Enantioselective Total Synthesis of (+)-Homochelidonine by a Pd$^{II}$-Catalyzed Asymmetric Ring-Opening Reaction of a meso-Azabicyclic Alkene with an Aryl Boronic Acid

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Angew. Chem. Int. Ed. 2007, 46, 433
Introduction

- Hexahydrobenzo[c]phenanthridine class of alkaloids
- 1 and 2 isolated from the roots of *Chelidonium majus*
- Cytotoxic, inhibits tubulin polymerization
- Major component of the drug Ukrain, a semisynthetic preparation from *C. majus* alkaloids
- Fully aromatic A and D rings, partially hydrogenated B and C rings, C11-hydroxy group and 3-contiguous syn-stereocenters
Total Synthesis of Chelidonine

- First total synthesis of \( dl \)-chelidonine using intramolecular [4+2] cycloaddition strategy

Total Synthesis of Homochelidonine

- 15 linear steps, 11 % overall yield

Homochelidonine: Retrosynthetic Analysis

• Ring-opening of azabicyclo-alkene with aryl boronic acid as the key step in synthesis

Pd-Catalyzed Alkylative Ring Opening

The product was obtained in good yield and as a single diastereomer

Proposed Mechanism

• Carbopalladation: rate-limiting step

Addition of Aryl Boronic Acids to Bicyclic Alkenes

Addition of heteroaryl boronic acids to oxa- and aza-bicyclic alkenes

Homochelidonine: Retrosynthetic Analysis

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Synthesis of the Intermediates

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Asymmetric Ring-Opening Reaction

Protecting Group Manipulations

- Acid-stable protecting group on the Nitrogen

**Scheme 6.** Synthesis of dihydronaphthalene 23: a) TMSI, NEt₃, CH₂Cl₂, reflux, 15 min; then CbzCl, RT, 3 h, 80%; b) [Pd(MeCN)₂Cl] (5 mol%), (S)-binap (5.5 mol%), 17, Cs₂CO₃, MeOH, RT, 6 h, 89%, 90% ee (80%, 99% ee after one recrystallization). Cbz = benzylxycarbonyl, TMS = trimethylsilyl.

Completion of the Synthesis

Scheme 7. Completion of the synthesis of (+)-1: a) HCl, iPrOH/THF, RT, 8 h, 75%; b) CBr₄, PPh₃, CH₂Cl₂, 0°C, 1 h; then NaH, DMF, 0°C, 3 h, 90%; c) NBS, THF/H₂O, RT, 90 min, 75%; d) KOTBu, THF, −78°C, 30 min, quant.; e) LiAlH₄, 1,4-dioxane, reflux, 12 h, 87%.

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Conclusion

• Enantioselective total synthesis of (+)-Homochelidonine was achieved in 14 steps with 15 % overall yield from 4,5-dibromoveratrole.

• A new and general strategy for the synthesis of hexahydrobenzo[c]phenanthridine alkaloids using highly enantioselective Pd(II)-catalyzed ring-opening reaction of a meso-azabicycle with aryl boronic acid has been established.

• Application of this methodology to the synthesis of other alkaloids is under investigation.
Phosphine Ligands
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\text{ROH} + \text{LiBr} + \text{CH}_2(\text{OCH}_3)_2 \xrightarrow{p-\text{TsOH (cat.)}} \begin{array}\text{ROCH}_2\text{OCH}_3 + \text{LiBr} + \text{CH}_3\text{OH}\end{array}
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