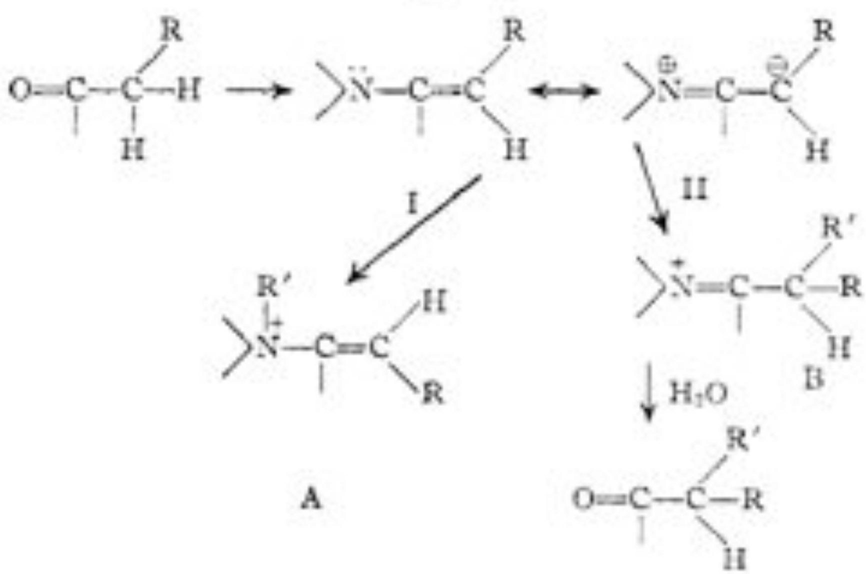
Enamine Catalysis: Fifty Years in the Making

- Stork's landmark 1954 publication outlines benefits of enamines vs enolates

A NEW SYNTHESIS OF 2-ALKYL AND 2-ACYL KETONES

Sir:

We have discovered a new method for the alkylation and acylation of ketones. The condensation products of ketones and secondary amines are well known.[1,2] It is evident that these substances can undergo reaction with proper electron acceptors either at N or C according to path I or II:



Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029.

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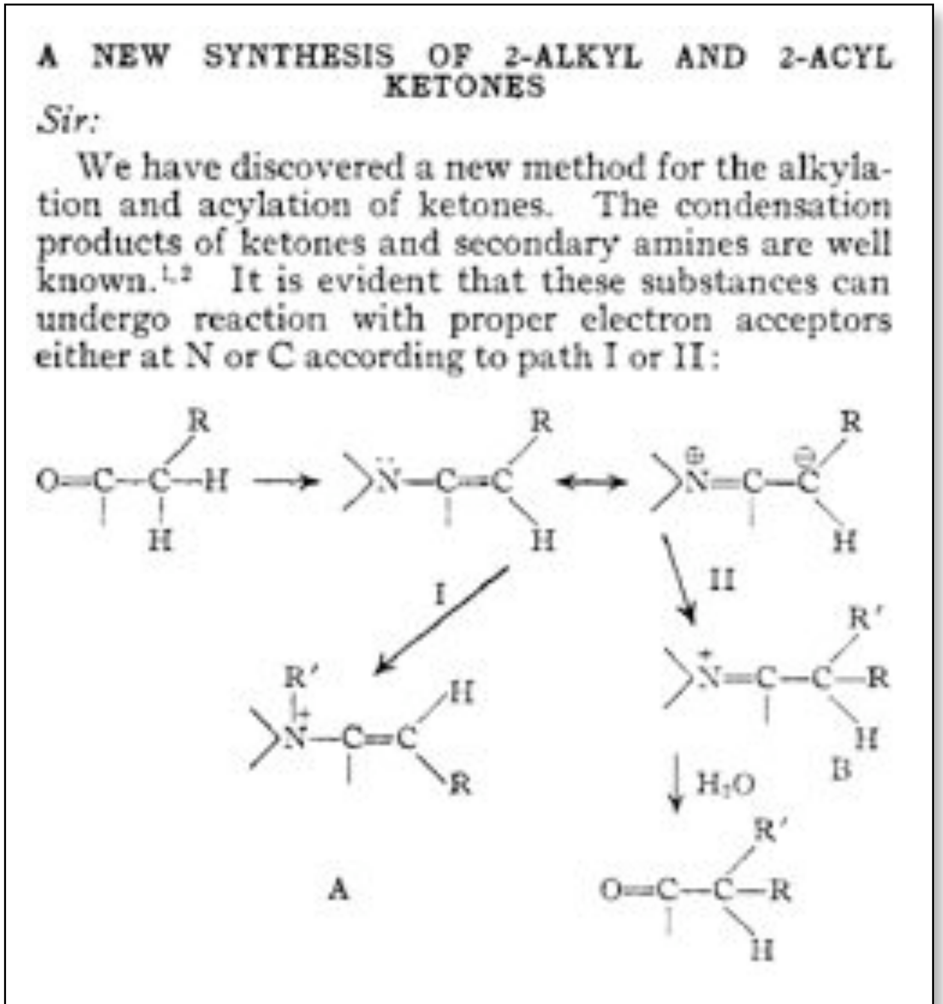

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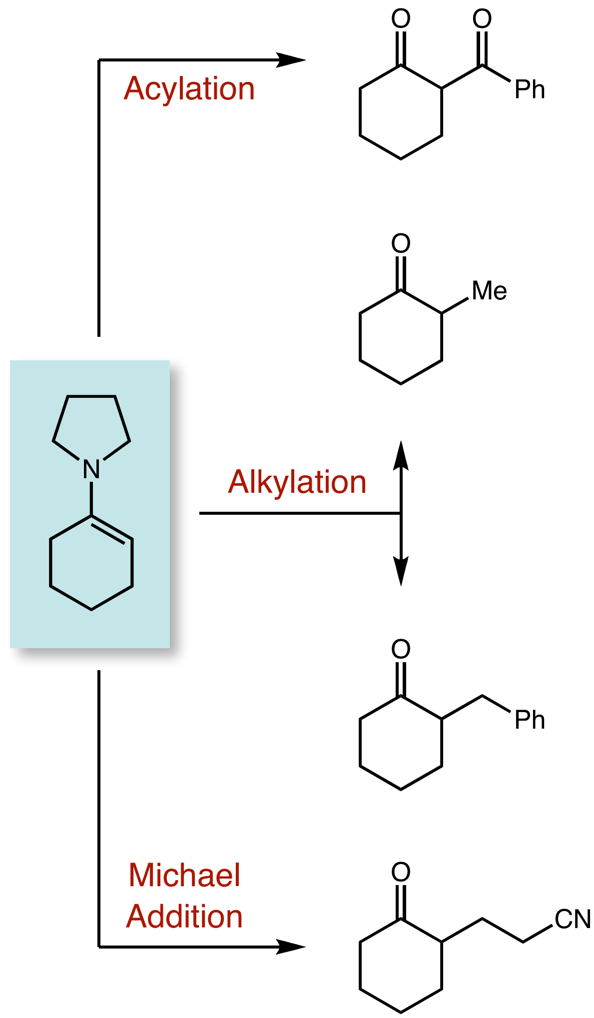
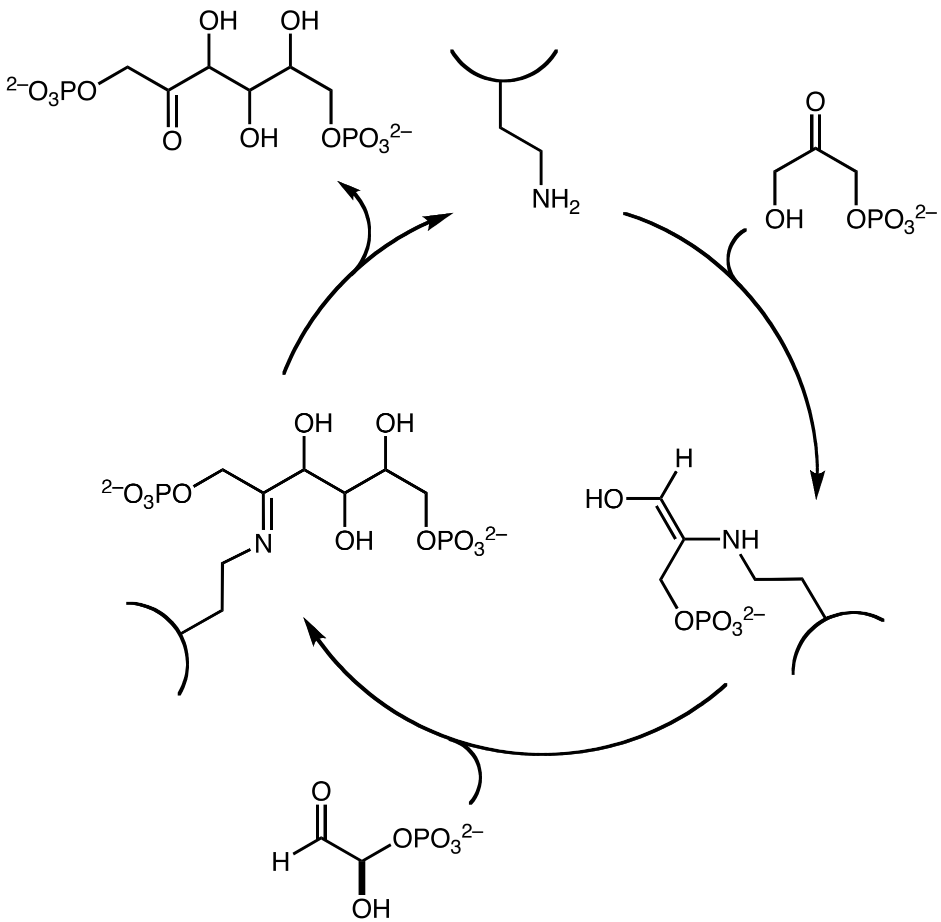


Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029.

Enamine Catalysis: Inspiration from Biology

■ Mechanism of class I aldolases is proposed to involve enamine intermediates



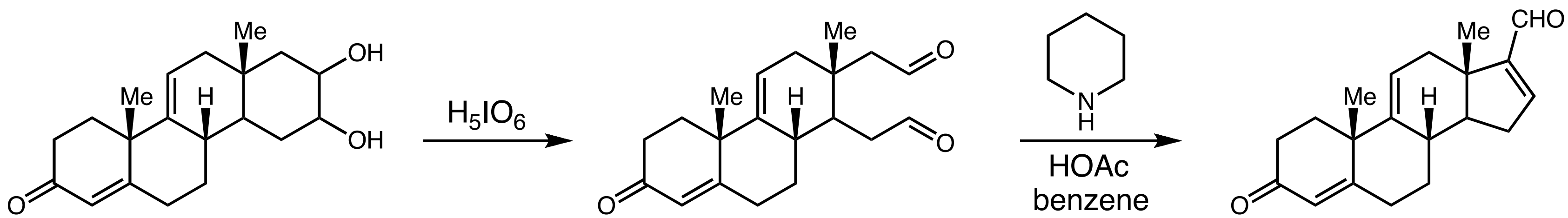
Fructose bisphosphate aldolase

Lysine reside is required for catalytic activity

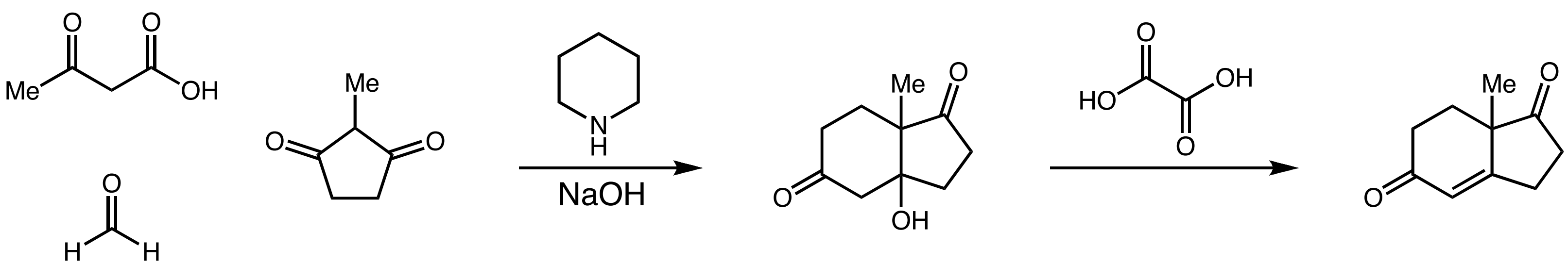
Rutter, W. J. *Fed. Proc. Am. Soc. Exp. Biol.* **1964**, *23*, 1248

Enamine Catalysis: Early Adoption in Total Synthesis

■ Woodward-Wieland-Miescher enamine cyclization for steroid synthesis



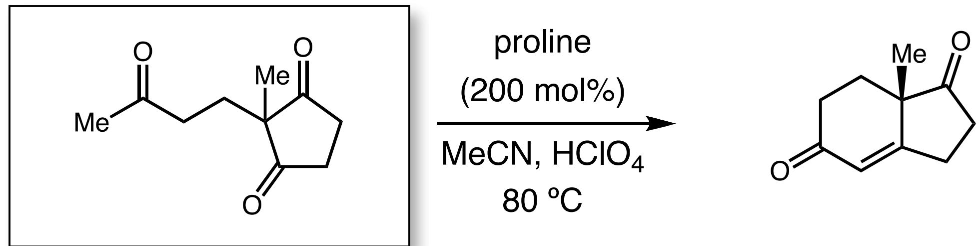
Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223



Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215

Hajos-Parrish-Eder-Sauer-Wiechart: Asymmetric Breakthrough

- Use of proline to deliver the Weiland-Miescher ketone in an asymmetric fasion



67% ee

New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures[**]

By *Ulrich Eder*, *Gerhard Sauer*, and *Rudolf Wiechert*[*]

Hajos-Parrish-Eder-Sauer-Wiechart: Asymmetric Breakthrough

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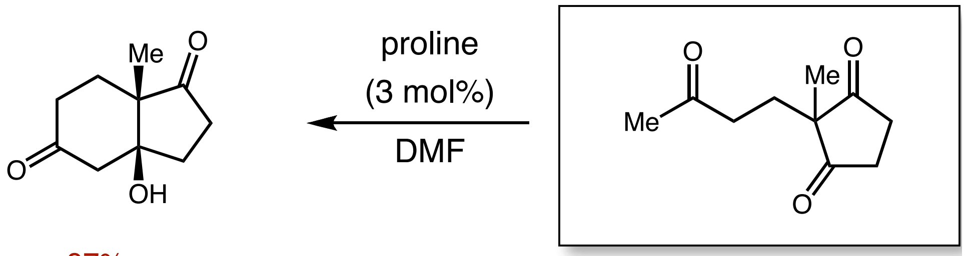

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Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry

Zoltan G. Hajos*[1] and David R. Parrish

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received August 20, 1973

Hajos-Parrish-Eder-Sauer-Wiechart: Asymmetric Breakthrough

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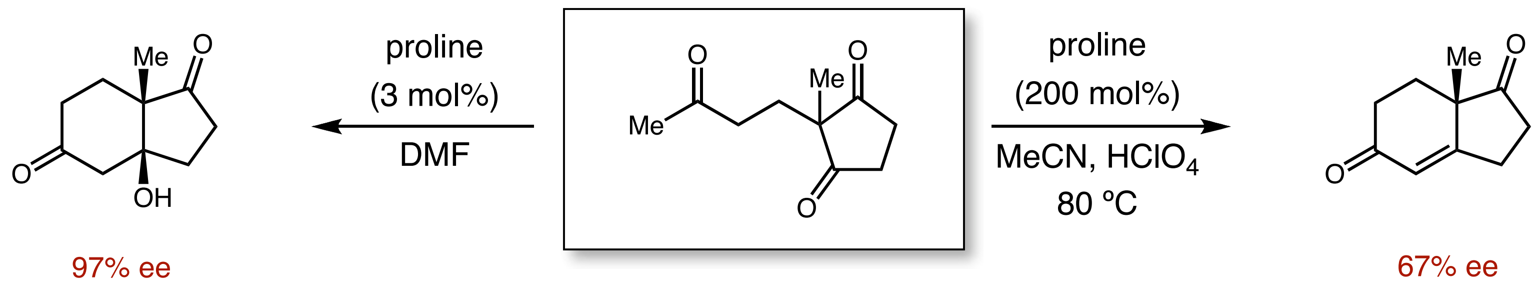

J. Org. Chem. **1974**, *39*, 1615.

Angew. Chem. Int. Ed. **1971**, *10*, 496.

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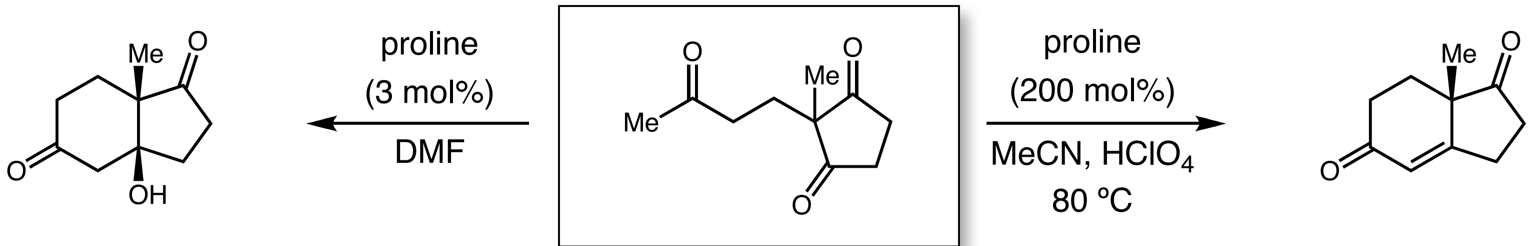

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J. Org. Chem. **1974**, *39*, 1615.

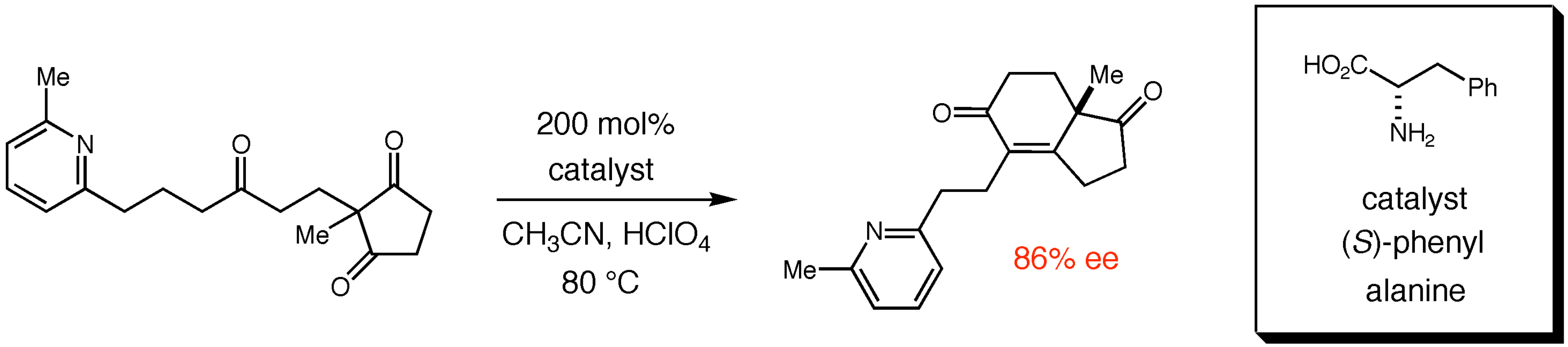
Angew. Chem. Int. Ed. **1971**, *10*, 496.

German Patent DE2102623 (July 29, 1971)

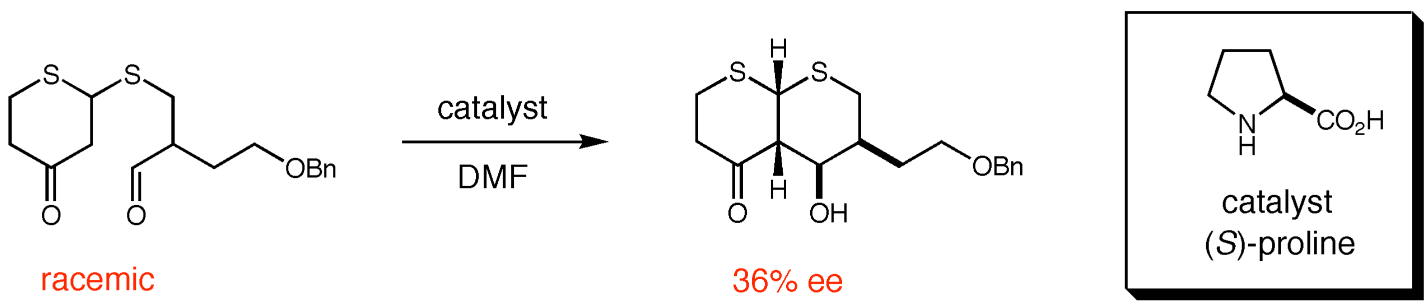
German Patent DE2014757 (Oct 7, 1971)

Enantioselective Organocatalysis, Early Examples: Enamine Catalysis

■ Intramolecular Aldol: Danishefsky–Cain *J. Am. Chem. Soc.* **1976**, *98*, 4975



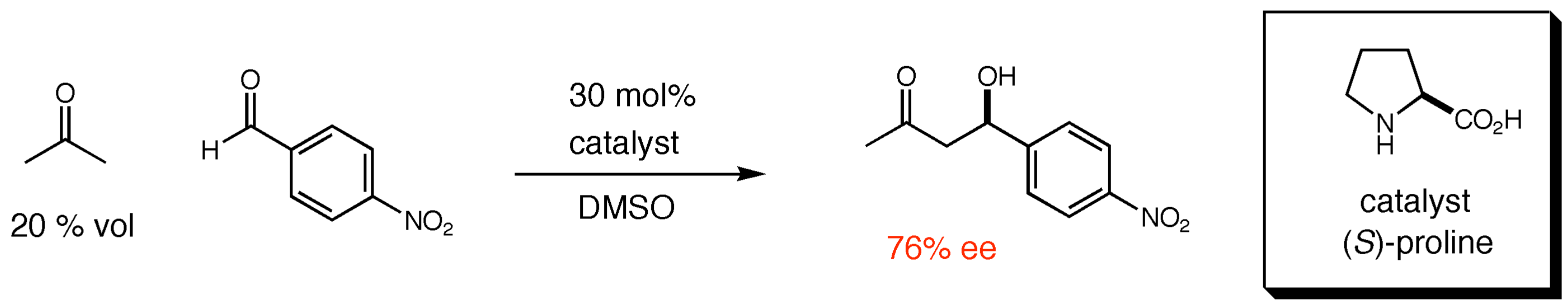
■ Erythromycin Synthesis: Woodward *J. Am. Chem. Soc.* **1981**, *103,* 3210



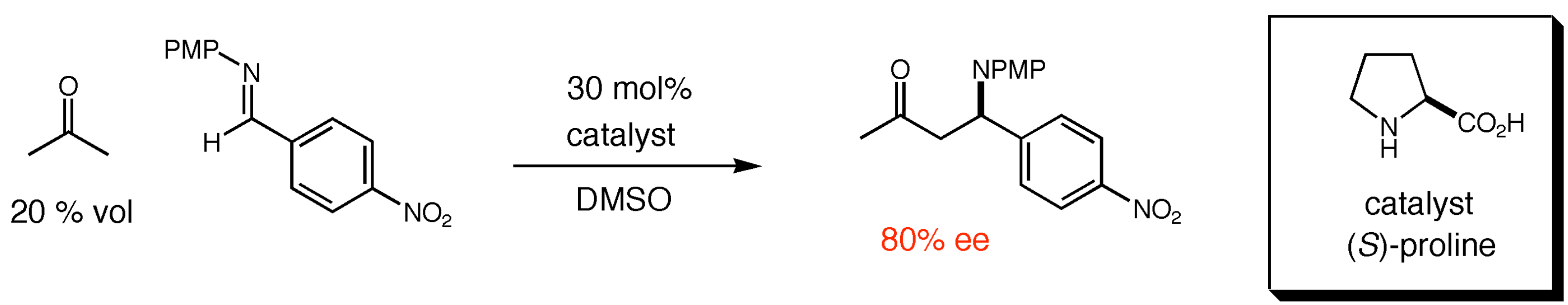
First examples of application of enamine catalysis to natural product synthesis

Enantioselective Organocatalysis, Modern Examples: Enamine Catalysis

■ Intermolecular Aldol: Barbas–List–Lerner *J. Am. Chem. Soc.* **2000**, *122*, 2395

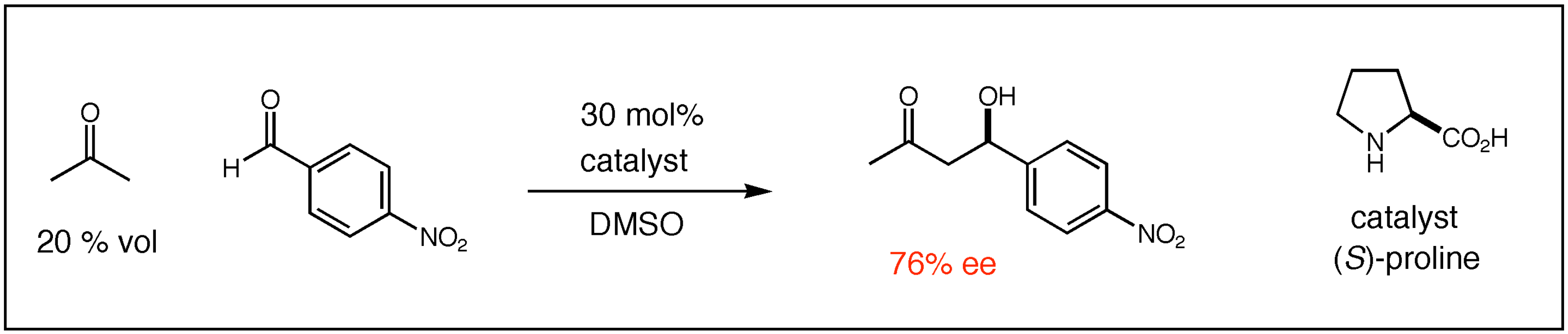


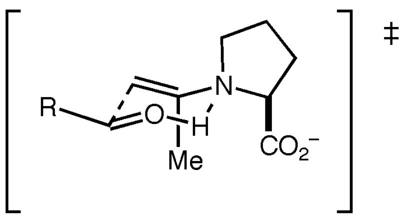
■ B-Amino Carbonyls: Barbas *Tetrahedron Lett*, **2001**, *49,* 199



First examples of application of enamine catalysis to intermolecular reactions

Enamine Aldol: Proposed Transition States to Date





Hajos–Parrish (1971)

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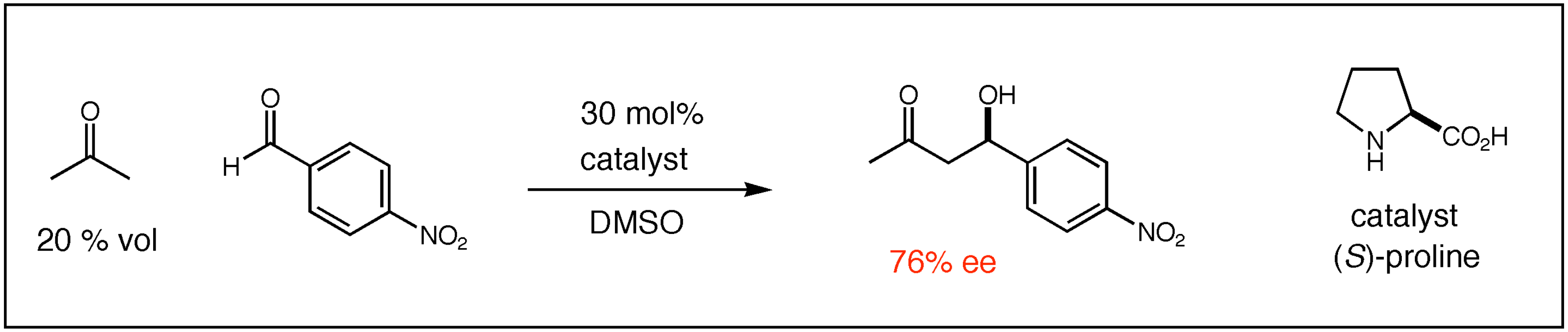

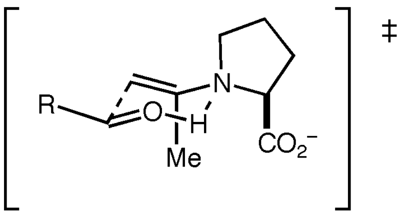

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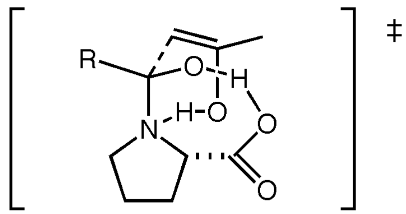

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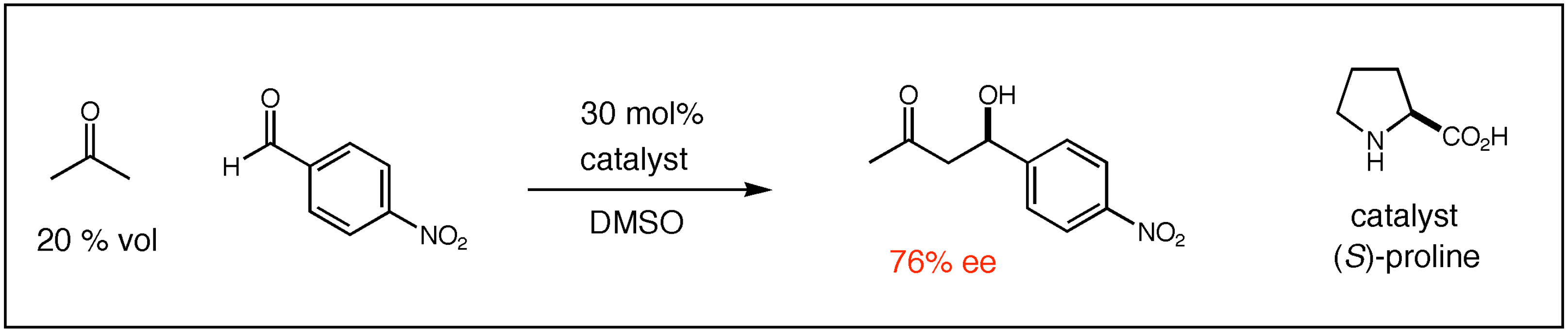

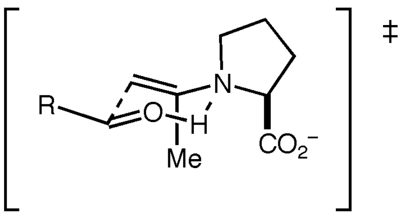

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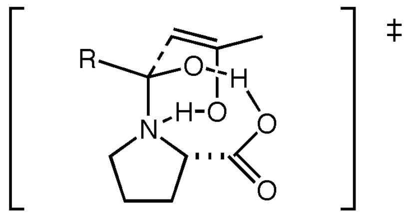

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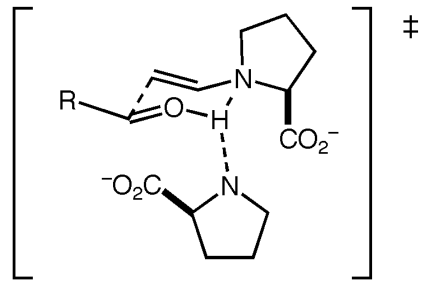

Agami (1987)

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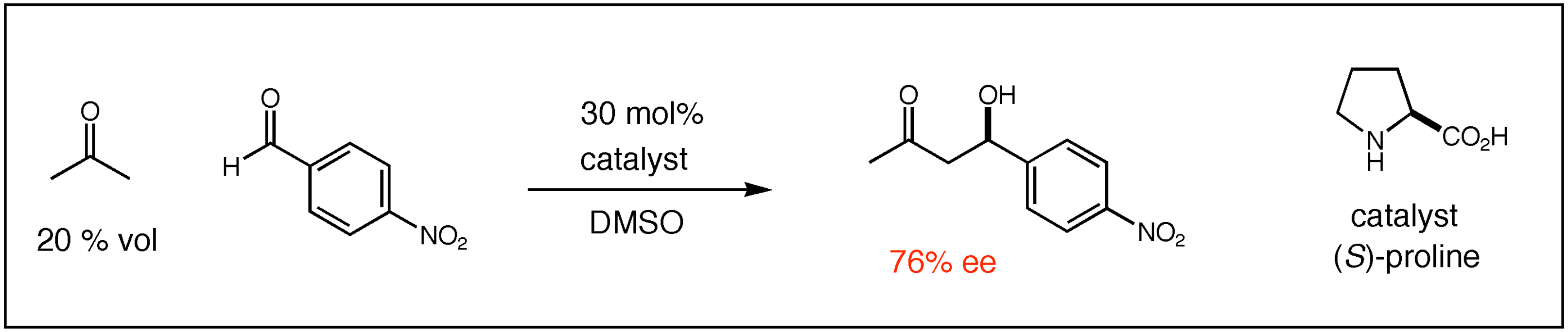

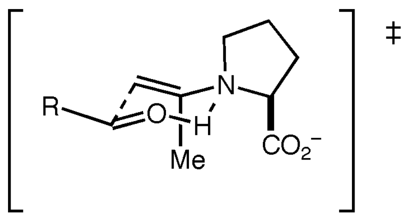

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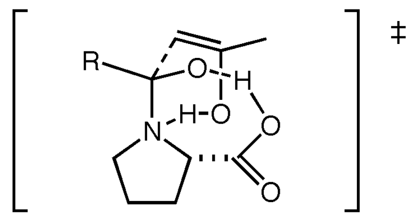

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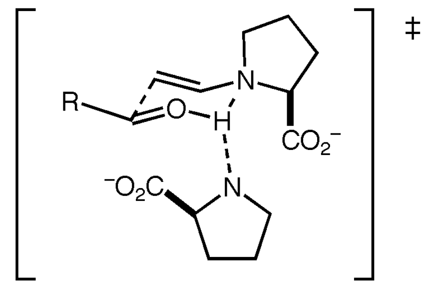

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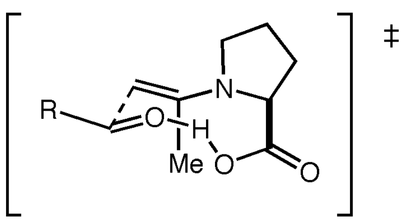

Barbas–List (2000)

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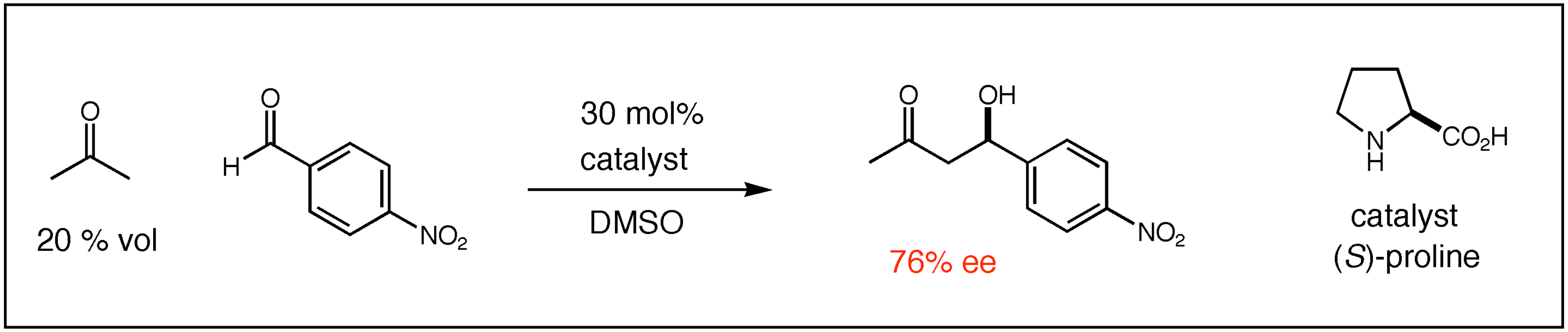

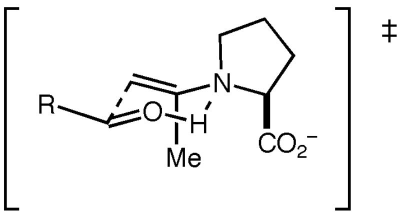

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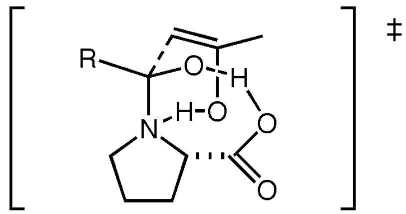

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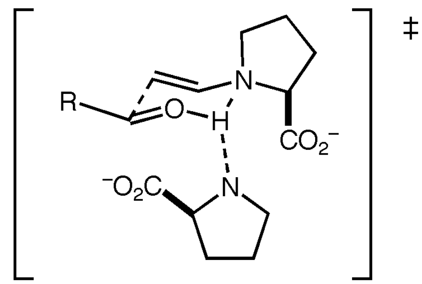

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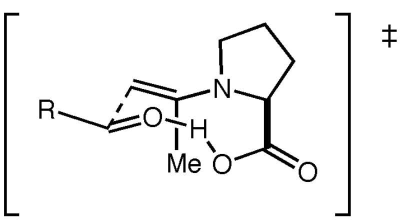

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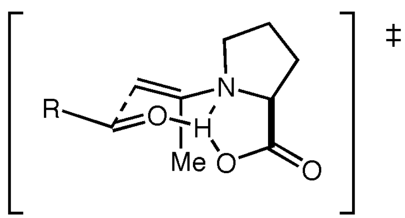

Houk (2002)

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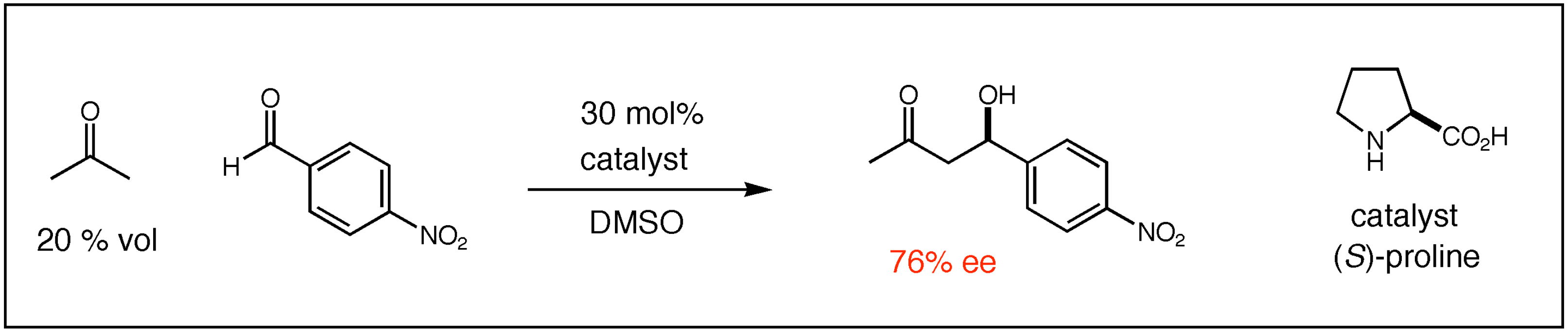

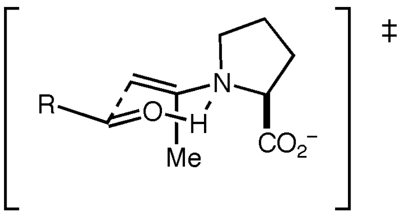

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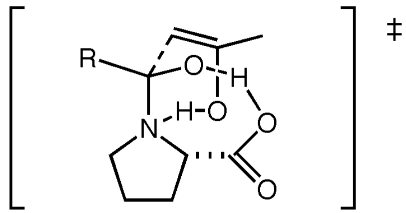

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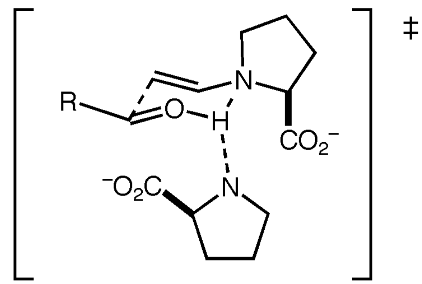

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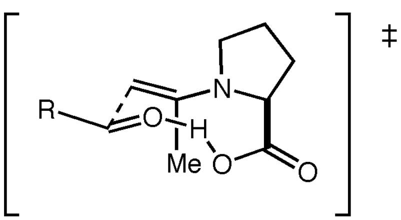

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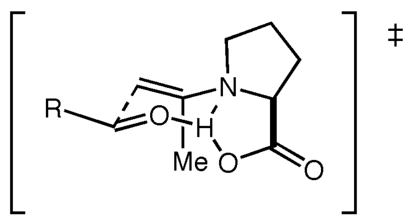

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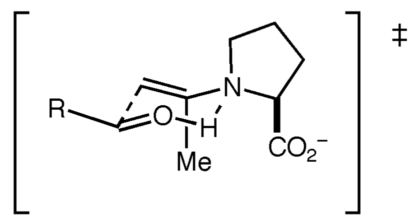
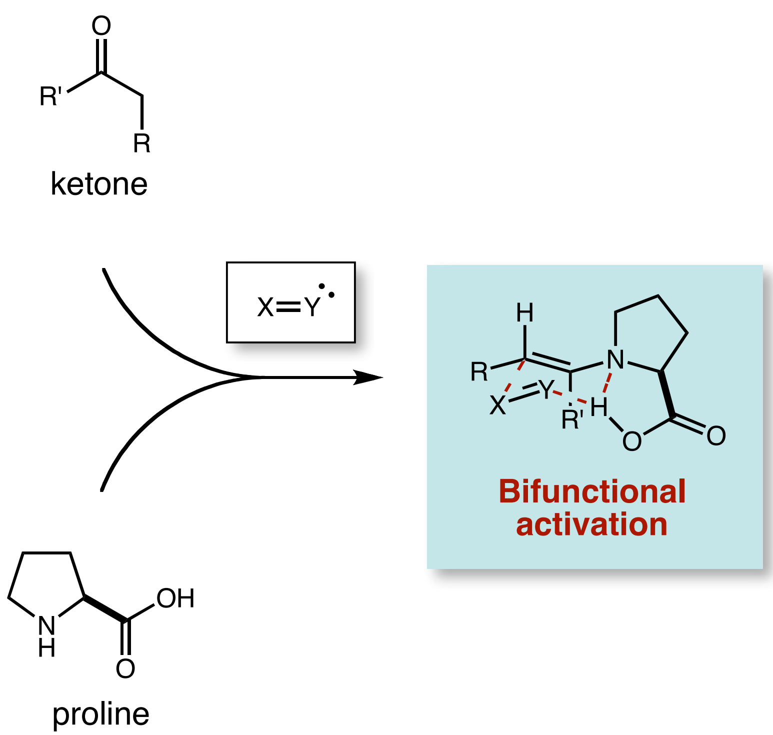


MacMillan (2003)

Bifunctional Enamine Catalysis: Generic Induction Platform

- Use of proline or proline-type activation a widely exploited mode of ketone activation



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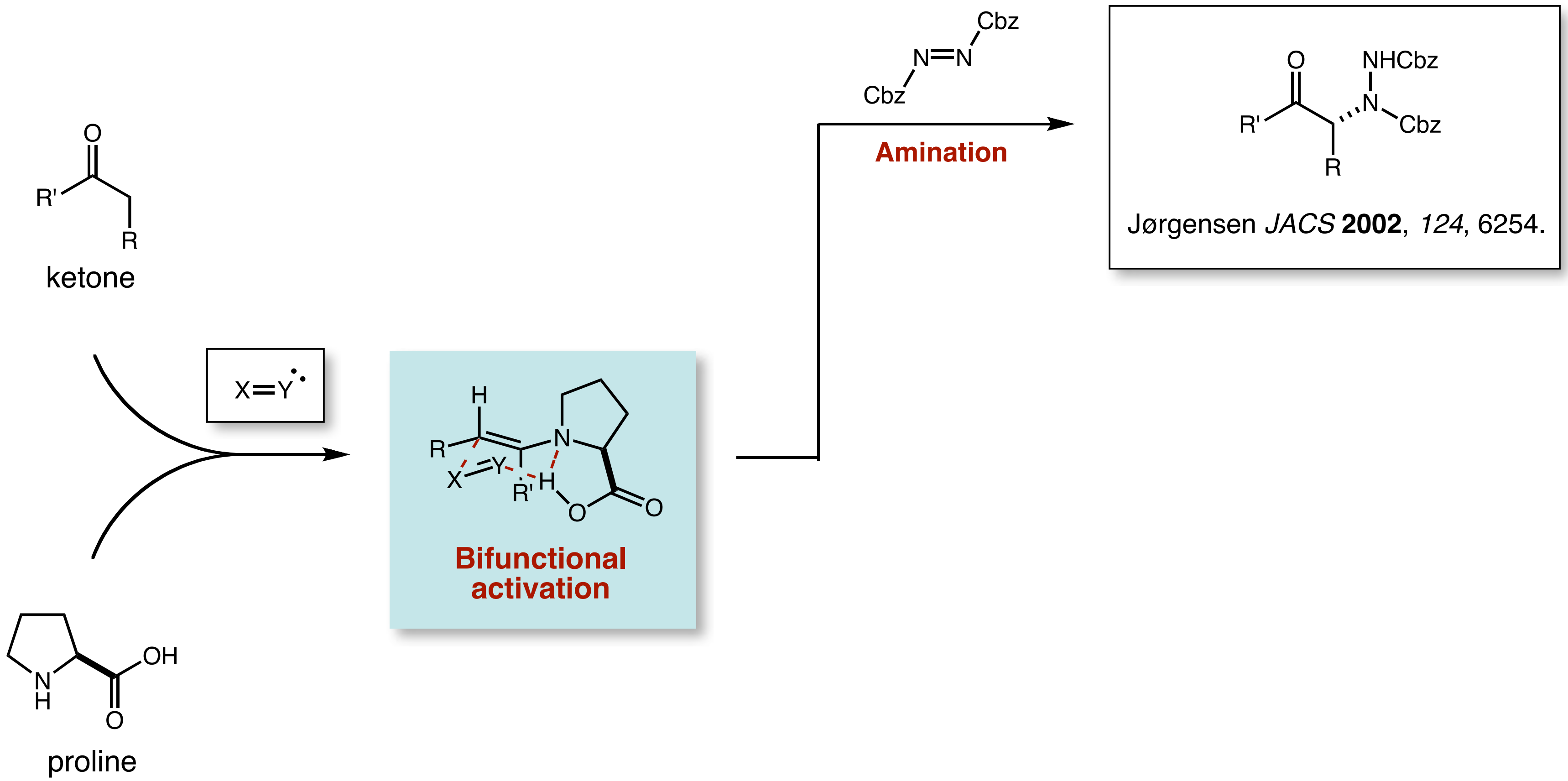

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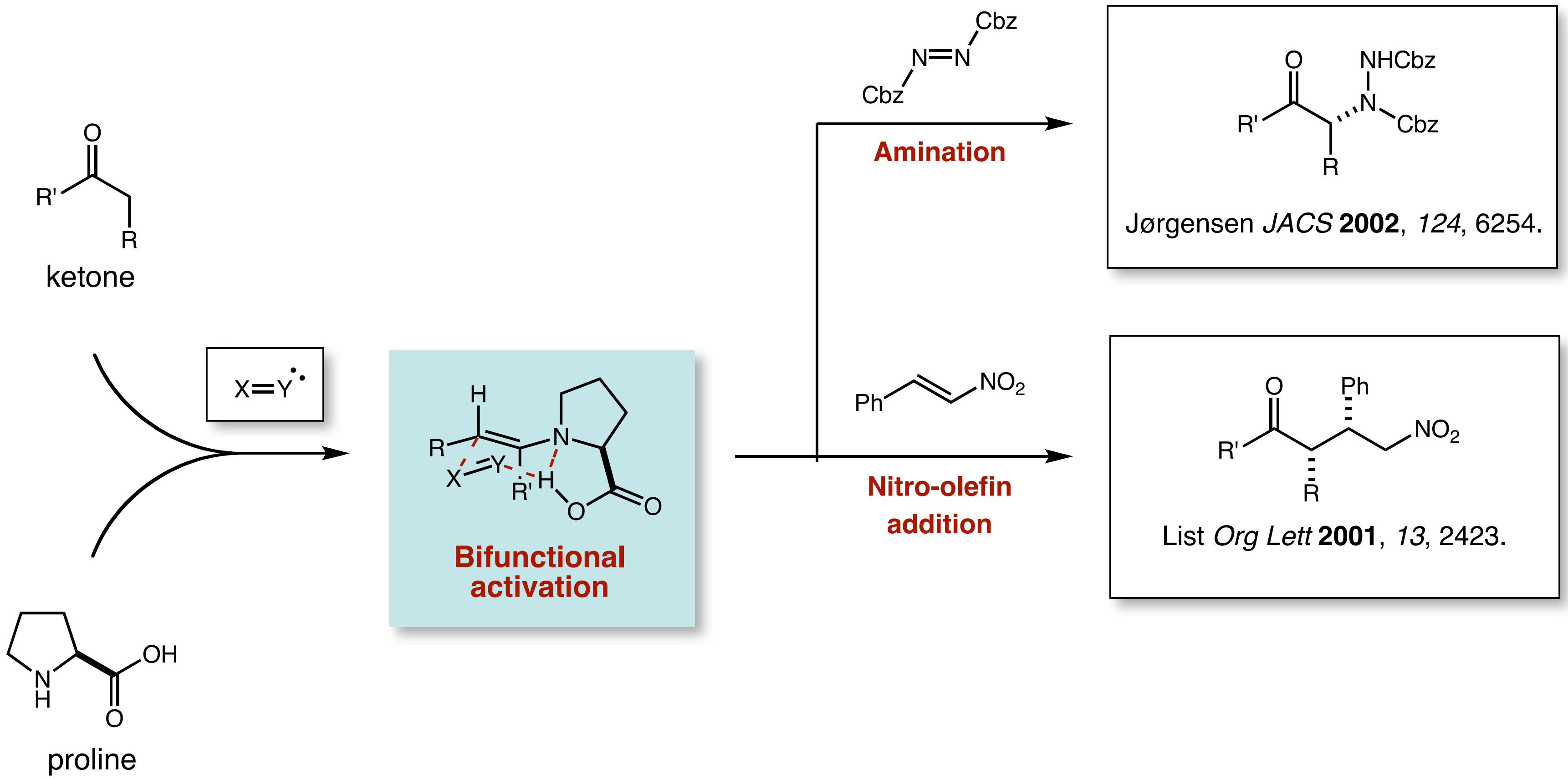

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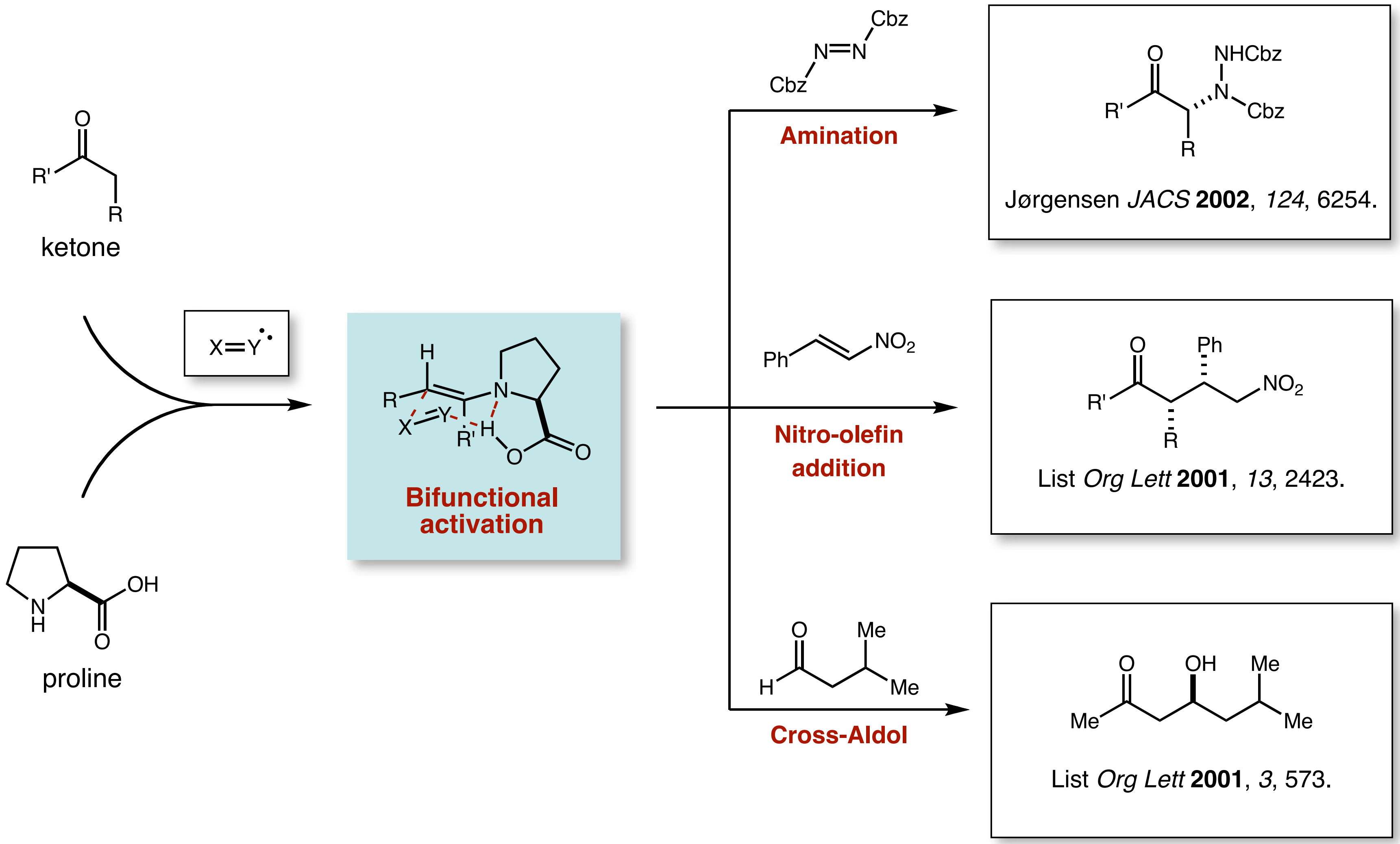
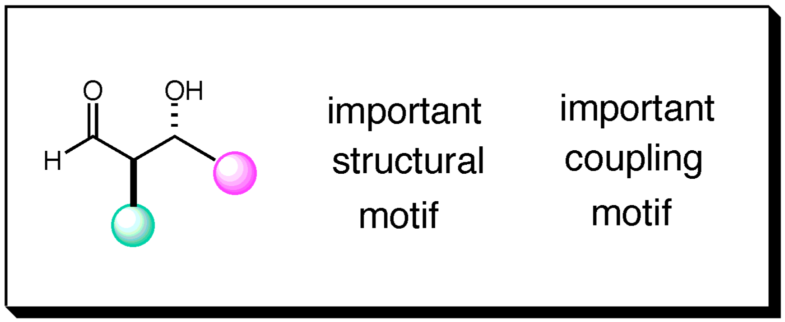
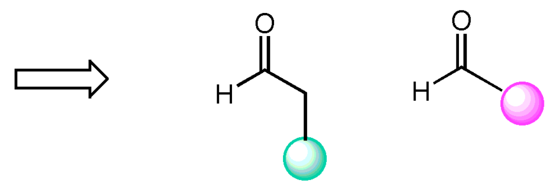


Development of a New Approach to the Enantioselective Aldehyde Aldol Reaction



Aldehyde–Aldehyde Aldol



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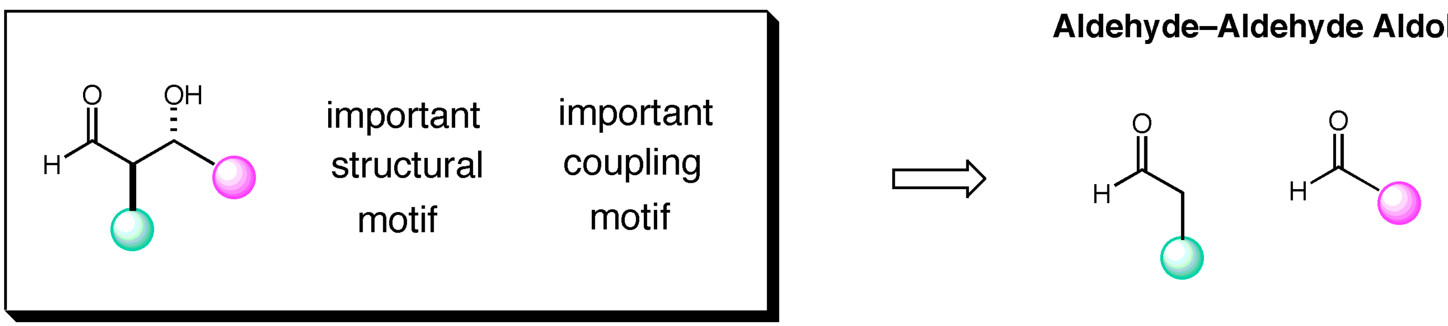
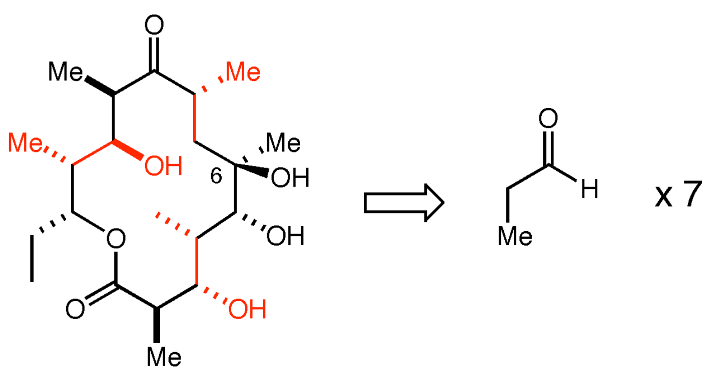
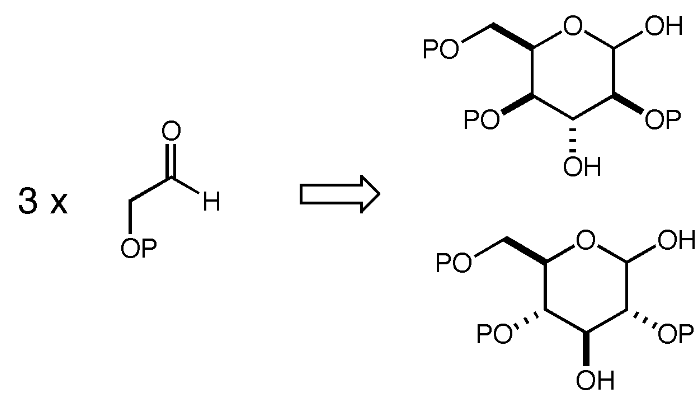


- Can we conduct organocatalytic aldehyde–aldehyde direct aldol reaction



erythronolide B: polyproionate synthesis



sugar synthesis

- Control of aldehyde–aldehyde aldol reactions would allow rapid synthesis of key organic structures

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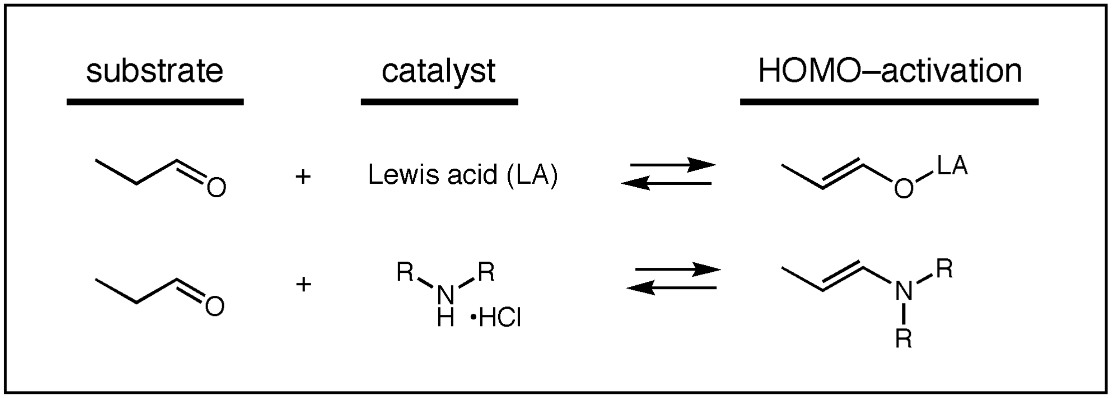

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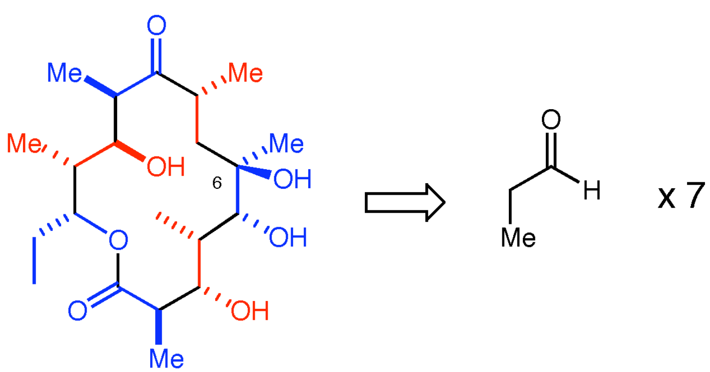

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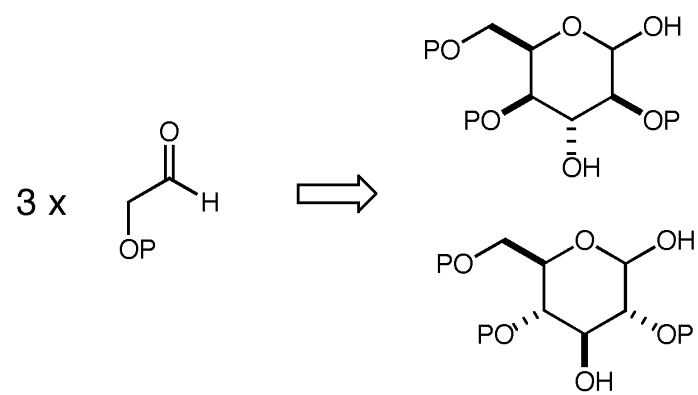

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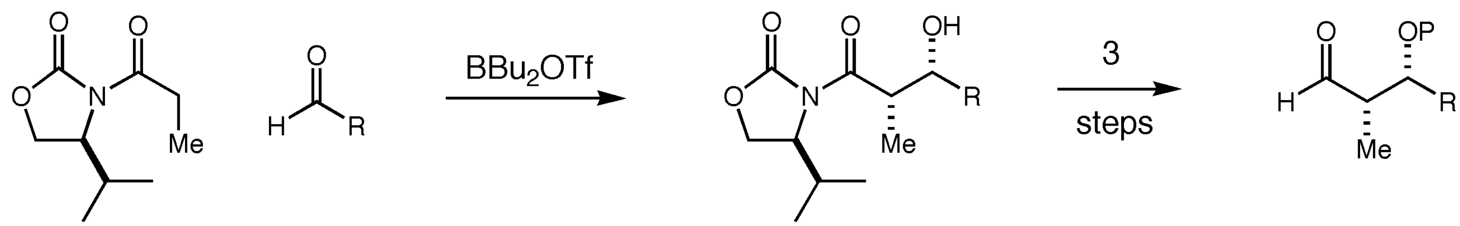
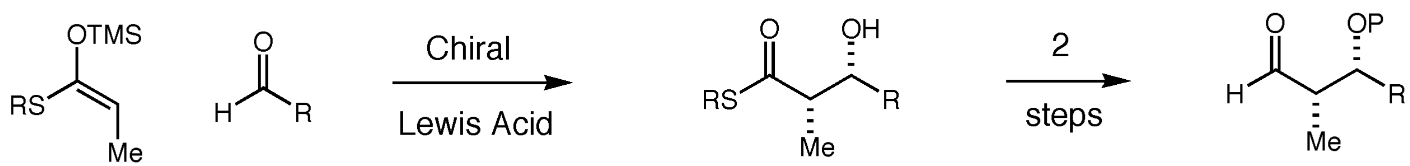
Classical and Modern Methods for Enantioselective Propionate Construction

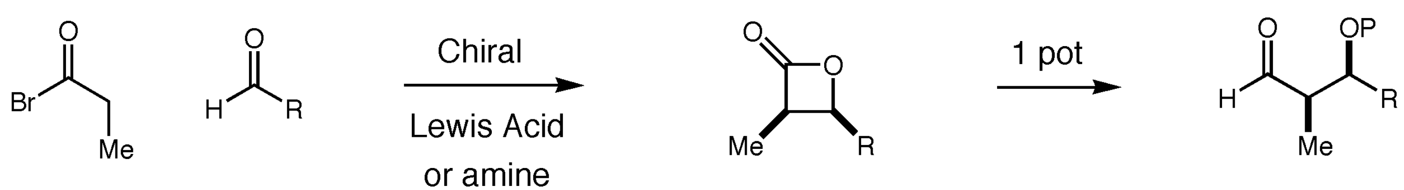
■ Auxiliary Controlled Aldol: Evans



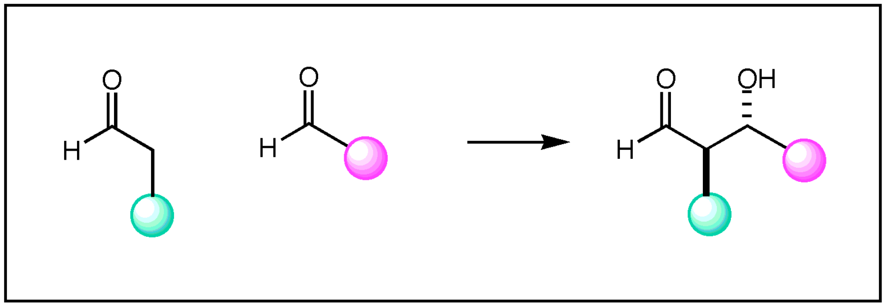
■ Chiral Lewis Acid Controlled Aldol: Mukaiyama



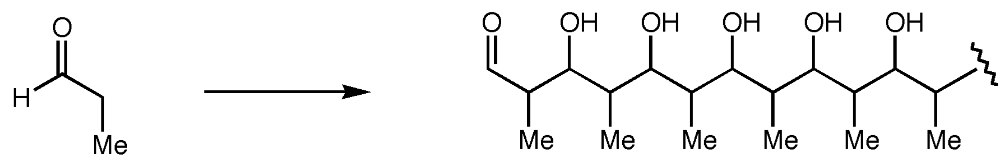
■ Chiral Lewis Acid or Amine Catalyzed Ketene [2 + 2]: Nelson



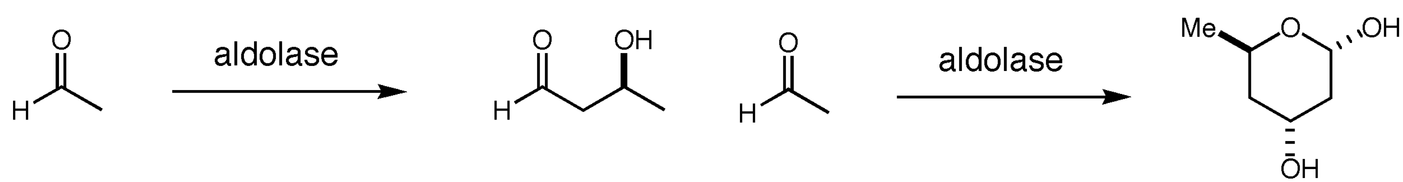
Aldehyde–Aldehyde Direct Aldol: Mechanistic Considerations



■ Aldehyde–aldehyde reaction is believed to lead to polymeric materials

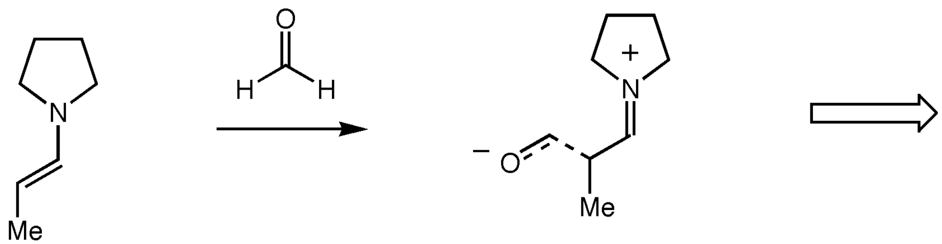


■ Aldolase mechanism shows that enamine aldol reaction should not polymerise

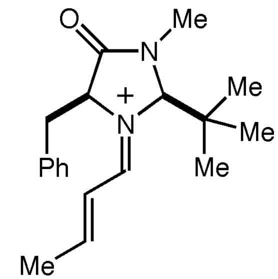


Imidazolidinones Should be Highly Effective Aldol Catalysts

- Calculated Late T.S. Implies Importance of Both Iminium Formation and Geometry Control (Houk)



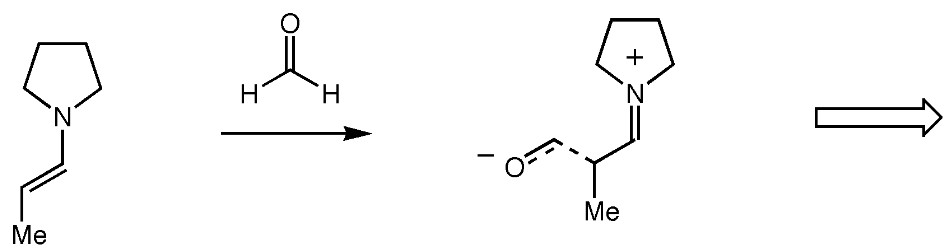
Transition State Iminium Ion



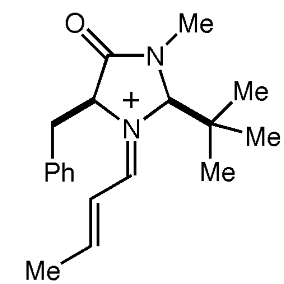
Rapidly Formed Iminium
Complete Geometry Control

Imidazolidinones Should be Highly Effective Aldol Catalysts

Calculated Late T.S. Implies Importance of Both Iminium Formation and Geometry Control (Houk)

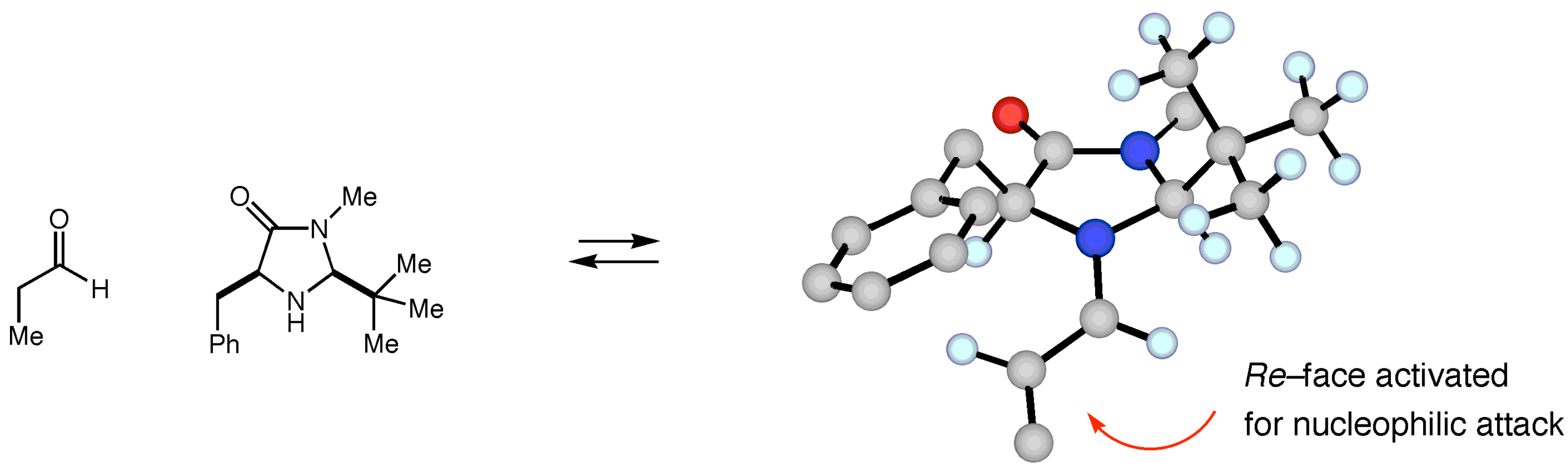


Transition State Iminium Ion



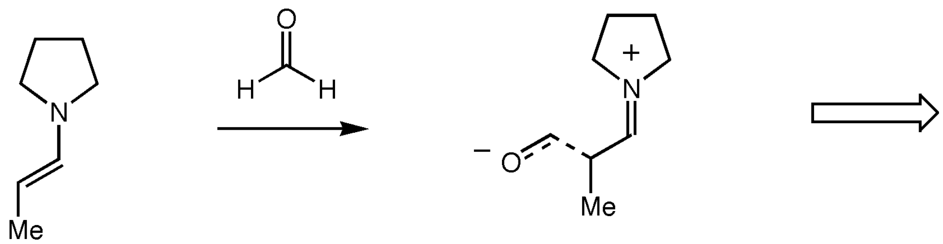
Rapidly Formed Iminium
Complete Geometry Control

Benzyl Group Shields Olefin π–Face: Clear Rationale for Enantiocontrol

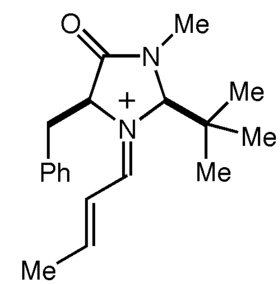


Imidazolidinones Should be Highly Effective Aldol Catalysts

- Calculations Suggest Iminium Formation in C–C Bond Formation (Houk)

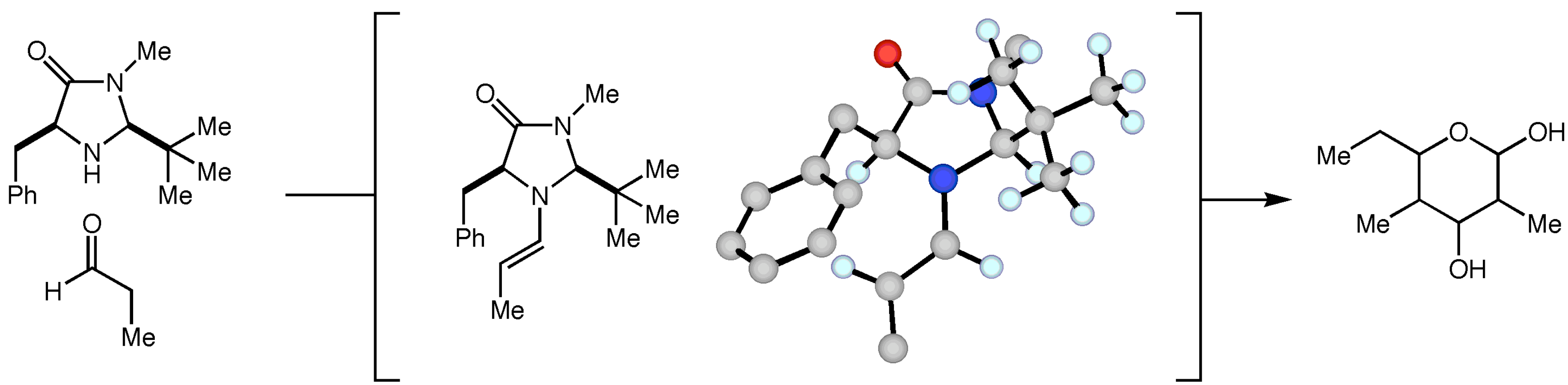


Transition State Iminium Ion



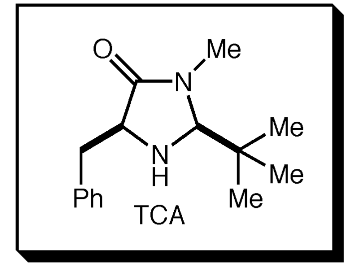
Rapidly Formed Iminium
Complete Geometry Control

- Can imidazolidinone catalyst function as a small molecule aldolase

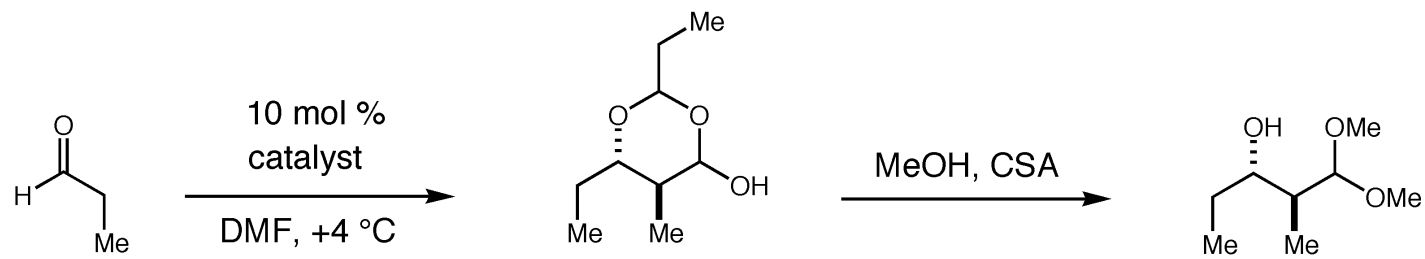


Imidazolidinone performs as a small molecule aldolase mimic

Valuable new method to access aldolate architecture



■ Trimerization of propionaldehyde



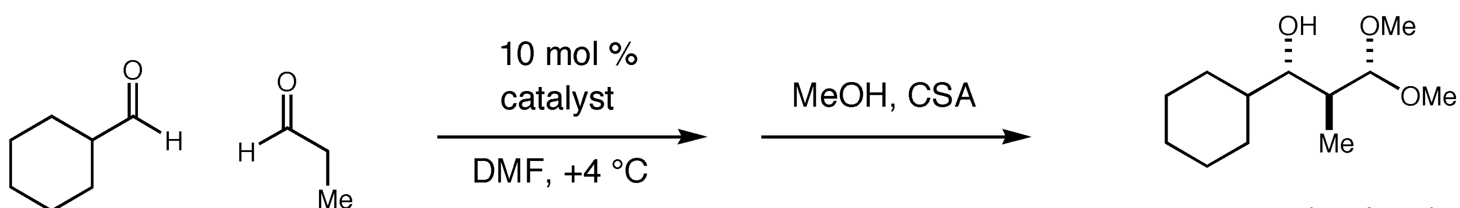
3 equiv.

86% yield

4:1 (*anti*:*syn*)

94% ee

■ Cross coupling to non-enolizable aldehydes



2 equiv.

5:1 (*anti*:*syn*)

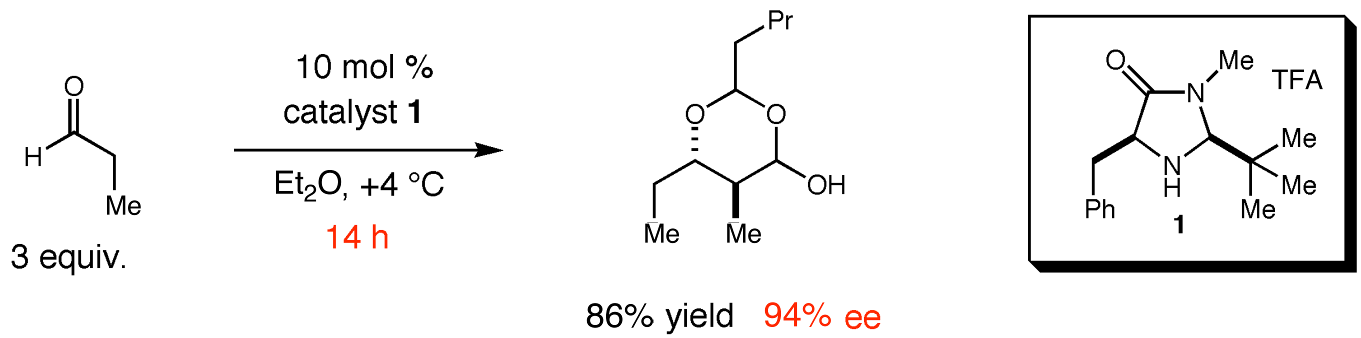
81% yield 97% ee

Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722.

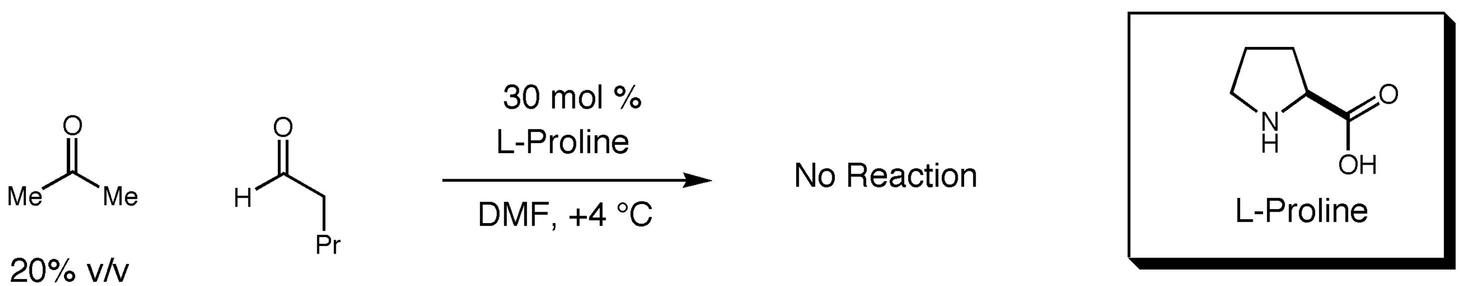
Why does Imidazolidinone perform well, yet Proline is unsuccessful

Why does the proline reaction work with isobutyraldehyde but not pentanal

■ Aldehyde–Aldehyde Aldol with Imidazolidinone



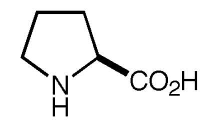
■ Reported Ketone–Aldehyde Aldol with Proline (Barbas, List, Lerner)



Can we determine if Proline forms enamines with aldehydes?

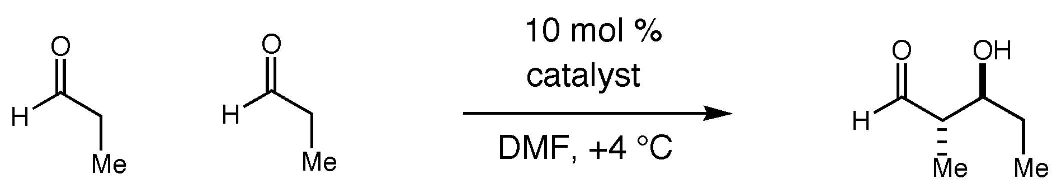
Proline and imidazolidinone provide complementary function

Studies are underway to determine mechanistic origin of phenomenon



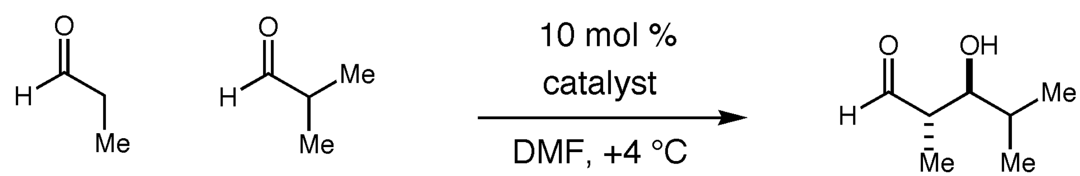
catalyst
(*S*)-proline

- Dimerization of propionaldehyde



80% yield
4:1 (*anti*:*syn*)
99% ee (*anti*)

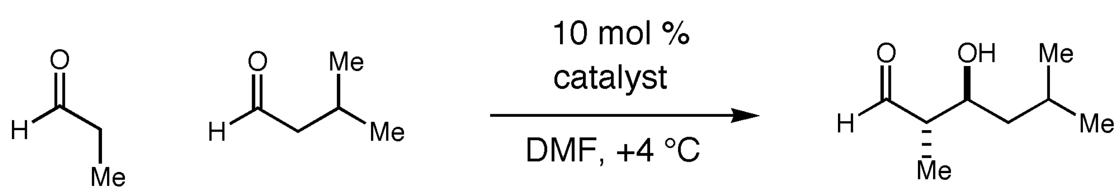
- Addition to non-enolizable aldehydes



1 equiv 2 equiv

82% yield
24:1 (*anti*:*syn*)
99% ee (*anti*)

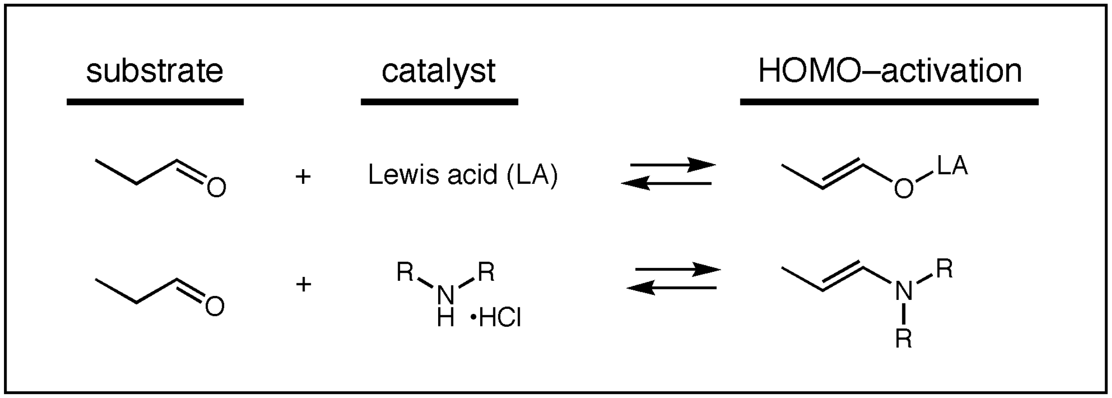
- Cross coupling of enolizable aldehydes



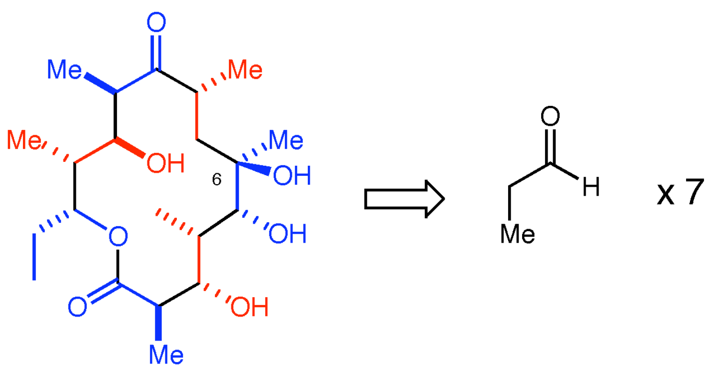
88% yield
5:1 (*anti*:*syn*)
97% ee (*anti*)

proline survey: with Northrup, A. B. J. Am. Chem. Soc. **2002**, *124*, 6798

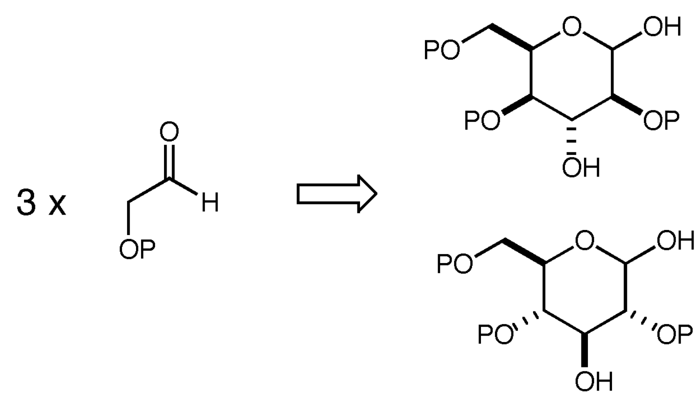
Development of a New Approach to the Enantioselective Aldehyde Aldol Reaction



■ Can we conduct organocatalytic aldehyde–aldehyde direct aldol reaction



erythronolide B: polyproionate synthesis

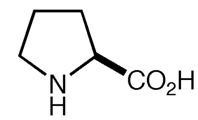


sugar synthesis

■ Control of aldehyde–aldehyde aldol reactions would allow rapid synthesis of key organic structures

Proline catalyzes α-oxy aldehyde dimerization

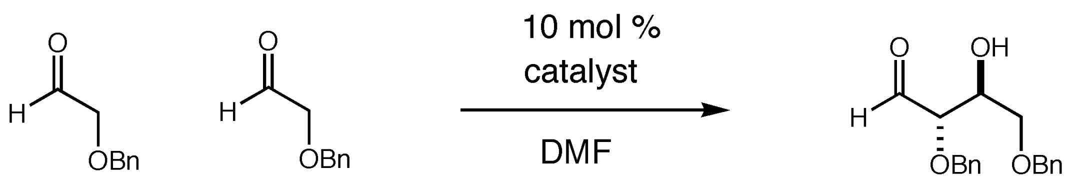
Rapid access to α,β,γ-trioxy butyraldehydes



catalyst

(*S*)-proline

- Dimerization of α-benzyloxyaldehydes

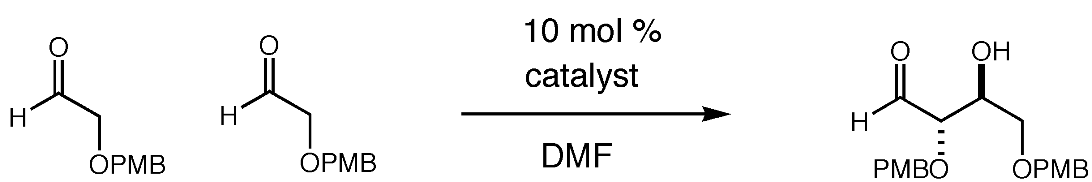


73% yield

4:1 (*anti*:*syn)*

98% ee (*anti*)

- Dimerization of α-PMB-oxyaldehydes

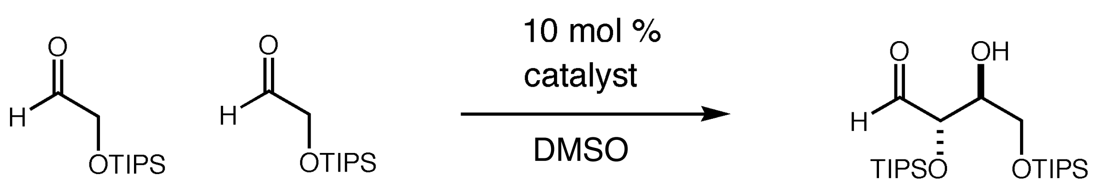


64% yield

4:1 (*anti*:*syn)*

97% ee (*anti*)

- Dimerization of α-silyloxyaldehydes



92% yield

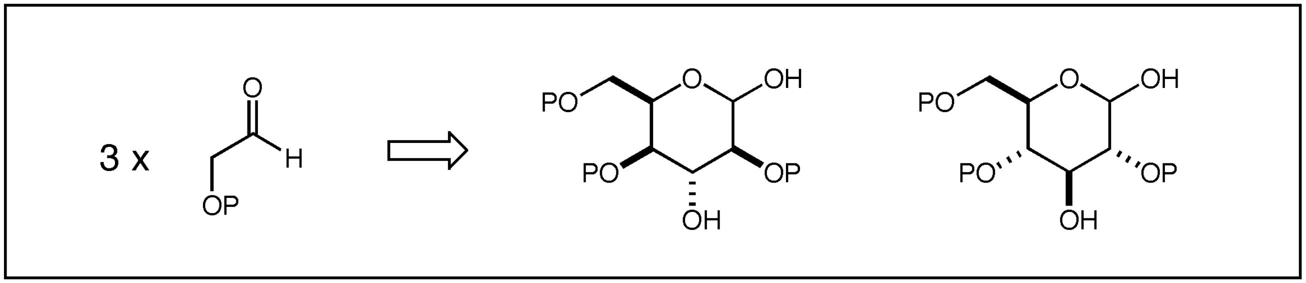
4:1 (*anti*:*syn)*

95% ee (*anti*)

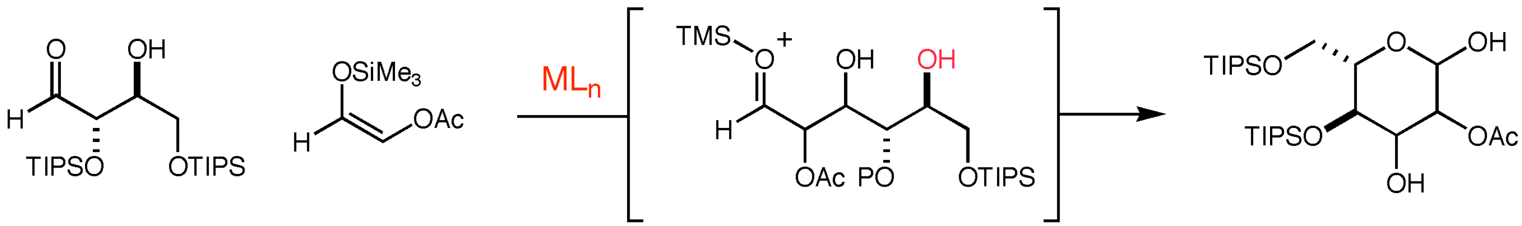
with Mangion, Northrup and Hettche. *Angew. Chem. Int. Ed.* **2004,** *43,* 2152

Development of a New Approach to the Enantioselective Carbohydrate Synthesis

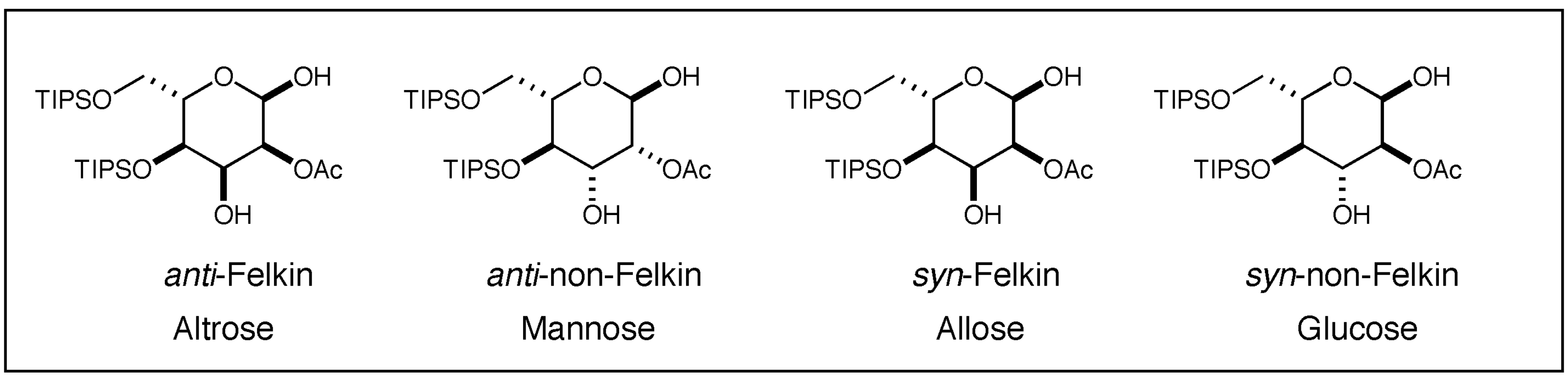
- Aldehyde–aldehyde aldol reactions allows conceptually new approach to carbohydrate synthesis



- Can we use a combination of organo and metal catalysis to rapidly generate carbohydrates



8 possible isomers



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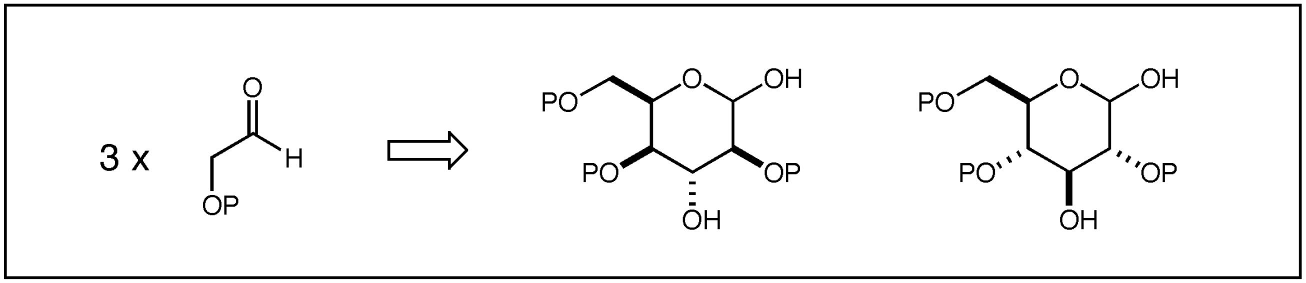

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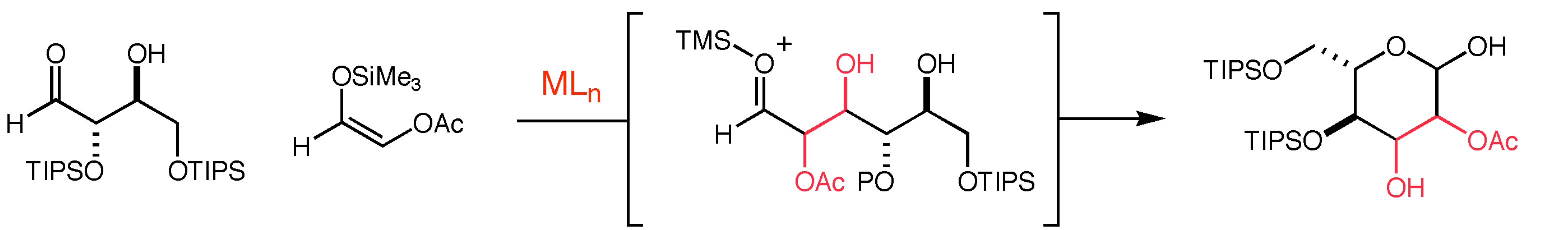

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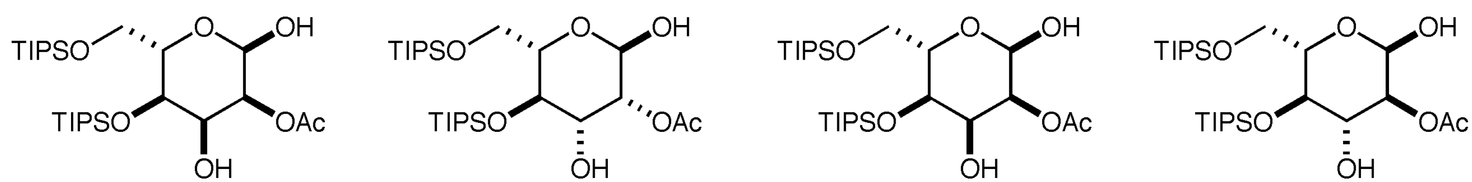
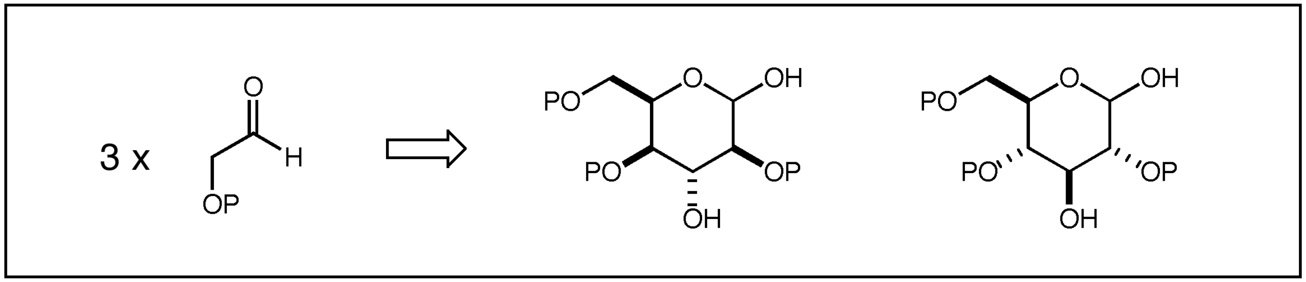
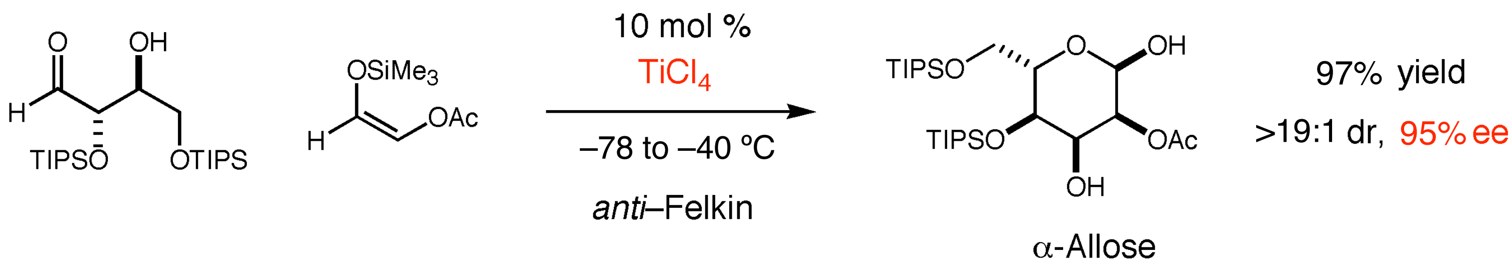


anti-Felkin Altrose | *anti*-non-Felkin Mannose | *syn*-Felkin Allose | *syn*-non-Felkin Glucose

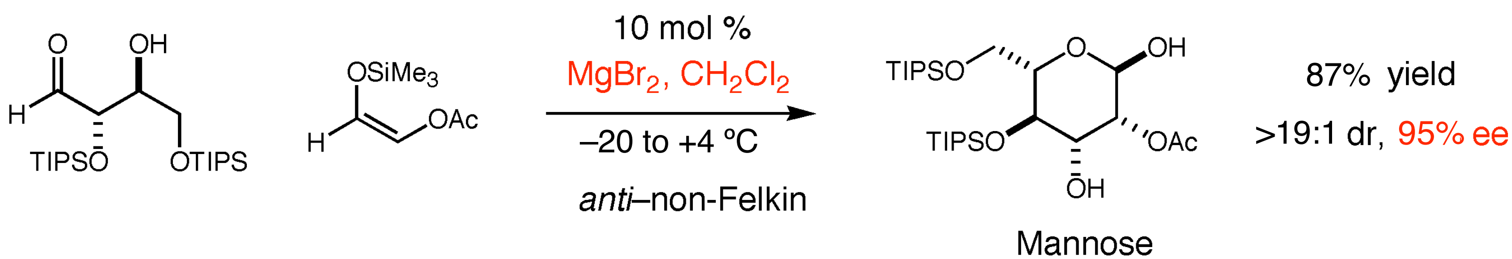
Development of a New Approach to the Enantioselective Carbohydrate Synthesis



- Synthesis of fully differentiated Allose in two chemical steps

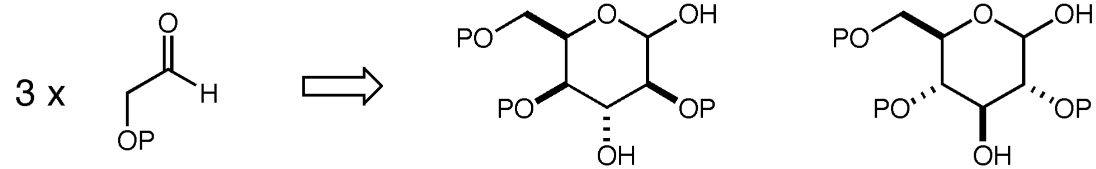


- Synthesis of fully differentiated Mannose in two chemical steps

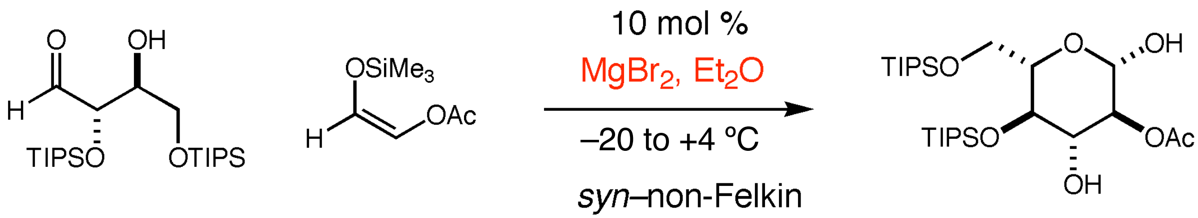


Merging catalysis technologies allows enantio- and diasteroselective access to carbohydrates

Development of a New Approach to the Enantioselective Carbohydrate Synthesis



■ Synthesis of fully differentiated Glucose in two chemical steps

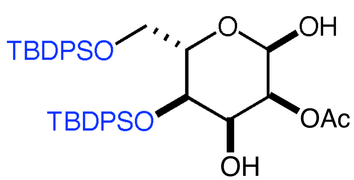


Glucose

79% yield

10:1 dr, 95% ee

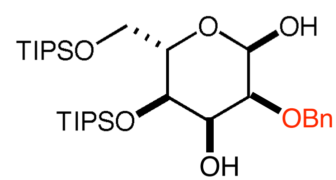
■ Two-Step Strategy is Compatable with a Variety of Protecting Groups



86% yield

>19:1 dr, 96% ee

allose

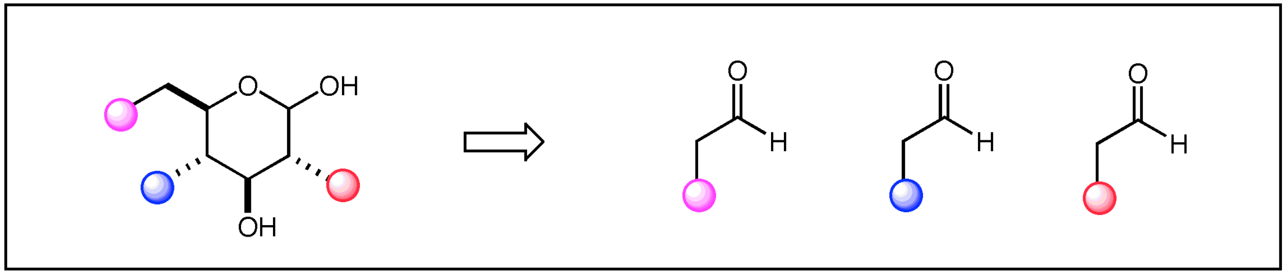


83% yield

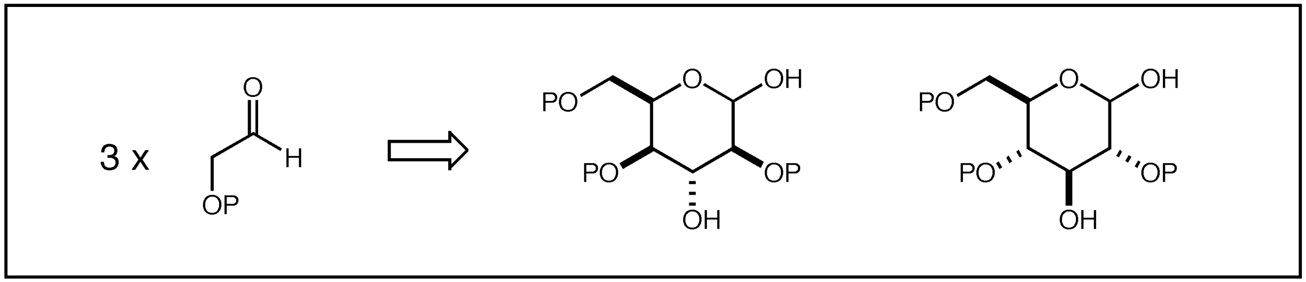
>19:1 dr, 95% ee

allose

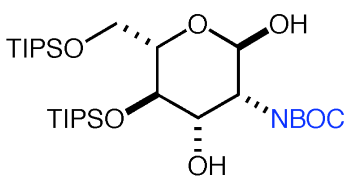
Two-Step Construction of Carbohydrates with Atomic Mutations



Development of a New Approach to the Enantioselective Carbohydrate Synthesis



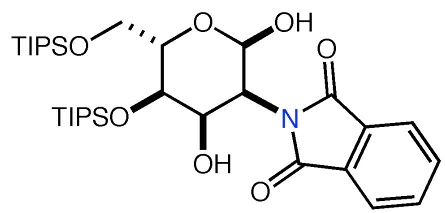
- Synthesis of fully differentiated mannosamine in two chemical steps



74% yield

10:1 dr, 95% ee

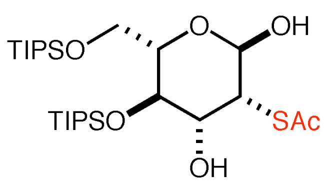
α-Mannosamine



82% yield

12:1 dr, 96% ee

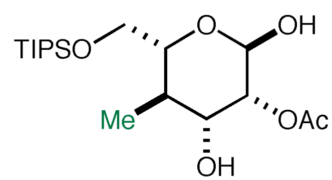
α-2-Amino-Allose



71% yield

19:1 dr, 95% ee

α-Thiomannose



68% yield

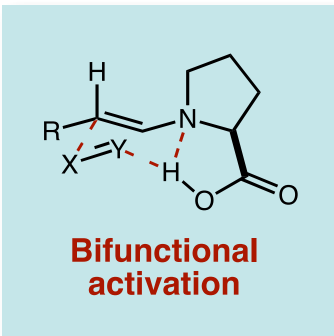
19:1 dr, 99% ee

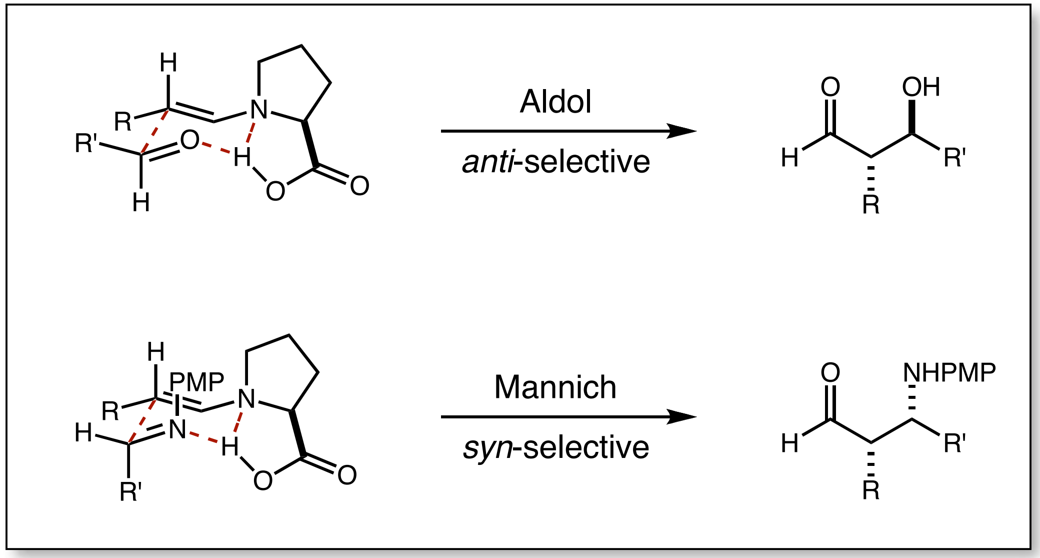
α-4-carboallose

with Northrup, *Science* **2004**, *305*, 1752

Predictable Stereochemistry for Aldol and Mannich

■ Use of proline or proline-type catalysts leads to *anti*-aldol or *syn*-Mannich





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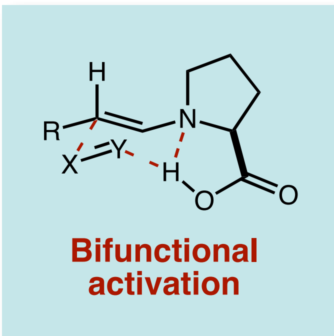
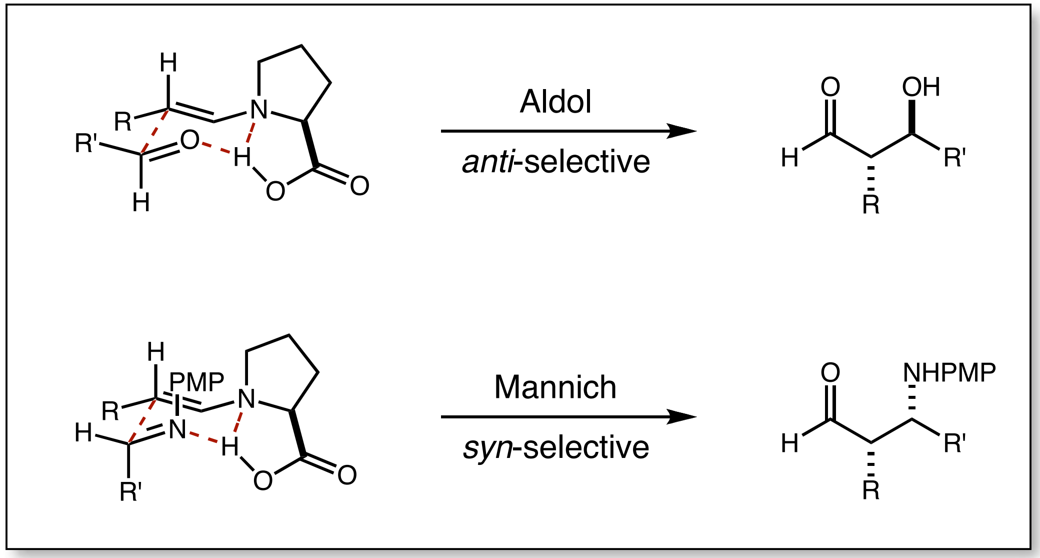
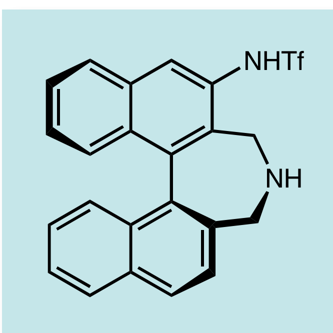
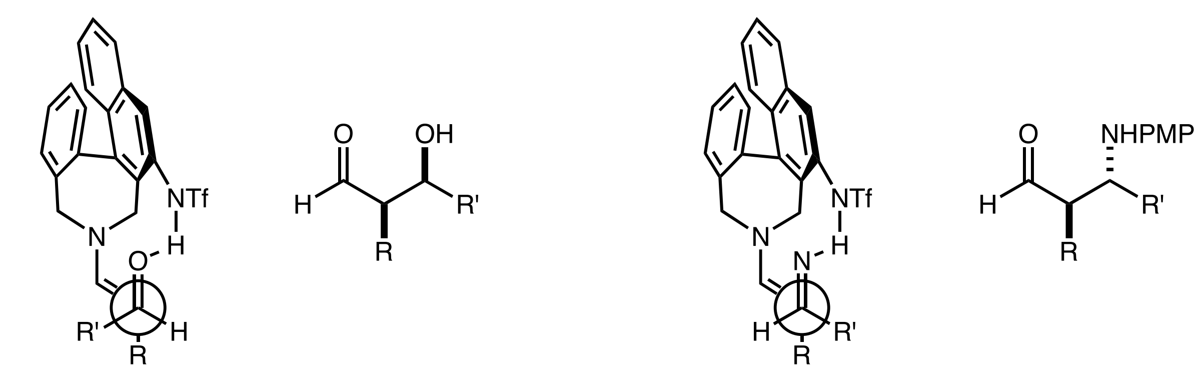




■ Maruoka's binaphthyl catalyst is a significant advance to access opposite stereoisomers



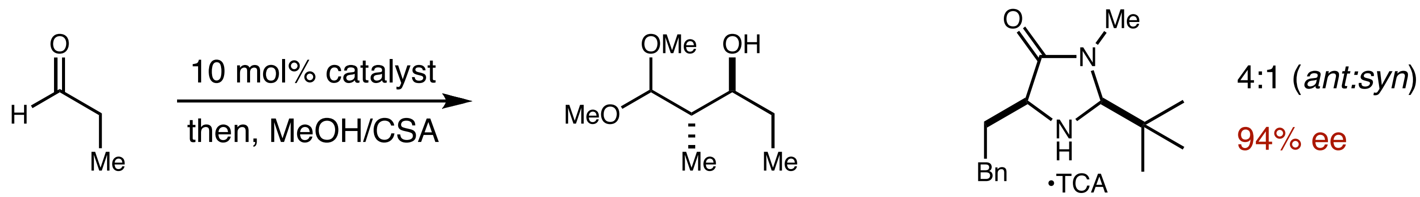


Syn-aldol: *ACIEE* **2004**, *43*, 6722

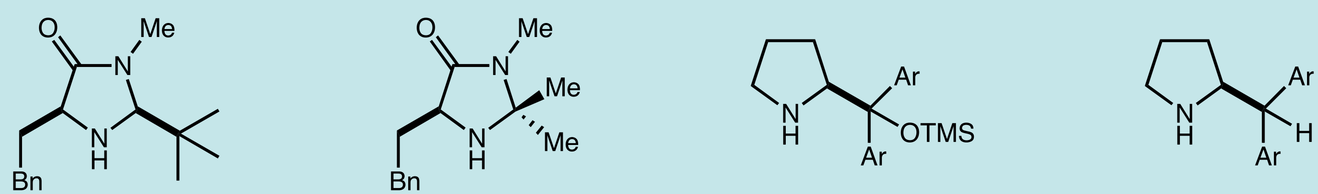
Anti-Mannich: *JACS* **2005**, *127*, 16408

Monofunctional Enamine Catalysis

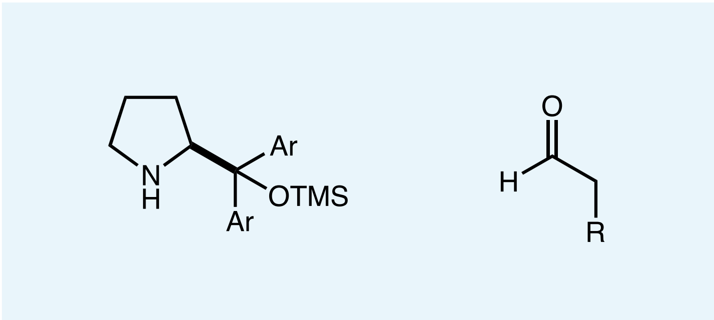
- Bifunctional activation is not absolutely required for selective catalysis



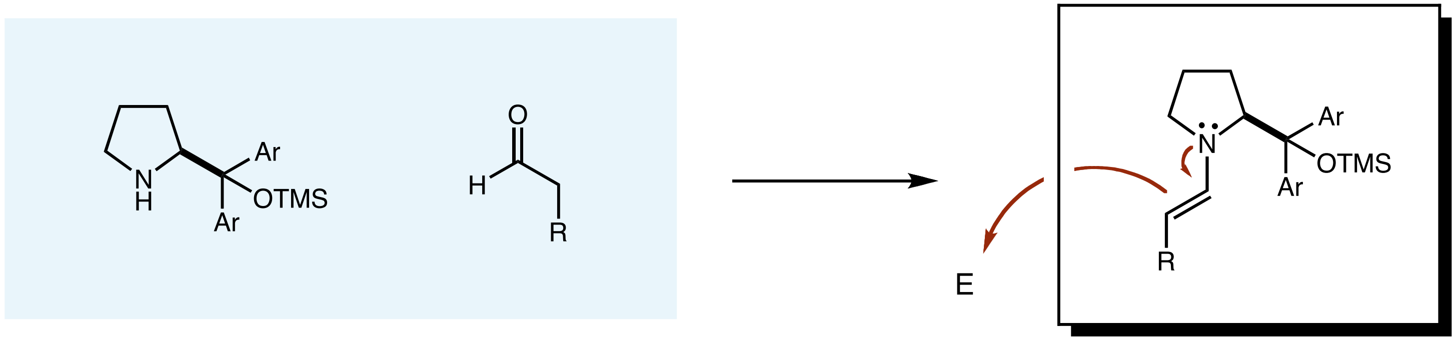
- Imidazolidinone and Jørgensen-type frameworks have been widely applied



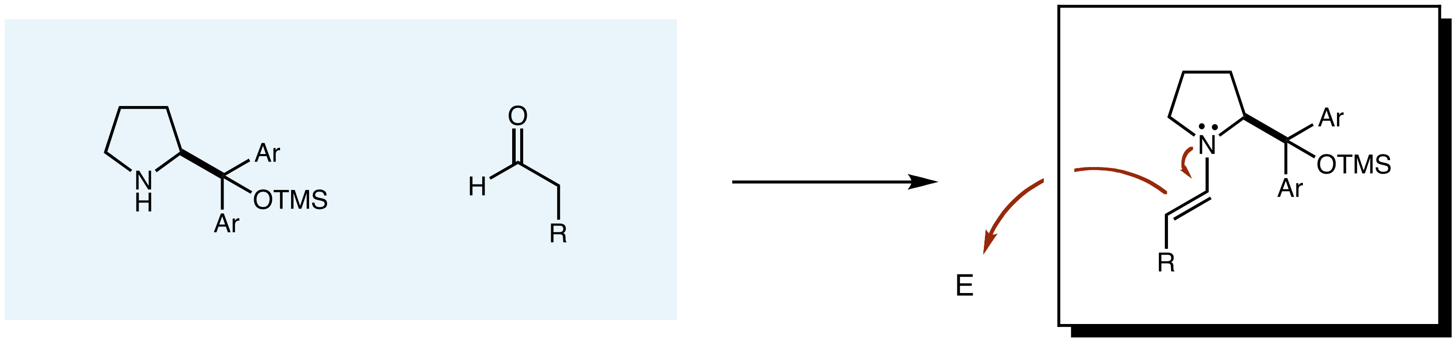
Enamine Chemistry with Jørgensen's Catalyst

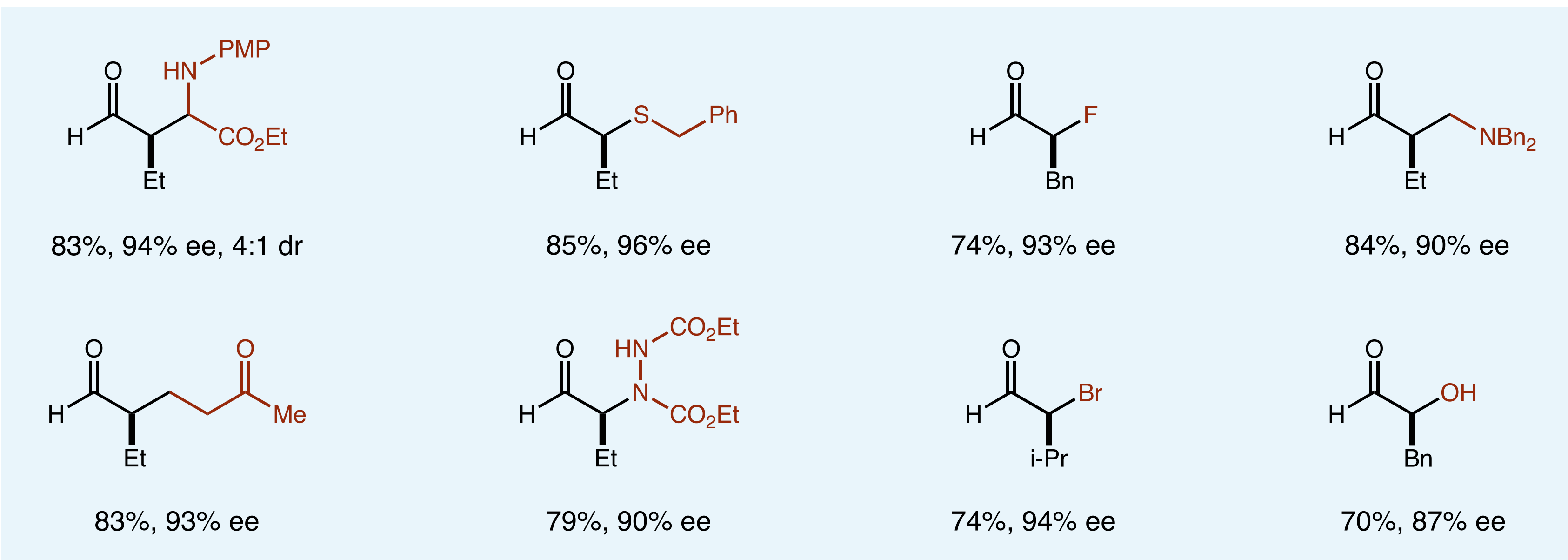


Enamine Chemistry with Jørgensen's Catalyst



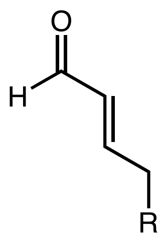
Enamine Chemistry with Jørgensen's Catalyst

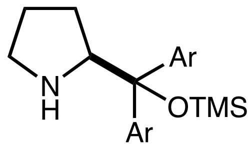




Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kaersgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.
Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804.
Ibrahem, I.; Zhao, G.-L.; Sunden, H.; Córdova, A. *Tettrahedron Lett.* **2006**, *47*, 4659.

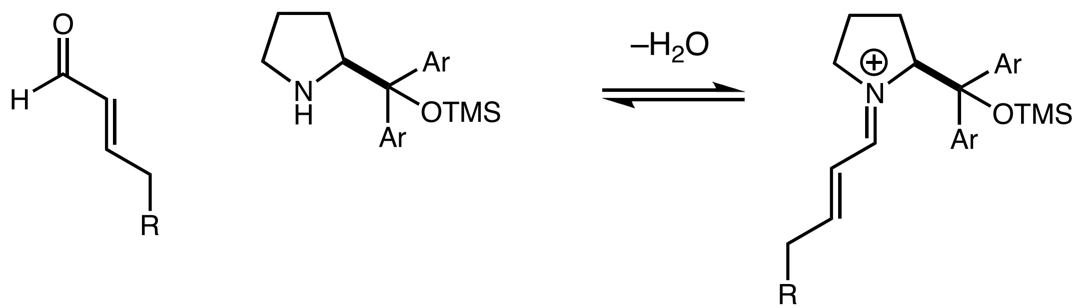
Dienamine Activation: γ-Amination of Enals





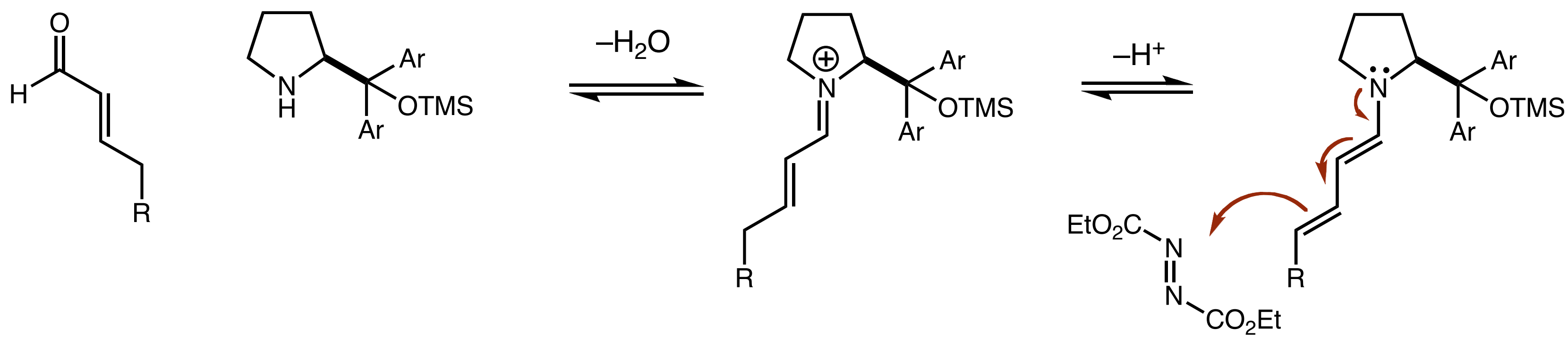
Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

Dienamine Activation: γ-Amination of Enals



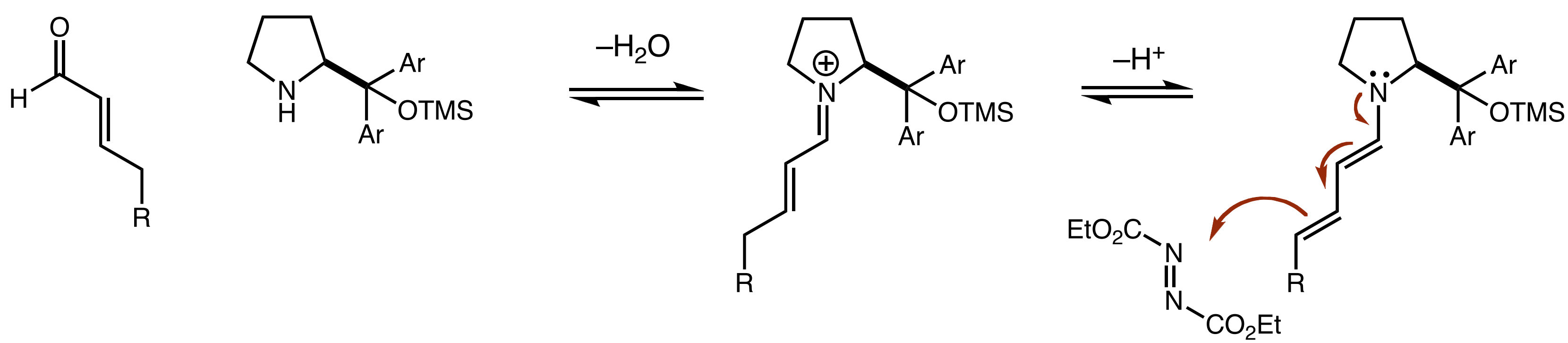
Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

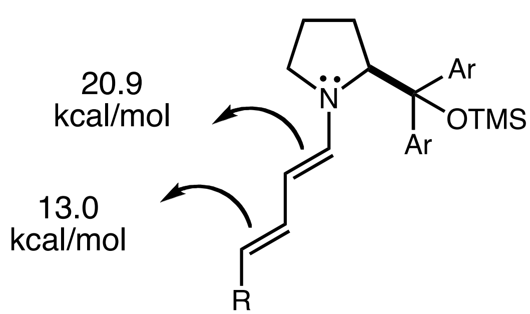
Dienamine Activation: γ-Amination of Enals



Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

Dienamine Activation: γ-Amination of Enals





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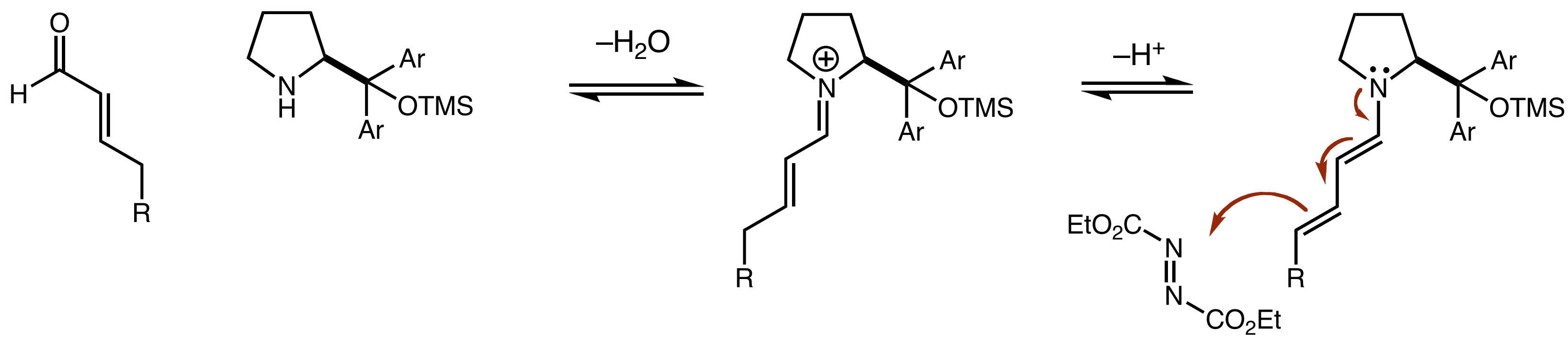

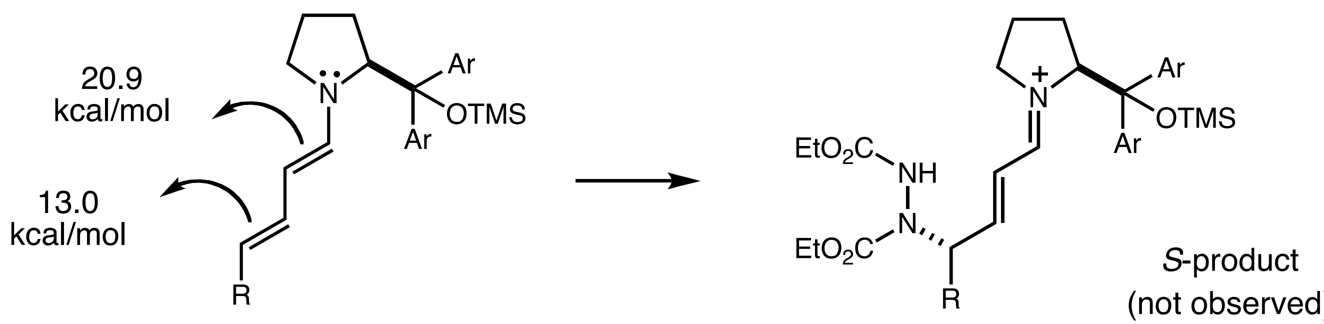

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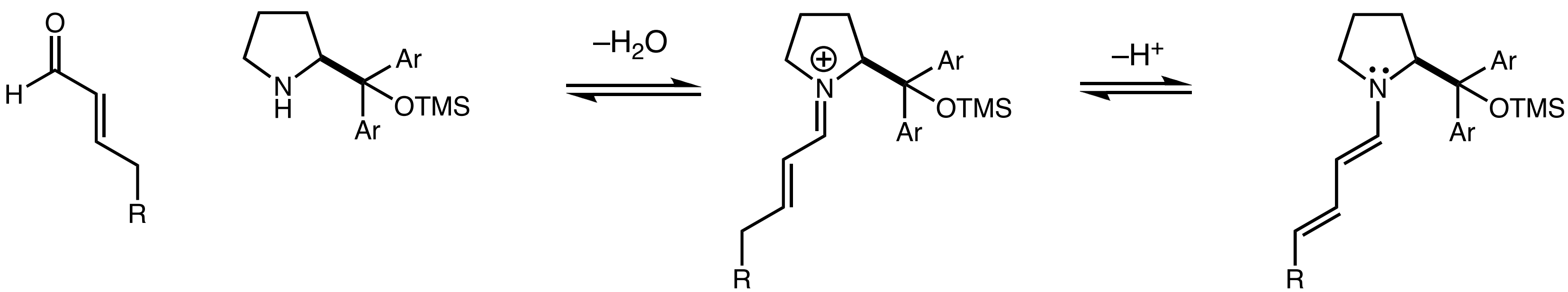

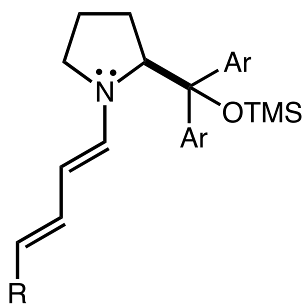

0 kcal/mol

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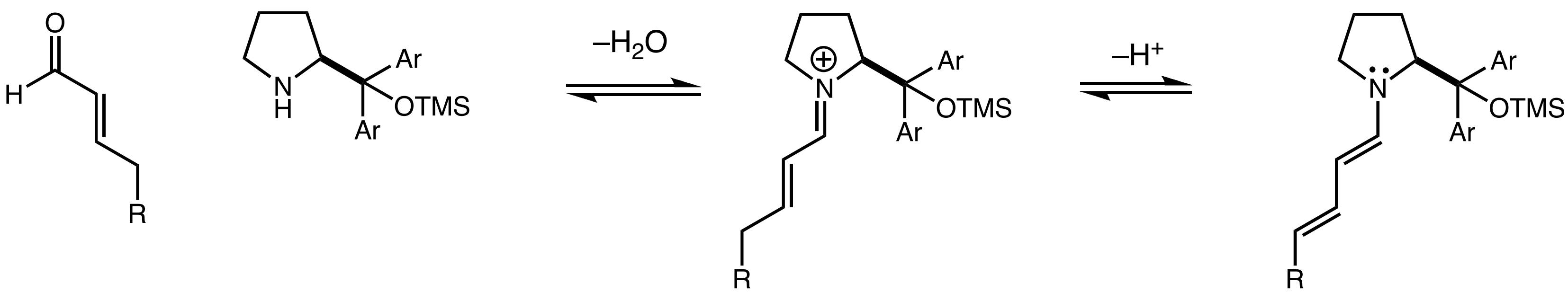

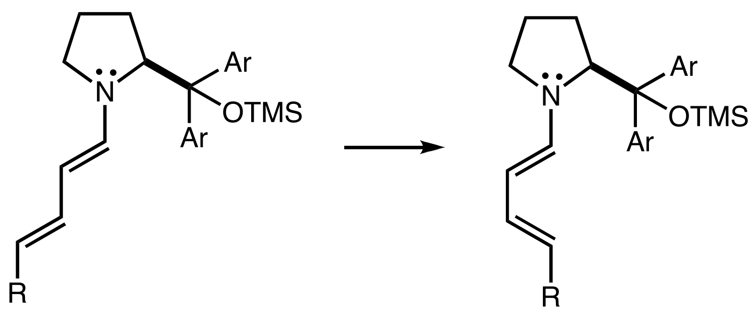

0 kcal/mol

7.5 kcal/mol

Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

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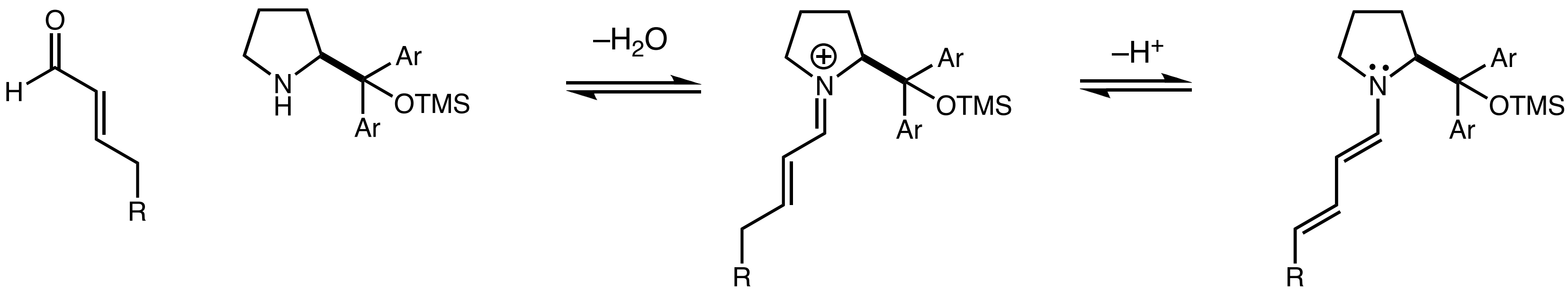
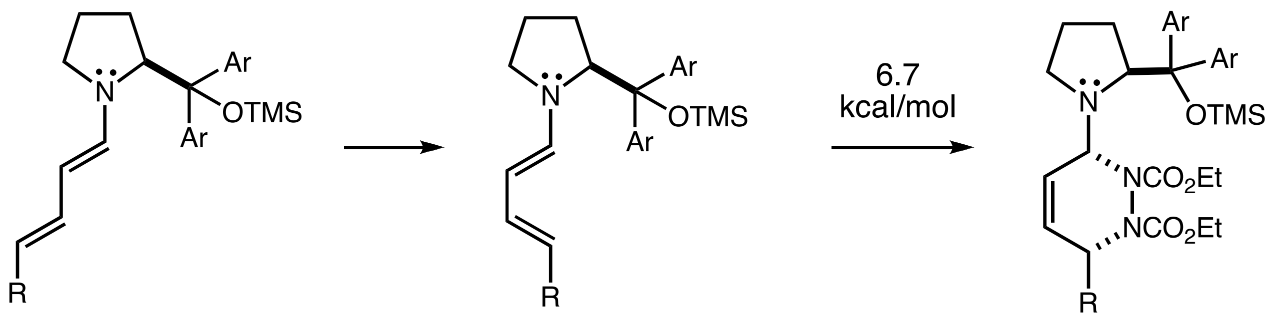
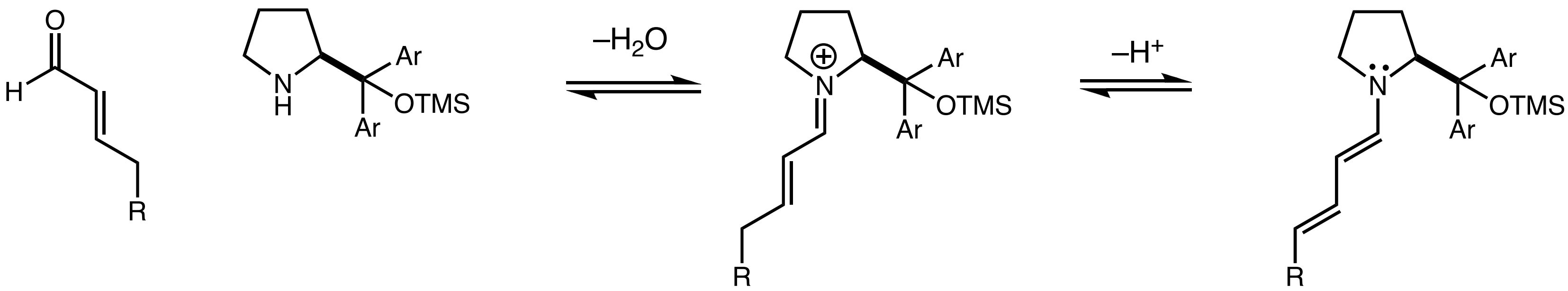


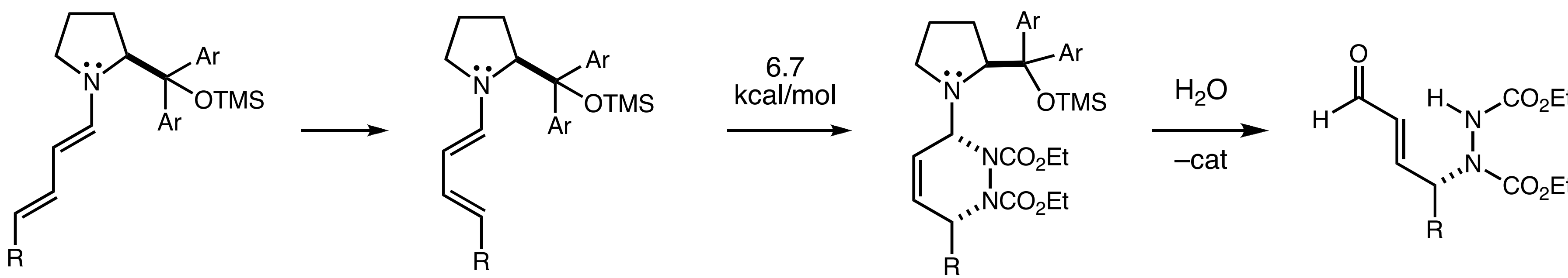


0 kcal/mol | 7.5 kcal/mol | –23.5 kcal/mol

Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

Dienamine Activation: γ-Amination of Enals





0 kcal/mol

7.5 kcal/mol

–23.5 kcal/mol

R–product

Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

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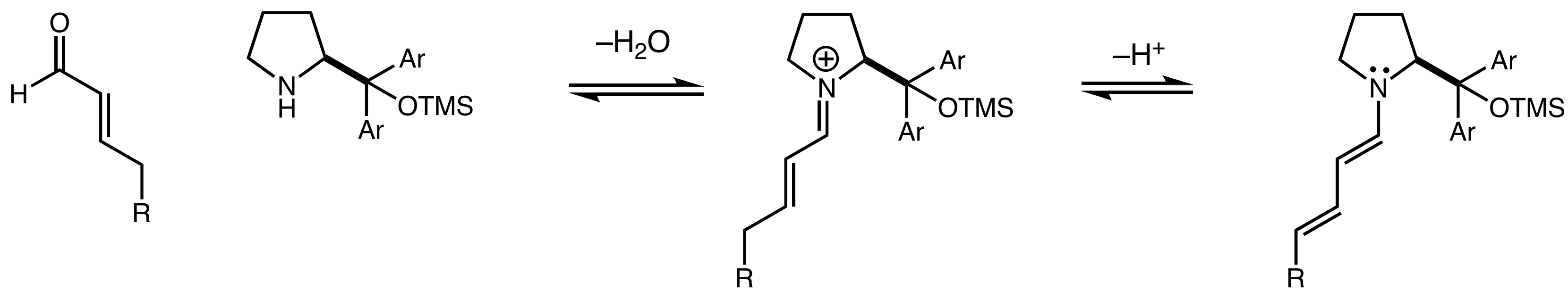
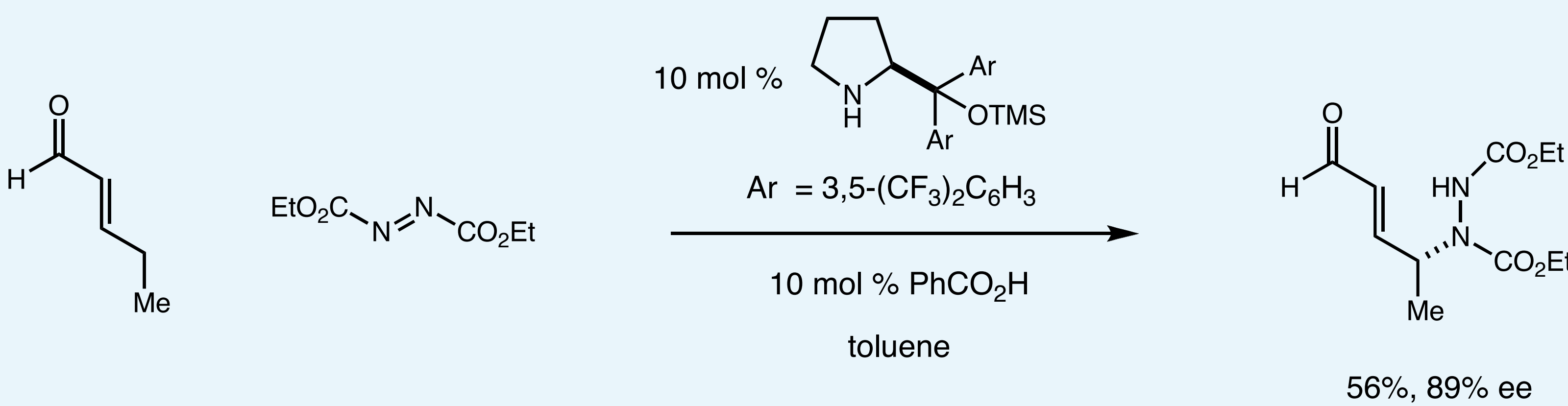
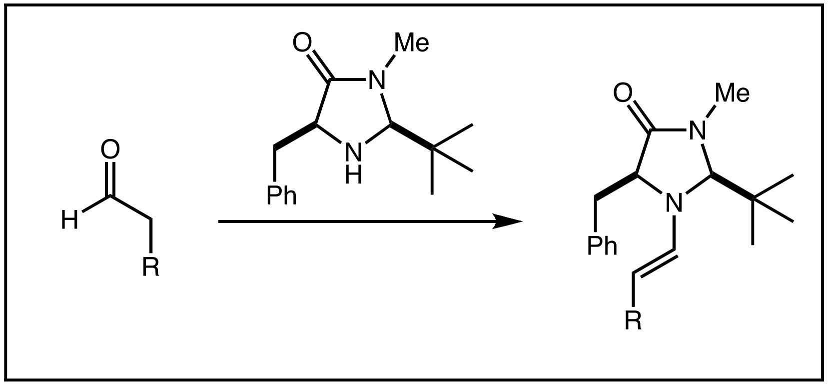


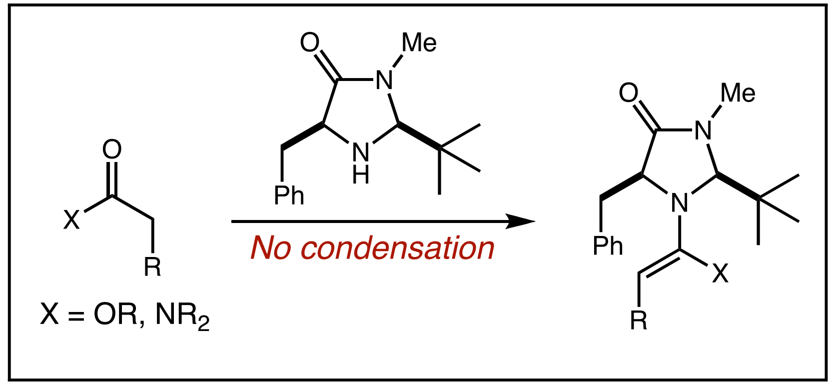


Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

HOMO-Raising Catalysis Beyond Enamine Activation

■ Enamine activation is extremely powerful, but does not extend to esters, amides, etc.





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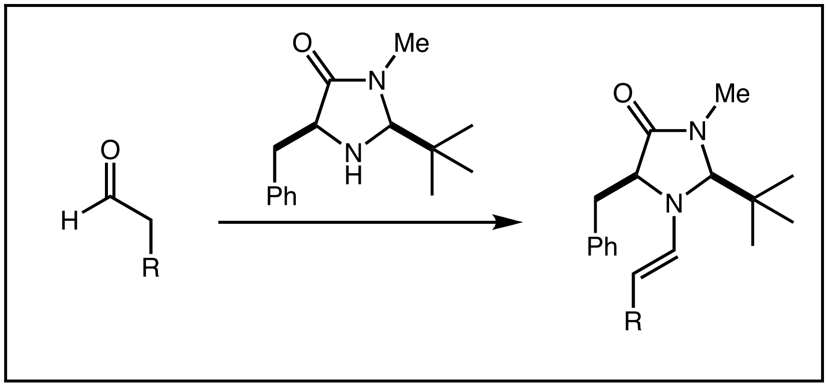
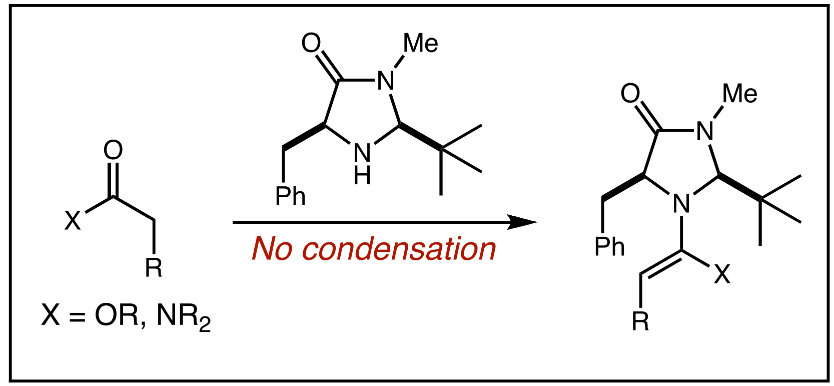
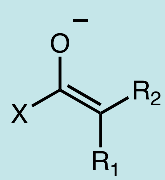
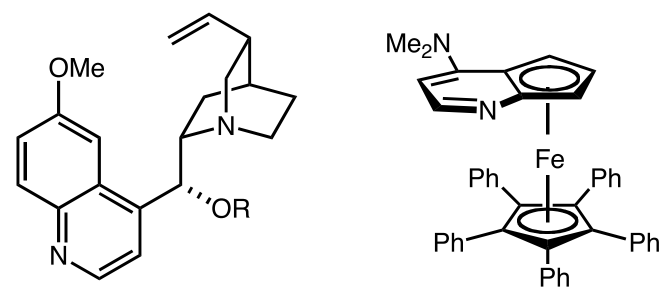






Is there an alternative way to generate chiral ester enolate equivalents?

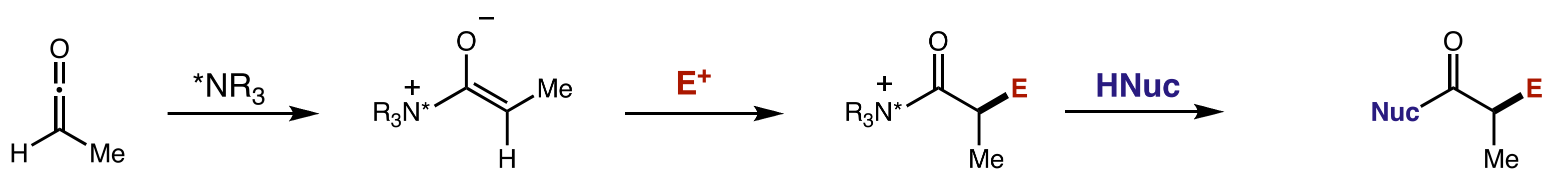


Chiral Ammonium Catalysis

Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596

Ketenes as Precursors for Ammonium Enolates

- Attack of nucleophilic tertiary amine on ketene leads directly to ammonium enolate



Enantioselective ester/amide
α-functionalization

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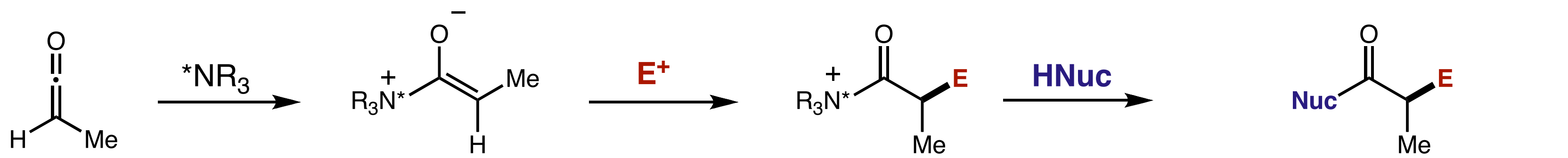
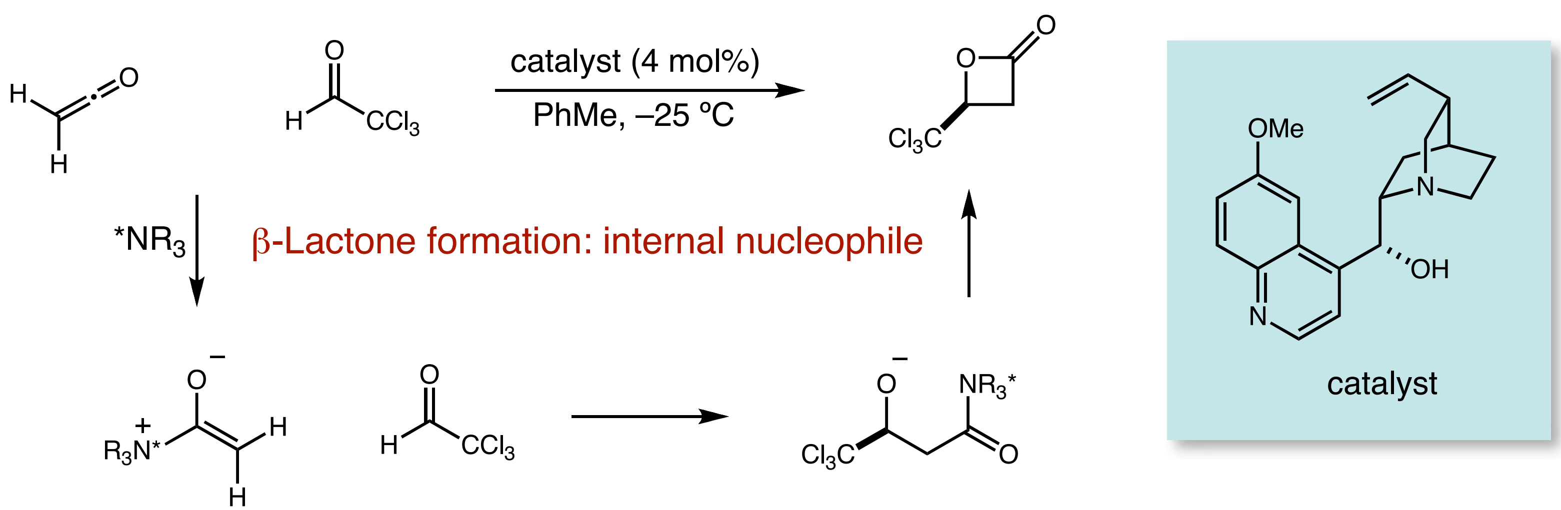


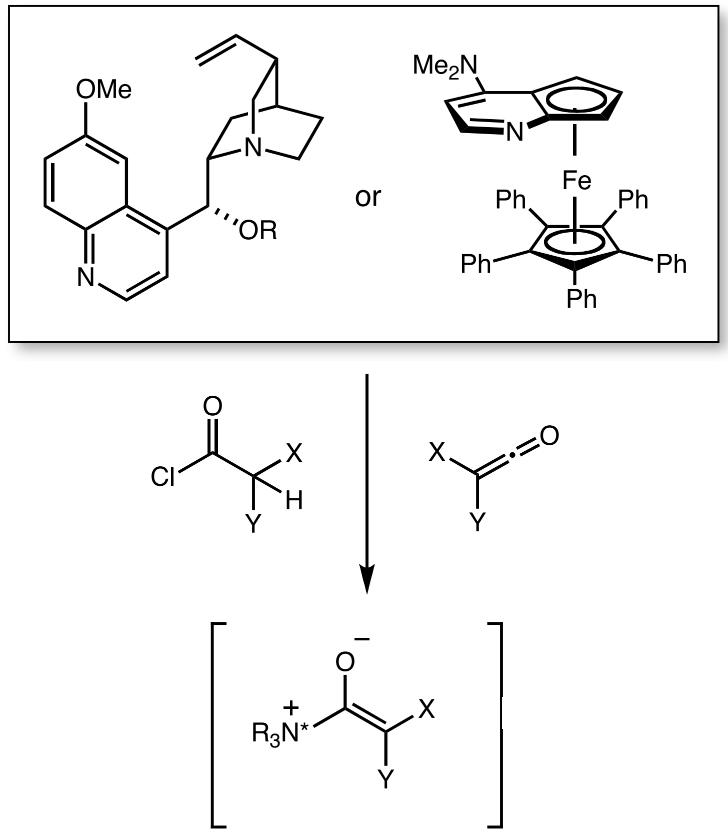
Enantioselective ester/amide
α-functionalization

■ First asymmetric example by Wynberg in 1982 (first racemic by Sauer in 1947)



Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166
Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444

Ammonium Enolates as Versatile Synthetic Intermediates



Gaunt, M. J. Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596
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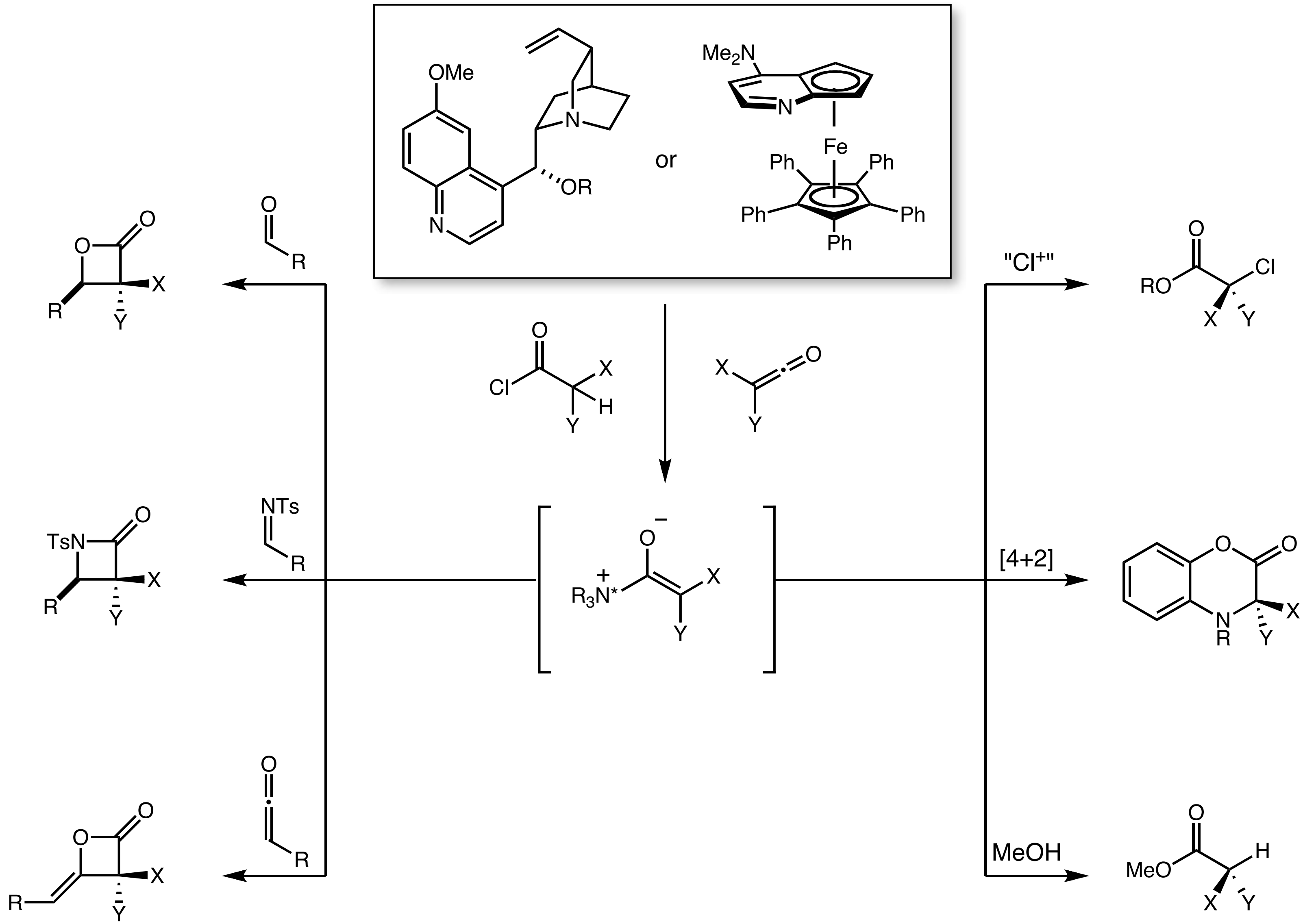

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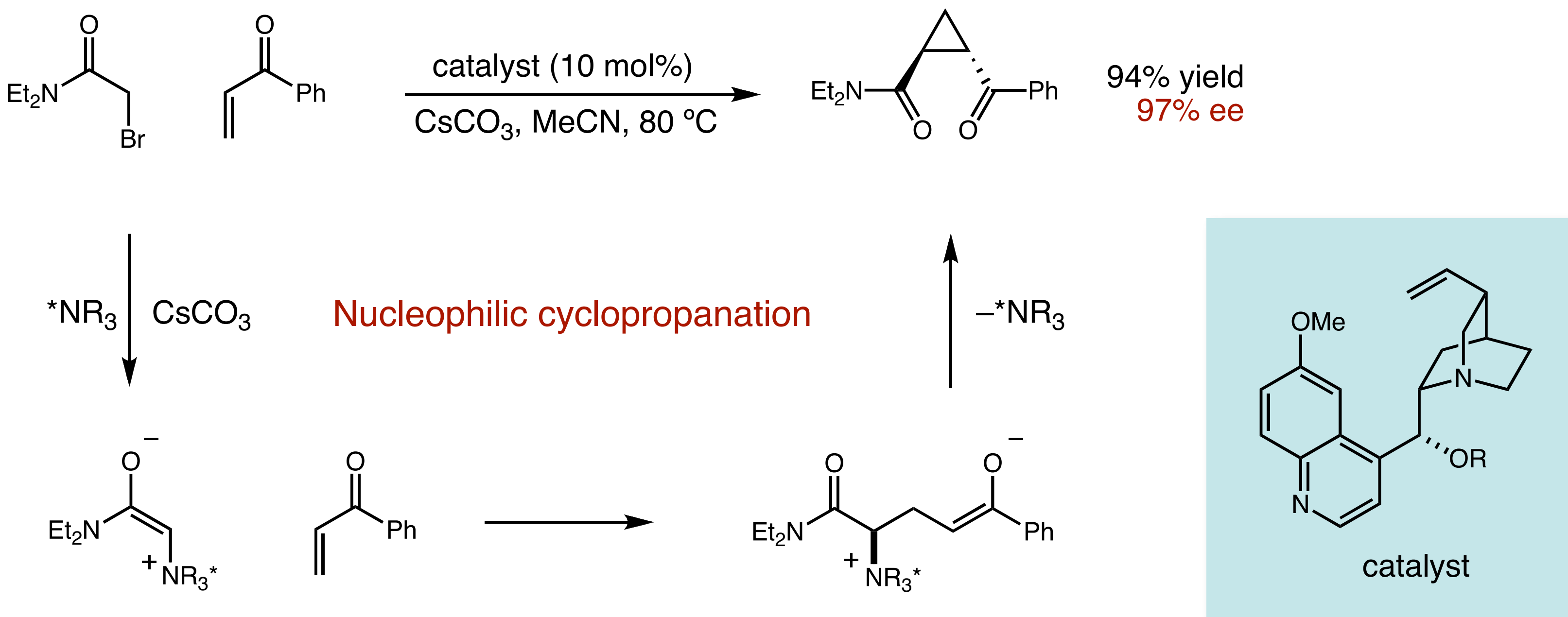
France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985

Alternative Methods to Access Ammonium Enolates

- Alkylation of α-bromocarbonyls lead to chiral ammonium ylides

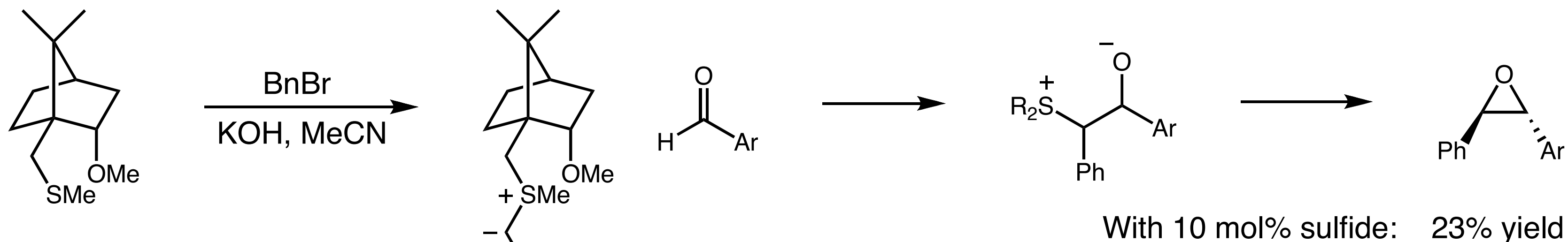


- Also applicable to Baylis-Hillman type reactivity

Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641

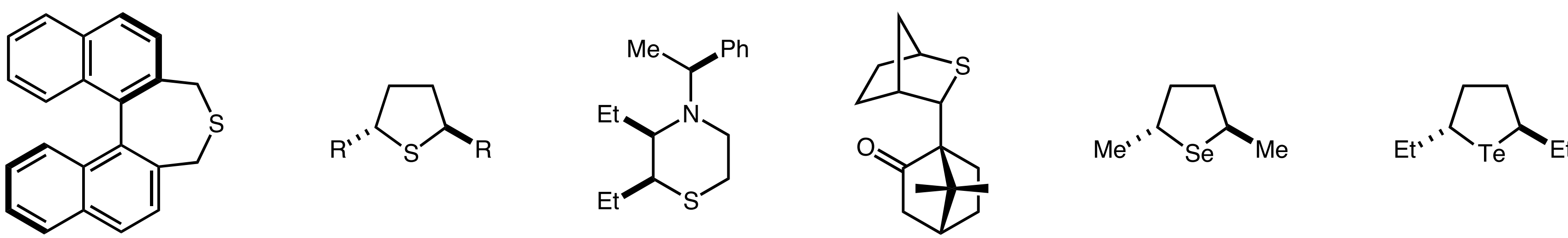
Asymmetric Ylides Formed from Chalcogenides

■ Combination with stronger bases/alkyl halides allows for asymmetric epoxide formation



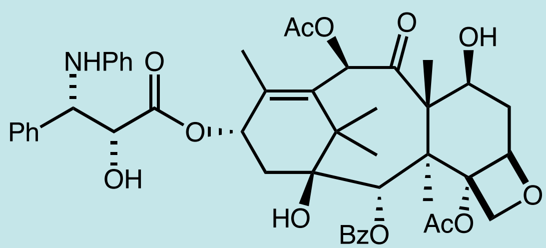
Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222

■ Vast array of structural types allows for epoxide, aziridine, cyclopropane formation, Baylis-Hillman



McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. A. *Chem. Rev.* **2007**, *107*, 5841

"The Taxol Problem" An illustrative example



Taxol

- Important ovarian, breast cancer treatment worldwide
- Originally available from Pacific Yew *Taxus Brevifolia* (extraction killed the source)

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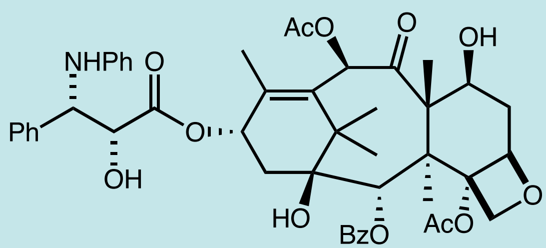

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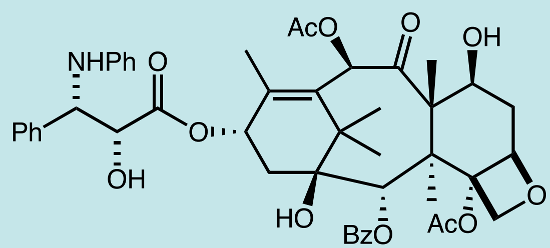

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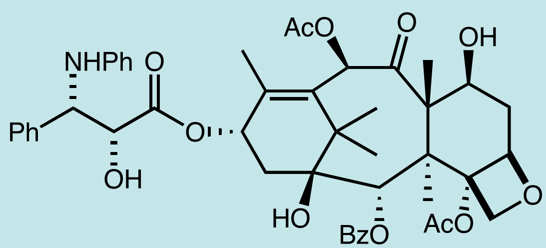
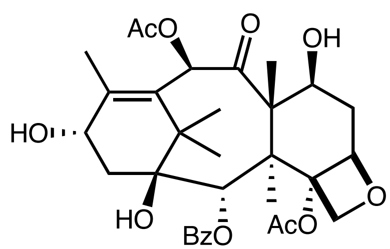


Taxol

11 Chemical steps ⇧ 7 isolation steps



10-deacetyl baccatin III (renewable source)

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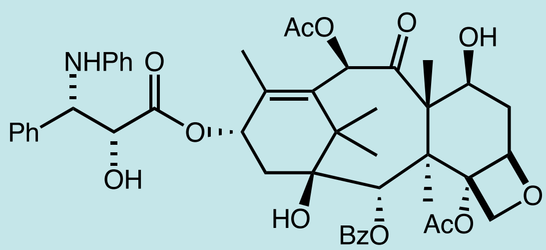

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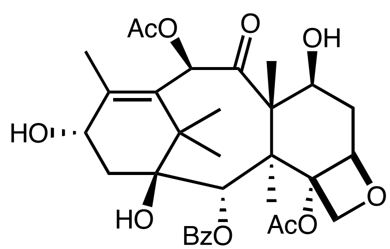

10-deacetyl baccatin III (renewable source)

- Now produced via fermentation from *Taxus Chinensis*

- What if the European or Chinese Yew did not produce baccatin in the pine needles?

The problem with a 40 step synthesis: Step Economy and Losses

- Why is chemical synthesis able to produce complexity on small scale but not large
  - For every step (operation) involved = exponential decrease in efficiency

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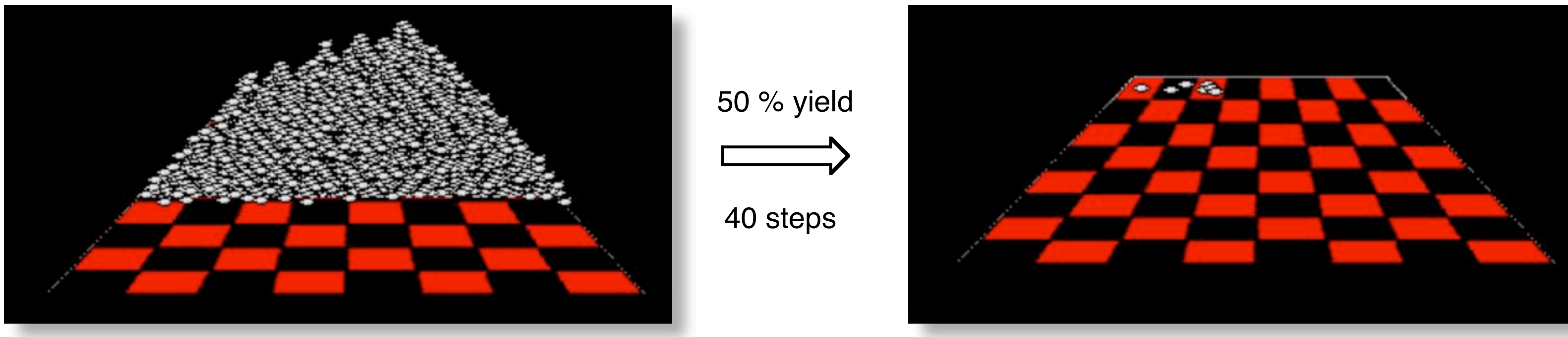

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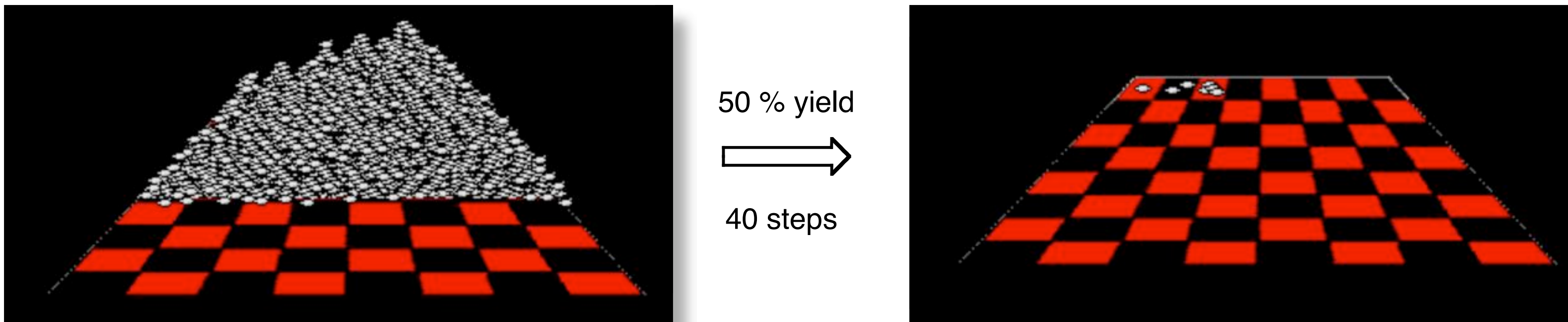
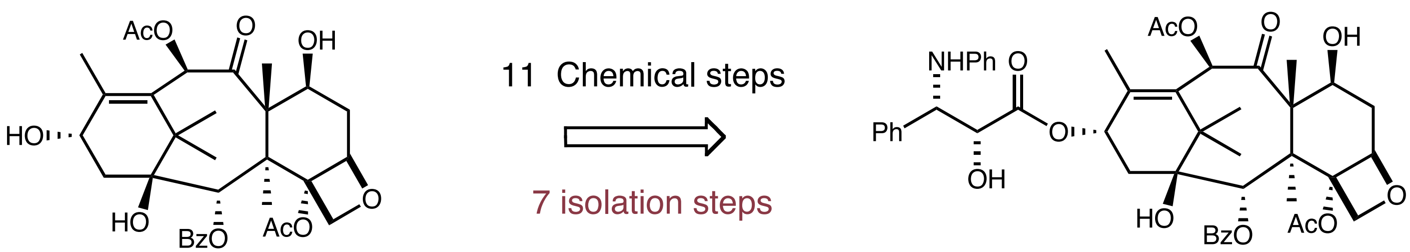


- Problems with taxol production arose from "stop and go" synthesis



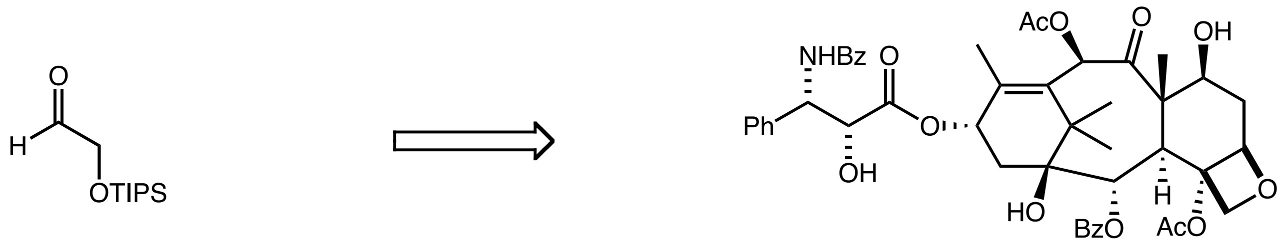
10-deacetyl baccatin III

Taxol

- "Stop and Go" isolation can greatly diminsh the overall efficiency of processes with high yielding steps

Benchtop Synthesis vs. Biosynthesis : Why is Nature Winning?

■ Nicolaou Synthesis of Taxol: Tour de force



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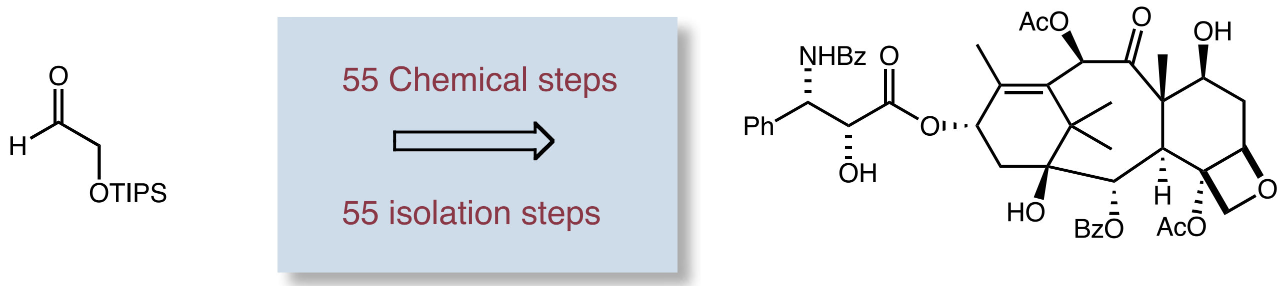

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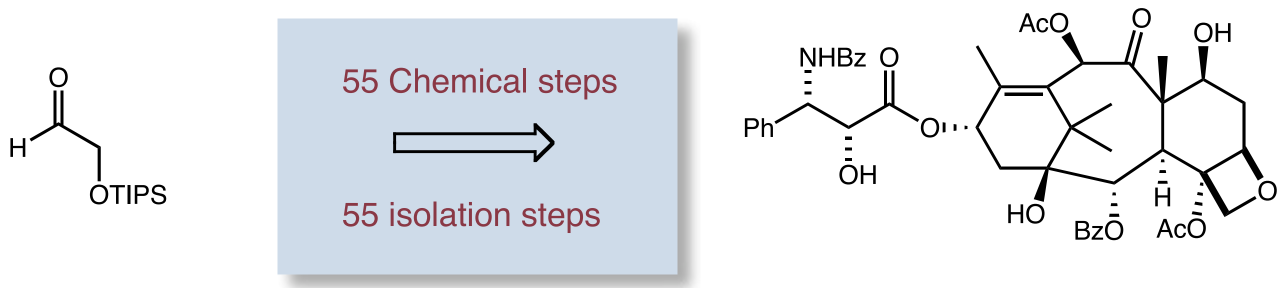
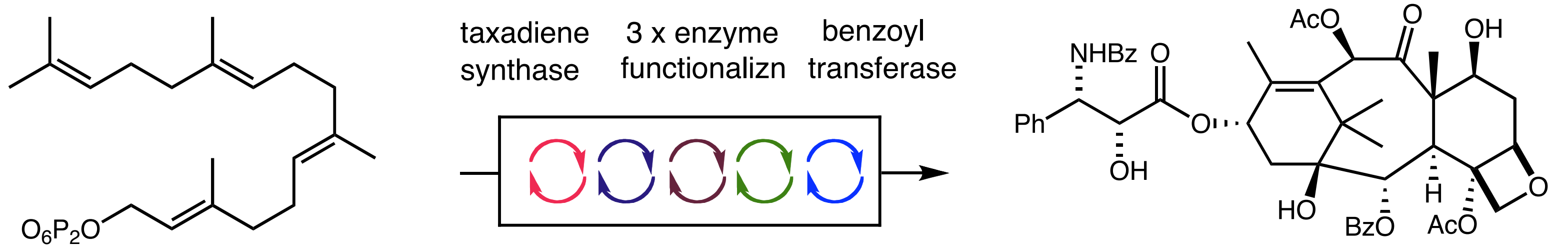


Taxol

■ Biology employs enzymatic cascade catalysis: Continuous process assembly lines



geranylgeranyl diphosphate

5 catalytic transformations
in one cascade process

Taxol

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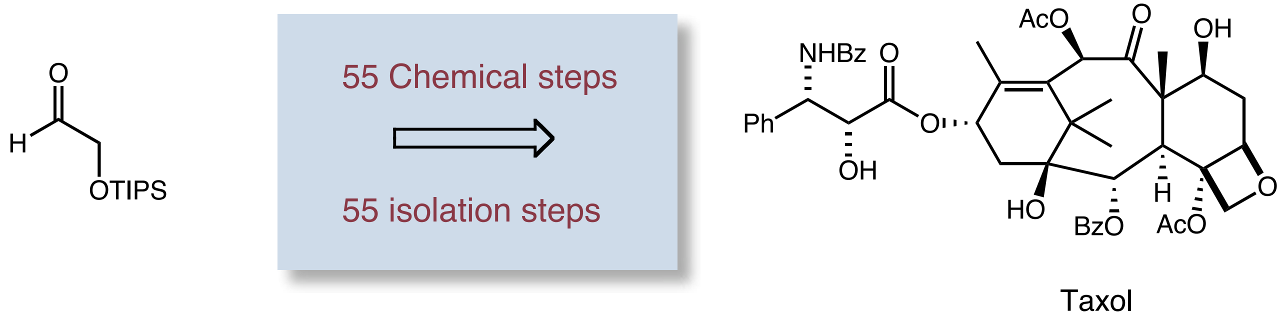

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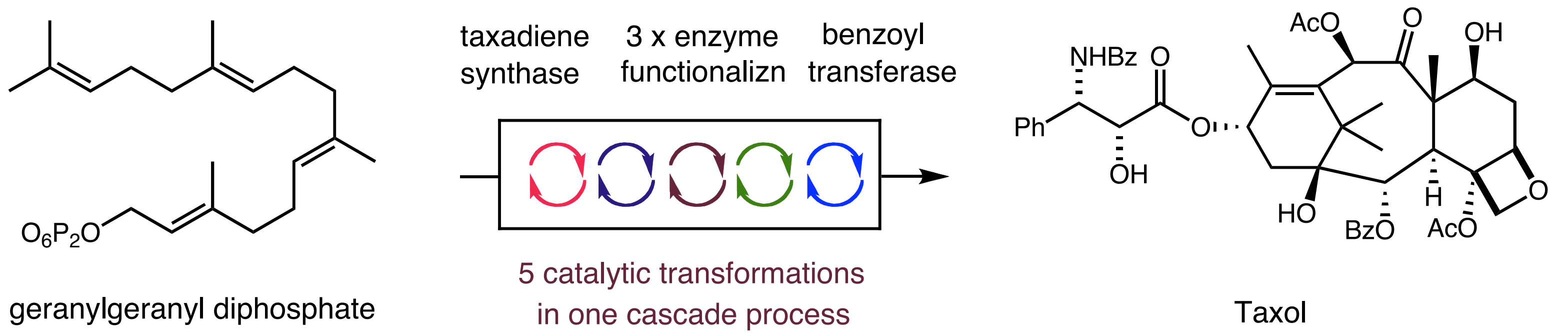
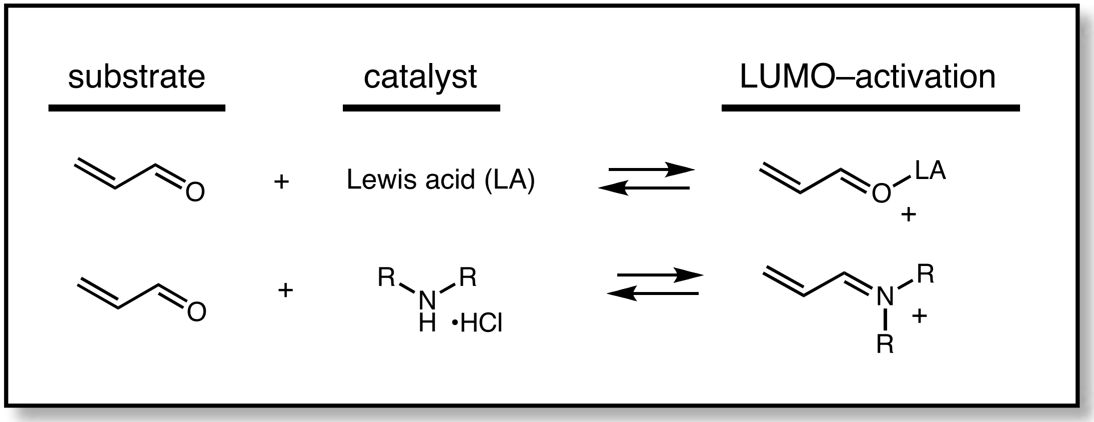
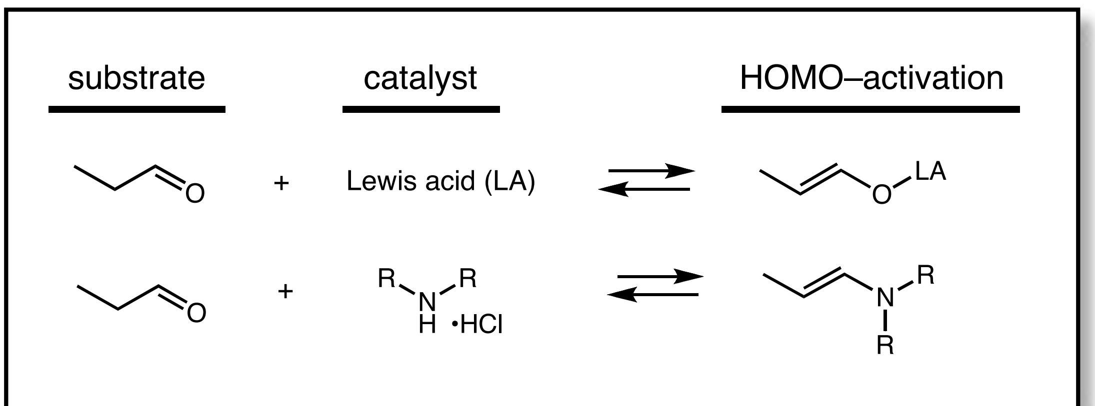


■ Why doesn't the field of chemical synthesis build complexity using cascade catalysis (biomimetic)

Design of Cascade–Catalysis Strategy: LUMO–HOMO Catalyst





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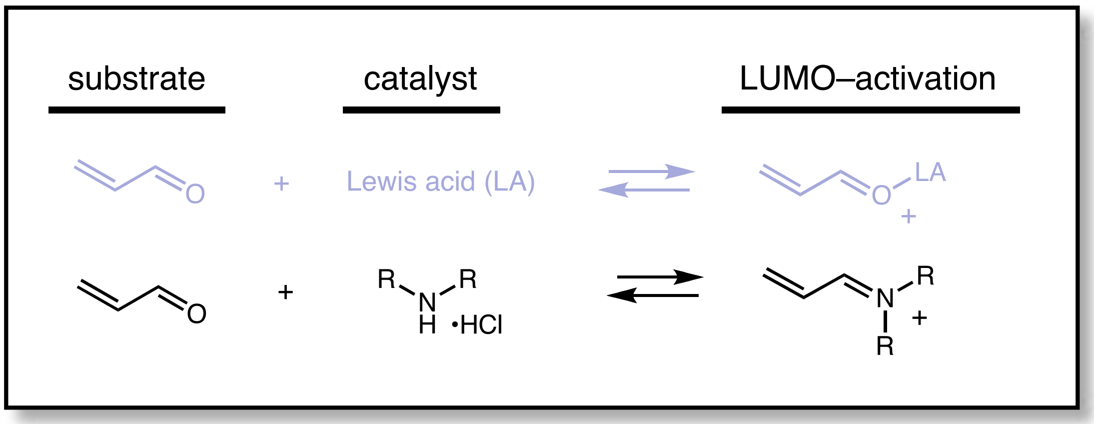
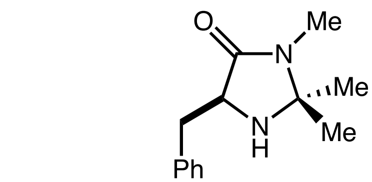
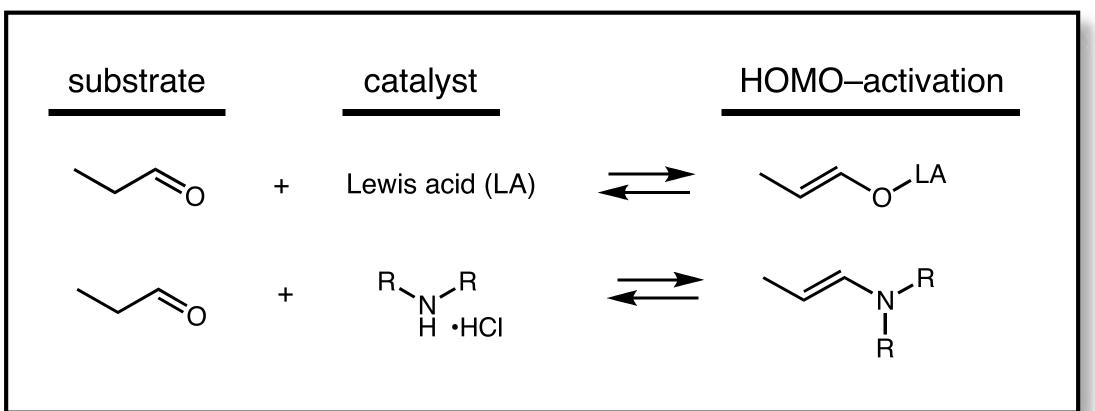




imidazolidinone
generation 1



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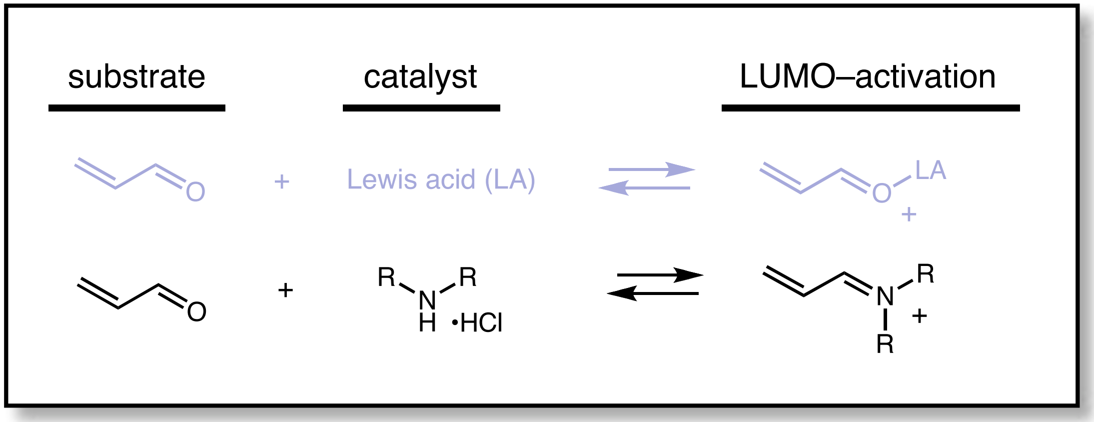

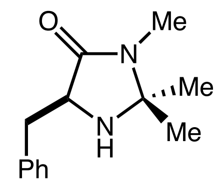

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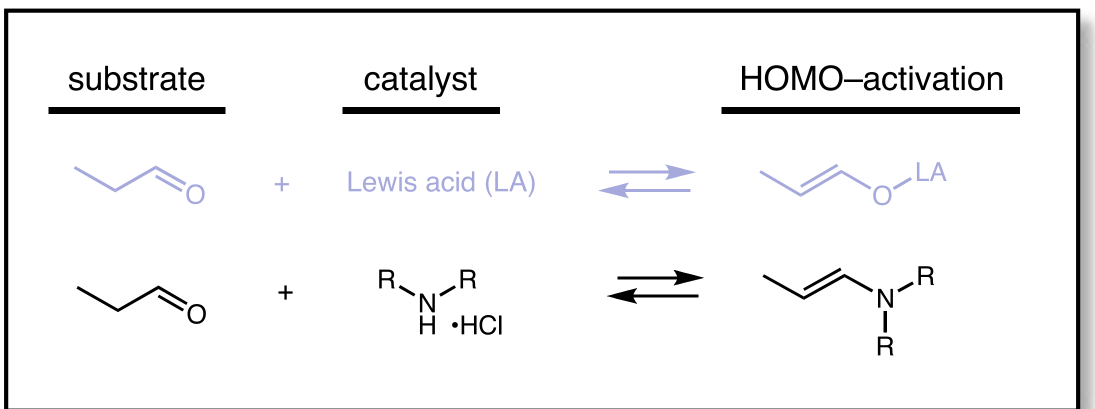
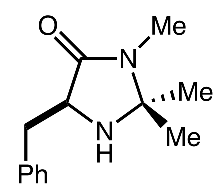


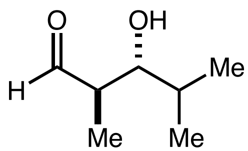


imidazolidinone
generation 1

Enamine activation strategy is useful for a variety of organocatalytic reactions

Aldehyde aldol

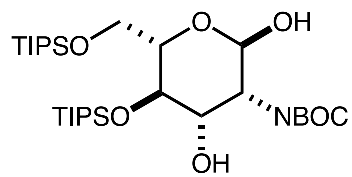
JACS **2002**, *124*, 6798



99% ee

Two step sugars

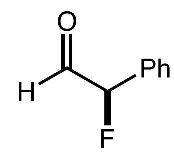
Science **2004**, *305*, 1752



95% ee

α-Fluorination

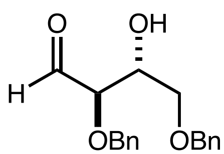
JACS **2005**, *127*, ASAP



99% ee

α-Oxy Aldol

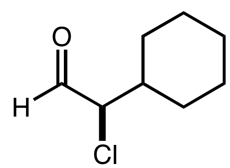
Angew Chemie **2004**, *43*, 2152



98% ee

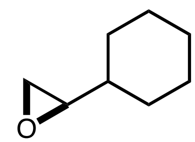
α-Chlorination

JACS **2004**, *126*, 4108



94% ee

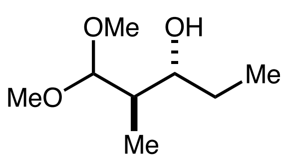
Epoxidation



98% ee

Imidazolidinone aldol

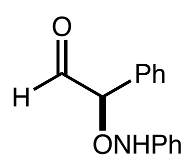
Angew Chemie **2004**, *43*, 6722



94% ee

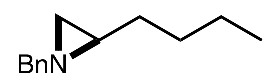
α-Oxyamination

JACS **2003**, *125*, 10808



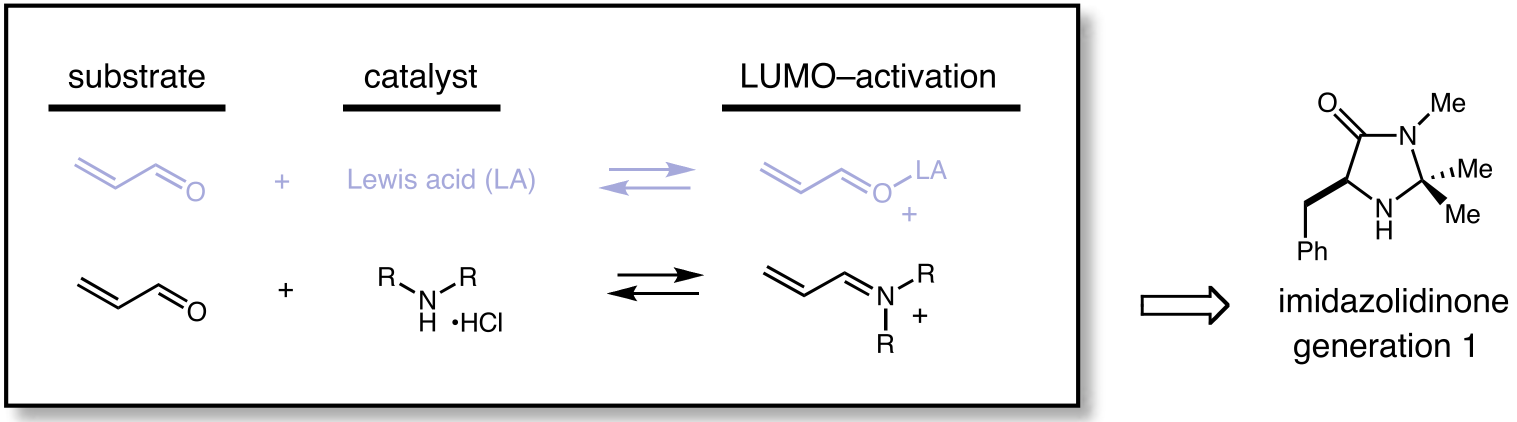
99% ee

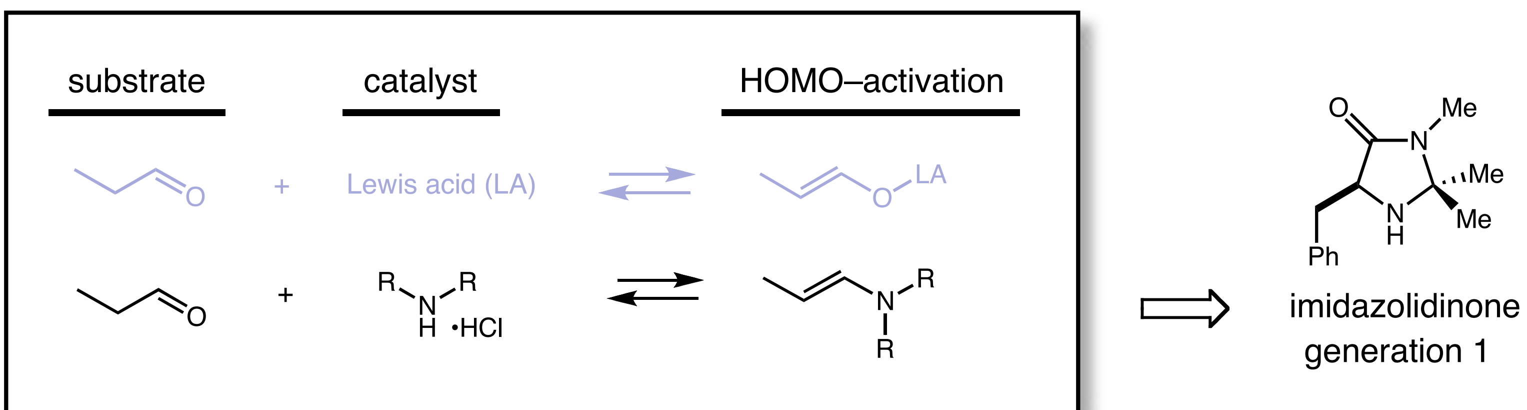
Aziridination



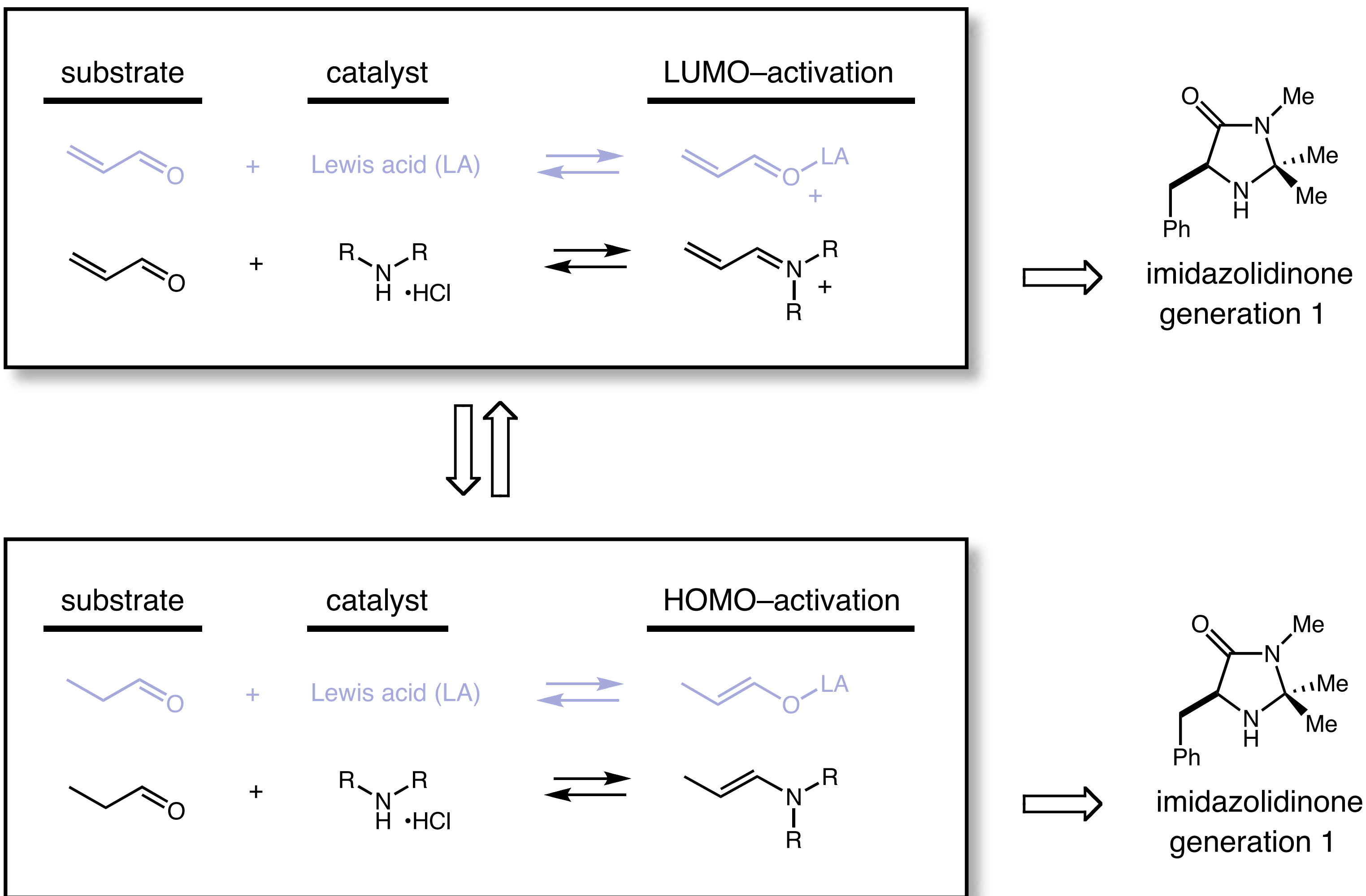
98% ee

Design of Cascade–Catalysis Strategy: LUMO–HOMO Catalyst





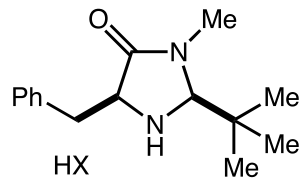
Design of Cascade–Catalysis Strategy: LUMO–HOMO Catalyst



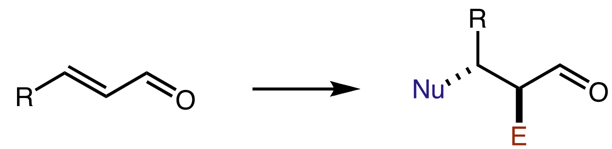
■ Can we merge LUMO-lowering and HOMO-raising catalysis using the same catalyst

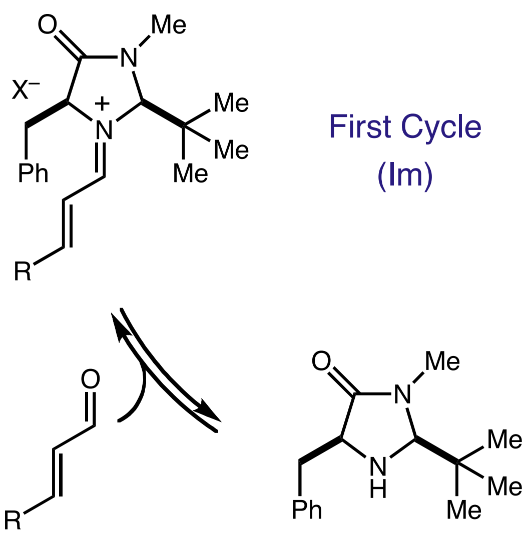
Merging LUMO-lowering and HOMO-raising with one catalyst

- **First step:** Iminium catalysis
- **Second step:** Enamine catalysis



imidazolidinone





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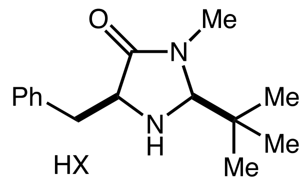
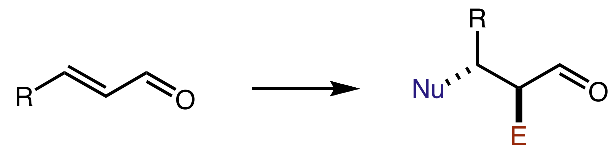
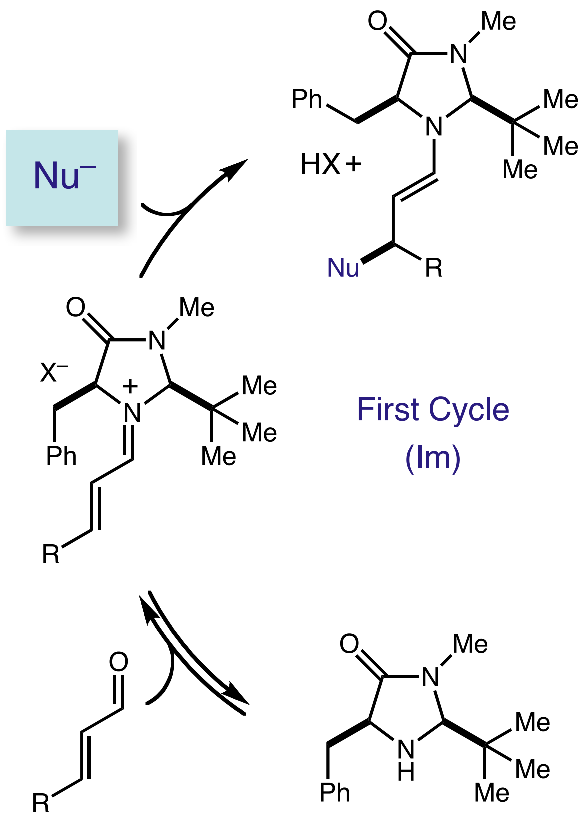
- **Second step:** Enamine catalysis



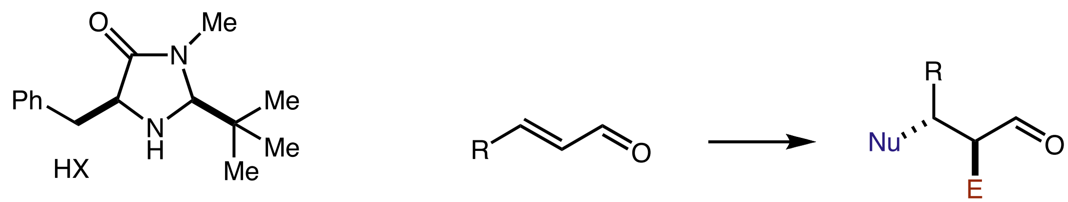
imidazolidinone



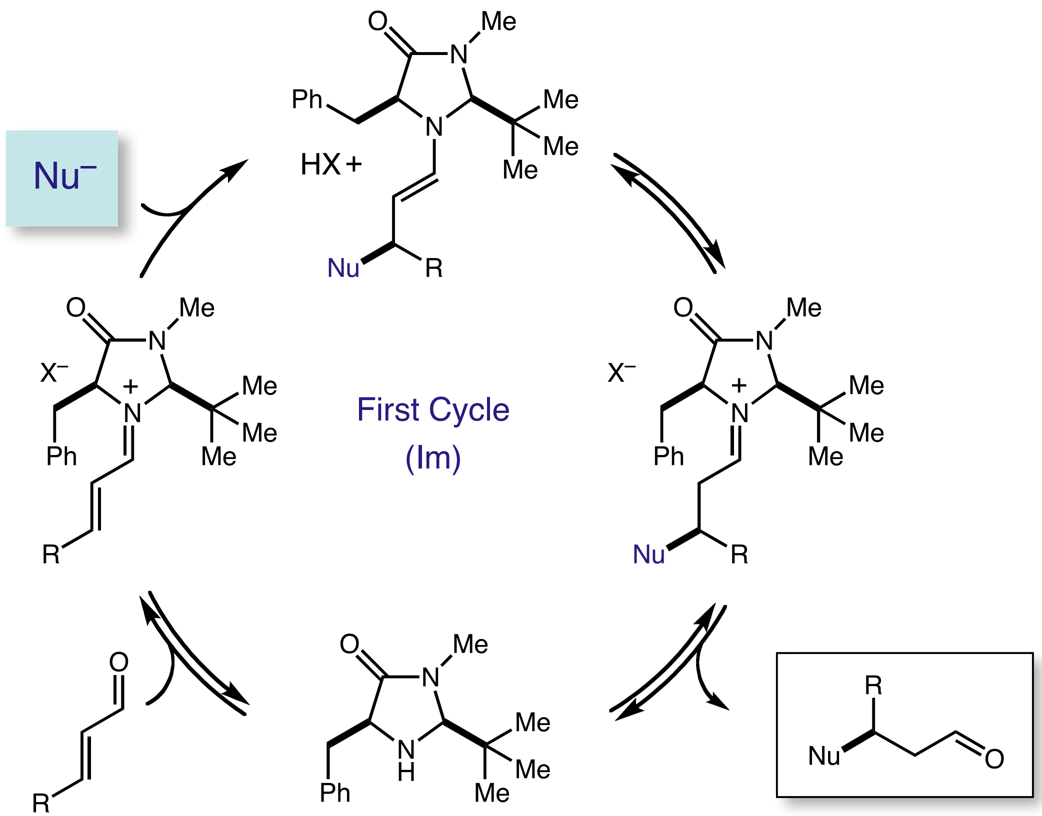


Merging LUMO-lowering and HOMO-raising with one catalyst

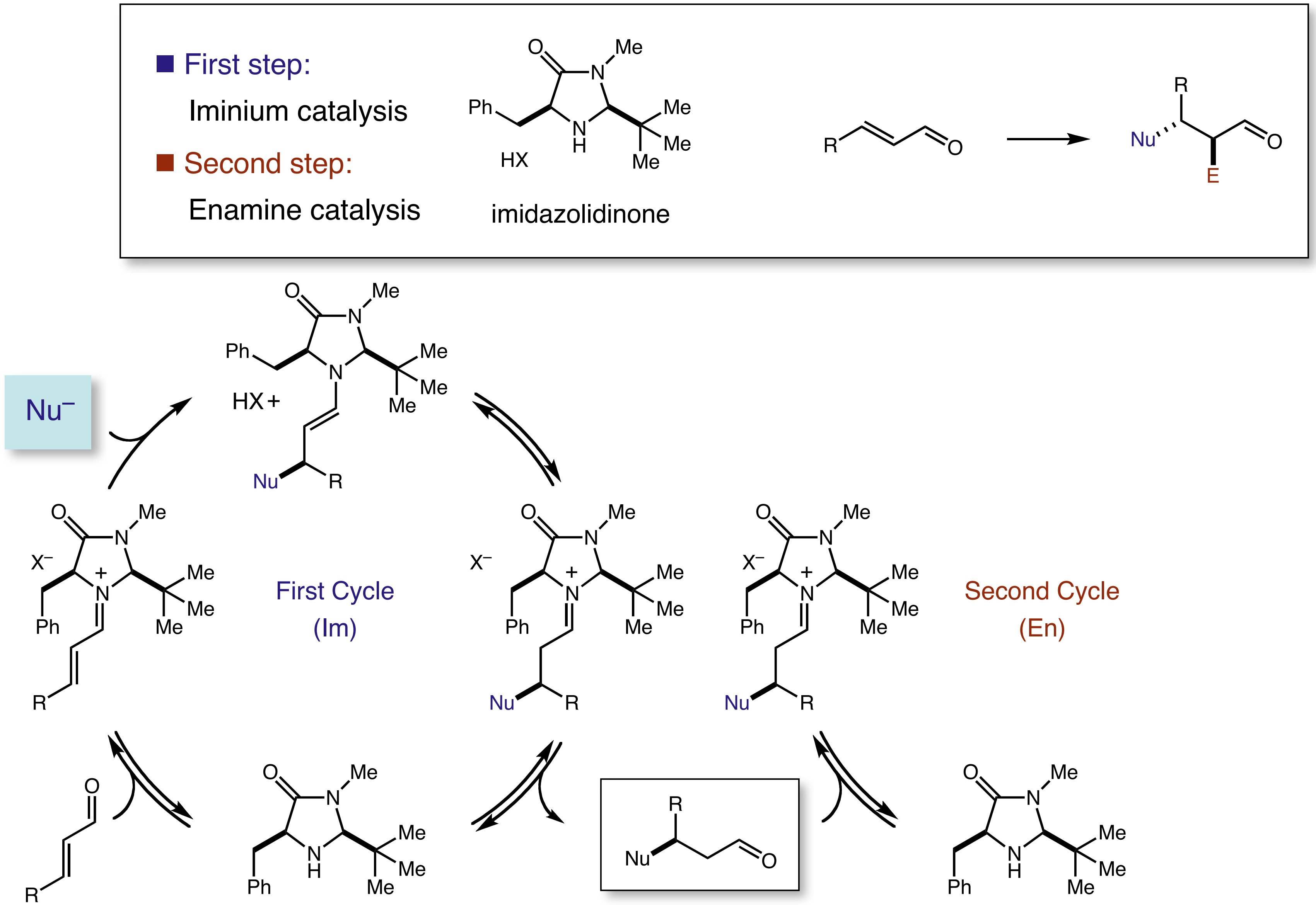
- **First step:**
  Iminium catalysis
- **Second step:**
  Enamine catalysis



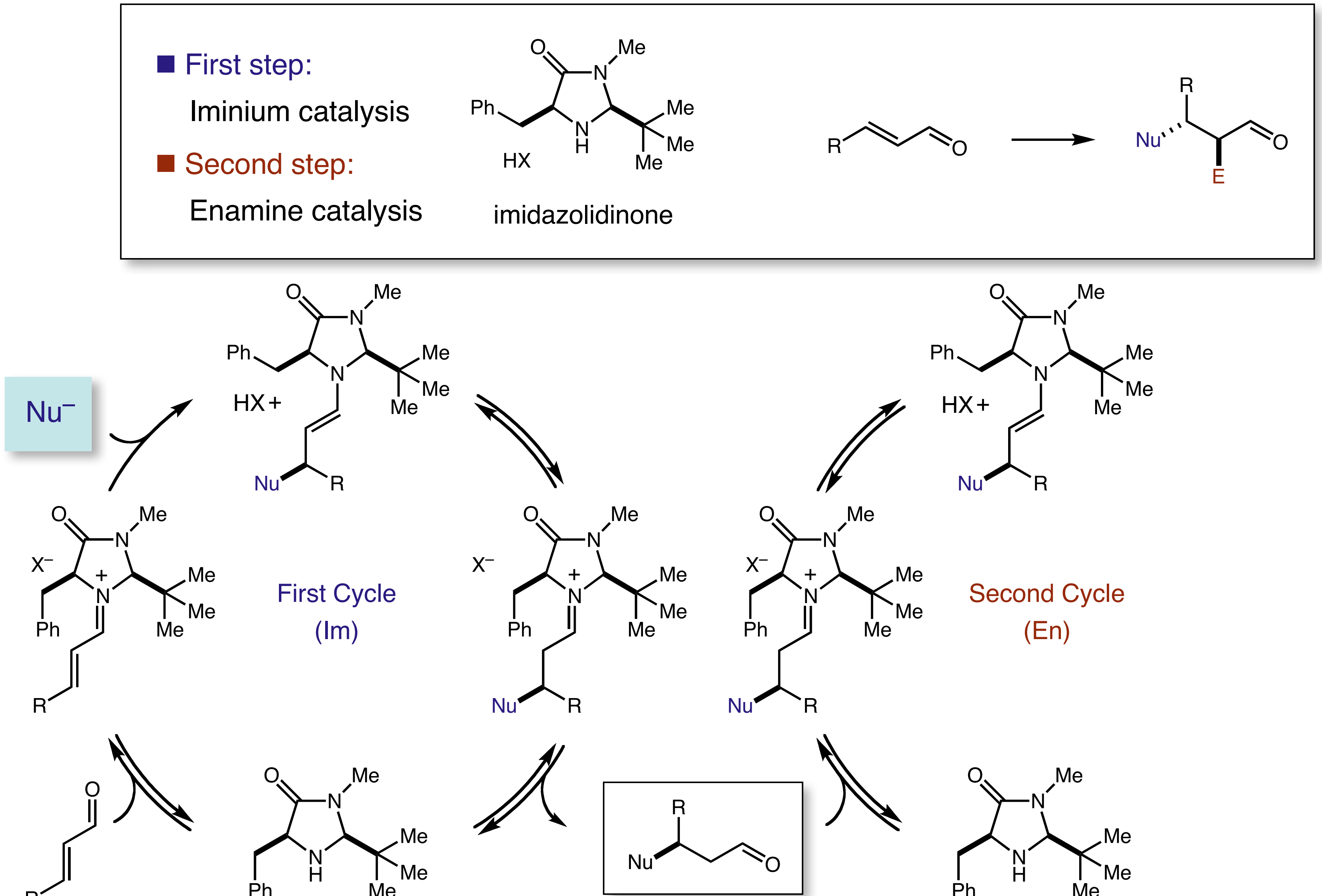
imidazolidinone



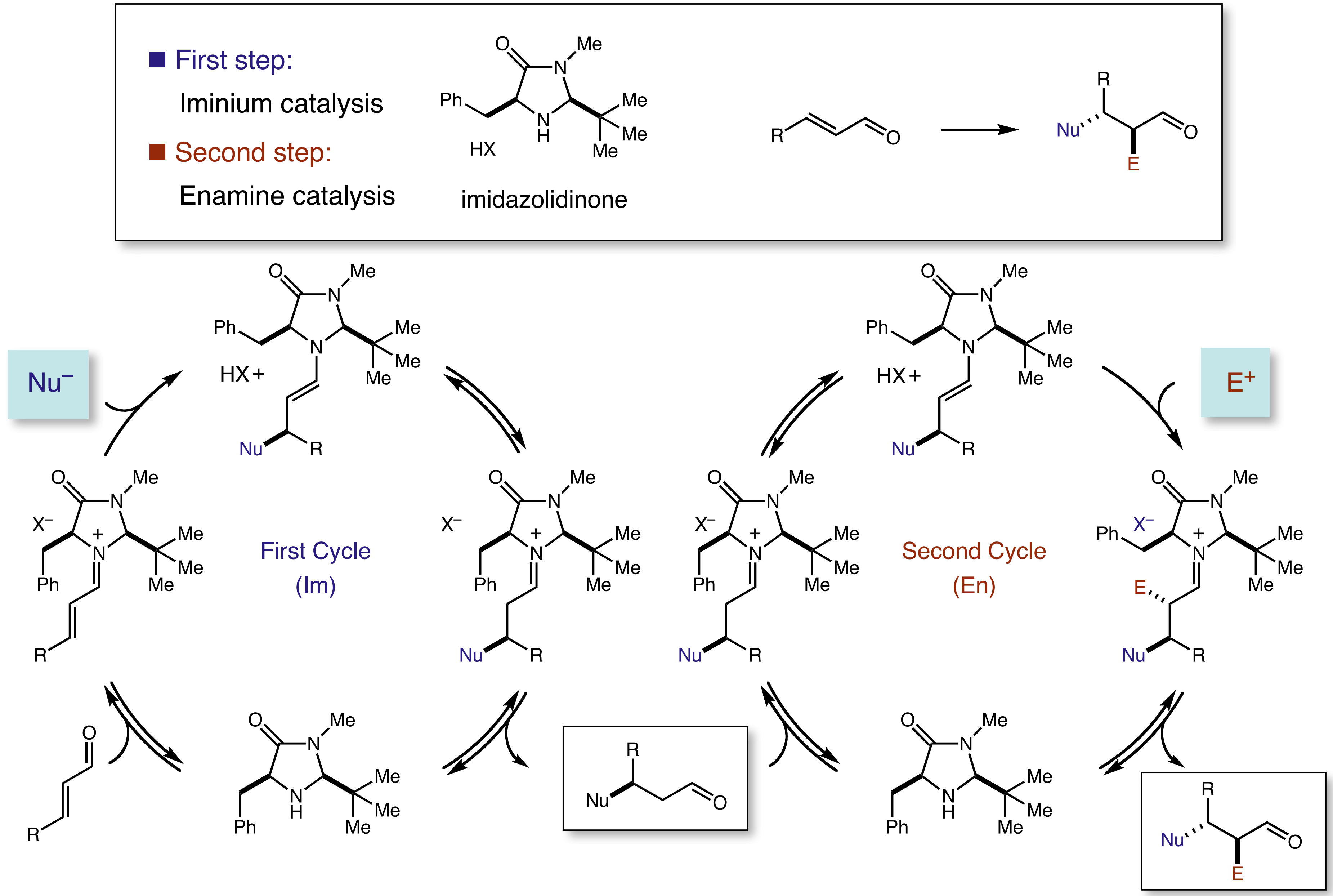
Merging LUMO-lowering and HOMO-raising with one catalyst



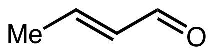
Merging LUMO-lowering and HOMO-raising with one catalyst



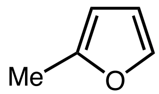
Merging LUMO-lowering and HOMO-raising with one catalyst



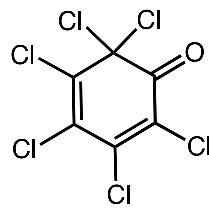
Cascade catalysis with imidazolidinones: preliminary results



substrate

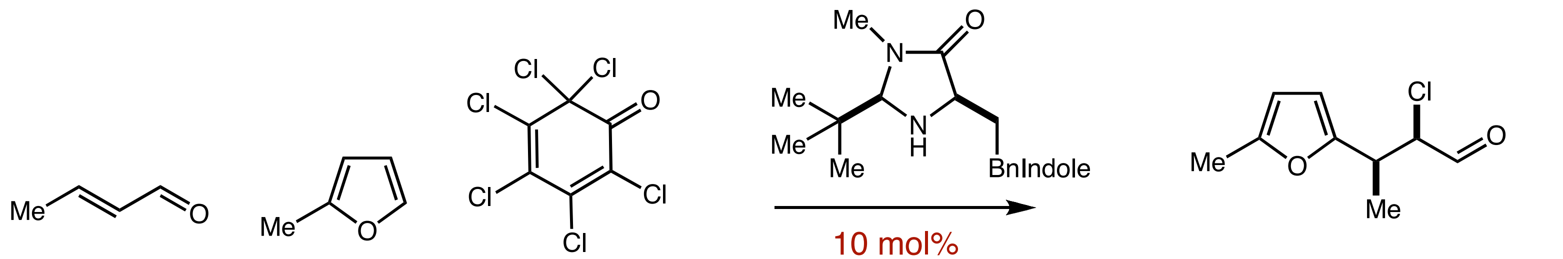


nucleophile



electrophile

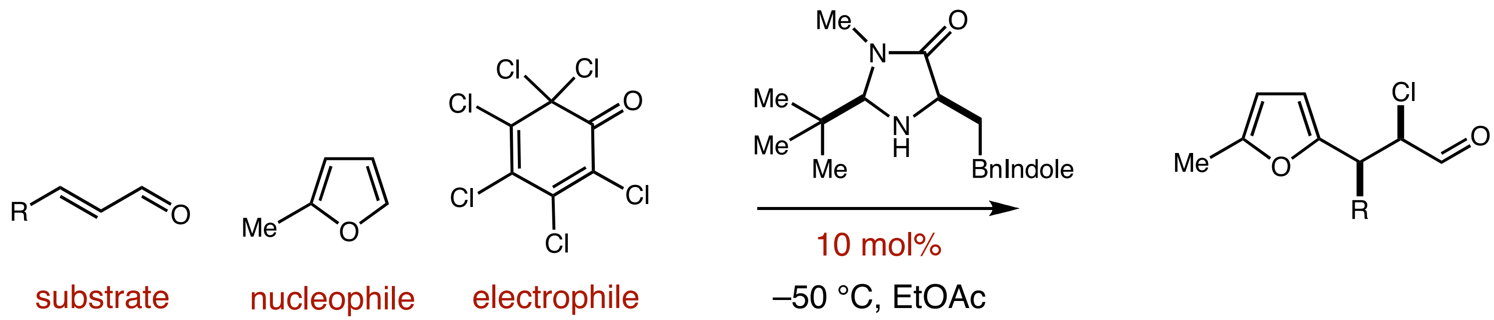
Cascade catalysis with imidazolidinones: preliminary results



substrate nucleophile electrophile

86% yield 14:1 dr 99% ee

Cascade catalysis with imidazolidinones: preliminary results

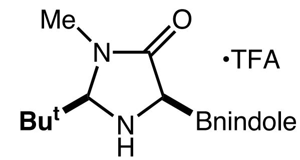


R	Temp °C	Yield	*syn*:*anti*	ee%
Me	–50	86%	14:1	*syn* 99% ee
Pr	–50	74%	13:1	*syn* 99% ee
CO_2Et	–40	80%	22:1	*syn* 99% ee
CH_2OAc	–40	82%	11:1	*syn* 99% ee

- Cascade-catalsysis appears general for a range of enal substrates
- Diastereoselectivity suggests that catalyst control is dominant in second cycle

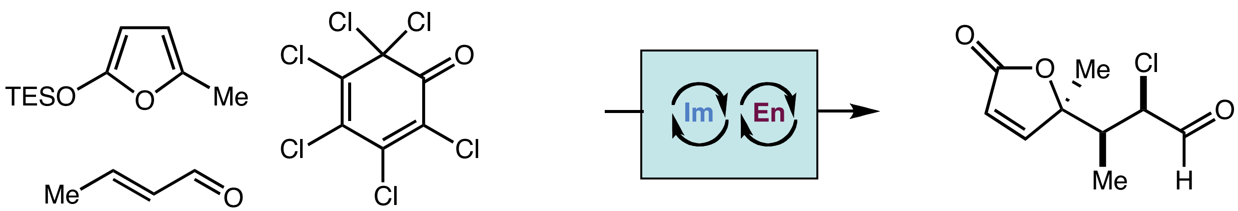
Enantioselective Organo–Cascade Catalysis

Rapid development of molecular complexity from simple materials



10 mol% catalyst

■ With a range of nucleophiles



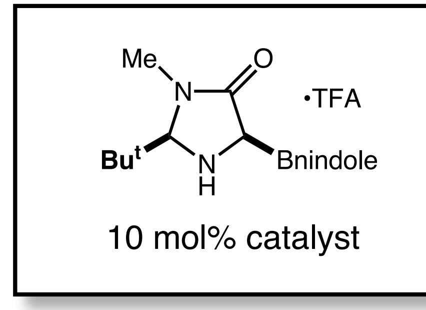
71% yield

syn:*anti* 25:1

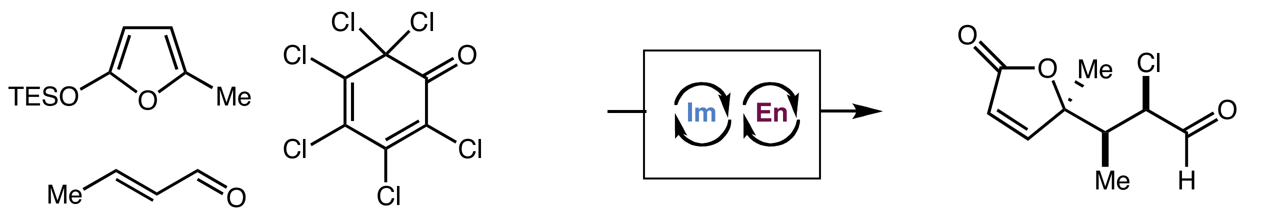
99% ee

Enantioselective Organo–Cascade Catalysis

Rapid development of molecular complexity from simple materials



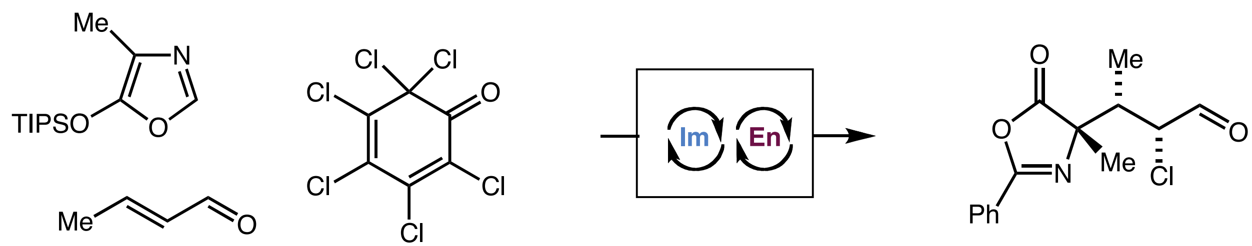
■ With a range of nucleophiles



71% yield

syn:*anti* 25:1

99% ee



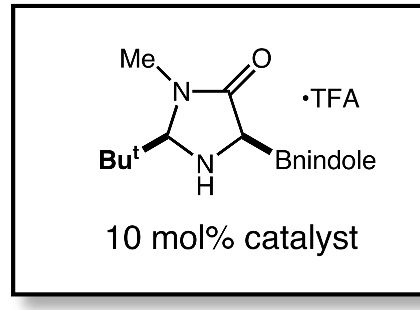
97% yield

syn:*anti* 9:1

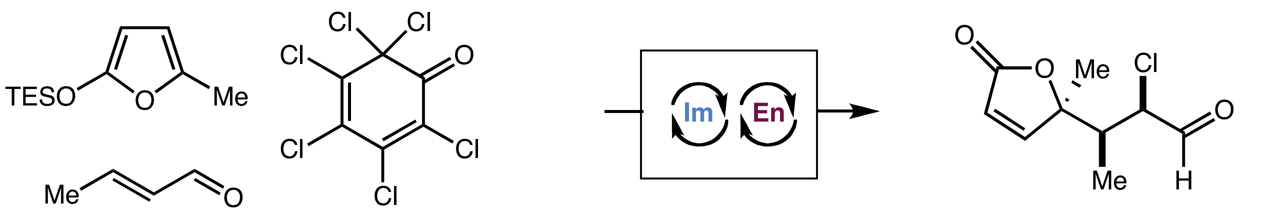
99% ee

Enantioselective Organo–Cascade Catalysis

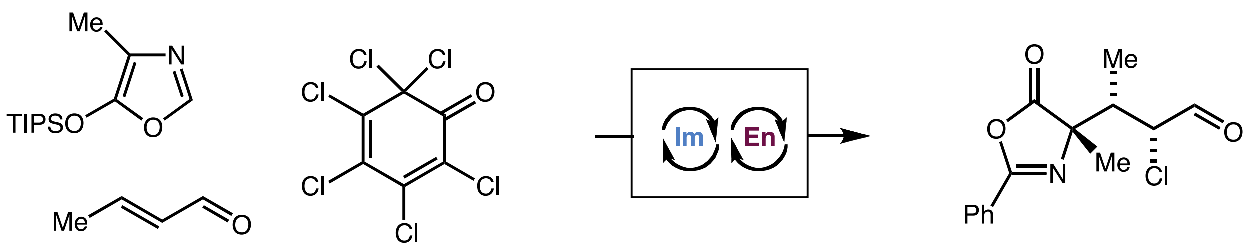
Rapid development of molecular complexity from simple materials



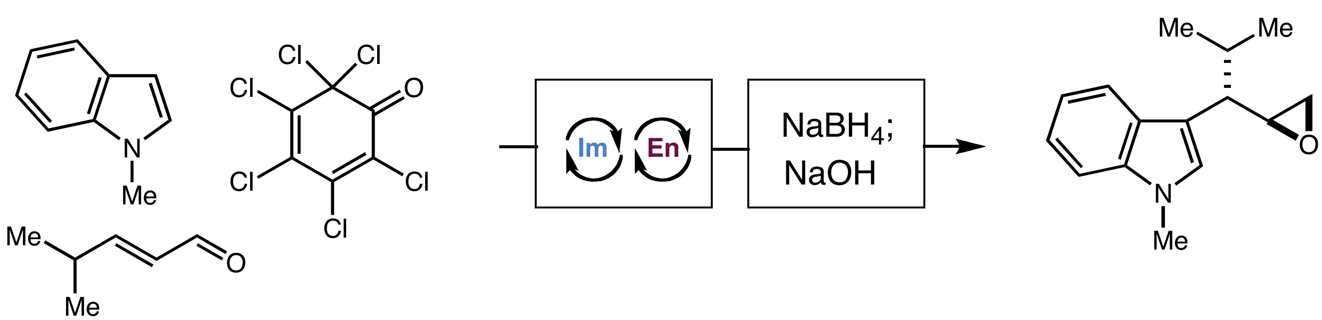
■ With a range of nucleophiles



71% yield
syn:*anti* 25:1
99% ee



97% yield
syn:*anti* 9:1
99% ee



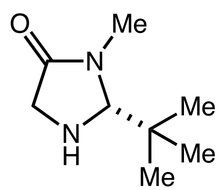
75% yield
syn:*anti* 12:1
99% ee

■ Processes are highly selective also using thiophenes, nitroalkanes

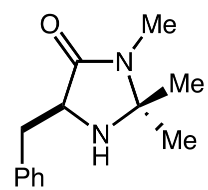
Cascade Catalysis Towards the Development of Modular Stereocontrol

catalyst combination A

enamine catalyst and **E**
added after consumption of **Nu**



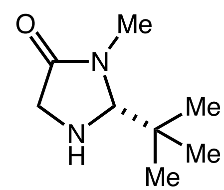
(5*S*)-iminium catalyst (7.5 mol%)



(2*R*)-enamine catalyst (30 mol%)

catalyst combination B

enamine catalyst and **E**
added after consumption of **Nu**



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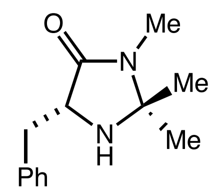
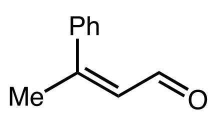
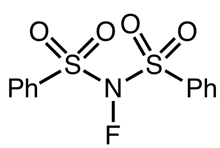
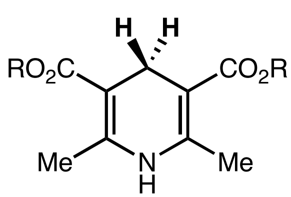


(2*S*)-enamine catalyst (30 mol%)





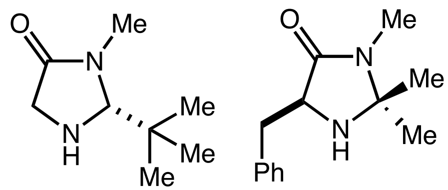


Cascade Catalysis Towards the Development of Modular Stereocontrol

catalyst combination A

enamine catalyst and **E**

added after consumption of **Nu**

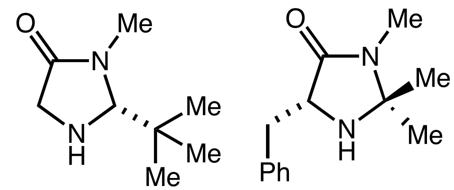


(5*S*)-iminium catalyst (7.5 mol%)	(2*R*)-enamine catalyst (30 mol%)

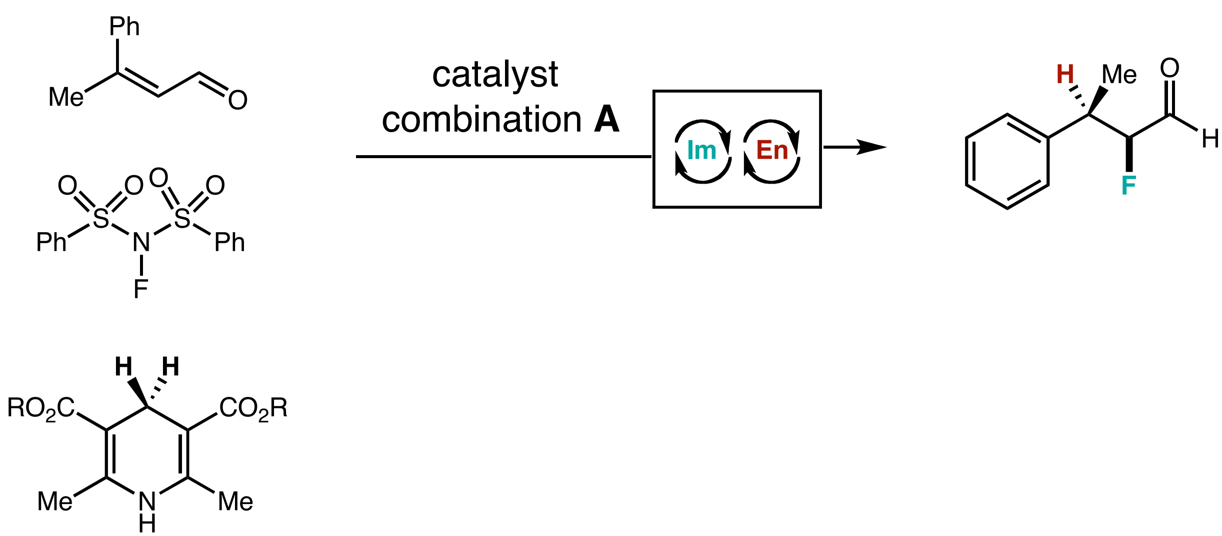
catalyst combination B

enamine catalyst and **E**

added after consumption of **Nu**



(5*S*)-iminium catalyst (7.5 mol%)	(2*S*)-enamine catalyst (30 mol%)



81% yield

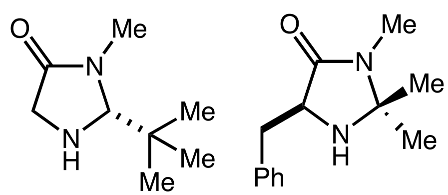
anti:*syn* 16:1

99% ee

Cascade Catalysis Towards the Development of Modular Stereocontrol

catalyst combination A

enamine catalyst and **E**
added after consumption of **Nu**

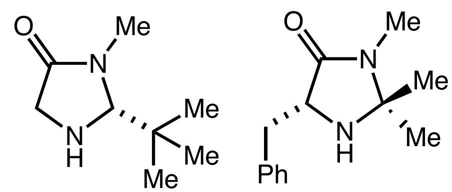


(5*S*)-iminium catalyst (7.5 mol%)

(2*R*)-enamine catalyst (30 mol%)

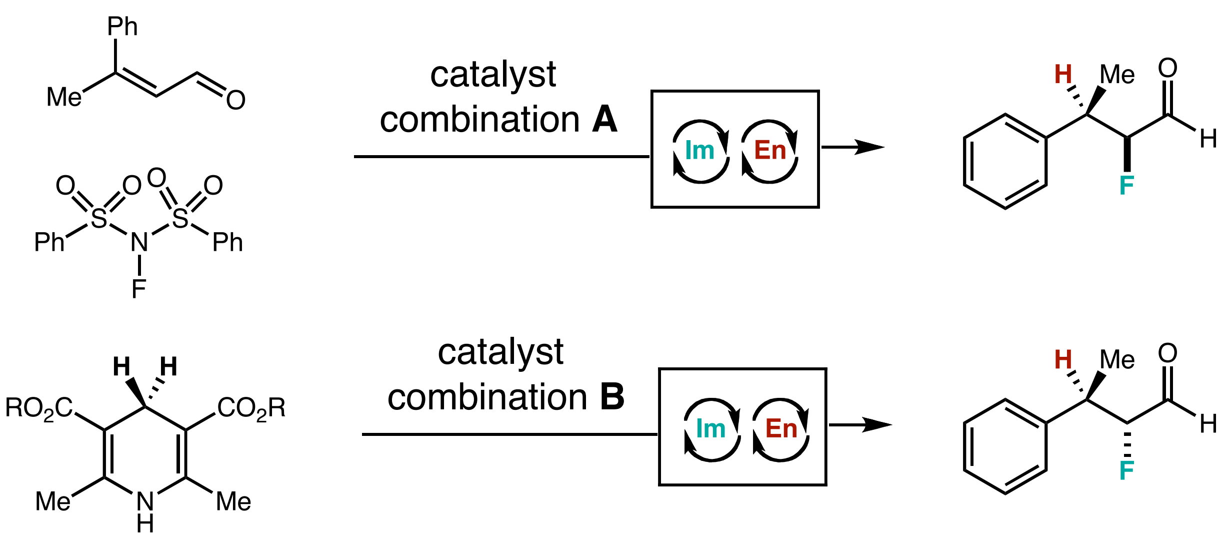
catalyst combination B

enamine catalyst and **E**
added after consumption of **Nu**



(5*S*)-iminium catalyst (7.5 mol%)

(2*S*)-enamine catalyst (30 mol%)



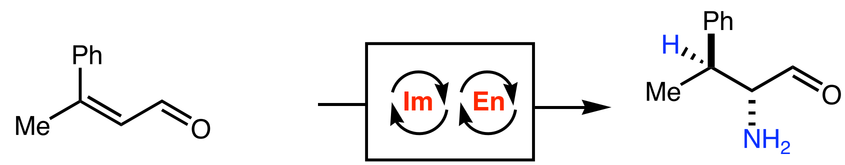
81% yield
anti:*syn* 16:1
99% ee

62% yield
syn:*anti* 9:1
99% ee

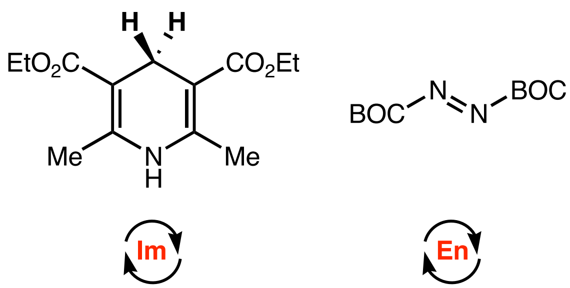
With Huang, Walji, Larsen. *J. Am. Chem. Soc.* **2005,** *127*, 15051

Cascade Catalysis Towards the Development of Modular Stereocontrol

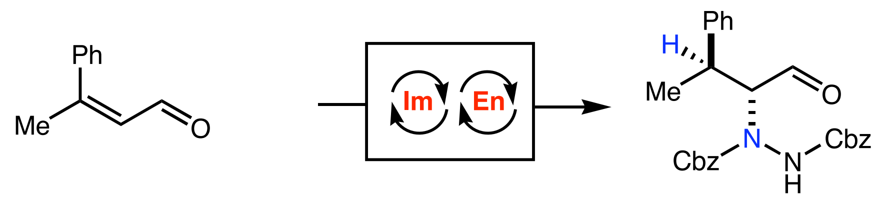
■ Olefin hydroamination



Cascade Catalysis Towards the Development of Modular Stereocontrol



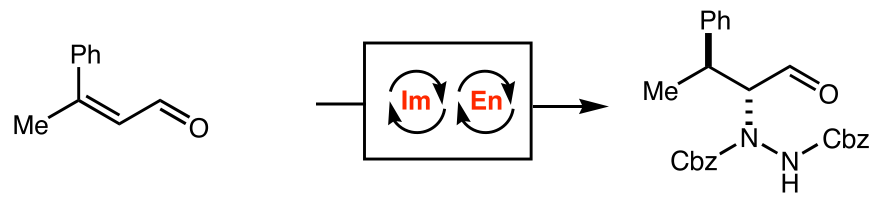
■ Olefin hydroamination



anti:syn 6:1 99% ee

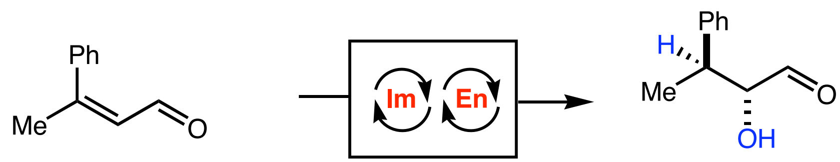
Cascade Catalysis Towards the Development of Modular Stereocontrol

■ Olefin hydroamination



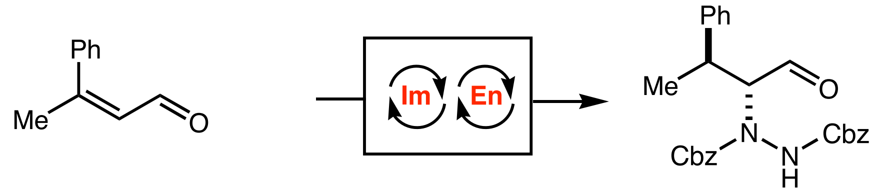
anti:syn 6:1 99% ee

■ Olefin hydrooxidation

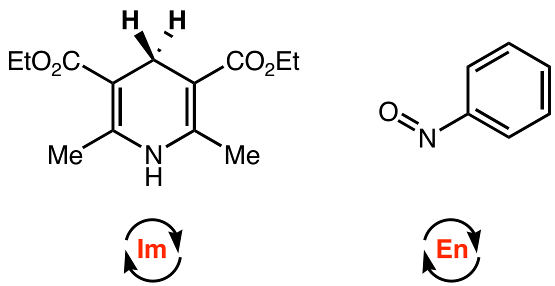


Cascade Catalysis Towards the Development of Modular Stereocontrol

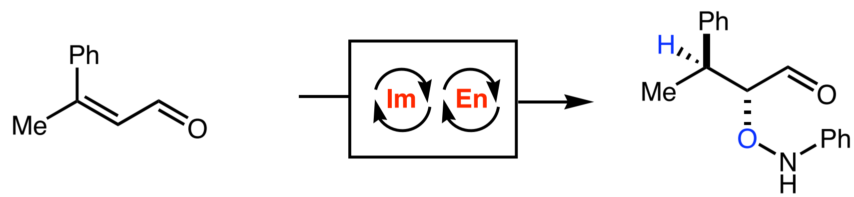
Olefin hydroamination



anti:syn 6:1   99% ee



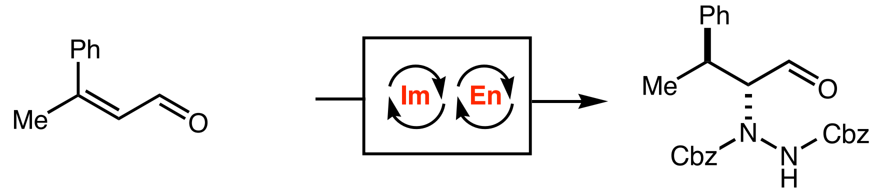
Olefin hydrooxidation



anti:syn 11:1   99% ee

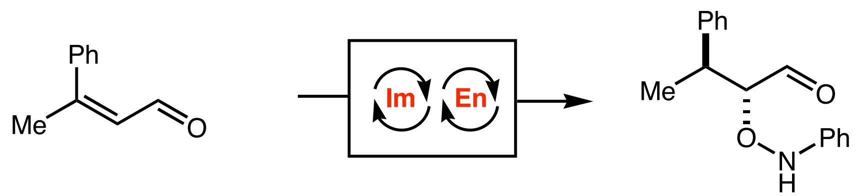
Cascade Catalysis Towards the Development of Modular Stereocontrol

■ Olefin hydroamination



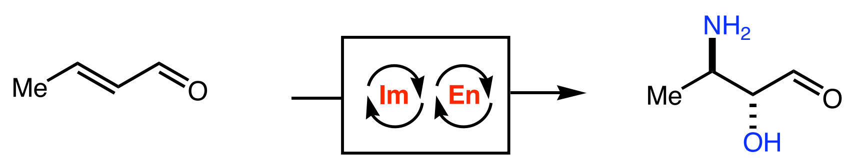
anti:syn 6:1 99% ee

■ Olefin hydrooxidation



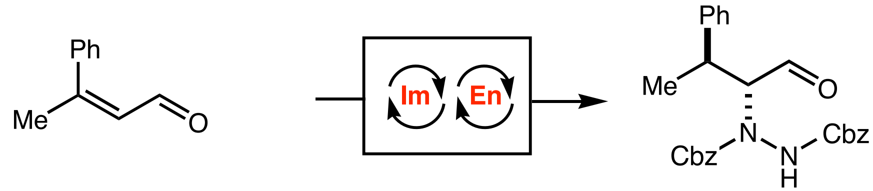
anti:syn 11:1 99% ee

■ Olefin aminohydroxylation



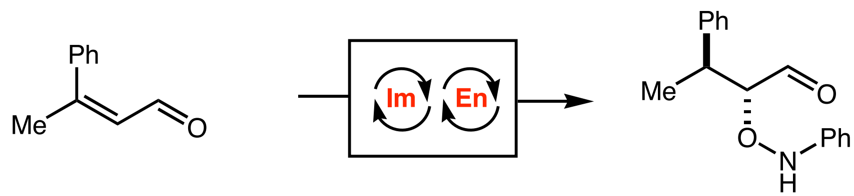
Cascade Catalysis Towards the Development of Modular Stereocontrol

- Olefin hydroamination

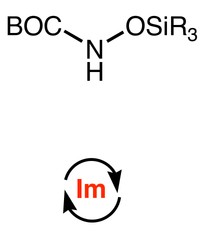


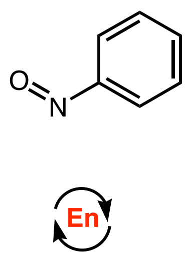
anti:syn 6:1 99% ee

- Olefin hydrooxidation

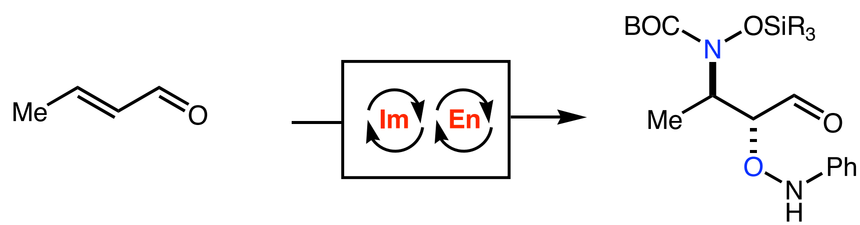


anti:syn 11:1 99% ee



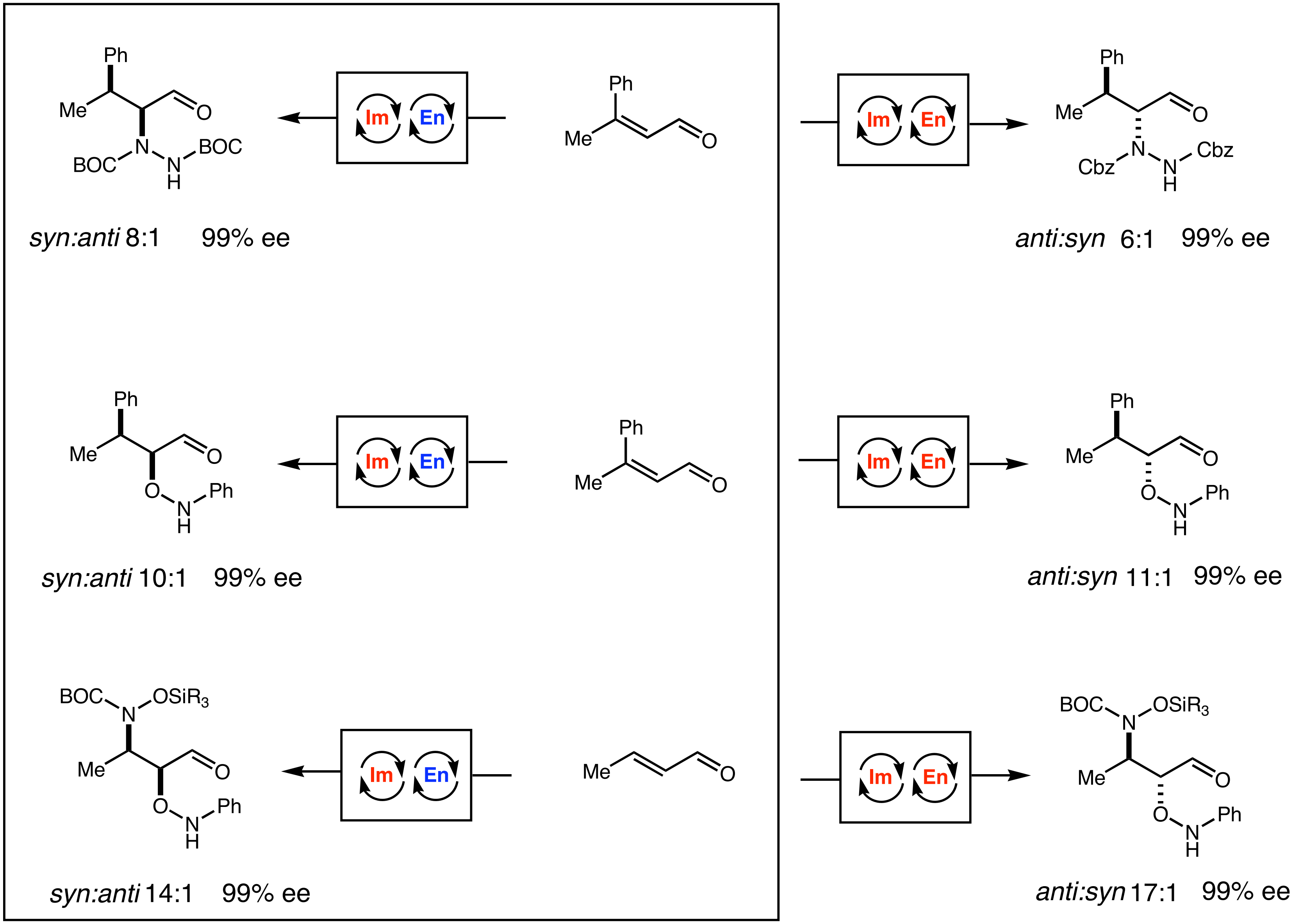


- Olefin aminohydroxylation



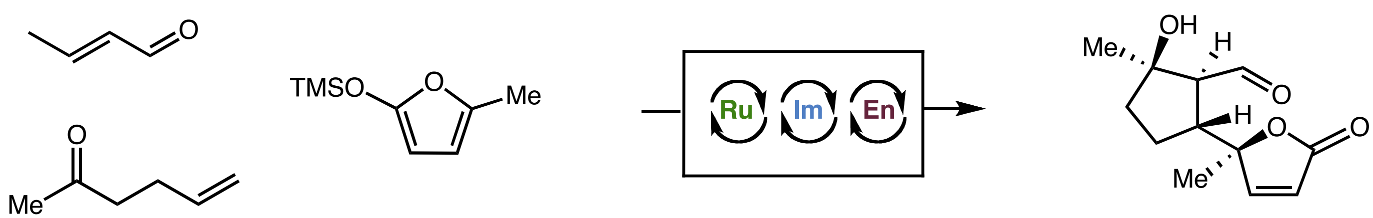
anti:syn 17:1 99% ee

Cascade Catalysis Towards the Development of Modular Stereocontrol



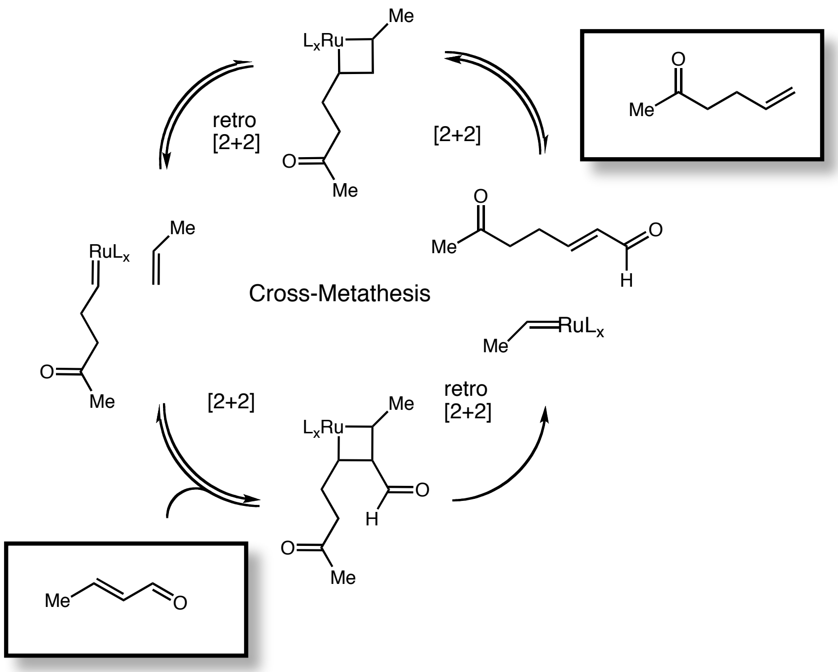
Cascade Catalysis: Merging Organo and Organometallic Catalysis

■ The structural core of aromadendranediol in one step



■ 11 carbon framework

■ 4 contiguous stereogenic centers



Cascade Catalysis:

Merging Organocatalysis

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Triple cascade catalysis should allow

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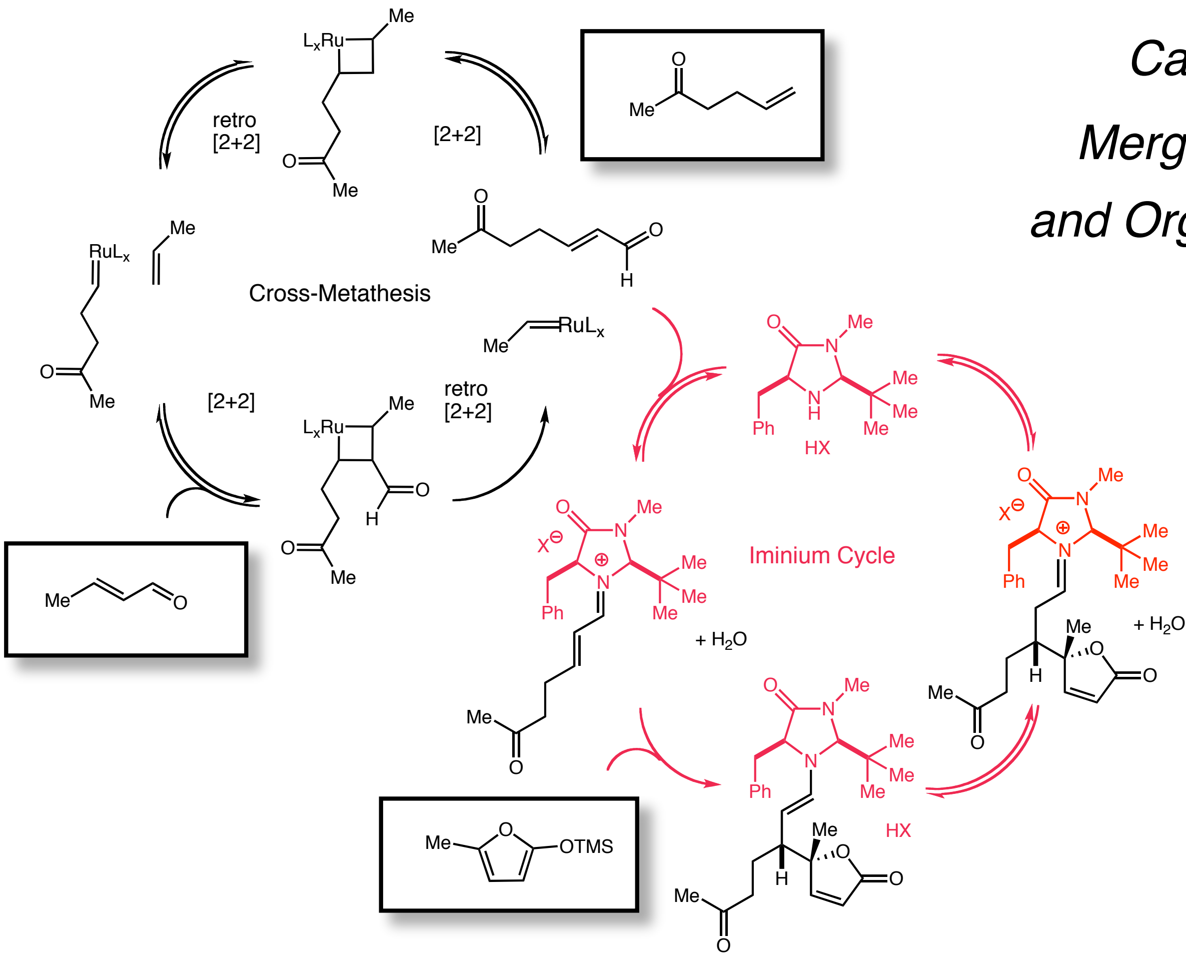

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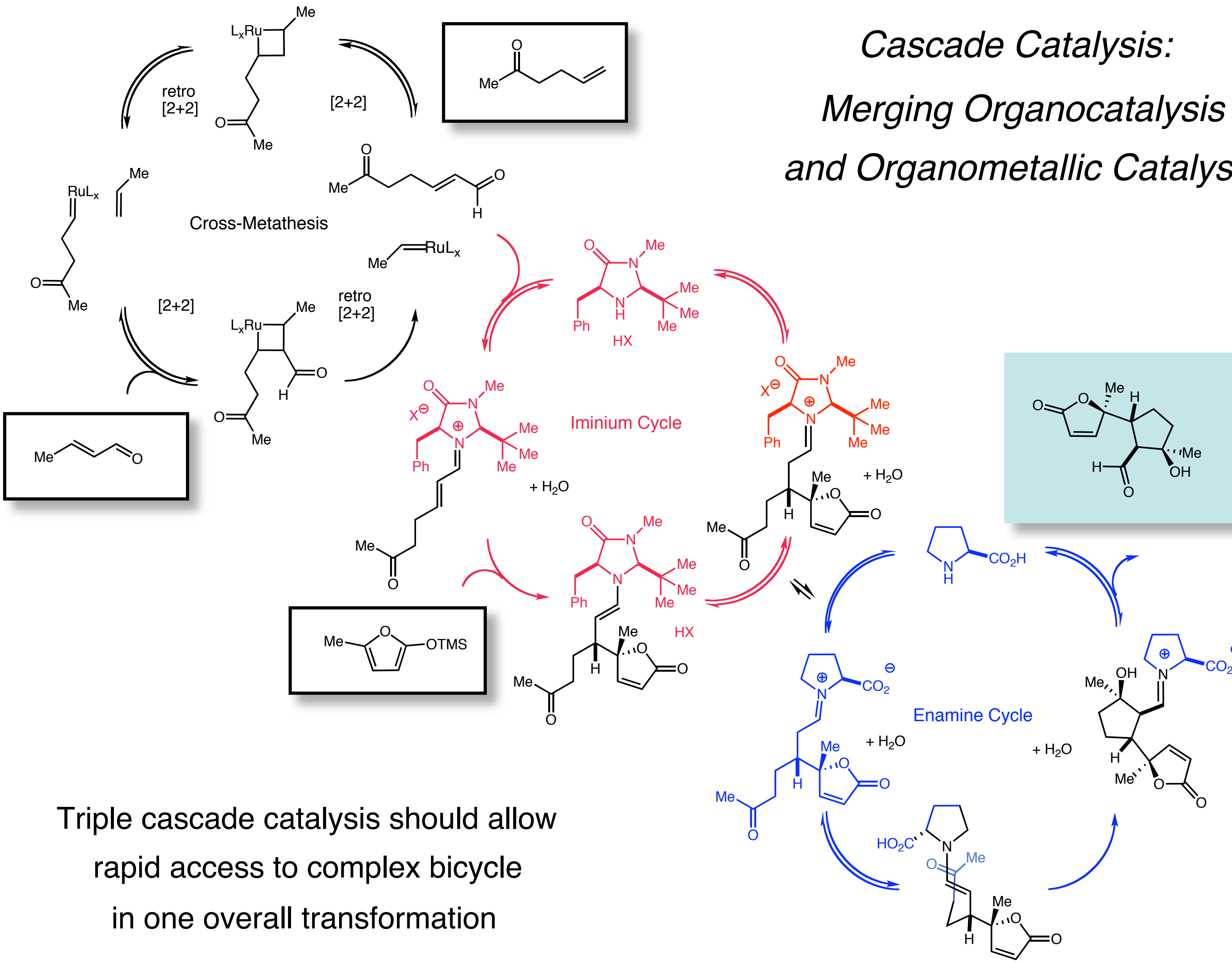

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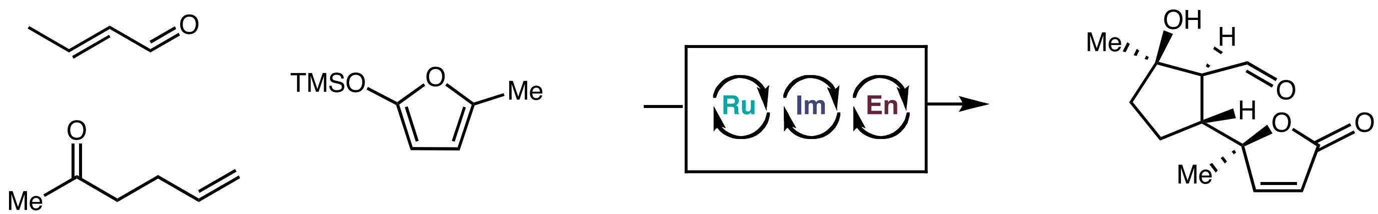

64% yield

5:1 dr

95% ee

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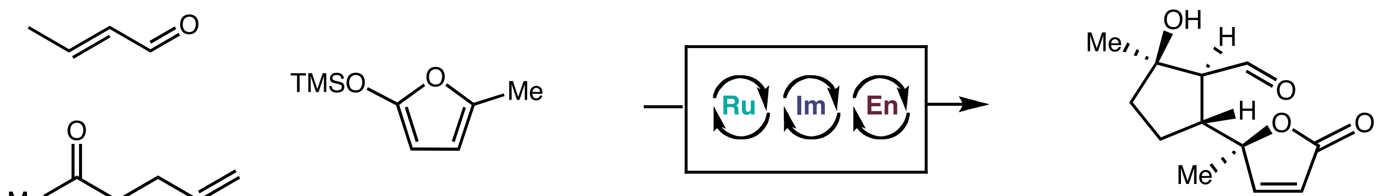

64% yield

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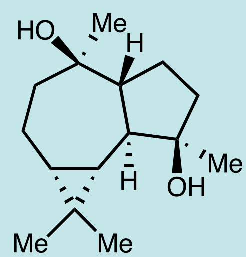
95% ee

5 steps

■ Aromadendranediol

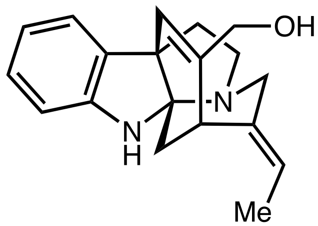
■ Analgesic in folk medicine

■ Previous synthesis 22 steps



Cascade Synthesis of the Sytrchnos Alkaloid Minfiensine

■ Strychnos alkaloid minfiensine and members of the akuammiline alkaloid family



minfiensine

■ Key strategy for minfiensine involving an organocatalytic Diels–Alder cyclization cascade

Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606

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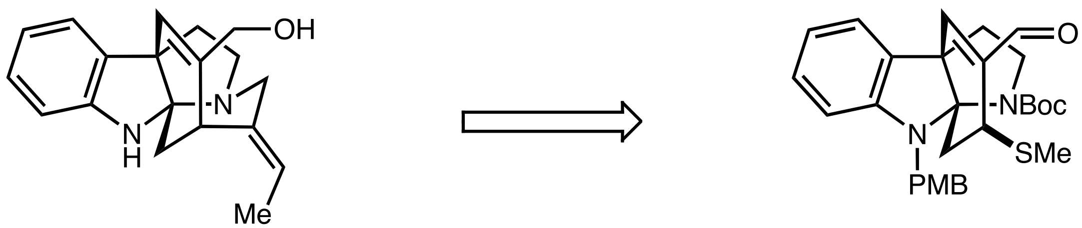

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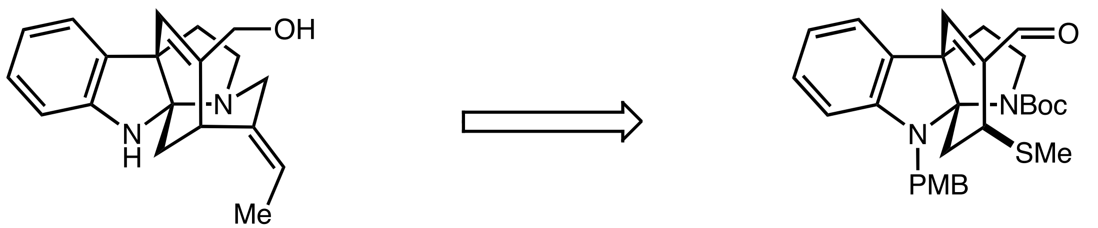

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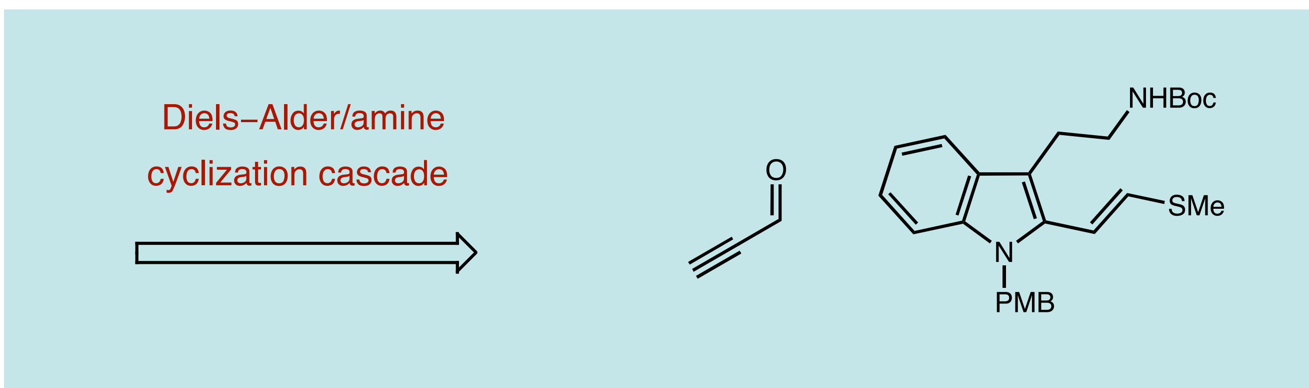

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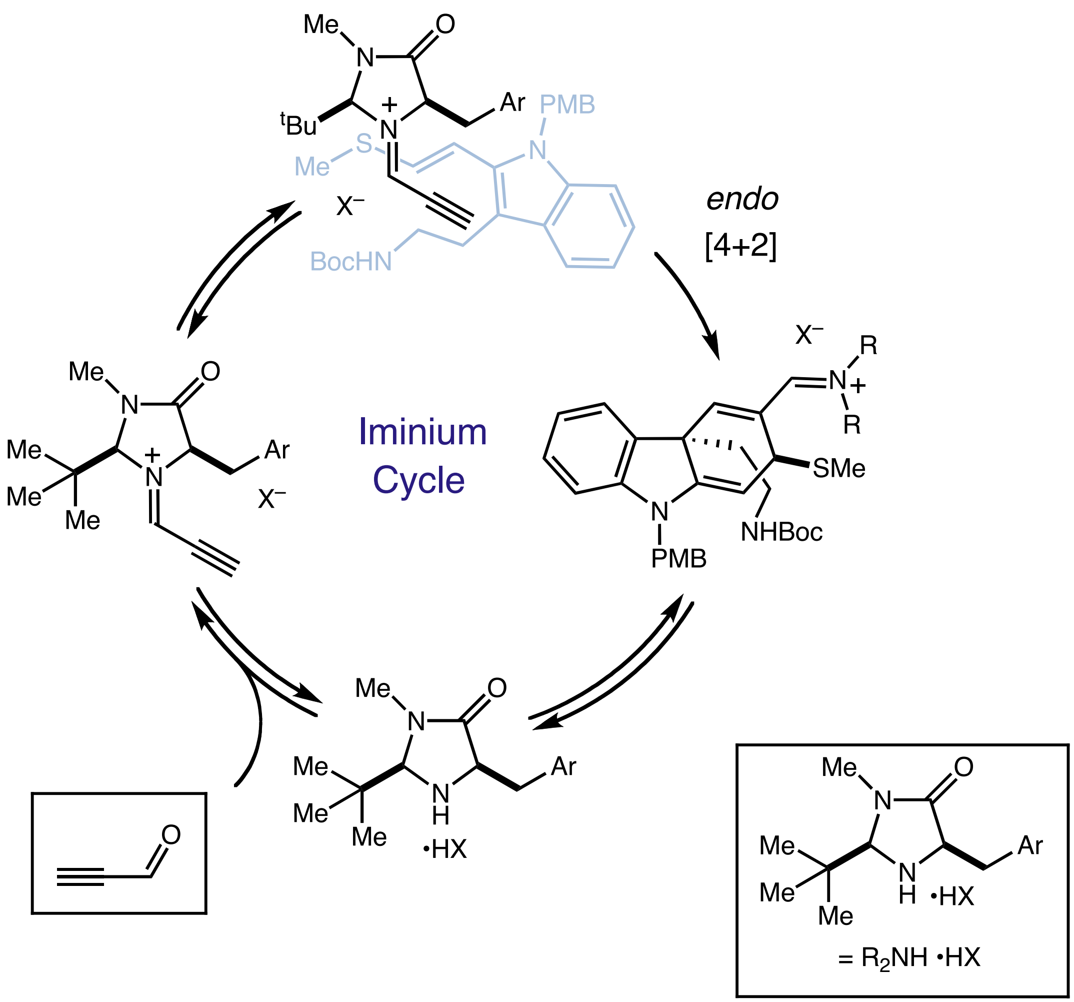

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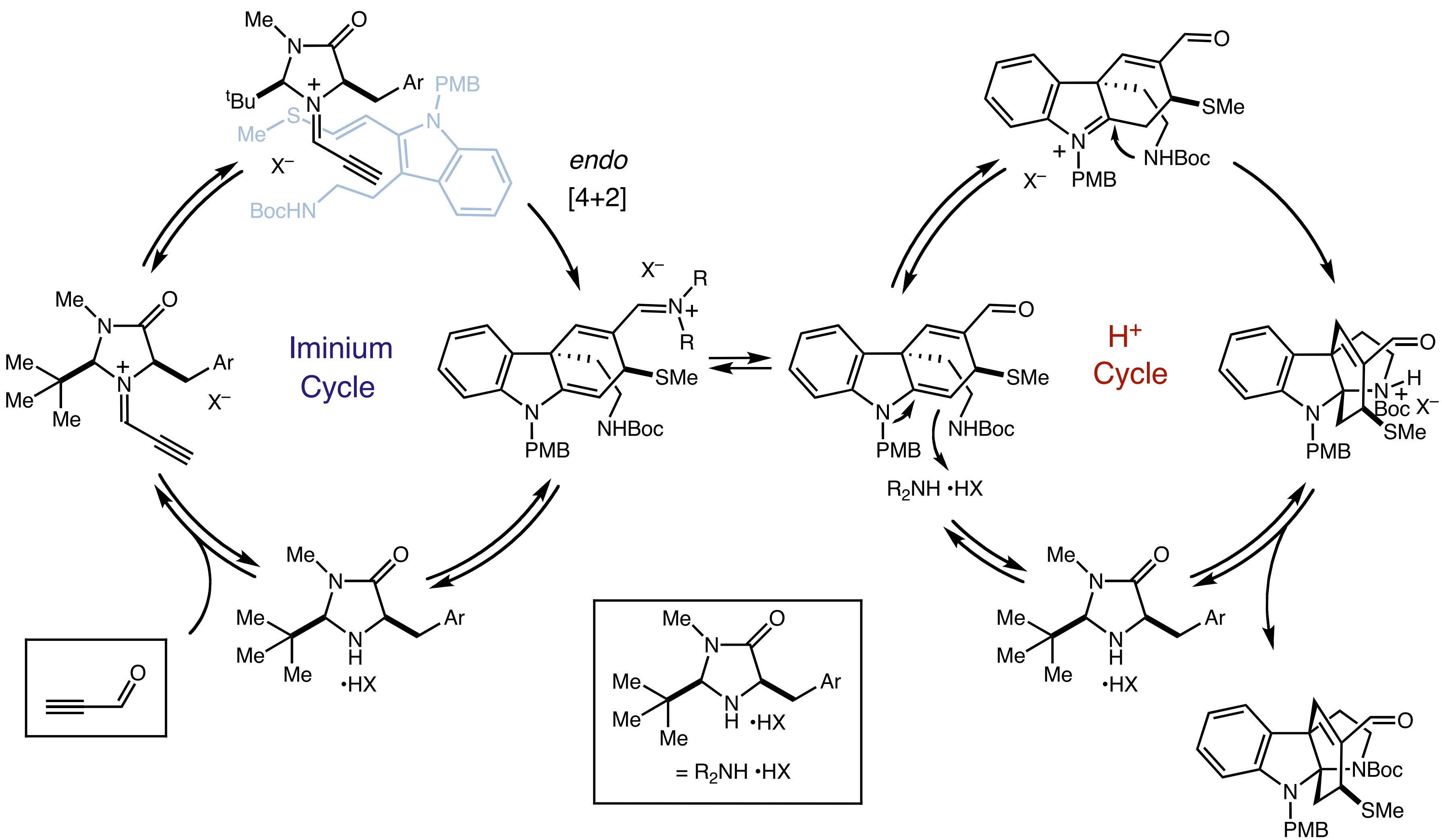

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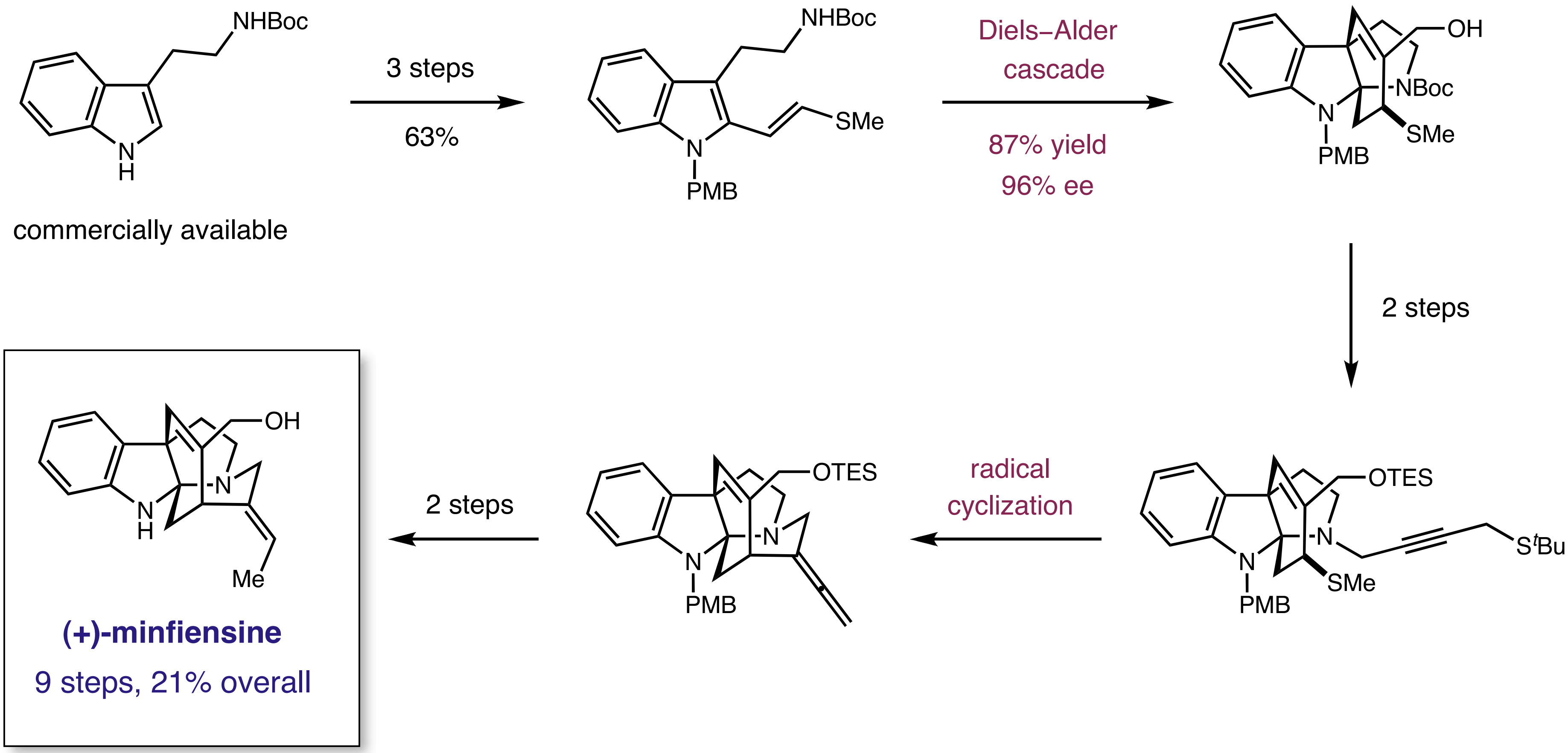
Cascade Synthesis of the Sytrchnos Alkaloid Minfiensine

■ Diels–Alder/Bronsted acid cascade provides rapid access to the enantioenriched core of minfiensine



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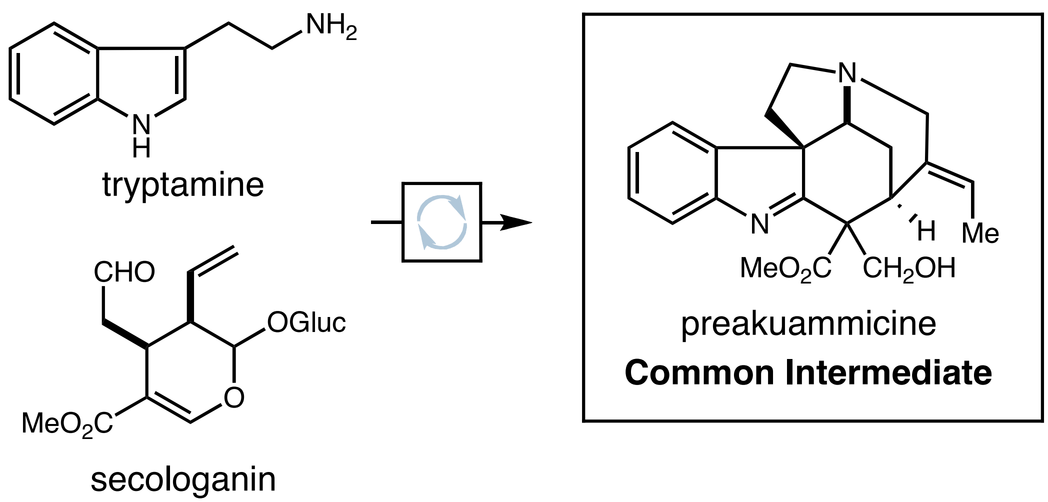
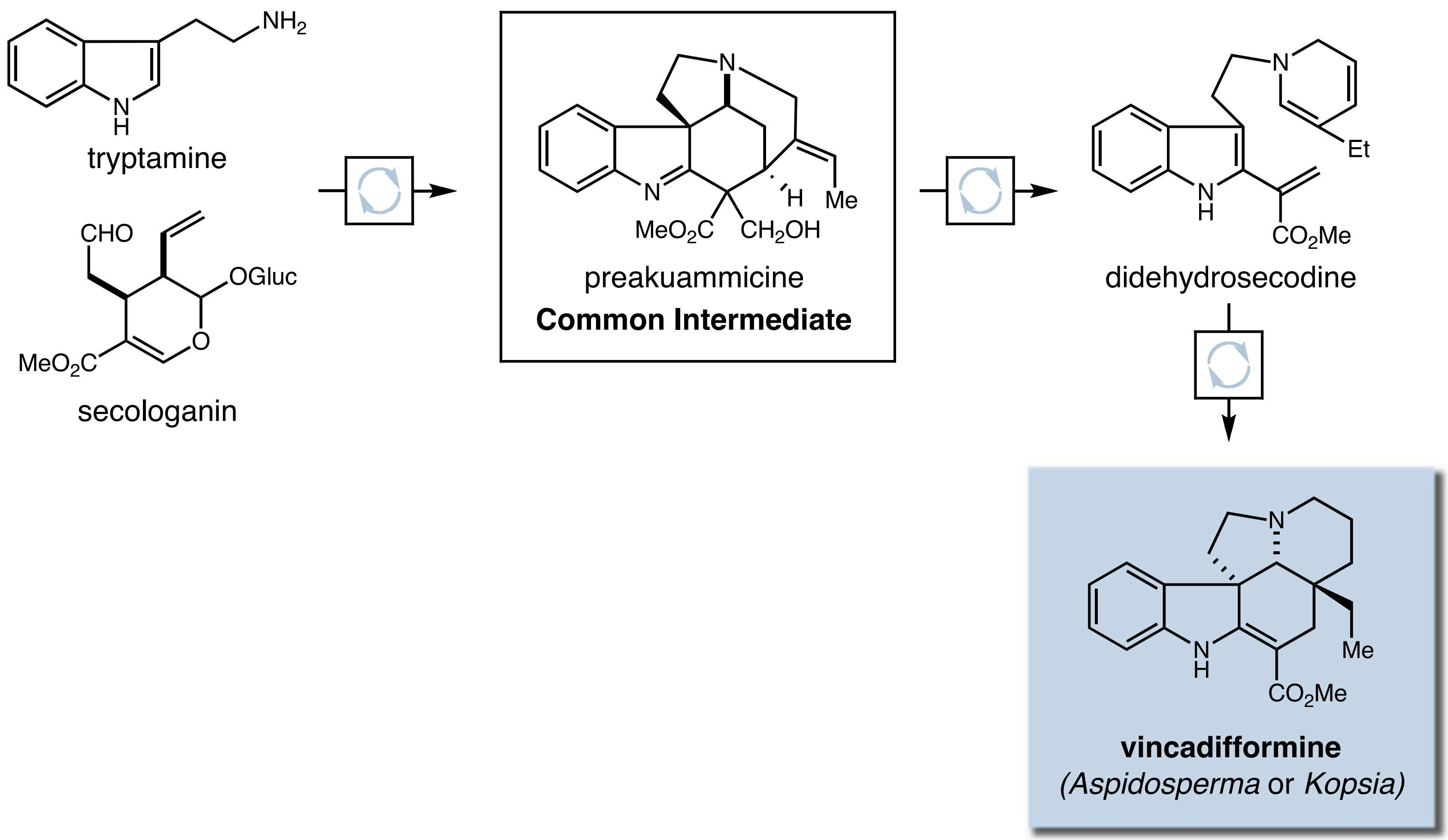
Organocascade Catalysis Inspired by Nature



Natures employs transform specific enzymes in continous catalytic cascades to rapidly access common biosynthetic intermediates and natural products.

Organocascade Catalysis Inspired by Nature



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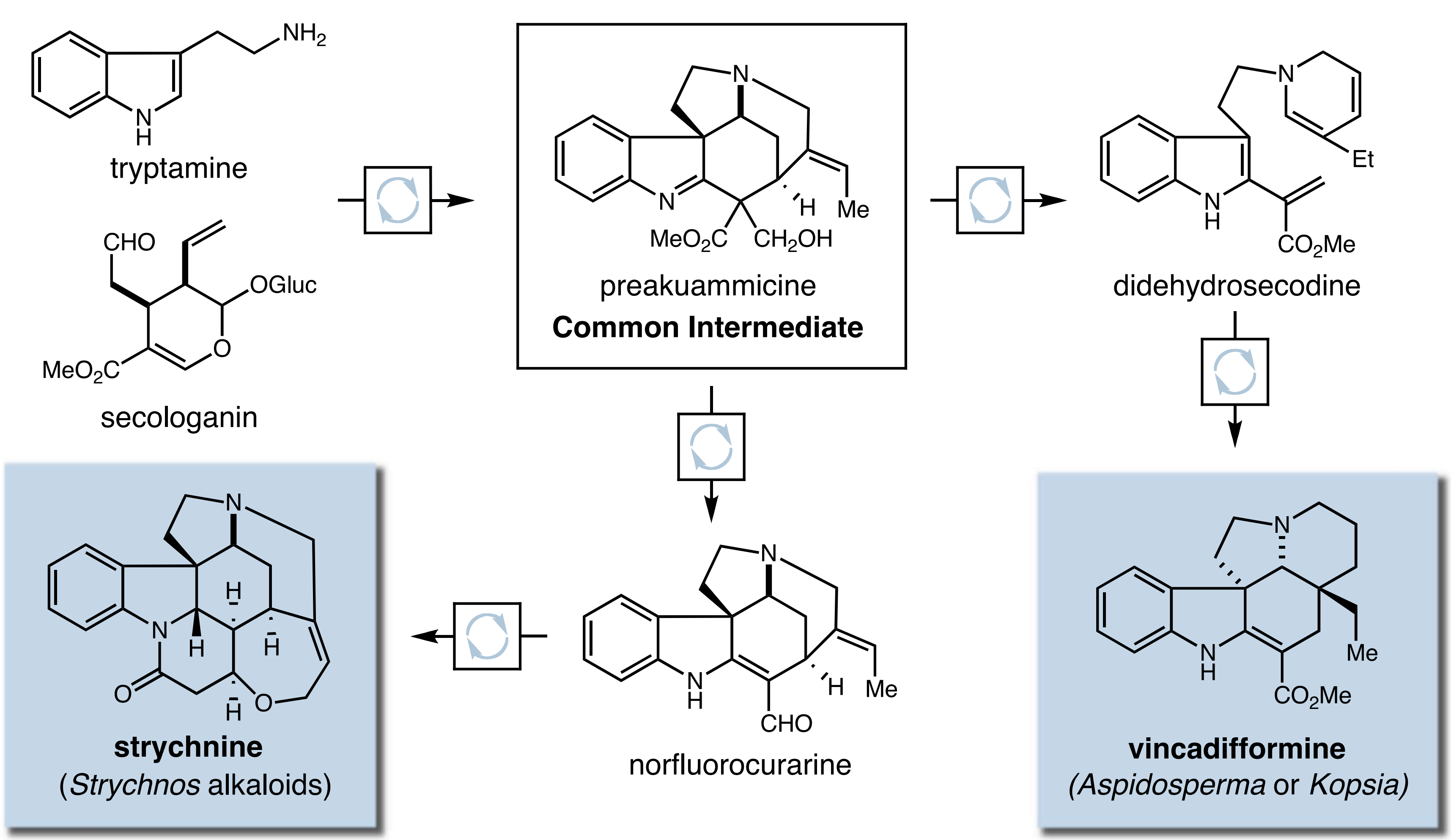

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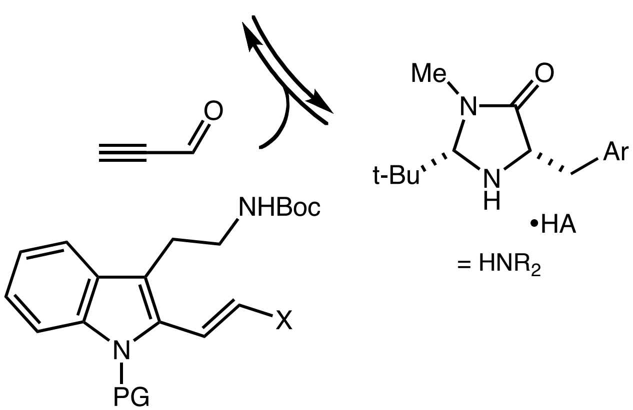
Proposed Diels-Alder/Michael Catalytic Cycle

- Double cascade would enantioselectively construct a highly functionalized spirocycle

First Cycle
(Im)



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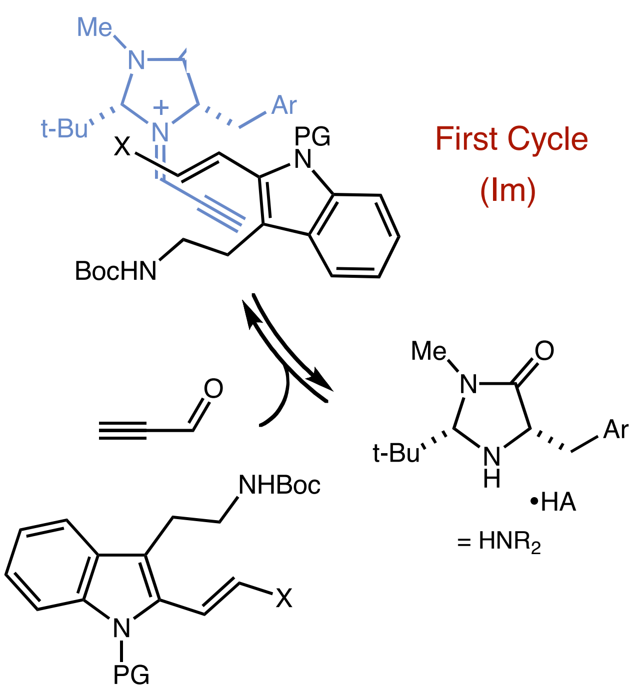

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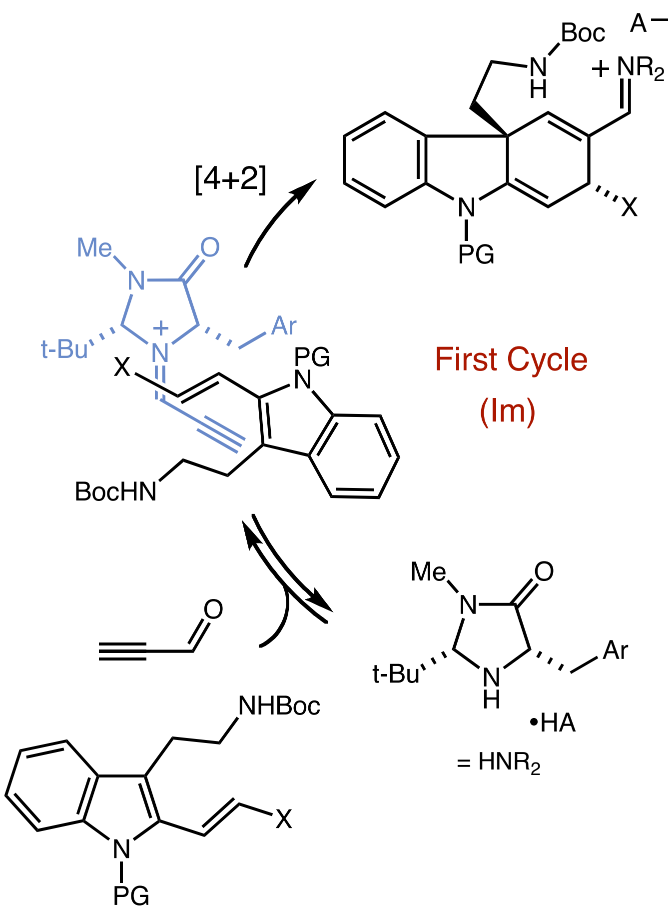

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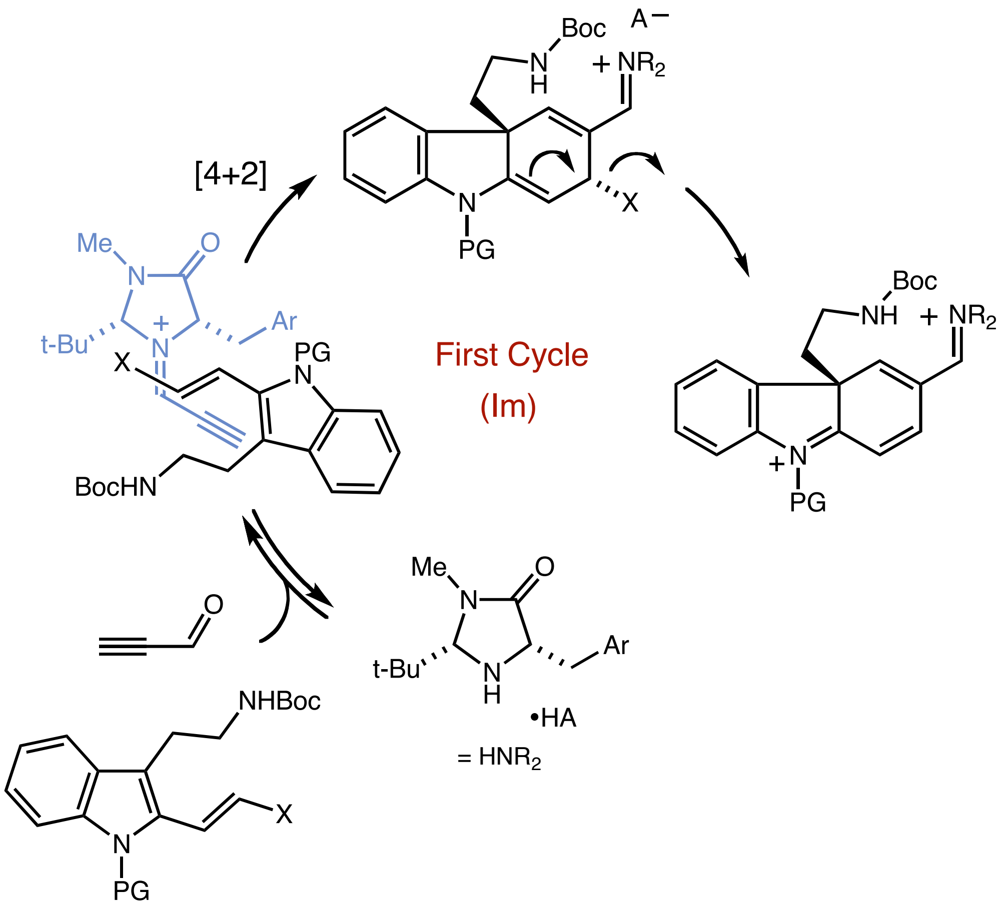

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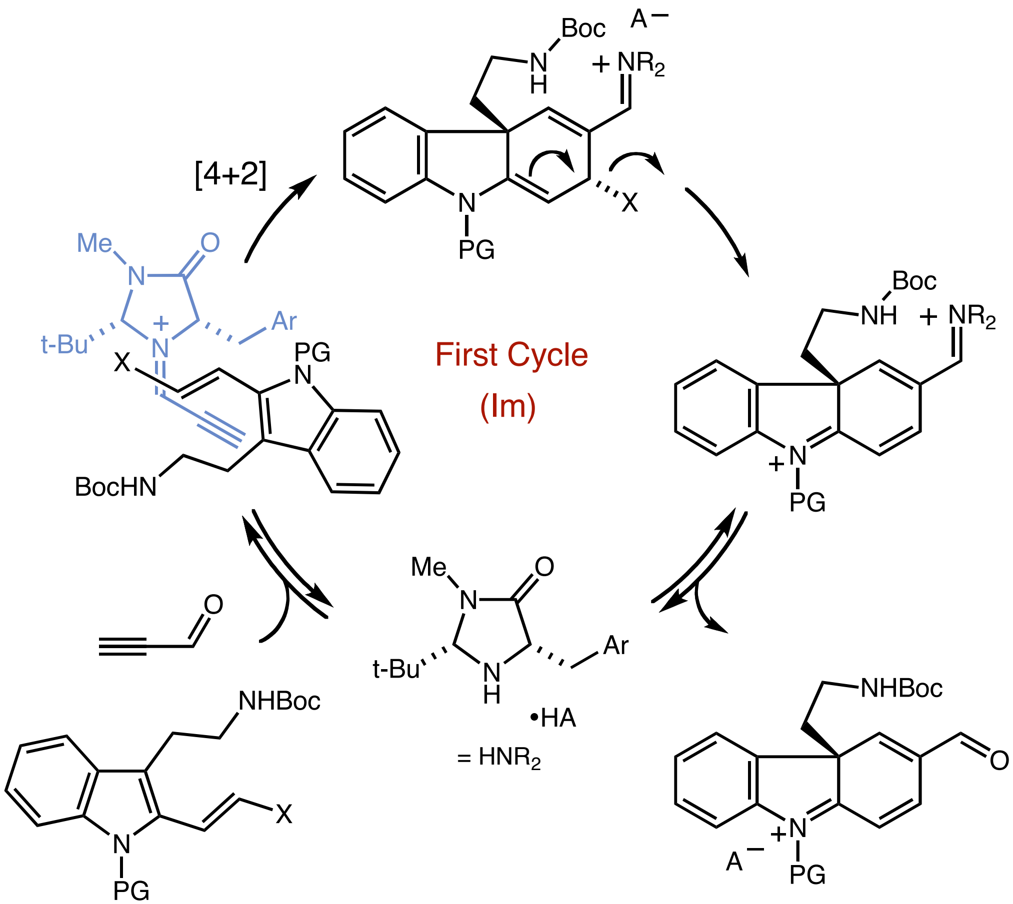

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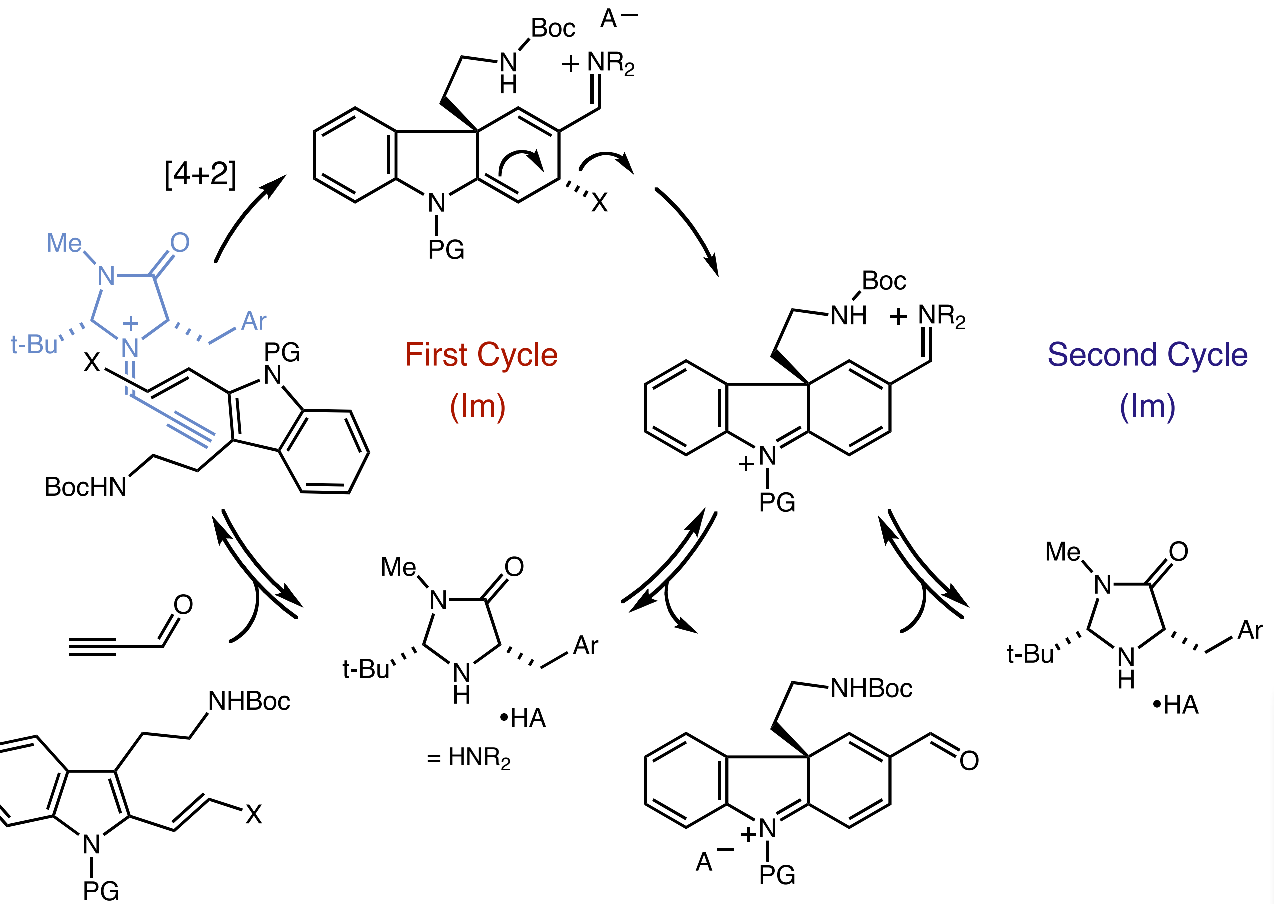

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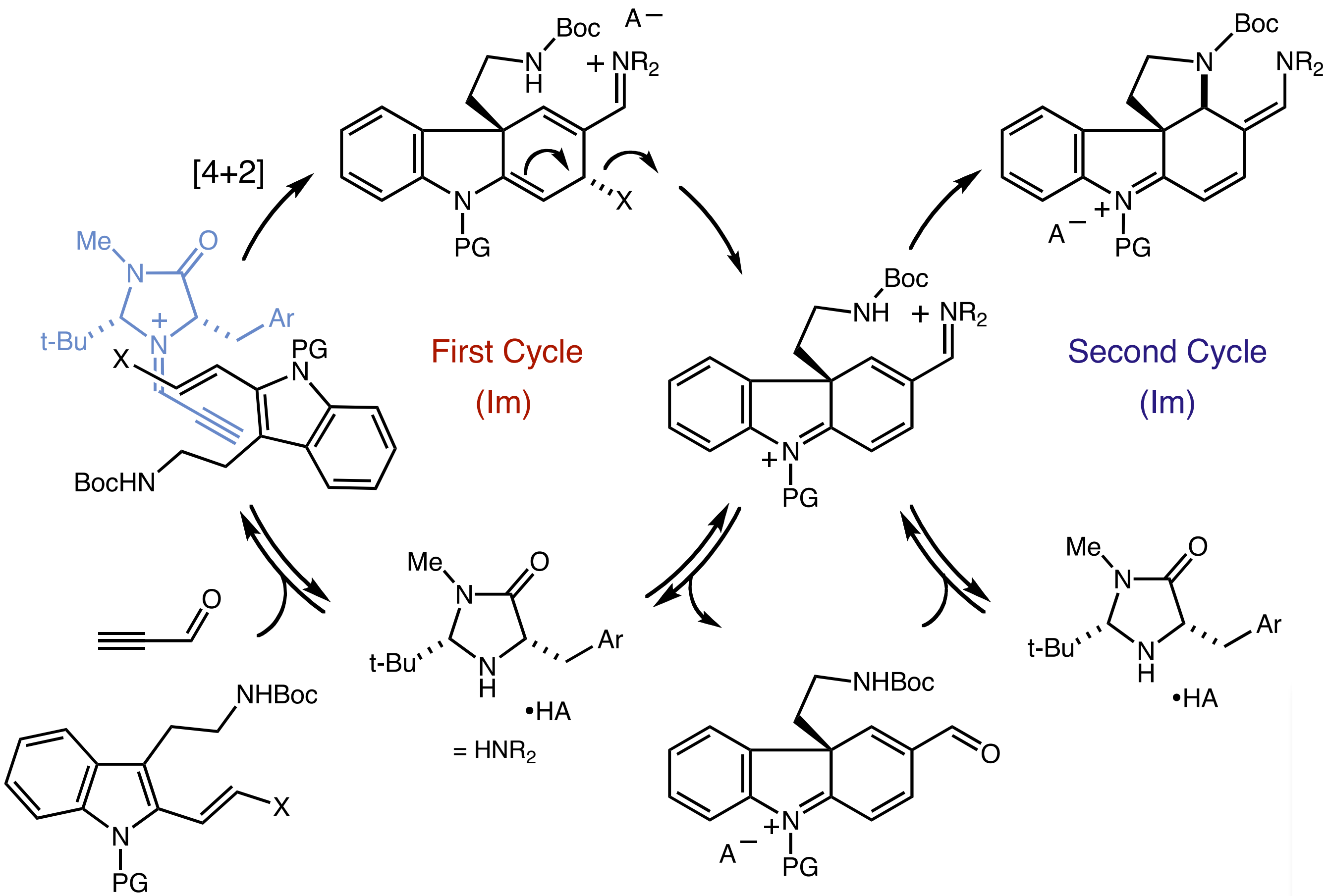

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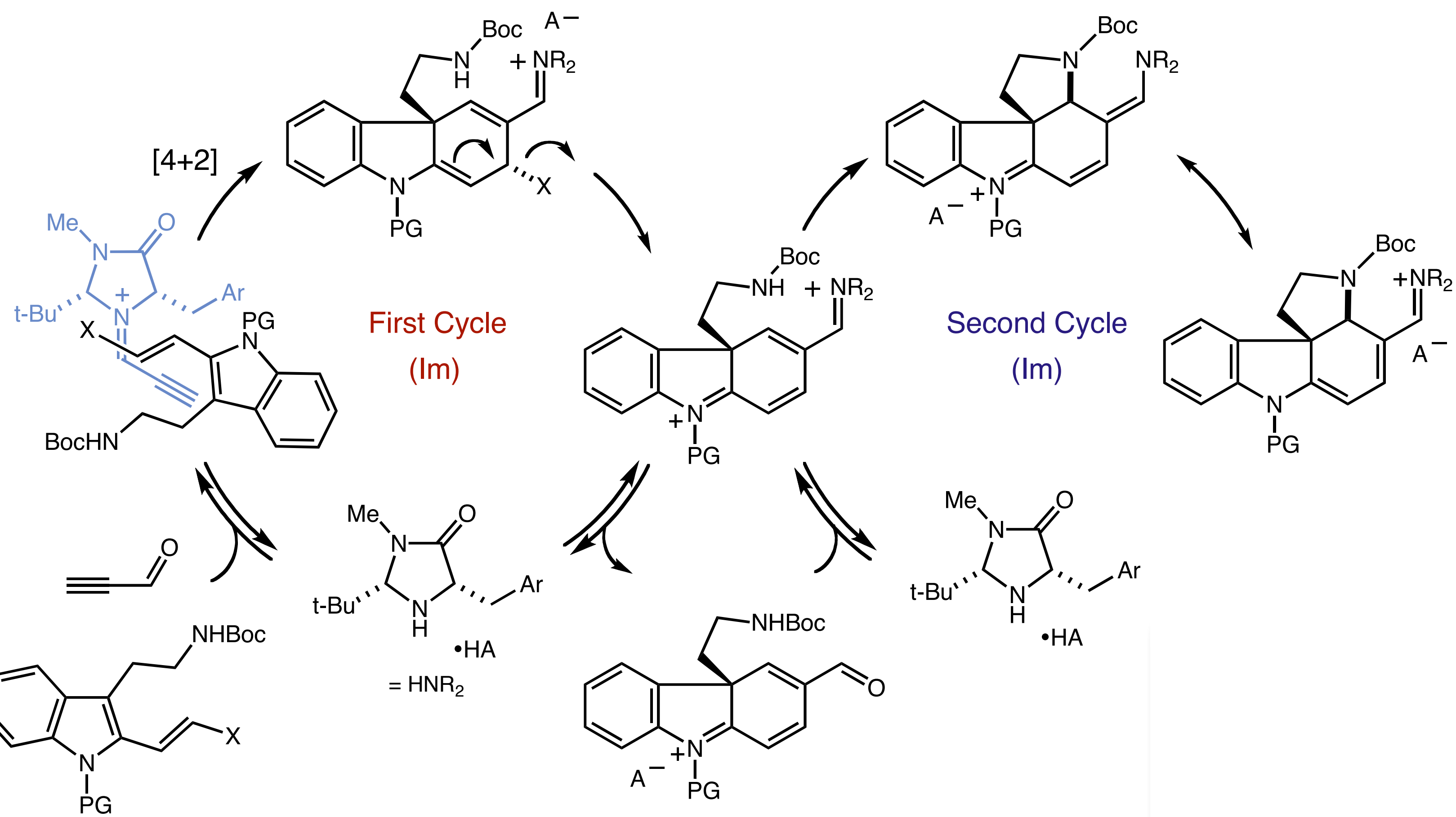

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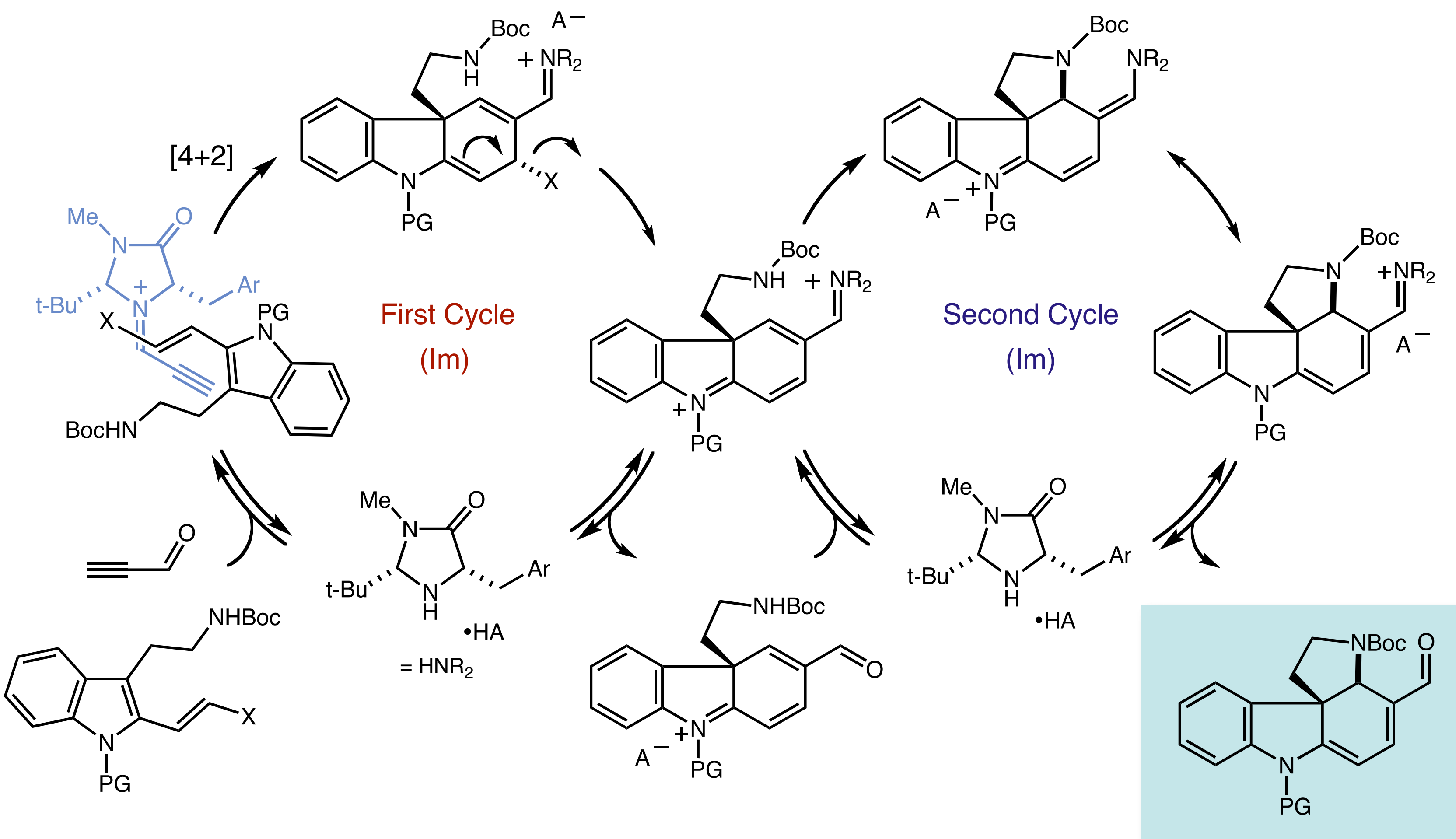
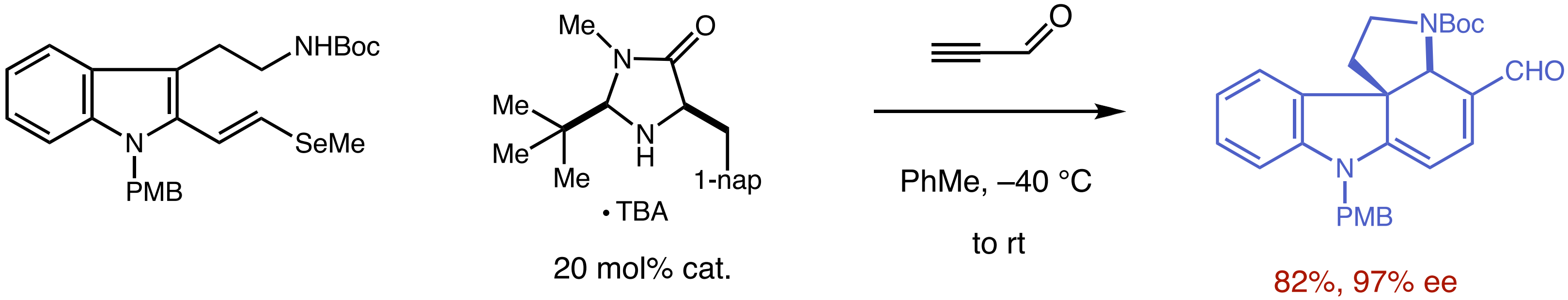


Bioinspired Cascade of a Common Intermediate for Indole Alkaloid Synthesis



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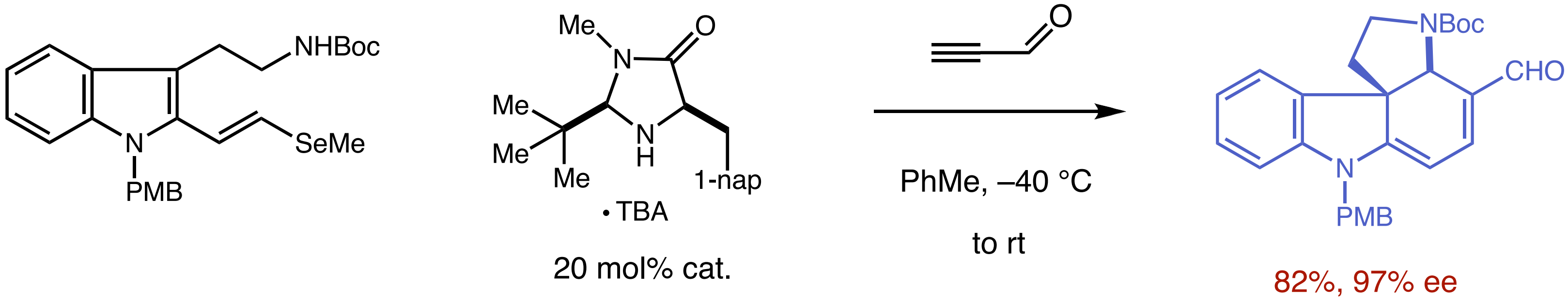
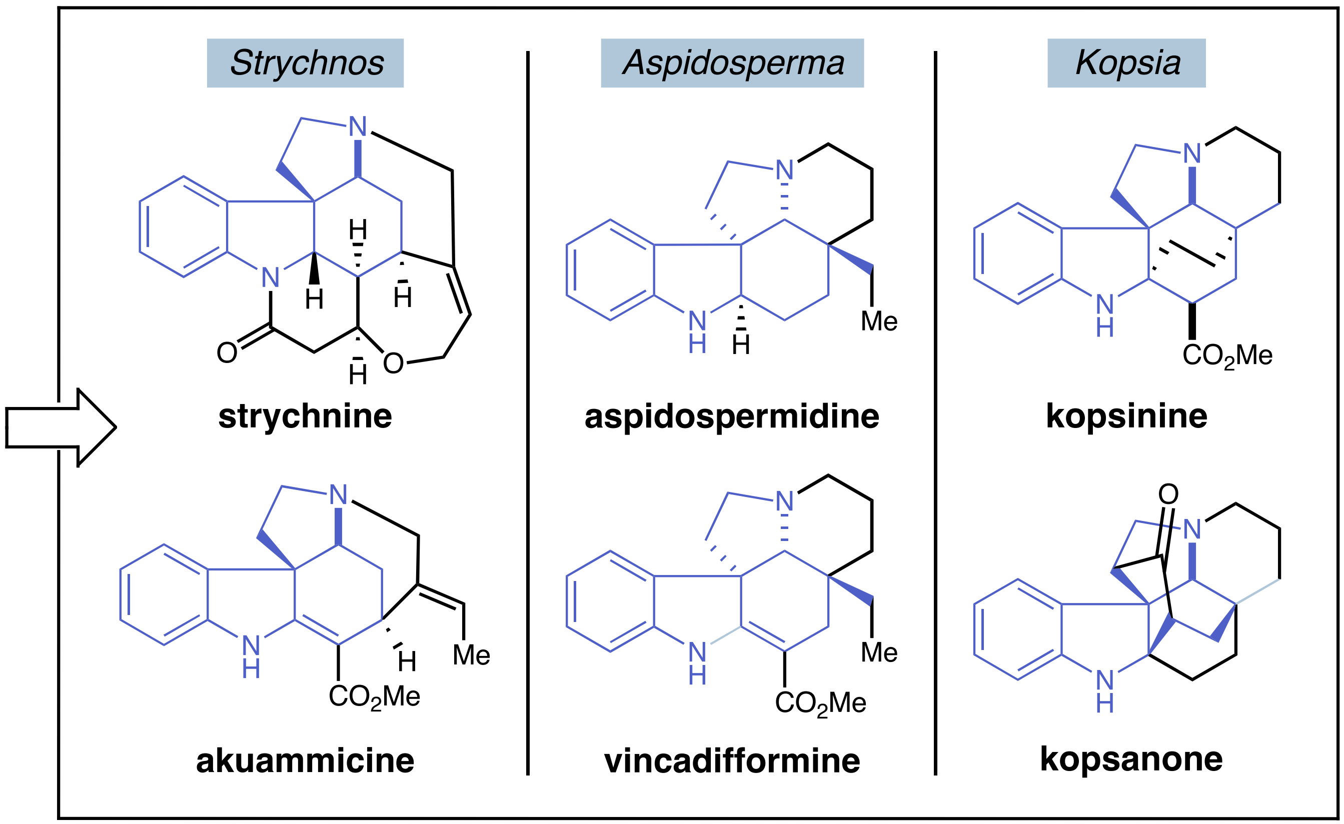
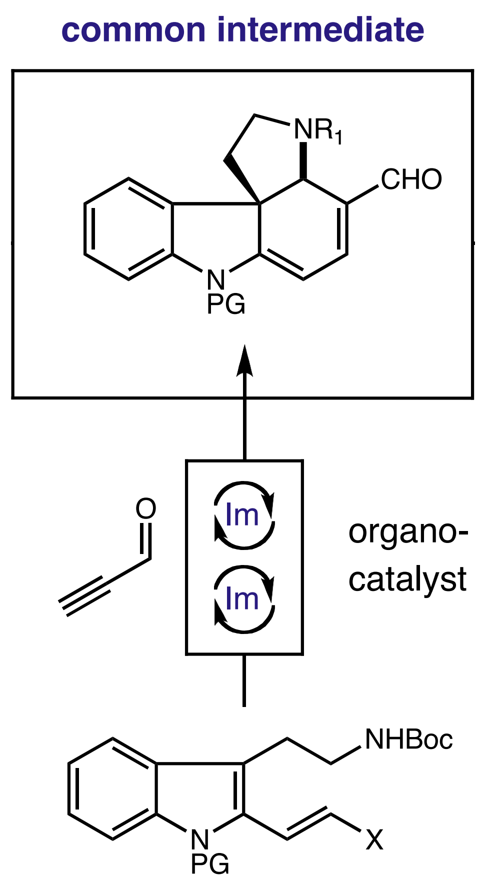




Synthesis of High Profile Alkaloids via Cascade Catalysis



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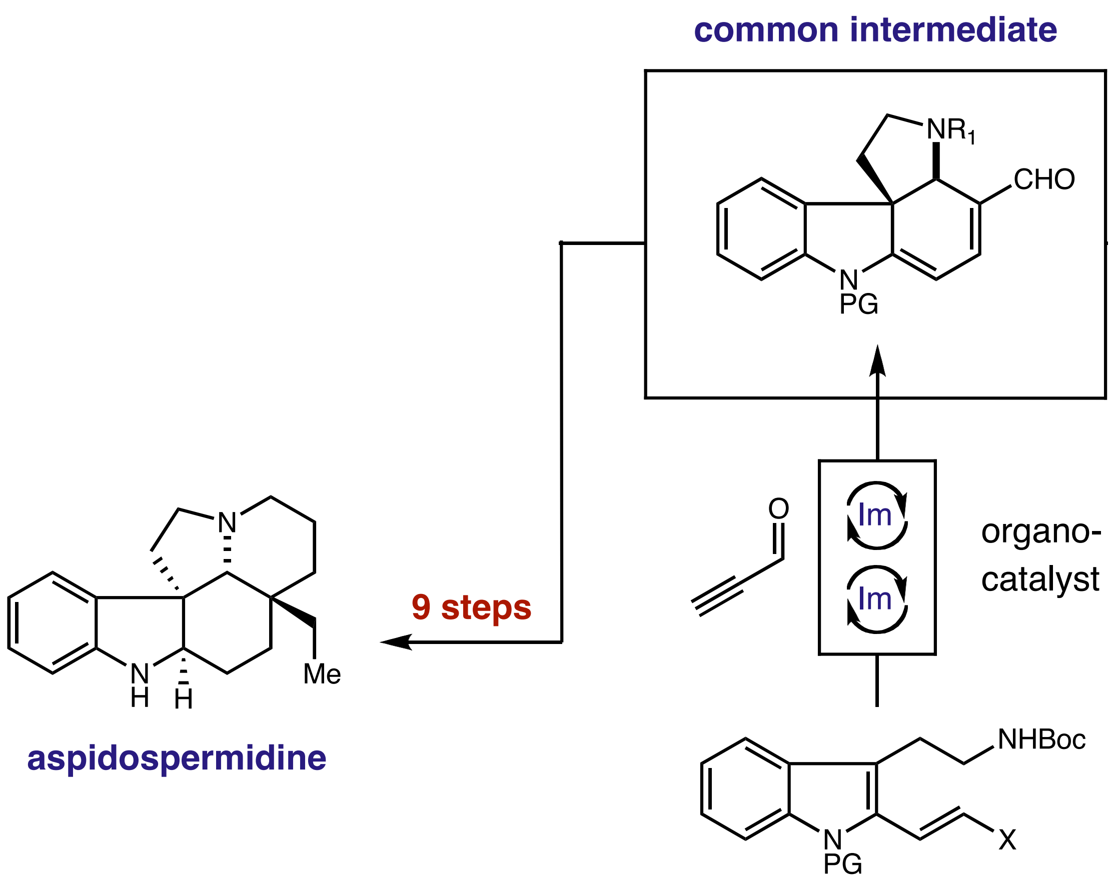

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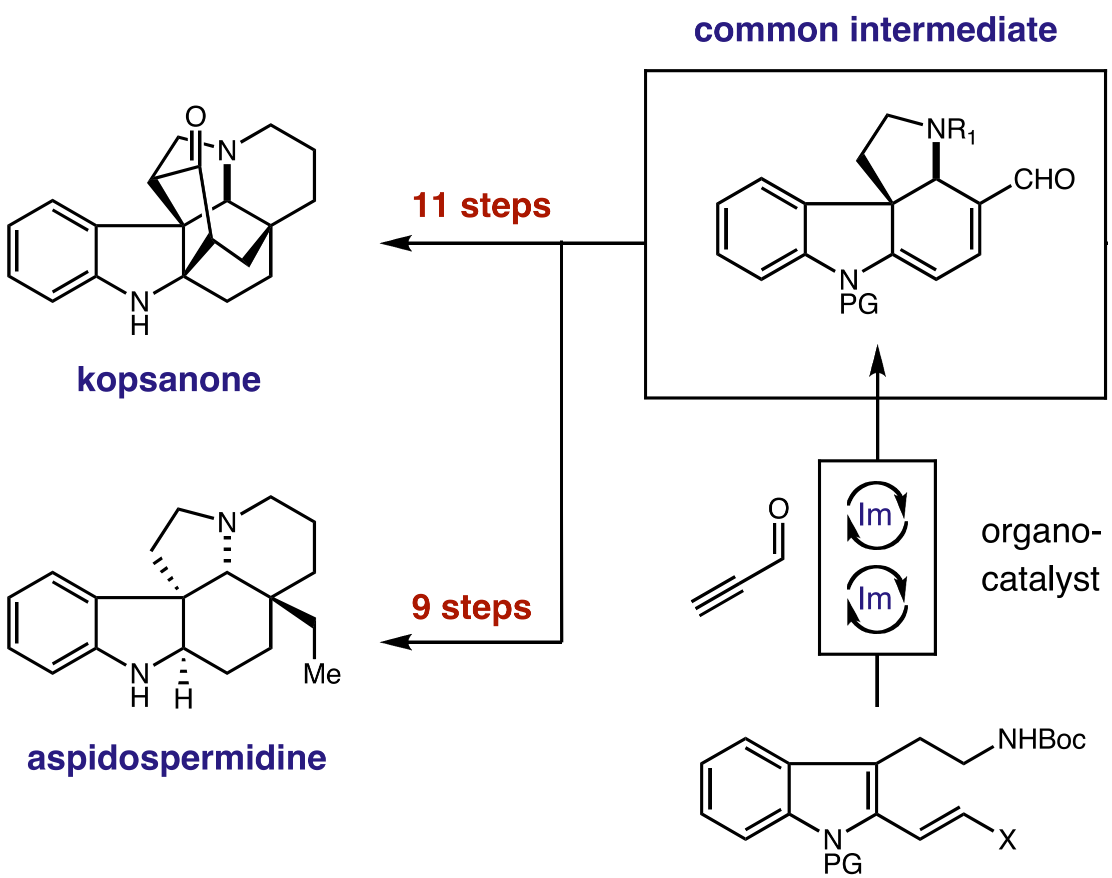

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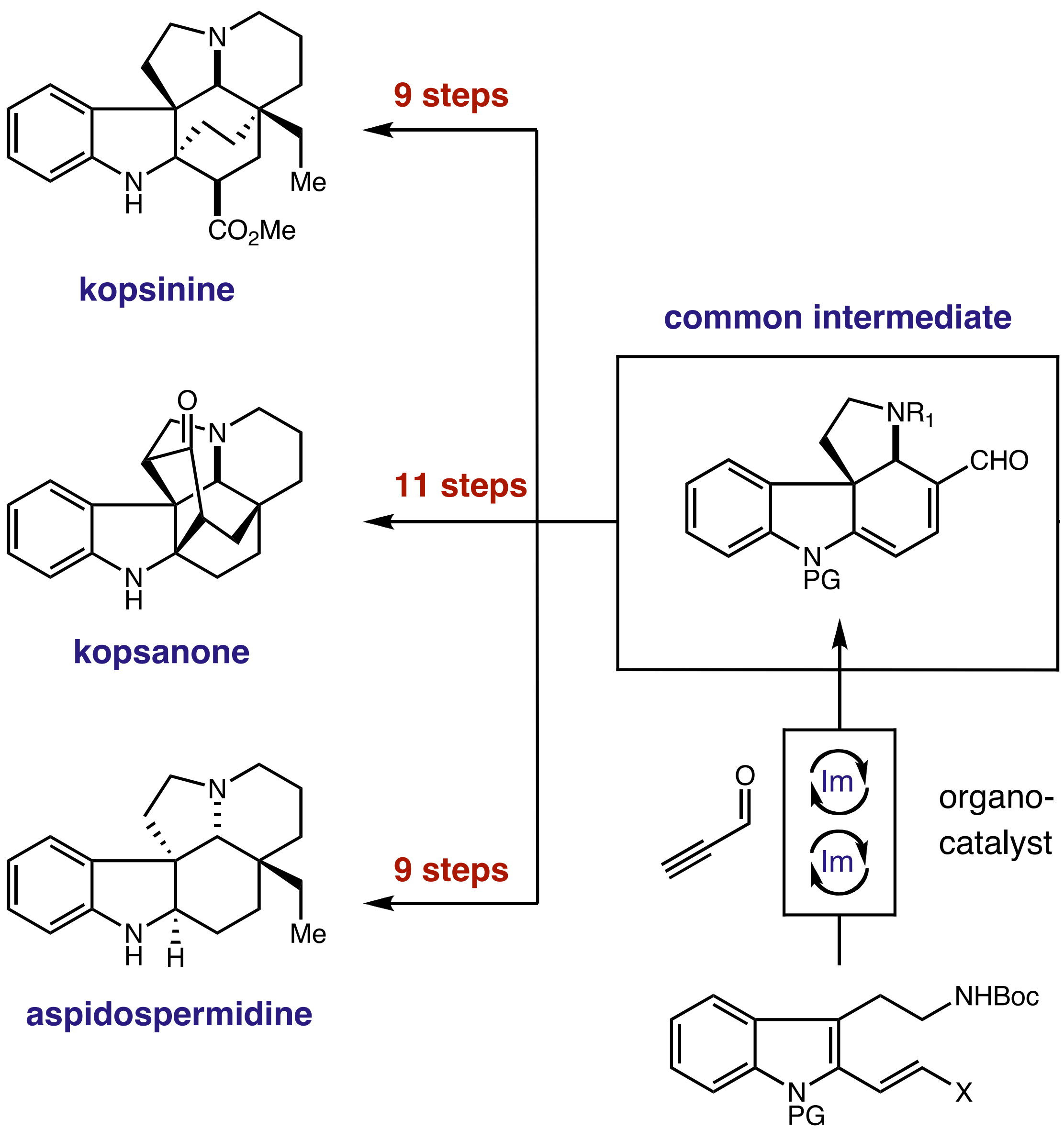

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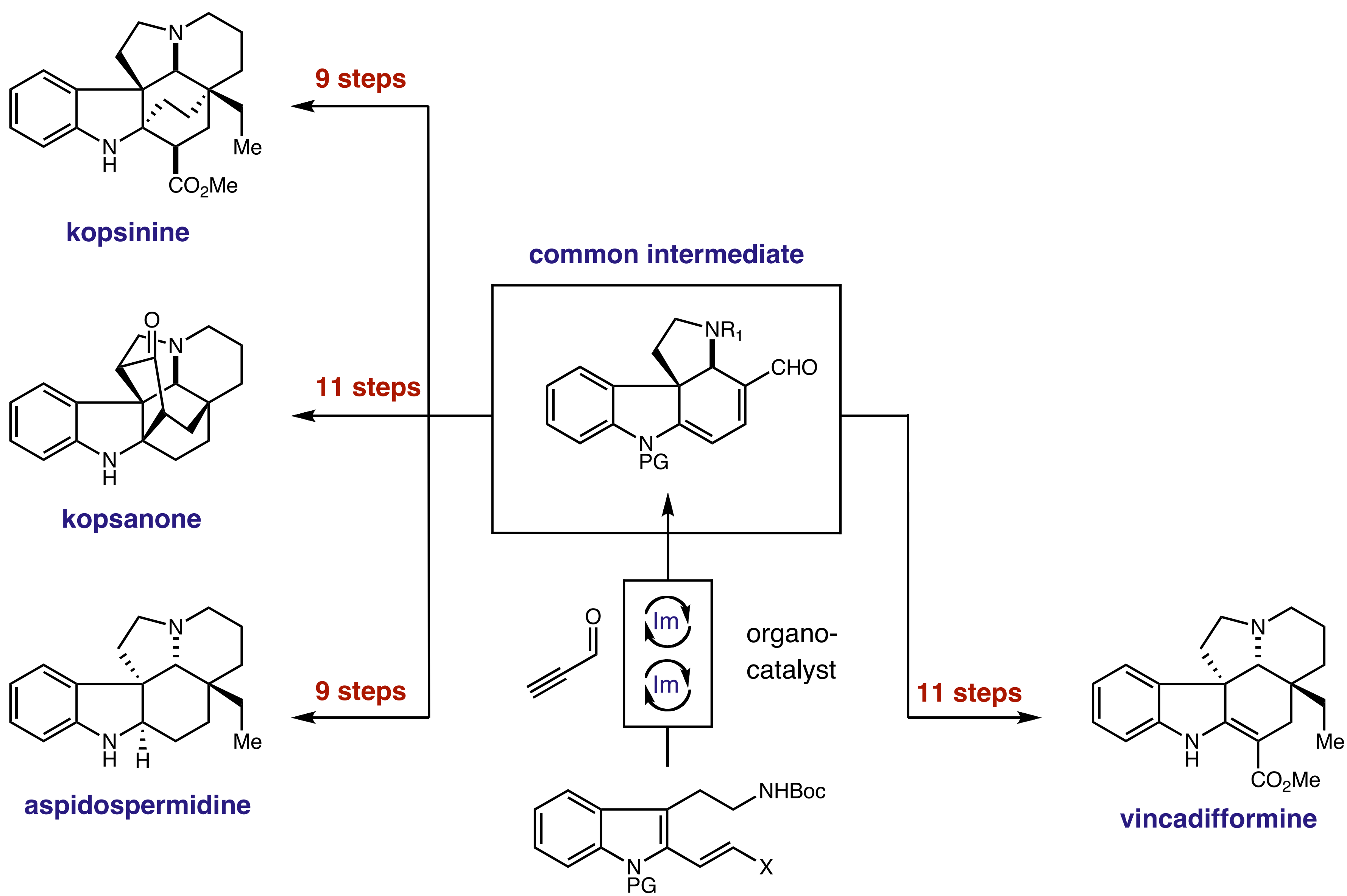

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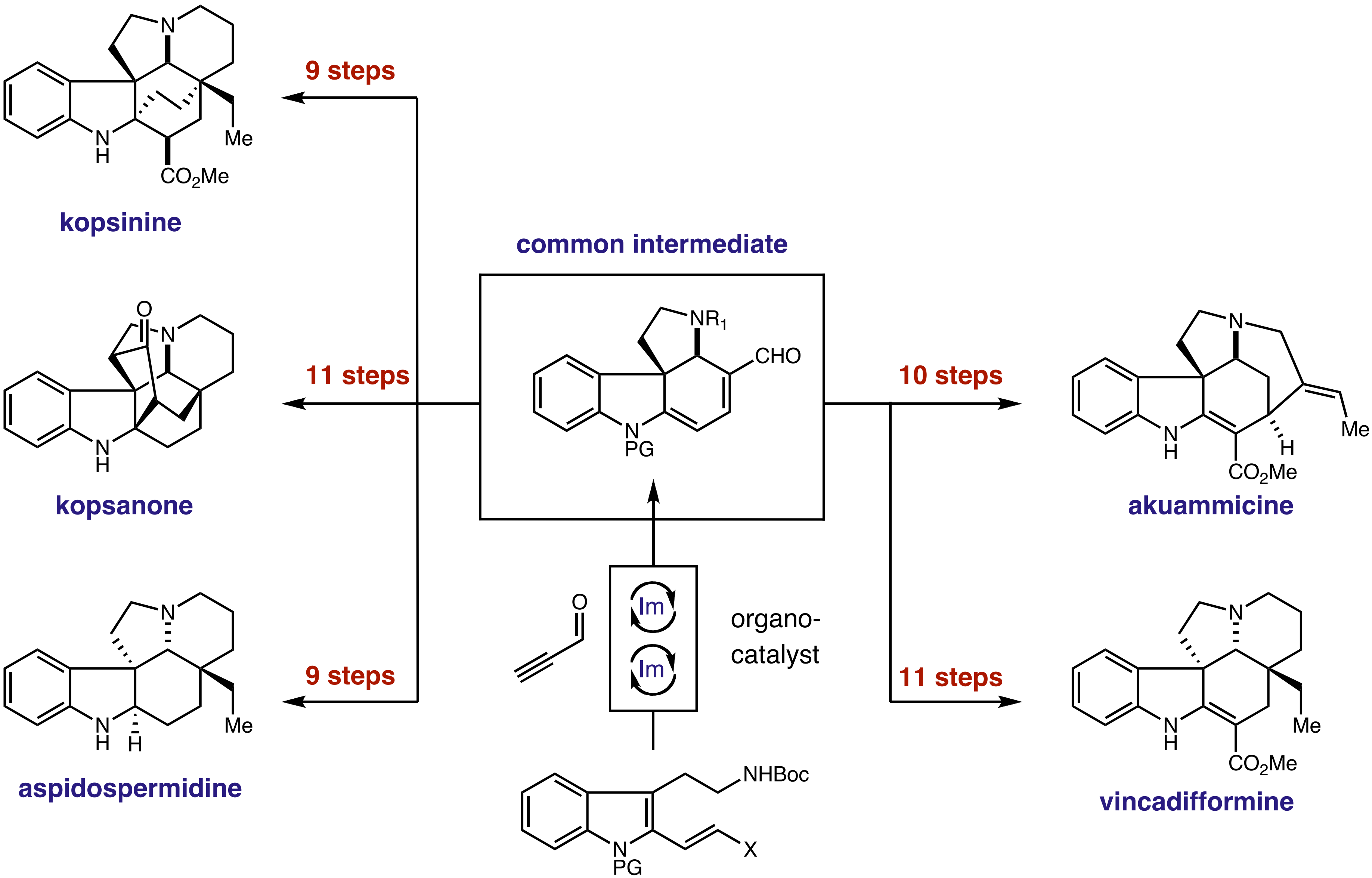

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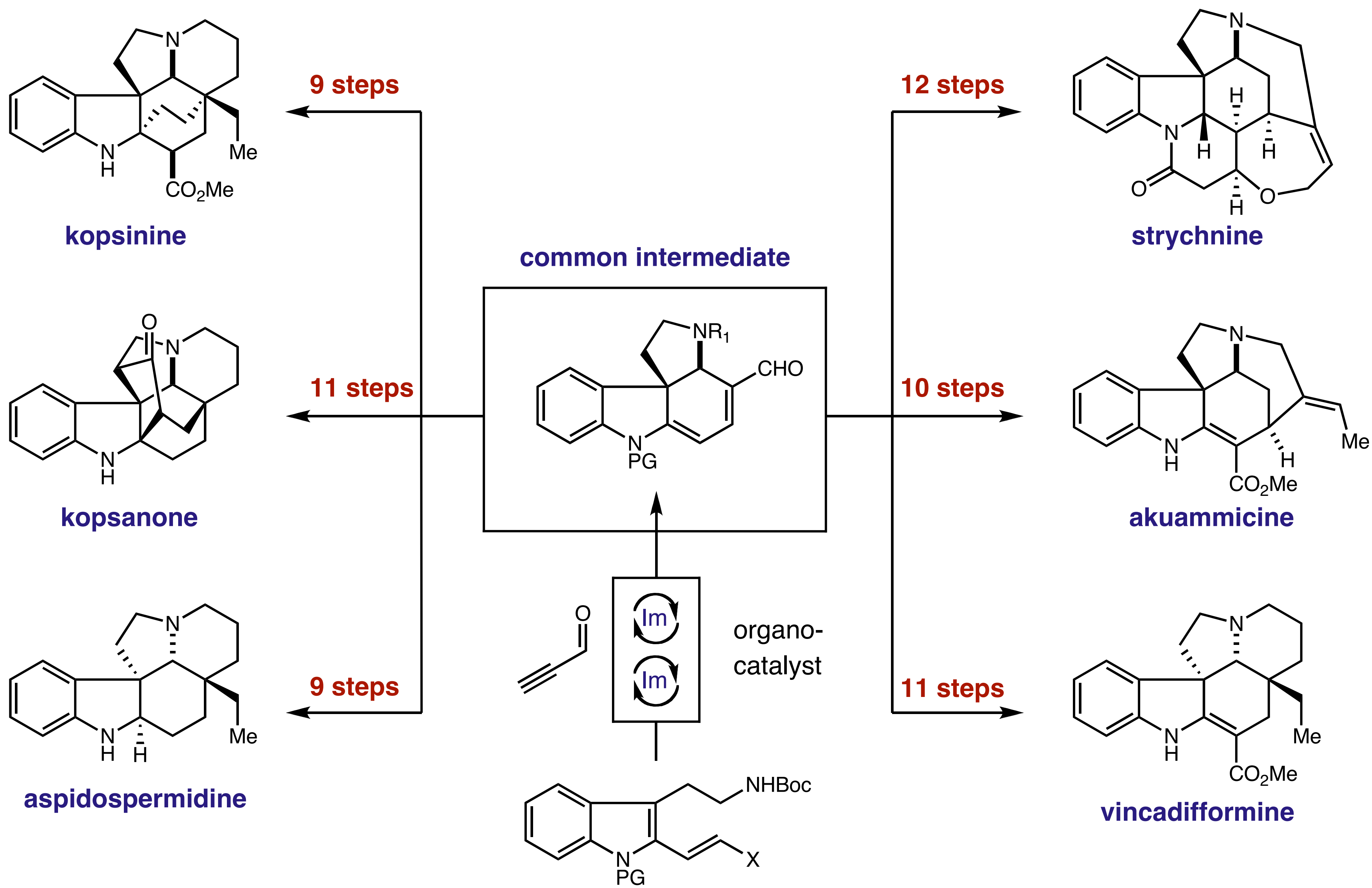

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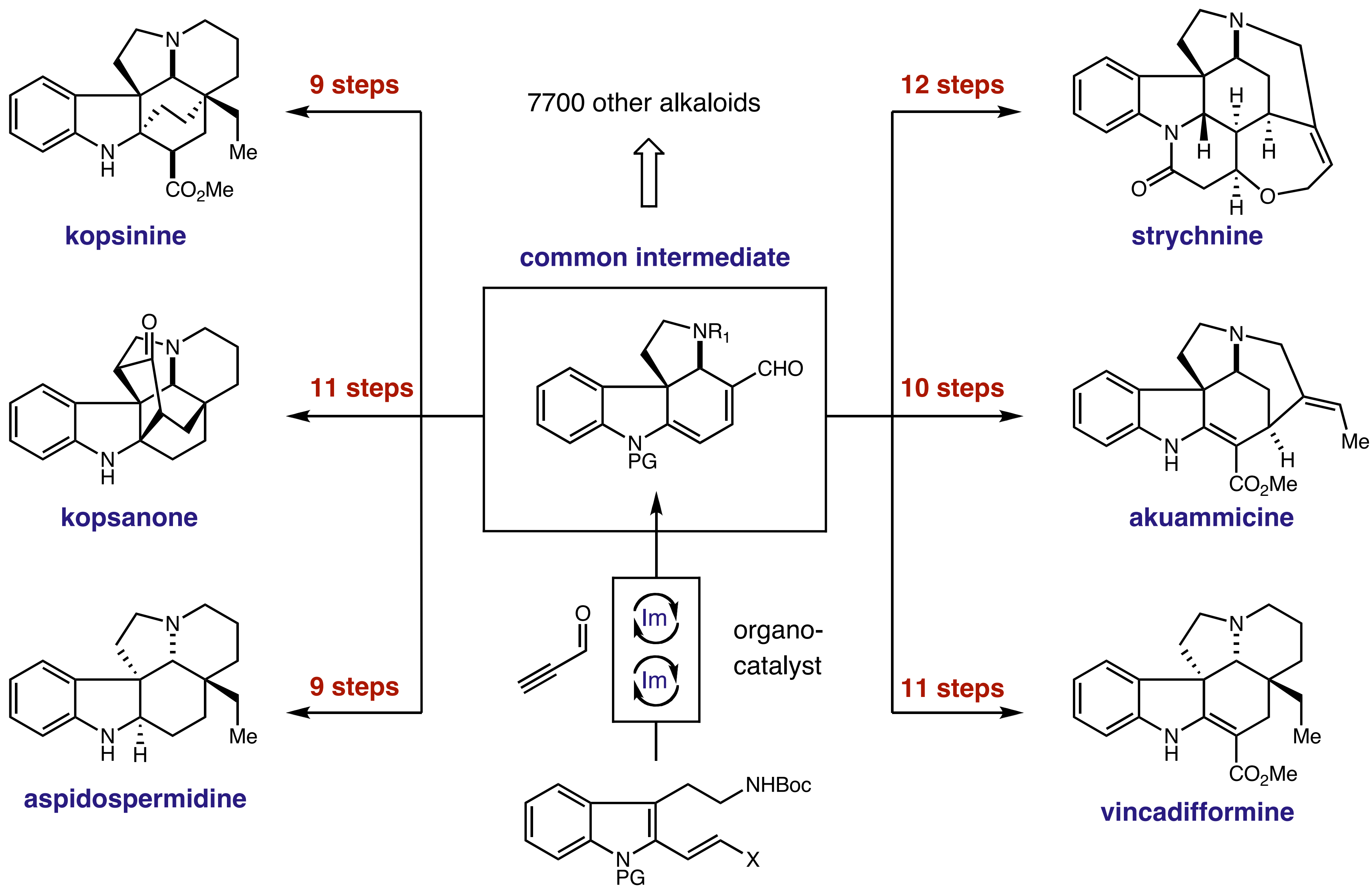

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