Synthesis of (-)-flustramine B: Enantioselective organocatalytic Pyrroloindoline Construction

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Wen-Jing Xiao, and David W. C. MacMillan*

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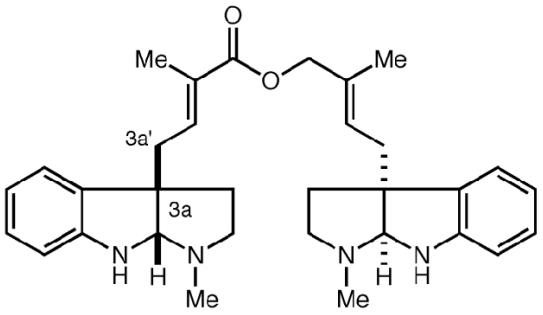
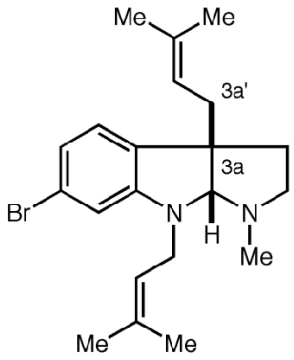
David W. C. MacMillan

- **1968**: Born in Scotland.
- **1987-1991:** B.S- University of Glasgow
- **1991-1996:** Doctoral studies with Professor Larry E. Overman at the University of California, Irvine
- **1996-1998:** Postdoctoral research fellow with Professor David A. Evans at Harvard University
- **1998:** Dave began his independent research career at the University of California, Berkeley
- **2006:** Appointed as the A. Barton Hepburn Professor of Chemistry at Princeton University
- **2011**: Appointed as James S. McDonnell Distinguished University Professor of Chemistry at Princeton University.

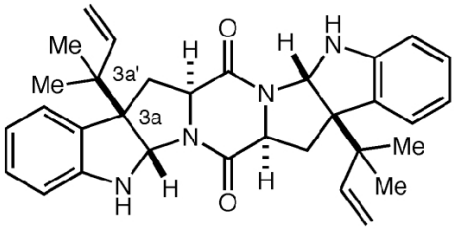
Pyrroloindoline Natural Isolates



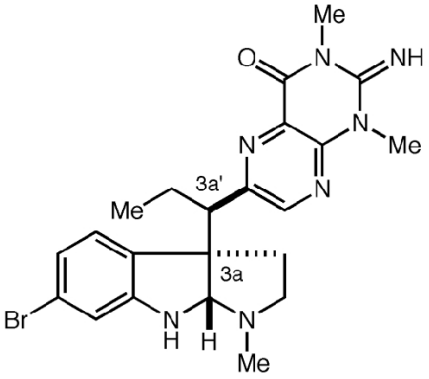
Pseudophrynamine A



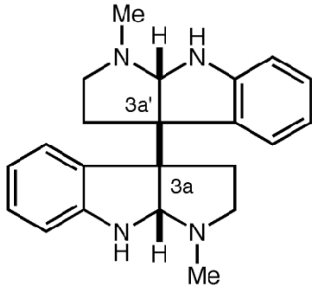
(–) Flustramine B



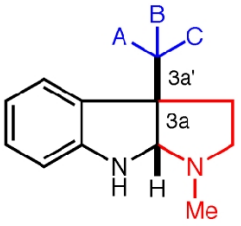
Amauromine



(–) Urochordamine A



(–) Chimonanthene



synthetic challenges

(1) Quaternary stereocenter C3a
(2) Diastereocontrol C3a-C3a'
(3) Pyrroloindoline ring system
(4) Enantioselective catalysis

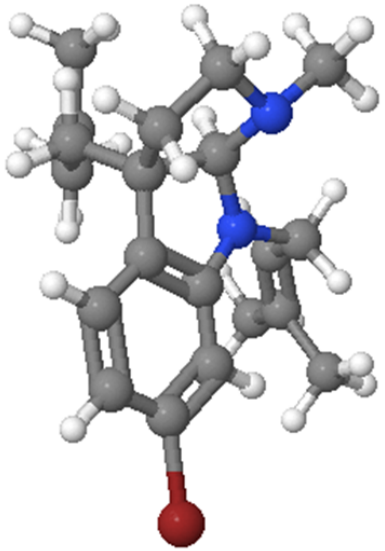
(-)-flustramine B

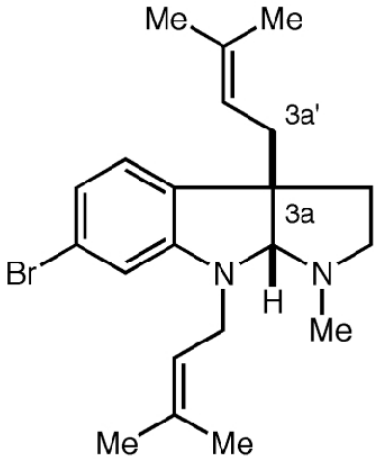
- Isolated from a widespread series of natural sources, including amphibians, plants and marine algae

- First described in the late 1930s, this alkaloid family has been found to exhibit remarkable biological properties across a broad spectrum of pharmacological screens

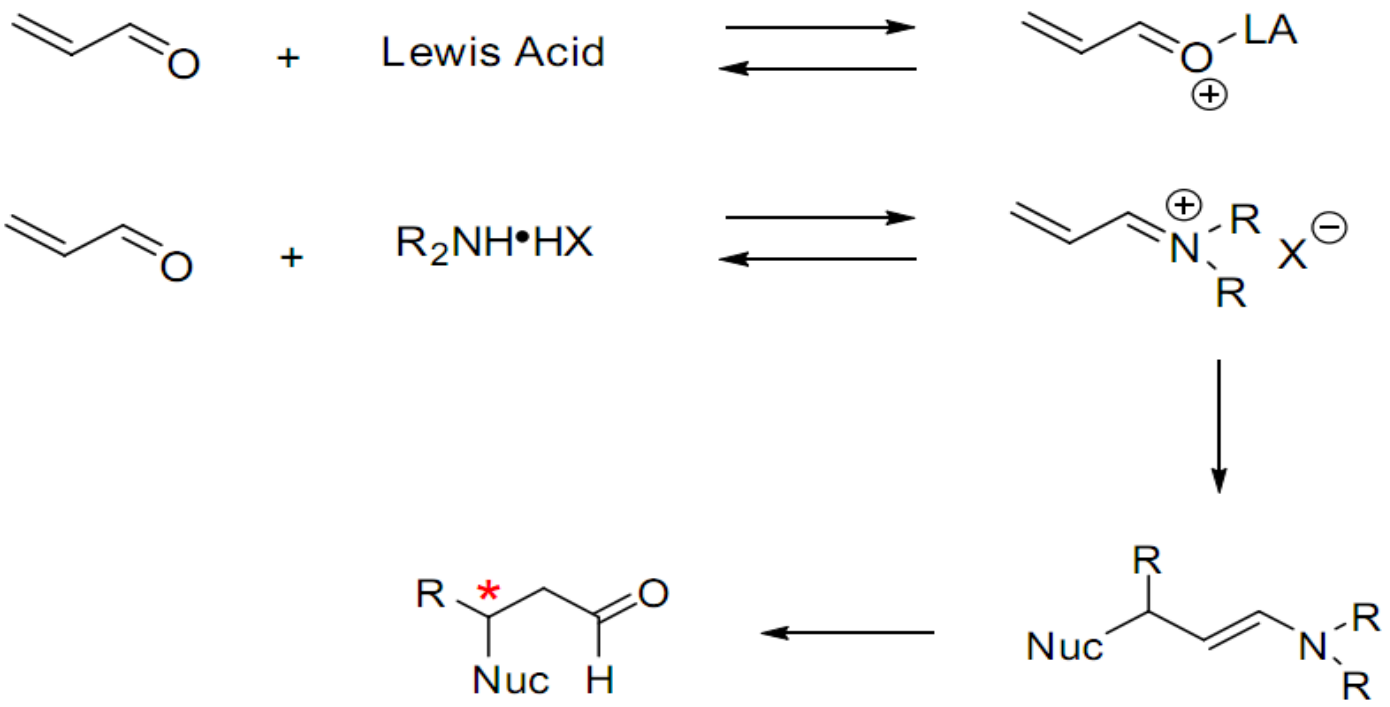
- exhibit potent anti-cancer activities against lymphocytic leukemia cell lines and cytotoxicity to HeLa cell lines

- Total synthesis has been published by Austin, Kim, Christopher, Xiao, and MacMillan





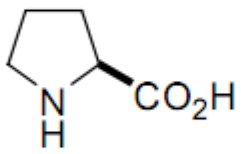
Iminium Activation: Concept Development



- Use chiral amines as LUMO-lowering catalysts instead of Lewis acids.

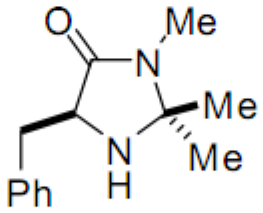
Development of effective amine catalyst

1. Increase reactivity of substrate.
2. Efficient and reversible iminium ion formation.
3. Control enantiofacial selectivity of the olefin.
   - thru organized T.S.
   - predictable d.b. geometry
4. Ease of catalyst preparation and implementation.

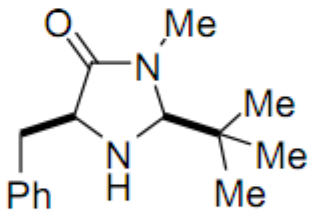


L-proline

List, Barbas, MacMillan, etc.



MacMillan 1st gen.
Imidazolidinone catalyst



MacMillan 2nd gen.
Imidazolidinone catalyst

Applications

- cycloadditions
- conjugate additions
- Friedel-Crafts alkylations

Alrichimica ACTA, **2006**, *39*, 79-87
JACS, **2000**, *122*, 4243

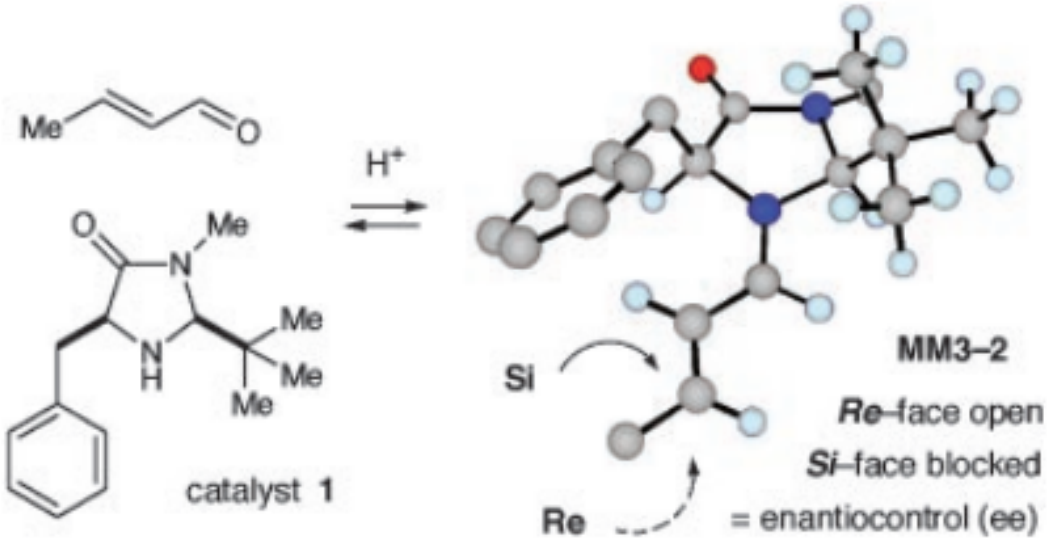


Fig. 2. Iminium catalysis concept: Imidazolidinone catalyst and corresponding iminium structure.

The catalyst activated iminium ion was formed with (E)-isomer selectivity to avoid nonbonding interactions between the substrate olefin and the bulky tert-butyl group

Pyrroloindoline Construction

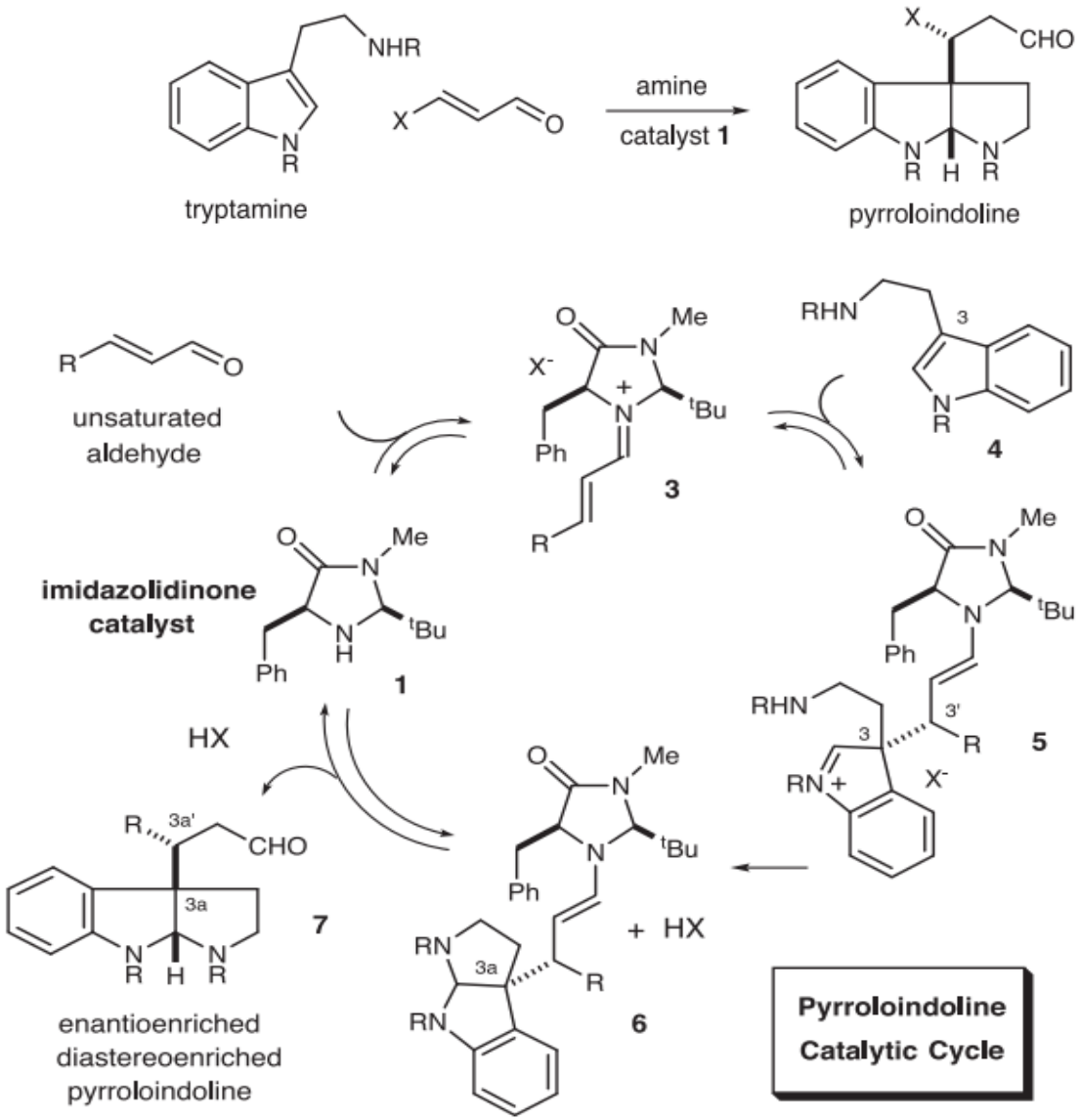
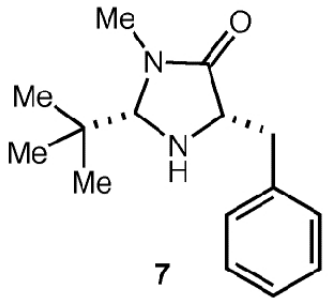


Fig. 3. Pyrroloindoline formation: Catalytic cycle.

Effect of Cocatalyst and Solvent on the Organocatalytic pyrroloindoline Construction



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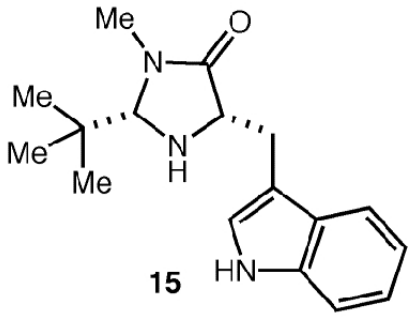
cocatalyst (HX)

a = TFA
b = HBr
c = $NCCH_2CO_2H$
d = *p*–TSA



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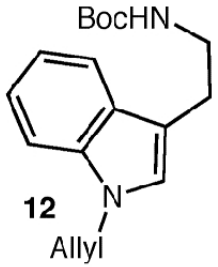

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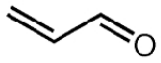
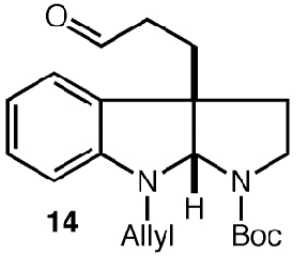


13

20 mol% amine

Solvent



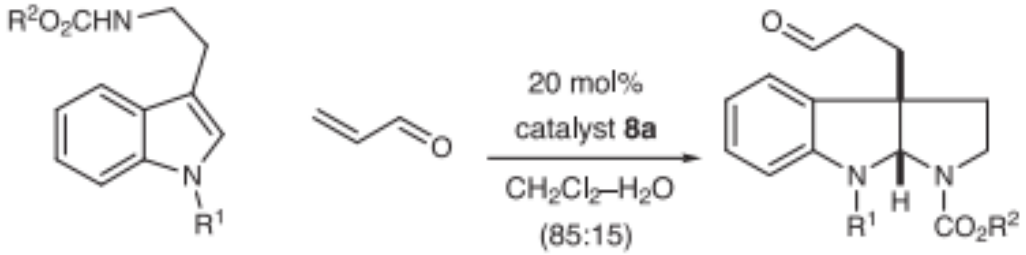
14

entry	solvent	dielectric	% H_2O	catalyst	temp (°C)	% yield	% ee[a]
1	MeOH	32.6	0	7c	–85	9	77
2	MeOH	32.6	10	7d	–40	64	69
3	Acetone	20.2	10	7d	–40	58	60
4	DME	7.2	10	7d	–40	18	21
5	$CHCl_3$	4.8	10	7d	–40	66	-45
6	Toluene	2.4	10	7d	–40	60	-59
7	Toluene	2.4	2	7b	+4	50	-84
8	CH_2Cl_2	9.1	15	7a	–85	79	70
9	CH_2Cl_2	9.1	15	15a	–85	85	89

[a] Product ratios determined by chiral HPLC.

Results of various protecting groups with Acrolein

Table 2. Enantioselective pyrroloindoline formation with representative *N*(1)- and *N*(10)-substituted tryptamines



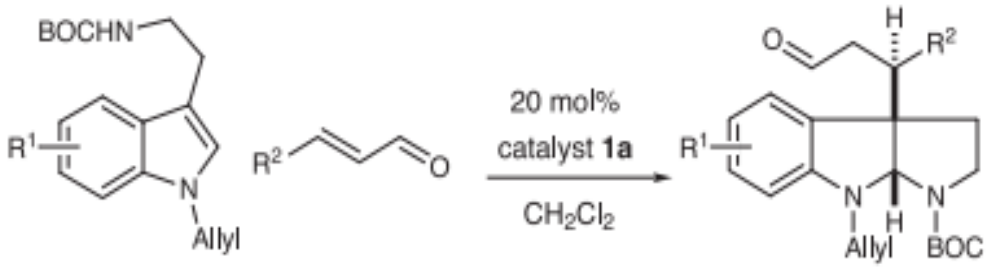
Entry	R^1	R^2	Time, h	Yield, %	ee,* %
1	Allyl	*t*-Bu	25	85	89
2	Allyl	Et	26	89	89
3	Prenyl	Et	24	89	89
4	Benzyl	Allyl	48	83	89
5	Benzyl	*t*-Bu	30	82	90†

*Product ratios determined by HPLC.

†Absolute configuration determined by chemical correlation.

Results With Substituted Acroleins

Table 3. Enantioselective pyrroloindoline formation with representative unsaturated aldehydes and indoles

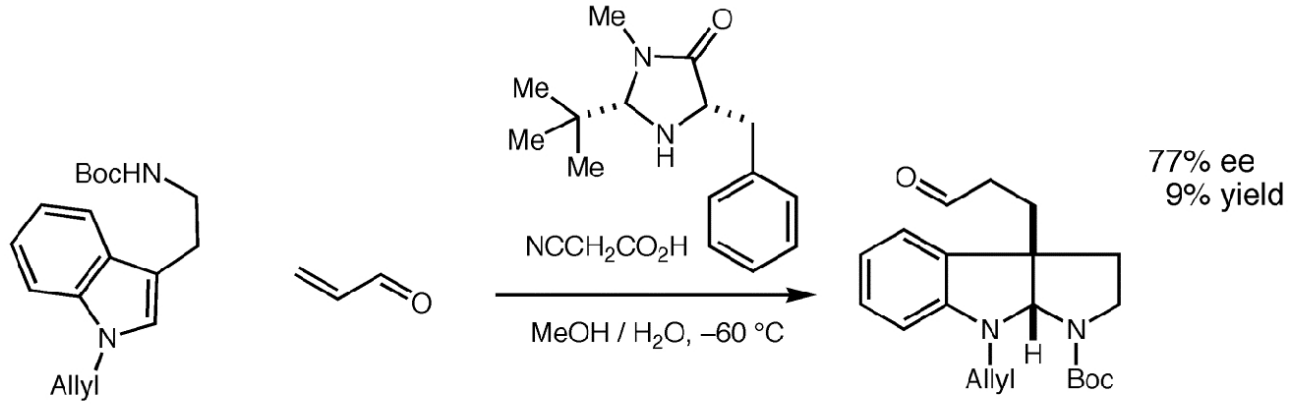


Entry	R^1	R^2	Time, h	Yield, %	ee,* %	dr†
1	H	COPh	64	92	94	13:1
2	H	CH_2OBz	44	66	91	22:1
3	H	CO_2Me	28	93	91	44:1‡
4	5-Me	CO_2Me	18	94	92	50:1
5	5-MeO	CO_2Me	20	99	90	10:1
6	6-Br	CO_2Me	36	86	97	31:1
7	7-Me	CO_2Me	30	97	99	17:1

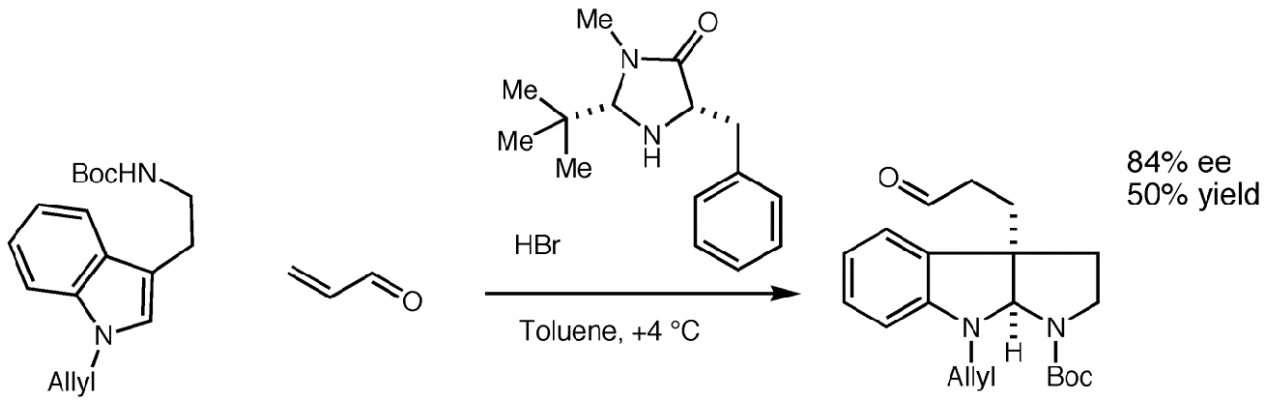
*Product ratios determined by chiral HPLC.
†dr, diastereomeric ratio.
‡Absolute configuration determined by x-ray crystallography.

Stereochemical Rationale For Acrolein

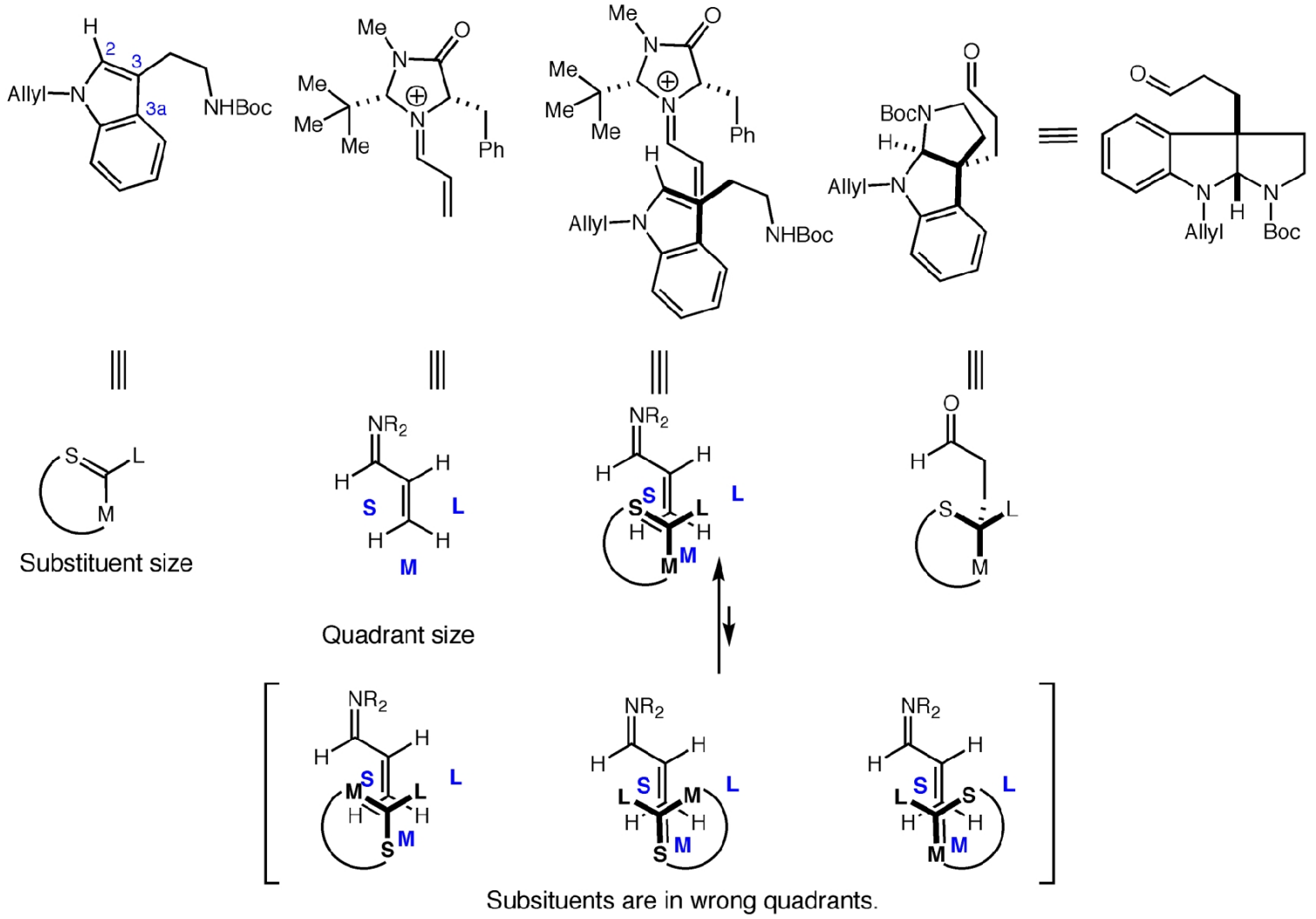
Equation1. Enantioselective construction of pyrroloindole core in Methanol



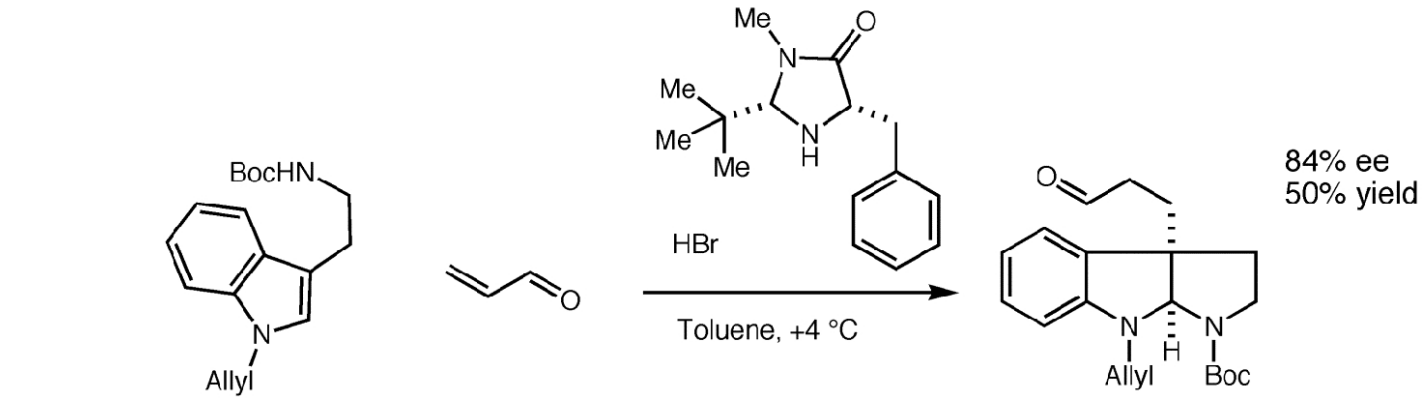
Equation 2. Enantioselective construction of pyrroloindole core in Toluene

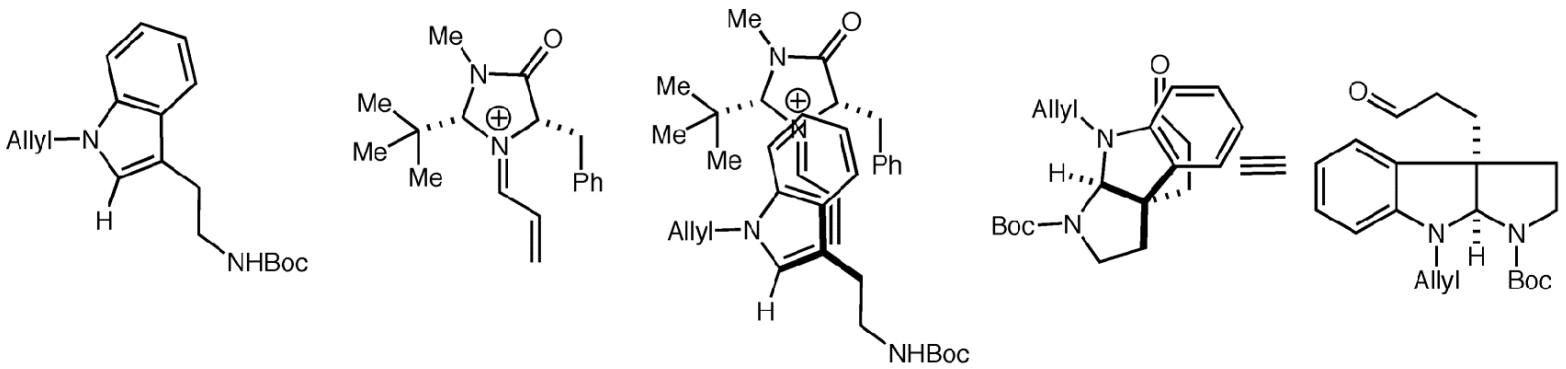


Equation1

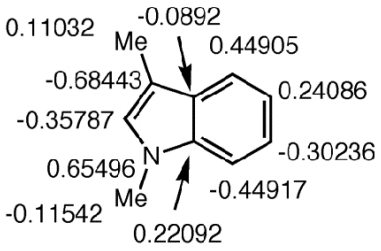

Substituent size
Quadrant size
Subsituents are in wrong quadrants.

Equation 2. Enantioselective construction of pyrroloindole core in Toluene

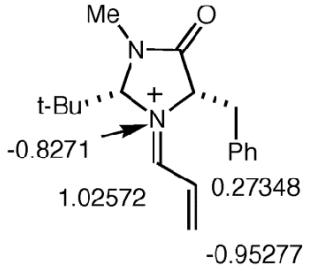




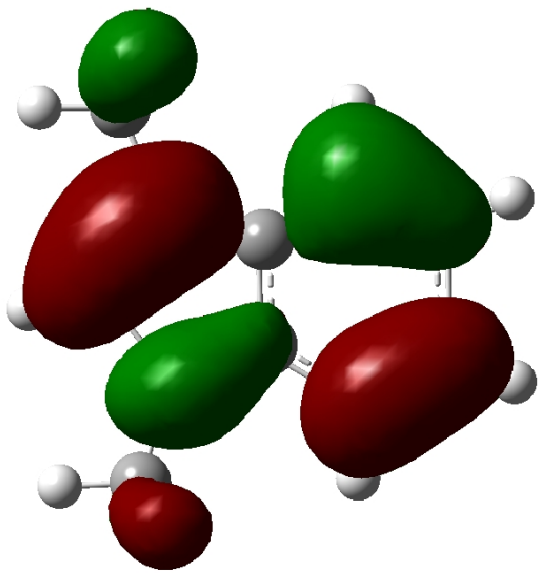
Frontier Molecular Orbital Explanation for Equation 2

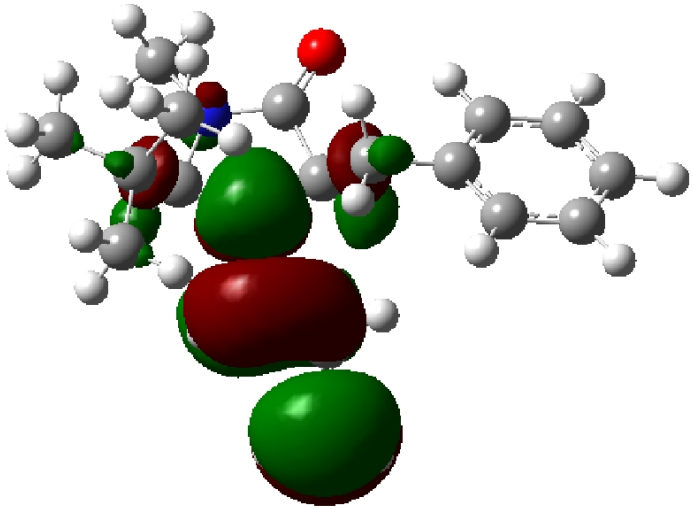


Frontier electron population for 1,3-dimethylindole HOMO

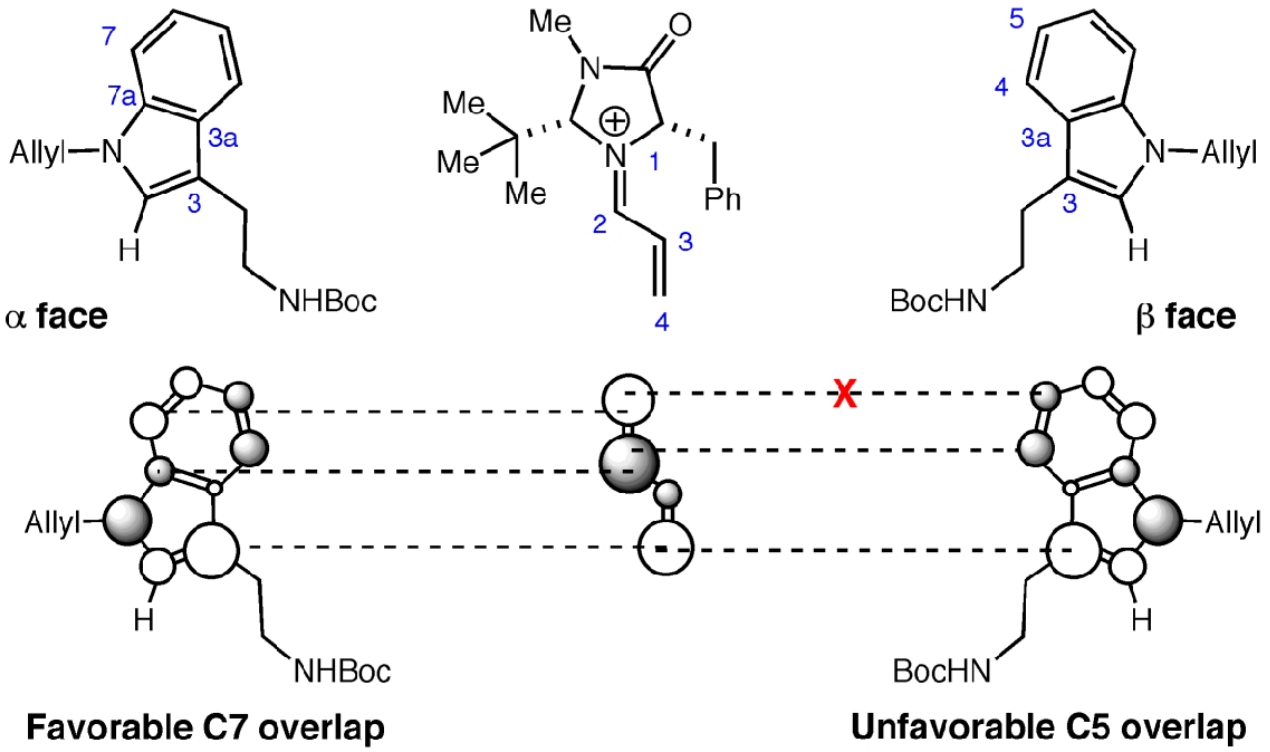


Frontier electron population for iminium LUMO

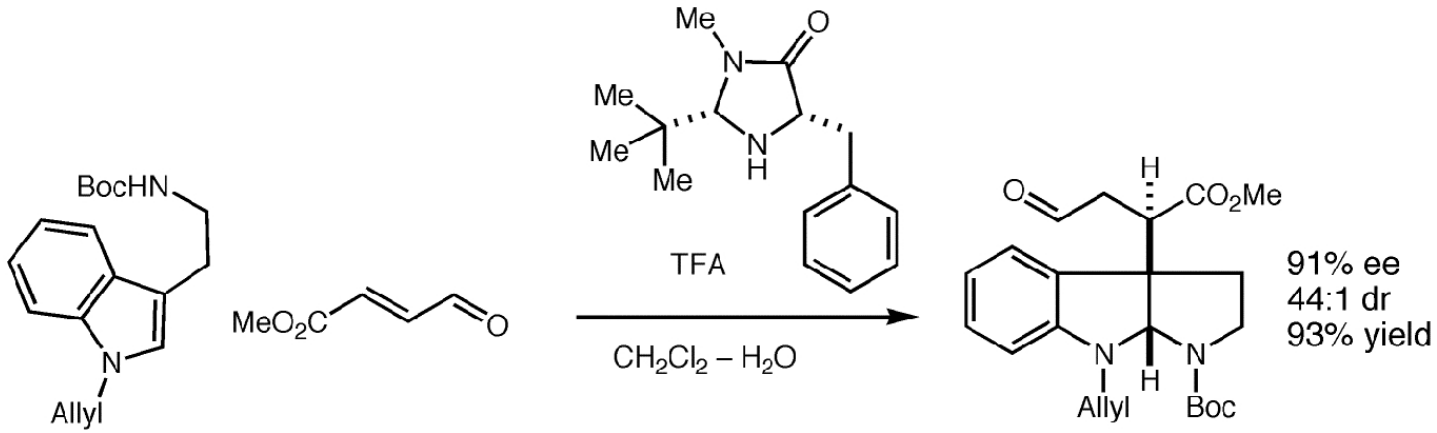


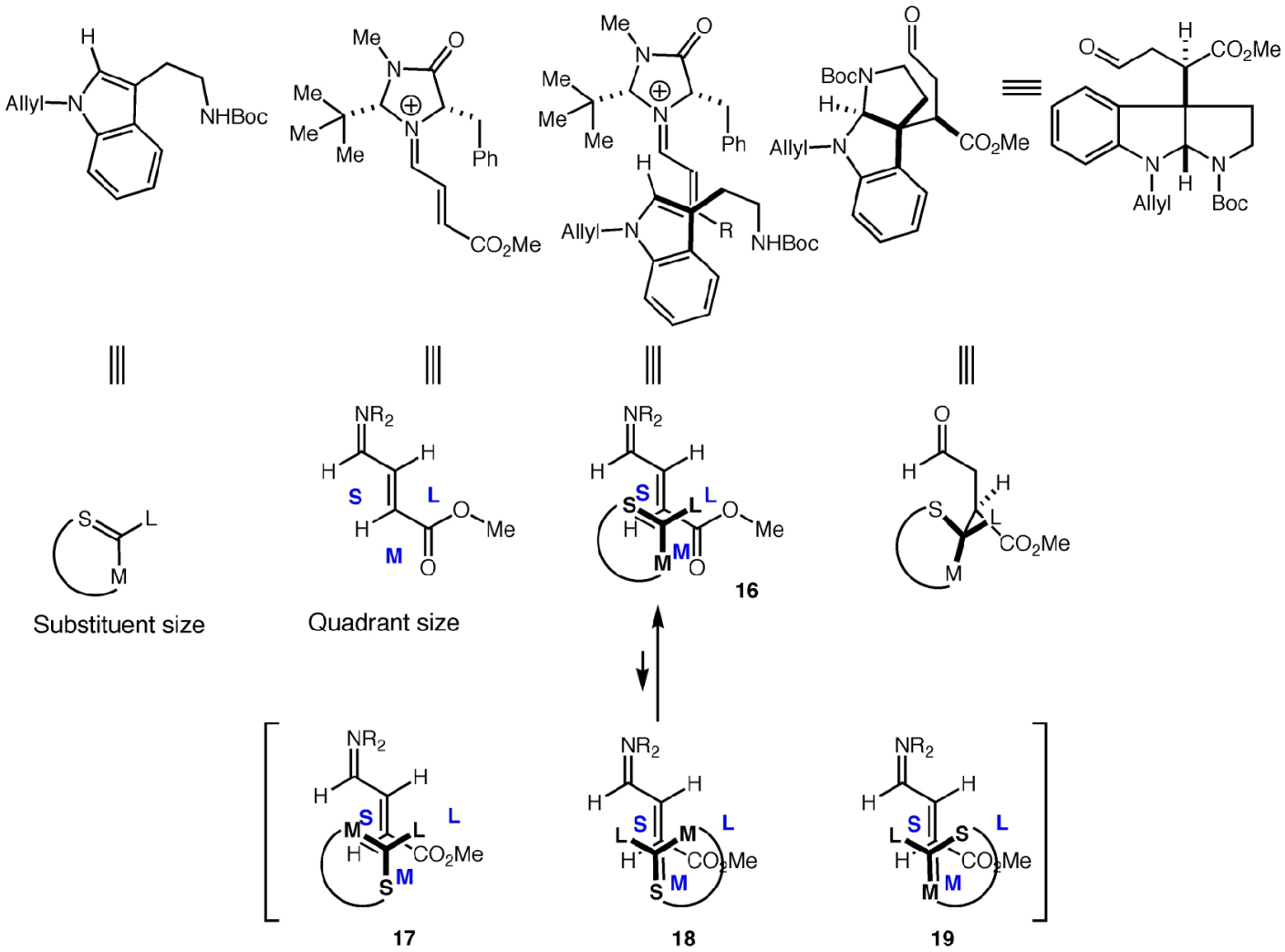


Tryptamine Facial Selectivity Due to Secondary Overlap

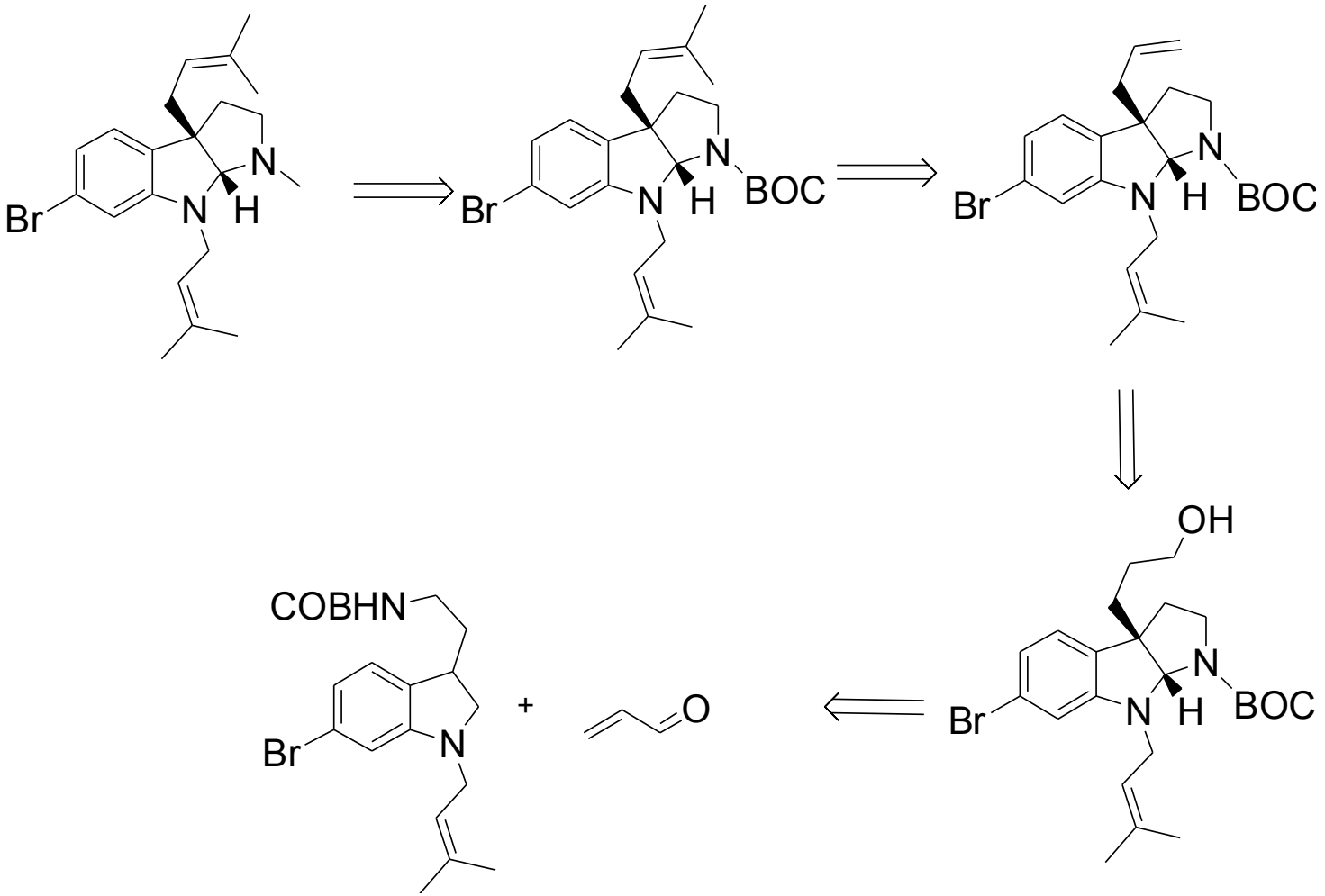


Stereochemical Rationale for β-Substituted Acroleins




Substituent size
Quadrant size
16
17
18
19

Retrosynthetic Analysis



(-)-Flustramine B Synthesis

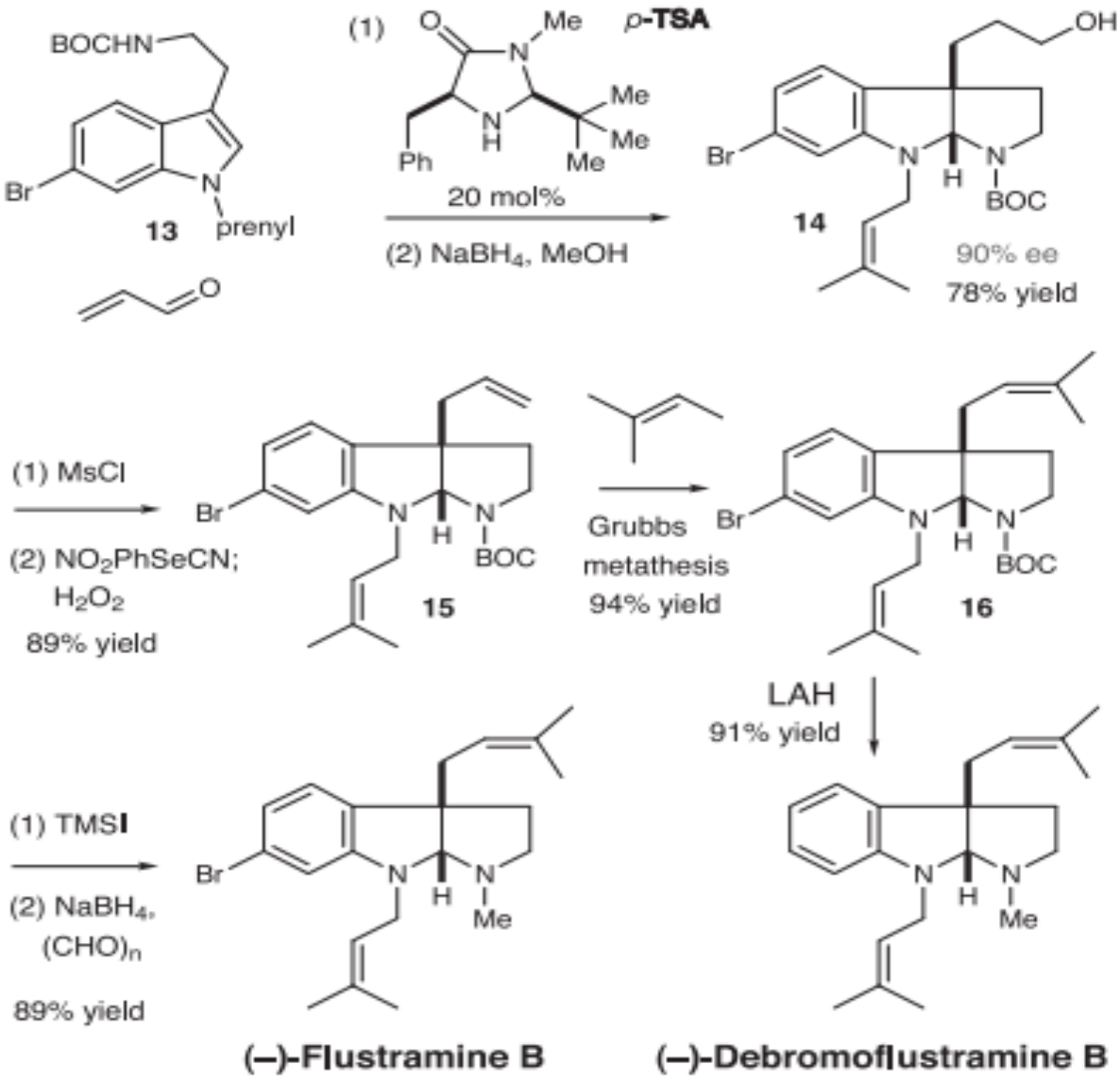


Fig. 4. Total synthesis of (−)-flustramine B

Conclusion

- The addition cyclization of tryptamines with α,β-unsaturated aldehydes in the presence of imidazolidinone catalysts provides pyrrolidinone adducts in high yield and excellent enantioselectivities.

- Application of this pyrroloindoline-forming reaction to natural product synthesis has been accomplished in the context of the enantioselective synthesis of (-)-Flustramine B

Thank you