Asymmetric Catalysis for Fine Chemicals Synthesis

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Hypoiodite-Catalyzed Oxidative Umpolung of Indoles for Enantioselective Dearomatization

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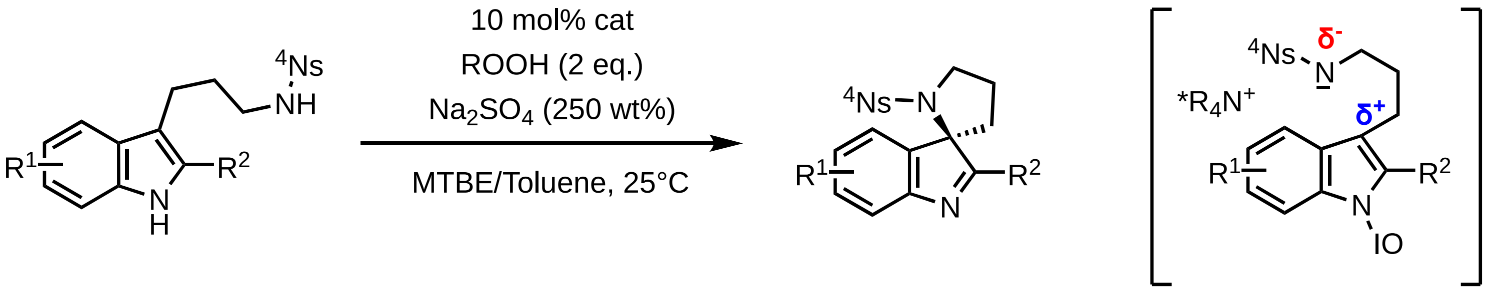
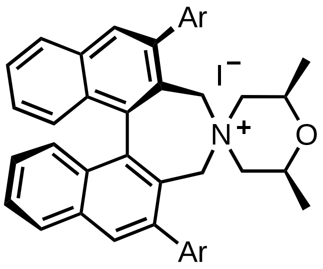
Introduction: Reaction and Reactivity

Spirocyclization

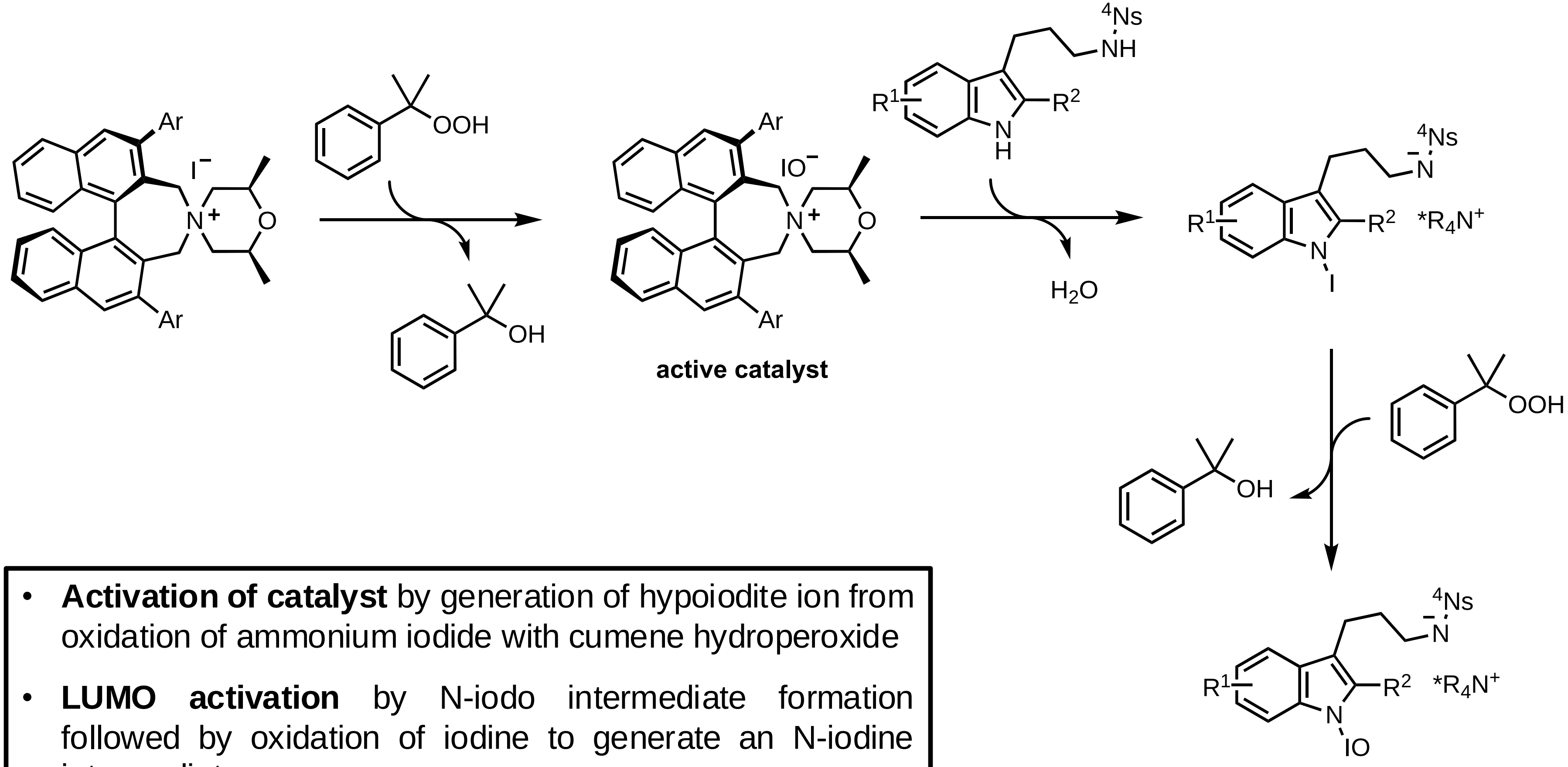




cat.

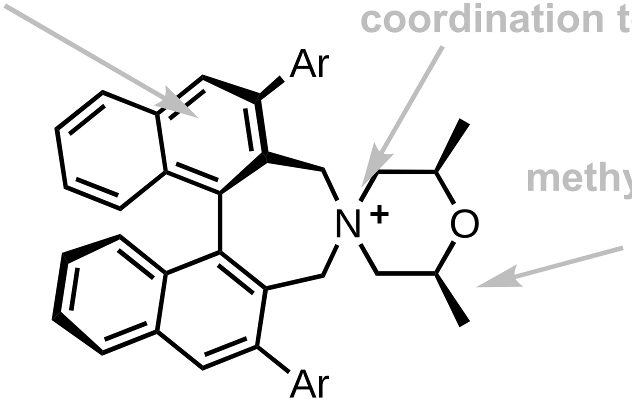
- The reaction is a **spirocyclization**.
- **Nucleophile**: sulfonamide attached to the C3 position of the indole
- **Electrophile**: C3 atom of indole (**umpolung**)
- **Bond formation**: Attack of sulfonamide on electron-deficient C3 atom of the indole
- **Catalyst**: bis(binaphthyl)-based chiral quaternary ammonium iodide

Principle of Activation



- **Activation of catalyst** by generation of hypoiodite ion from oxidation of ammonium iodide with cumene hydroperoxide
- **LUMO activation** by N-iodo intermediate formation followed by oxidation of iodine to generate an N-iodine intermediate
- **Asymmetric induction** from the binaphthol ligand and methyl groups

Asymmetric Induction

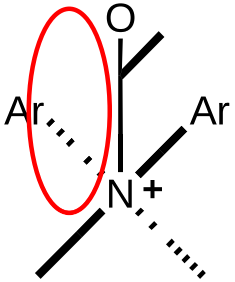


π-π interactions

coordination to substrate

methyl groups blocking one catalyst face

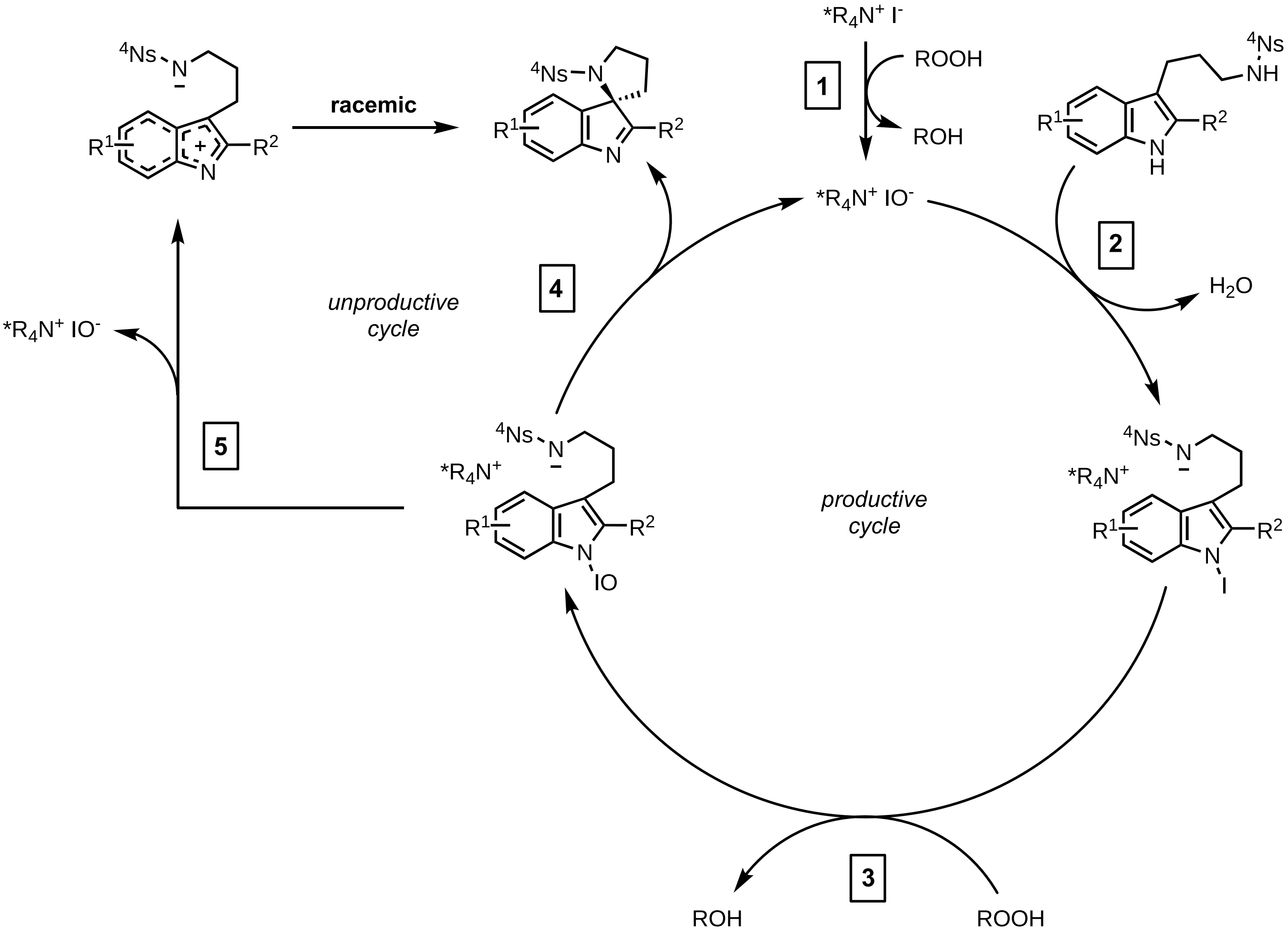
$*R_4N^+$



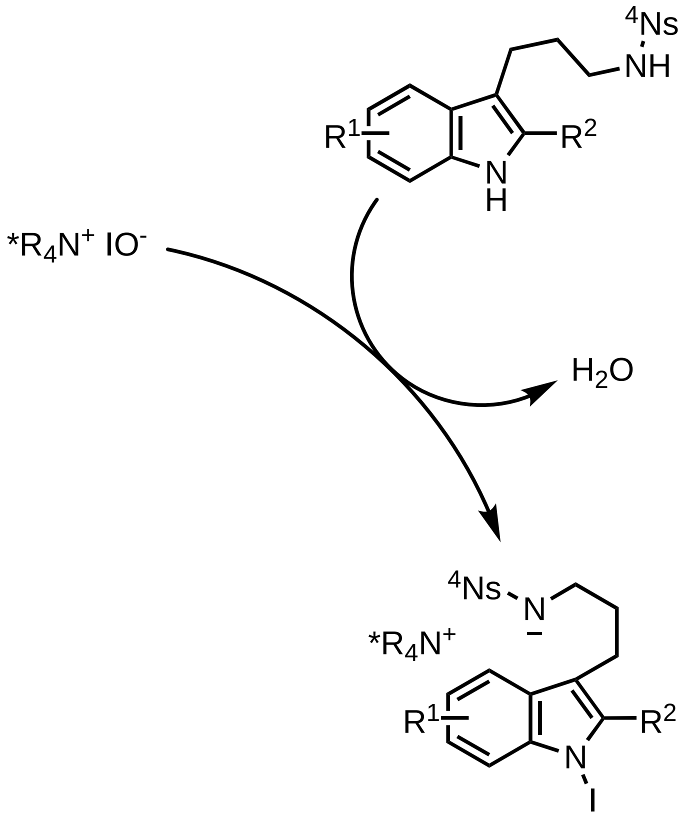
top view on $*R_4N^+$

- Exact **transition state** is still unknown
- Potential interactions: π-π stacking, ion-pair
- **Cation-induced asymmetry** from the binaphthol ligand and methyl groups

Catalytic Cycle

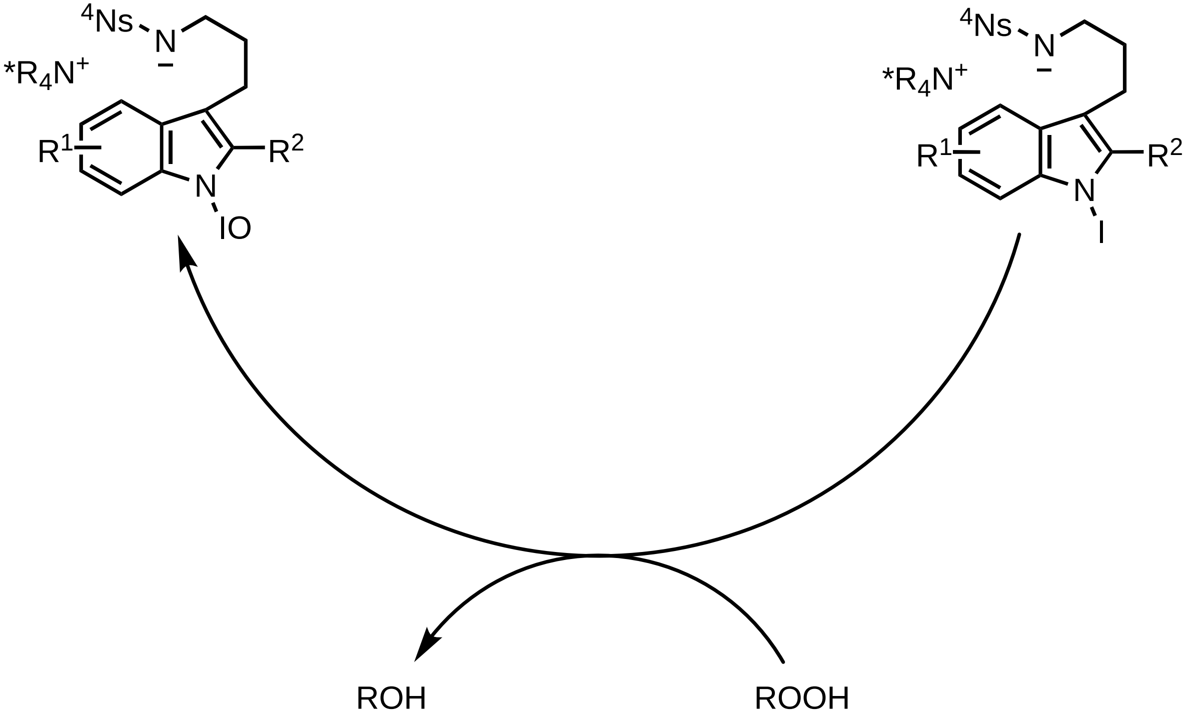


Catalytic Cycle 2



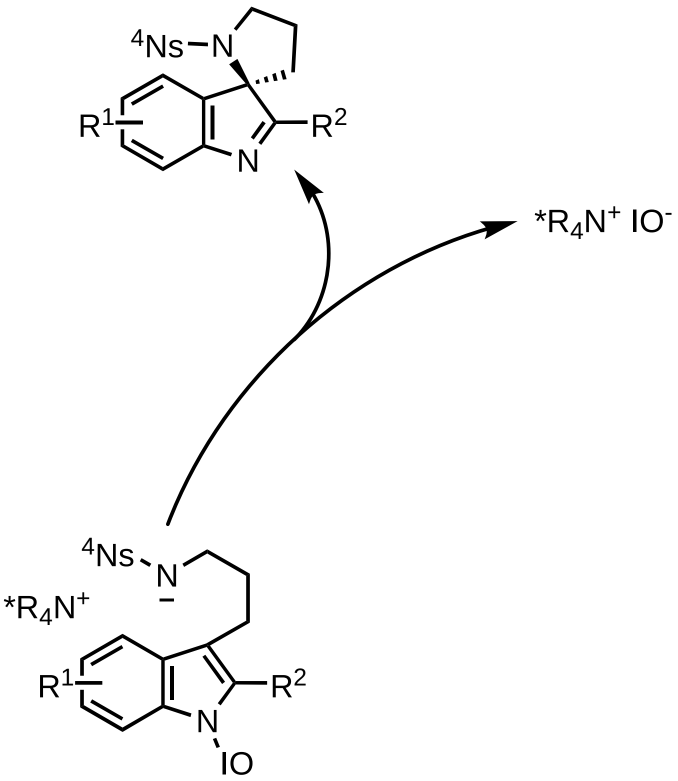
1st LUMO activation by N-iodo intermediate formation

Catalytic Cycle 3



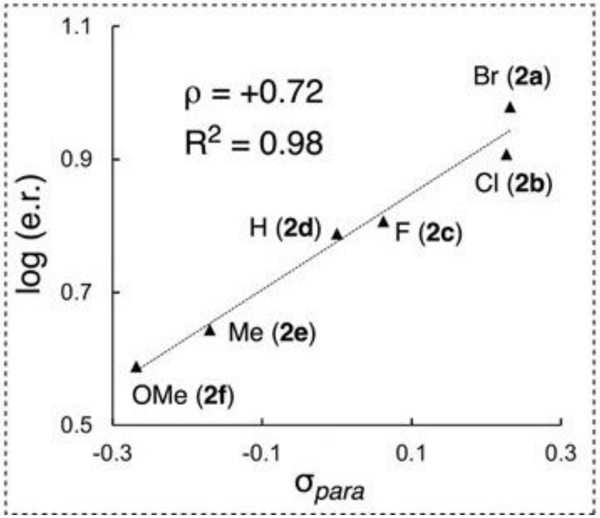
2nd LUMO activation by oxidation of iodine to generate an N-iodine(III) intermediate

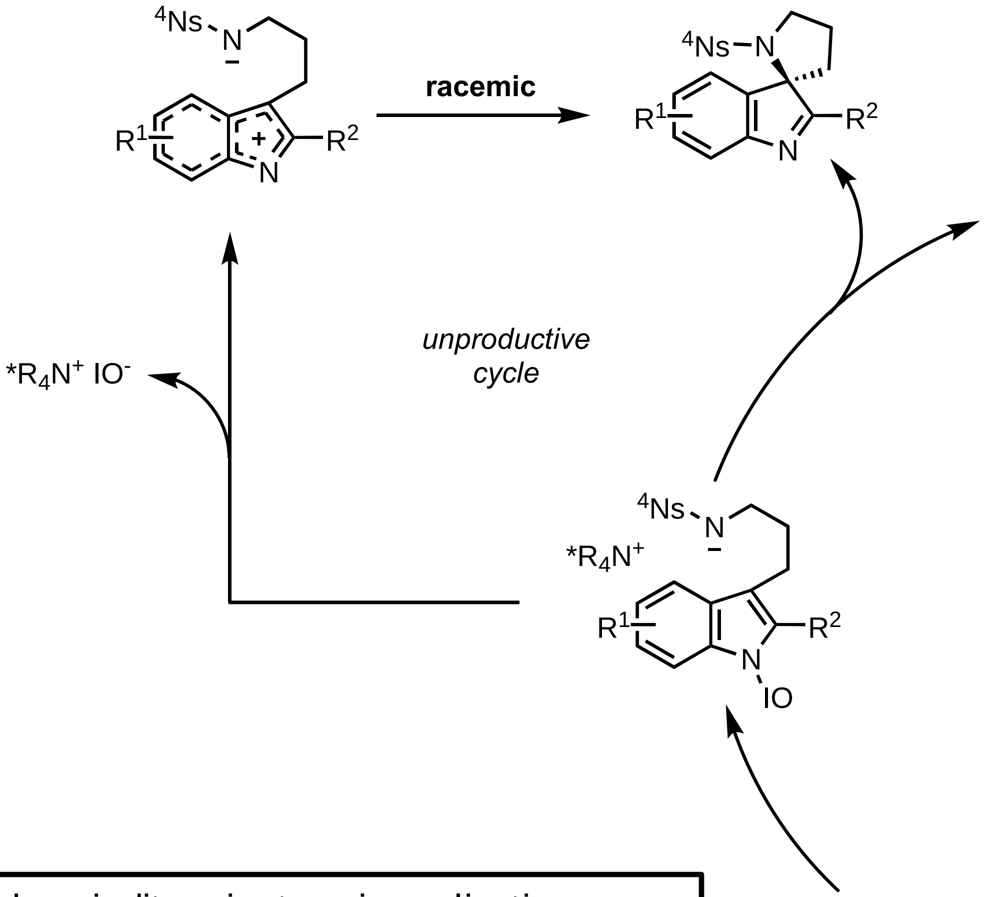
Catalytic Cycle 4



Bond formation and **catalyst turnover** by simultaneous reductive elimination of ammonium hypoiodite and spirocyclization

Catalytic Cycle 5



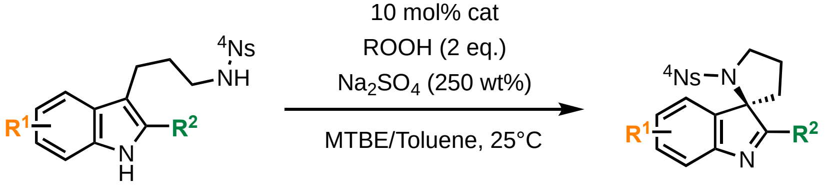


Side reaction: dissociation of ammonium hypoiodite prior to spirocyclization

Prevention of this pathway by installing:

- Electron-withdrawing substitutents on C5 of the indole (R^1 group)
- Pyrazole as electron-deficient auxiliary at the C2 position (R^2 group)

Scope



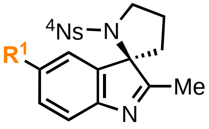
10 mol% cat

ROOH (2 eq.)

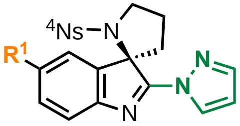
Na_2SO_4 (250 wt%)

MTBE/Toluene, 25°C

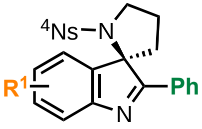
C4-C7 substitution



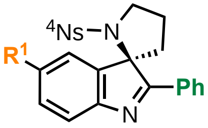
R^1 = Br: 87%, 81% ee (99% ee)^b
Cl: 85%, 78% ee (95% ee)^b
F: 85%, 73% ee (99% ee)^b
H: 84%, 72% ee (93% ee)^b
Me: 86%, 63% ee (94% ee)^b
OMe: 80%, **59% ee** (88% ee)^b



R^5 = H: 99%, 82% ee
Br: 97%, 86% ee
OMe: 81%, 81% ee

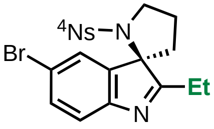


R^1 = 7-Br: 99%, 75% ee
5,7-F_2: 98%, 86% ee
6,7-Cl_2: 94%, 83% ee
4,6-Cl_2: 89%, 86% ee

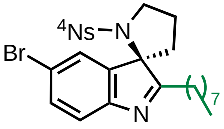


R^1 = Br: 96%, 94% ee
Cl: 90%, 92% ee
F: 98%, 93% ee
OCF_3: 81%, 92% ee
H: 82%, 85% ee

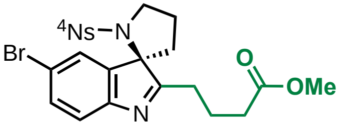
C2 substitution



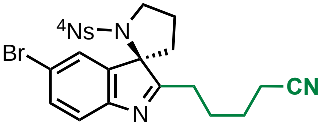
93%, 89% ee



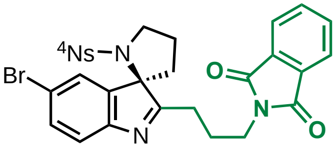
86%, 91% ee



93%, 88% ee

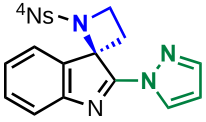


90%, 93% ee



78%, 98% ee

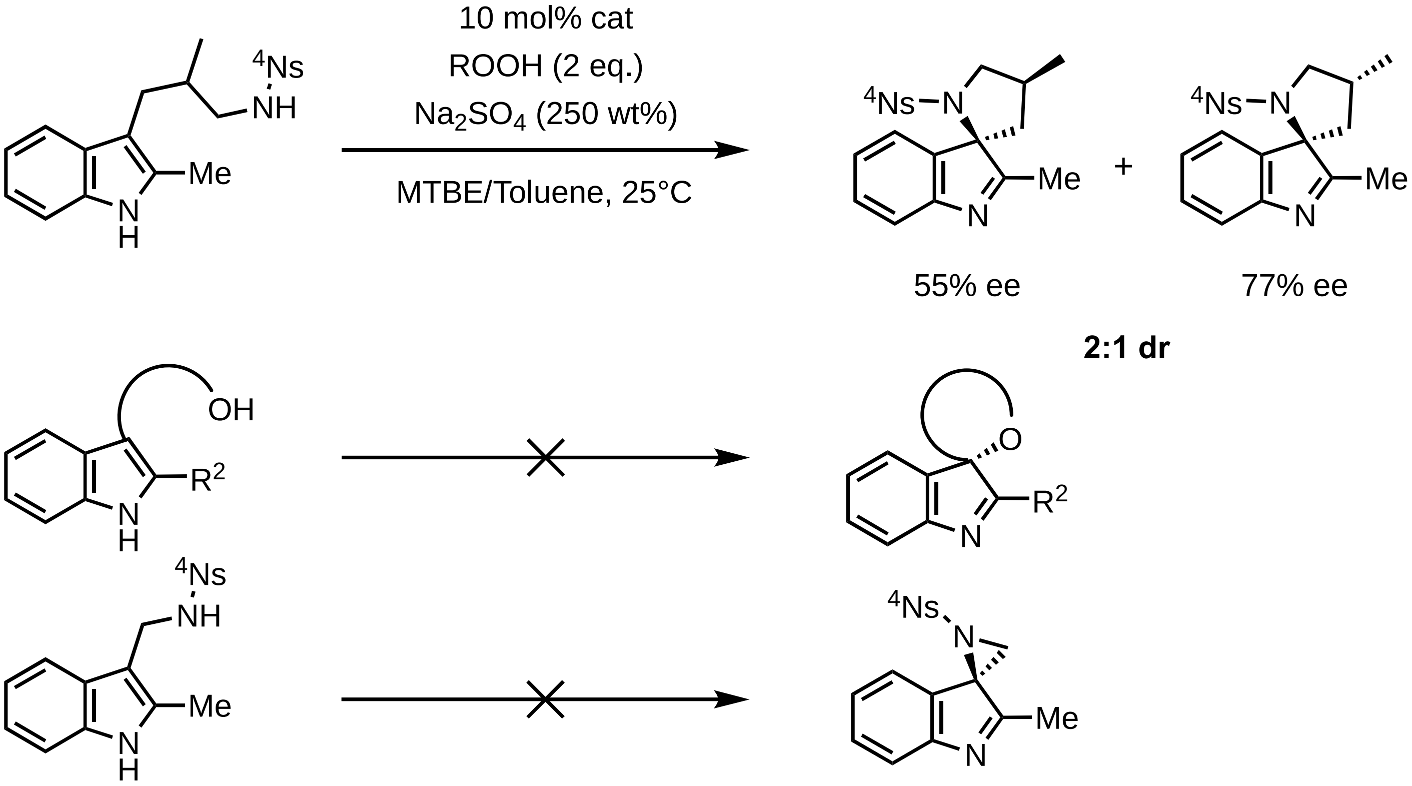
Ring size



63%, 82% ee

- Very high yields and good ees observed.
- **b**: after single recrystallization

Synthetic Limitations



- Poor **diastereoselectivity**
- Replacing **N by O** for spirocyclization
- Reducing the **ring size** of the spiro moiety

Tanaka, H.; Ukegawa, N.; Uyanik, M.; Ishihara, K. Supporting Information, 2022. ja2c01852_si_001.pdf.

Critical Analysis: Novelty

Strong points

- Enantioselective dearomatization reaction
- Design of new catalyst
- Synthetic utility, relatively easy transformations from the product

Weaker points

- No testing of substituents on spiro ring
- No investigation of stereoconvergence

Critical Analysis: Practicability

Strong points

- Mild conditions
- Good enantioselectivities and high yields
- Broad scope (various substitutions on indole, ring sizes for spiro moiety)

Weaker points

- Complex synthesis of catalyst (12 steps, 44%)
- High catalyst loading (10 mol%)
- Poor diastereoselectivity
- Racemic pathway in catalytic cycle

Critical Analysis: Sustainability

Strong points

- Metal-free catalyst
- Mild conditions (room temperature)
- Solvents are OK (toluene and MTBE classified as «yellow» solvents)
- Good atom economy (intramolecular reaction)

Weaker points

- Harsher conditions for synthesis of substrates (48 hours, 80°C)
- «Red» solvents (DCM) for substrate synthesis
- Many synthetic steps required to access catalyst (involving Suzuki cross-coupling)

Questions

Question 1

How is it possible for the reaction to be 0th order in the substrate?

Question 2

This reaction proceeds via Umpolung of the reactivity of Indole. What are the two possible structures of the intermediate with inverted reactivity? Which results are supporting this structure?

Question 3

Electron-donating substituents on the indole gave lower er. What could be an explanation? How was the issue solved?