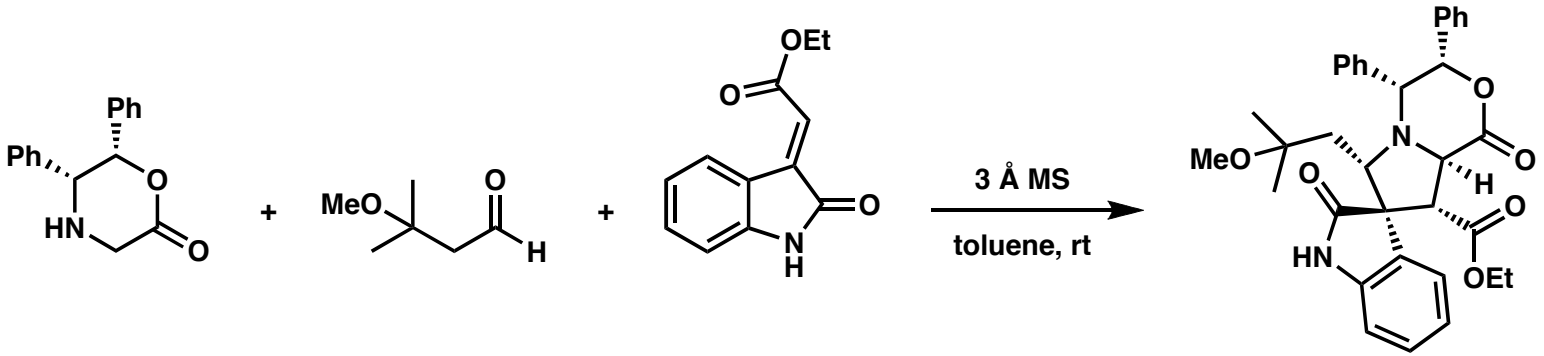
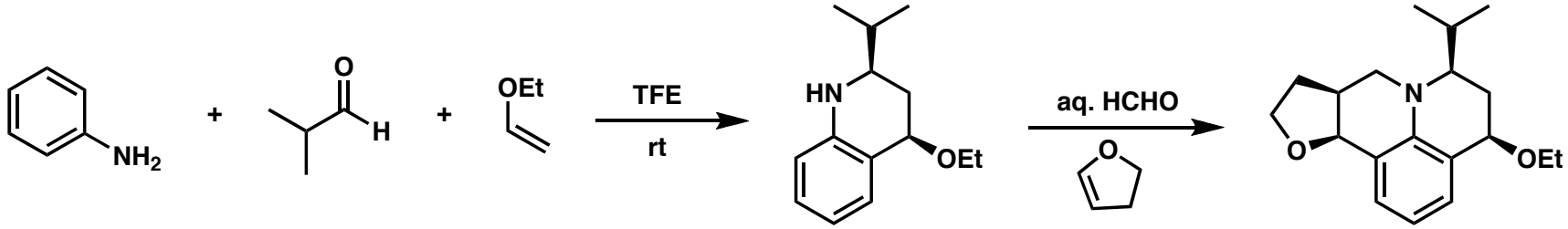
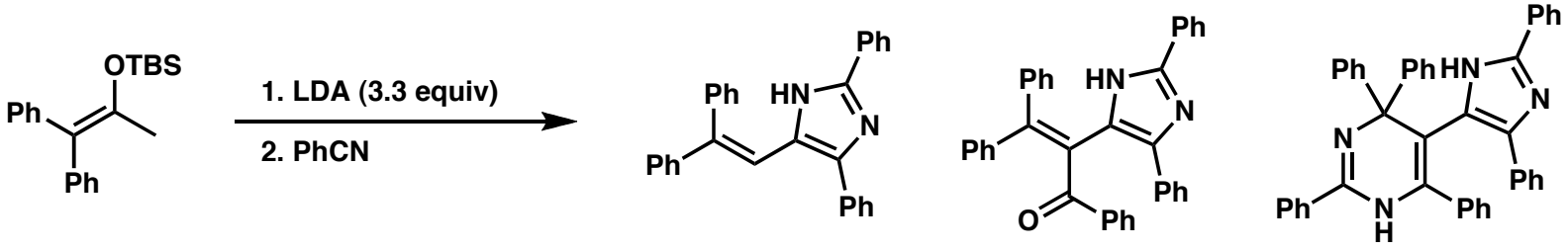


Multicomponent Reactions in Total Synthesis

Generation of Complex Polyfunctionalized Molecules Using Convergent One-Pot Transformations



Kevin Allan
Stoltz Group Literature Meeting
Monday, February 5, 2007
8:00 PM
147 Noyes



3-CR **4-CR** **5-CR**

Multicomponent Reactions in Total Synthesis

- Introduction to Multicomponent Reactions

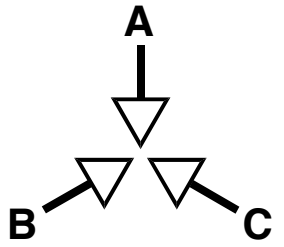
- Reactions Involving Activated Carbonyl Species
  - Mannich Reaction / Petasis (Boronic Acid Mannich) Reaction
  - Biginelli Dihydropyrimidinone Synthesis
  - Passerini Reaction
  - Ugi Reaction

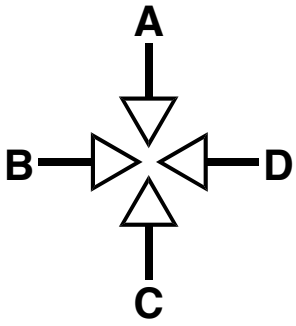
- Cycloadditions
  - Povarov Reaction
  - Knoevenagel / Hetero-Diels-Alder Cycloaddition
  - 1,3-Dipolar Cycloadditions

- Multiple Anion Capture
  - Heterospirocyclic Compounds and Medium-Sized Lactones
  - Radialene-Shaped Pyrroles
  - Allene Dianions and Nitrile Oligomers

- One-Pot Total Syntheses
  - Nitaramine
  - Glyantrypine, Fumiquinazoline F, Fiscalin B
  - Schlerotigenin, Circumdatin F, Asperlicin C

- Conclusions





Reviews:
Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89.
Multicomponent Reactions. Zhu, J.; Bienaymé, H., eds. Wiley-VCH; Weinheim, **2005**.
Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, *10*, 1471-1499.
Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187-191.
Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321-3329.
Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 499-516.
Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115-122.

Multicomponent Reactions

An Introduction

"Multicomponent reactions (MCRs) are processes involving sequential reactions among three or more reactant components that co-exist in the same reaction mixture. In order to be efficient, MCRs rely on components that are compatible with each other and do no undergo alternative irreversible reactions to form other products or by-products."

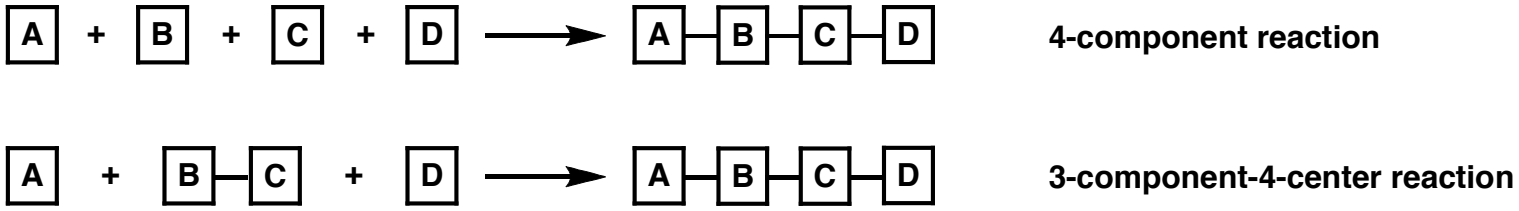
-- Jieping Zhu in *Multicomponent Reactions*

- Addendum: The products of multicomponent reactions comprise a portion of each individual reactant component.

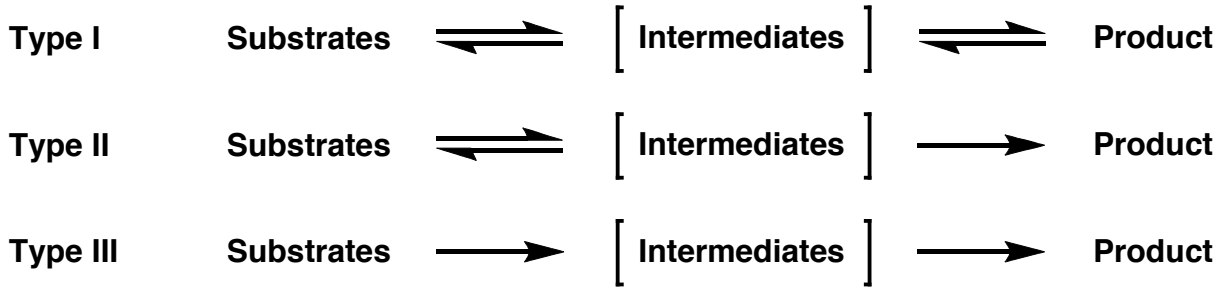
- Multicomponent reactions are sometimes referred to as tandem or domino reactions.

- Multicomponent reactions may be further classified by the number of molecules and the number of functional groups participating in the reaction.

  Example:



- Multicomponent reactions are also classified by the reversibility of steps leading to the product.

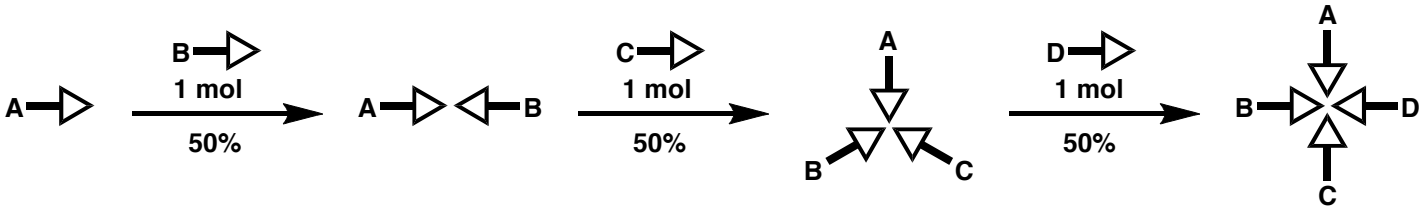


Ugi, I. *J. Prakt. Chem.* **1997**, *399*, 499-516.
Bienaymé, H. *Chem. Eur. J.* **2000**, *6*, 3321-3329.

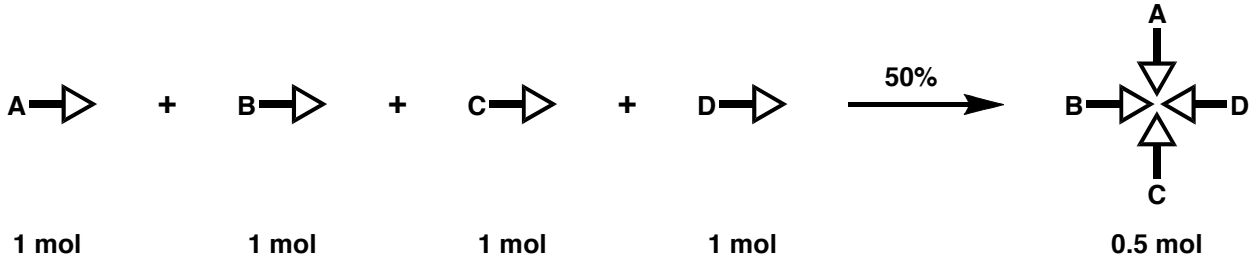
Multicomponent Reactions

A New Approach to Total Synthesis

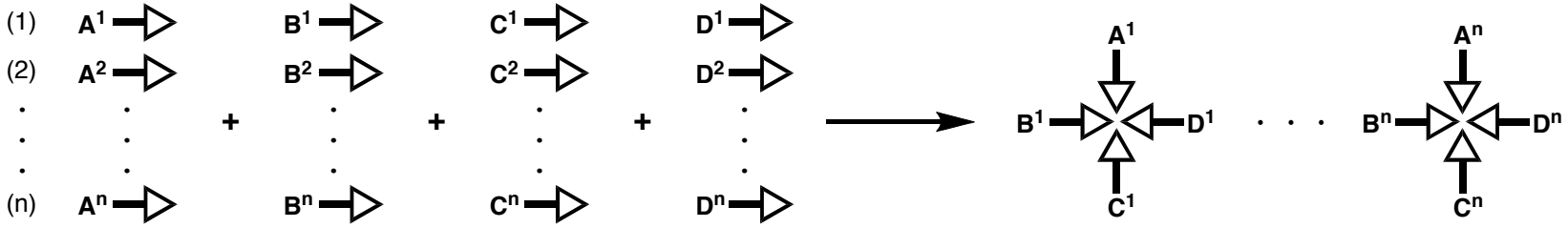
- Linear total syntheses require significant amounts of time and money to advance starting materials to complex targets.



- MCRs minimize cost in the form of time and material by generating complex targets in a single convergent step.



- MCRs typically run at mild temperatures and do not require many reagents in excess of the participating substrates. This has made them ideal for combinatorial library synthesis as well as industrial pharmaceutical synthesis.



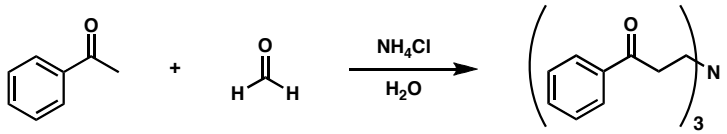
m component reaction with **n** types of each component → $\mathbf{n^m}$ products

n = 5 (20 SM cmpds) → 625 products
n = 10 (40 SM cmpds) → 10,000 products
n = 50 (200 SM cmpds) → 6.25 mill products

Mannich Reaction

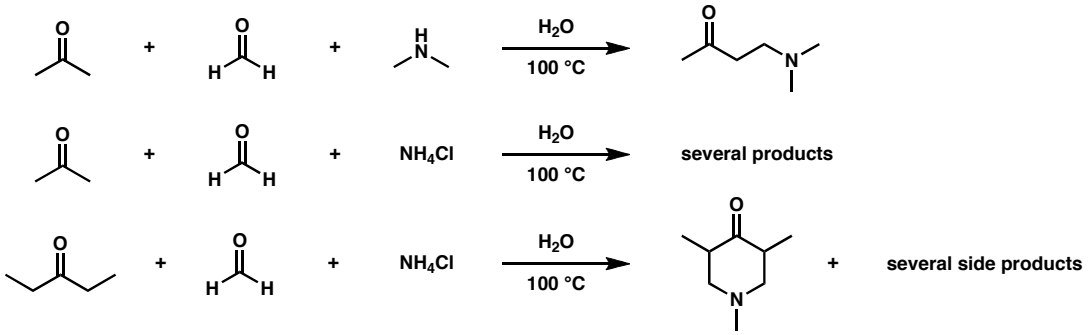
Three-Component Synthesis of β-Aminocarbonyls

- In 1903, B. Tollens and C. M. van Marle observed the formation of a tertiary amine from the treatment of an aqueous solution of acetophenone and formaldehyde with ammonium chloride.



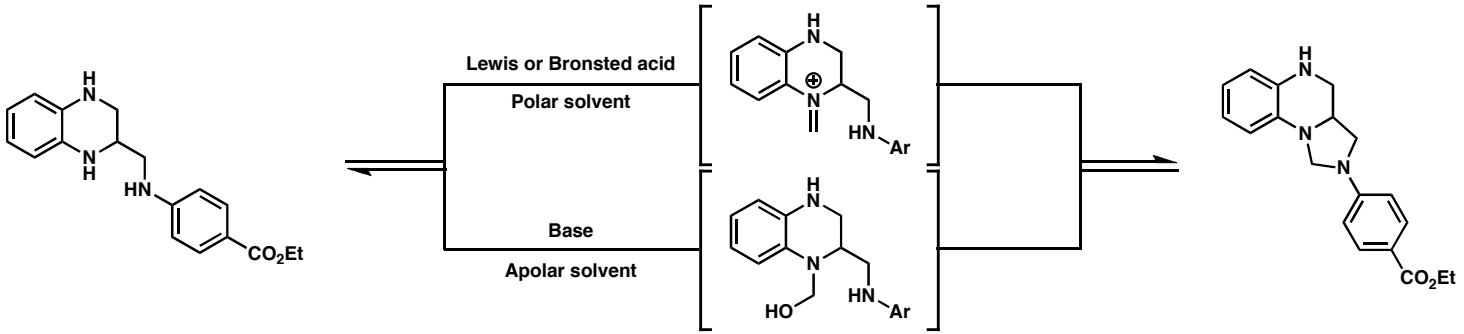
Tollens, B.; van Marle, C. M. *Ber.* **1903**, *36*, 1347-1351.

- In 1917, Carl Mannich (Berlin, Germany) reported the formation of a number of β-aminoketones under the same conditions.



Mannich, C. *Archiv. Pharm.* **1917**, *255*, 261-276.
Mannich, C. *J. Chem. Soc. Abstr.* **1917**, *112*, 634-635.

- The Mannich reaction is a Type I MCR that proceeds under both acidic and basic conditions, though acidic conditions are more common. In 1969, Stephen Benkovic (Penn State) performed kinetics experiments over a broad pH range that supported the formation of a pH-dependent steady state iminium intermediate under acidic conditions. Under basic conditions, a carbinolamine intermediate presides.

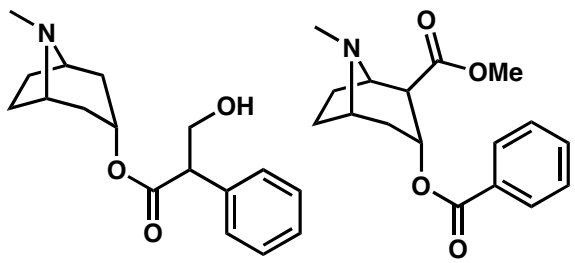


Benkovic, S. J. *J. Am. Chem. Soc.* **1969**, *91*, 1860-1861.

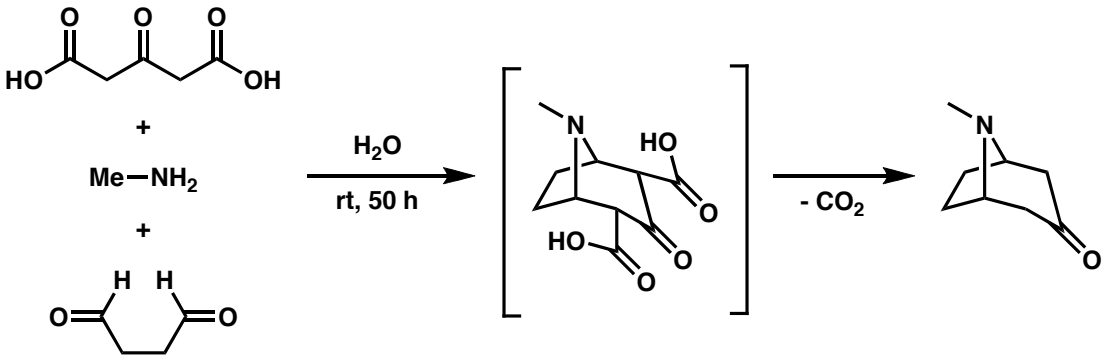
Mannich Reaction

Select Total Syntheses

Robinson's Synthesis of Tropinone:

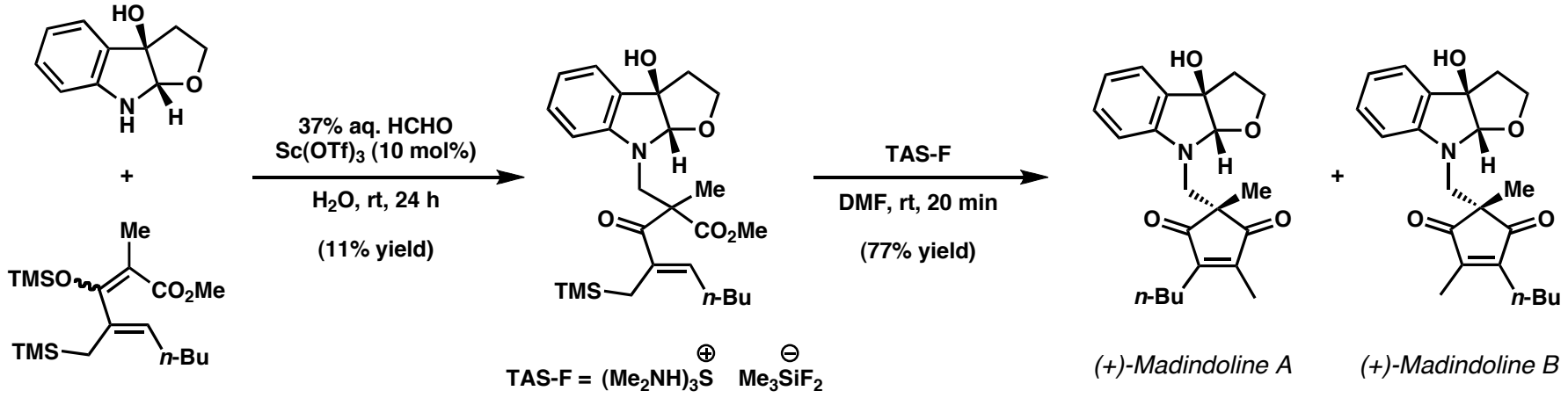


Atropine *Cocaine*



Robinson, R. *J. Chem. Soc.* **1917**, 762-768.

Omura's Synthesis of (+)-Madindoline A and B:



TAS-F = $(Me_2NH)_3S^{\oplus}$ $Me_3SiF_2^{\ominus}$

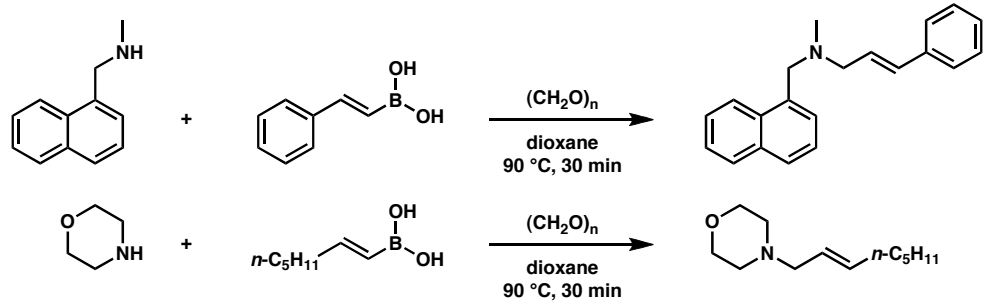
(+)-Madindoline A *(+)-Madindoline B*

Omura, S. *Tetrahedron Lett.* **2006**, *47*, 6761-6764.

Petasis (Boronic Acid Mannich) Reaction

Three-Component Synthesis of Allyl, Propargyl, and Benzylamines

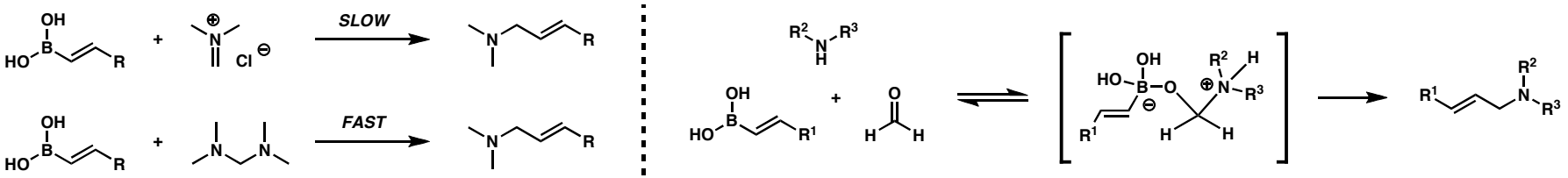
- In 1993, Nicos A. Petasis (USC) described the preparation of tertiary allylic amines from paraformaldehyde, secondary amines, and vinyl boronic acids under acid-free conditions. Yields ranged from 75-96%.



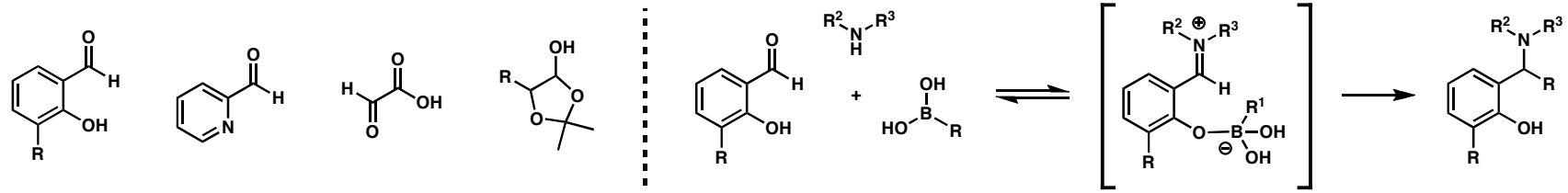
Petasis, N. A. *Tetrahedron Lett.* **1993**, *34*, 583-586.

- The Petasis reaction is a Type II reaction, though the precise mechanism is still disputed:

  - Petasis noted that in the absence of acid, it was unlikely that significant amounts of the iminium salt would form. Also, boronic acids did not readily add to preformed iminium salts, though they did react with diamines. Based on these observations, Petasis proposed the formation of an intermediate ammonium borate complex followed by internal delivery of the vinyl nucleophile.



  - However, the vast majority of cases in the literature employ an aldehyde substrate containing a directing group near the carbonyl, indicating a necessity for formation of a two-center ionic complex. In these cases, a protic solvent is typically used (MeOH, EtOH, TFE).

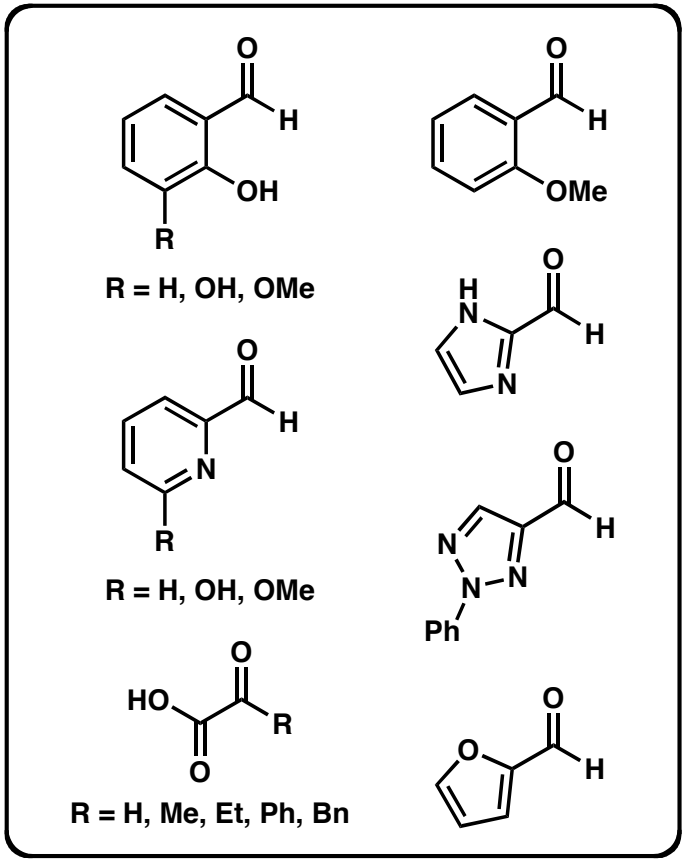


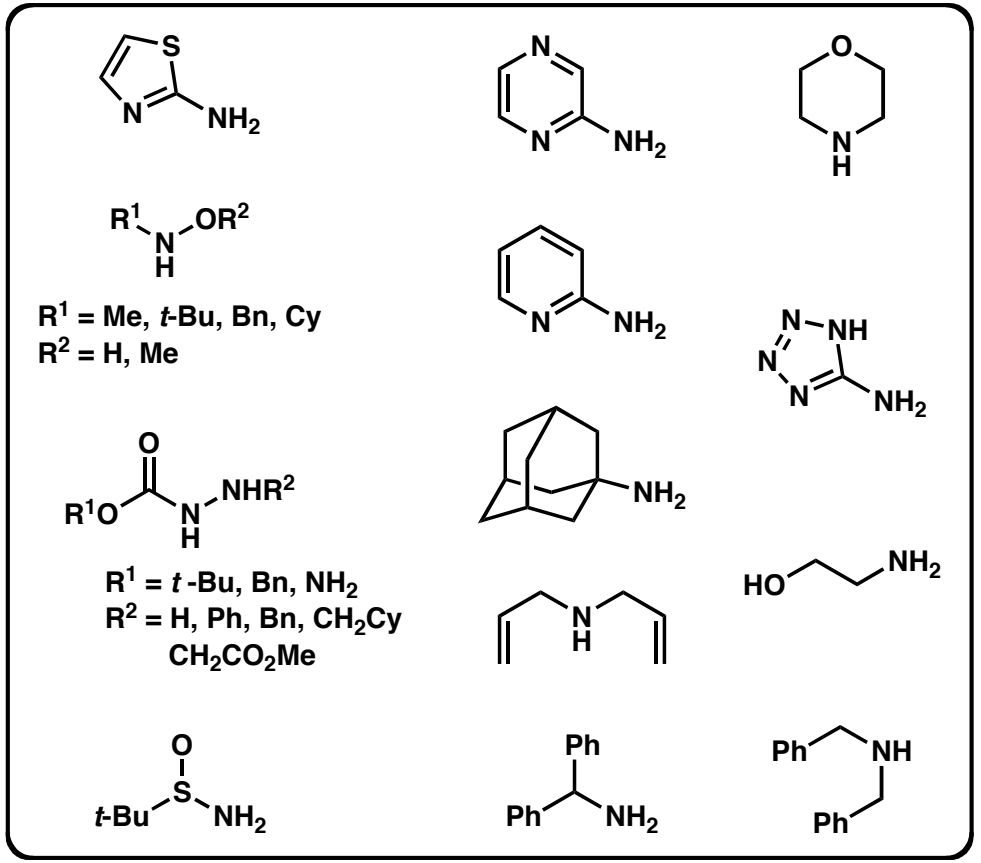
Bryce, M. R.; Hansen, T. K. *Tetrahedron Lett.* **2000**, *41*, 1303-1305.
Schreiber, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3635-3638.

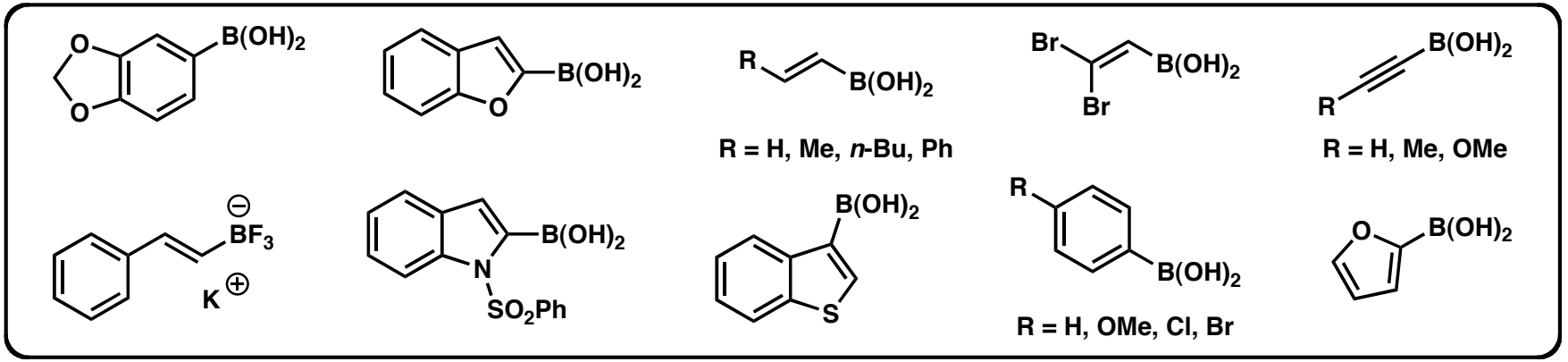
Petasis, N. A. *Tetrahedron Lett.* **2001**, *42*, 539-542.
McReynolds, M. D.; Hanson, P. R. *Chemtracts* **2001**, *14*, 796-801.

Petasis (Boronic Acid Mannich) Reaction

Substrate Scope

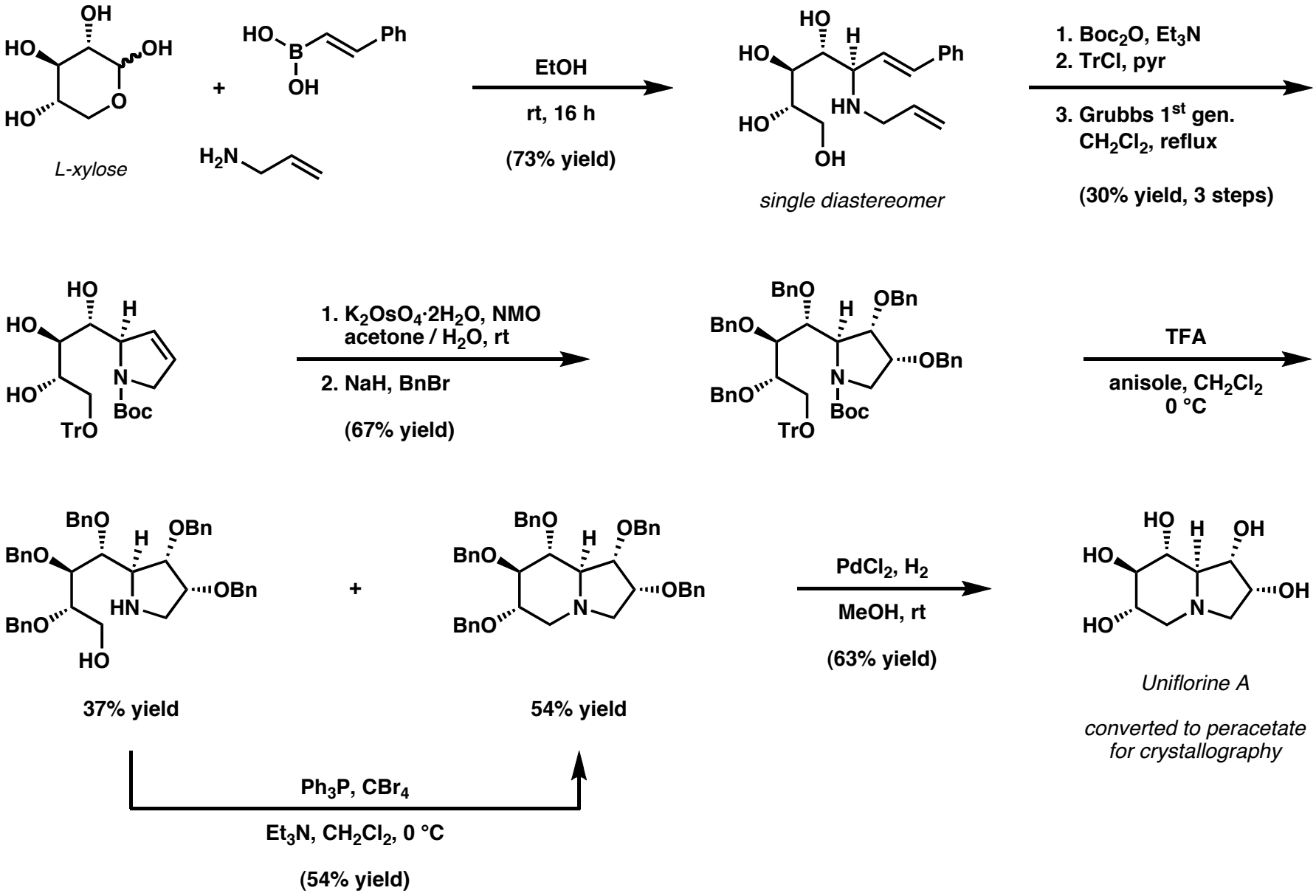






Petasis (Boronic Acid Mannich) Reaction

Pyne's Total Synthesis of Uniflorine A

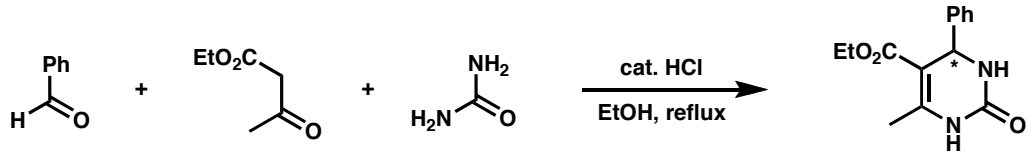


Pyne, S. G. *J. Org. Chem.* **2004**, *69*, 3139-3143.

Biginelli Reaction

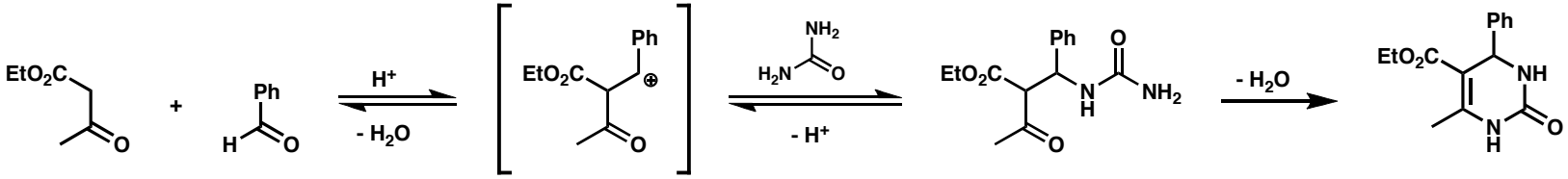
Three-Component Synthesis of Substituted Dihydropyrimidinones

- In 1891, Pietro Biginelli (Florence, Italy) discovered a three-component condensation of aldehydes, ureas, and β-ketoesters under strongly acidic conditions that produced dihydropyrimidinones.



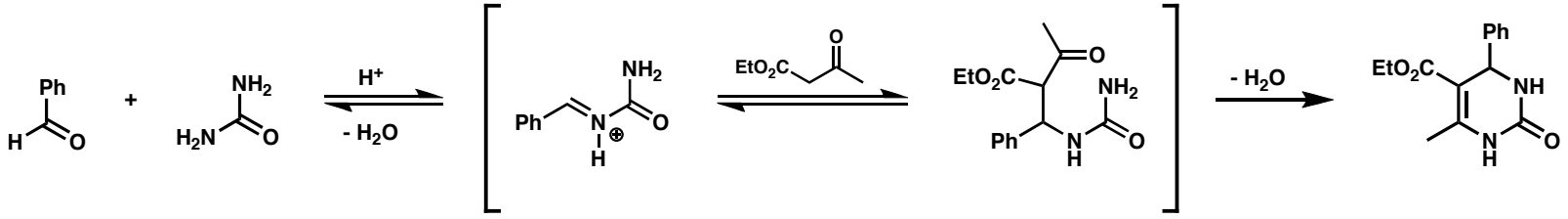
Biginelli, P. *Ber.* **1891**, *24*, 2962-2967,
Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360-416.

- In 1973, Sweet et al. proposed a Type II mechanism in which the first, rate-limiting step involved aldol condensation of the β-ketoester and aldehyde substrates, followed by S_N1 loss of H_2O to form a β-carbocation. Quenching with urea and condensation with the ketone then closed the ring.



Sweet, F.; Fissekis, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 8741-8749.

- In 1997, Kappe et al. proposed at alternate mechanism in which the urea and aldehyde substrates first condensed to form an *N*-acyliminium intermediate that was then quenched by addition of the β-ketoester.



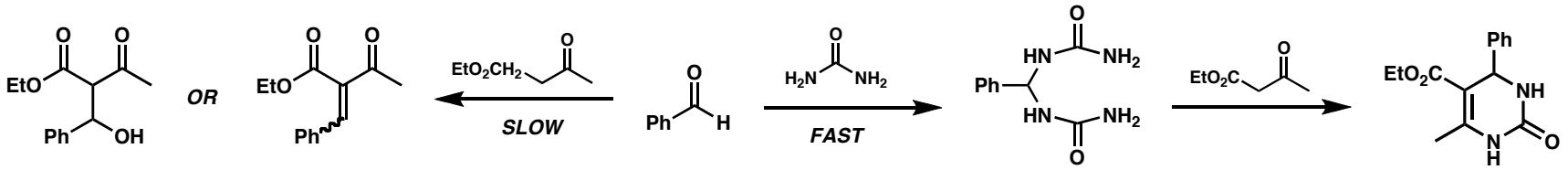
Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201-7204.
Kappe, C. O. *Acc. Chem. Res.* **2000**, *32* 879-889.

Biginelli Reaction

Three-Component Synthesis of Substituted Dihydropyrimidinones

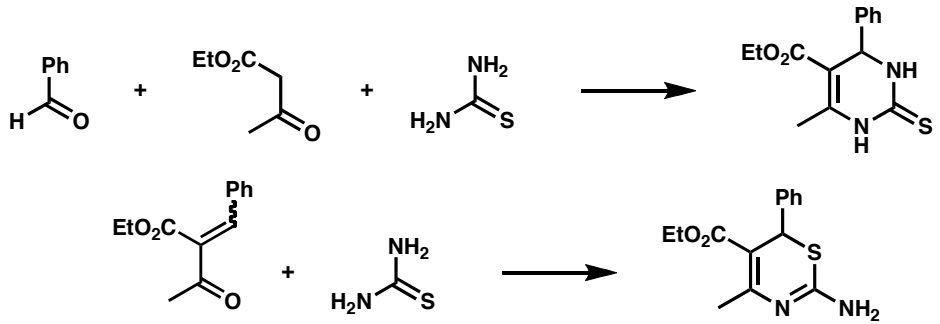
- Two observations support Kappe's mechanism:

1. Ethyl acetoacetate and benzaldehyde are slow to condense under the reaction conditions, while urea and benzaldehyde quickly form *bis*-ureides. In addition, the expected dihydropyrimidine product forms upon addition of ethyl acetoacetate to the *bis*-ureide.



Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201-7204.

2. Thioureas form dihydropyrimidine-2-thiones under the 3-CR conditions, but form 2-amino-1,3-thiazines when added to enones.



Kappe, C. O. *J. Heterocycl. Chem.* **1989**, *26*, 55-64.

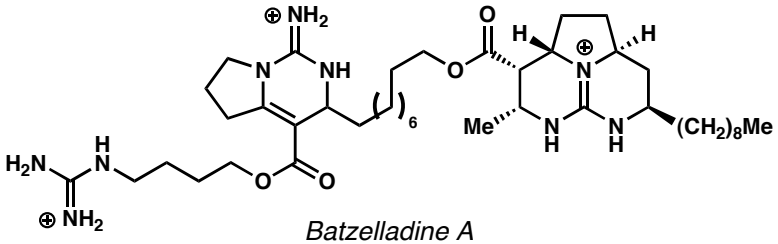
- Additionally, isolation of sterically and electronically modified intermediates support urea-ketone condensation as the last step (supports both proposed mechanisms).

slow to cyclize *slow to eliminate*

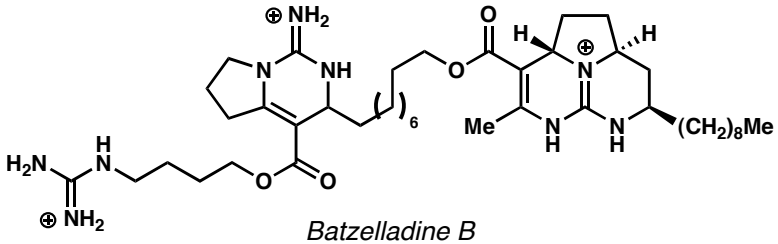
Hu, E. H. *J. Org. Chem.* **1998**, *63*, 3454-3457.
Kappe, C. O. *Heterocycles* **1999**, *51*, 77-84.

Biginelli Reaction

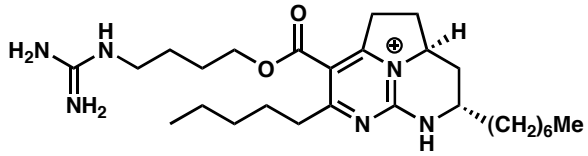
Application to the Total Synthesis of the Batzella Alkaloids



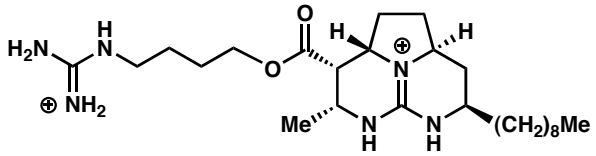
Batzelladine A



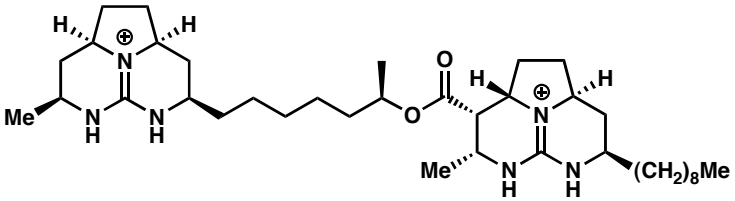
Batzelladine B



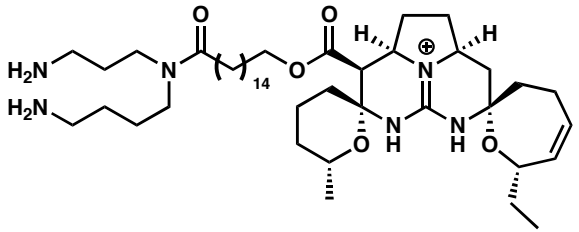
Dehydrobatzelladine C



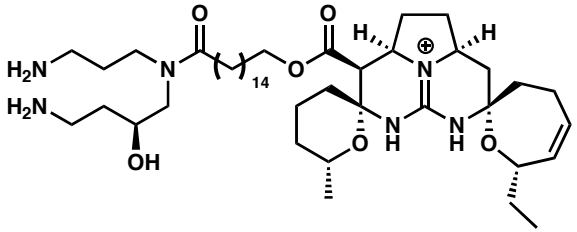
Batzelladine D



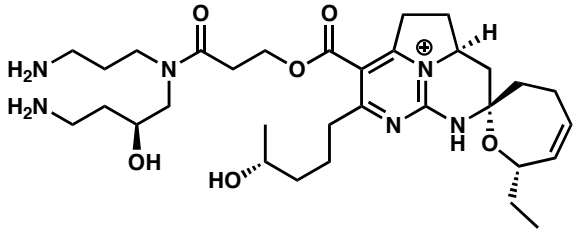
Batzelladine F



Ptilomycalin A



Crambescidin 800



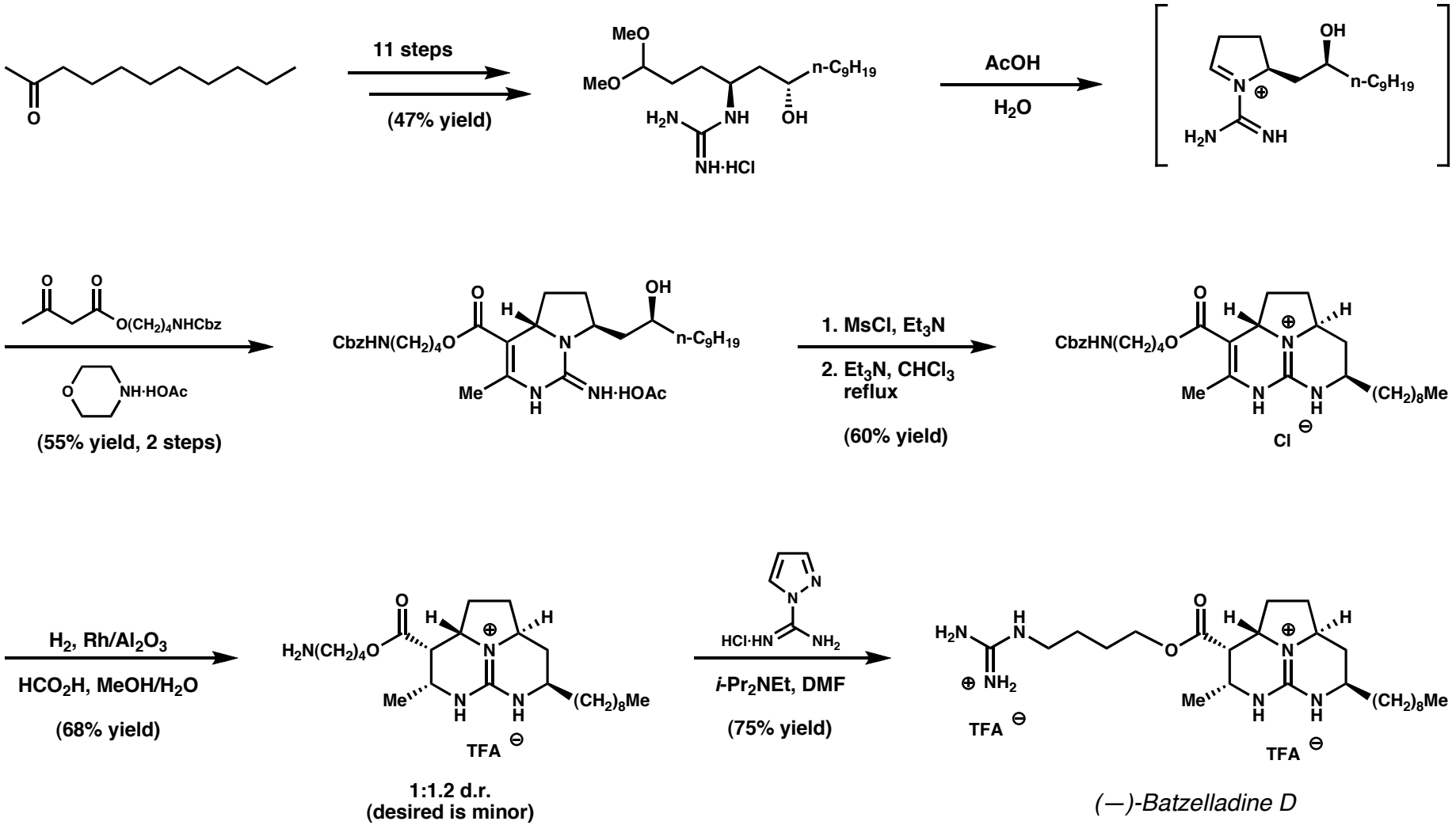
Crambidine

Isolations:

Batzelladines A-E: Patil, A. D. *J. Org. Chem.* **1995**, *60*, 1182-1188.
Batzelladines F-I: Patil, A. D. *J. Org. Chem.* **1997**, *62*, 1814-1819.
Ptilomycalin A: Kashman, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8925-8926.
Crambescidin 800: Minale, L. *Tetrahedron* **1995**, *51*, 3675-3682.
Crambidine: Kashman, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8472-8479.

Biginelli Reaction

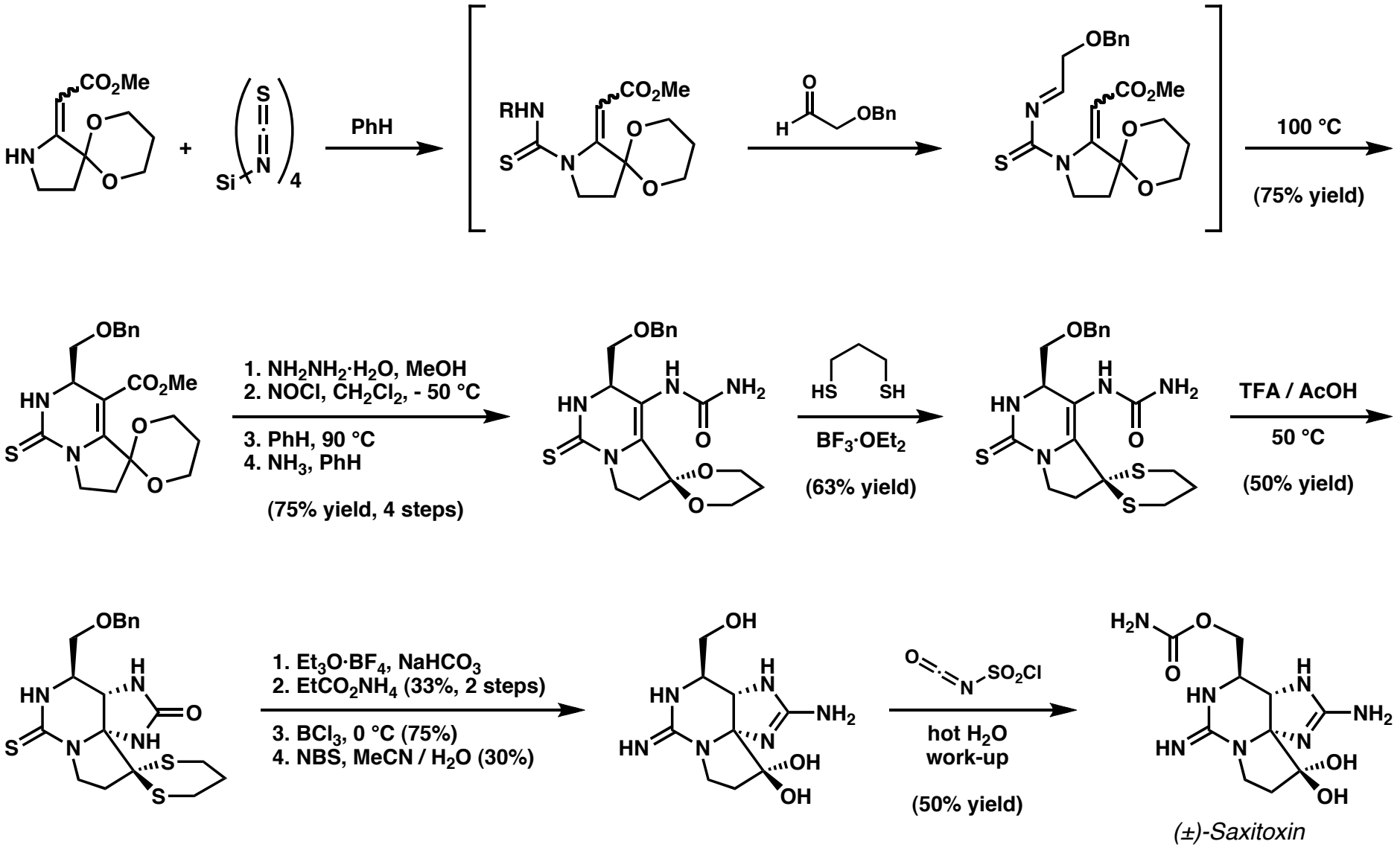
2-Component 3-Center: Overman's Synthesis of (—)-Batzelladine D



Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1512-1519.
Overman, L. E. *Org. Lett.* **1999**, *1*, 2169-2172.

Biginelli Reaction

Modified Biginelli: Kishi's Total Synthesis of (±)-Saxitoxin

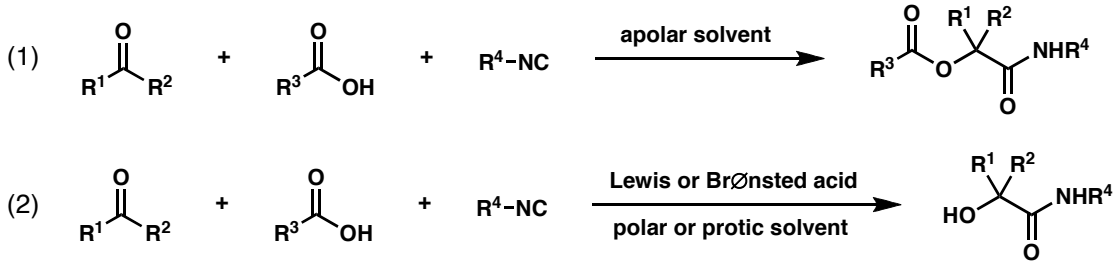


Busby, G. W., III. Ph.D. Dissertation, Harvard University, **1974**.
Kishi, K. Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818-2819.

Passerini Reaction

Three-Component Synthesis of α-Acyloxyamides

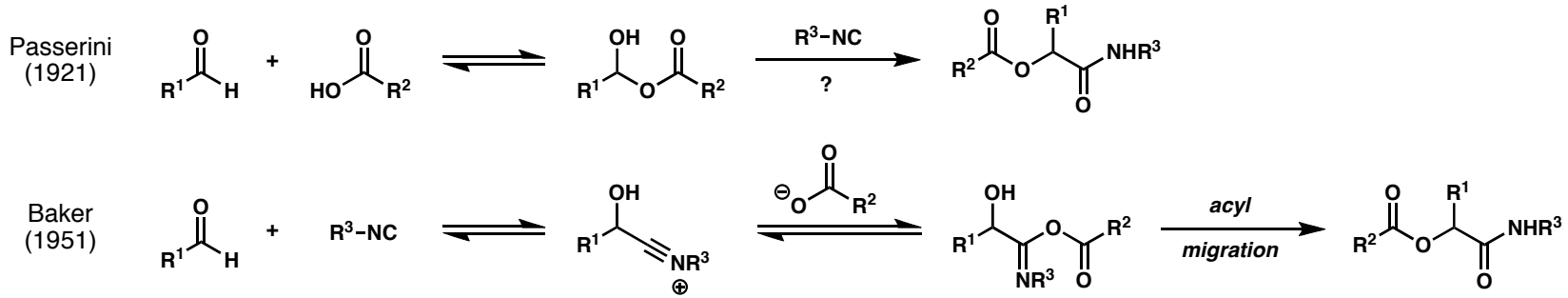
- In 1921, Mario Passerini (Florence, Italy) discovered the three-component condensation of isocyanides, acids, and aldehydes/ketones. It was the first synthetically useful reaction involving isocyanides. The reaction is typically run in apolar solvents (THF, CH_2Cl_2) to avoid cleavage of the acyl substituent, but can be run in alcohol to generate α-hydroxyamides.



* same product is formed if R^3CO_2H is replaced by H_2O in (2)

Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181-189.

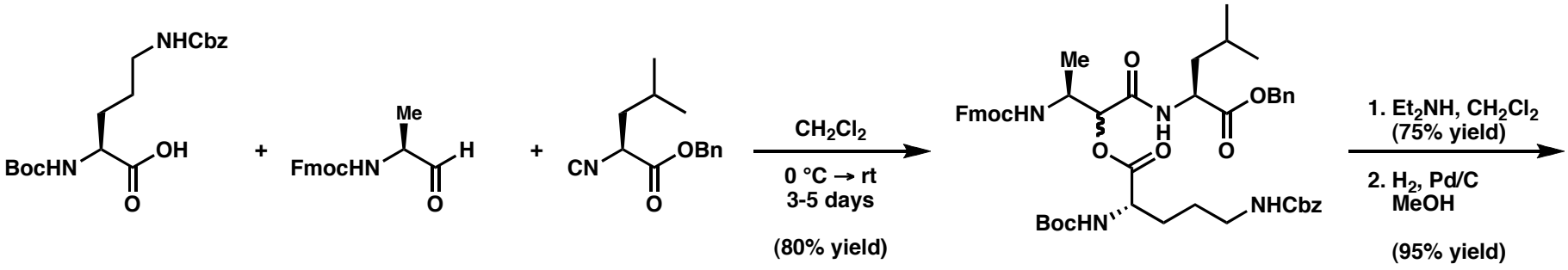
- The originally proposed mechanism involved condensation between the acid and aldehyde, followed by attack by the isocyanide. However, it was unclear how the second step would proceed to product. In 1951, Baker proposed the Type II mechanism that is accepted today involving isocyanide attack upon the aldehyde, followed by quenching of the cation by the carboxylate and subsequent rearrangement.

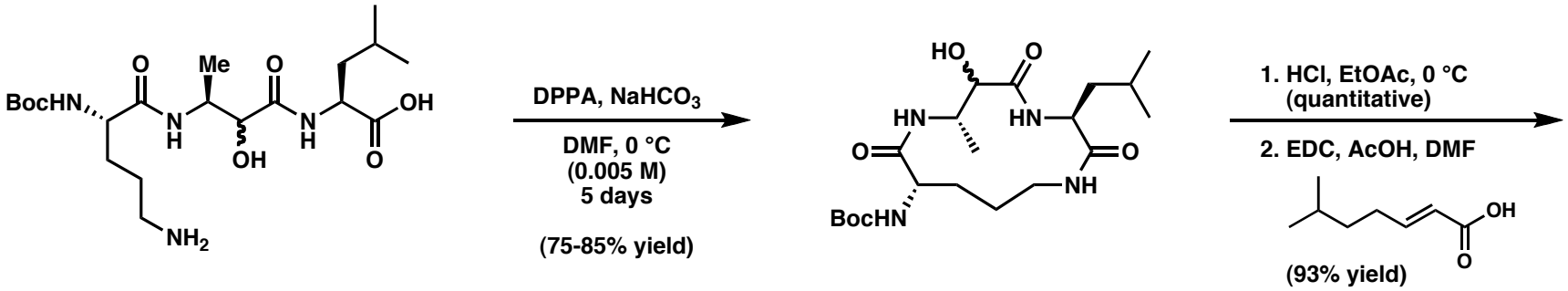


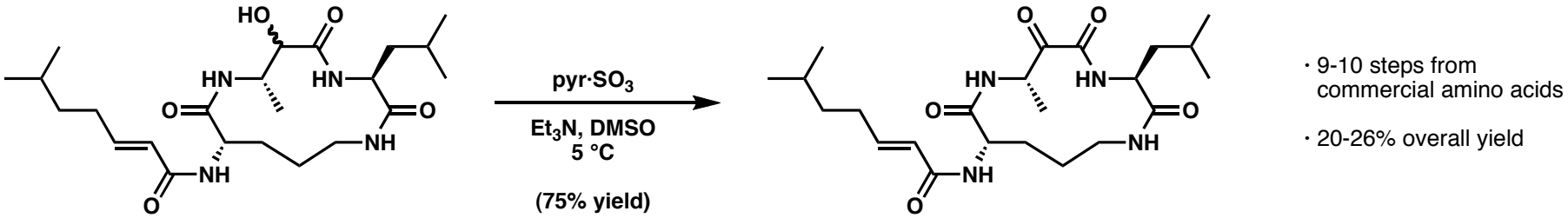
Baker, R. H. *J. Am. Chem. Soc.* **1951**, *73*, 699-702.

Passerini Reaction

Semple's Total Synthesis of Eurystatin A







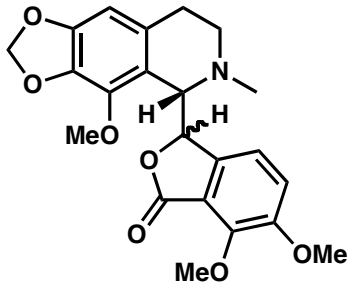
Eurystatin A

- 9-10 steps from commercial amino acids
- 20-26% overall yield

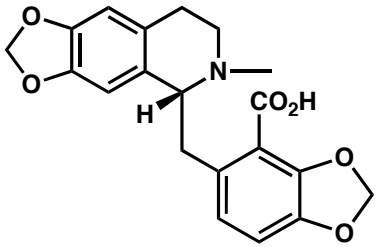
Semple, J. E. *Tetrahedron Lett.* **2001**, *42*, 6271-6274.

Passerini Reaction

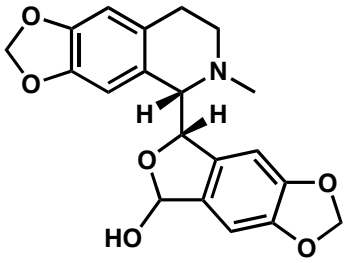
2-Component 3-Center: Falck's Four-Step Synthesis of (±)-Hydrastine



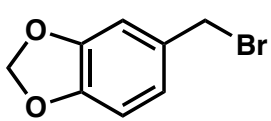
Noscapine



(+)-Coryximine



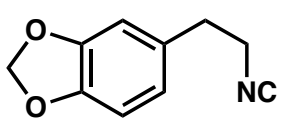
(+)-Egenine

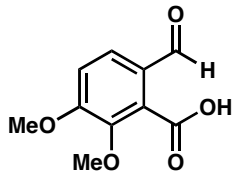


$LiCH_2NC$

THF
- 78 °C → rt

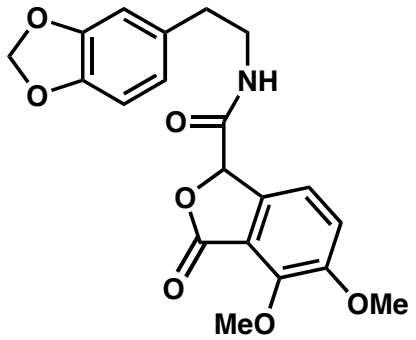
(88% yield)





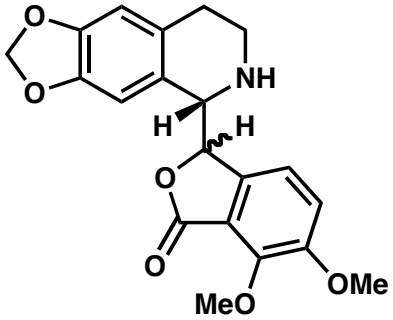
CH_2Cl_2, rt
3 h

(71% yield)



1. $POCl_3$, MecN

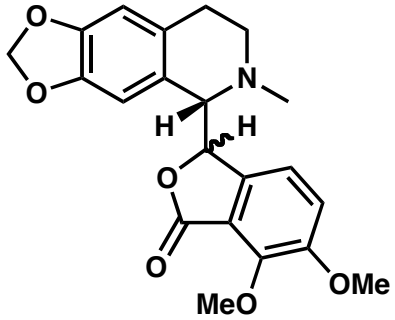
2. PtO_2, H_2



$NaBH_3CN$

HCHO

(58% yield, 3 steps)



(±)-Hydrastine

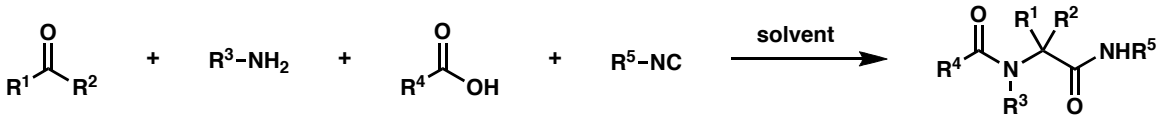
approx. 1:1 mixture of naturally interconverting isomers

Falck, J. R. *Tetrahedron Lett.* **1981**, *22*, 619-620.

Ugi Reaction

Four-Component Synthesis of α-Acylamidoamides

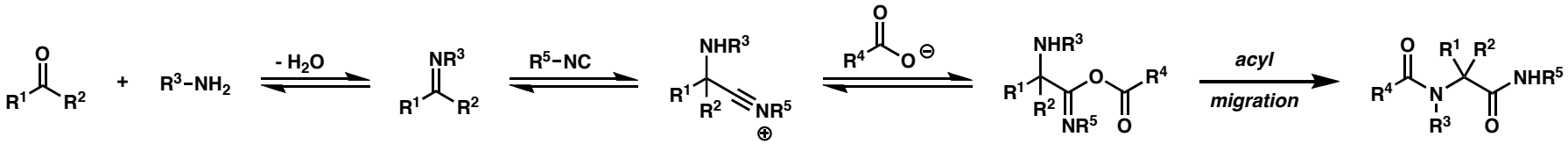
- In 1959, Ivar Ugi (Ludwig Maximilians Universität, Munich) discovered the four-component coupling of isocyanides, carboxylic acids, amines, and aldehydes/ketones to form α-acylamidoamides.



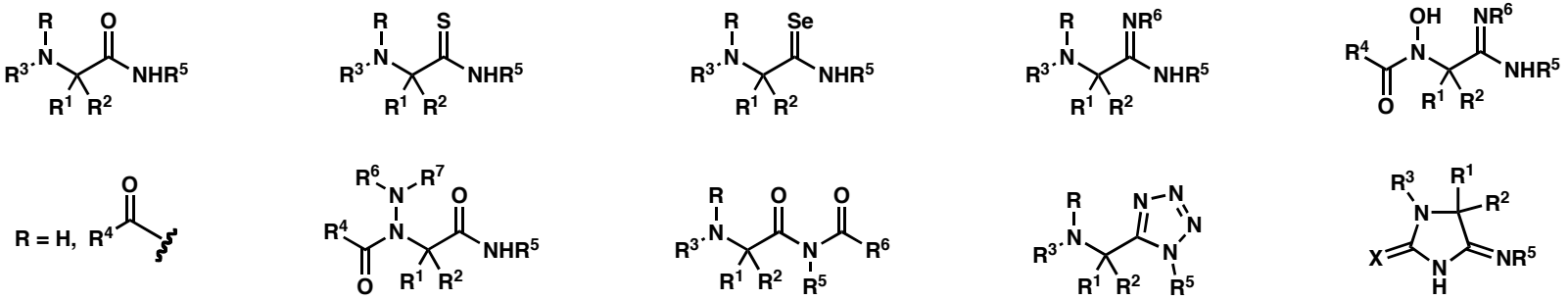
"Had Passerini been conversant with present day views on reaction mechanisms while studying the reaction which now bears his name, he would probably have added ammonia or the primary amines to his three starting materials and thereby discovered the α-amino alkylation of isonitriles and acids."

Ugi, I. *Angew. Chem.* **1959**, *71*, 386.
Ugi, I. *Angew. Chem.* **1960**, *72*, 267-268.

- The reaction is a Type II MCR and the mechanism mirrors that of the Passerini reaction, only preceded by the condensation of the carbonyl and amine species.



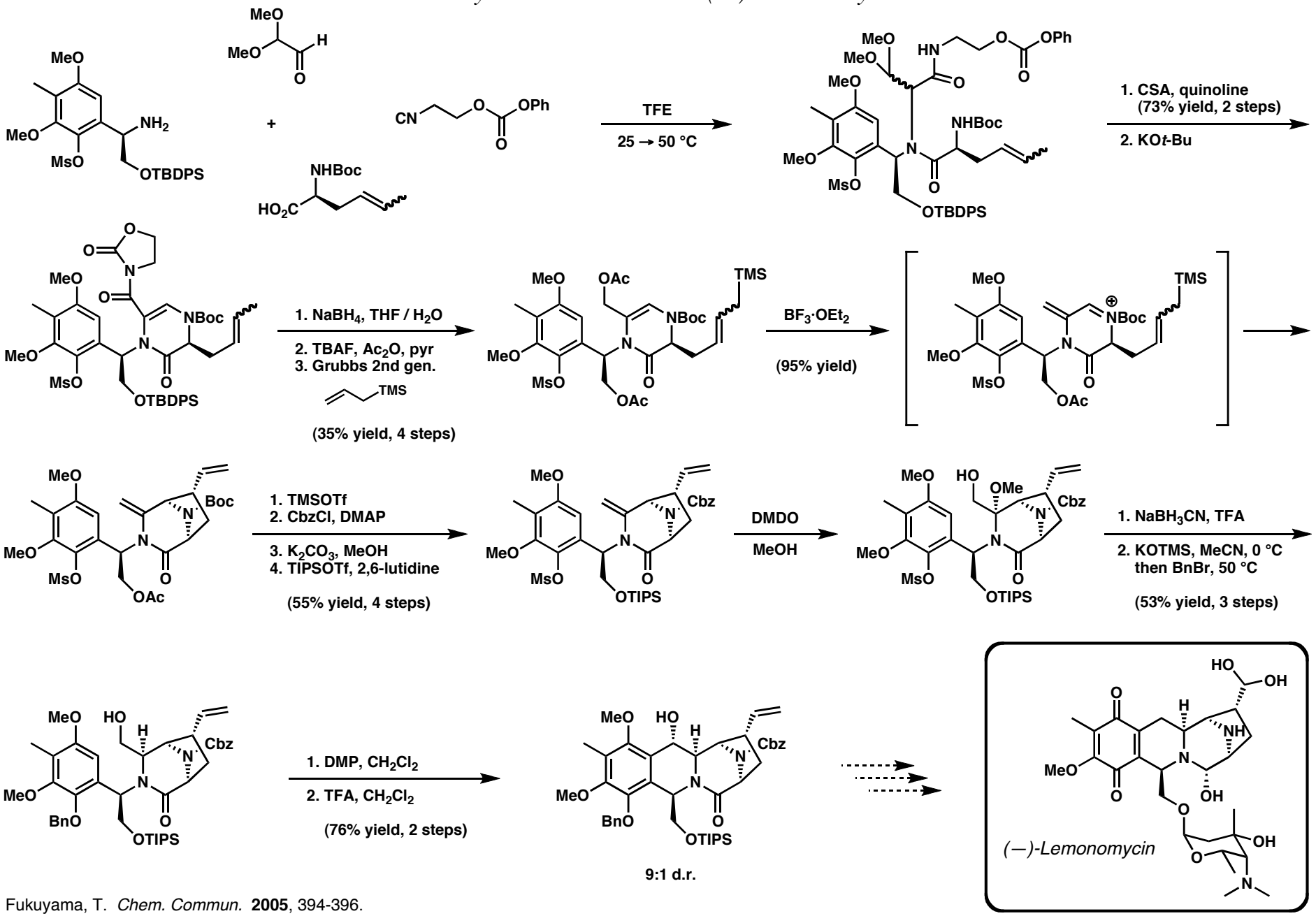
- The Ugi reaction has been applied to the synthesis of a broad range of product structures by substituting the amine and carboxylic acid components.



Ugi, I.; Dömling, A. *Endeavour* **1994**, *18*, 115-122.

Ugi Reaction

Fukuyama's Route Toward (—)-Lemonomycin

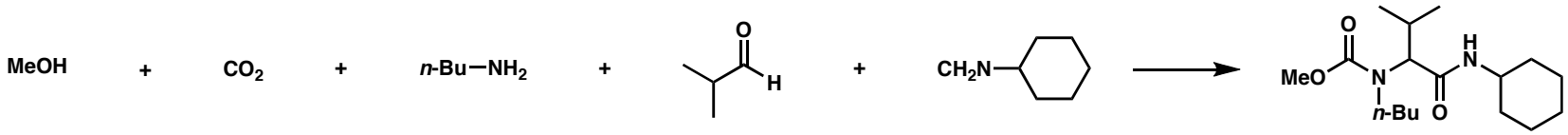


Fukuyama, T. *Chem. Commun.* **2005**, 394-396.

Ugi Reaction

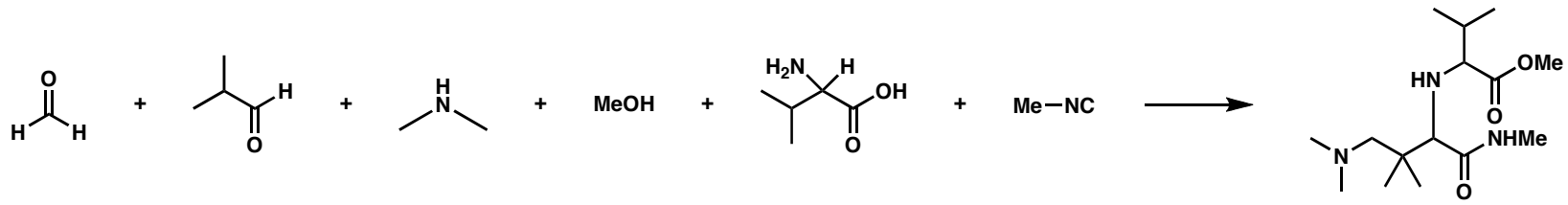
Beyond Four-Component Reactions

· Five-component reaction:



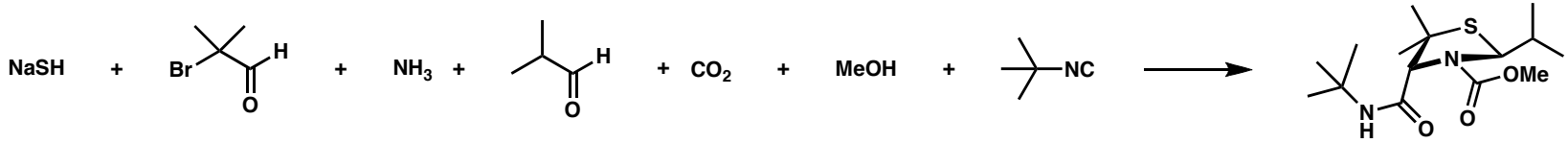
Haslinger, E. *Monatsh. Chem.* **1978**, *109*, 749-750.

· Six-component (seven-center) reaction (Mannich-Ugi):



Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115-122.

· Seven-component reaction (Asinger-Ugi):

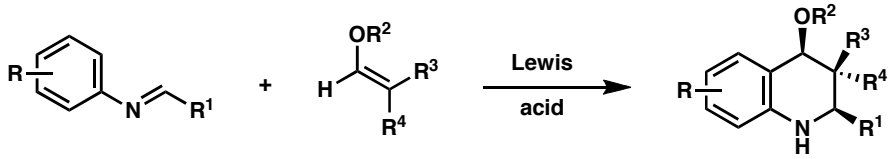


Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115-122.

Povarov Reaction

Three-Component Synthesis of Substituted Tetrahydroquinolines

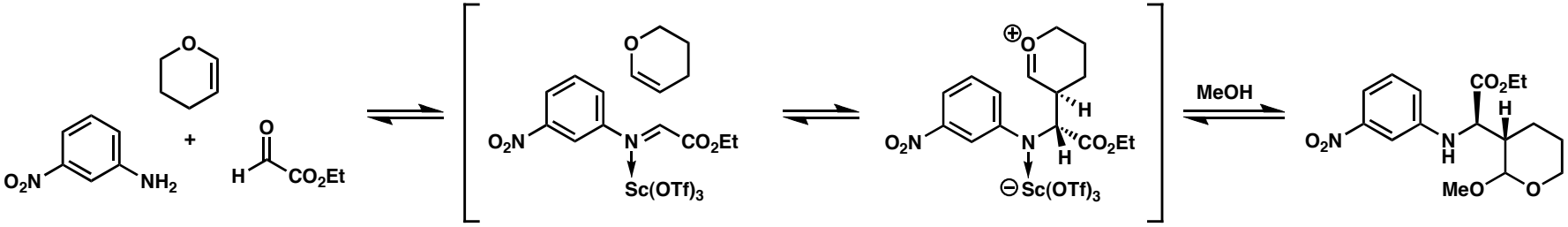
- In 1965, L. S. Povarov discovered a Lewis acid-catalyzed cycloaddition between *N*-aryl imines and vinyl ethers.



Povarov, L. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1963**, 955.
Povarov, L. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1963**, 2039.
Povarov, L. S. *Russ. Chem. Rev.* **1965**, *34*, 639.
Povarov, L. S. Doctoral Thesis, Institute of General and Inorganic Chemistry, Academy of Sciences of the USSR, Moscow, 1966.

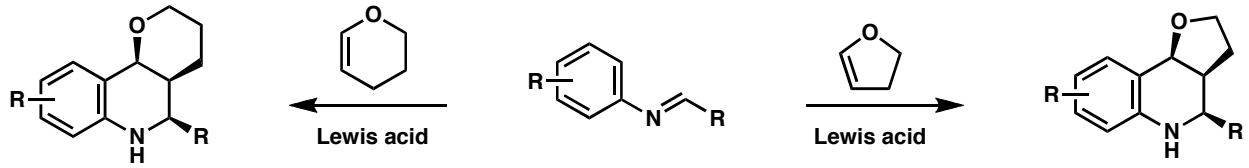
- The mechanism is disputed, though classified as Type II due to the irreversibility of rearomatization in the final step.

  - Though casually referred to as an aza-Diels-Alder cycloaddition, the Povarov is most often proposed as a non-concerted, two-step ionic mechanism. This is supported by trapping experiments (Type I).



Lavilla, R. *Angew. Chem. Int. Ed.* **2005**, *44*, 6521--6525.

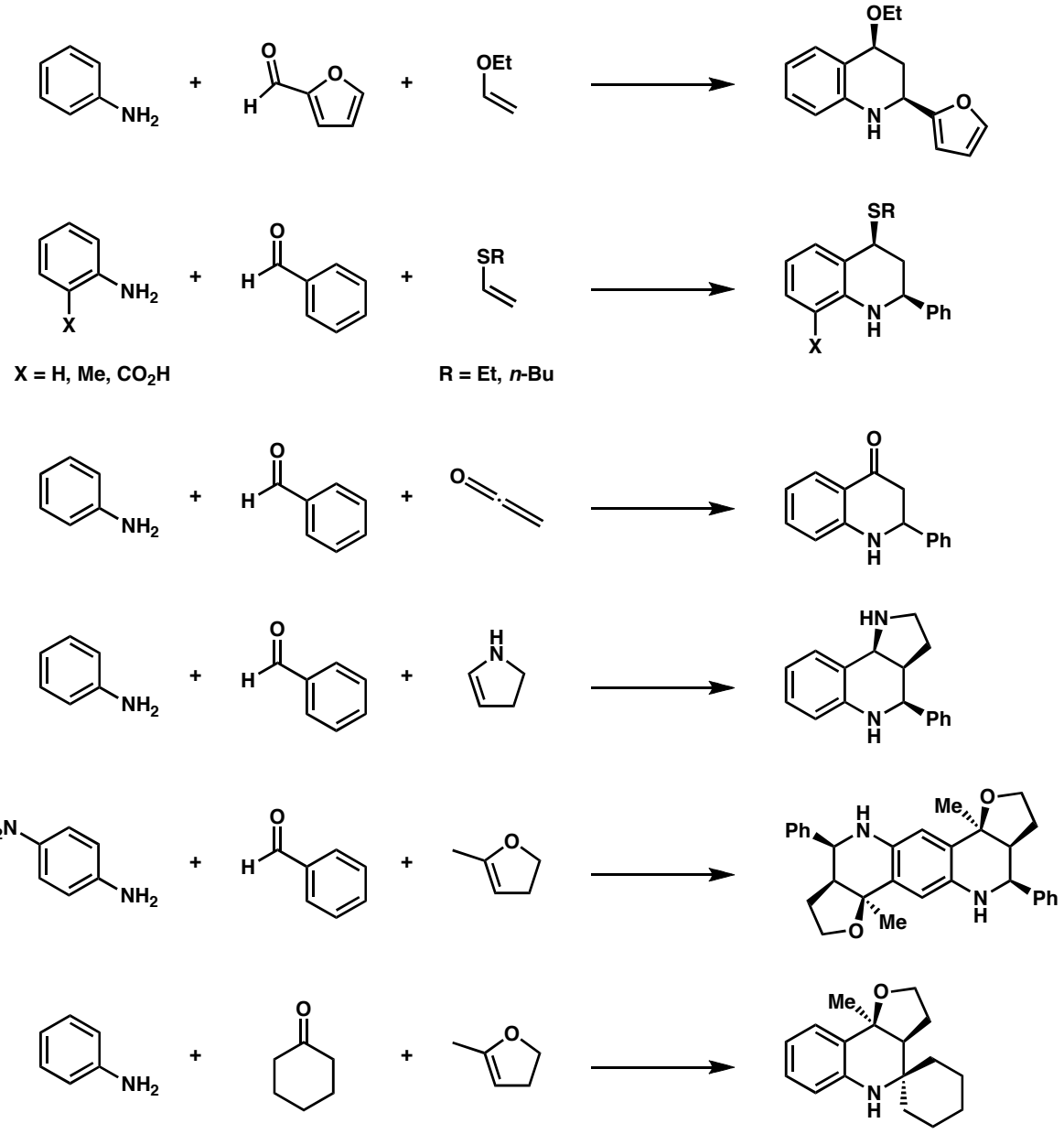
  - However, a step-wise mechanism does not explain the observation that only one stereoisomeric product is generated in reactions with dihydrofuran and dihydropyran.



Lucchini, V. *J. Chem. Soc. Perkin Trans. I* **1992**, 259-266.

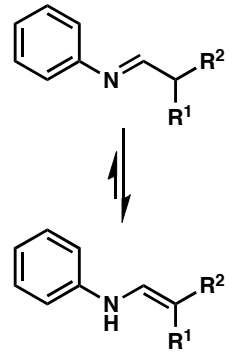
Povarov Reaction

Substrate Scope



X = H, Me, CO_2H

R = Et, *n*-Bu

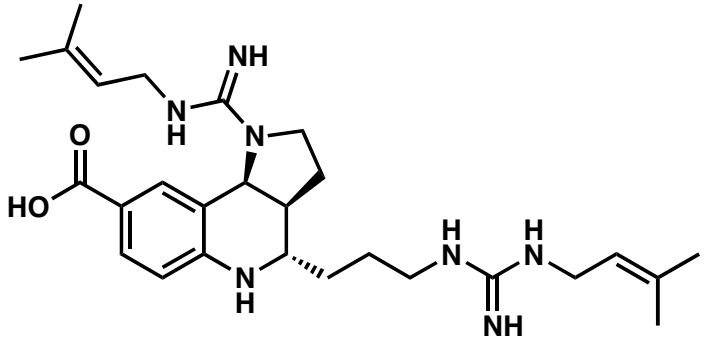


- The carbonyl component is typically limited to aryl substituents due to tautomerization of aliphatic imines to the corresponding enamines.
- Original conditions used *p*-TsOH as the catalyst and heated to 100-200 °C.
- More recently, transition metal and lanthanide triflates have been shown to catalyze the Povarov reaction between RT and 50 °C.

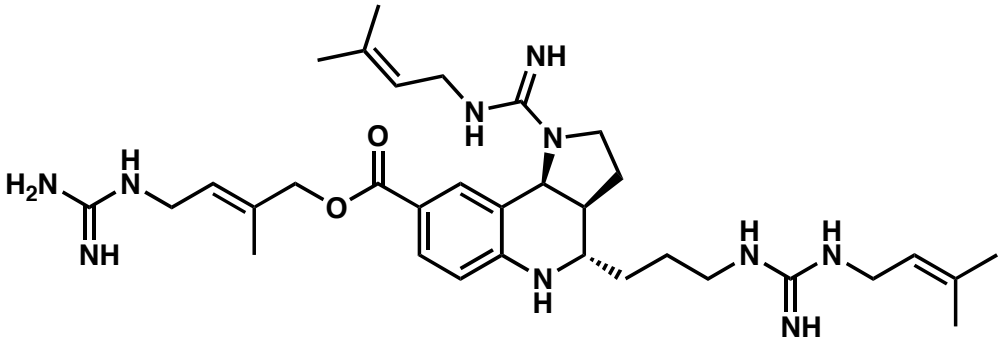
Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656-670.
Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7569-7573.
Lavilla, R. *J. Comb. Chem.* **2005**, *7*, 33-41.
Legros, J. *Synlett* **2006**, 1899-1902.

Povarov Reaction

Total Syntheses of (±)-Martinellic Acid and (±)-Martinelline



Martinellic Acid



Martinelline

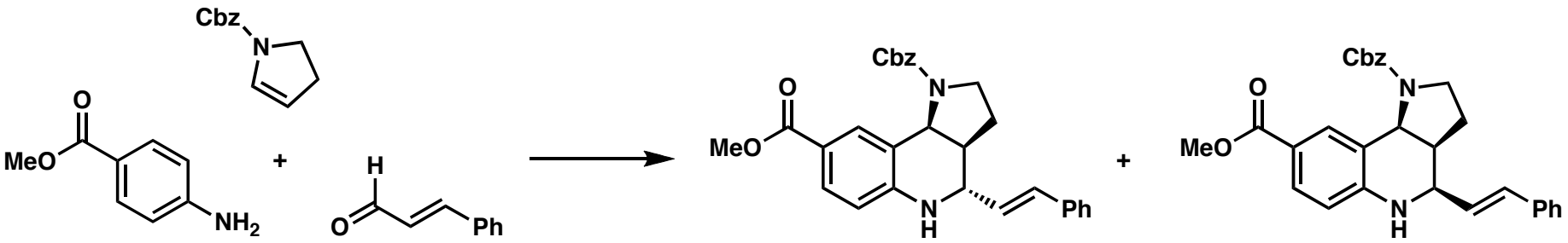
- Root extracts of the *Martinella iquitosensis* vine, found in Amazonian lowland rainforests.
- Used by indigenous peoples to treat eye ailments, including inflammation and conjunctivitis.
- Display modest antibiotic activity and micromolar binding of G-protein coupled receptors.

Cook, K. *J. Ethnopharmacol.* **1984**, *11*, 337-343.
Witherup, K. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682-6685.

Povarov Reaction

Total Syntheses of (±)-Martinellic Acid and (±)-Martinelline

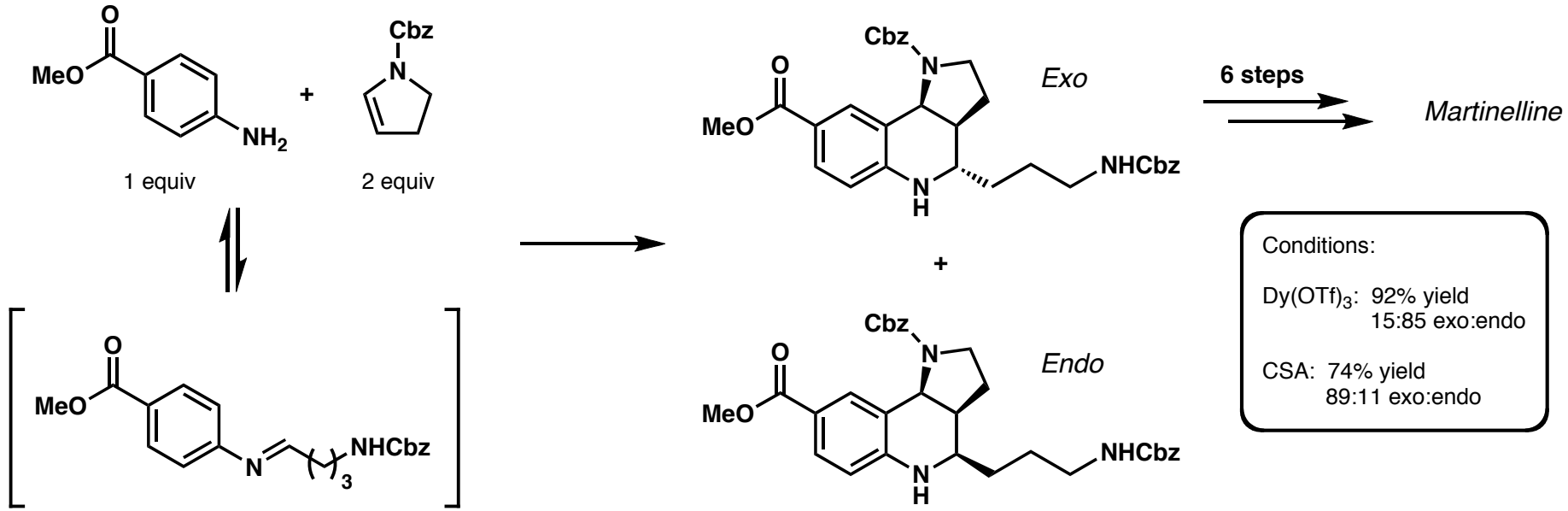
Stevenson's Approach to the Tricyclic Core:



Conditions:
A. $InCl_3$ (12 mol%), MeCN, 25 °C, 12 h → 40% yield, 1.1:1 d.r.
B. $Y(OTf)_3$ (1 mol%), MeCN, 25 °C, 2 h → 47% yield, 1:1 d.r.
C. $LiBF_4$ (100 mol%), MeCN, 25 °C, 12 h → 43% yield, 1:1 d.r.

Stevenson, P. J. *Tetrahedron* **2006**, *62*, 3977-3984,

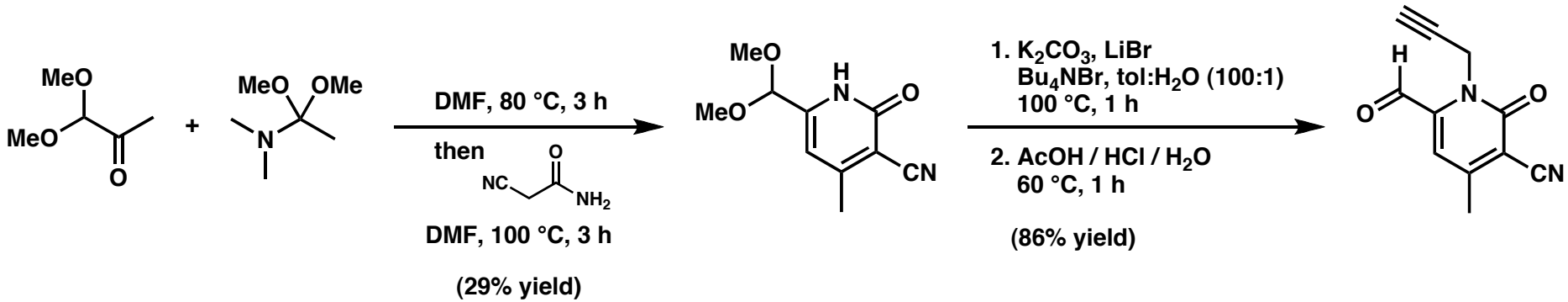
Batey's Approach (Modified Povarov):

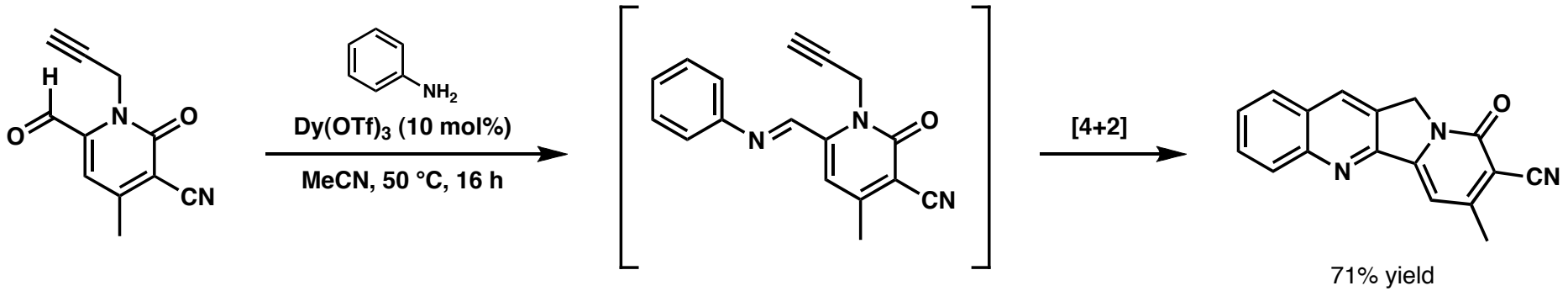


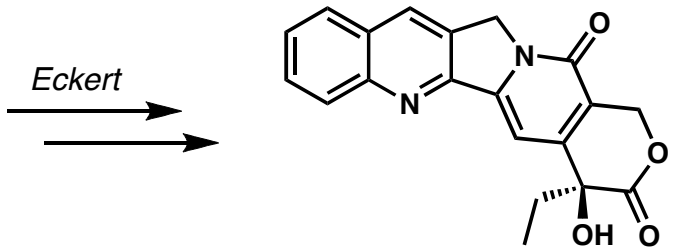
Batey, R. A. *Org. Lett.* **2002**, *4*, 2913-2916.

Povarov Reaction

2-Component 3-Center: Batey's Formal Total Synthesis of Camptothecin





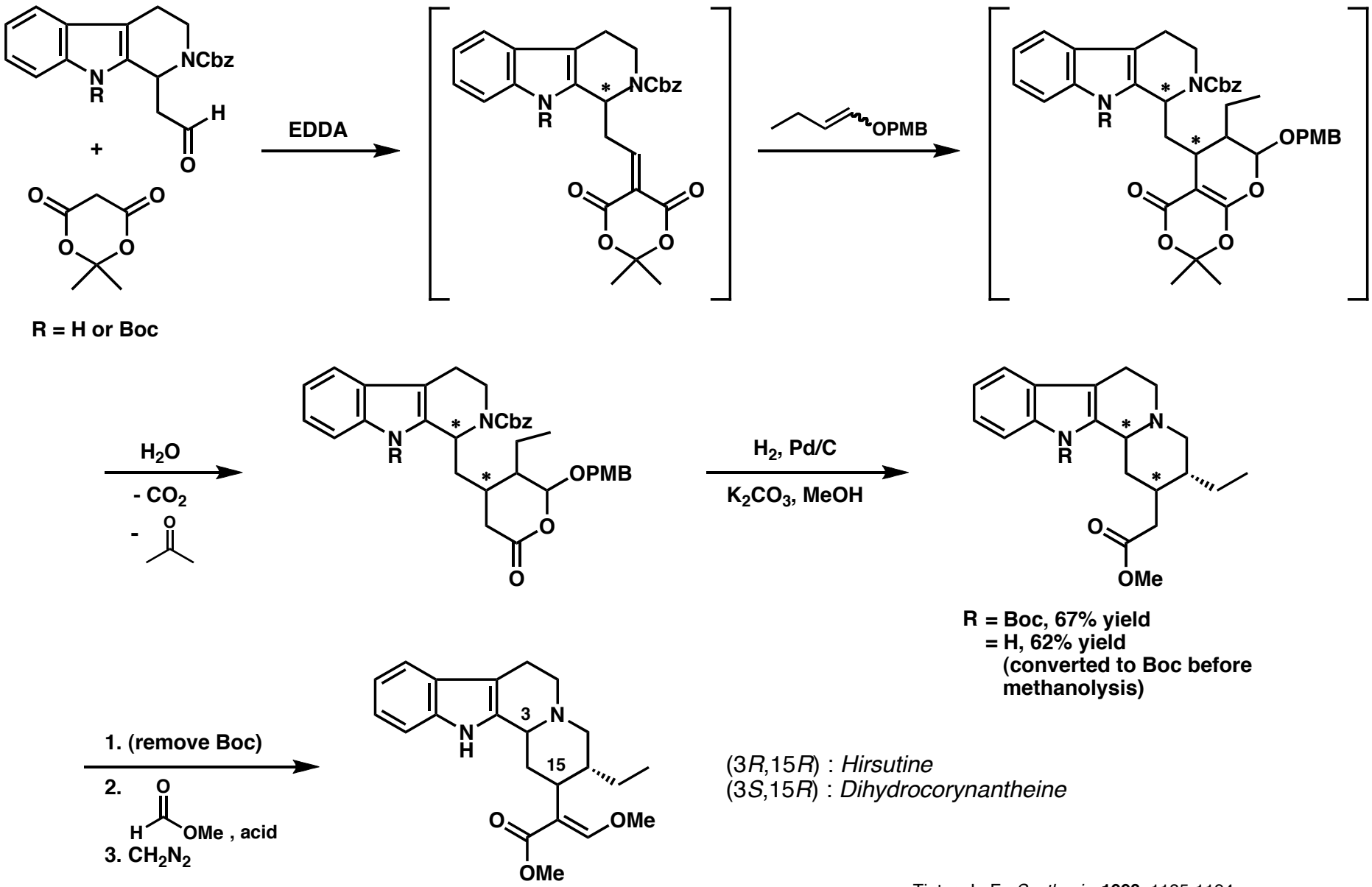


Camptothecin

Batey, R. A. *Org. Lett.* **2004**, *6*, 4913-4916.
Eckert, H. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 208-210.

Knoevenagel Condensation / Hetero-Diels-Alder Cycloaddition

Tietze's Total Synthesis of Hirsutine



(3*R*,15*R*) : *Hirsutine*
(3*S*,15*R*) : *Dihydrocorynantheine*

Tietze, L. F. *Synthesis* **1998**, 1185-1194.
Tietze, L. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 2045-2047.

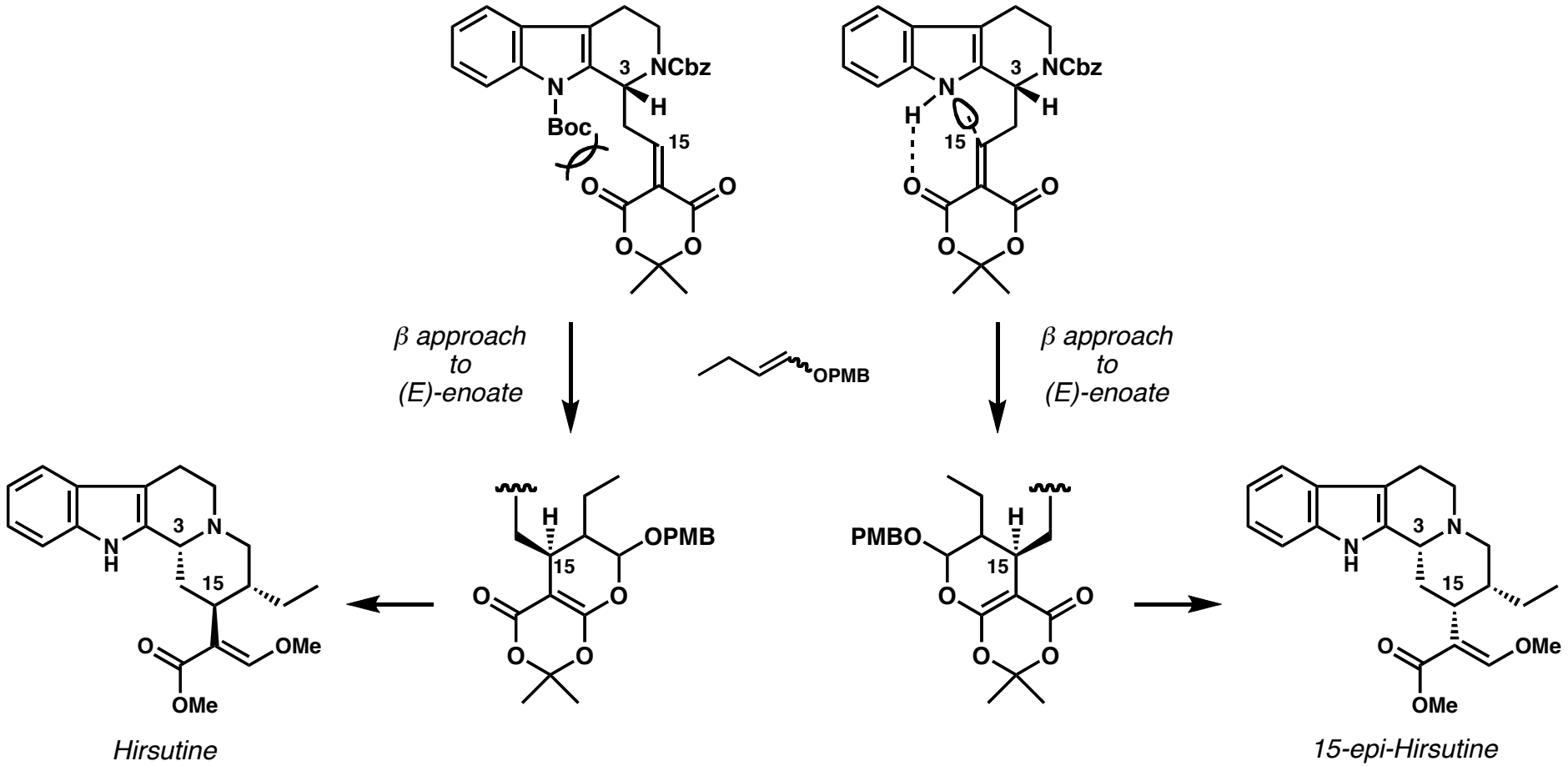
Knoevenagel Condensation / Hetero-Diels-Alder Cycloaddition

Hirsutine: Origin of Stereoselectivity

- Either enantiomer—(3*R*) or (3*S*)—is available by condensation of piperidyl nitrogen with (—)-camphanic acid to form separable diastereomeric amides. Enantiomerically pure (3*R*) substrate advanced to hirsutine.

- During the cycloaddition, *N*-Boc causes Meldrum's acid moiety to swing away from indole, while *N*-H causes it to swing toward indole in order to participate in H-bonding and partial donation of the nitrogen lone pair into the enoate π-system.

- The enol approaches the (*E*)-1-oxa-1,3-butadiene over the H at C(3) instead of the alkyl chain.

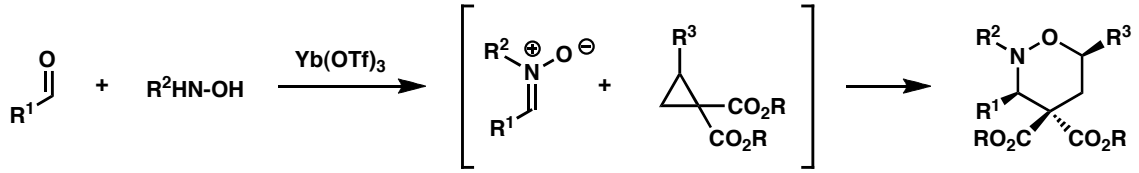


Tietze, L. F. *Synthesis* **1998**, 1185-1194.
Tietze, L. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 2045-2047.

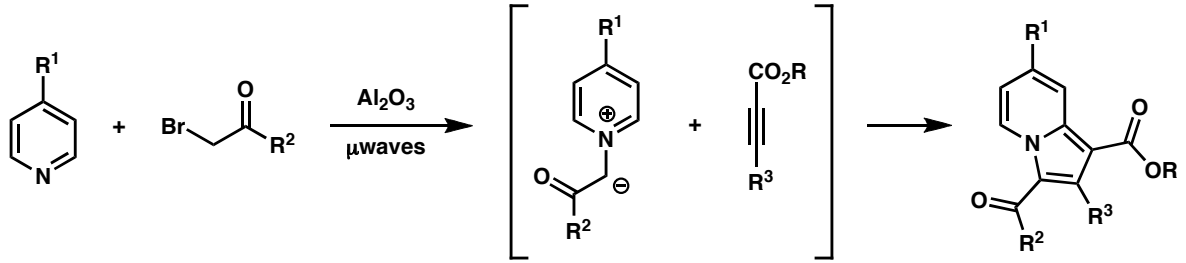
Dipolar Cycloadditions

Methods for Dipole Construction

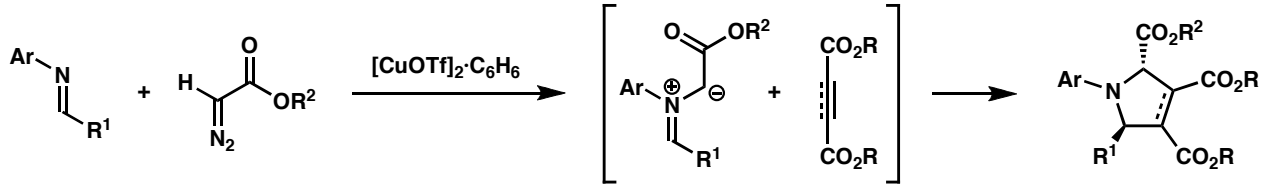
Multicomponent dipolar cycloadditions typically involve two-component formation of the 1,3-dipole followed by reaction with a suitable dipolarophile.



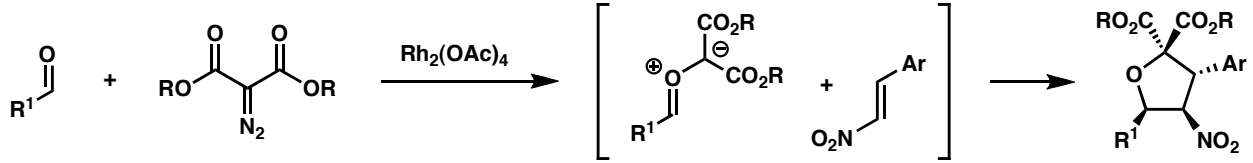
Kerr, M. A.
Org. Lett. **2004**, *6*, 139-141.



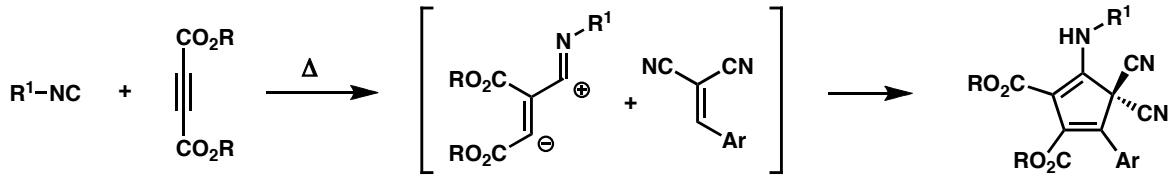
Boruah, R. C.
Org. Lett. **2003**, *5*, 435-438.
Müller, T. J. J.
Helv. Chim. Acta **2005**, *88*, 1798-1812.



Scheidt, K. A.
Org. Lett. **2003**, *5*, 3487-3490.



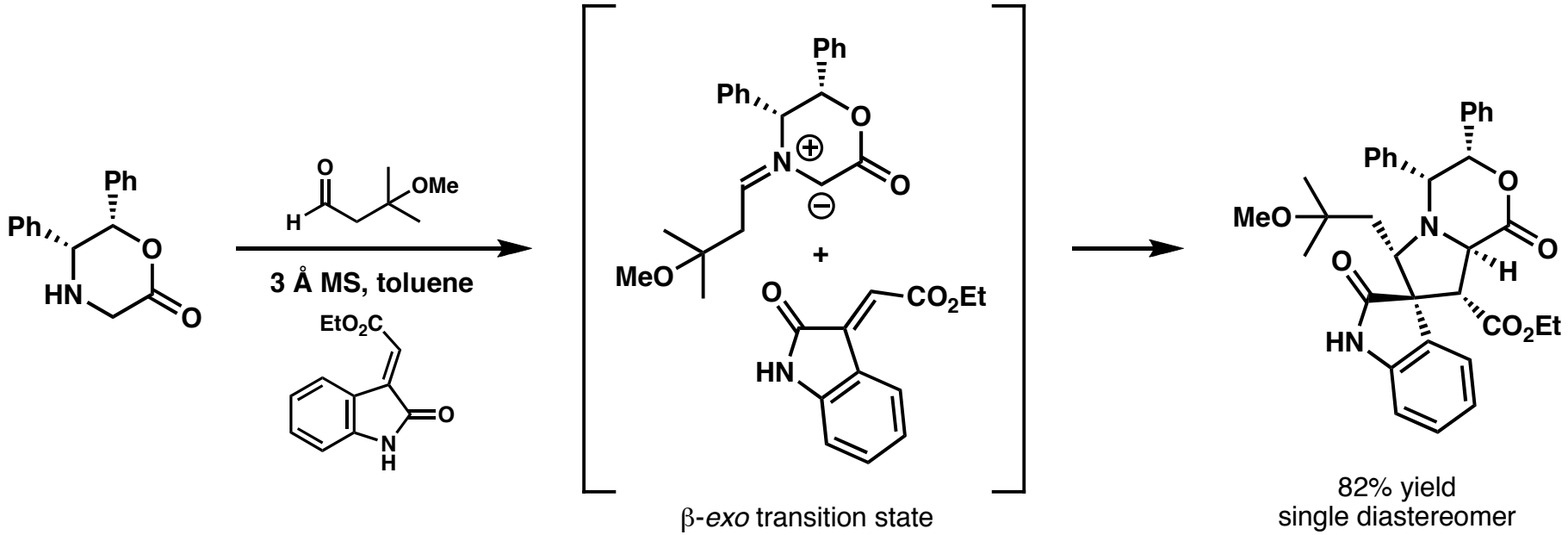
Nair, V.
J. Org. Chem. **2004**, *69*, 1413-1414.



Nair, V.
Org. Lett. **2004**, *6*, 767-769.

Dipolar Cycloadditions

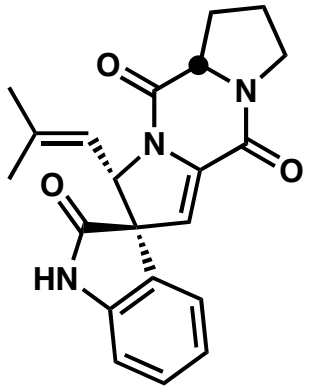
Williams' Total Synthesis of (—)-Spirotryprostatin B



β-*exo* transition state

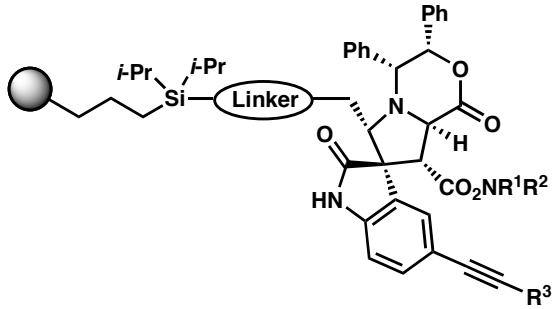
82% yield
single diastereomer

8 steps



(—)-Spirotryprostatin B

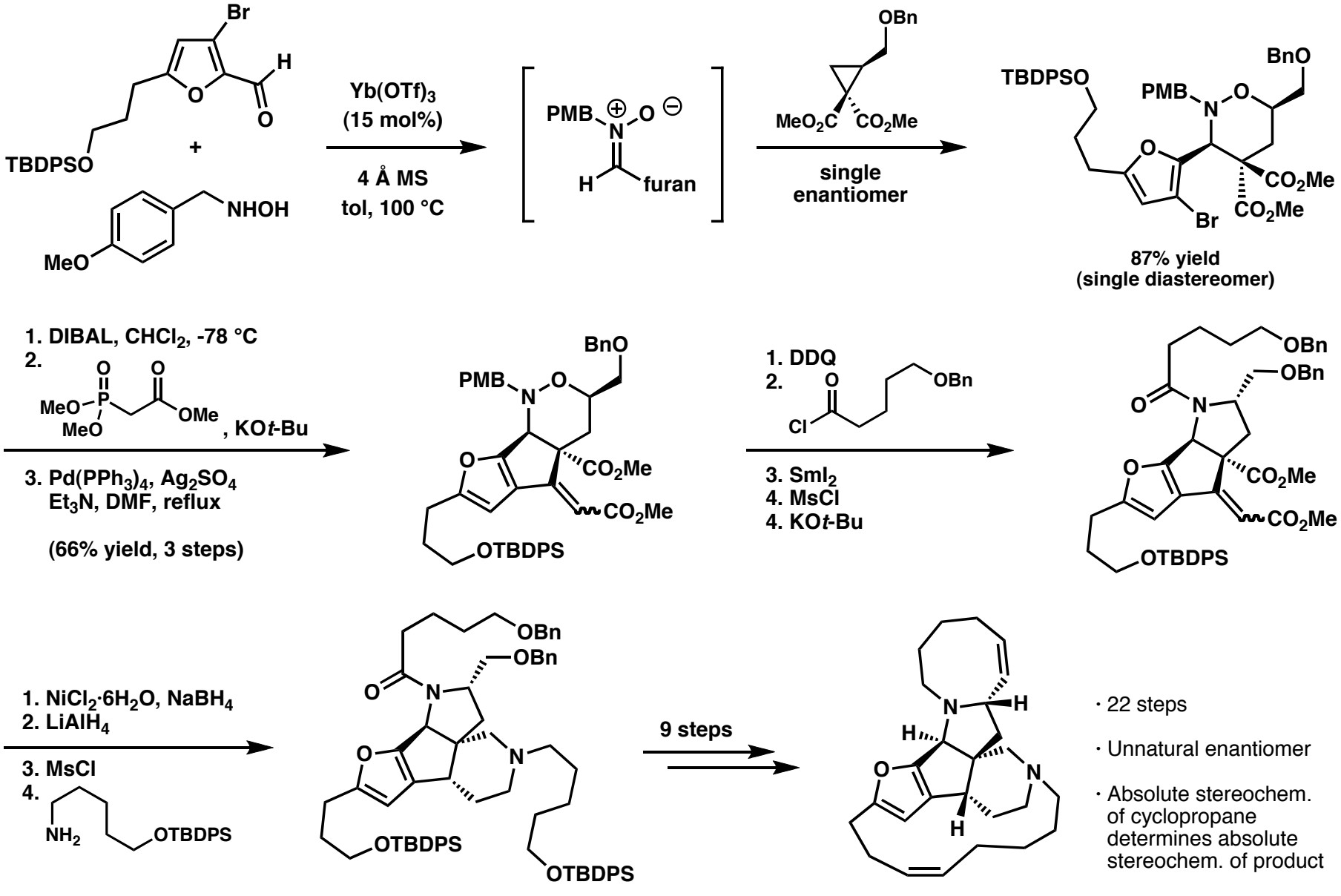
- 16% overall yield
- (+)-spirotryprostatin available from enantiomer of oxazinone substrate.
- Schreiber later used this reaction to construct a library of >3000 structural variants using split-pool synthesis on microbeads.



Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666-5667.
Williams, R. M. *Tetrahedron* **2002**, *58*, 6311-6322.
Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077-16086.

Dipolar Cycloadditions

Kerr's Total Synthesis of (+)-Nakadoumarin A



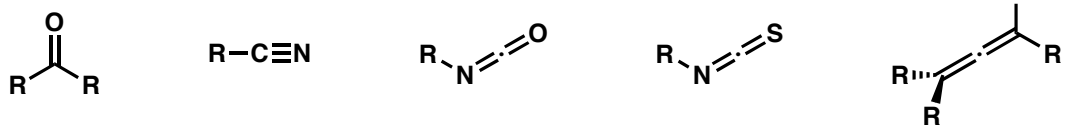
Kerr, M. A. *Org. Lett.* **2005**, *7*, 953-955.
Kerr, M. A. *J. Am. Chem. Soc.* **2007**, ASAP.

Multiple Anion Capture

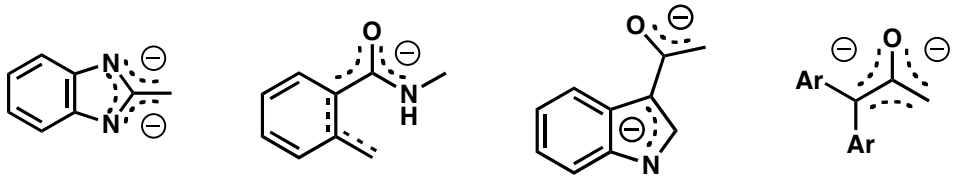
Dianion Relay for Structural Elaboration

Multiple anion capture is a process by which a resonance-stabilized dianion attacks a relais ("relay", electrophile) species to form a secondary dianion, which is then quenched by a second electrophile.

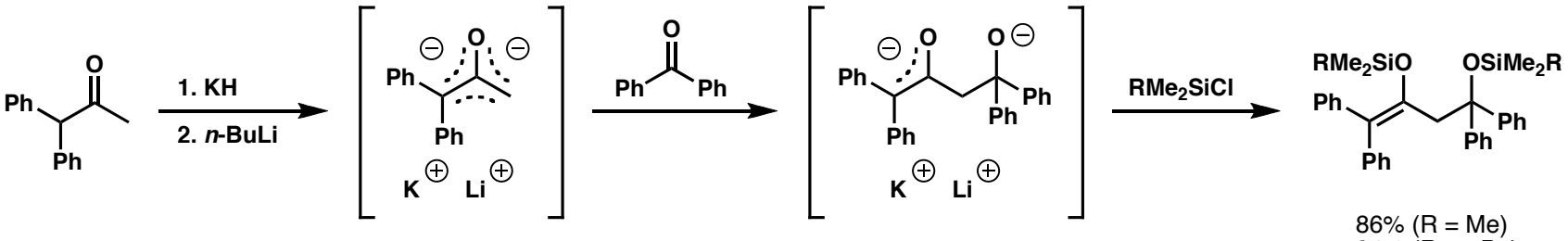
· Relais species =



· Dianions =



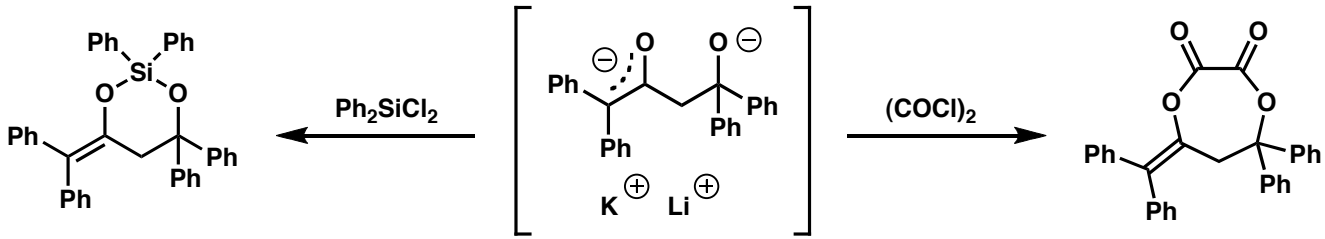
· If the second electrophile contains one electrophilic site, then two equivalents are necessary and the product is a linear homologation of the substrate.



"Y-shaped" dianion

86% (R = Me)
84% (R = *t*-Bu)

· If the second electrophile contains two electrophilic sites, then only one equivalent is necessary and the product is a ring.



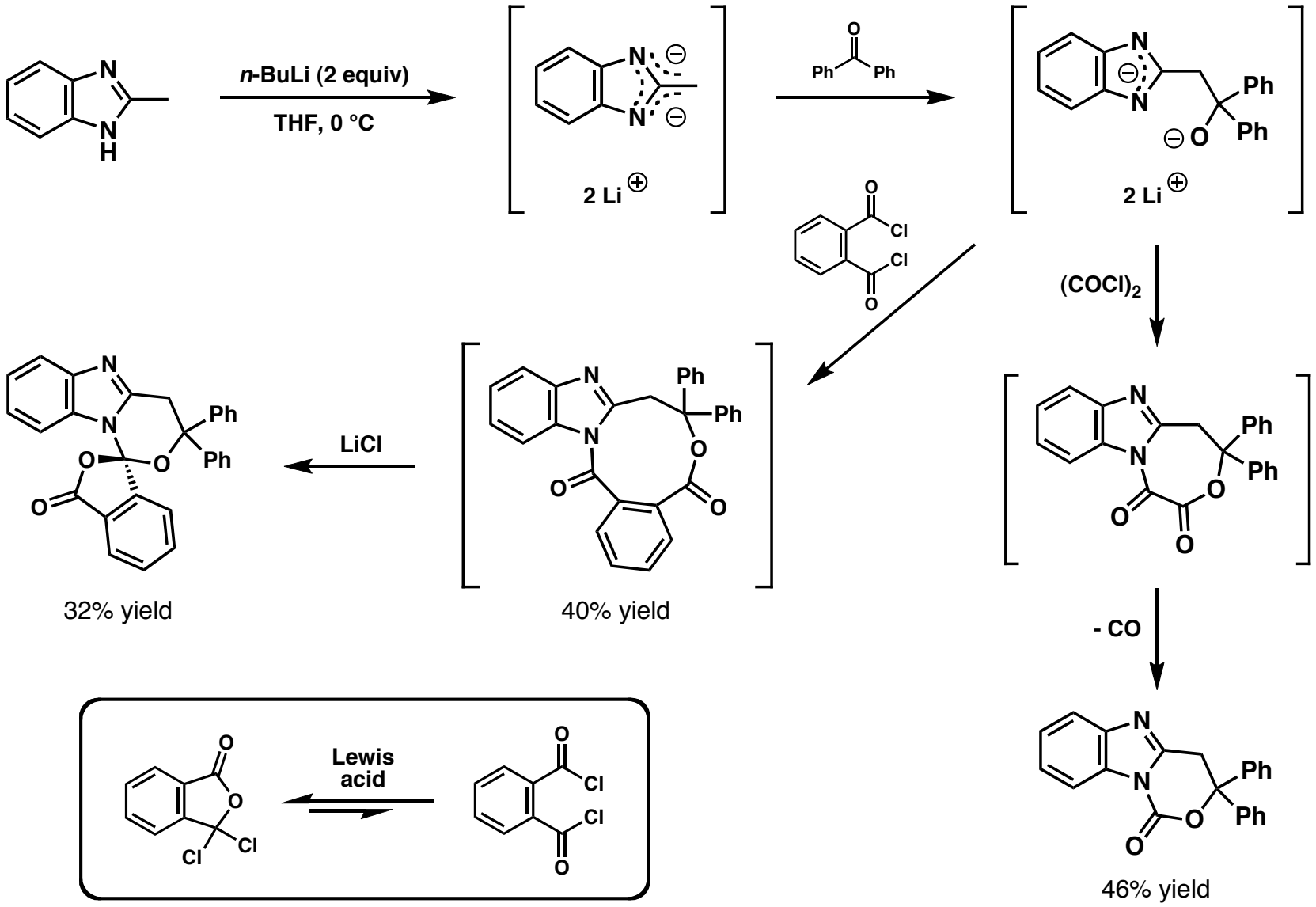
76% yield

36% yield

Langer, P. *Eur. J. Org. Chem.* **2001**, 1511-1517.
Langer, P. *Chem. Eur. J.* **2001**, *7*, 3858-3866.
Padwa, A. *J. Am. Chem. Soc.* **1988**, *110*, 1617-1618.
Ketchum, R. *J. Org. Chem.* **1985**, *50*, 3431-3434.
Trimitsis, G. B. *J. Org. Chem.* **1983**, *48*, 2957-2962.

Multiple Anion Capture

Synthesis of Medium-Sized Lactones and Heterospirocyclic Isobenzofuranones



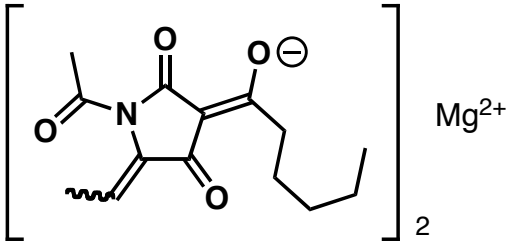
$AlCl_3$ catalyzed: Naik, N. *Synth. Commun.* **1988**, *18*, 625.

Langer, P. *Eur. J. Org. Chem.* **2001**, 1511-1517.
Naik, N. *Synth. Commun.* **1988**, *18*, 625-632.

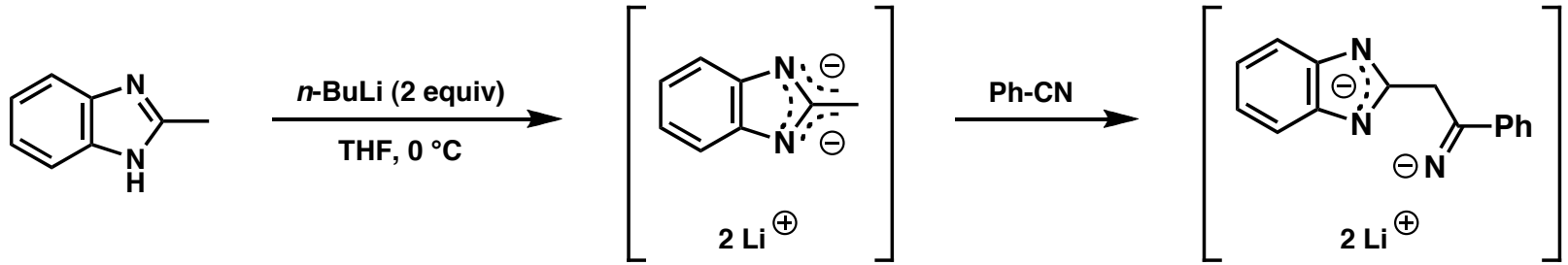
Multiple Anion Capture

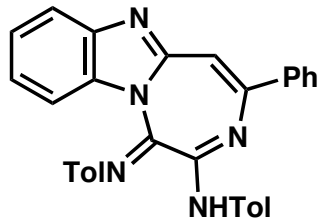
Synthesis of Radialene-Shaped Pyrroles

Radialenes are cyclic compounds containing only sp^2-hybridized ring atoms and exocyclic double bonds.



Magnesidin





Not observed!

Langer, P.; Döring, M. *Synlett.* **1998**, 399-401.
Langer, P. *Eur. J. Org. Chem.* **2001**, 2617-2627.

Multiple Anion Capture

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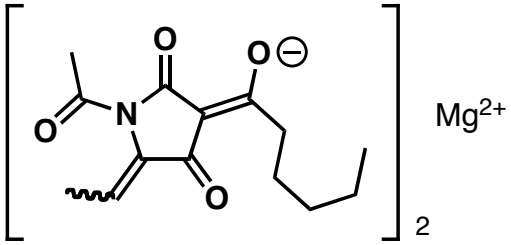
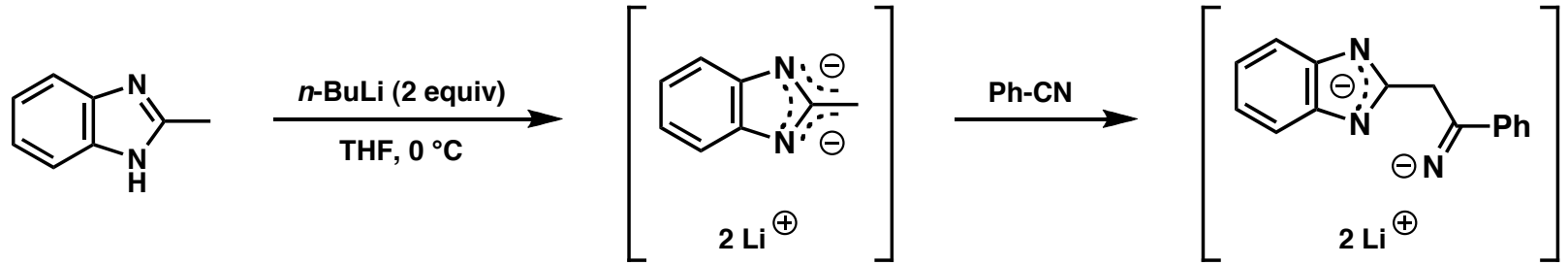
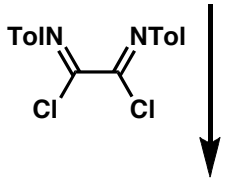
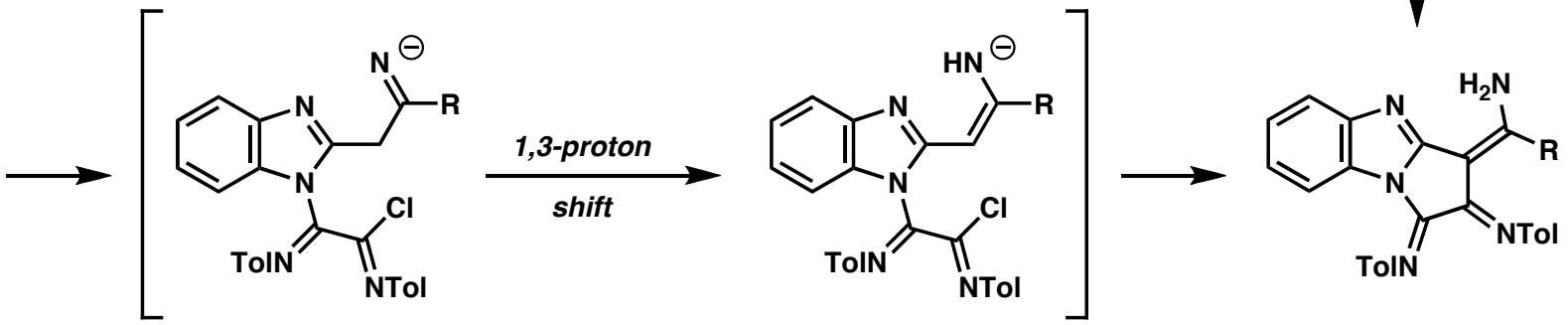


Magnesidin



Regioselectivity (C vs. N attack) proposed to be the product of relative HOMO energies (AM1: C lower than N) as well as HSAB effects.





40% yield

Langer, P.; Döring, M. *Synlett.* **1998**, 399-401.
Langer, P. *Eur. J. Org. Chem.* **2001**, 2617-2627.

Multiple Anion Capture

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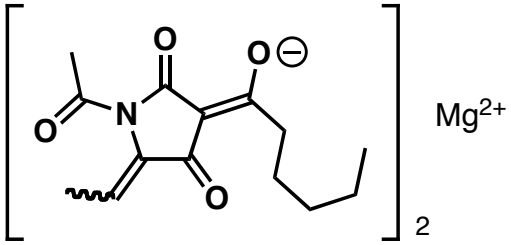
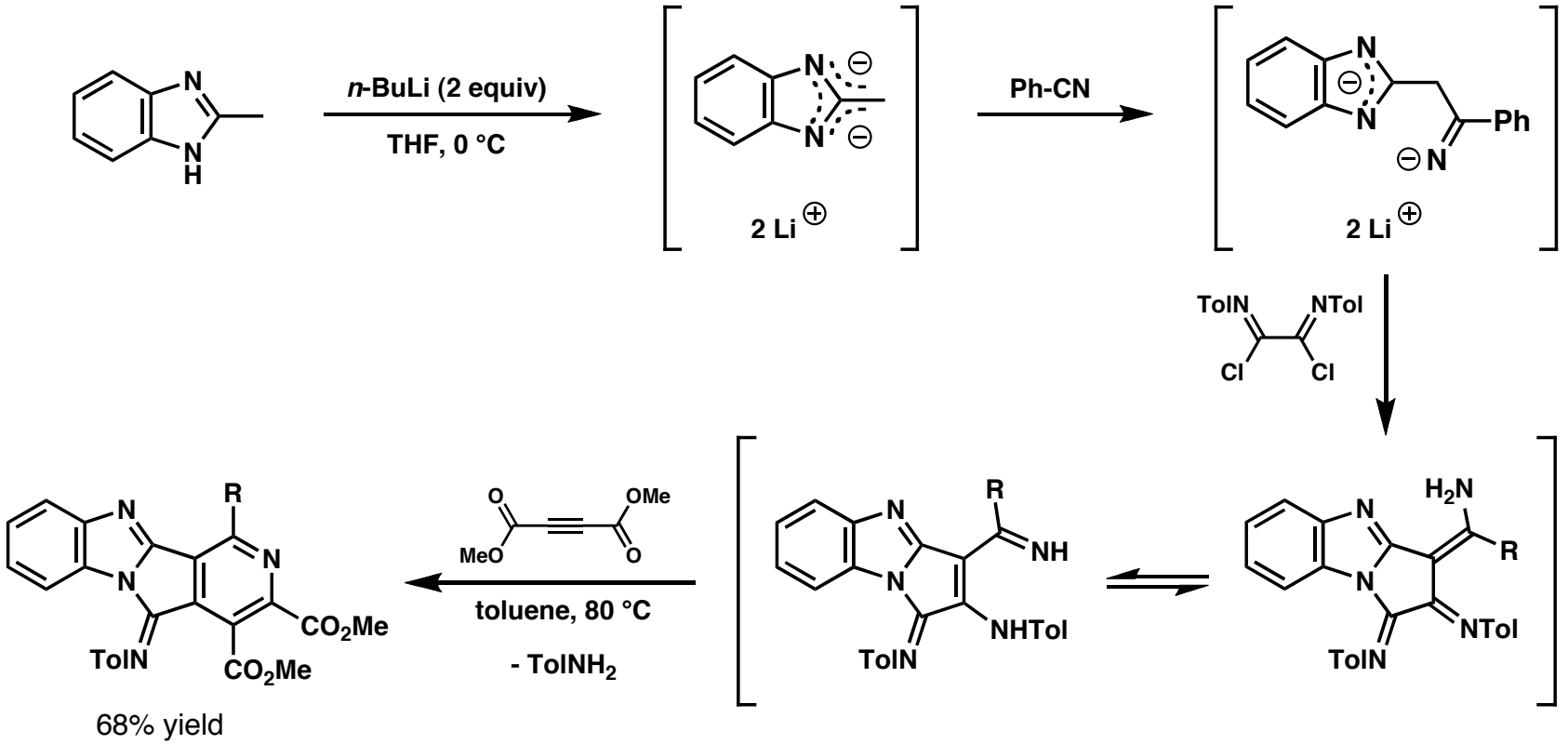
Radialenes are cyclic compounds containing only sp^2-hybridized ring atoms and exocyclic double bonds.



Magnesidin

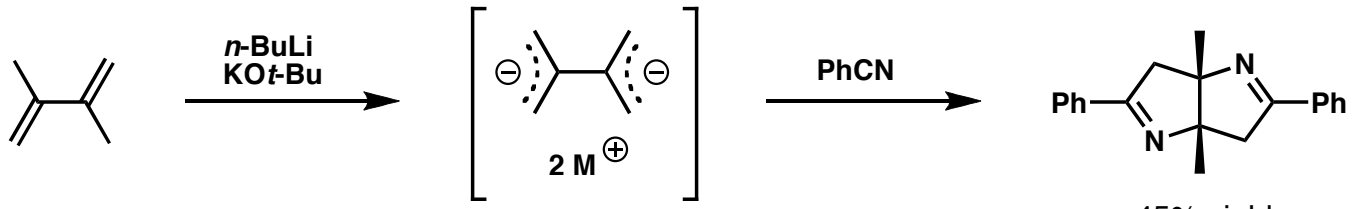


68% yield

Langer, P.; Döring, M. *Synlett.* **1998**, 399-401.
Langer, P. *Eur. J. Org. Chem.* **2001**, 2617-2627.

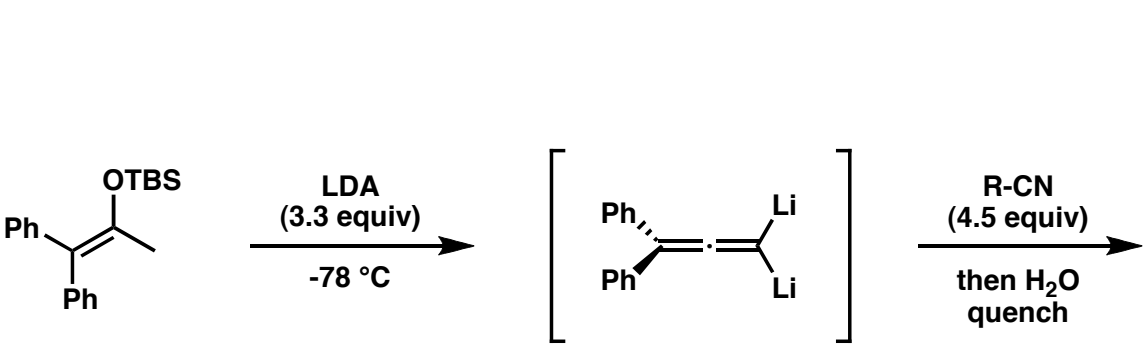
Multiple Anion Capture

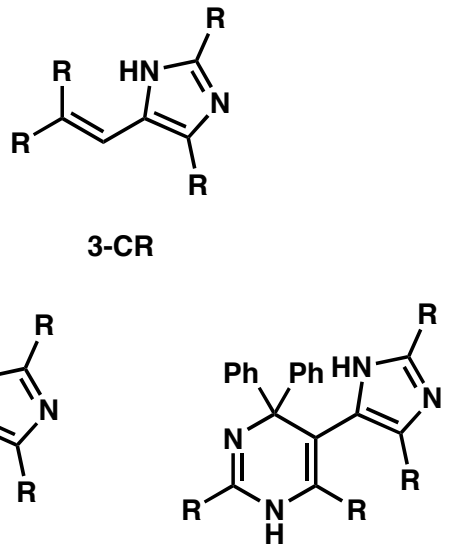
Synthesis of Nitrile Oligomers Using Allene Dianions



45% yield

Bates, R. B. *J. Org. Chem.* **1979**, *44*, 2290-2291.
Bates, R. B. *J. Org. Chem.* **1980**, *45*, 168-169.



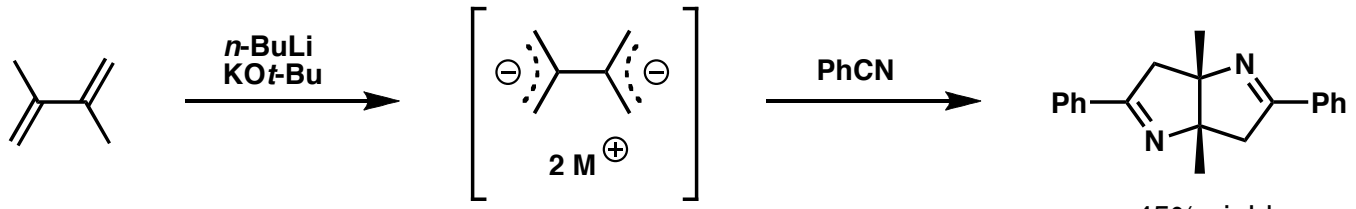


R	3-CR	4-CR	5-CR
Ph	0	12	51
t-Bu	0	66	0
4-Tol	0	28	0
3-Tol	40	0	trace

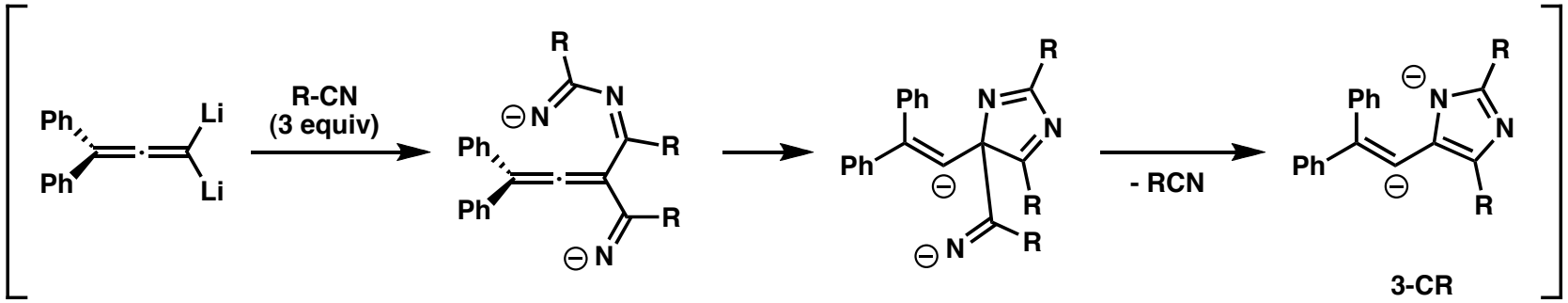
Langer, P. *Eur. J. Org. Chem.* **2003**, 1948-1953.

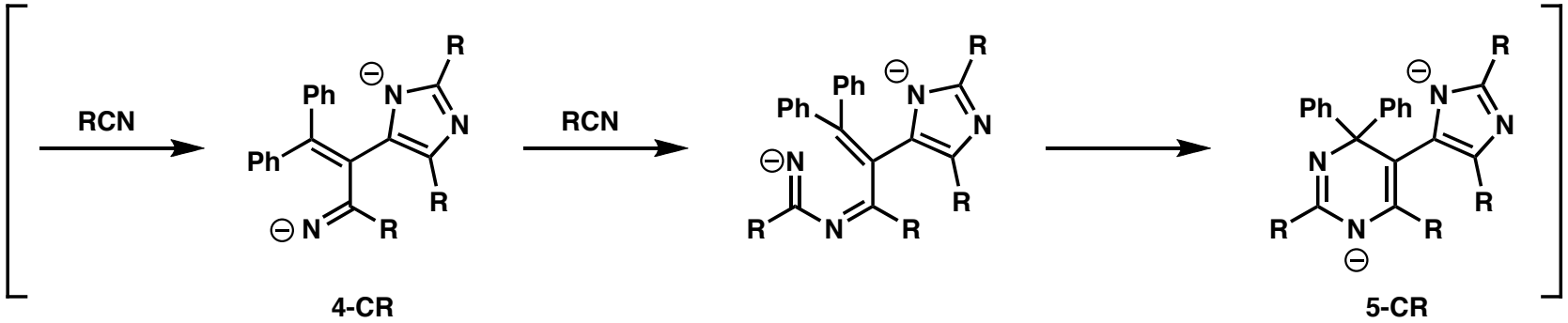
Multiple Anion Capture

Synthesis of Nitrile Oligomers Using Allene Dianions



Bates, R. B. *J. Org. Chem.* **1979**, *44*, 2290-2291.
Bates, R. B. *J. Org. Chem.* **1980**, *45*, 168-169.

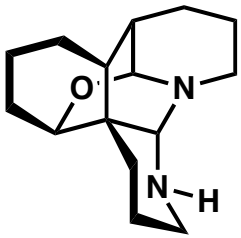




Langer, P. *Eur. J. Org. Chem.* **2003**, 1948-1953.

One-Pot Total Synthesis

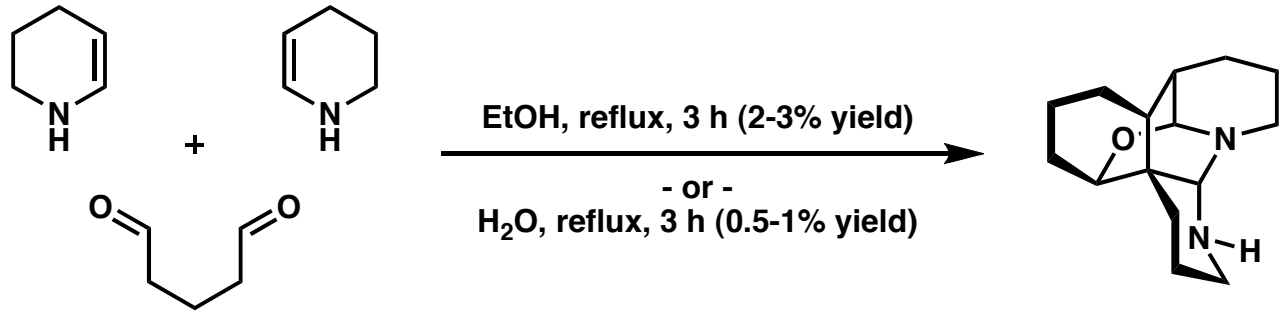
Poupon's Biomimetic Synthesis of Nitraramine



Nitraramine

- isolated from the desert shrub *Nitraria schoberi* found in Asia, Australia, and the Middle East
- exhibits "serotonin-like" activity in *in vitro* bioassays
- thought to be the product of condensation of three C_5 subunits derived from lysine

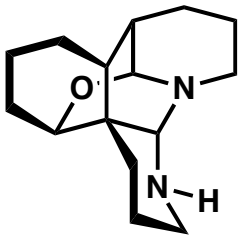
Nitraria schoberi



Poupon, E. *Org. Lett.* **2005**, *7*, 2497-2499.

One-Pot Total Synthesis

Poupon's Biomimetic Synthesis of Nitraramine



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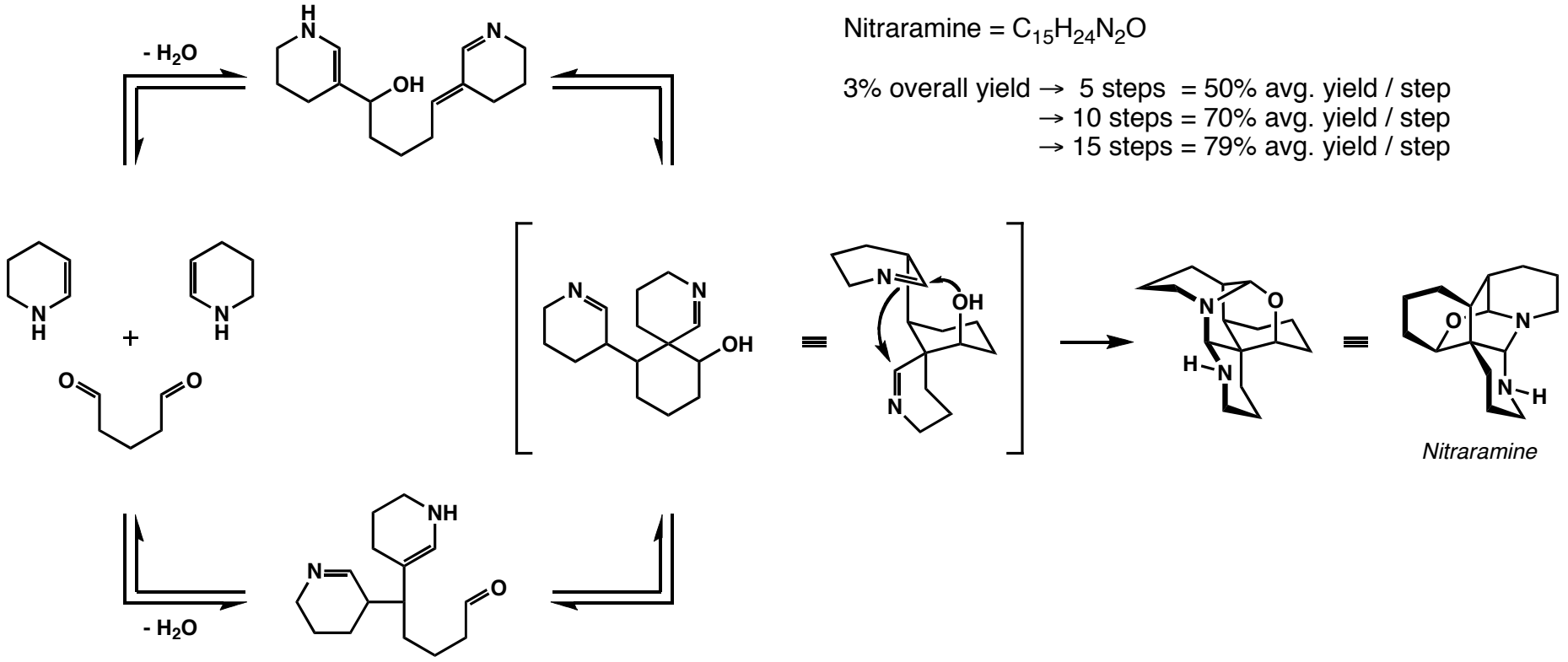
Nitraria schoberi



Nitraramine = $C_{15}H_{24}N_2O$

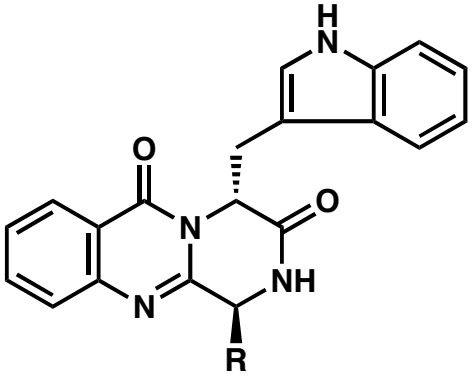
3% overall yield → 5 steps = 50% avg. yield / step
→ 10 steps = 70% avg. yield / step
→ 15 steps = 79% avg. yield / step

Nitraramine

Poupon, E. *Org. Lett.* **2005**, *7*, 2497-2499.

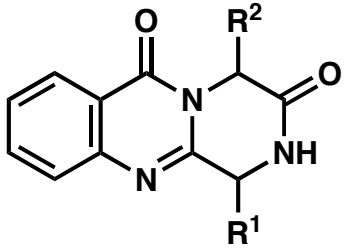
One-Pot Total Synthesis

Liu's Synthesis of the Quinazolinone Fungal Metabolites

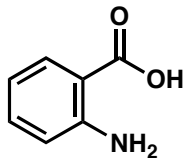


R = H, glyantrypine
= Me, Fumiquinazoline F
= i-Pr, Fiscalin B

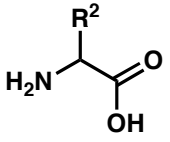
- Substance P (neurokinin) antagonists
- Display analgesic / anti-inflammatory properties

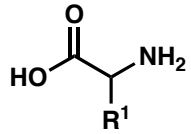


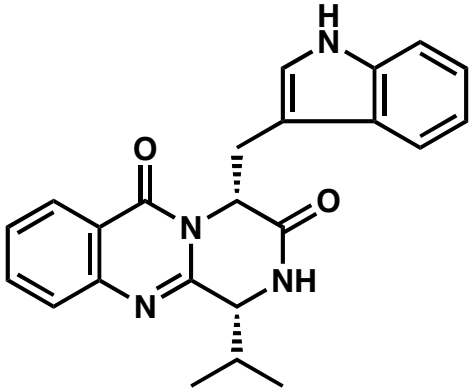
pyrazino[2,1-*b*]quinazoline-3,6-dione core



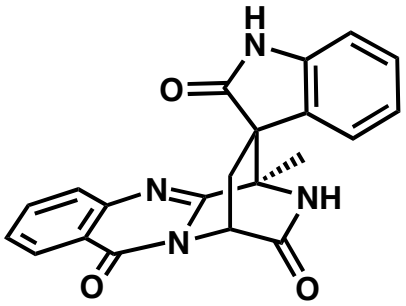
anthranilic acid



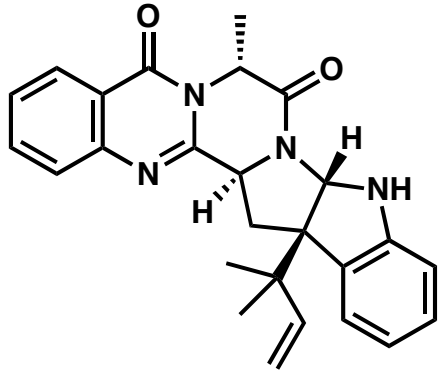




Fumiquinazoline G



Alantrypinone



Ardeemin

Glyantrypine: Mantle, P. G. *J. Chem. Soc. Perkin Trans. I* **1992**, 1495-1496.
Fumiquinazoline F: Numata, A. *Tetrahedron Lett.* **1992**, *33*, 1621-1624.
Fiscalin B: Cooper, R. *J. Antibiot.* **1993**, *46*, 545-553.
Fumiquinazoline G: Numata, A. *J. Chem. Soc. Perkin Trans. I* **1995**, 2345-2353.
Alantrypinone: Larsen, T. O. *J. Nat. Prod.* **1998**, *61*, 1154-1157.
Ardeemin: McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 374-379.

One-Pot Total Synthesis

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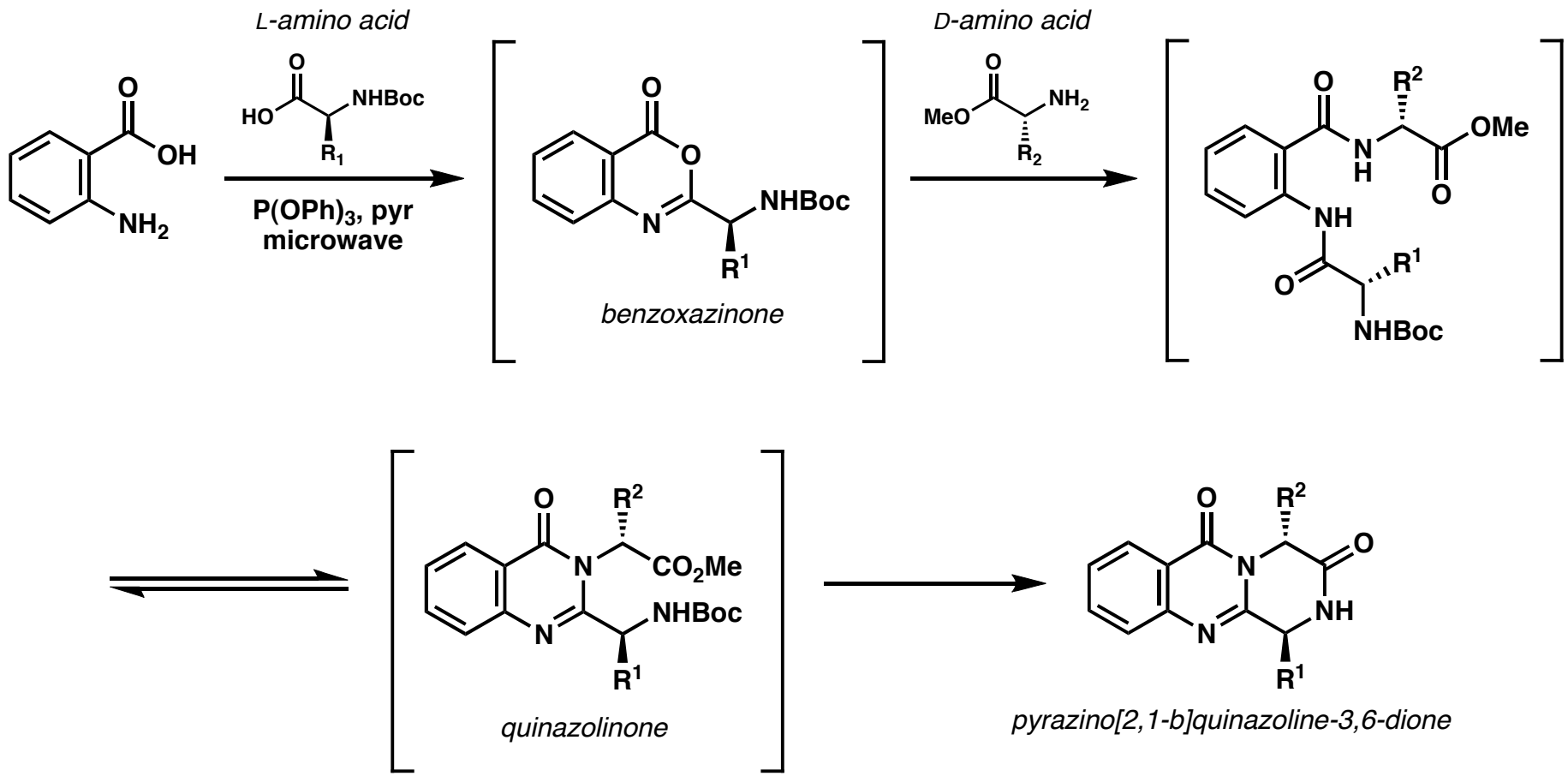
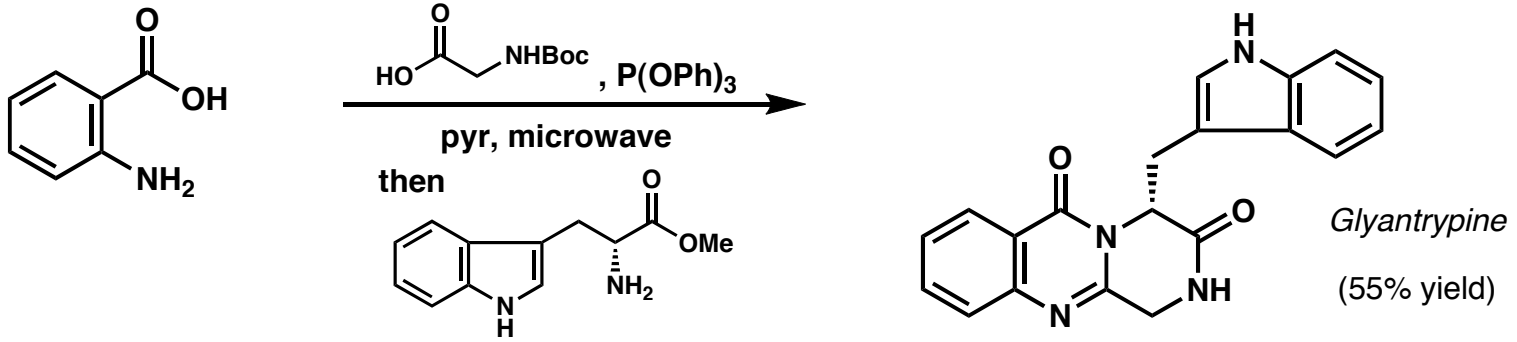
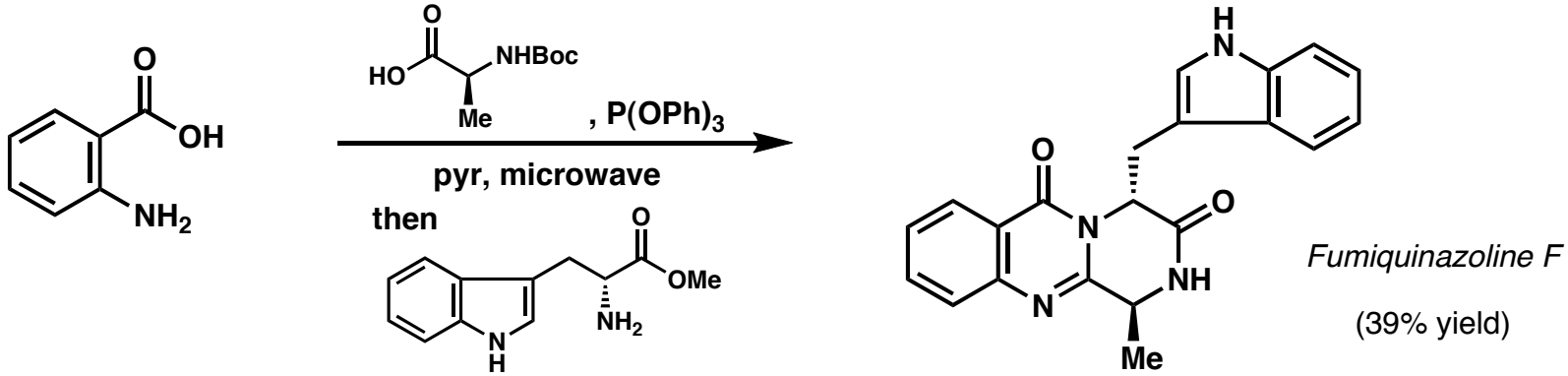


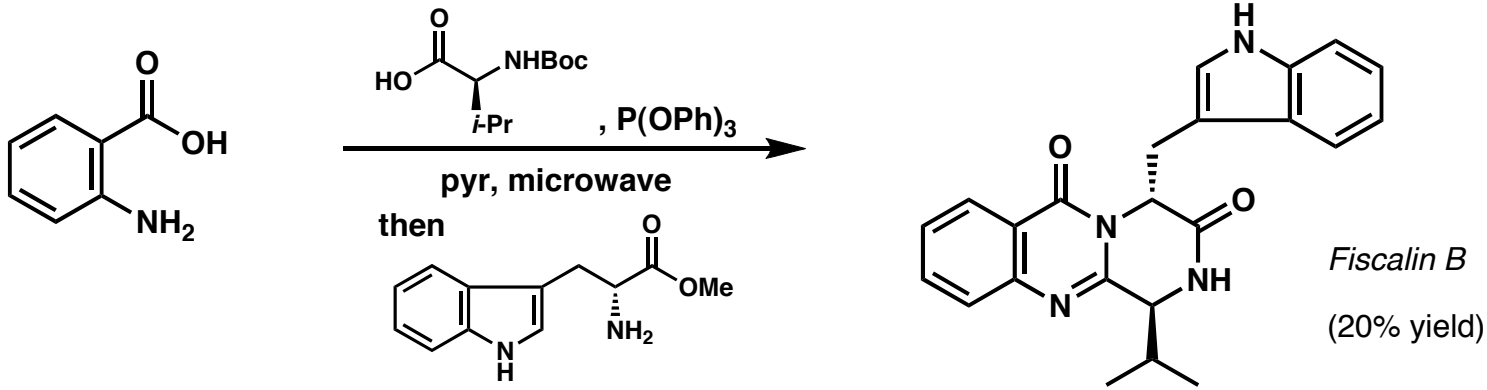
Liu, J.-F. *Tetrahedron Lett.* **2005**, *46*, 1241-1244.
Liu, J.-F. *J. Org. Chem.* **2005**, *70*, 6339-6345.

One-Pot Total Synthesis

Liu's Synthesis of the Quinazolinone Fungal Metabolites



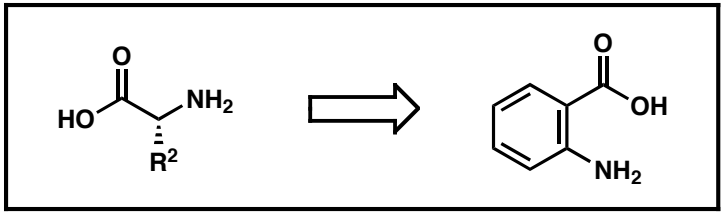


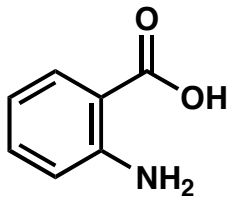


Liu, J.-F. *Tetrahedron Lett.* **2005**, *46*, 1241-1244.
Liu, J.-F. *J. Org. Chem.* **2005**, *70*, 6339-6345.

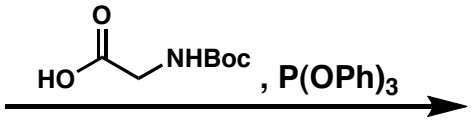
One-Pot Total Synthesis

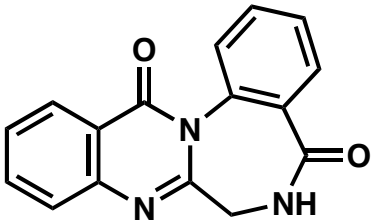
Liu's Synthesis of the Quinazolinobenzodiazepine Fungal Metabolites





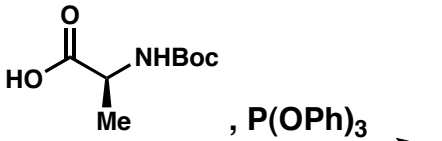
2 equiv

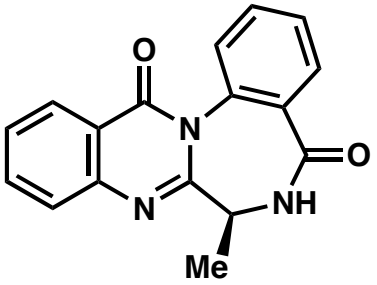




Sclerotigenin

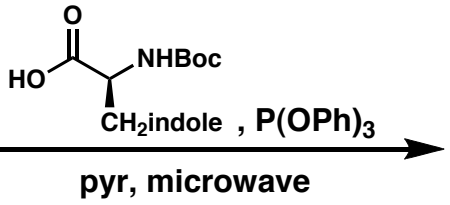
(55% yield)

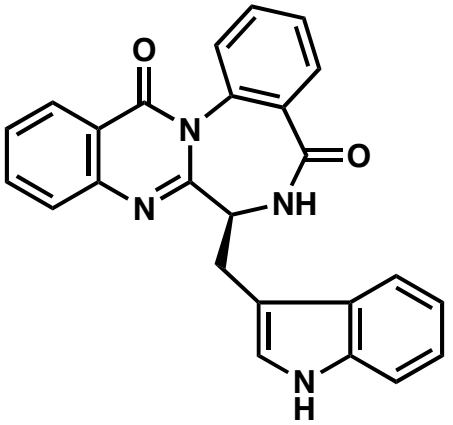




Circumdatin F

(32% yield)





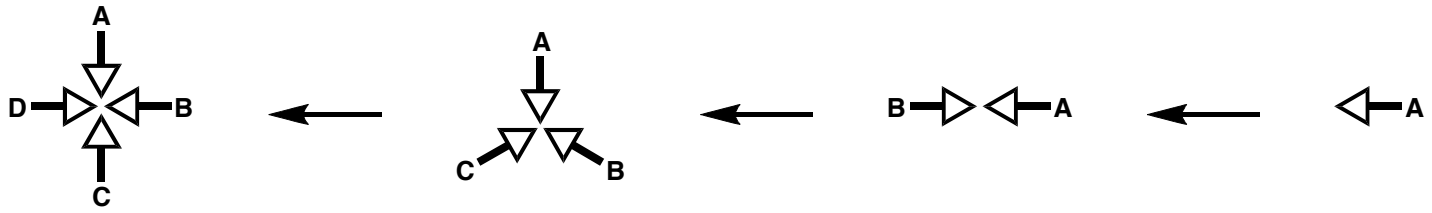
Asperlicin C

(20% yield)

Liu, J.-F. *J. Org. Chem.* **2005**, *70*, 10488-10493.
Sclerotigenin: Gloer, J. B. *J. Nat. Prod.* **1999**, *62*, 650-652.
Circumdatin F: Rahbæk, L. *J. Nat. Prod.* **1999**, *62*, 904-905.
Asperlicin: Lotti, V. J. *J. Antibiot.* **1988**, *41*, 875-877.

Multicomponent Reactions

Summary and Conclusions



- Multicomponent reactions are capable of condensing 3, 4, 5, 6, and even 7 reactant species in a single reaction mixture.

- MCRs are underused in total synthesis. Though the most obvious applications lie in the realm of library synthesis, the extreme convergence afforded by these reactions provides a quick, efficient, and low-cost alternative to current linear syntheses.

  Remember: In comparison to an analogous multi-step sequence, a low-yielding MCR is not as costly.

- Most MCRs have a broad substrate scope capable of tolerating diverse functionality in addition to the reactive centers. This can set up MCR products for further cascade transformations.

- Limitation: The more components that a MCR employs, the more complex the target it generates. The more complex the target, the less generally applicable it becomes in total synthesis.

- The library of known multicomponent reactions is far from complete! New combinations of existing reactions are always possible and a firm understanding of reaction mechanism can lead to the discovery of novel modes of reactivity.