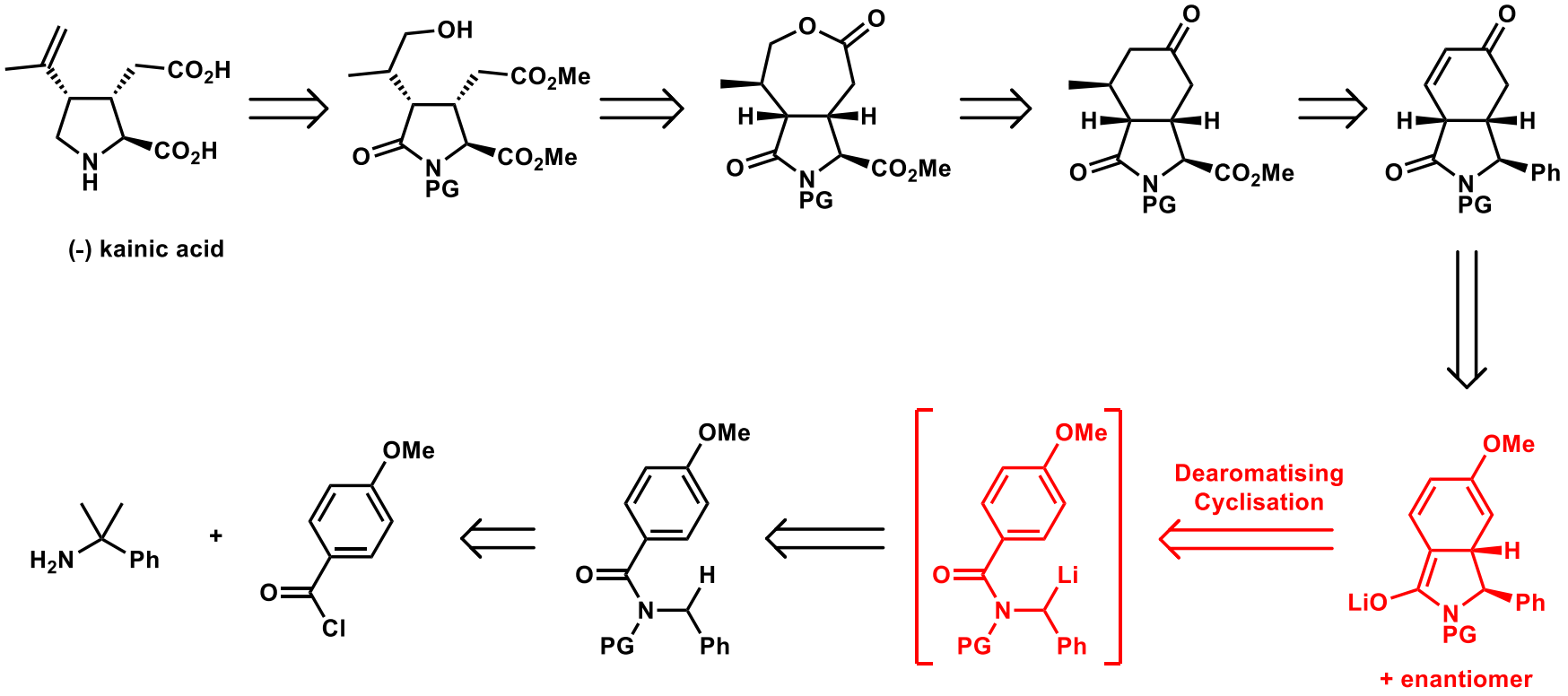


(-)-kainic acid (1)

1. C^2–C^3 Bond Formation Pathways

J. Clayden: *Chem. Commun*. **2000**, 317–318.

Retrosynthetic Analysis



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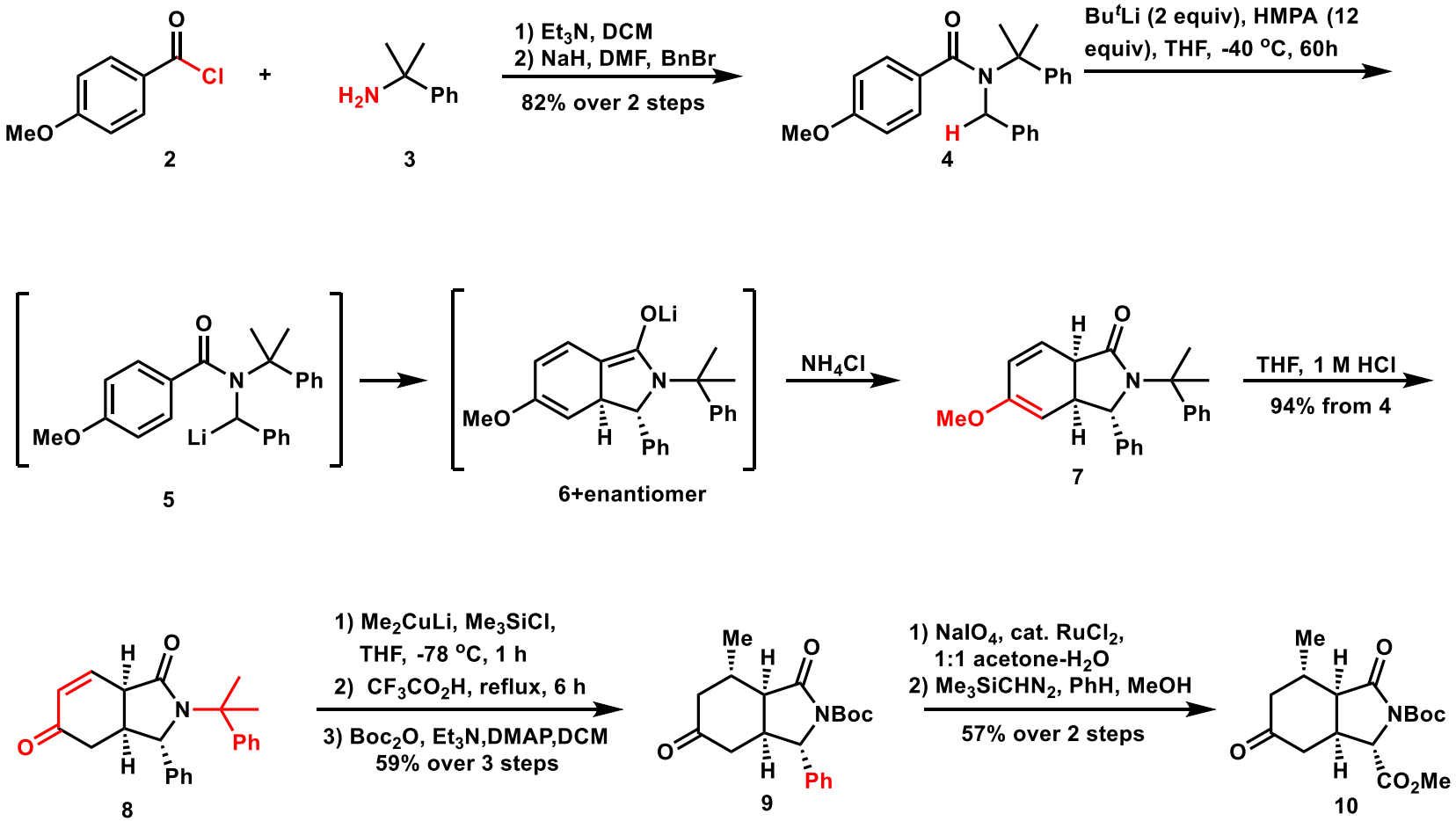

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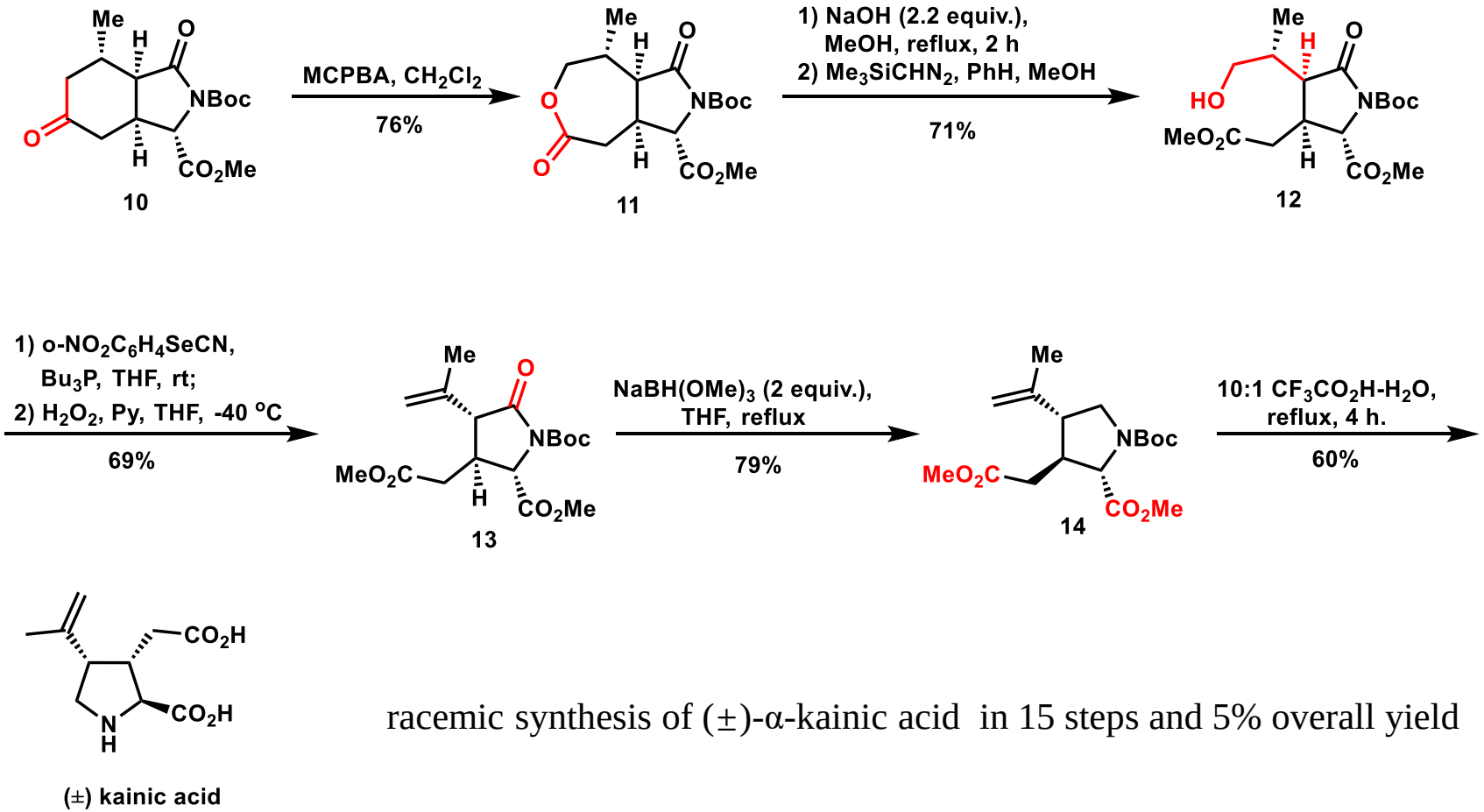

racemic synthesis of (±)-α-kainic acid in 15 steps and 5% overall yield

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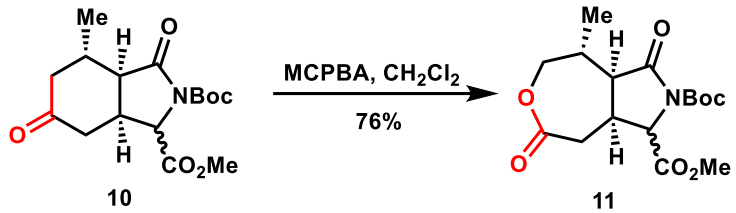
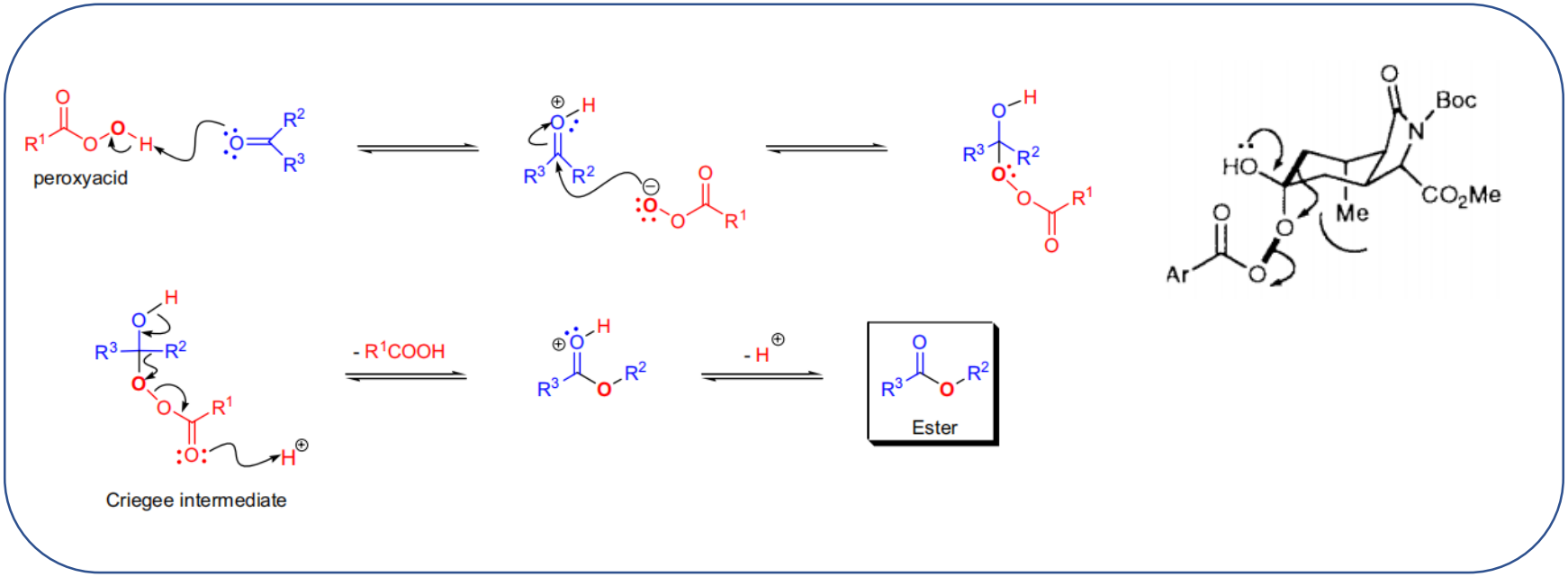
J. Clayden: *Chem. Commun*. **2000**, 317–318.



Baeyer-Villiger oxidation:



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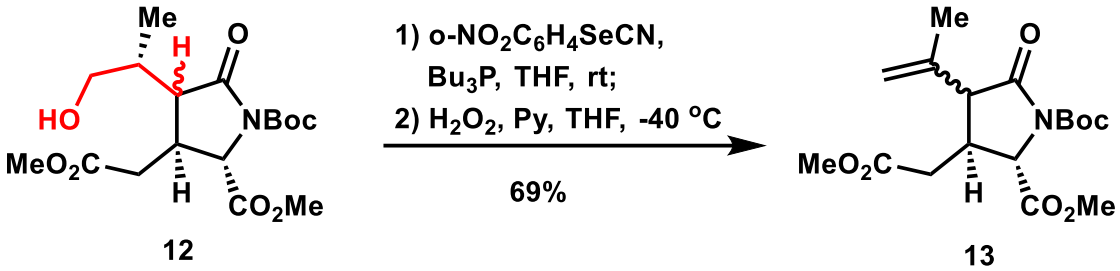
J. Clayden: *Chem. Commun*. **2000**, 317–318.



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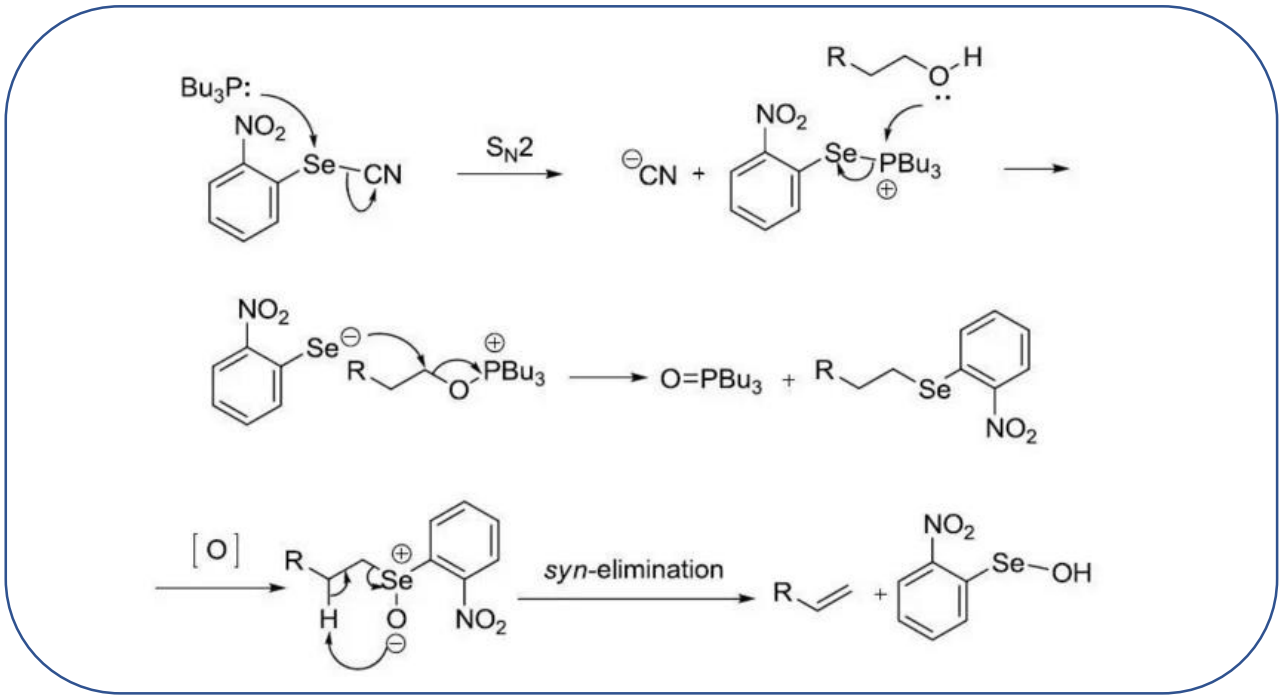

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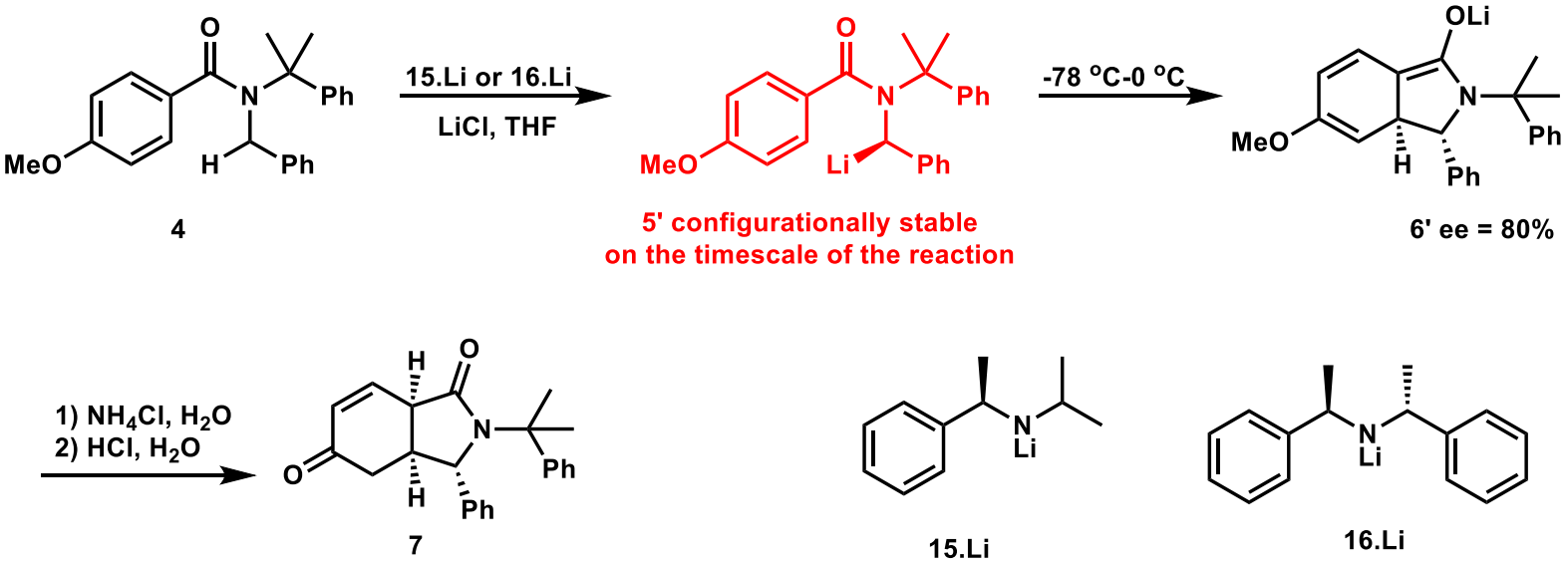
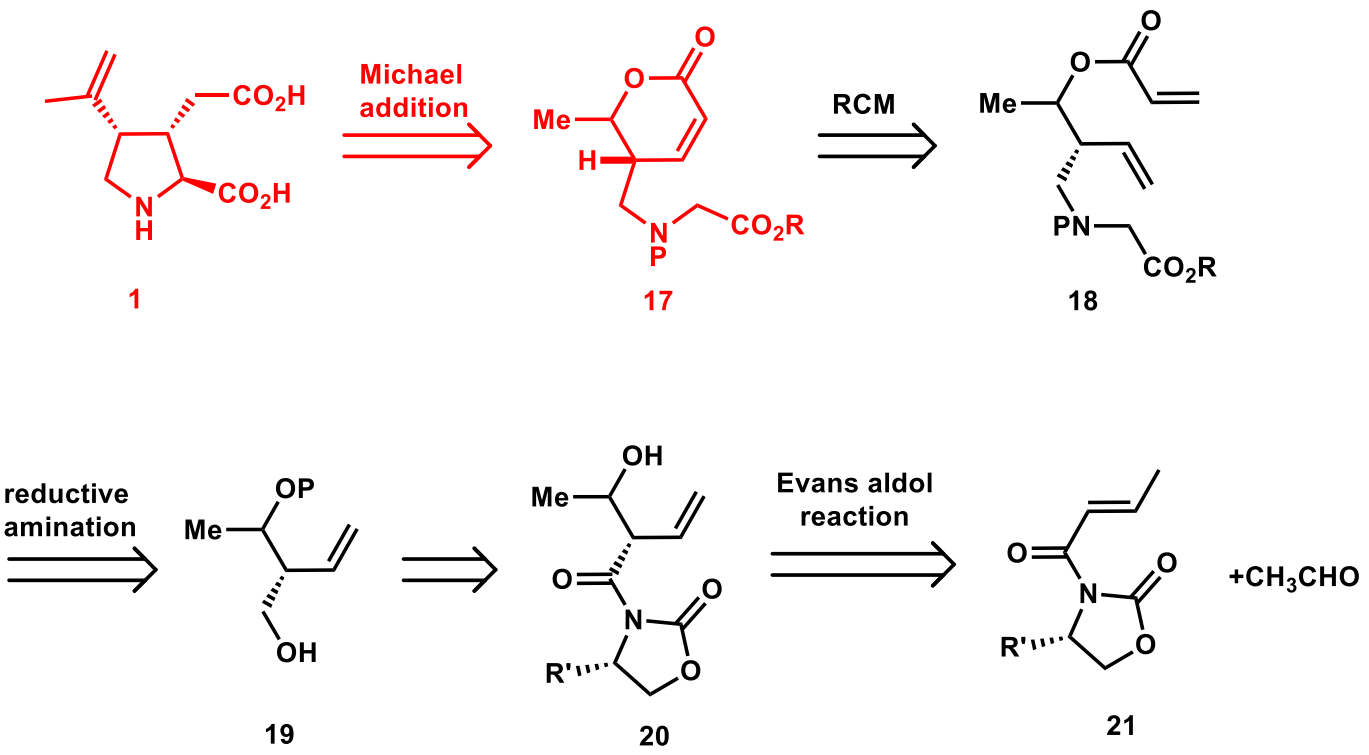
J. Clayden: *Chem. Commun*. **2002**, 38–39.
Tetrahedron. **2002**, 58, 4727–4733.



1.C^2–C^3 Bond Formation Pathways

T. Fukuyama: *Org. Lett*. **2007**, 9, 1635–1639.

Synthetic Strategy for (-)-Kainic Acid (1)



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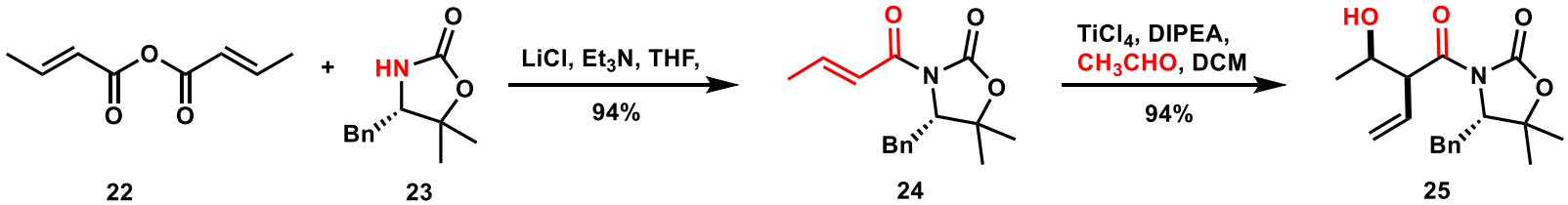
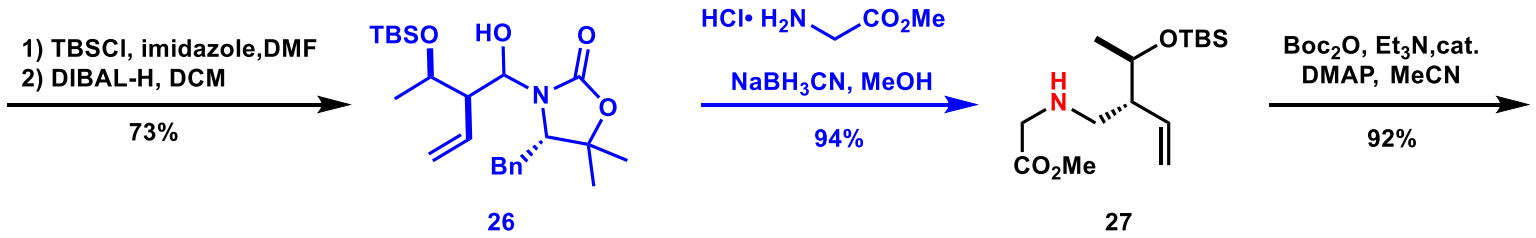
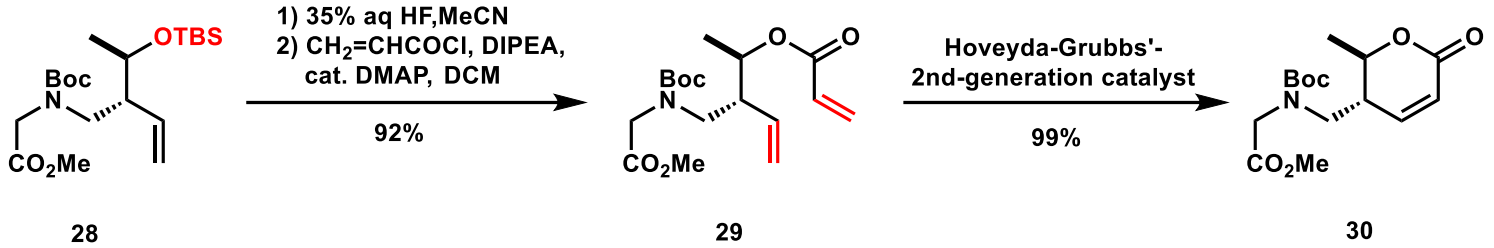
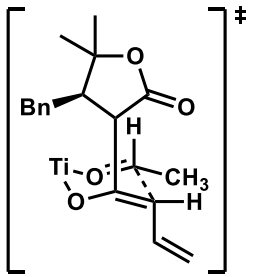
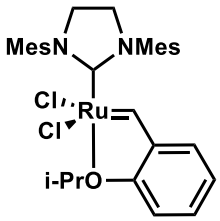






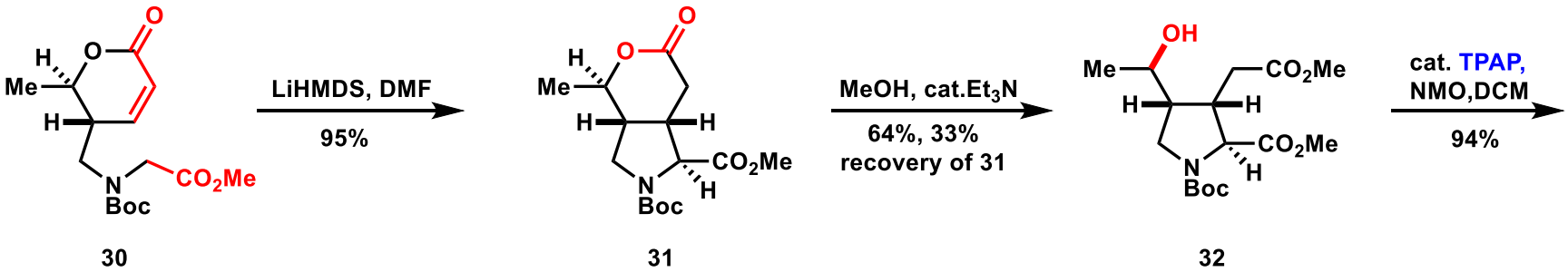


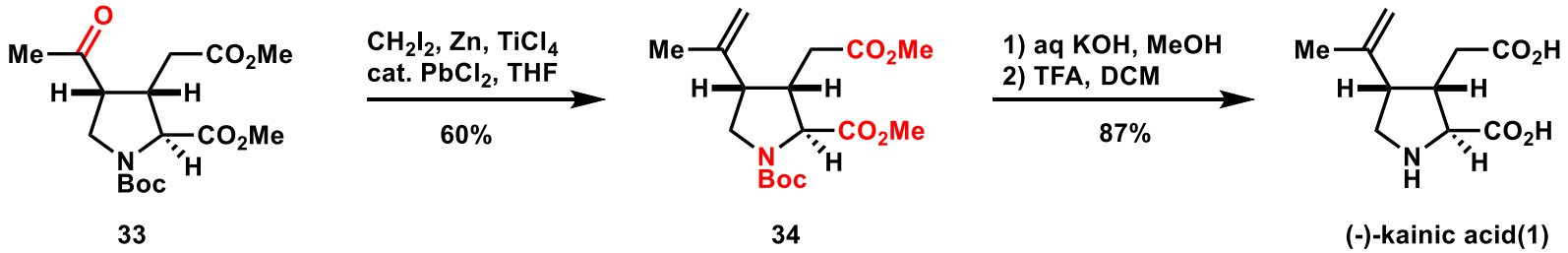


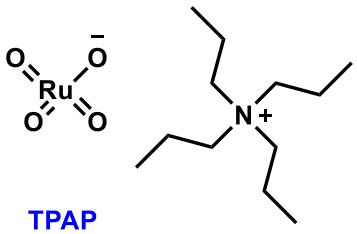
Hoveyda-Grubbs'
2nd Generation cat.

1. C^2–C^3 Bond Formation Pathways

T. Fukuyama: *Org. Lett*. **2007**, 9, 1635–1639.







13% overall yield in 13 steps from the Evans-type chiral auxiliary

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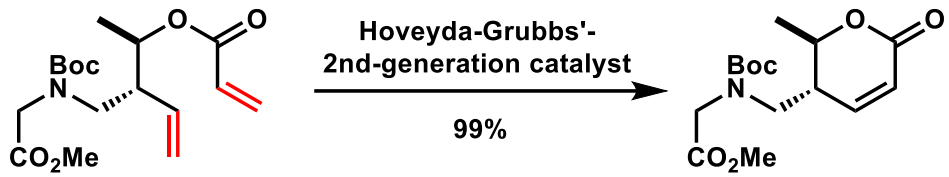
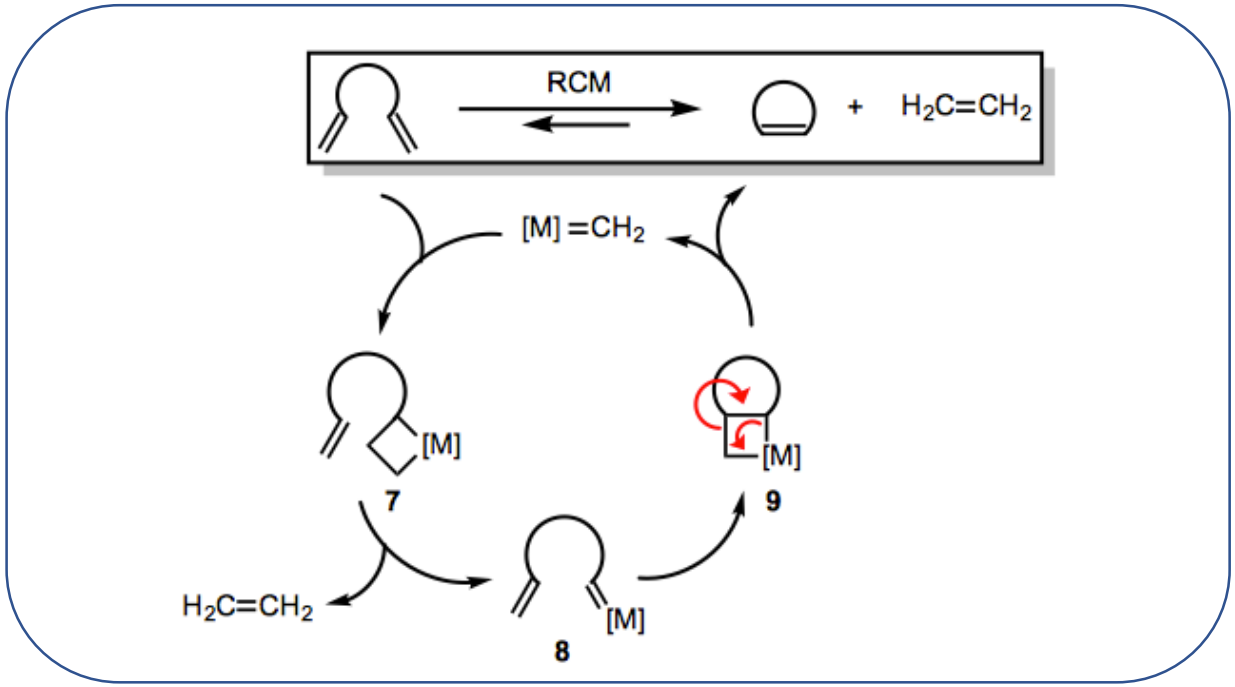
T. Fukuyama: *Org. Lett.* **2007**, 9, 1635–1639.



29 30

Ring-closing metathesis



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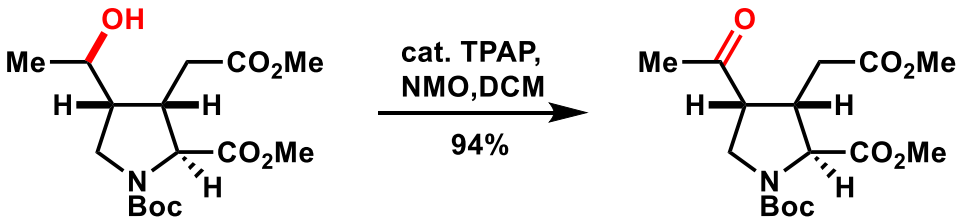
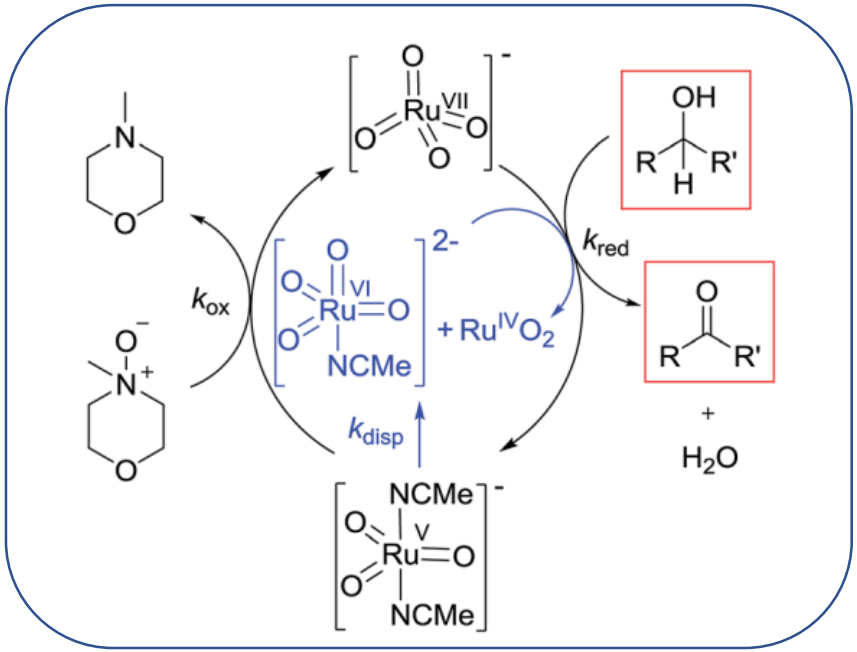


32 33

Ley–Griffith oxidation



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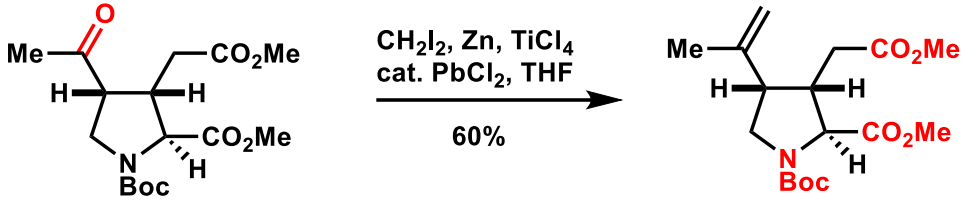
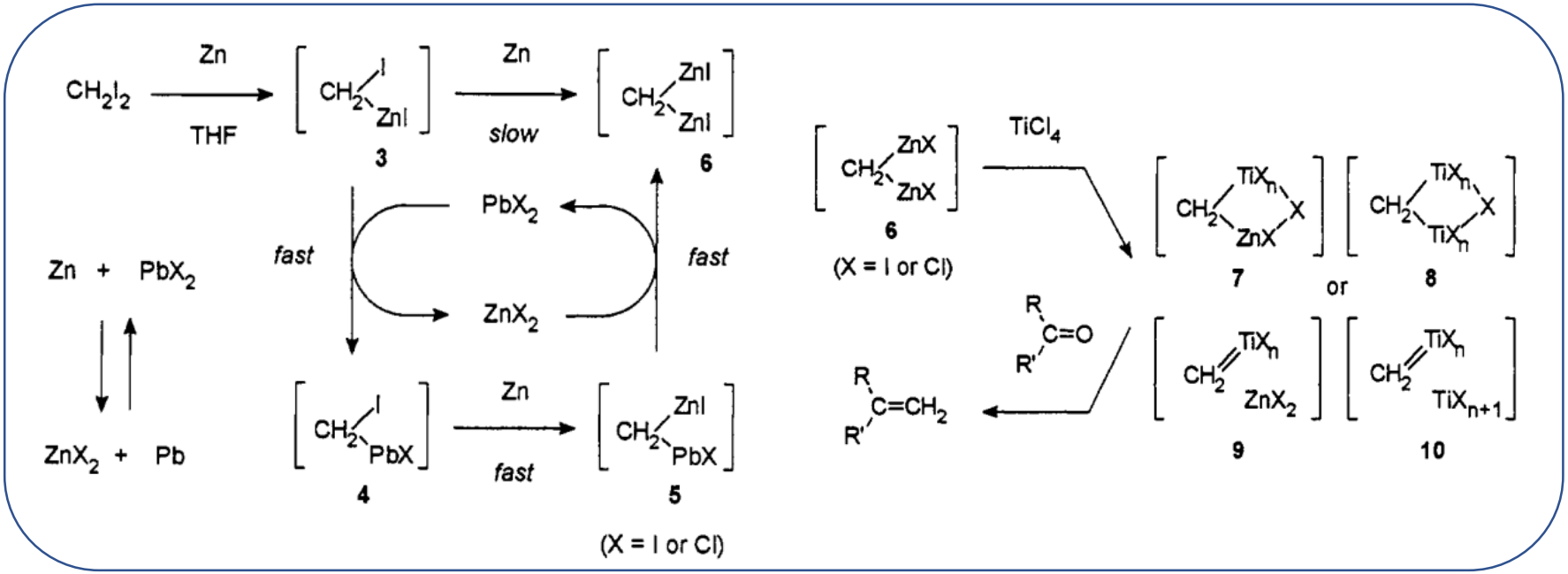


33 34

Mechanism

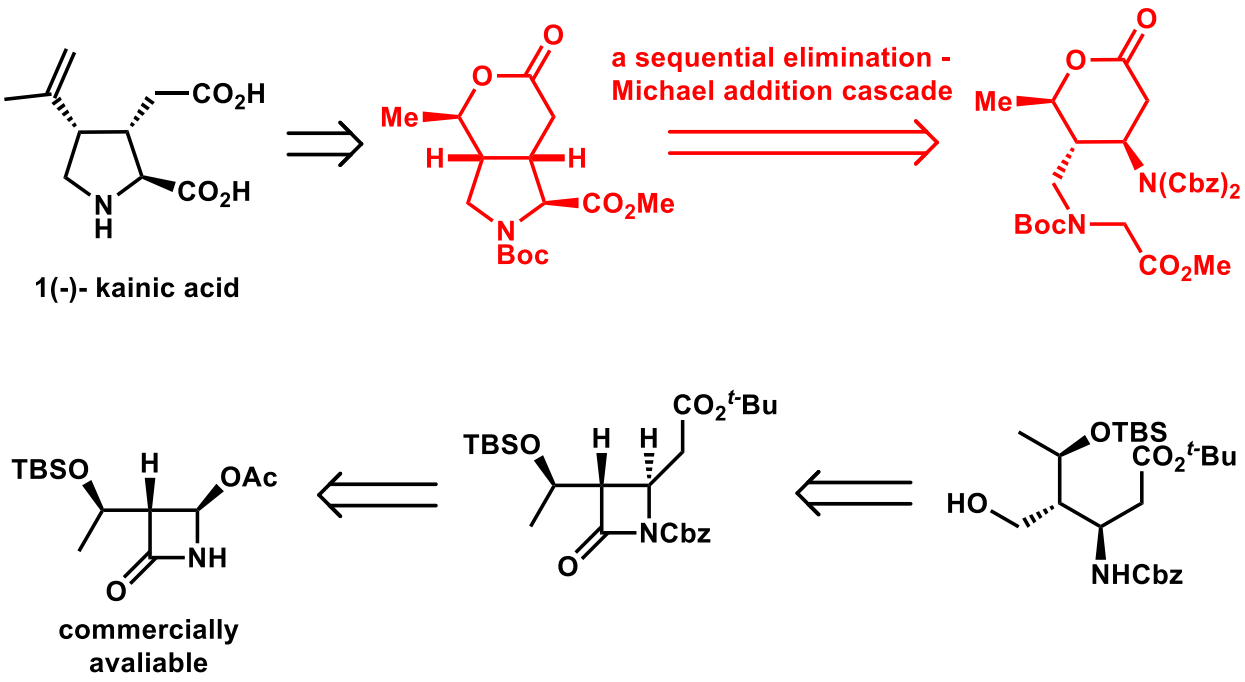


Takai, K, et al, *J.Org. Chem.* **1994**, 59, 2668.

1. C^2–C^3 Bond Formation Pathways

T. Fukuyama: *Org. Lett*. **2008**, 10, 1711–1714.

Strategy for Second-Generation Synthesis



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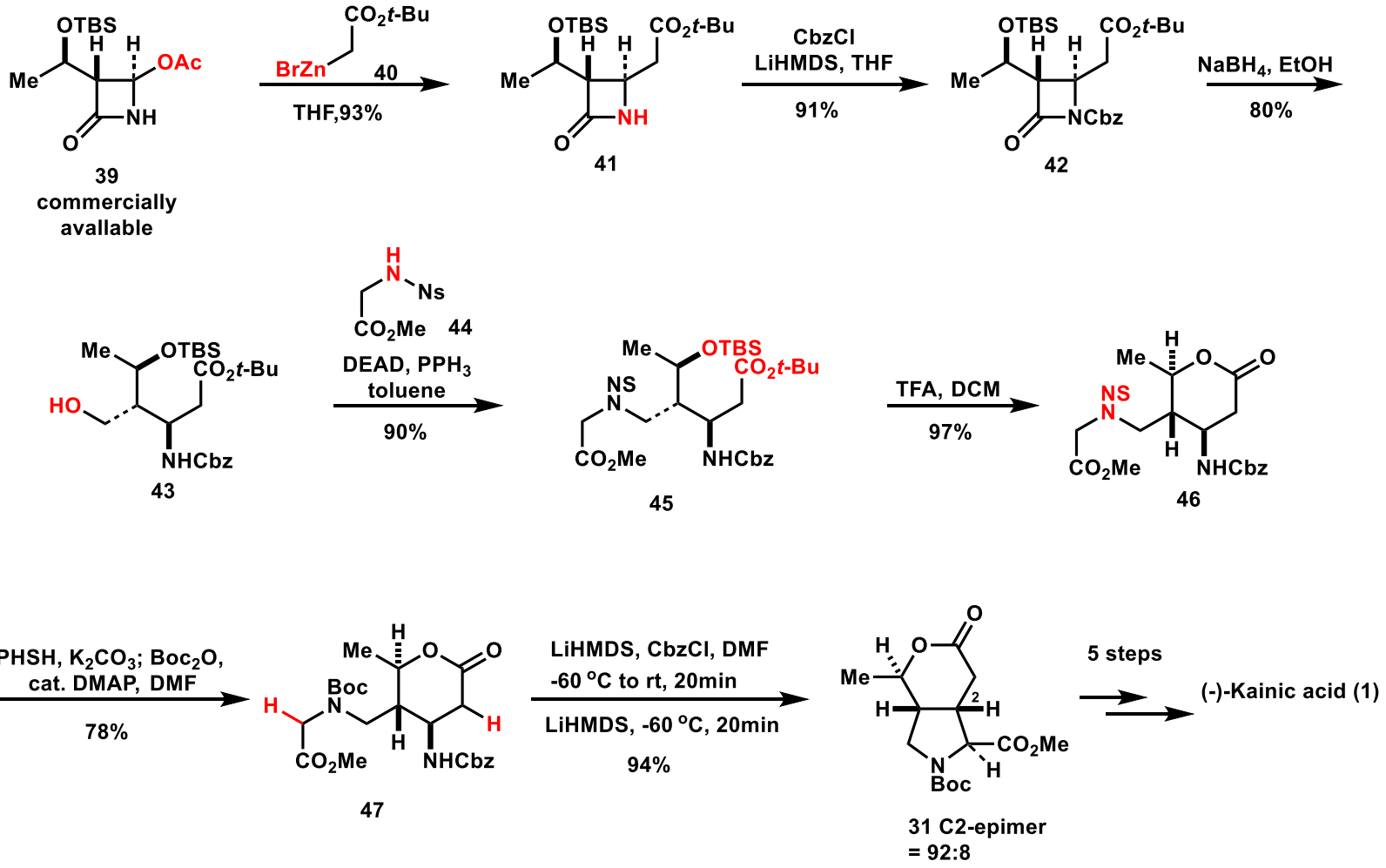
T. Fukuyama: *Org. Lett.* **2008**, 10, 1711–1714.



12 steps in 14% overall yield.

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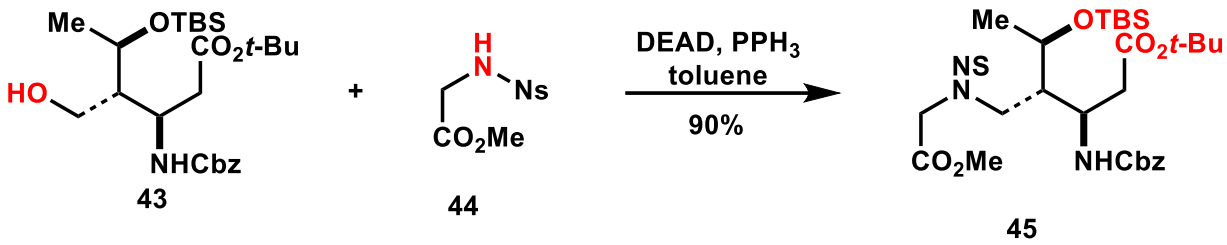
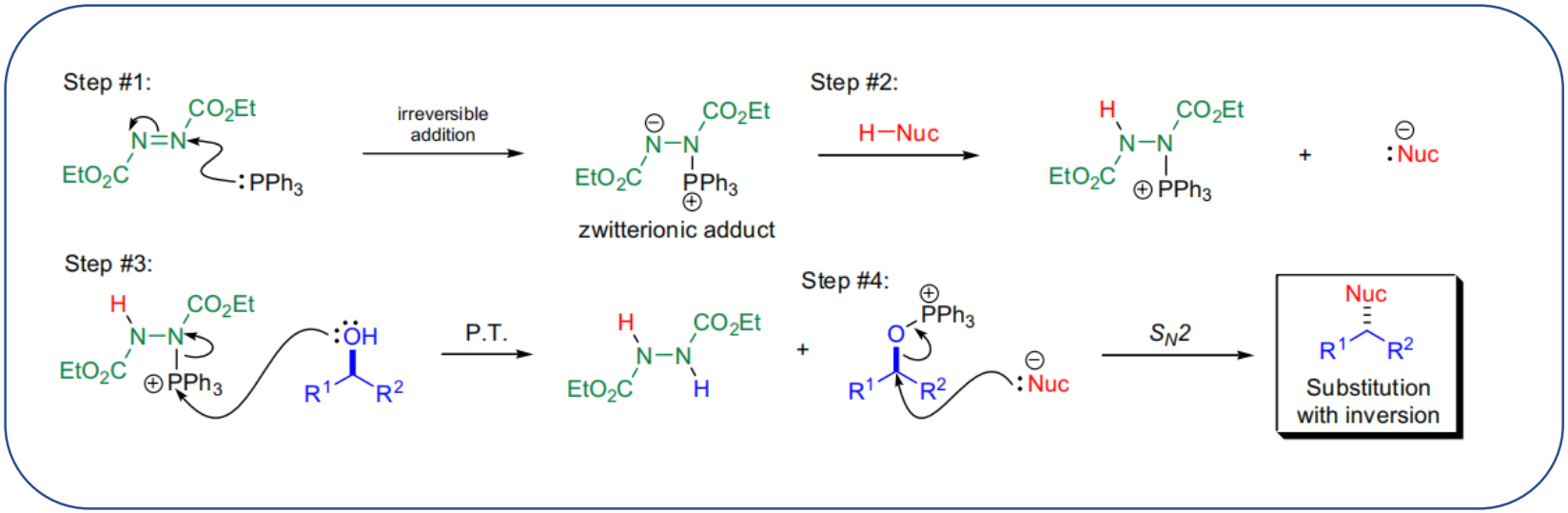
T. Fukuyama: *Org. Lett*. **2008**, 10, 1711–1714.



Mitsunobu reaction



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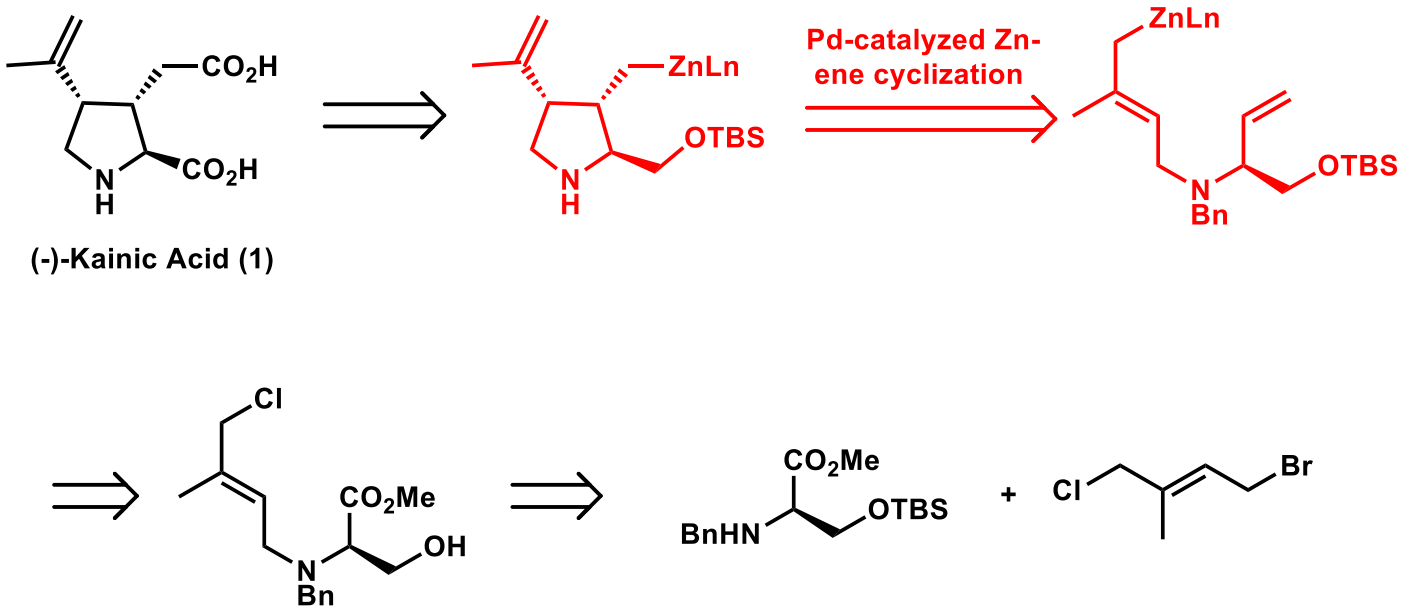
J. M. Chalker: *Org. Lett*. **2007**, 9, 3825–3828.

Retrosynthesis of (-)-Kainic Acid



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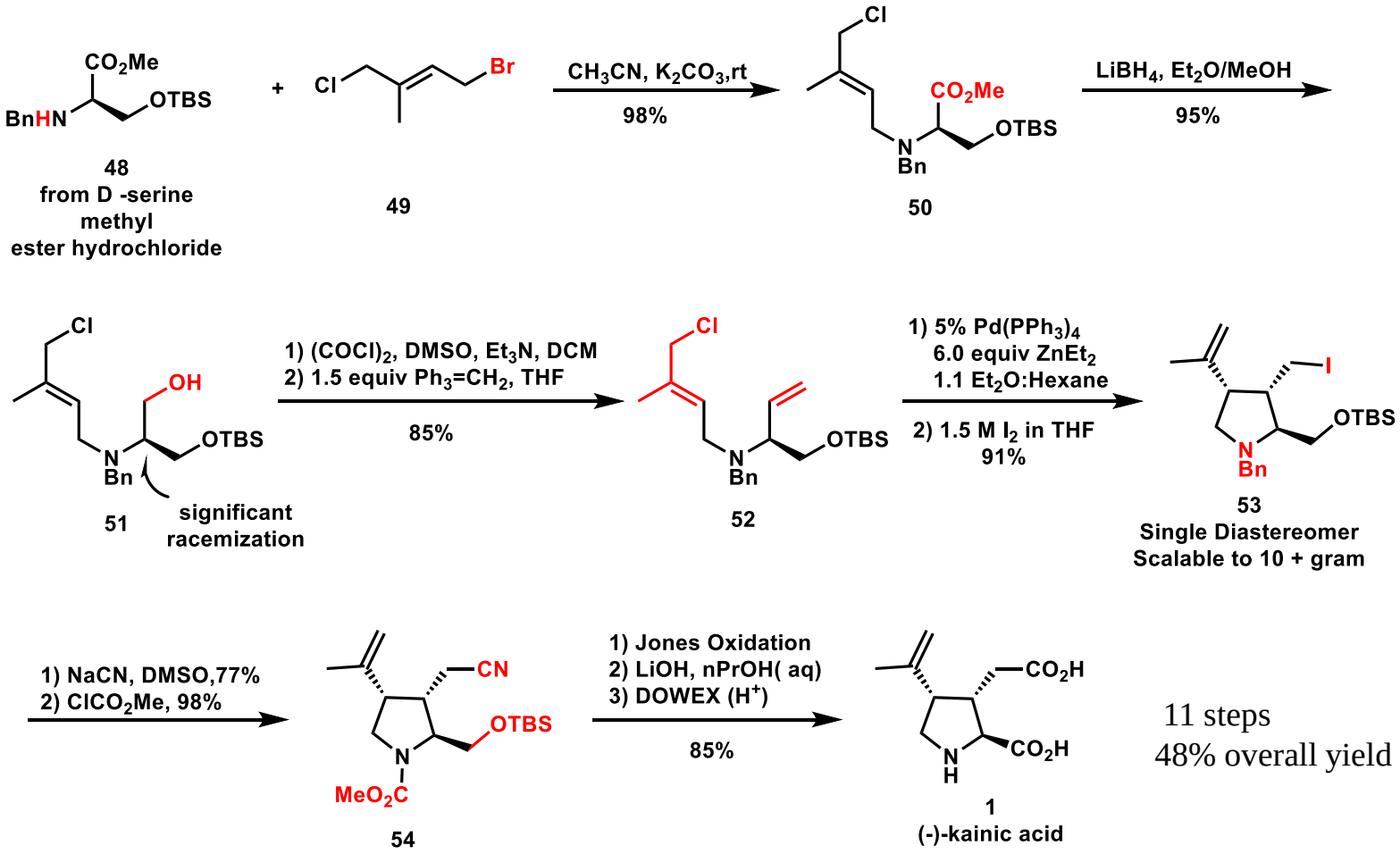

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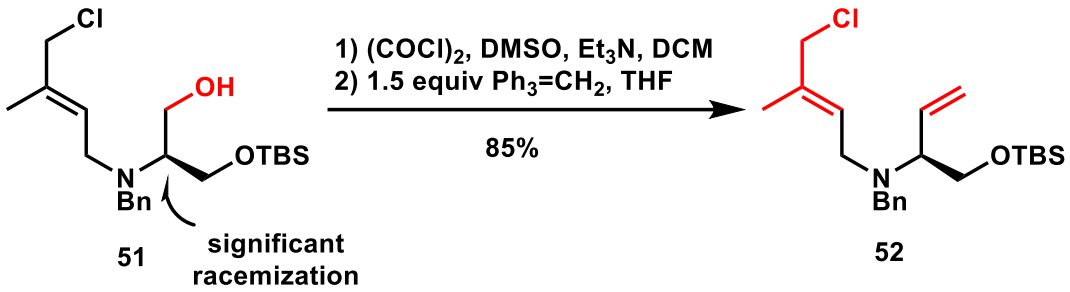
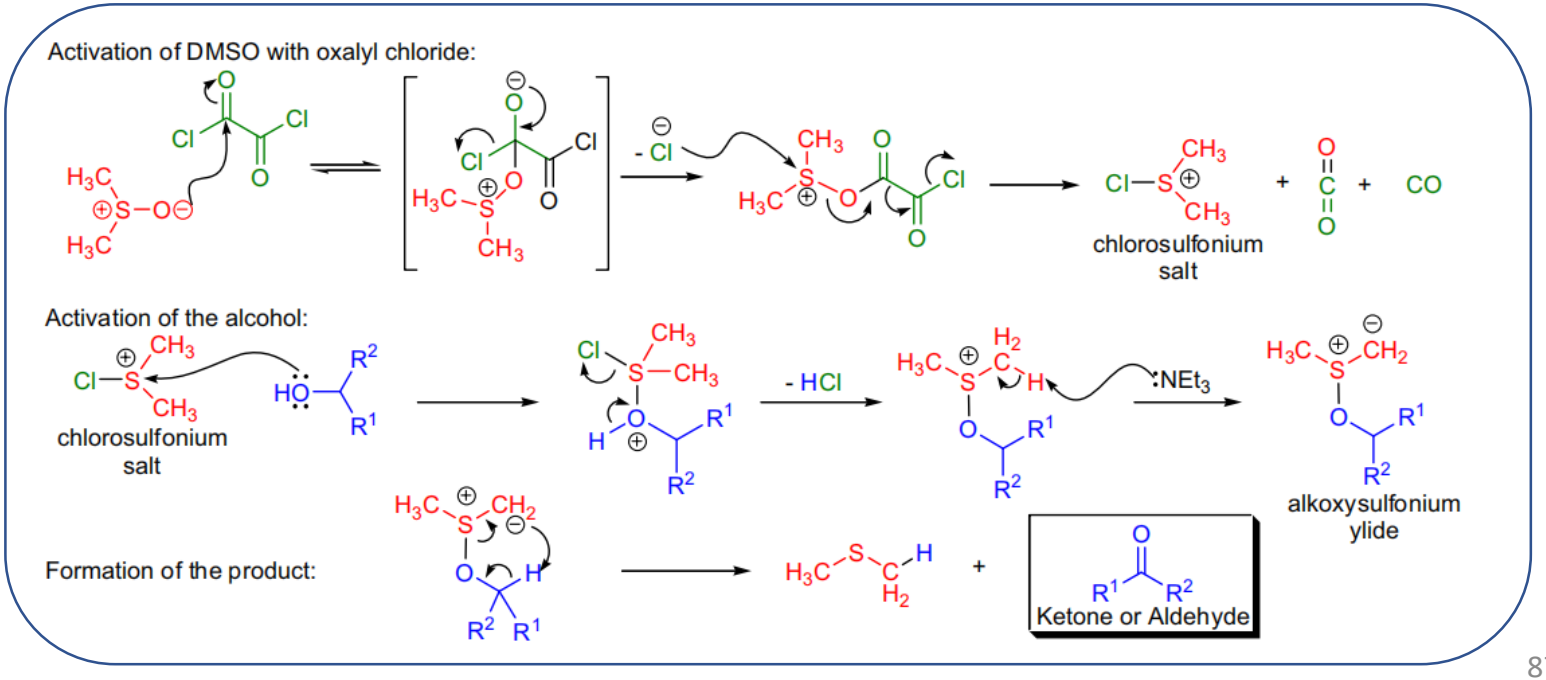


Swern oxidation

1. silyl group migration in alcohol
2. racemization of the related aldehyde.



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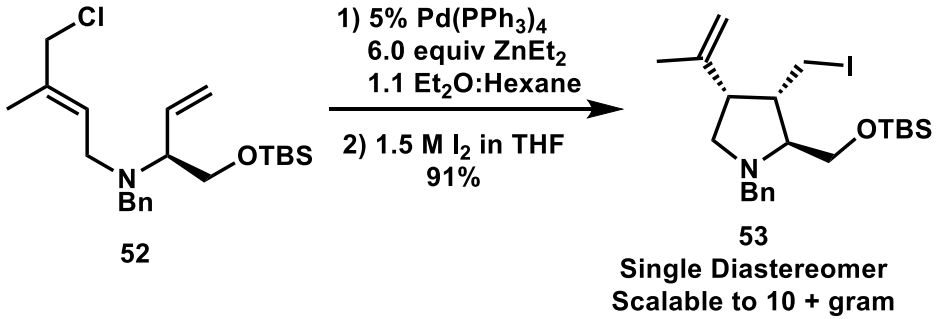
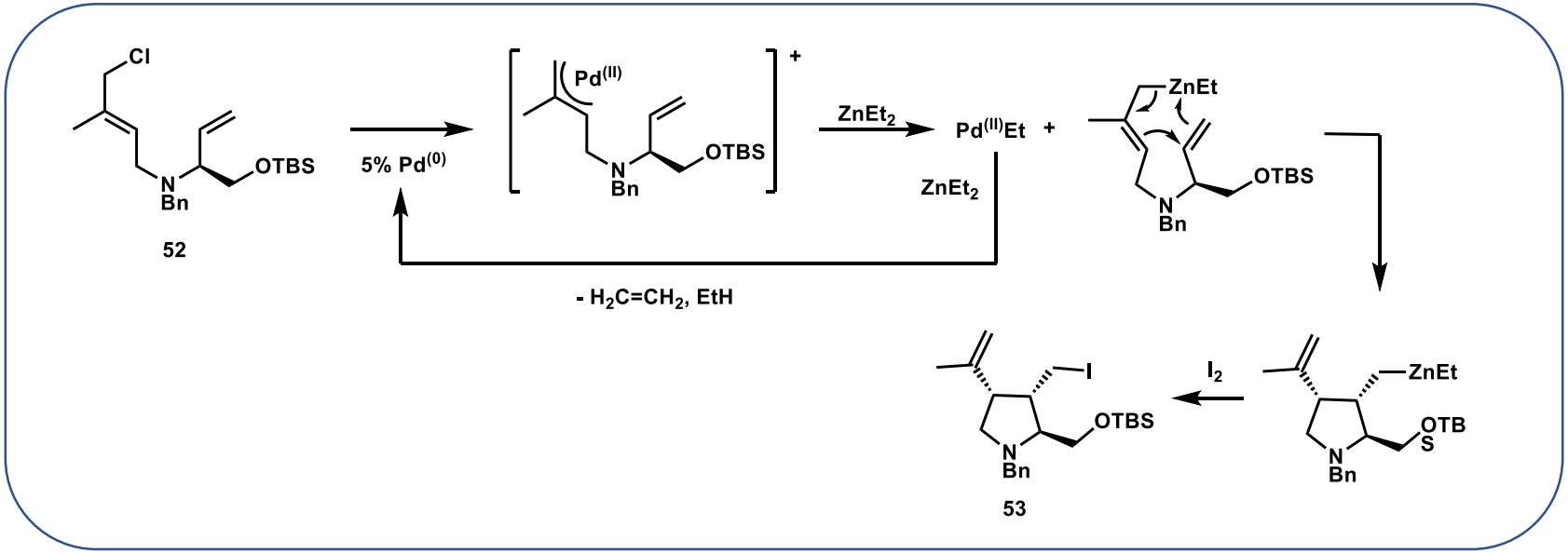


Pd-Catalyzed Zn-ene Cyclization



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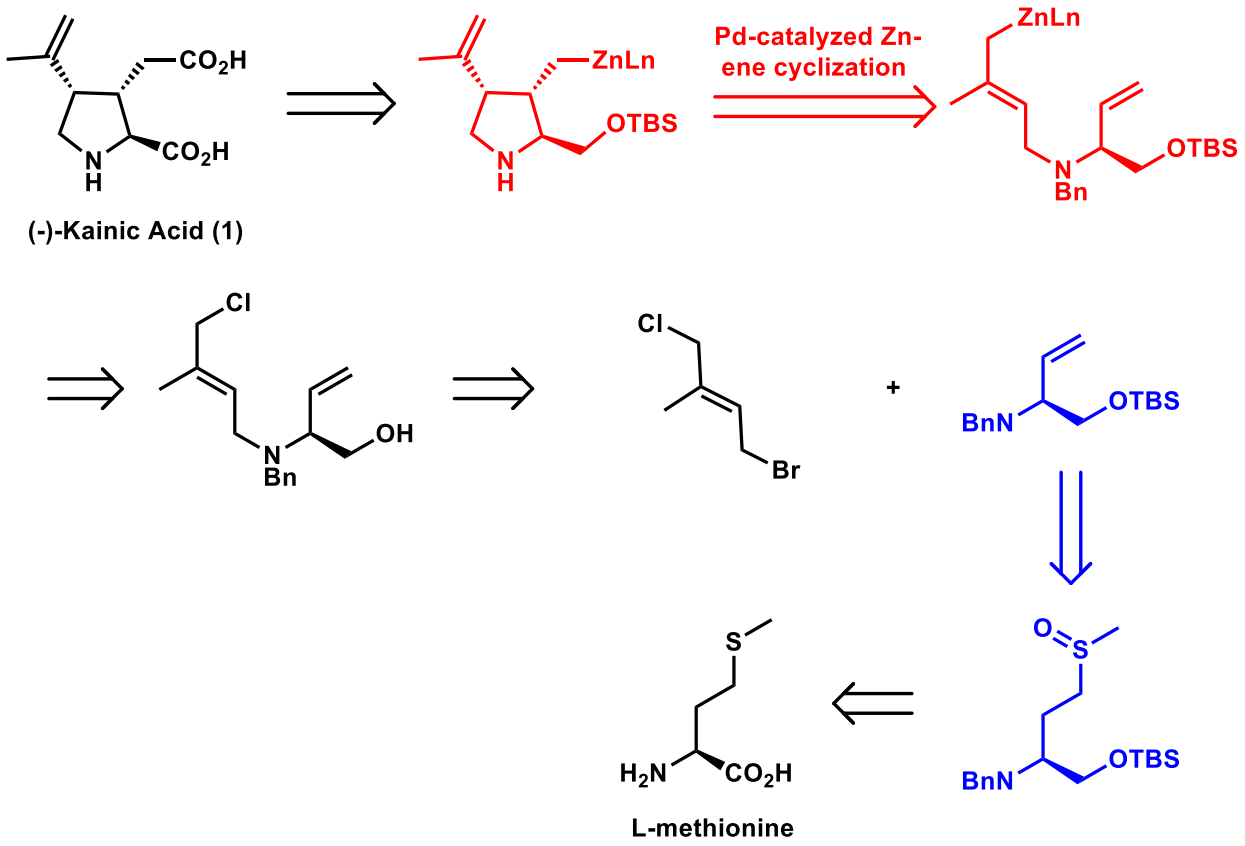
Retrosynthesis of (-)-Kainic Acid



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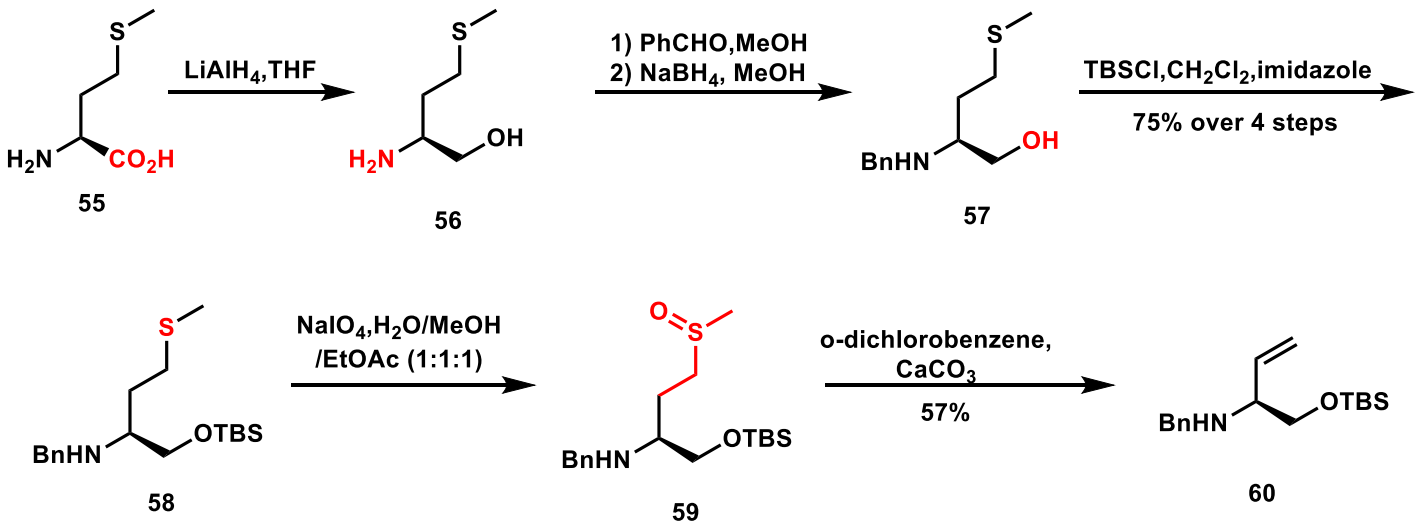

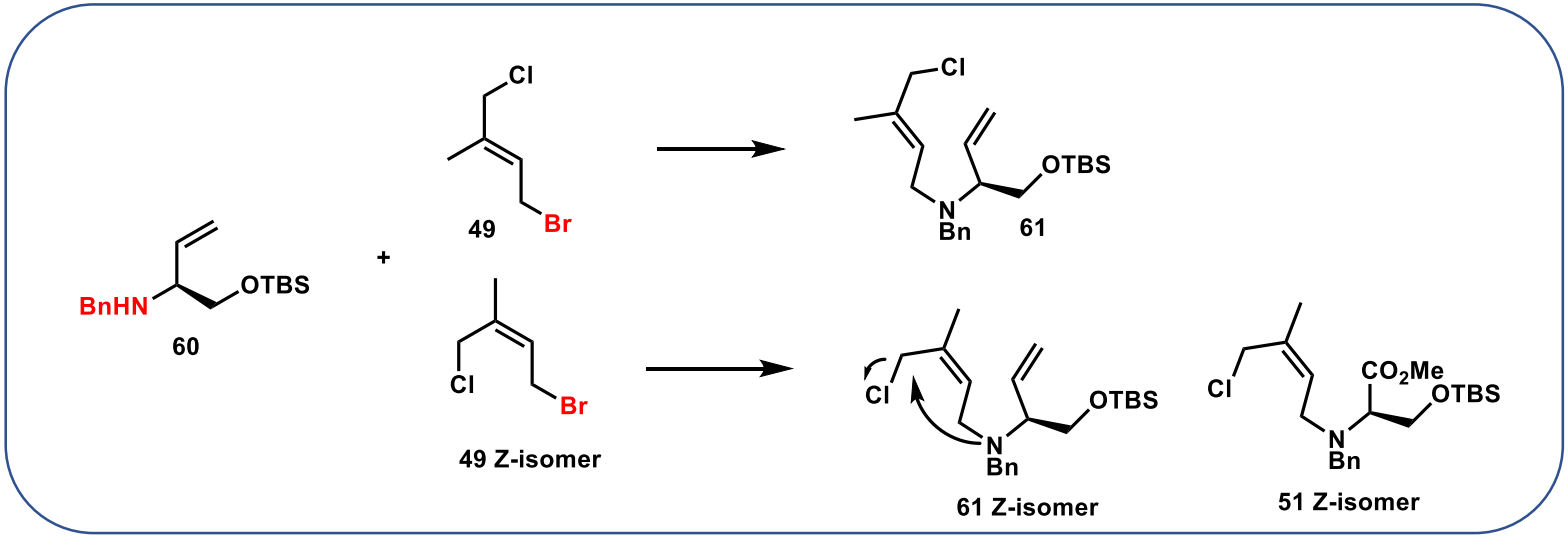

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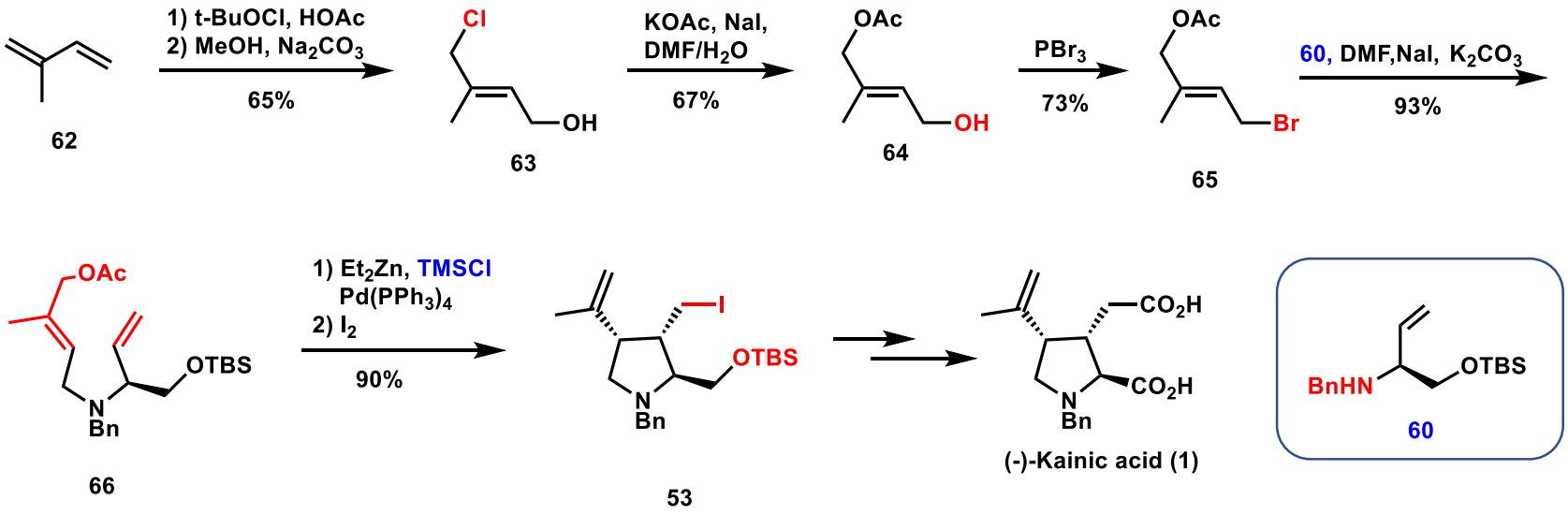
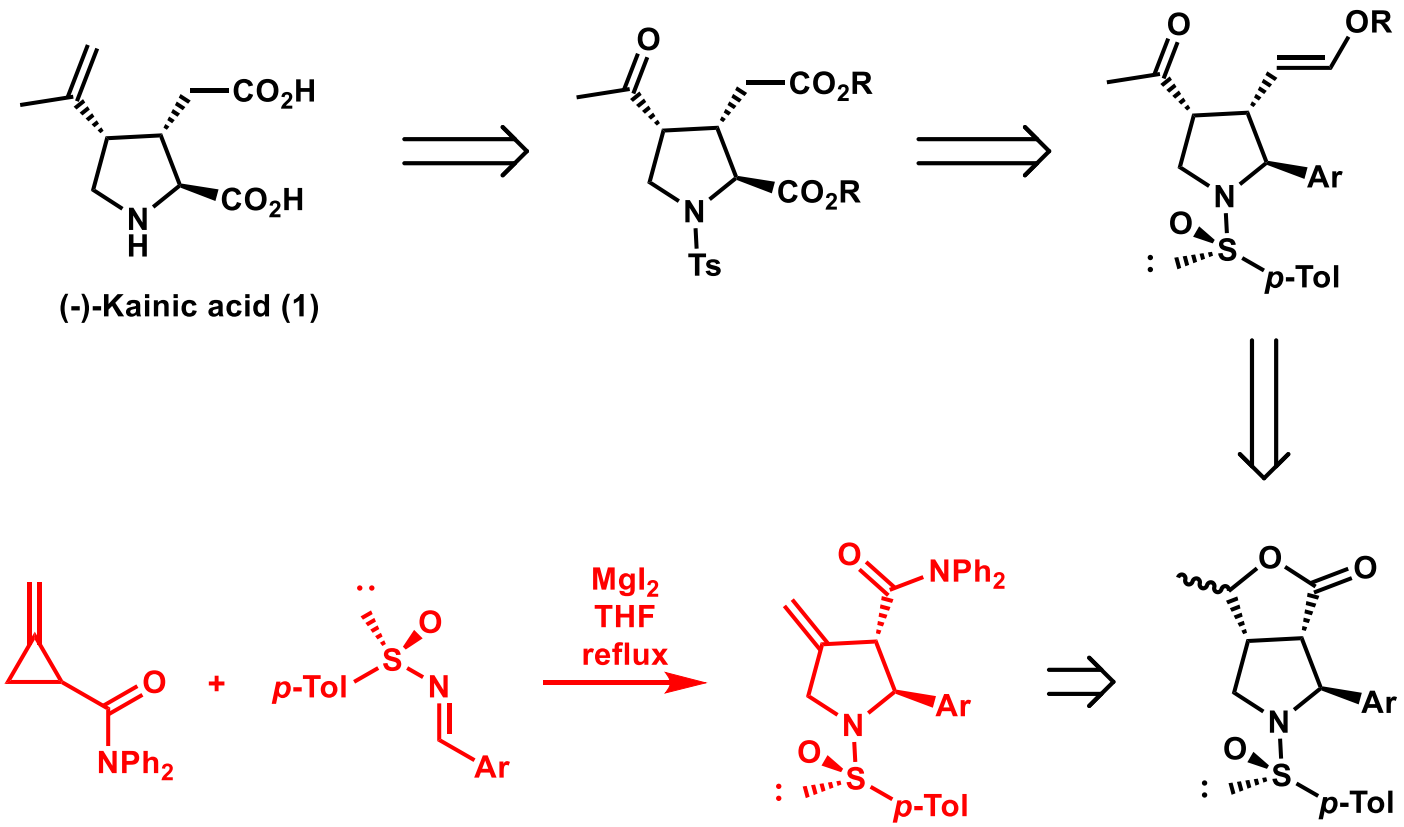


13 steps 37% overall yield

3. Cycloaddition Pathways

M. Lautens: *Org. Lett.* **2005**, 7, 3045–3047.

Retrosynthetic Analysis



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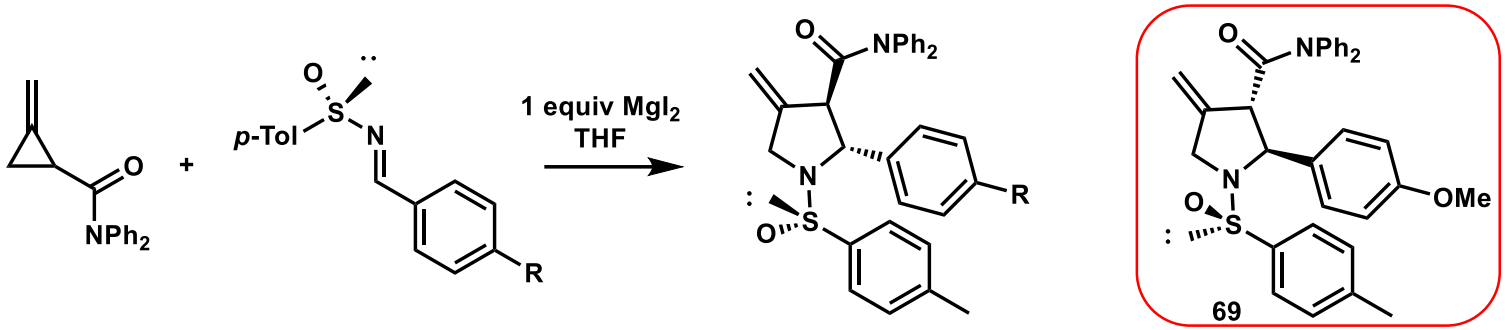
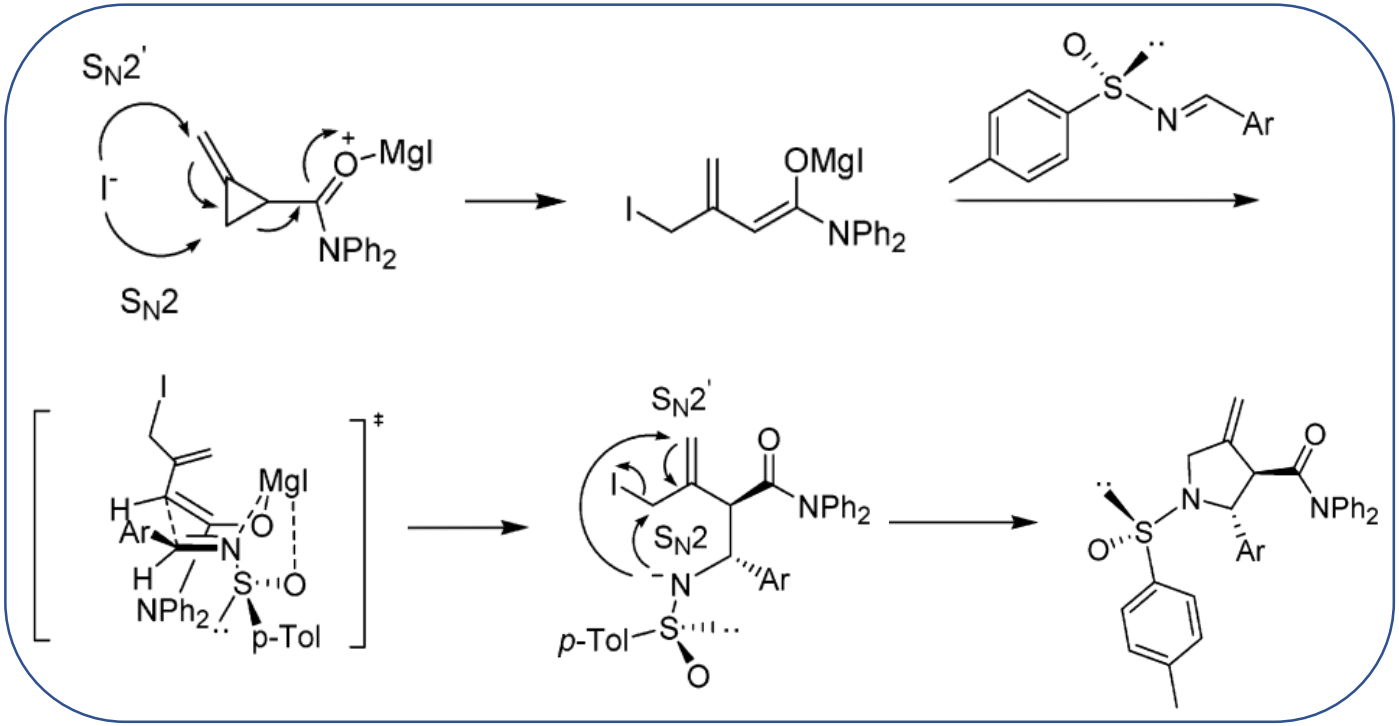
M. Lautens: *Org. Lett*. **2004**, 6, 3309.



Mechanism



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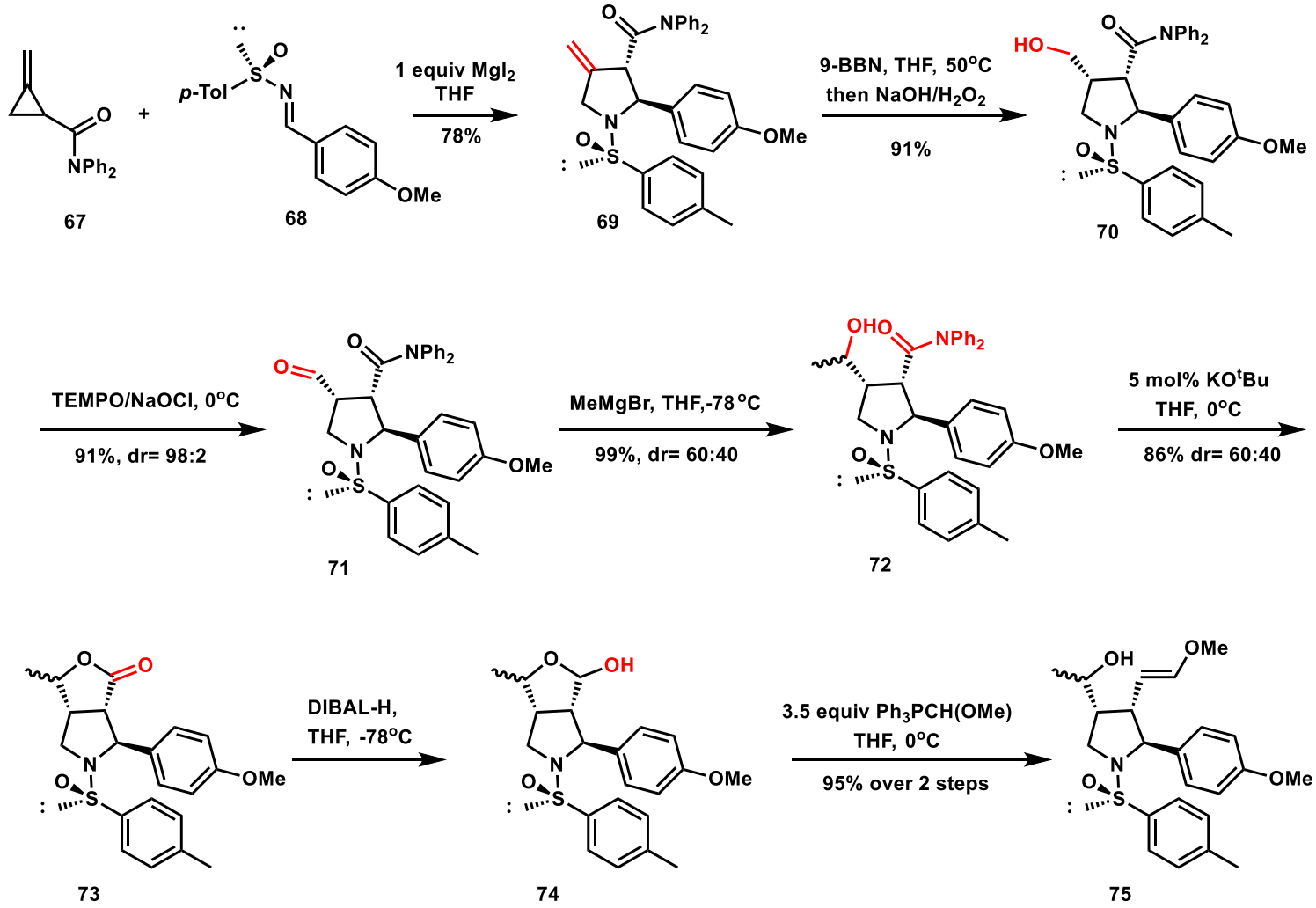

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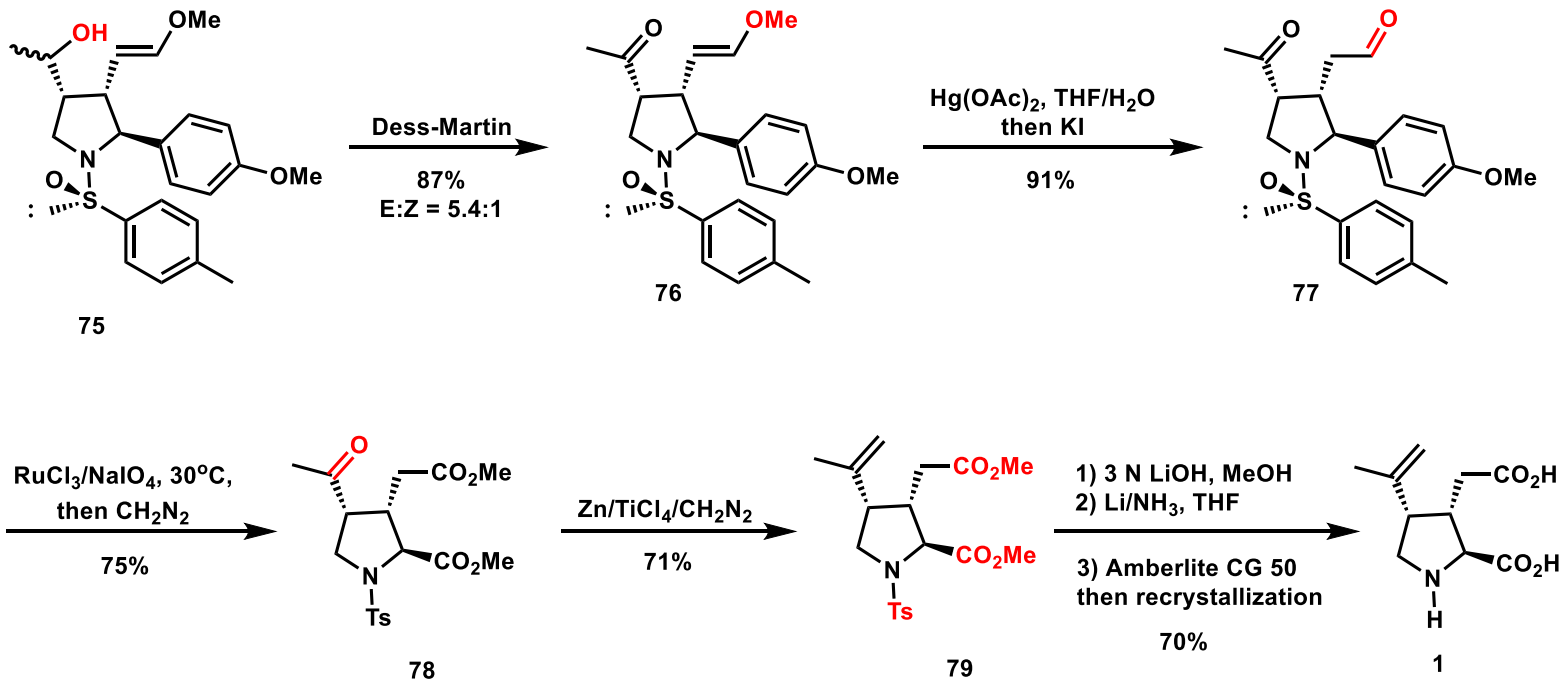

13 steps 15% overall yield

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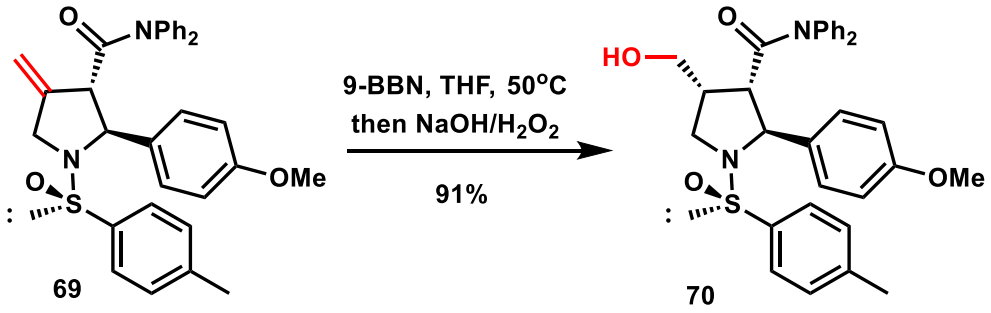
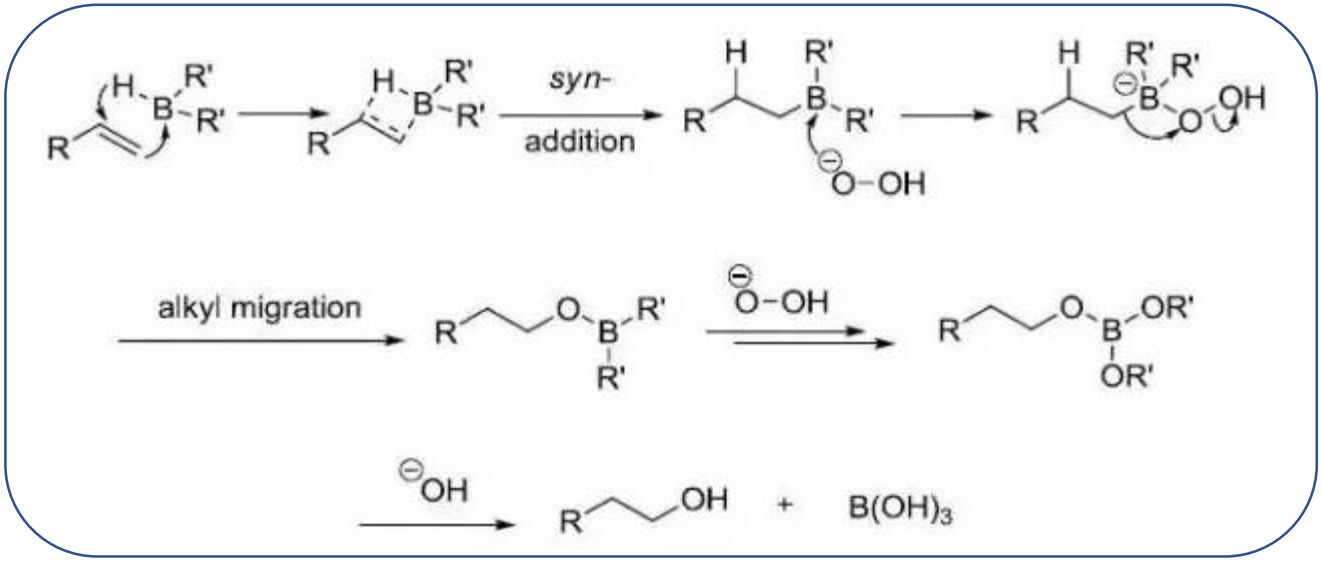
M. Lautens: *Org. Lett.* **2005**, 7, 3045–3047.



Brown hydroboration reaction



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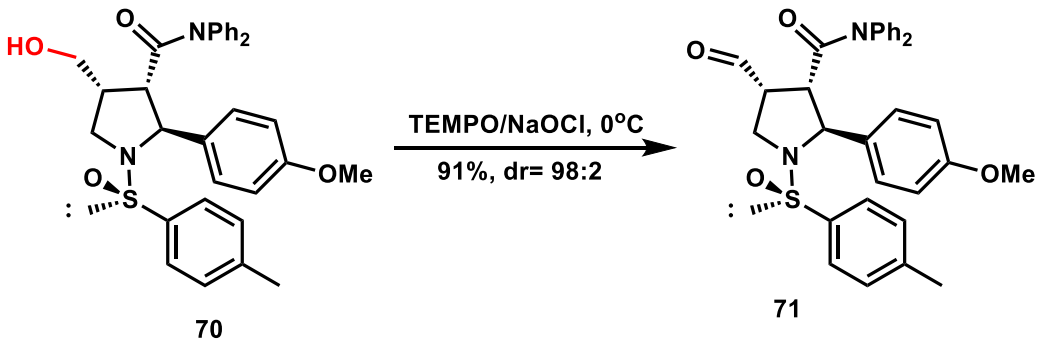
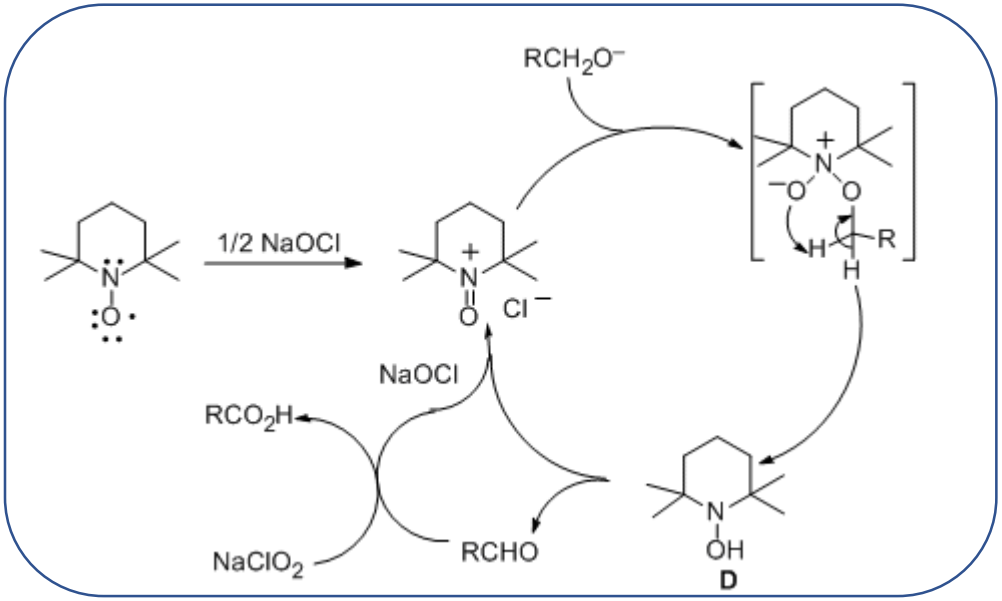


TEMPO/NaOCl Catalyzed Oxidation



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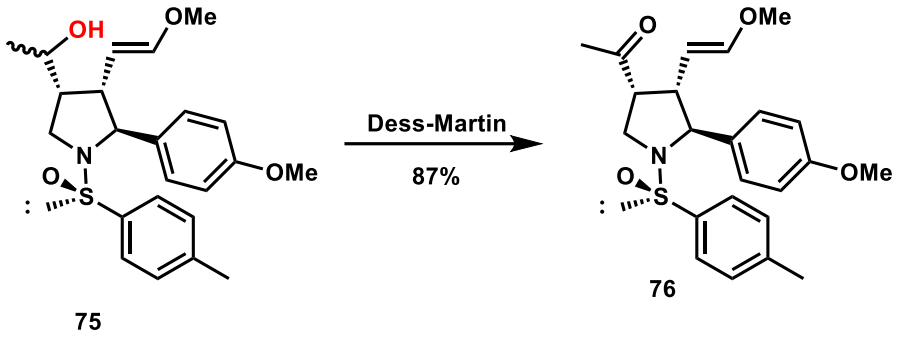
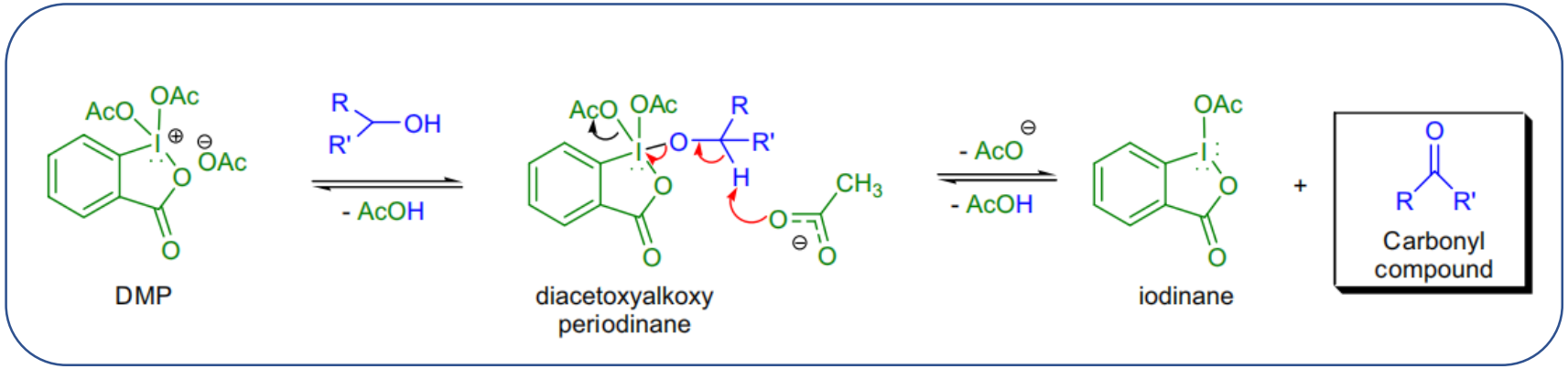
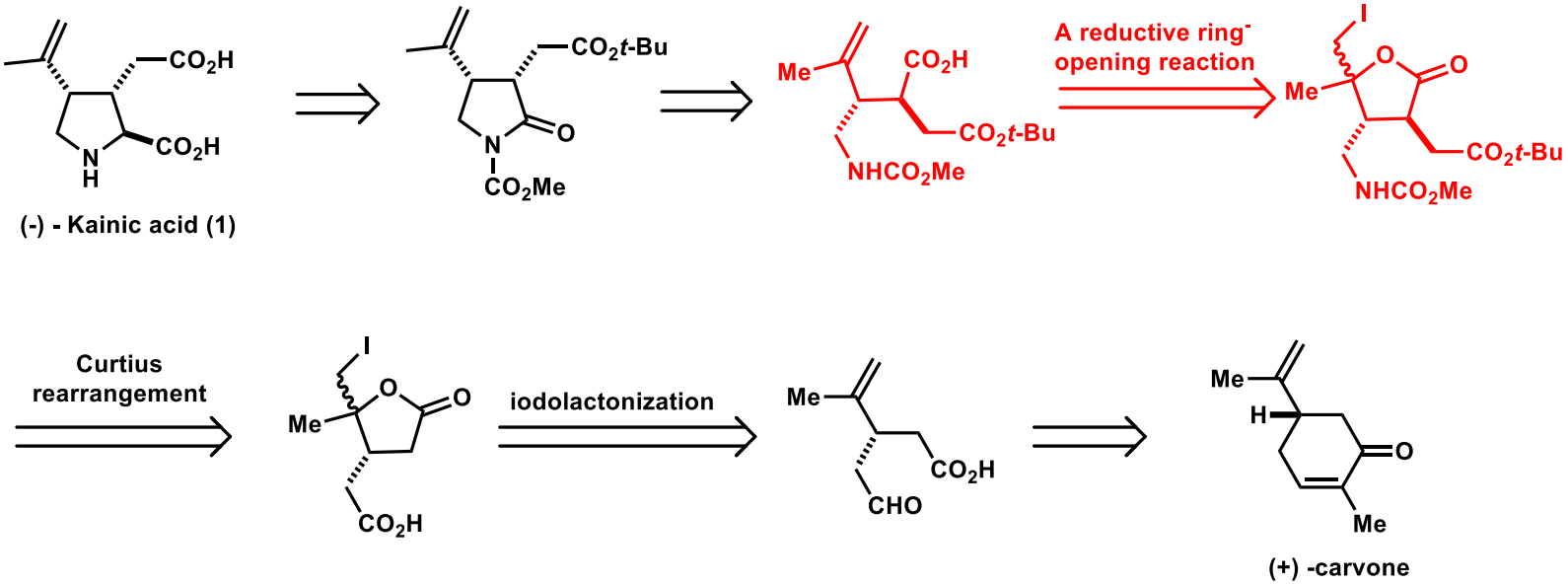


Dess-Martin oxidations



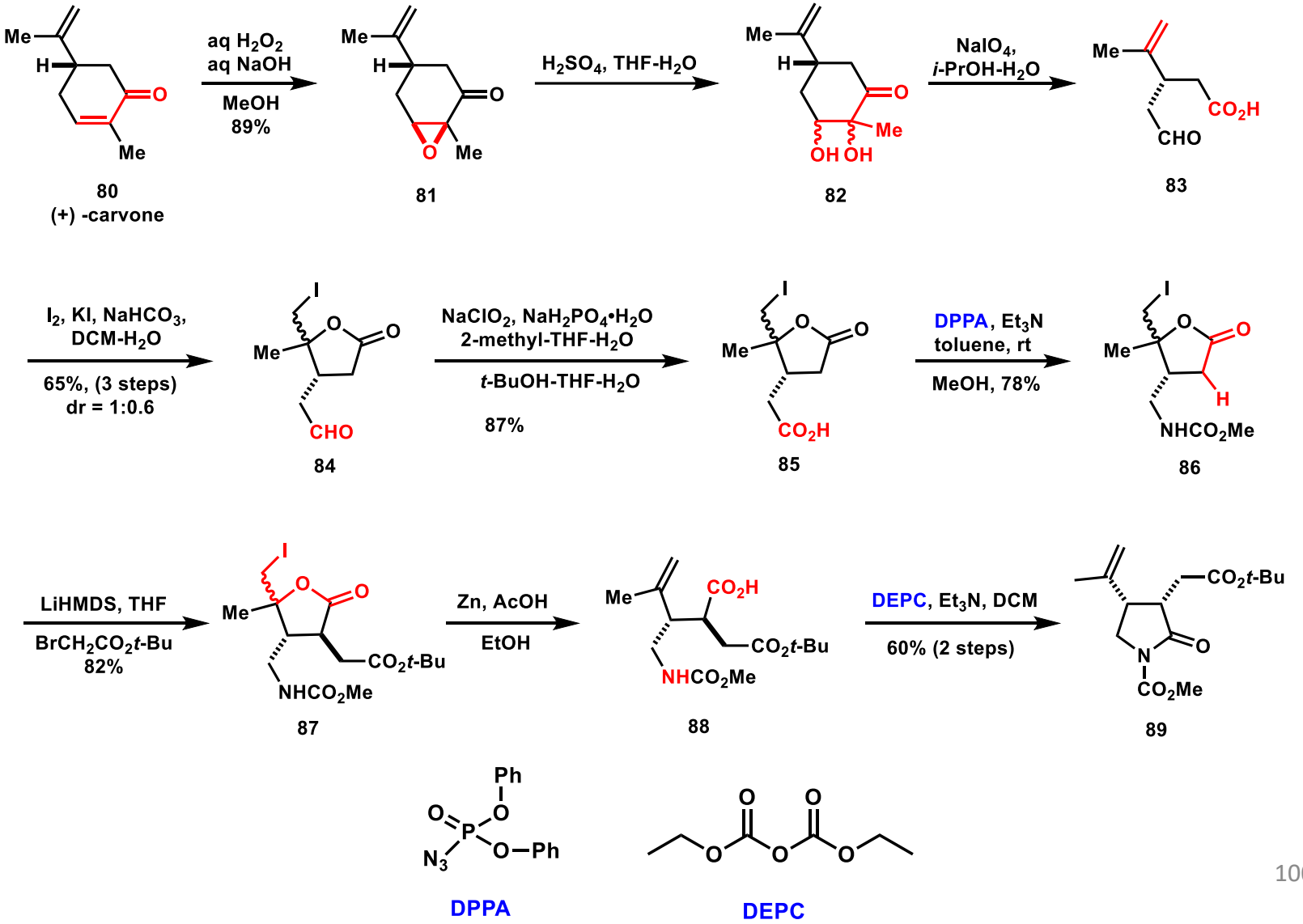
4. C–N Bond Formation Pathways

T. Fukuyama: *Org. Lett*. **2011**, 13, 2068–2070.



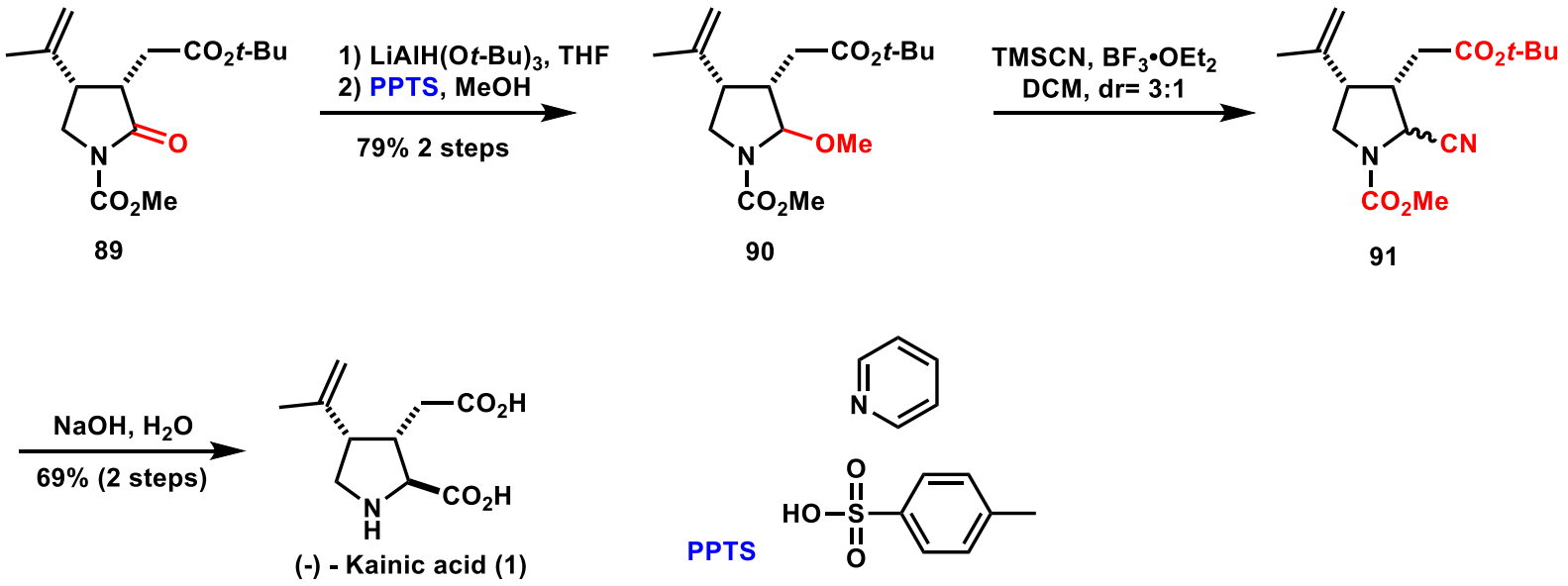
4. C–N Bond Formation Pathways

T. Fukuyama: *Org. Lett*. **2011**, 13, 2068–2070.



4. C–N Bond Formation Pathways

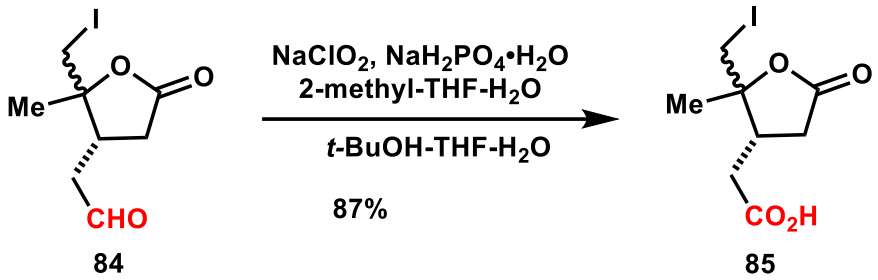
T. Fukuyama: *Org. Lett*. **2011**, 13, 2068–2070.



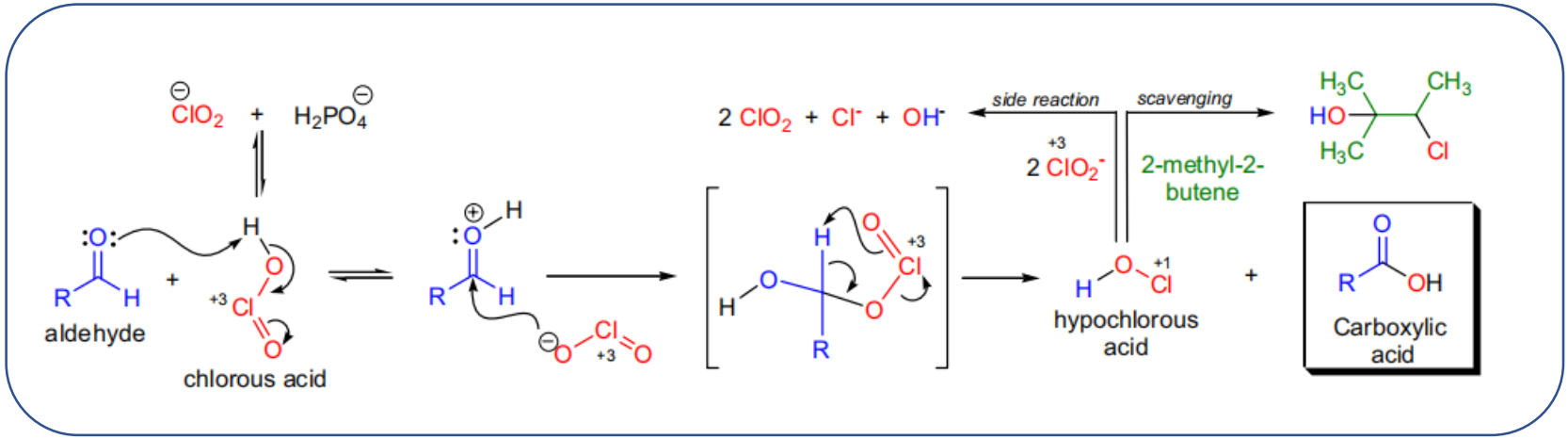
13 steps 10.3% overall yield

4. C–N Bond Formation Pathways

T. Fukuyama: *Org. Lett*. **2011**, 13, 2068–2070.

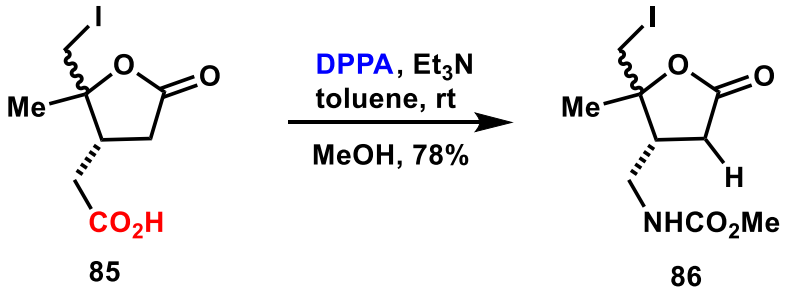


Pinnick oxidation

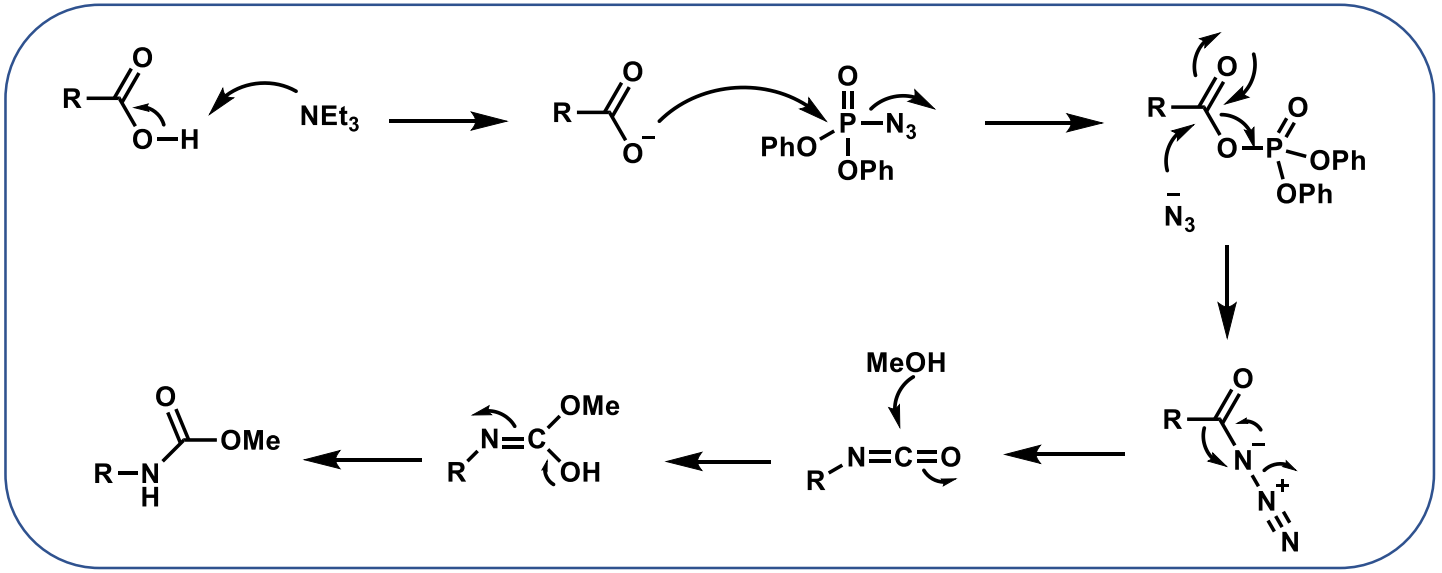


4. C–N Bond Formation Pathways

T. Fukuyama: *Org. Lett*. **2011**, 13, 2068–2070.

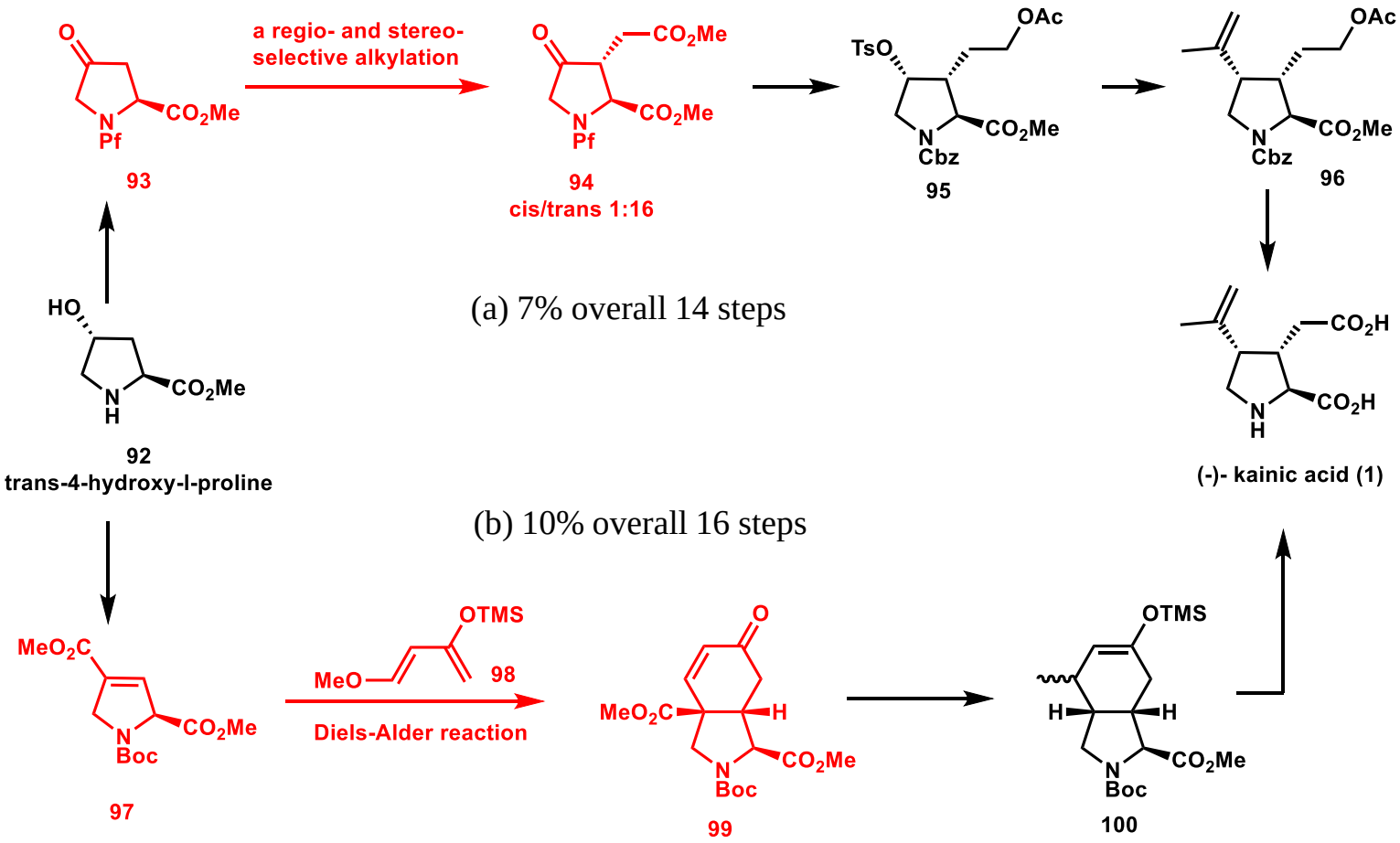


Curtius rearrangement



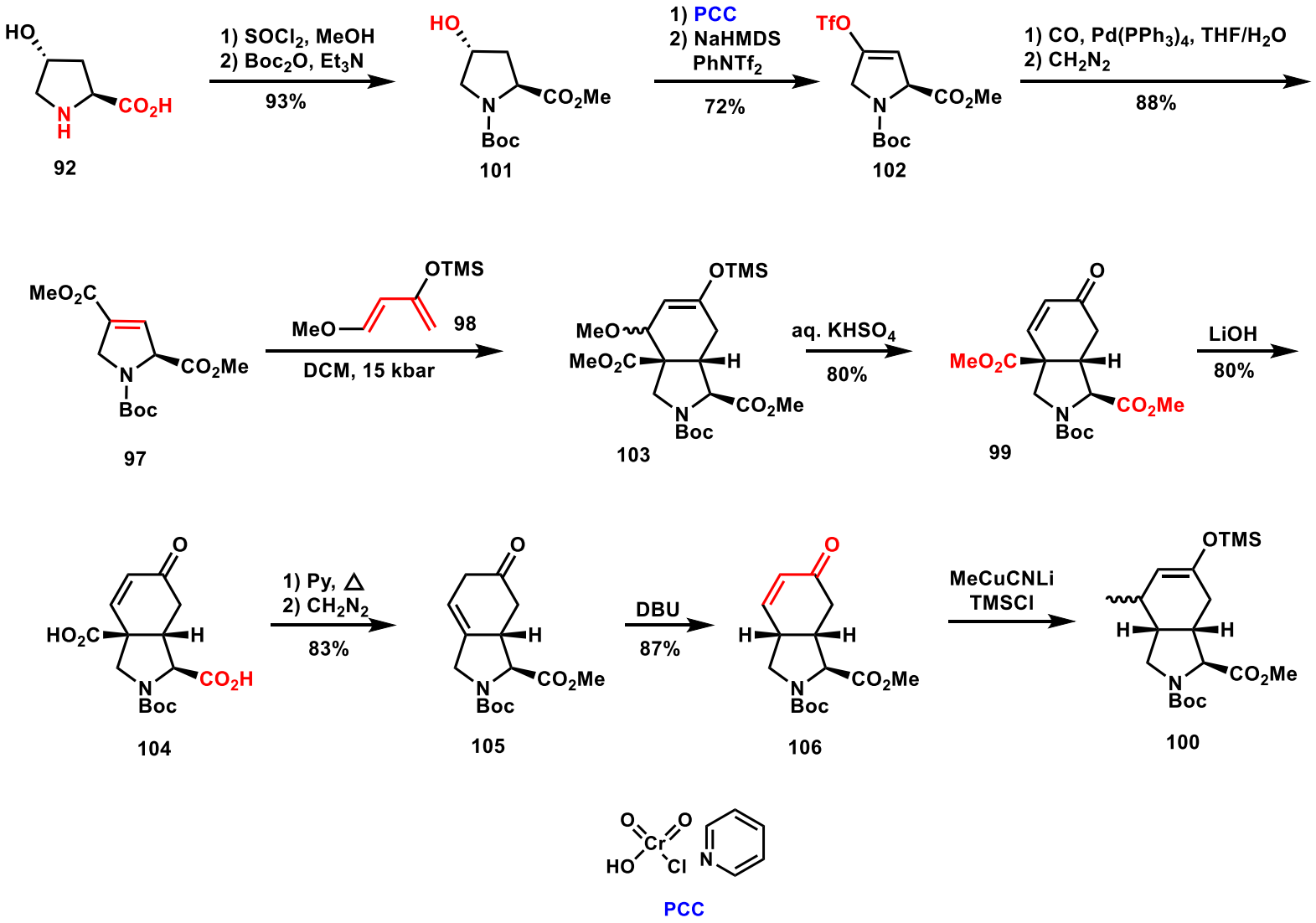
5. Starting from an Existing Pyrrolidine Ring

J.-F. Poisson: (a) *J. Org. Chem.* **2005**, 70, 10860–10863.
(b) *Org. Lett.* **2006**, 8, 5665–5668.



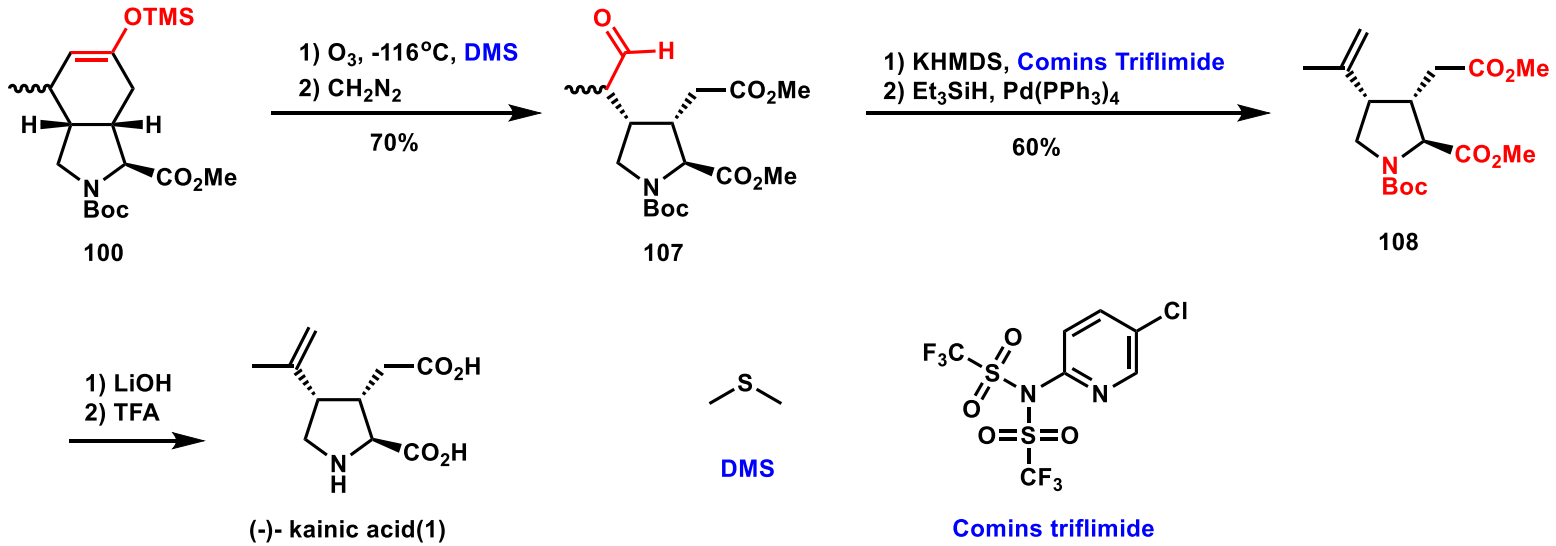
5. Starting from an Existing Pyrrolidine Ring

J.-F. Poisson: *Org. Lett.* **2006**, 8, 5665–5668.



5. Starting from an Existing Pyrrolidine Ring

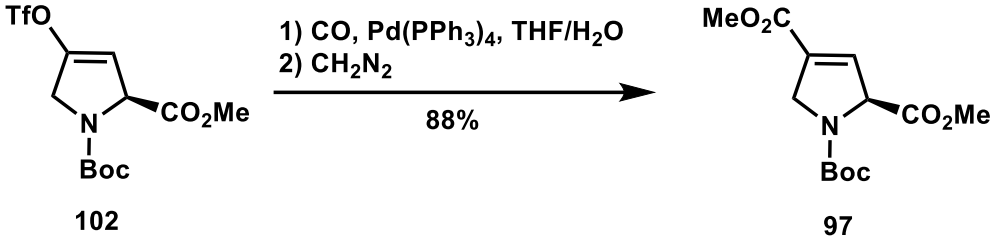
J.-F. Poisson: *Org. Lett.* **2006**, 8, 5665–5668.



(b) 10% overall 16 steps

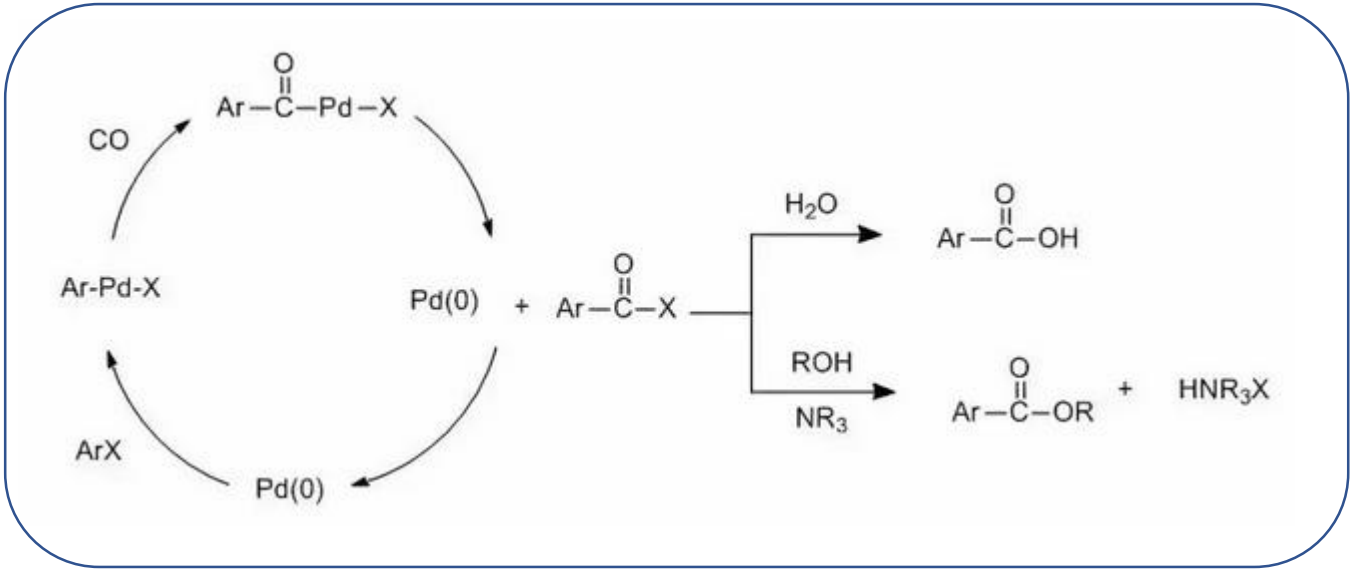
5. Starting from an Existing Pyrrolidine Ring

J.-F. Poisson: *Org. Lett.* **2006**, 8, 5665–5668.



102 97

Mechanism



Summary

1. C^2–C^3 Bond Formation Pathways

J. Clayden: Dearomatising Cyclisation

T. Fukuyama: Michael addition

2. C^3–C^4 Bond Formation Pathways

J. M. Chalker: Pd-catalyzed Zn-ene cyclization

3. Cycloaddition Pathways

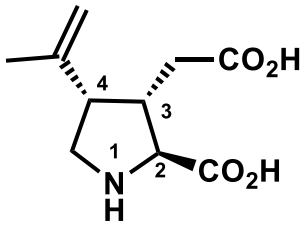
M. Lautens: MgI_2 -mediate cyclization

4. C–N Bond Formation Pathways

T. Fukuyama: A reductive ring opening reaction

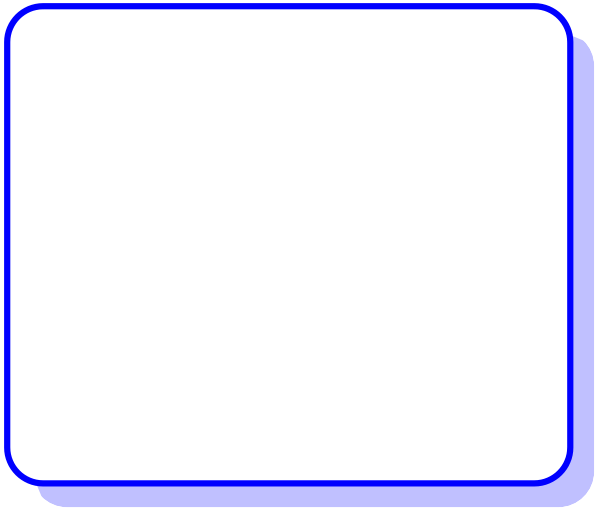
5. Starting from an Existing Pyrrolidine Ring

J.-F. Poisson: Diels-Alder reaction



(-)-kainic acid (1)

Total Syntheses of (–)-α-Kainic Acid (2011-2020)



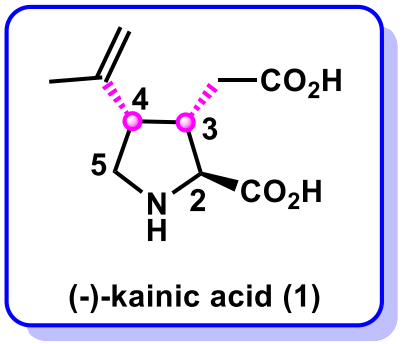
Reporter: Mingze Yang

Supervisors: *Prof.* Tao Ye

***Dr.* Yian Guo**

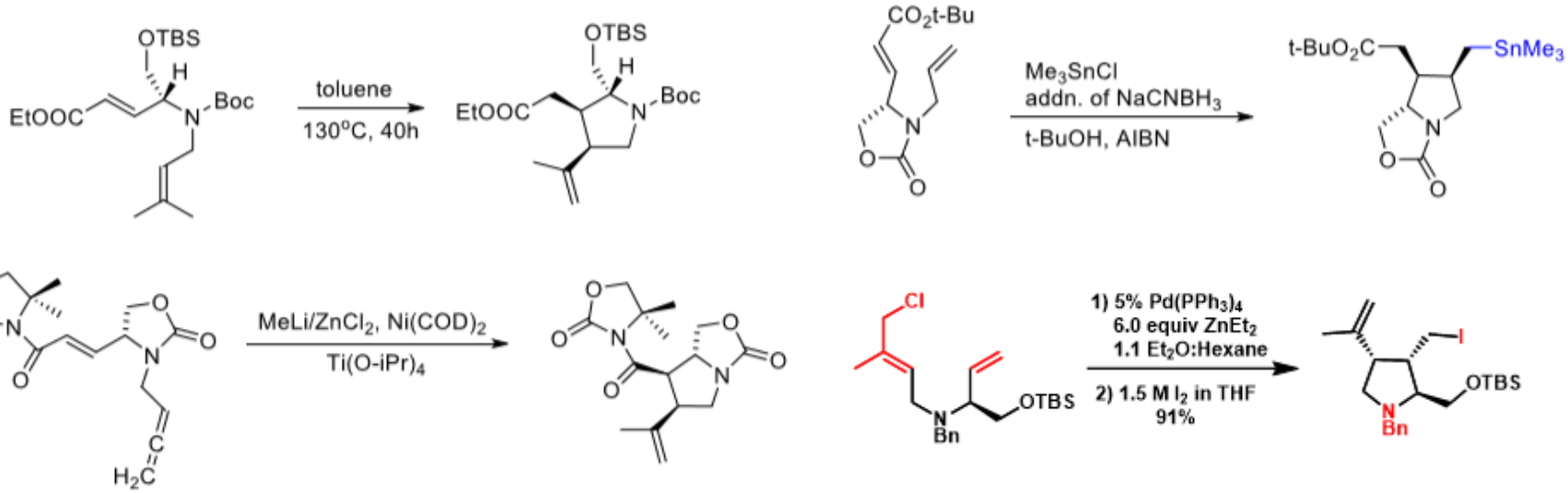
Oct 19th, 2020

Structure Analysis I (the key syn C4-C3)



I: The key syn C4-C3

I-a: Major Ene reaction

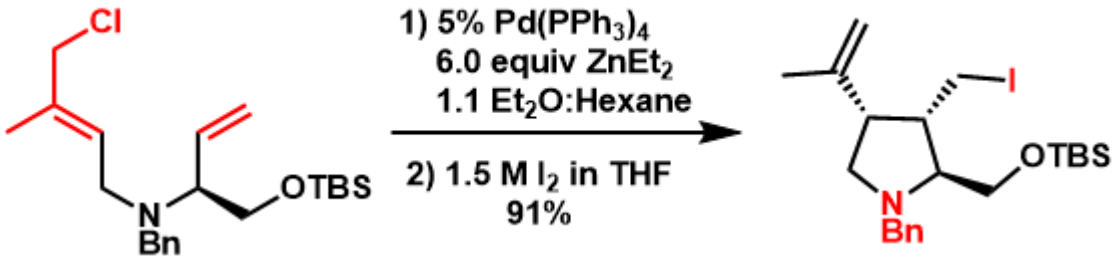


Note: Ene reaction – relative syn C4-C3

The center of C2 – face selectivity

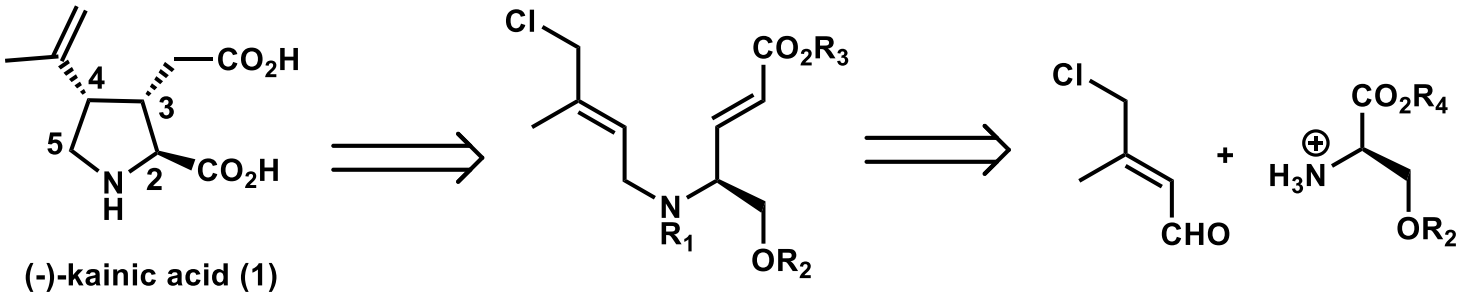
I-a: Ene reaction

SmI_2-mediated intramolecular coupling



J. M. Chalker: *Org. Lett*. **2007**, 9, 3825

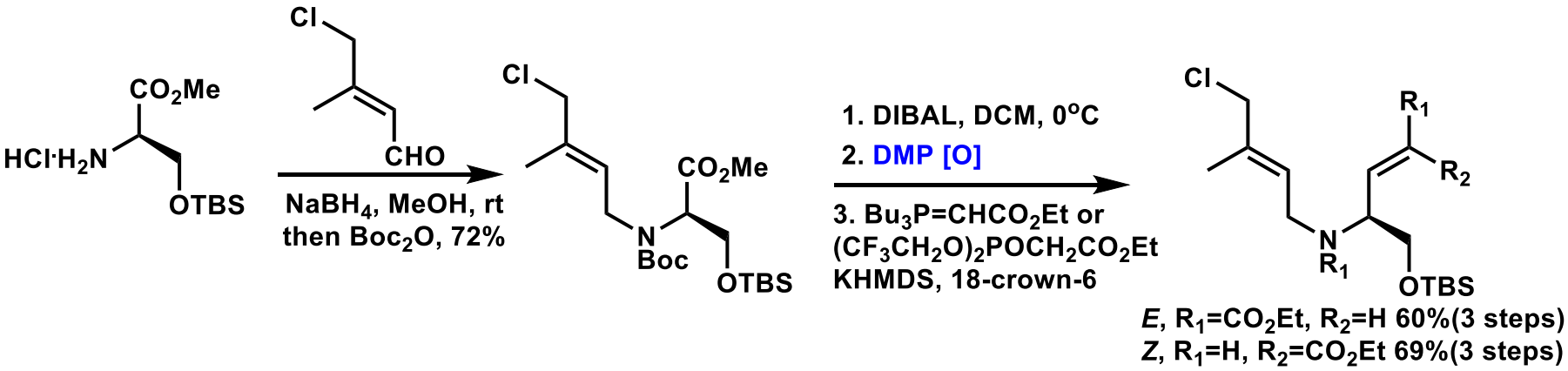
Retrosynthetic analysis of kainic acid



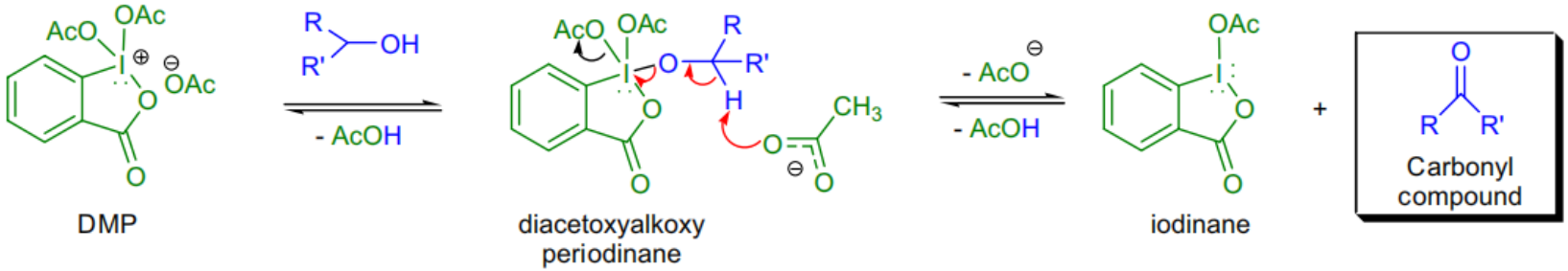
Fuyuhiko Matsuda et. al. *Org. Biomol. Chem*. **2017**, *15*, 6557

I-a: SmI_2-mediated intramolecular coupling

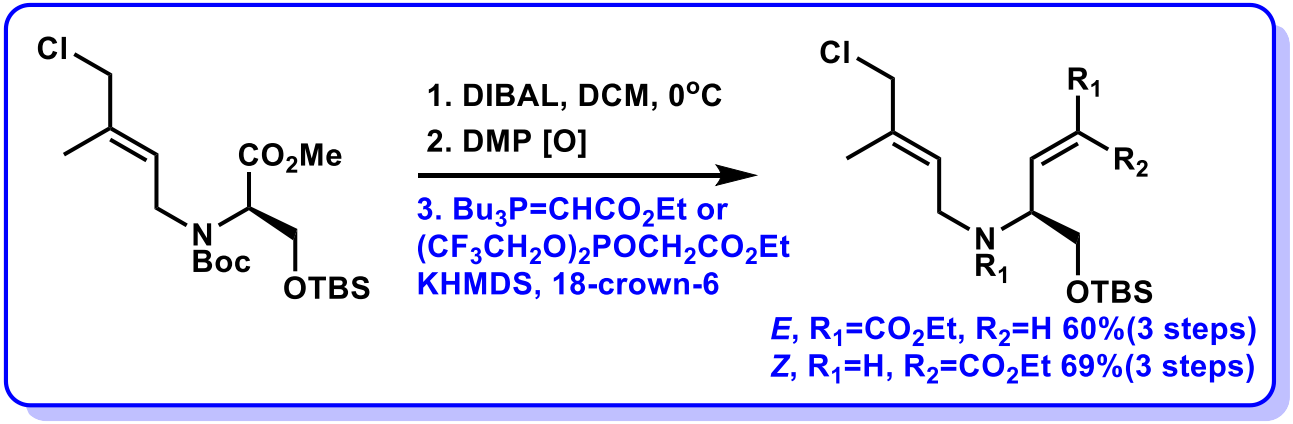
Synthesis of the intermediate



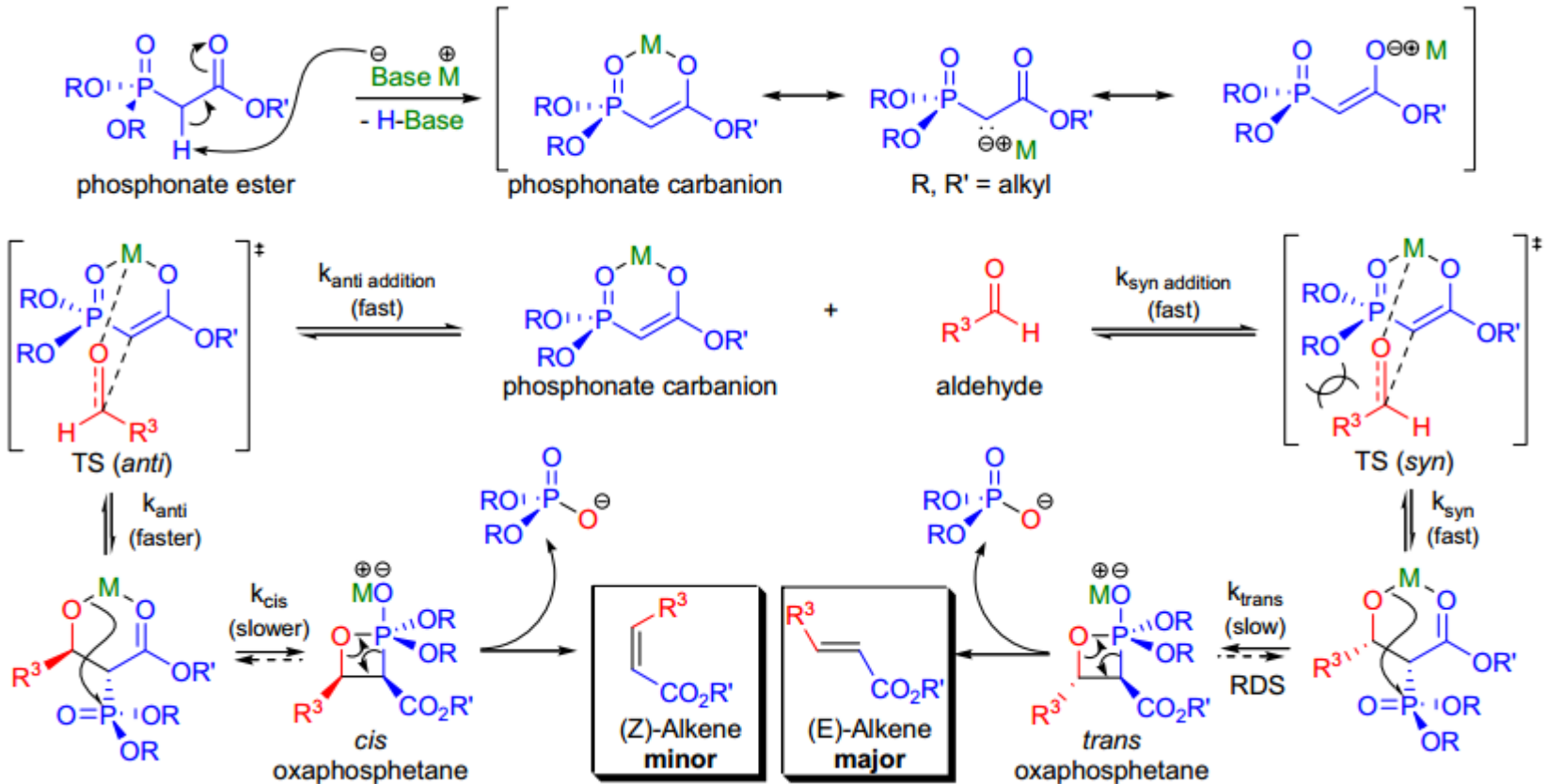
Dess-Martin oxidations



I-a: SmI_2-mediated intramolecular coupling

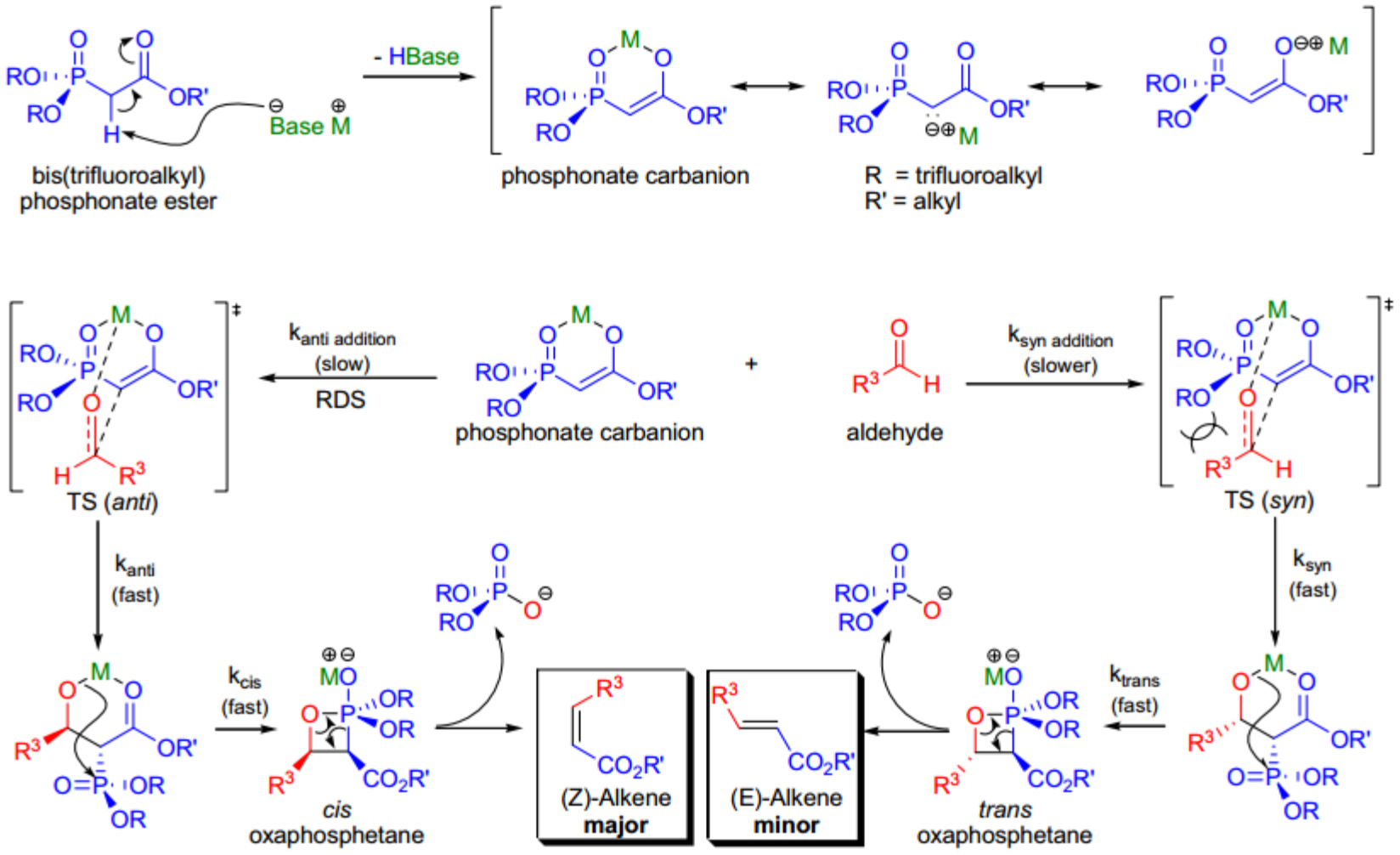


HWE olefination



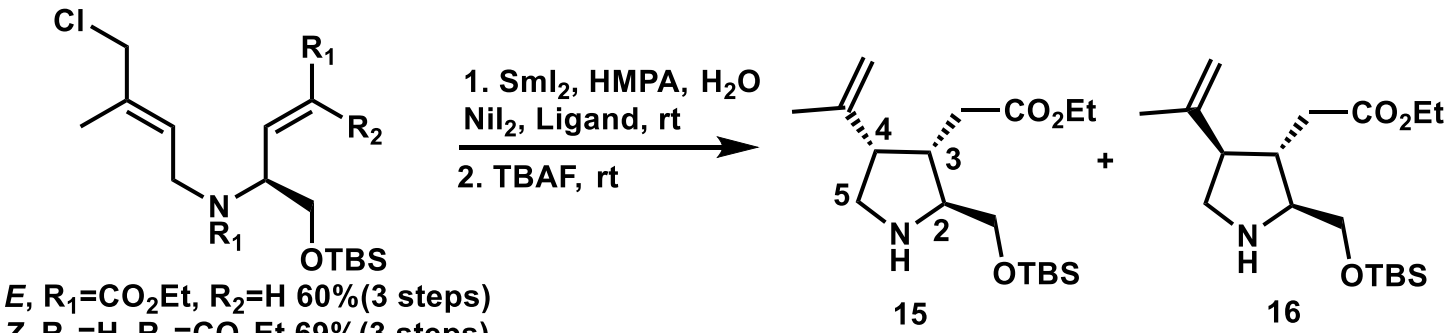
I-a: SmI_2-mediated intramolecular coupling

Still-Gennari modified HWE olefination



I-a: Ene reaction

SmI_2-mediated intramolecular coupling



E, R_1=CO_2Et, R_2=H 60%(3 steps)
Z, R_1=H, R_2=CO_2Et 69%(3 steps)

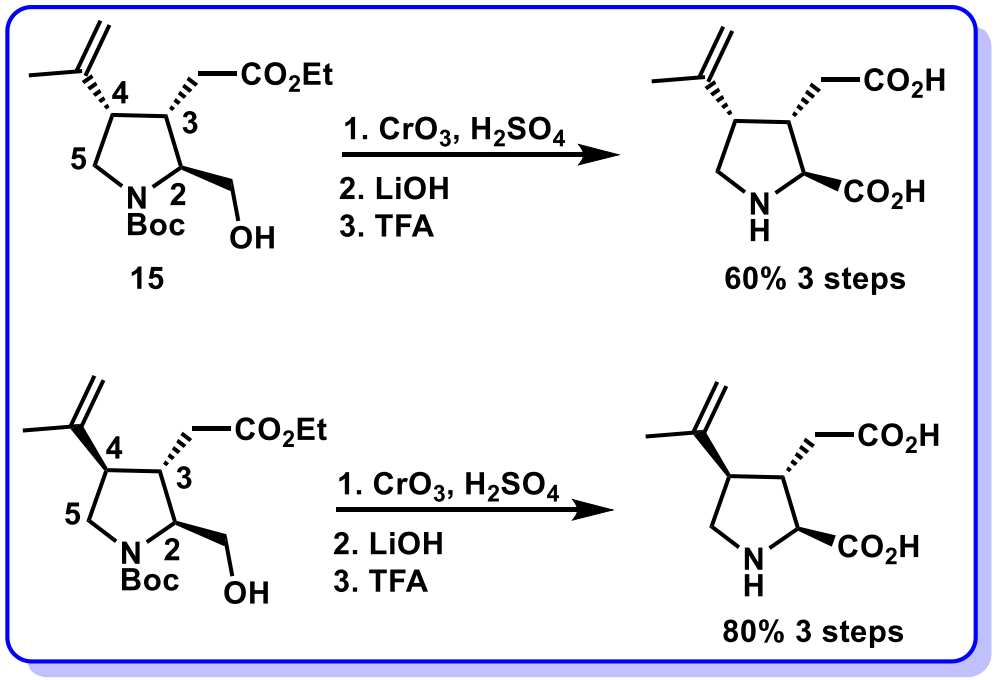
Entry	Substrate	HMPA (equiv.)	H_2O (equiv.)	NiI_2 (equiv.)	Ligand[b]	Yield[c] (%)	15 : 16 [d]
1	*E*-14	24	10	0	None	68	28 : 72
2	*E*-14	60	10	0	None	64	18 : 82
3	*E*-14	0	0	0.3	None	55	32 : 68
4	*E*-14	0	10	0.3	None	61	31 : 69
5	*E*-14	0	0	0.05	PPh_3	54	36 : 64
6	*E*-14	0	0	0.05	dppm	41	29 : 71
7	*E*-14	0	0	0.05	dppe	40	36 : 64
8	*E*-14	0	0	0.05	dppp	50	48 : 52
9	*E*-14	0	0	0.05	dppb	54	37 : 63
10	*E*-14	0	0	0.05	Ethylenediamine	38	29 : 71
11	*E*-14	0	0	0.05	1,10-Phenanthroline	41	36 : 64
12	*E*-14	0	0	0.05	2,2′-Bipyridylamine	43	48 : 52
13	*E*-14	0	0	0.05	2,2′-Bipyridine	45	62 : 38
14	*E*-14	0	10	0.05	2,2′-Bipyridine	51	58 : 42
15	*Z*-14	60	10	0	None	73	38 : 62
16	*Z*-14	0	10	0.3	None	56	45 : 55
17	*Z*-14	0	0	0.05	2,2′-Bipyridine	66	62 : 38
18	*Z*-14	0	10	0.05	2,2′-Bipyridine	69	50 : 50

[a] 6.0 equiv. of SmI_2 was used. [b] 0.2 equiv. of ligand was used. [c] Combined yield after silica gel chromatography. [d] Ratio estimated by ^1H NMR.

Fuyuhiko Matsuda et. al. *Org. Biomol. Chem.* **2017**, *15*, 6557

I-a: Ene reaction

Total synthesis of Kainic Acid



Jones oxidation

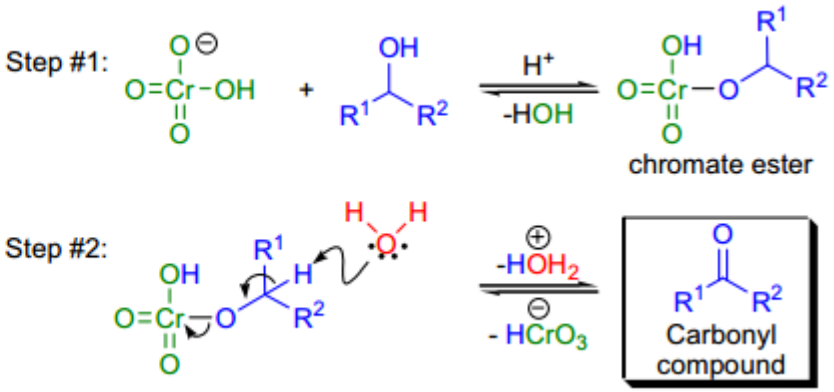
Complete mechanism which accounts for the observed stoichiometry:

$R^1R^2CHOH + Cr^{(VI)} \longrightarrow R^1R^2C{=}O + Cr^{(IV)} + 2\,H^+$

$R^1R^2CHOH + Cr^{(IV)} \longrightarrow R^1R^2C{=}O + Cr^{(II)} + 2\,H^+$

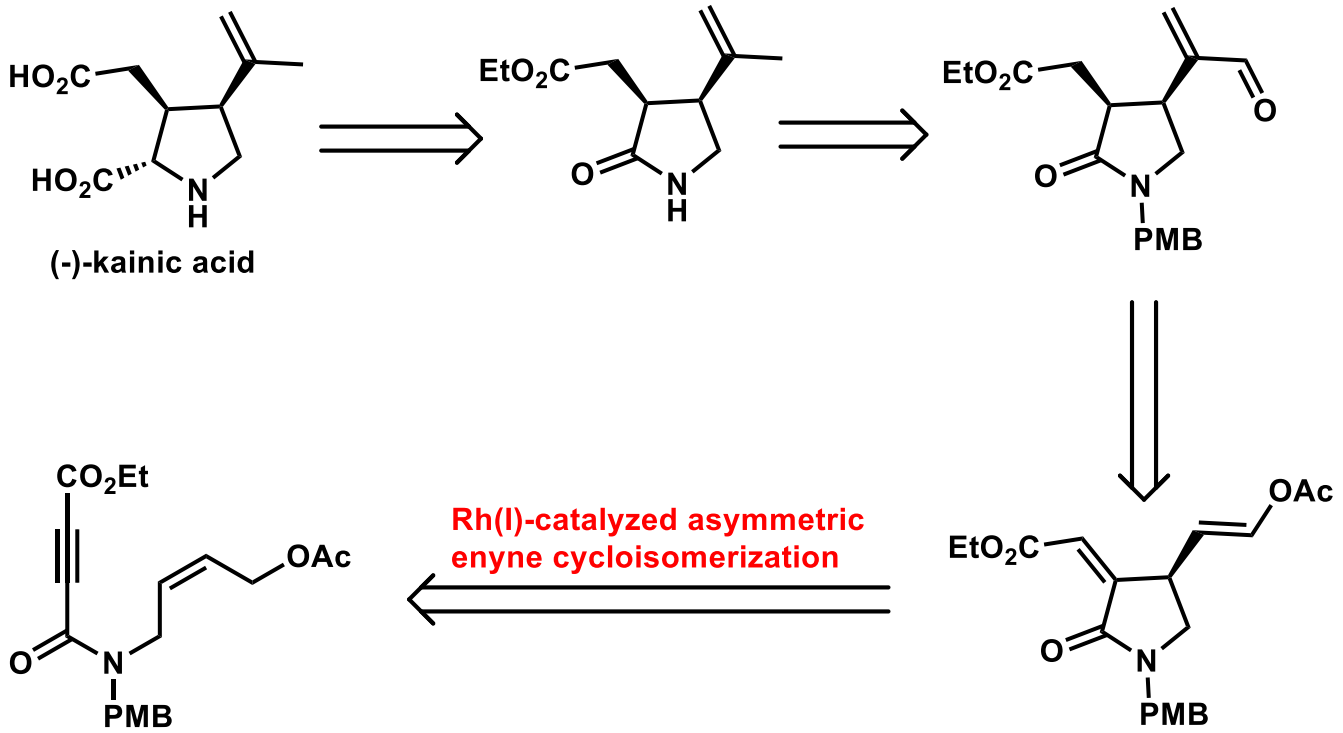
$Cr^{(II)} + Cr^{(VI)} \longrightarrow Cr^{(III)} + Cr^{(V)}$

$R^1R^2CHOH + Cr^{(V)} \longrightarrow R^1R^2C{=}O + Cr^{(III)} + 2\,H^+$



Rh(I)-catalyzed asymmetric enyne cycloisomerization

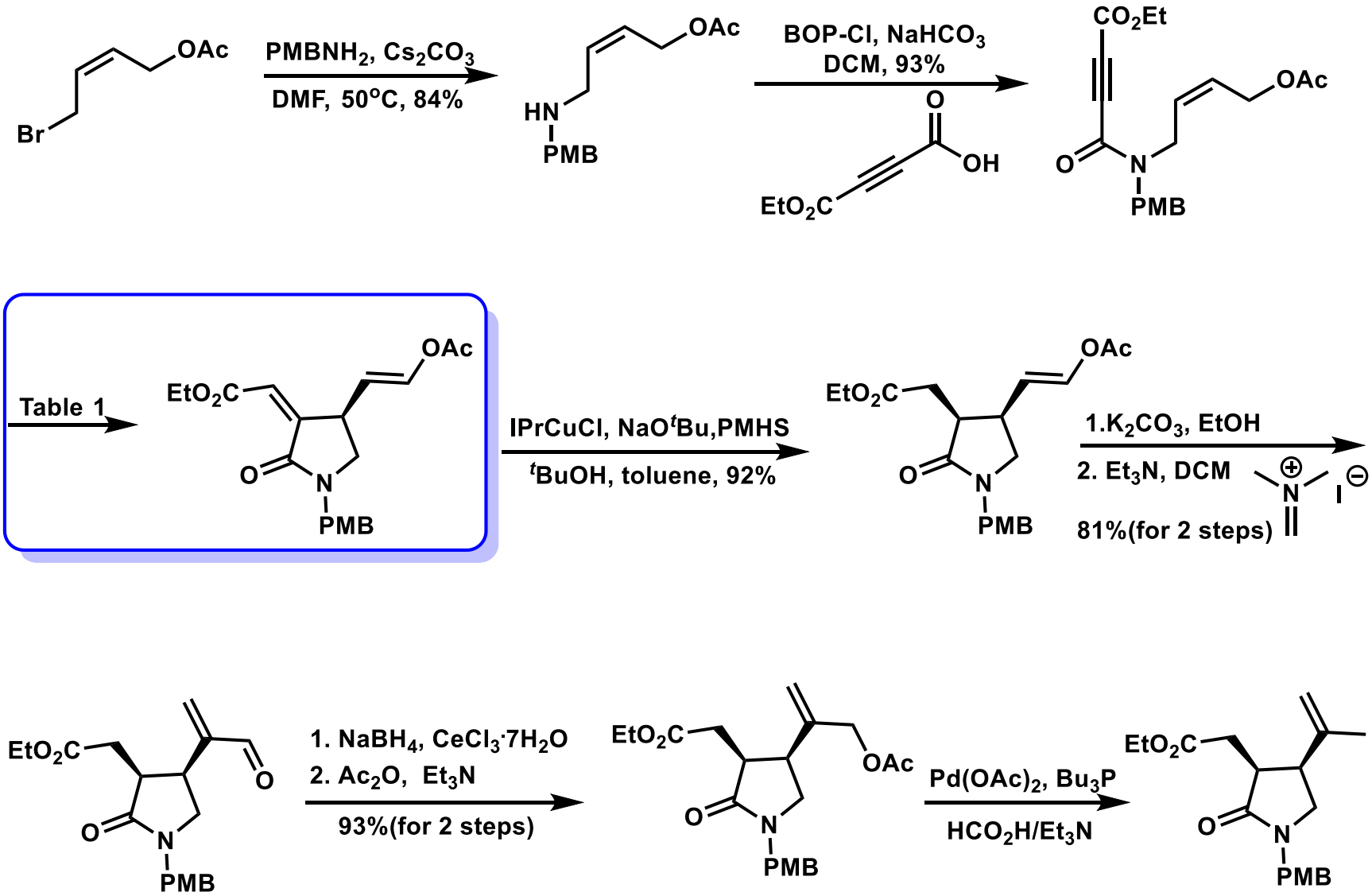
Retrosynthetic analysis



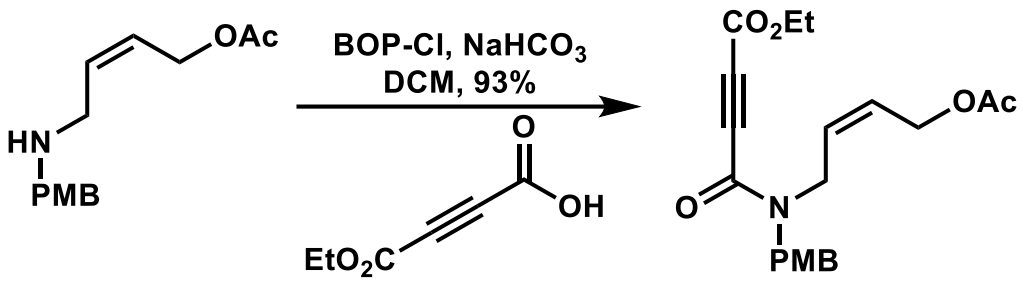
Xumu Zhang et. al. *Chem. Commun*. **2018**, *54*, 727

I-a: Rh(I)-catalyzed asymmetric enyne cycloisomerization

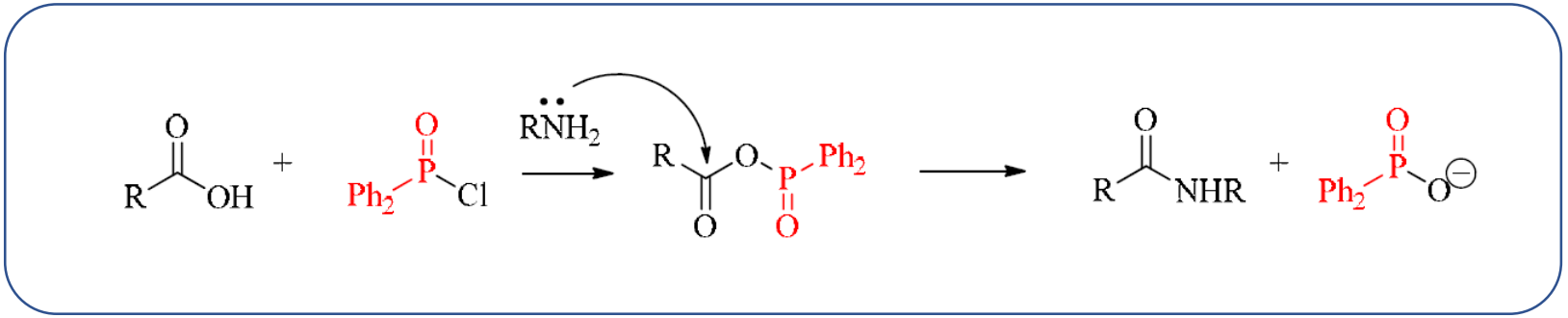
Synthesis of the intermediate



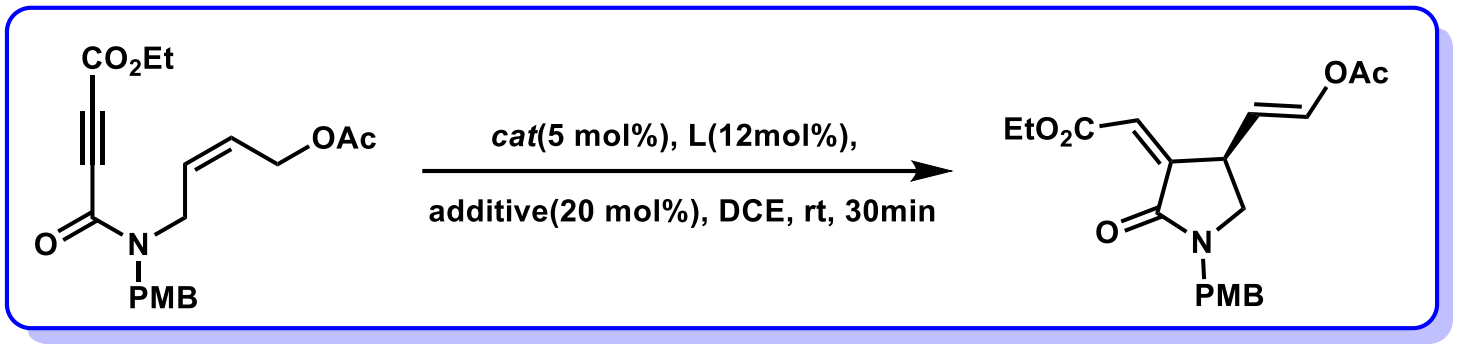
I-a: Rh(I)-catalyzed asymmetric enyne cycloisomerization



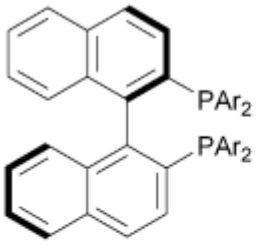
- **Amidation mediated by BOP-Cl**



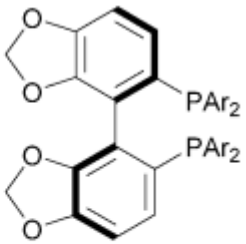
I-a: Optimization of the Rh(I)-catalyzed asymmetric cycloisomerization of enyne



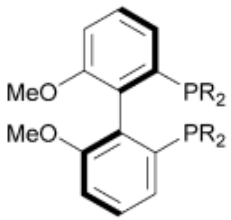
Entry	Catalyst/ligand	Additive	Yield[b] (%)	ee[c]
1	$[Rh(COD)Cl]_2$/**L1**	$AgBF_4$	98	81
2	$[Rh(NBD)Cl]_2$/**L1**	$AgBF_4$	96	78
3	$[Rh(CH_2CH_2)_2Cl]_2$/**L1**	$AgBF_4$	98	79
4	$[Rh(COD)Cl]_2$/**L2**	$AgBF_4$	97	69
5	$[Rh(COD)Cl]_2$/**L3**	$AgBF_4$	92	53
6	$[Rh(COD)Cl]_2$/**L4**	$AgBF_4$	<5	—
7	$[Rh(COD)Cl]_2$/**L5**	$AgBF_4$	99	77
8	$[Rh(COD)Cl]_2$/**L6**	$AgBF_4$	21	71
9	$[Rh(COD)Cl]_2$/**L7**	$AgBF_4$	24	73
10	$[Rh(COD)Cl]_2$/**L8**	$AgBF_4$	96	61
11	$[Rh(COD)Cl]_2$/**L9**	$AgBF_4$	N.R.	—
12	$[Rh(COD)Cl]_2$/**L10**	$AgBF_4$	98	91
13	$[Rh(COD)Cl]_2$/**L10**	AgOTf	98	92
14	$[Rh(COD)Cl]_2$/**L10**	$AgSbF_6$	96	90
15[d]	$[Rh(COD)Cl]_2$/**L10**	AgOTf	98 (95)[e]	92



Ar = C_6H_5 **L1**

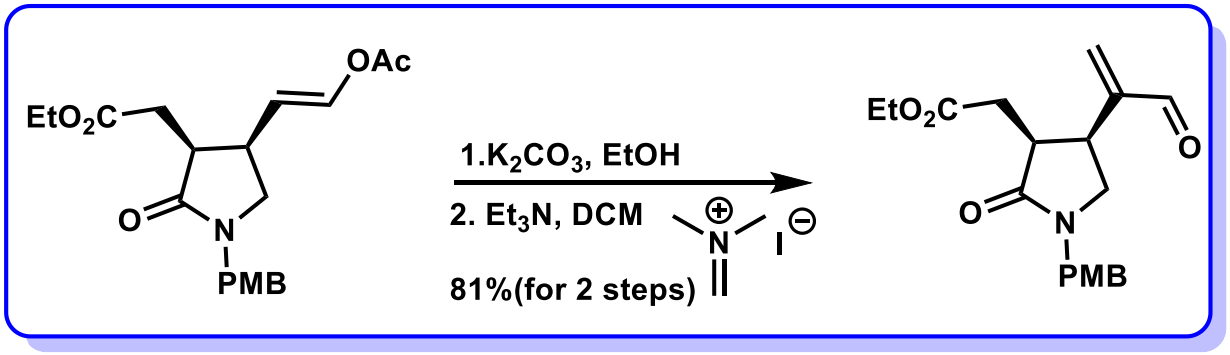


Ar = C_6H_5 **L2**
3,5-*di*-Me-C_6H_3 **L3**
3,5-*di*-^{t}Bu-4-OMe-C_6H_2 **L4**

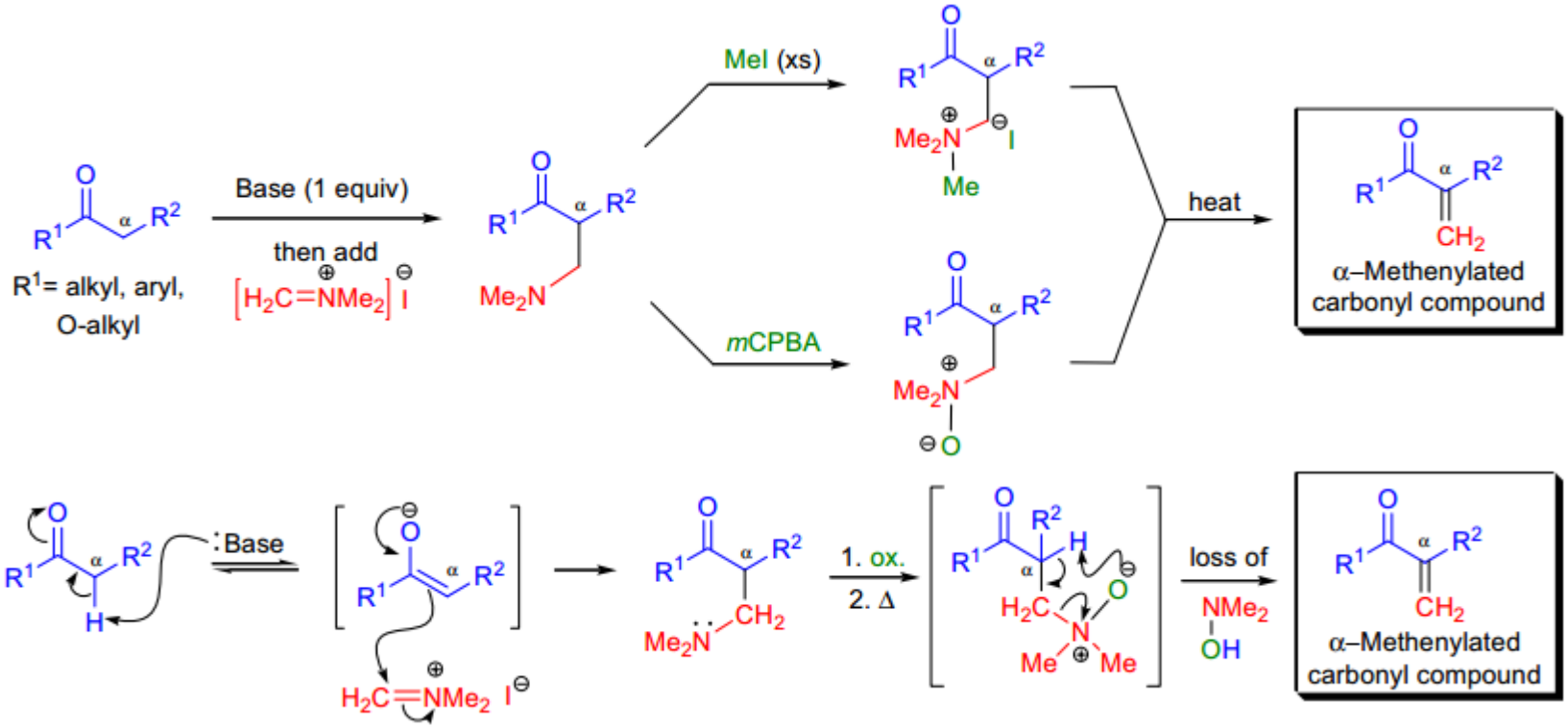


R = C_6H_5 **L5**
3,5-*di*-^{t}Bu-4-OMe-C_6H_2 **L6**
3,5-*di*-^{t}Bu-C_6H_3 **L7**
3,5-*di*-Me-C_6H_3 **L8**
^{i}Pr **L9**
3,4,5-*tri*-OMe-C_6H_2 **L10**

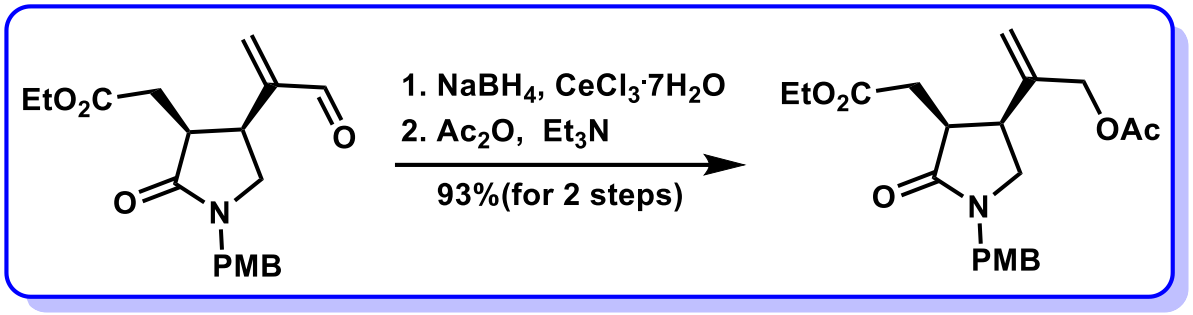
I-a: Rh(I)-catalyzed asymmetric enyne cycloisomerization



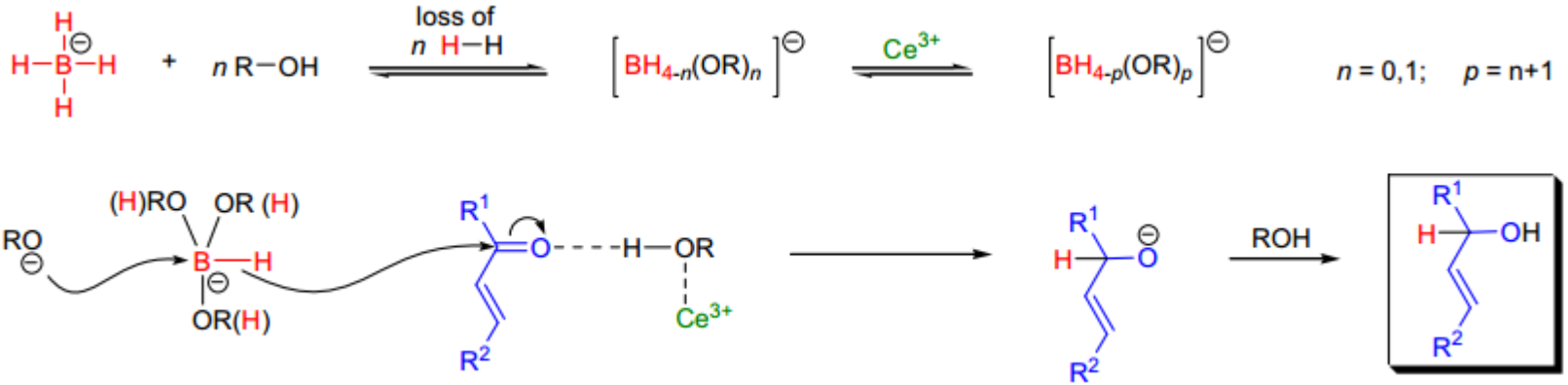
Eschenmoser methenylation



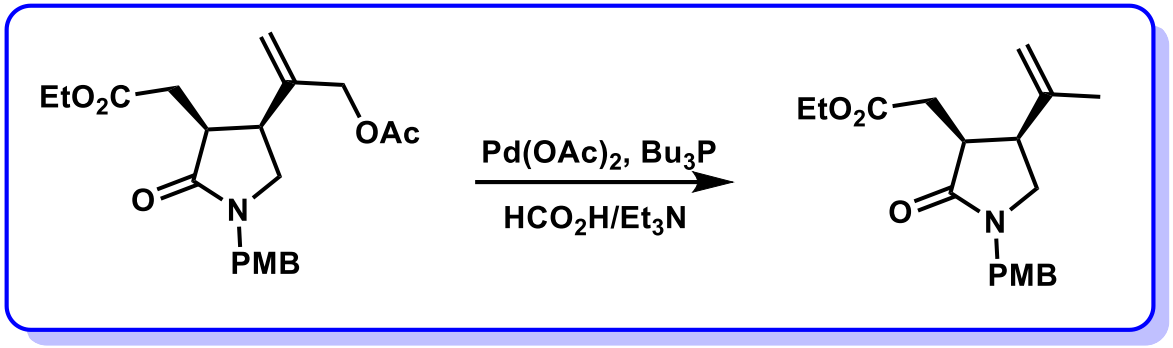
I-a: Rh(I)-catalyzed asymmetric enyne cycloisomerization



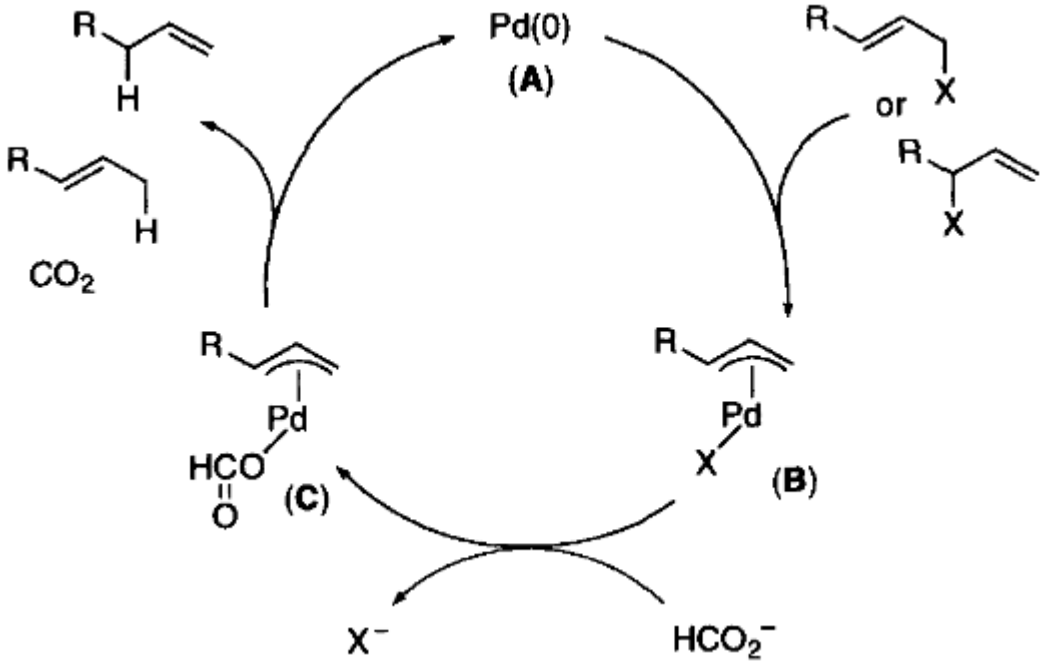
Luche reduction



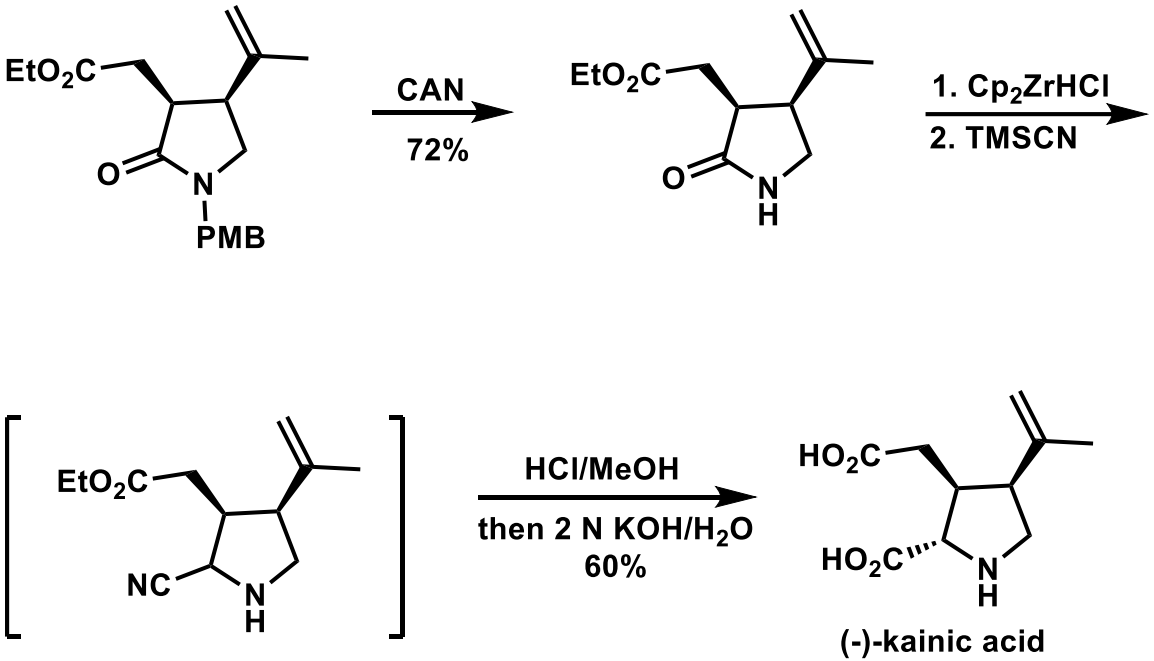
I-a: Rh(I)-catalyzed asymmetric enyne cycloisomerization



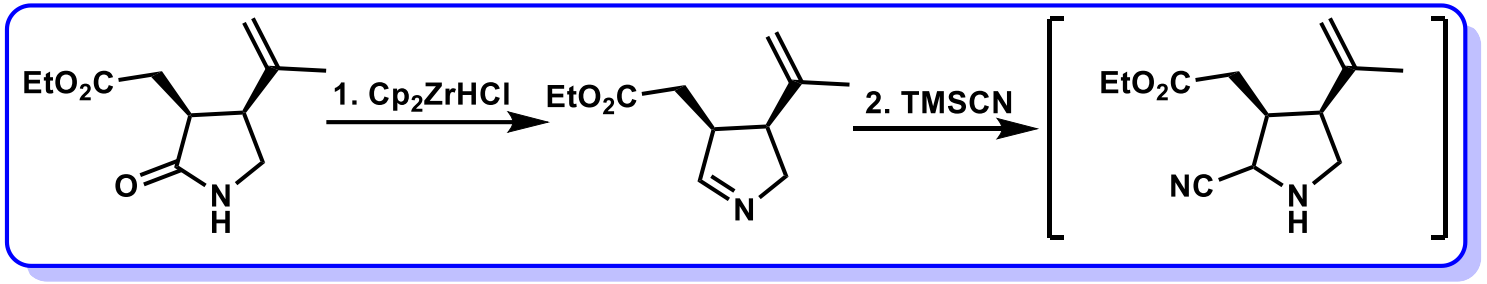
- **Palladium catalyzed hydrogenolysis of allylic acetate**



I-a: Synthesis of (-)-kainic acid.

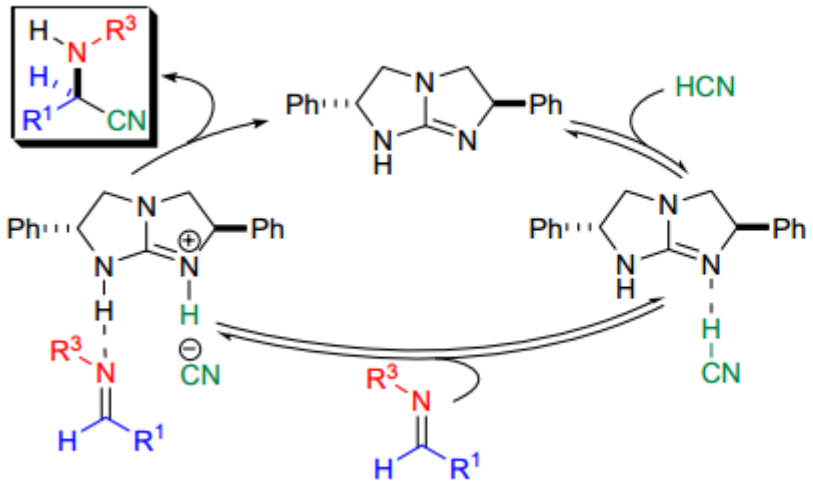


I-a: Synthesis of (-)-kainic acid.

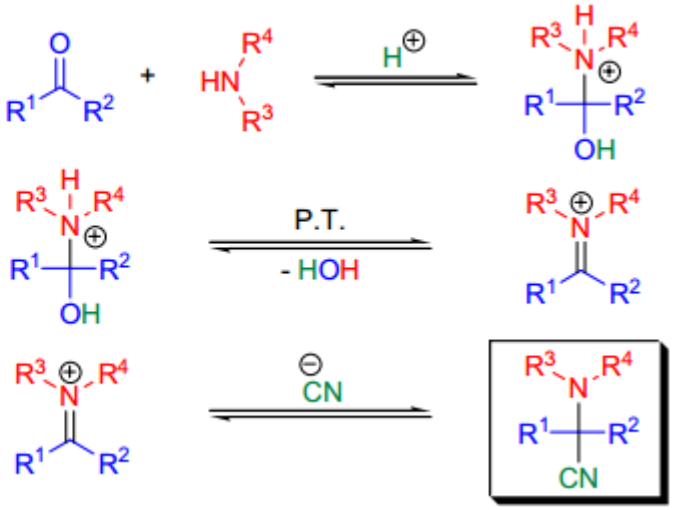


Strecker reaction

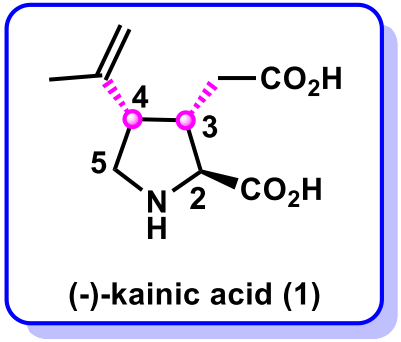
Mechanism in the presence of an organocatalyst (Corey, 1999):



Mechanism of the classical Strecker reaction:



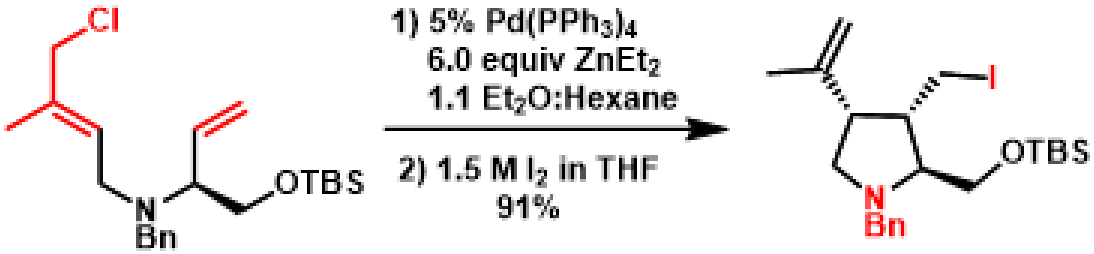
Structure Analysis I (the key syn C4-C3)



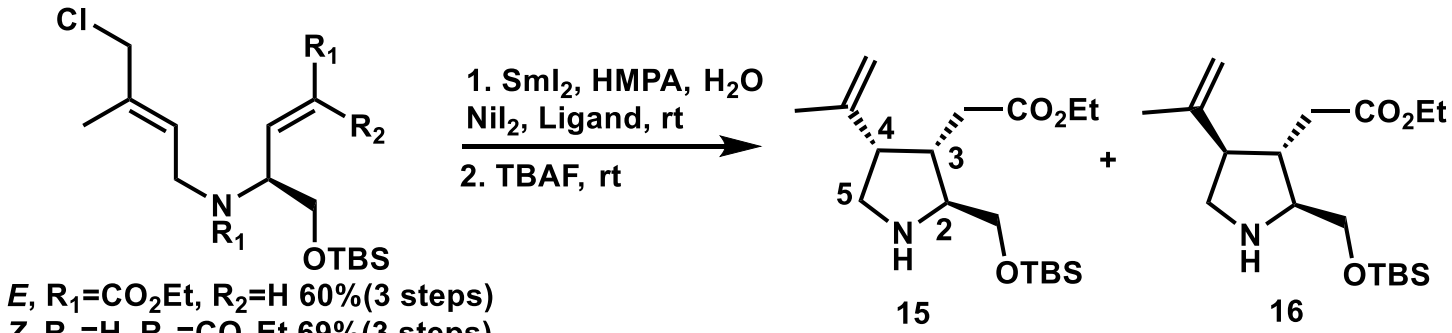
(-)-kainic acid (1)

I: The key syn C4-C3

I-b: S_N2' reaction



J. M. Chalker et. al. *J. Org. Chem.* **2011**, *76*, 7912

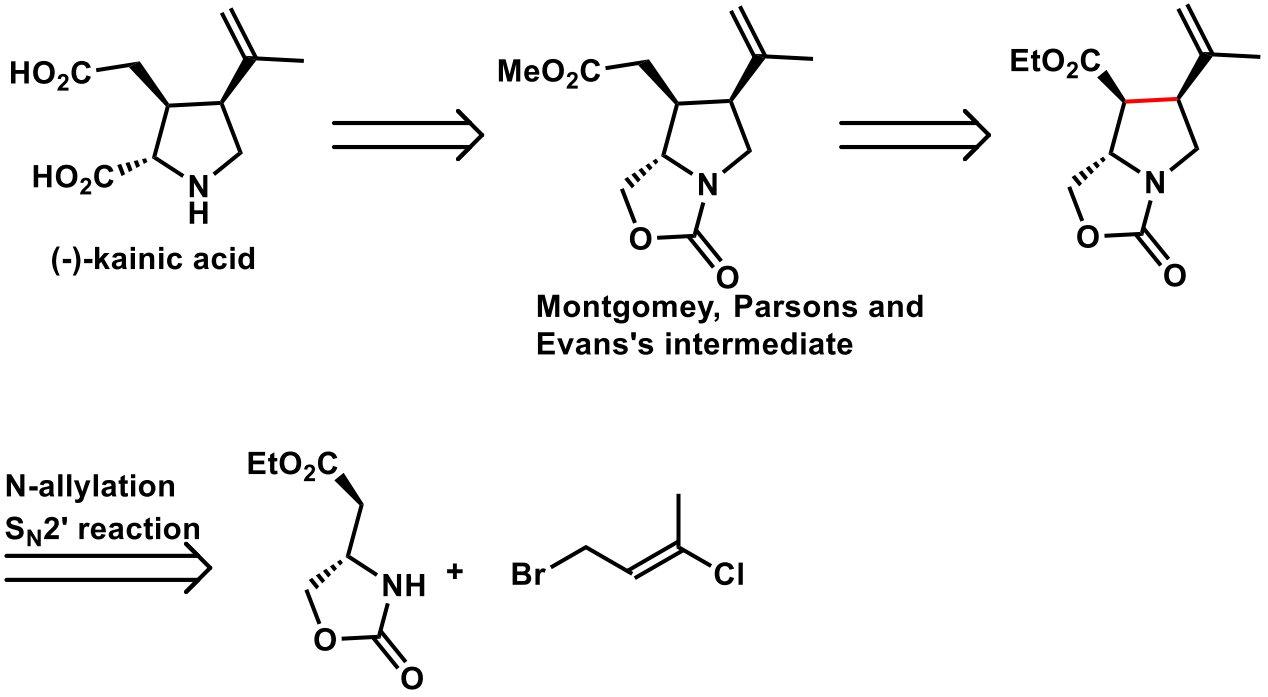


E, R_1=CO_2Et, R_2=H 60%(3 steps)
Z, R_1=H, R_2=CO_2Et 69%(3 steps)

Fuyuhiko Matsuda et. al. *Org. Biomol. Chem.* **2017**, *15*, 6557

I-b: S_N2' reaction

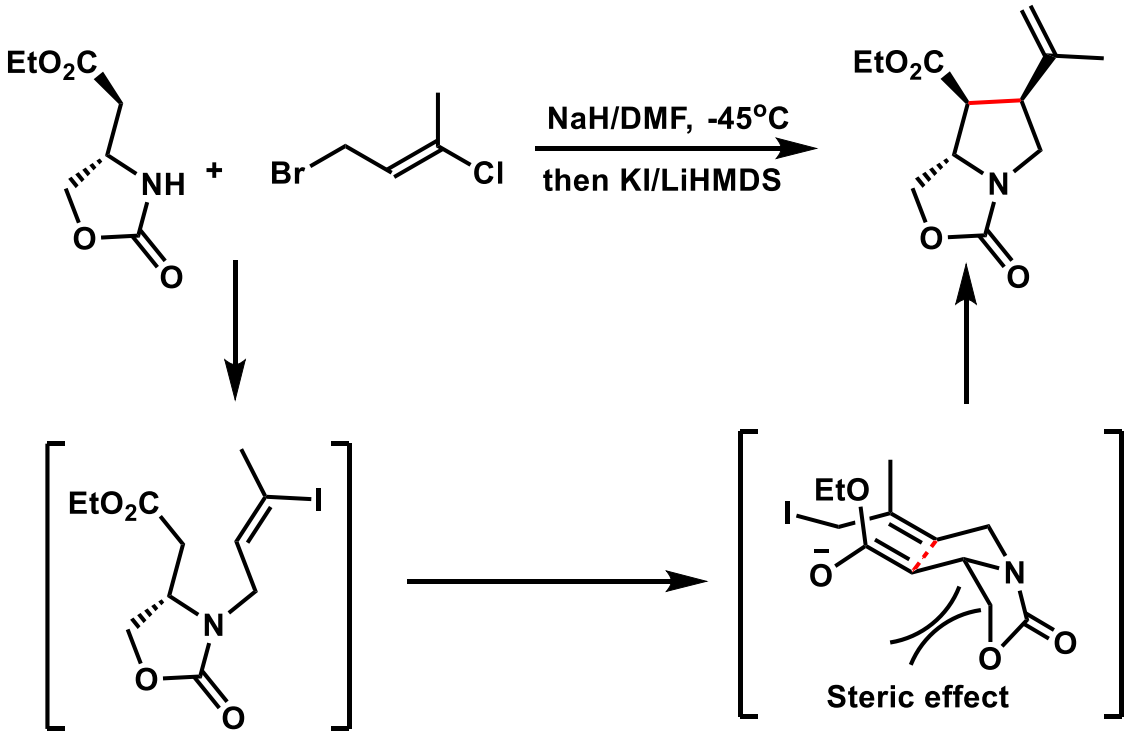
Retrosynthetic analysis



Jun Yang et. al. *Tetrahedron*. **2016**, *72*, 5502

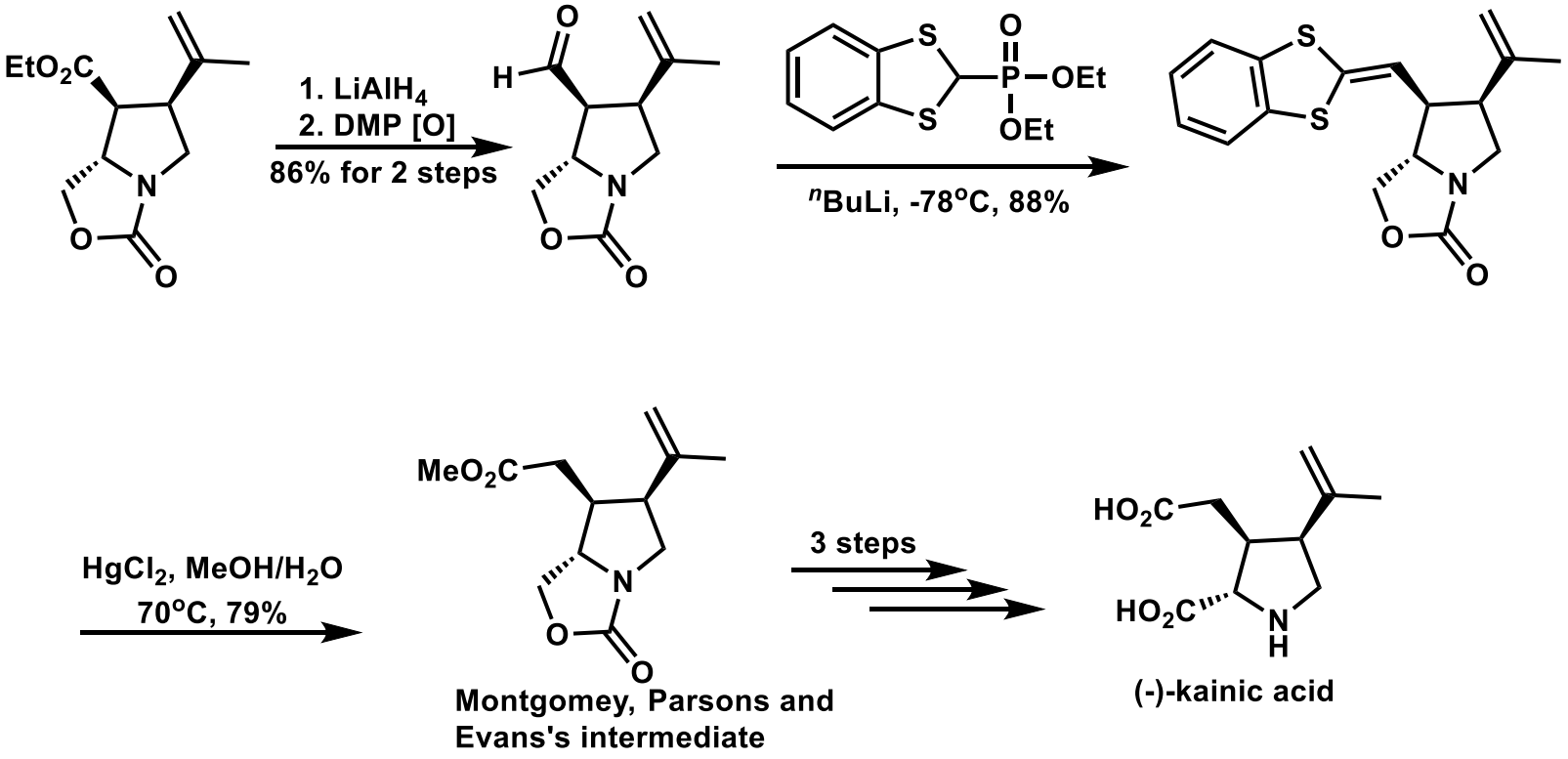
I-b: S_N2' reaction

Synthesis of the intermediate



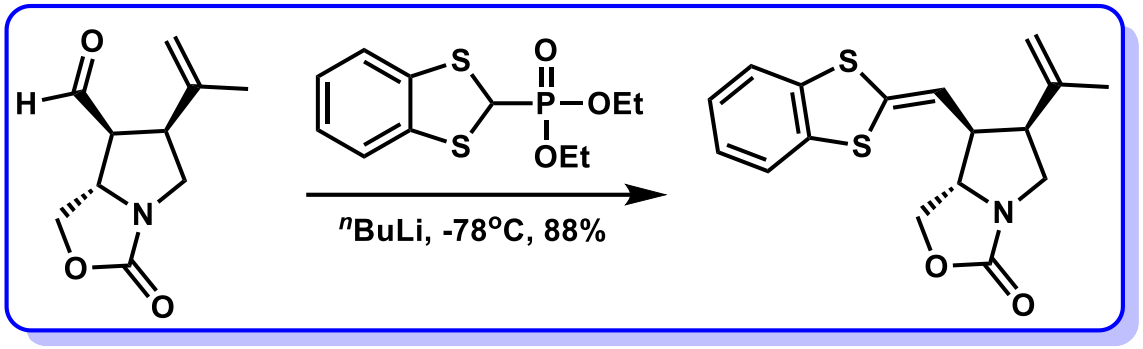
Jun Yang et. al. *Tetrahedron*. **2016**, *72*, 5502

I-b: Formal Total Synthesis of (-)-kainic acid.

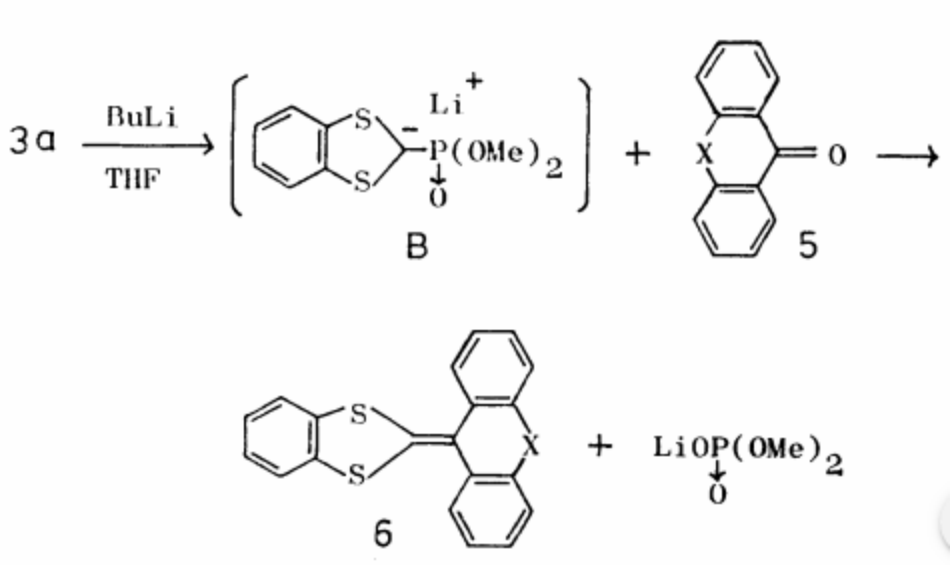


Jun Yang et. al. *Tetrahedron*. **2016**, *72*, 5502

I-b: Formal Total Synthesis of (-)-kainic acid.

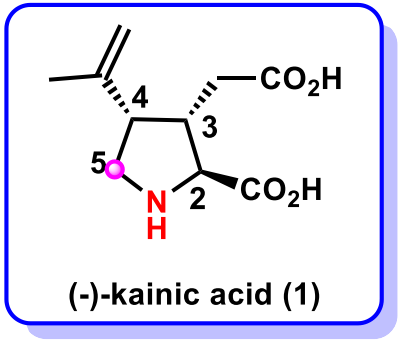


Wittig-horner reaction



Jun Yang et. al. *Tetrahedron*. **2016**, *72*, 5502

Structure Analysis II (the key C1-C5)



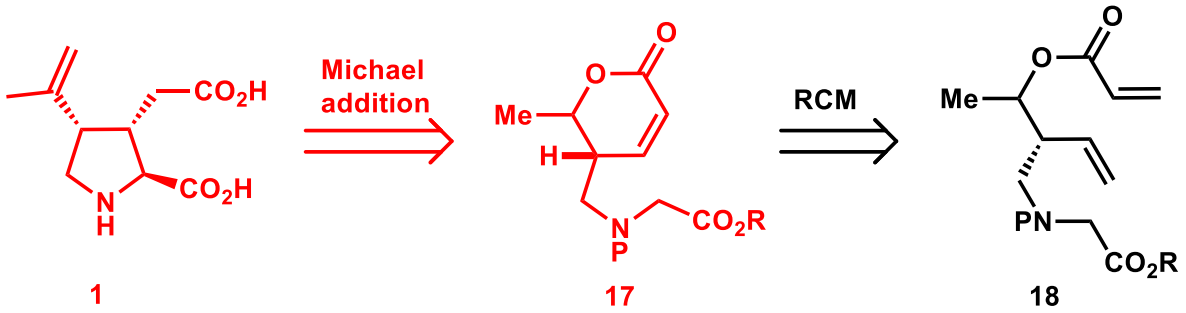
(-)-kainic acid (1)

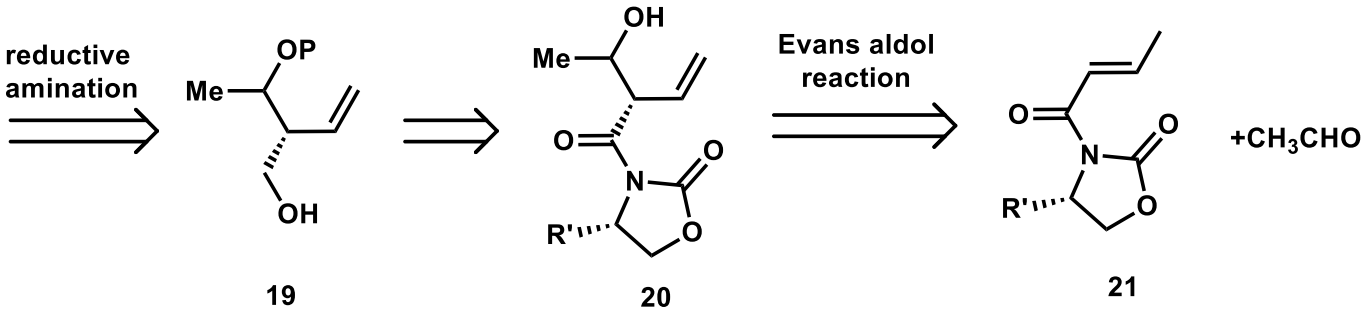
II: The key C1-C5

II-a: The nucleophilicity of N

(Michael addition)

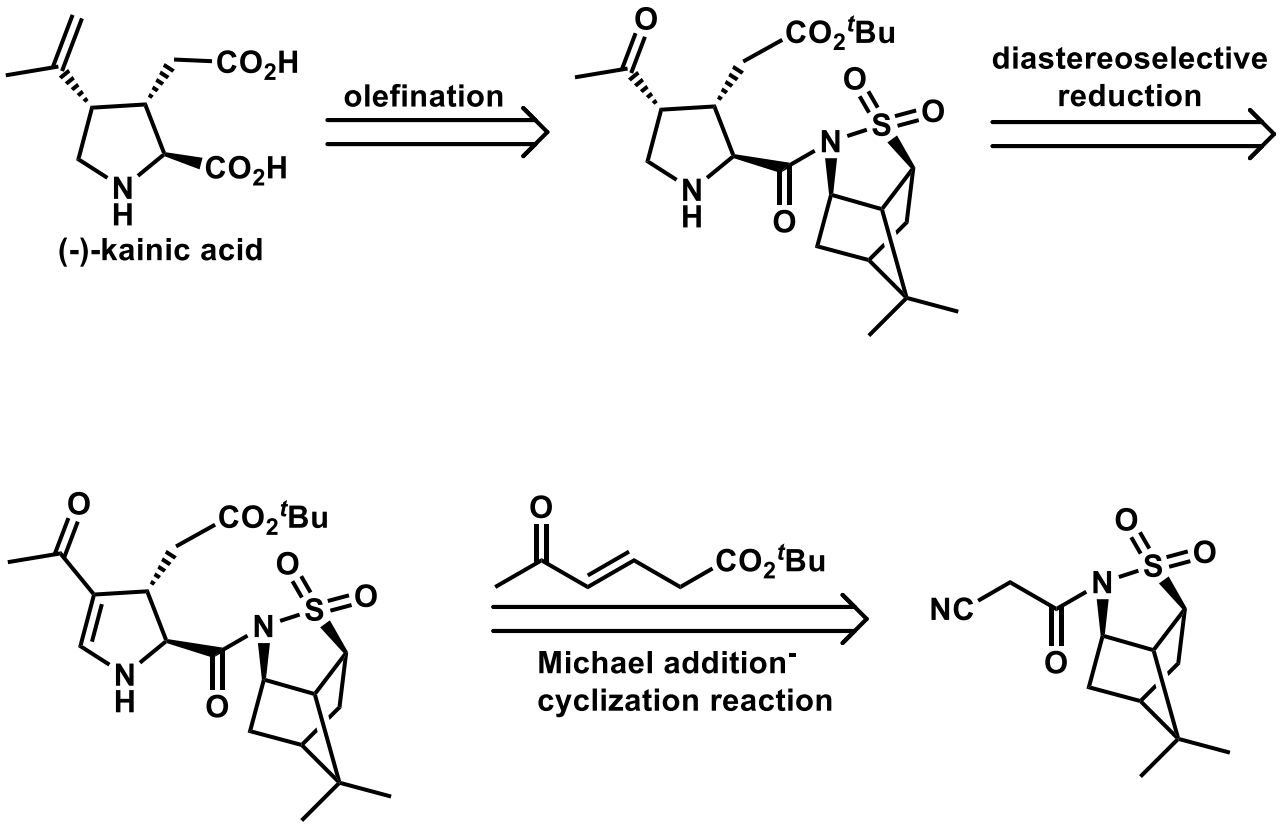
T. Fukuyama: *Org. Lett.* **2007**, 9, 1635–1639.





II-a: Cu catalyzed Michael addition−cyclization reaction

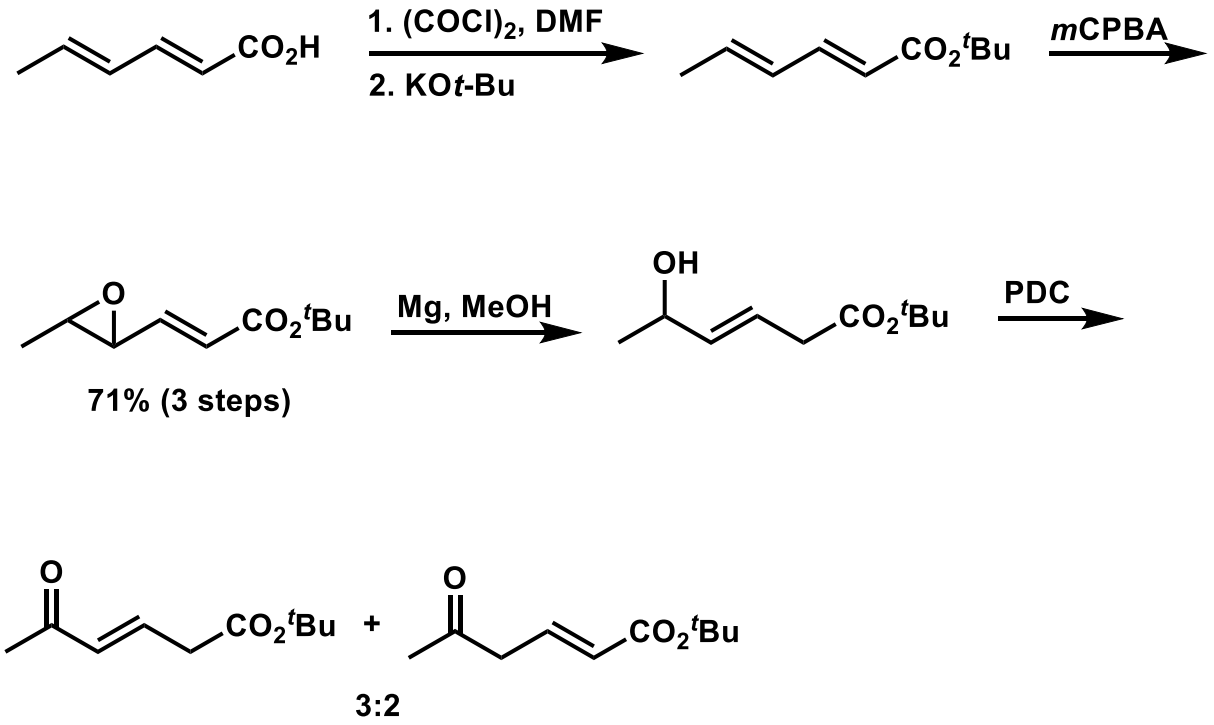
Retrosynthetic analysis



Tetsuro Shinada et. al. *Org. Lett.* **2014**, *16*, 2550

II-a: Cu catalyzed Michael addition−cyclization reaction

Synthesis of the Michael Addition Reaction Acceptor

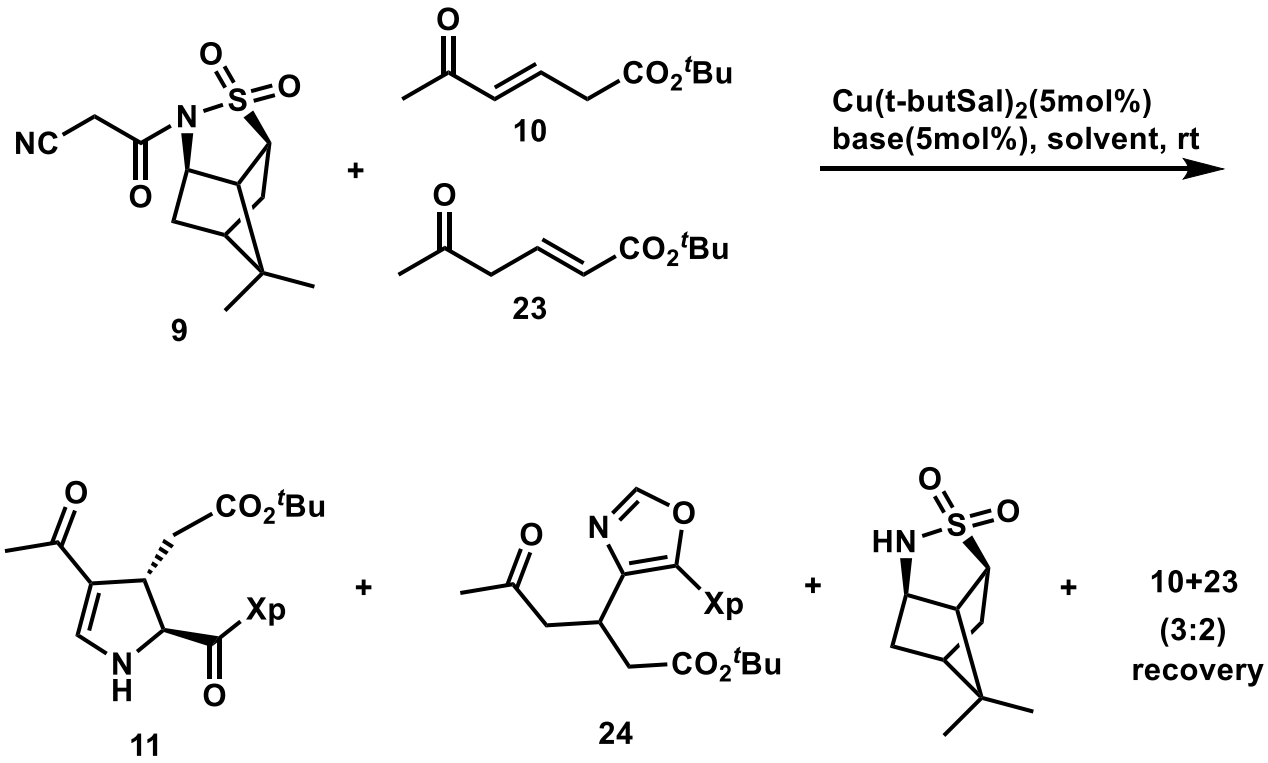


https://www.sohu.com/a/142106393_610519

Tetsuro Shinada et. al. *Org. Lett.* **2014**, *16*, 2550

II-a: Cu catalyzed Michael addition−cyclization reaction

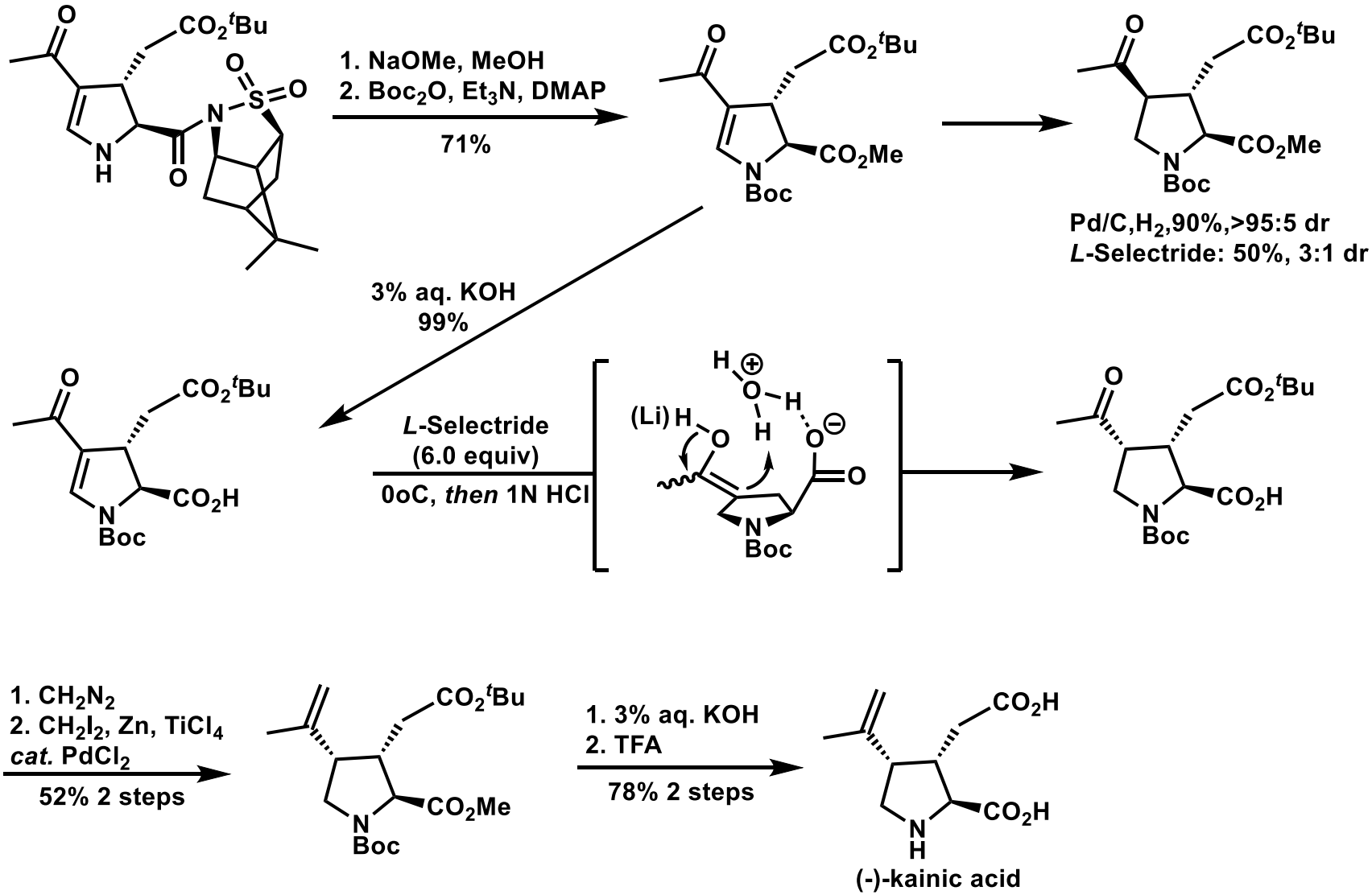
Synthesis of Chiral Pyrroline



entry	base	solvent (0.1 M)	acceptor (equiv)	time (min)	**11** (%)	**24** (%)	**25** (%)
1	Et_3N	DCE	1	16 h	trace	trace	45
2	DBU	DCE	1	120	11	10	55
3	TBD	DCE	1	120	20	14	46
4	none	DCE	1	60	24	20	14
5[a]	none	THF (0.5 M)	2	40	54	24	9

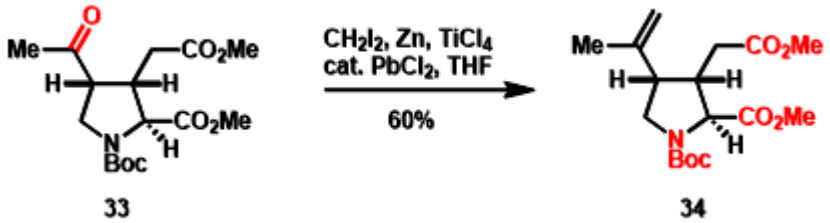
II-a: Cu catalyzed Michael addition−cyclization reaction

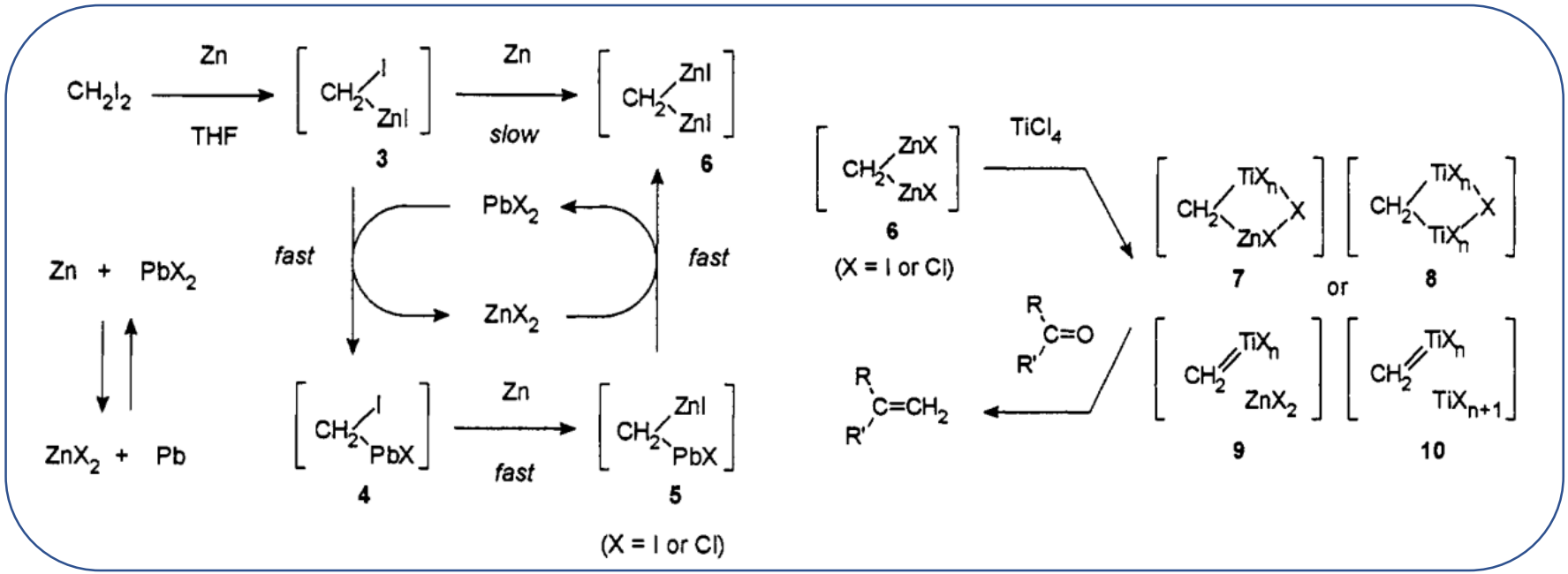
Total Synthesis of Kainic Acid via Stereoselective Reduction of Pyrrolines



II-a: Cu catalyzed Michael addition−cyclization reaction

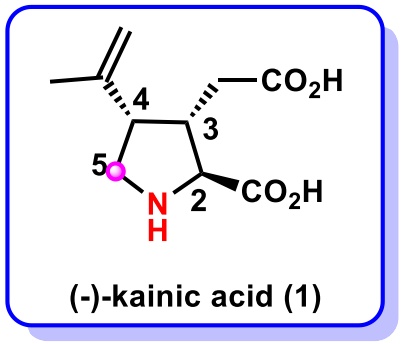
T. Fukuyama: *Org. Lett.* **2007**, 9, 1635–1639.





Takai, K, et al, *J.Org. Chem.* **1994**, 59, 2668.

Structure Analysis II (the key C1-C5)



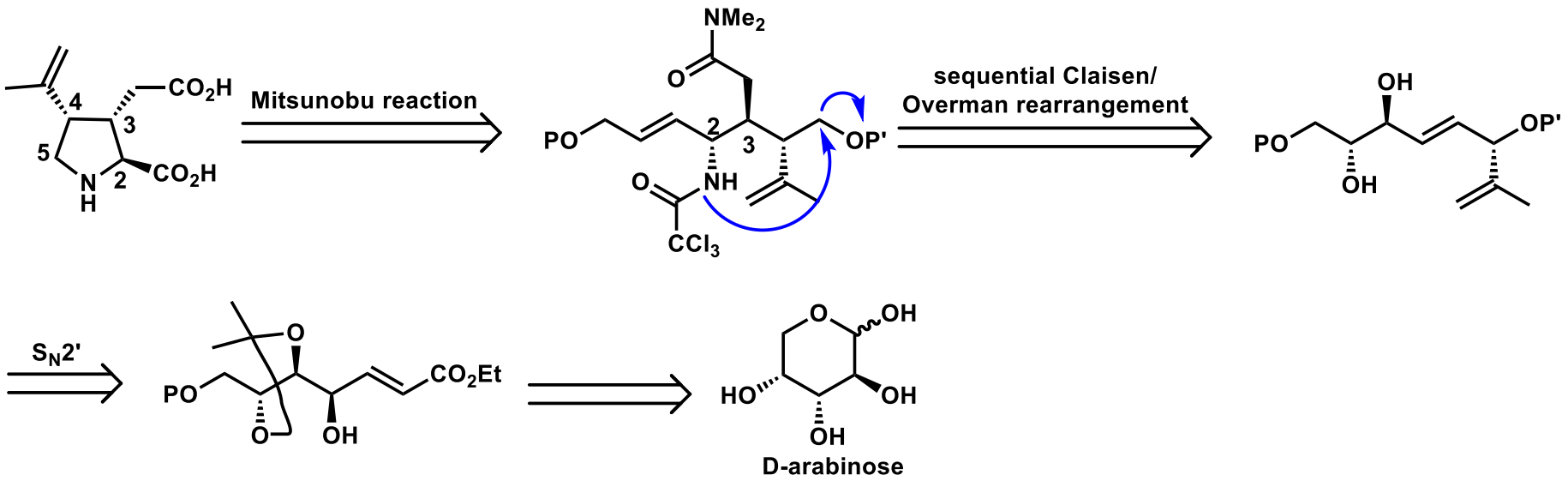
(-)-kainic acid (1)

II: The key C1-C5

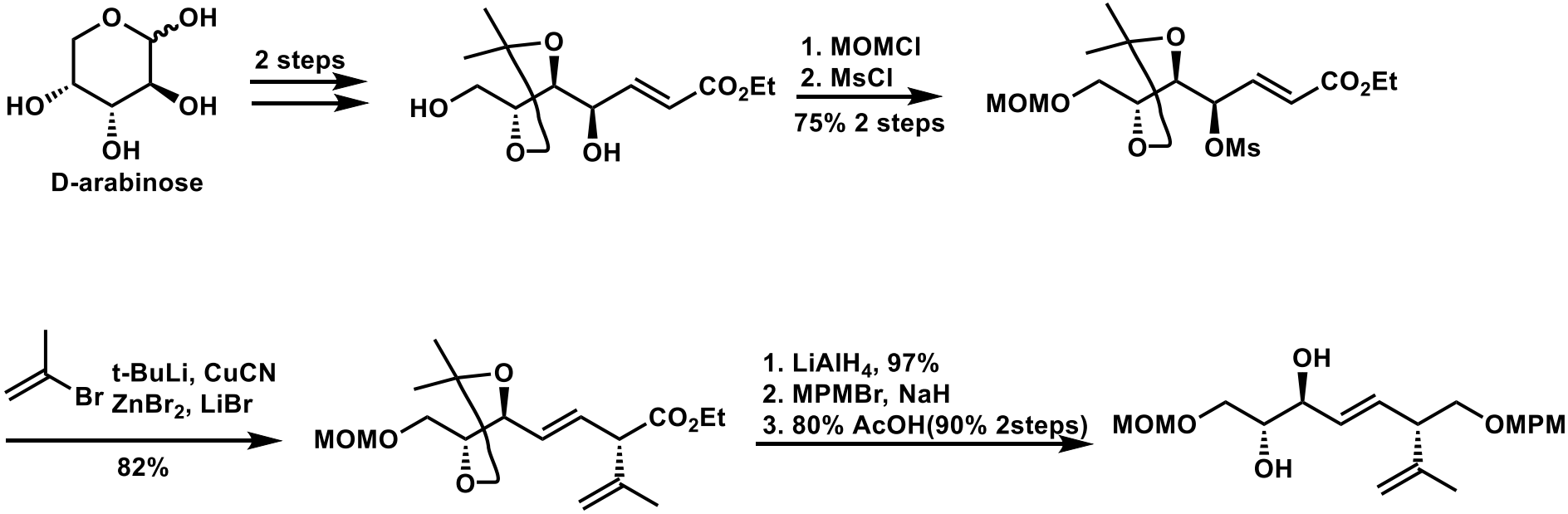
II-b: The nucleophilicity of N

(S_N2 reaction)

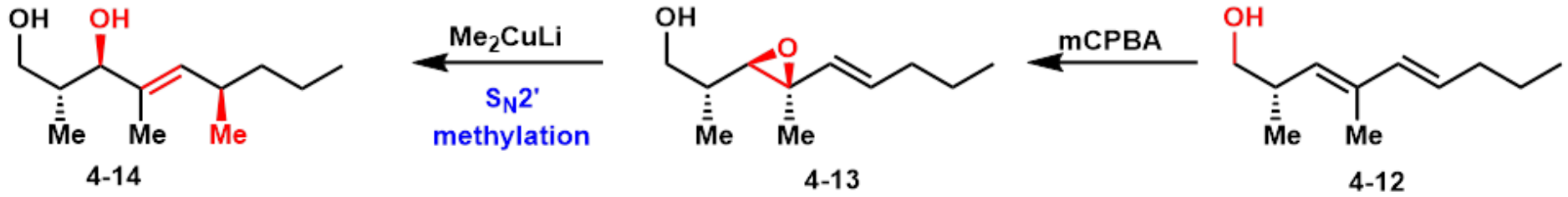
Noritaka Chida: *Org. Lett.* **2010**, 12, 5756.



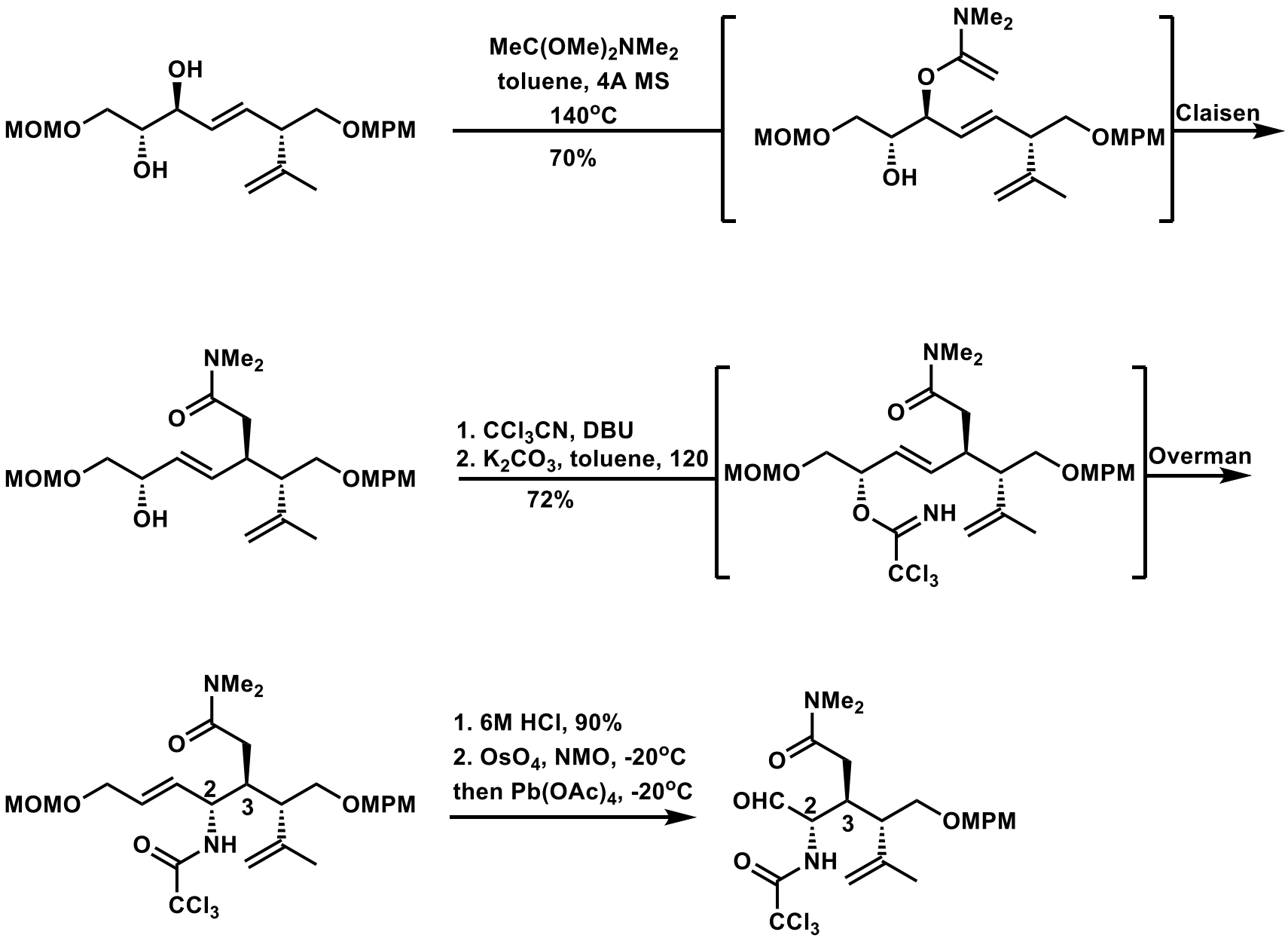
II-b: Sequential Sigmatropic Rearrangements



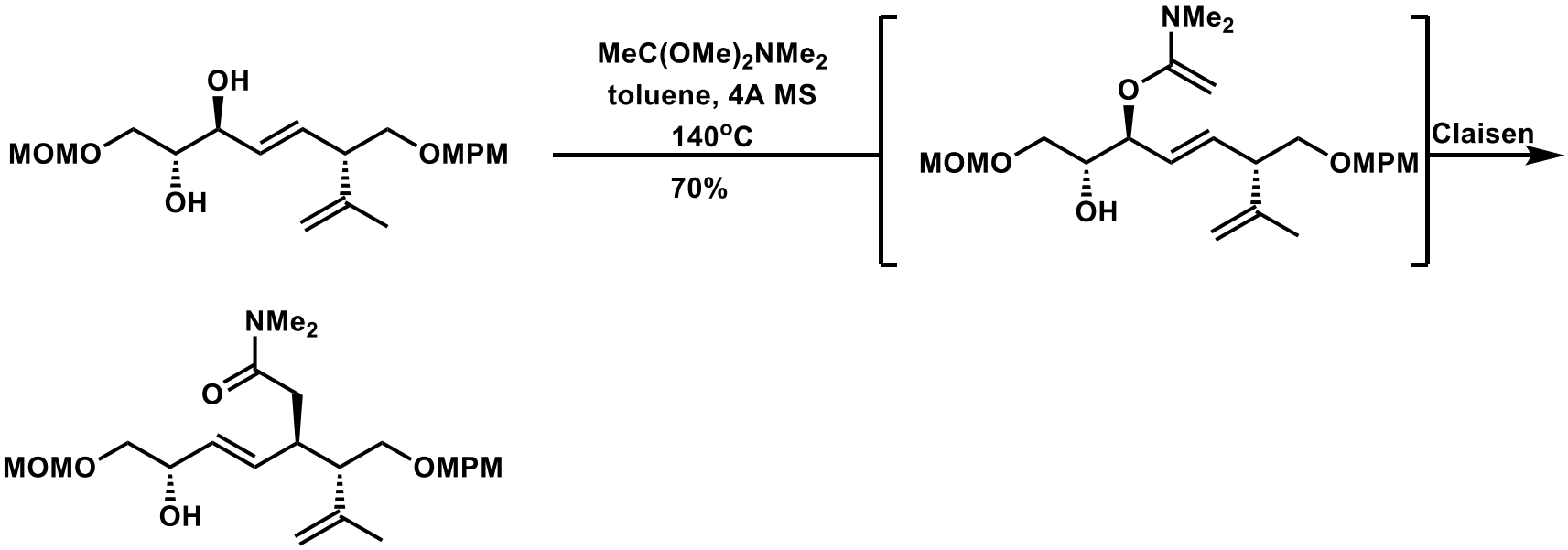
Chirality transfer



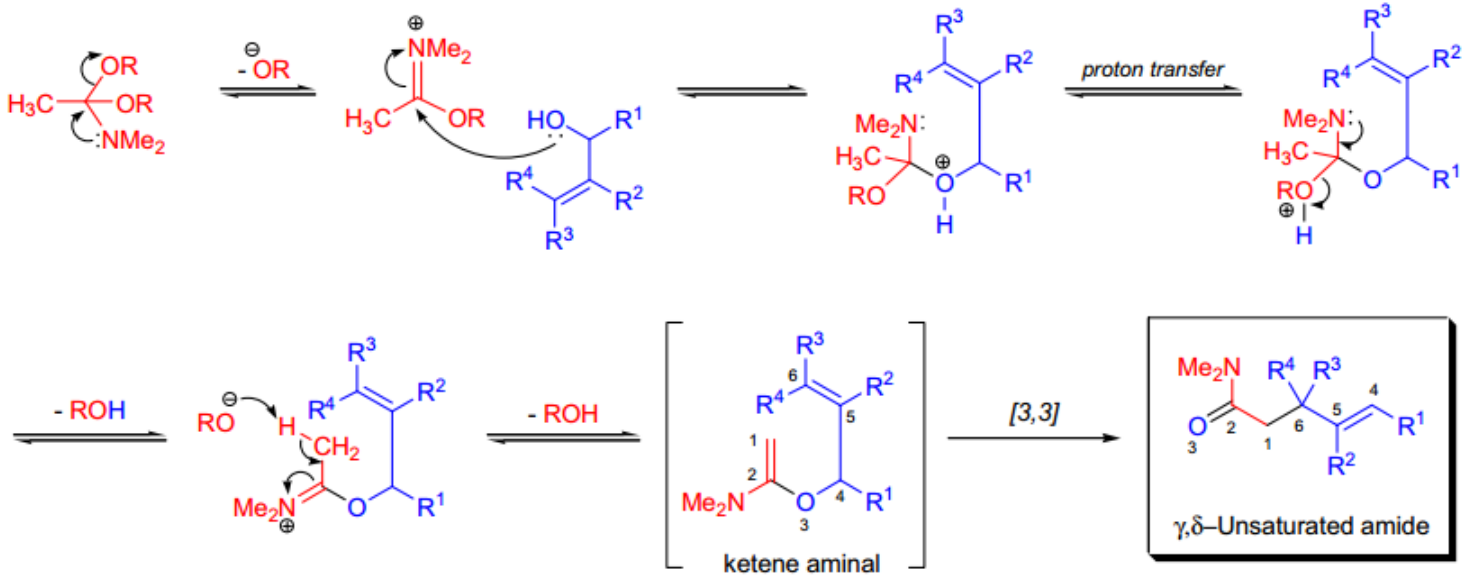
II-b: Sequential Sigmatropic Rearrangements



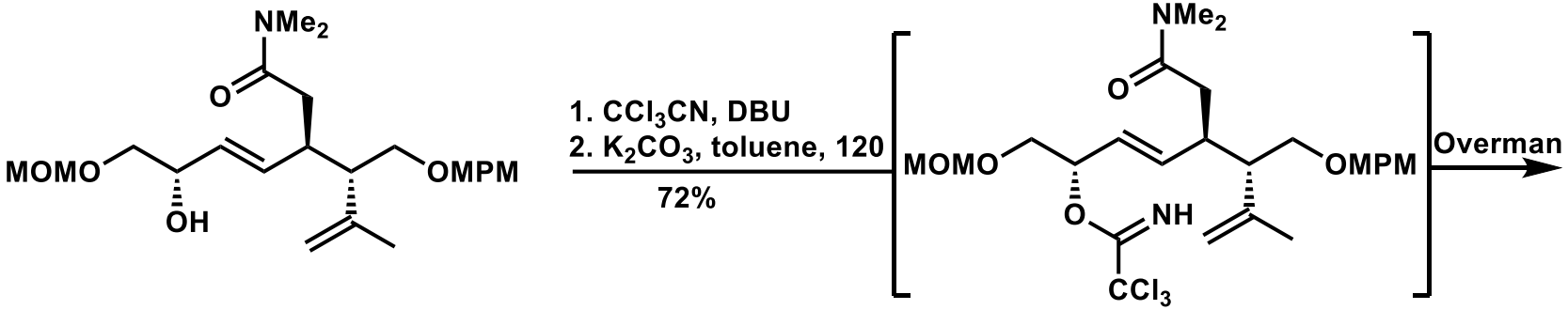
II-b: Sequential Sigmatropic Rearrangements

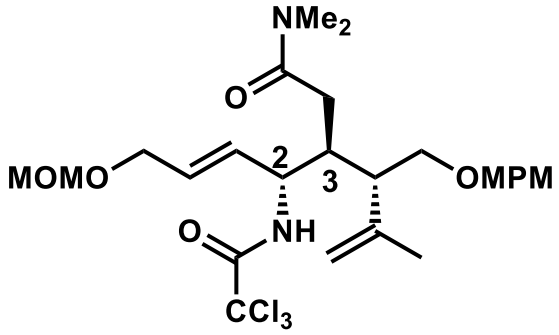


Eschenmoser-Claisen rearrangement

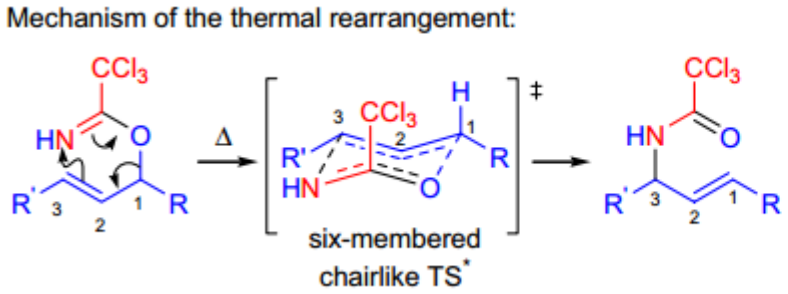


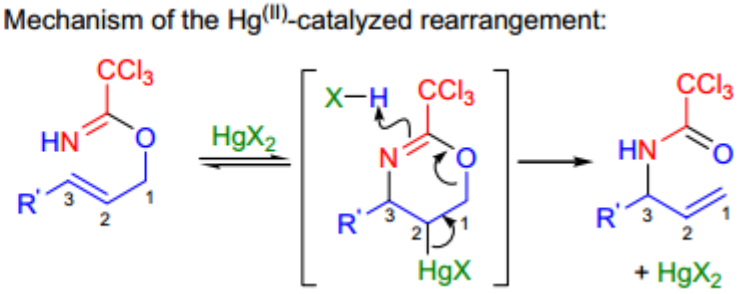
II-b: Sequential Sigmatropic Rearrangements



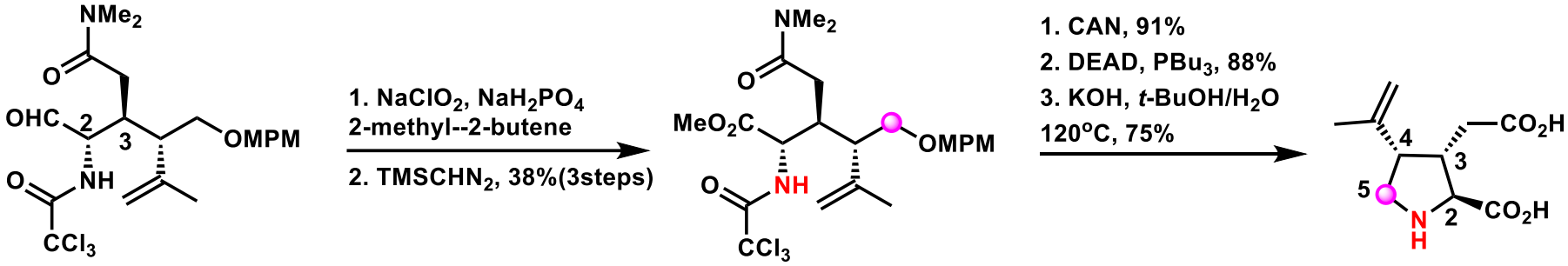


☐ Overman rearrangement

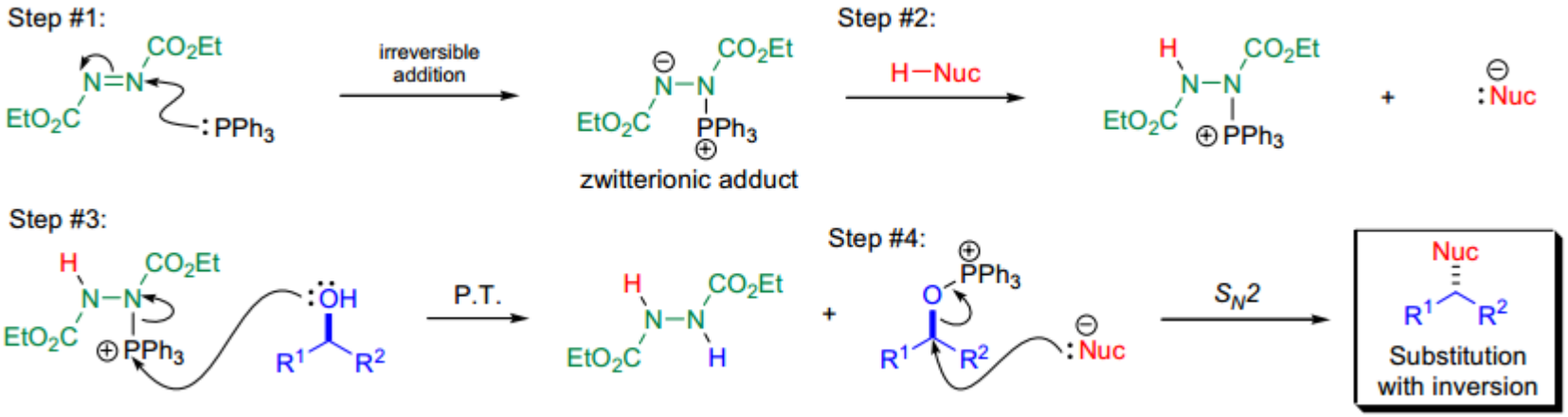




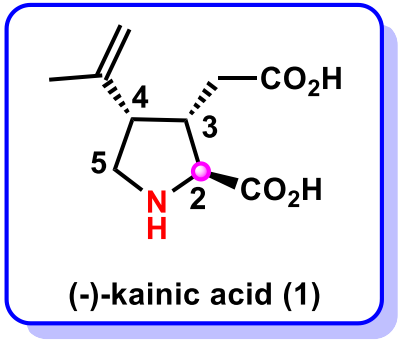
II-b: The nucleophilicity of N (S_N2 reaction)



Mitsunobu reaction



Structure Analysis III (the key C1-C5)



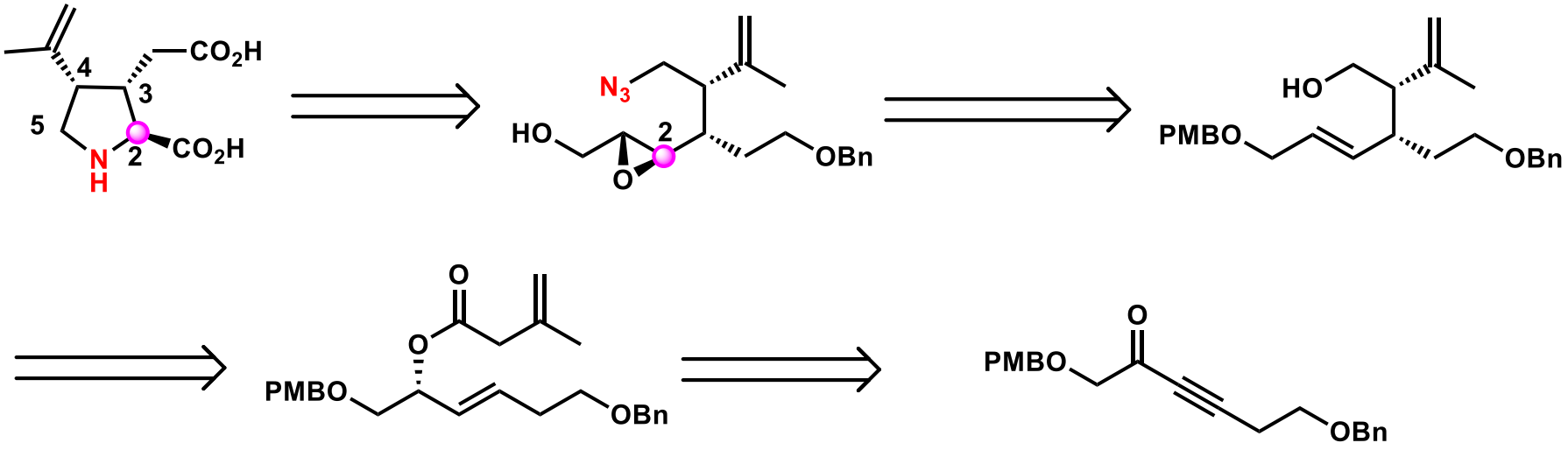
(-)-kainic acid (1)

III: The key C1-C2

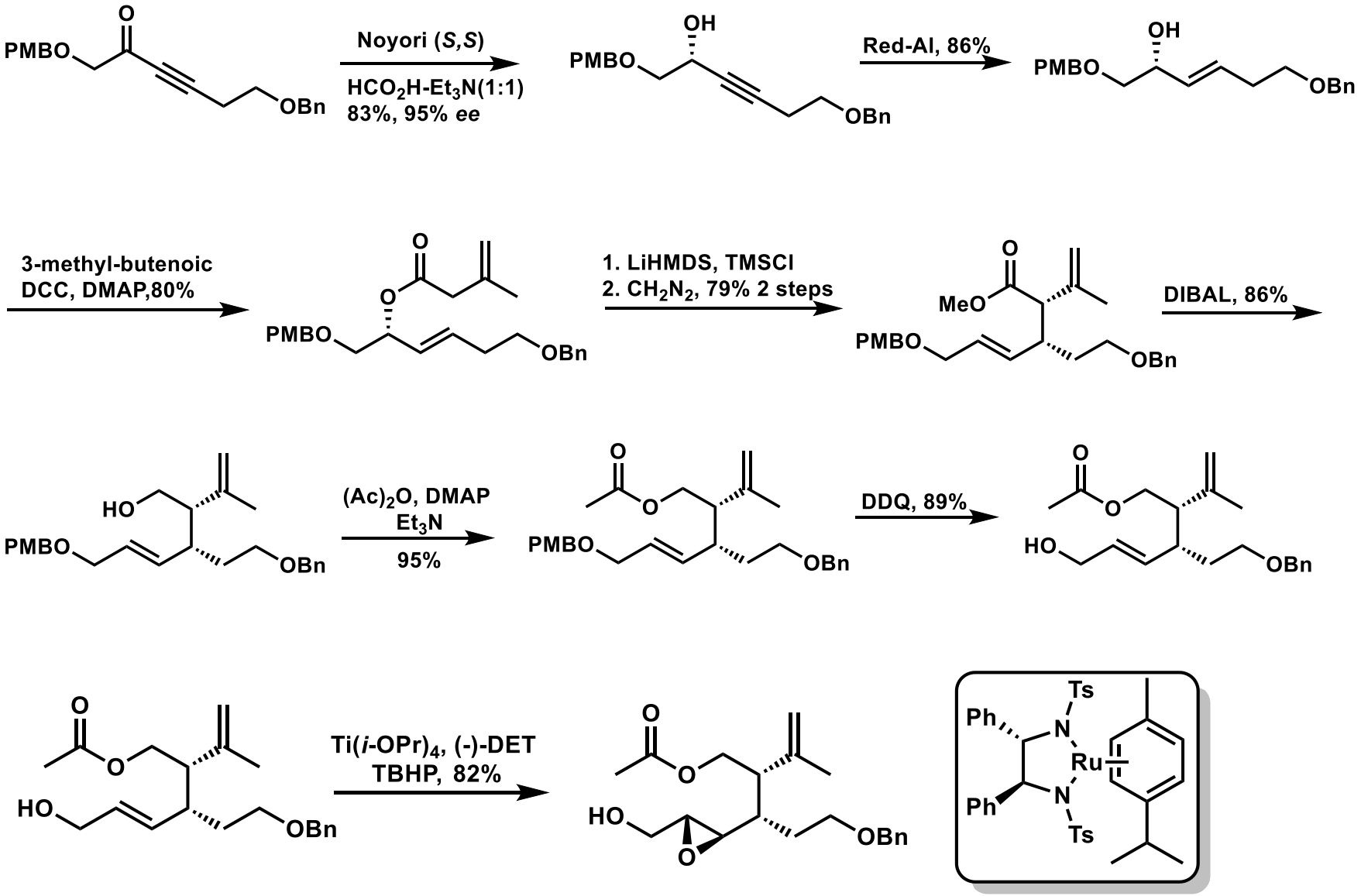
III-a: The nucleophilicity of N

(S_N2 reaction)

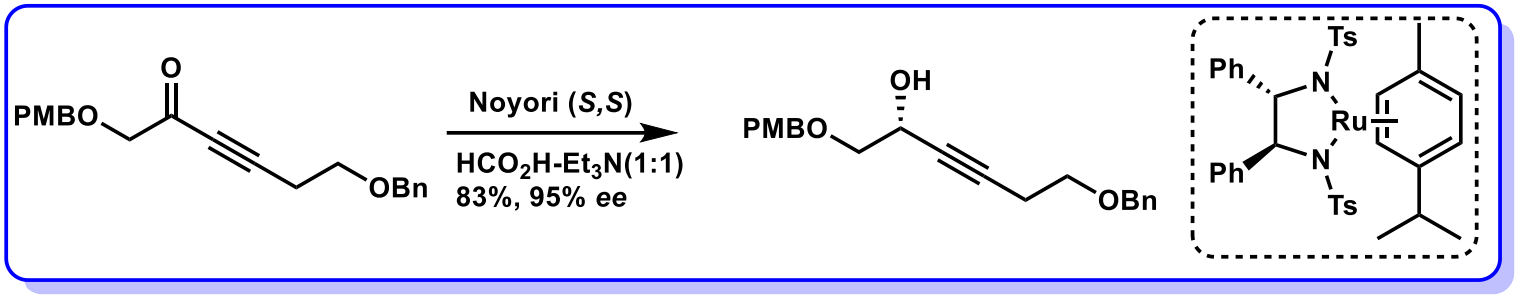
Srivari Chandrasekhar: *J. Org. Chem.*. **2013**, 78, 3355.



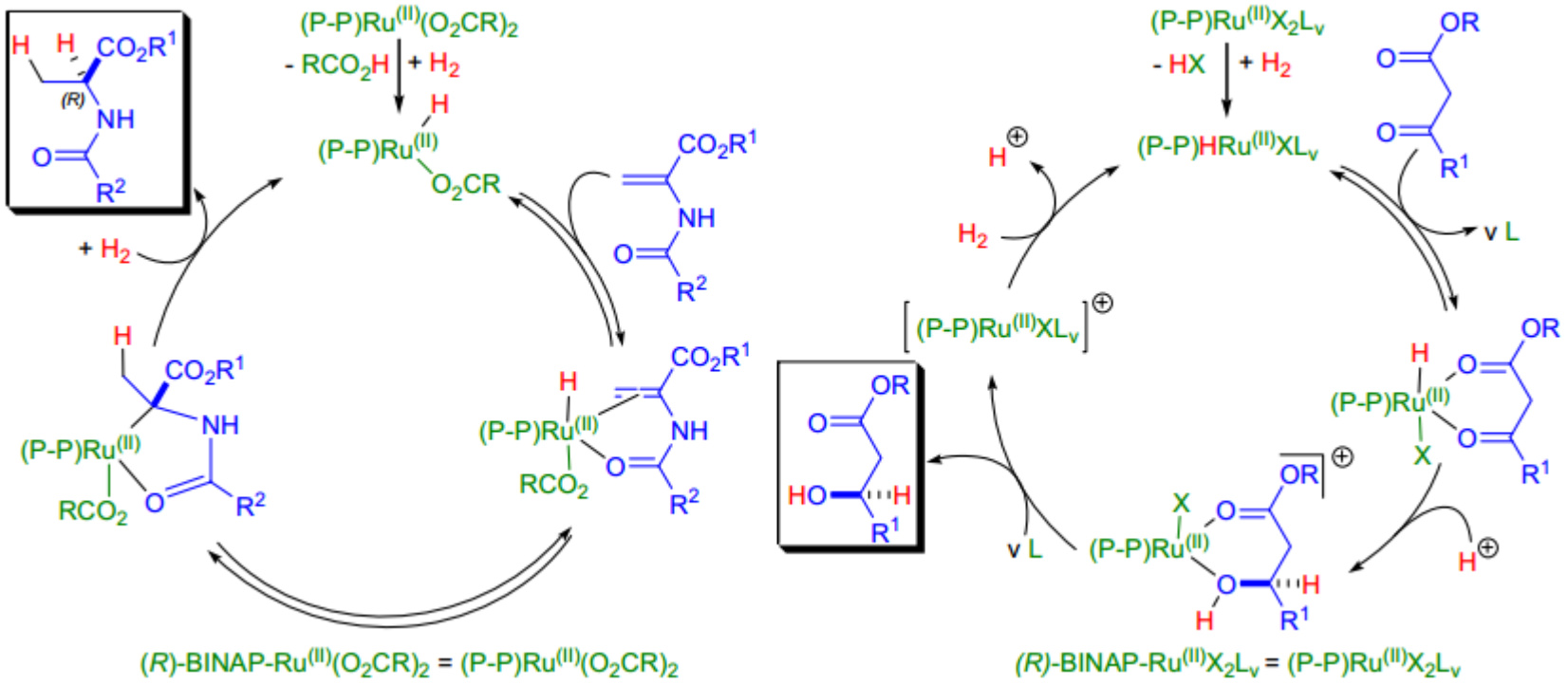
III-a: Synthetic of Epoxy Alcohol



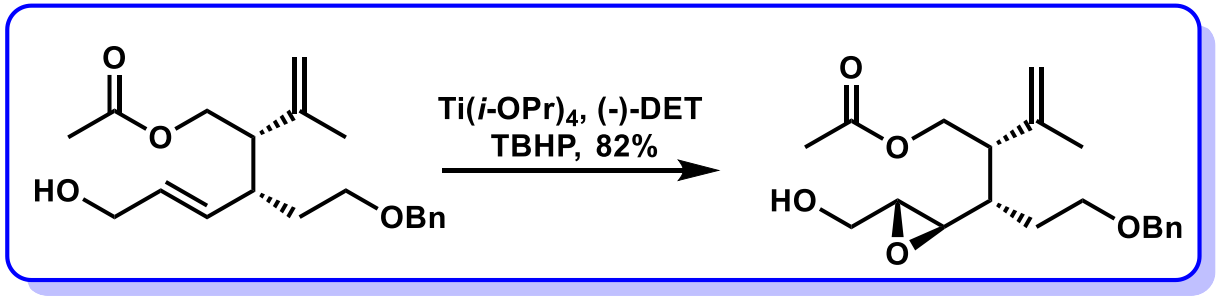
III-a: Synthetic of Epoxy Alcohol



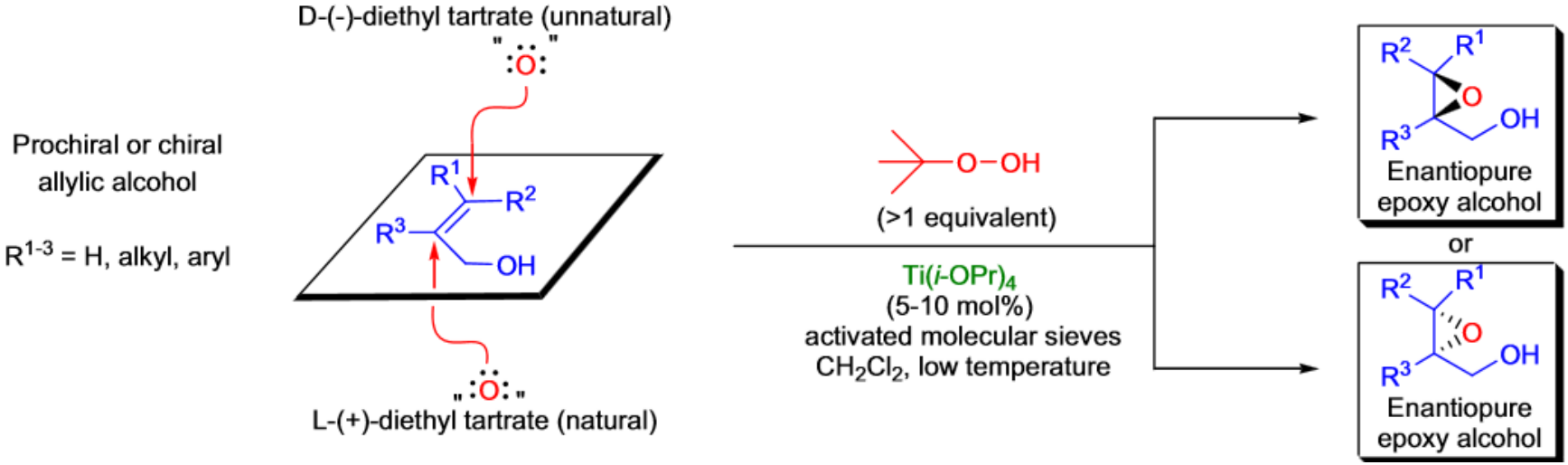
Noyori asymmetric hydrogenation



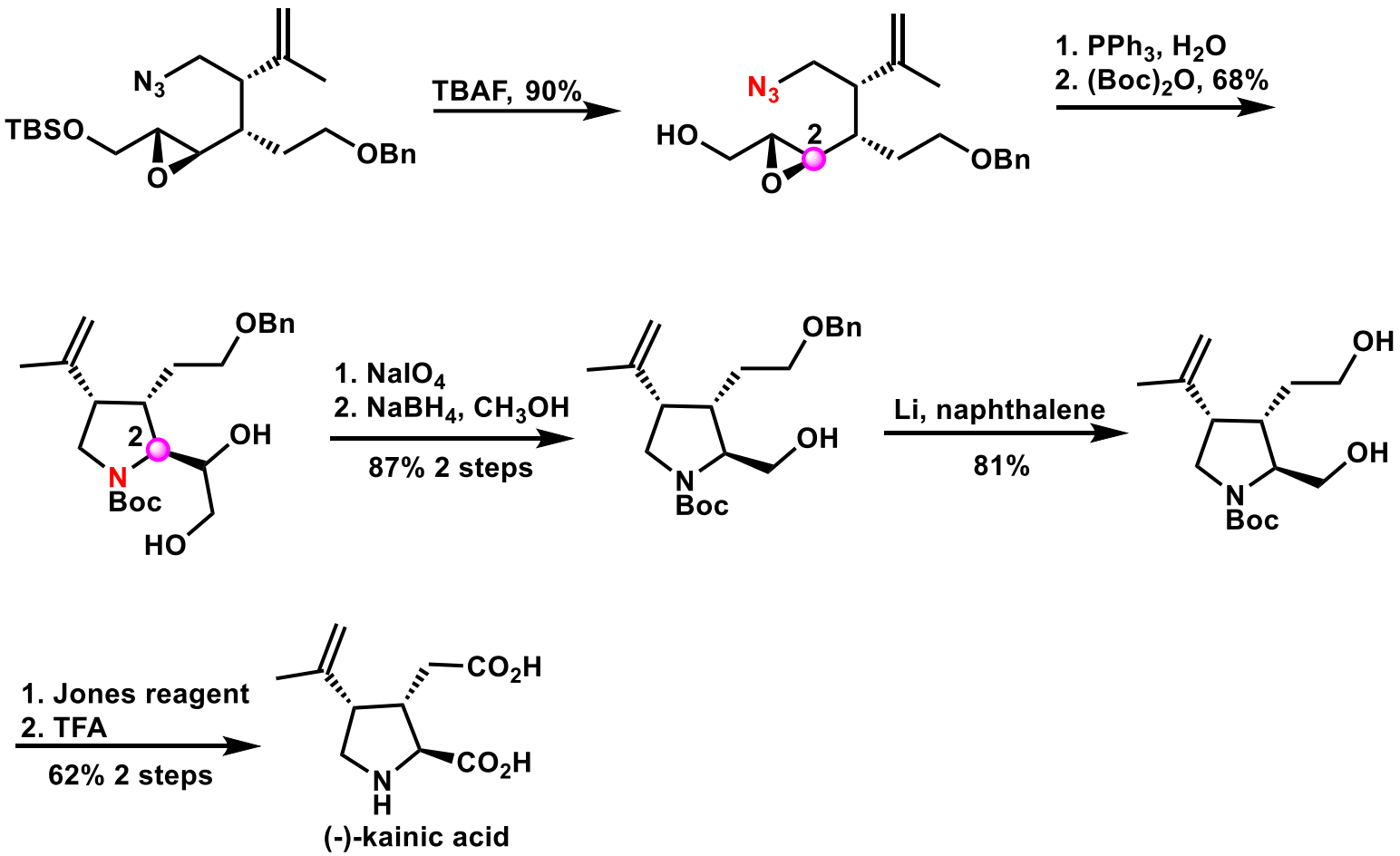
III-a: Synthetic of Epoxy Alcohol



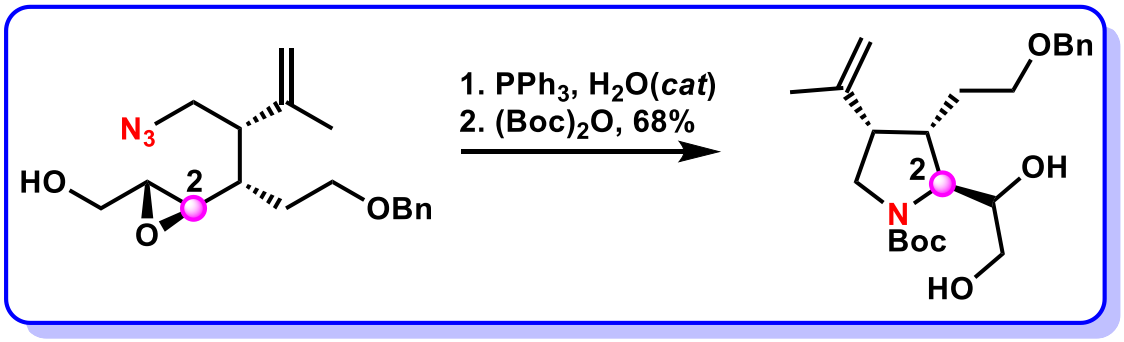
Sharpless Asymmetric Epoxidation



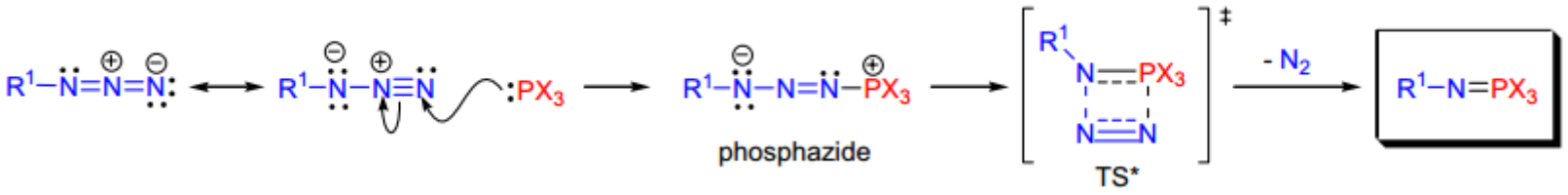
III-a: The nucleophilicity of N (S_N2 reaction)



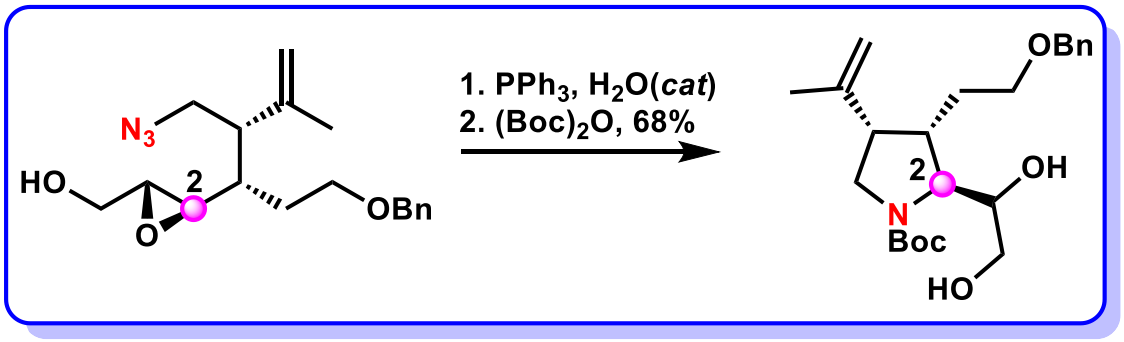
III-a: The nucleophilicity of N (S_N2 reaction)



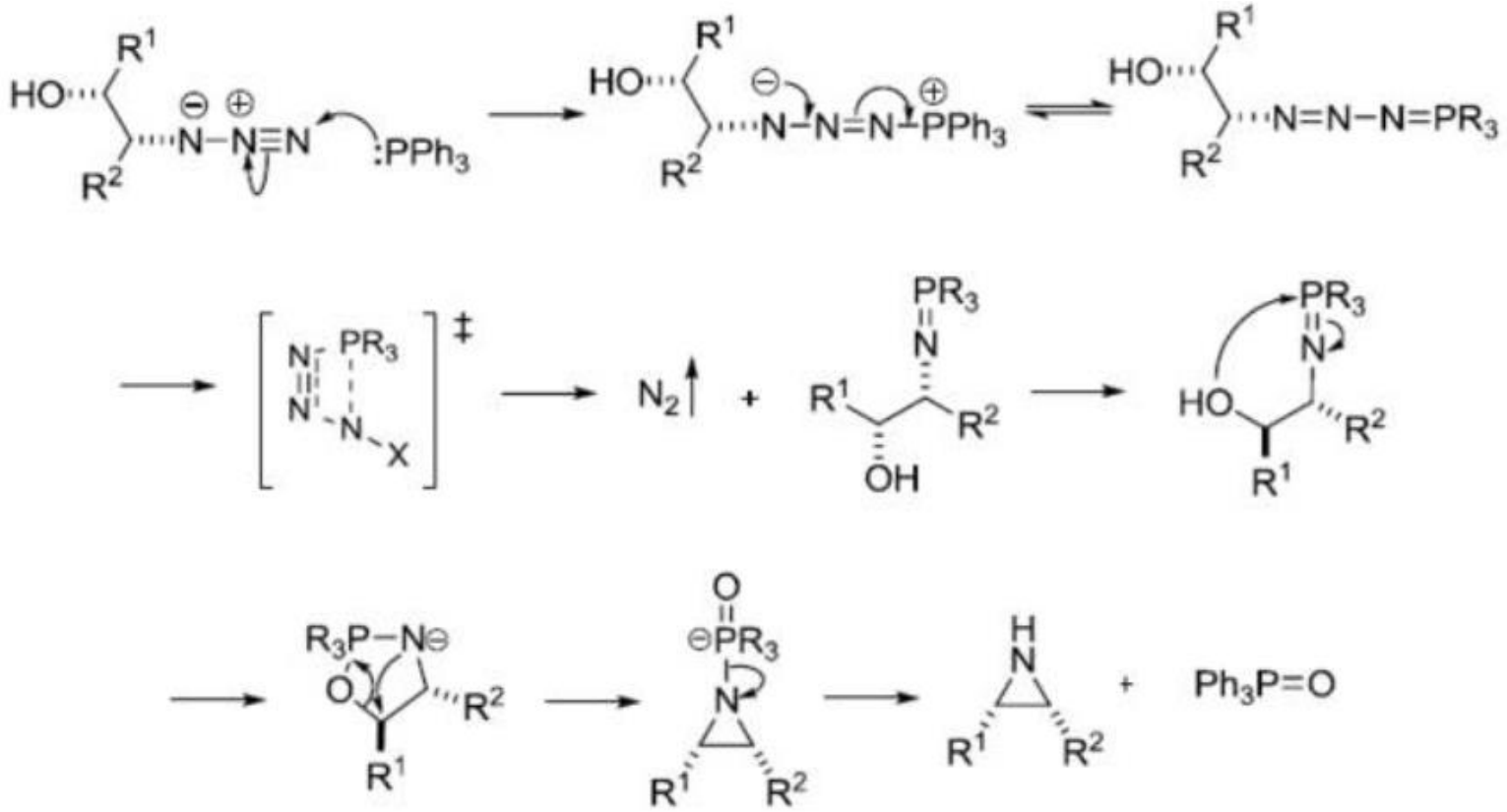
Staudinger reaction



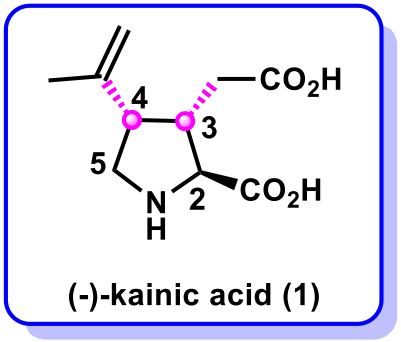
III-a: The nucleophilicity of N (S_N2 reaction)



- 5-exo-tet cyclization VS Blum–Ittah reaction



Summary



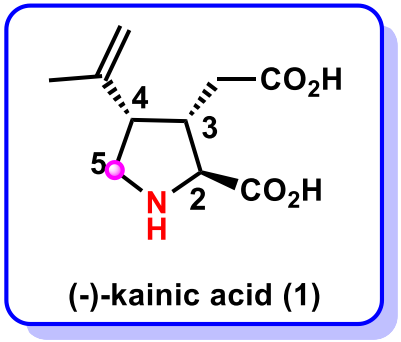
(-)-kainic acid (1)

I: The key syn C4-C3

I-a: Major Ene reaction

I-b: S_N2' reaction

I-c: D-A reaction



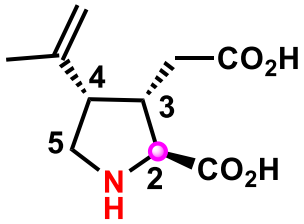
(-)-kainic acid (1)

II: The key C1-C5

II-a: The nucleophilicity of N (Michael addition)

II-b: The nucleophilicity of N (S_N2 reaction)

Summary

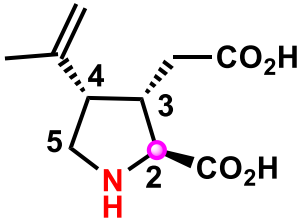


(-)-kainic acid (1)

III: The key C1-C2

III-a: The nucleophilicity of N

(S_N2 reaction)



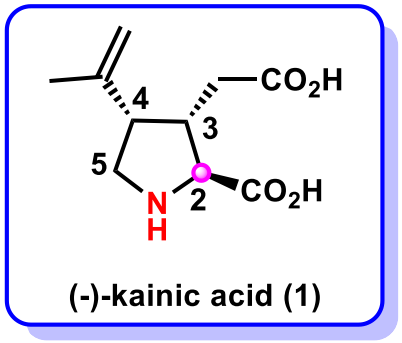
(-)-kainic acid (1)

III: The key C1-C2

III-b: The nucleophilicity of N

(Michael addition)

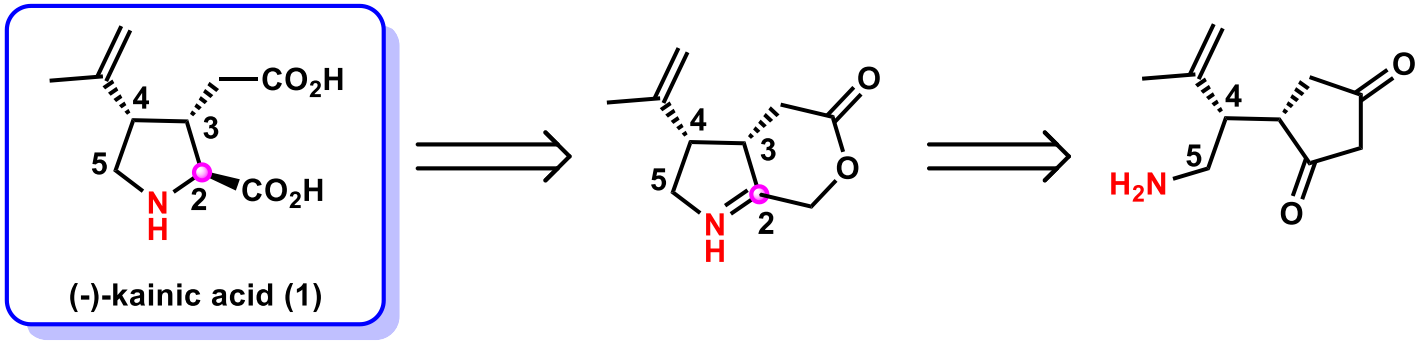
Summary



(-)-kainic acid (1)

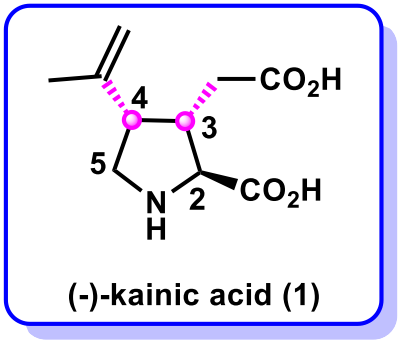
III: The key C1-C2

III-c: The nucleophilicity of N (imination)



(-)-kainic acid (1)

Summary



(-)-kainic acid (1)

IV: The key cycle

IV-a: [3+2] cycloaddition