Enantioselective Synthesis of Chiral Piperidines via the Stepwise Dearomatization/Borylation of Pyridines

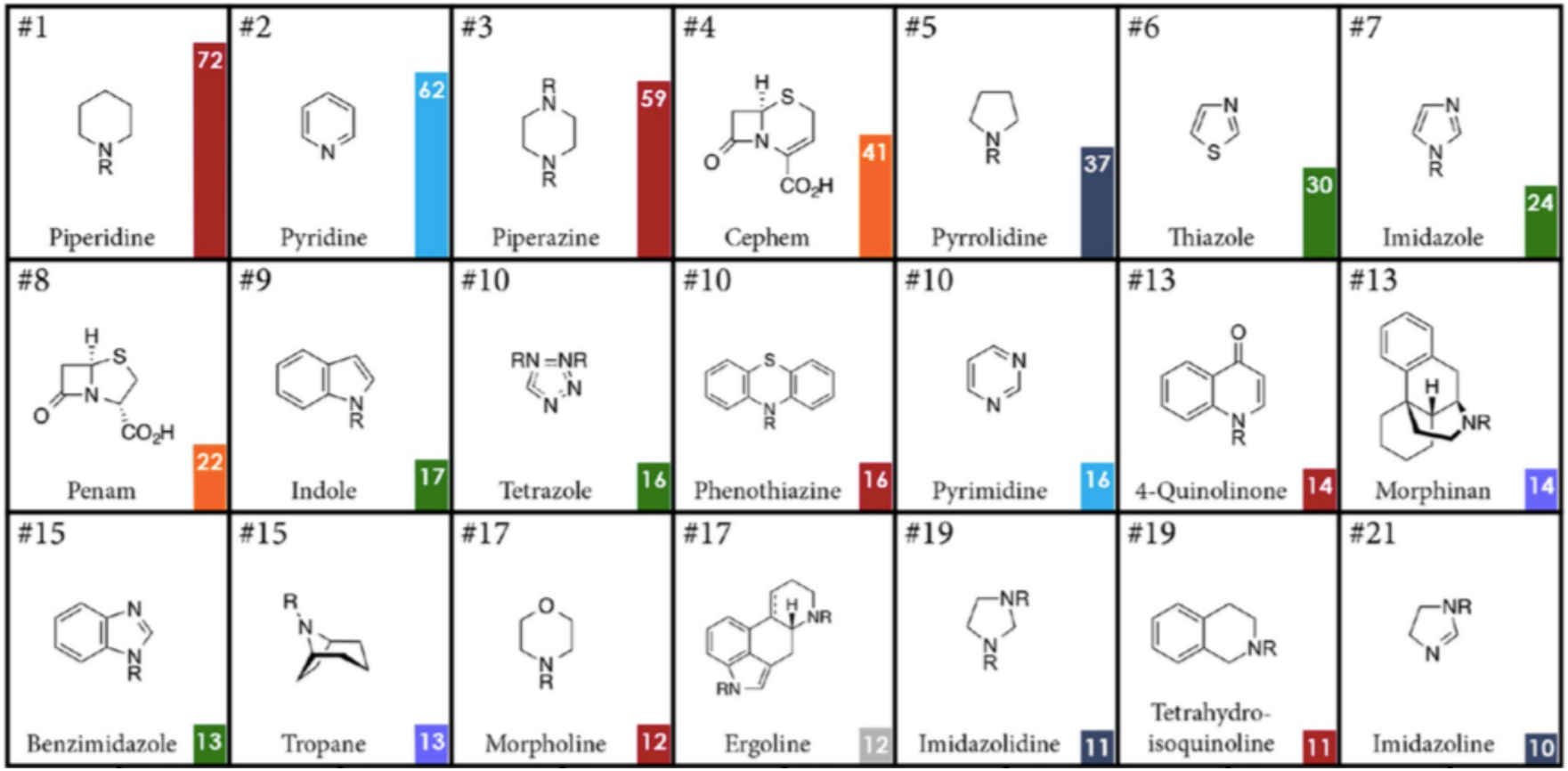
Koji Kubota, Yuta Wantanabe, Keiichi Hayama, and Hajame Ito

JACS ASAP 10.1021/jacs.6b01375

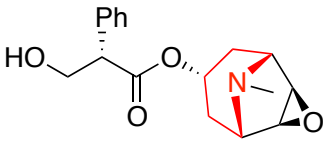
Wipf Group | Current Literature 4-9-16

James Johnson

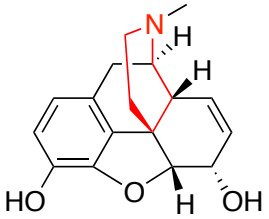
Piperidines a Privileged Heterocycle



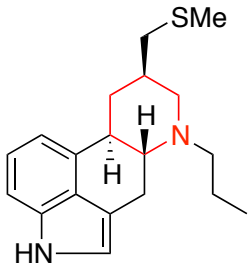
From a selection of 640 FDA approved drugs.
J. Med. Chem. **2014**, 57, 10257−10274



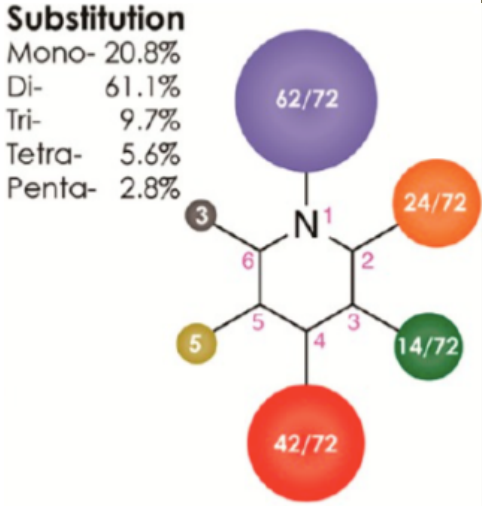
scopolamine

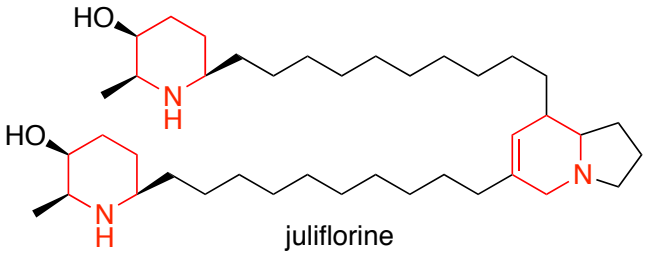


morphine

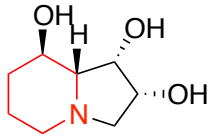


pergoline

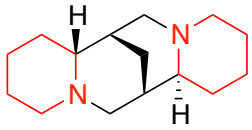




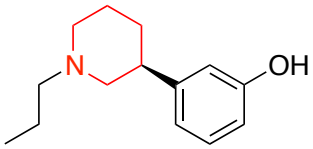
juliflorine



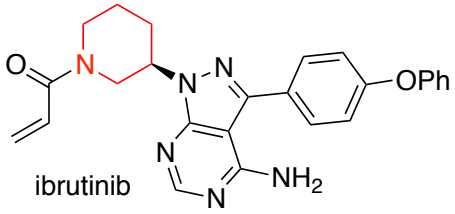
swainsonine



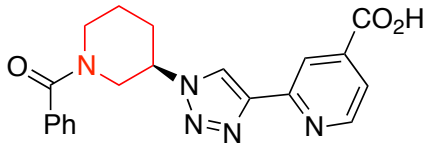
(-)-sparteine



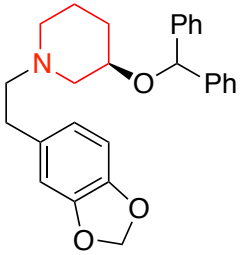
(-)-preclamol



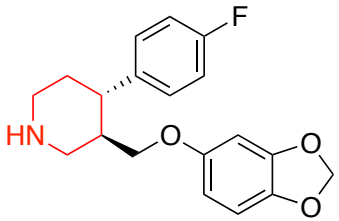
ibrutinib



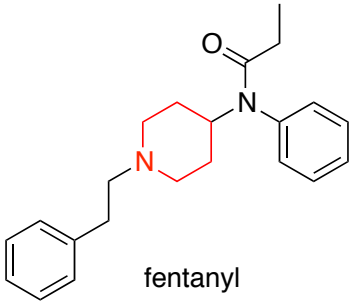
KDM2A inhibitor



zamifenacine



(-)-paroxetine



fentanyl

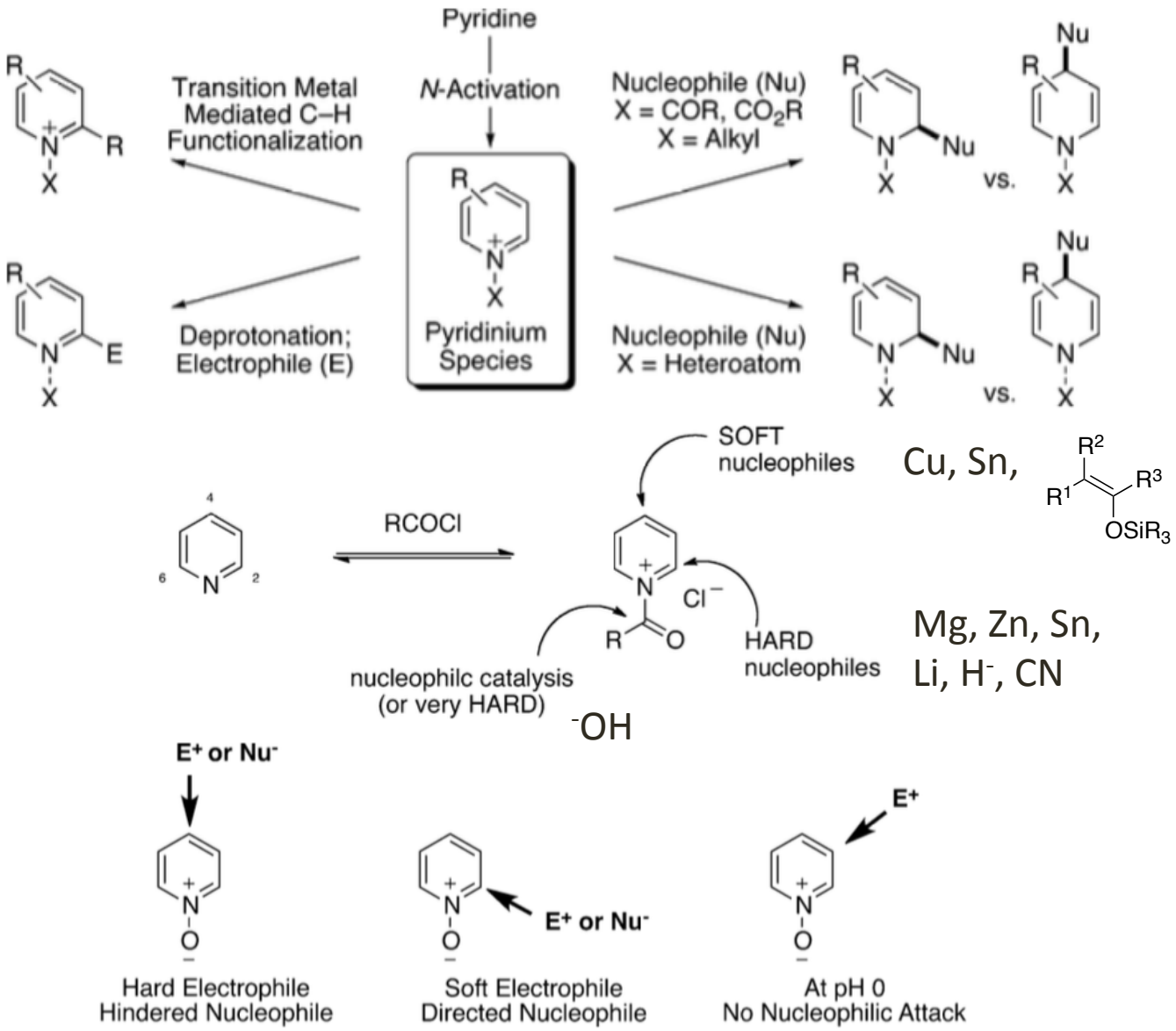
J. Med. Chem. **2014**, 57, 10257−10274
Nat. Prod. Rep. **2008**, 25, 139–165

Common Synthesis of Piperidines

- Nucleophilic substitution
  - Reaction of amines with halides, activated alcohols, three membered rings
- Reductive amination
  - Intra/intermolecular reductive amination
- Reaction of amides with alkenes and alkynes
  - Intramolecular Michael addition, radical 1,4 reaction of amines with alkenes, hydroamination, reaction of amines with alkynes
- Reaction of dienes, enynes and diynes
  - Ring-closing metathesis Intramolecular ene reactions, ene reactions (type I), ene reactions (type III)
  - Formal ene reactions (ene halogenocyclization, π-allyl complexes, palladium cross-coupling, iminium cations)
- Radical cyclizations
  - Radical cyclization of N-chloro amino alkenes, radical cyclization using samarium or tin
- Dieckmann condensation
- Cycloadditions
  - Imino Diels-Alder, Aza-diene Diels-Alder
- Dearomatization of pyridines

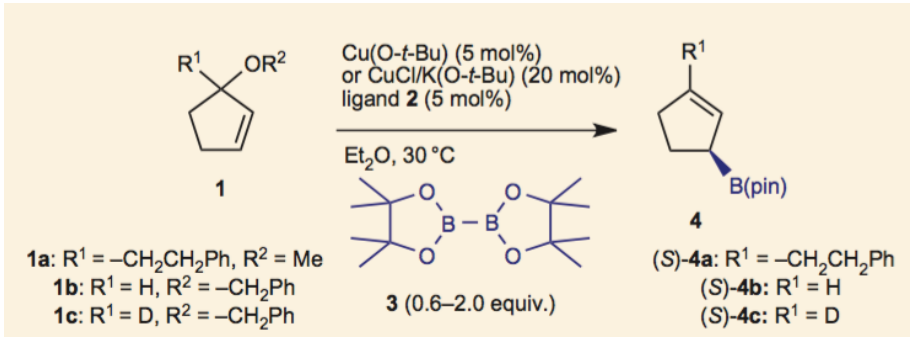
Tetrahedron **2004**, 60, 1701–1729,
Nat. Prod. Rep. **2008**, 25, 139–165
Synthesis **2000**, 13, 1781–1813

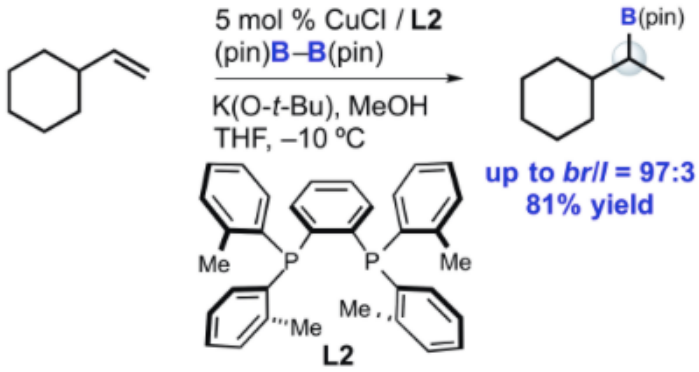
Dearomatization of Pyridines

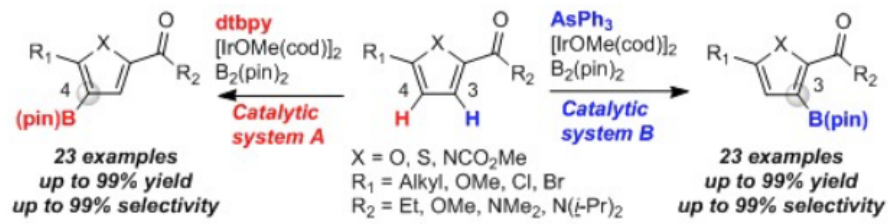


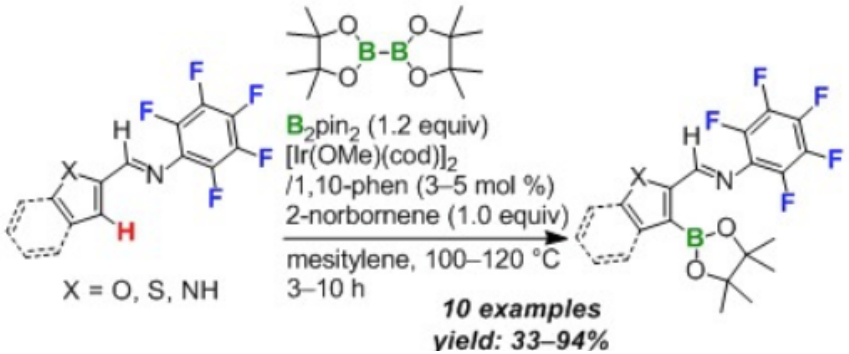
Chem. Rev. **2012**, 112, 2642–2713

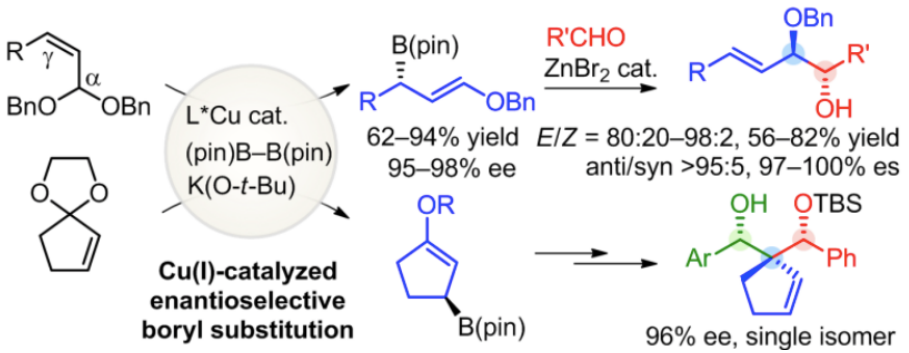
Ito Group Previous work

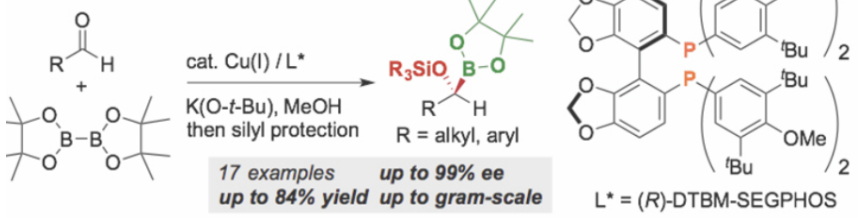






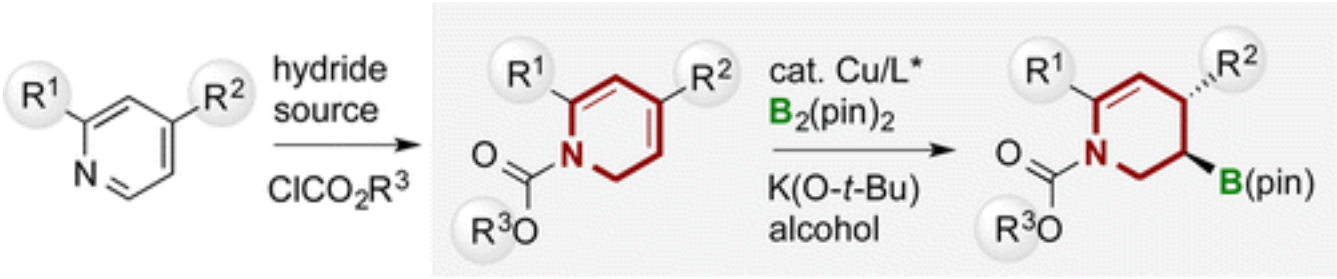






Chem. Commun. 2016 ASAP. Chem. Eur. J. **2015**, *21*, 25, 9236 – 9241, *Angew. Chem. Int. Ed.* **2015**, *54*, 8809 – 8813.
J. Am. Chem. Soc. **2015**, *137*, 1, 420 – 424., *J. Am. Chem. Soc.* **2014**, *136*, 47, 16515 – 16521
Nature Chemistry **2010**, *2*, 972 - 976

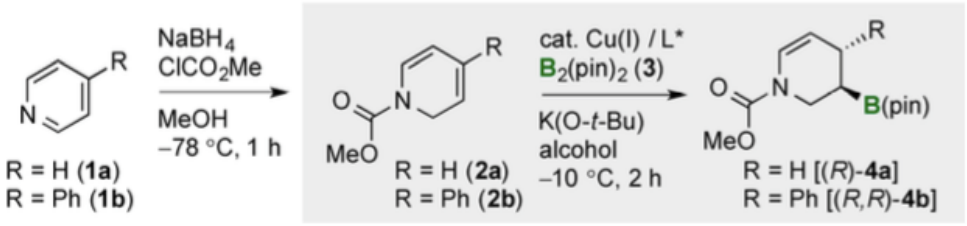
Title Paper



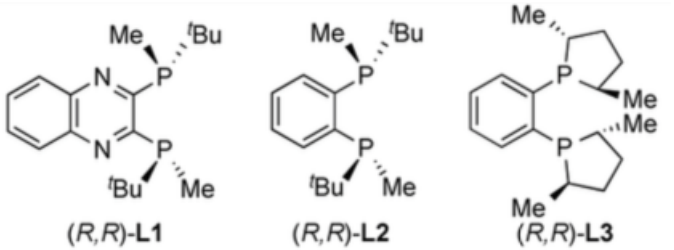
- ***Unprecedented regio-, diastereo- and enantioselective***
- ***Readily available starting materials***
- ***Chiral boryl-tetrahydropyridines: Novel building blocks***

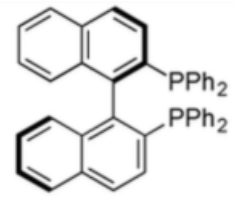
DOI: 10.1021/jacs.6b01375

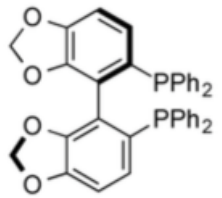
Reaction Optimization

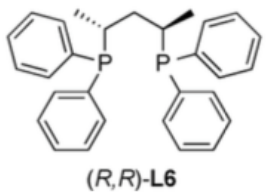


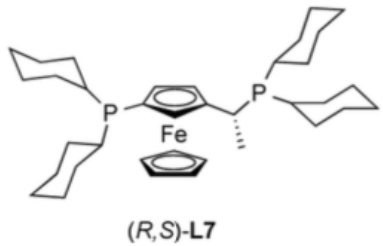
entry	R	chiral ligand	alcohol	d.r.	yield (%)[b]	ee (%)[c]
1	H (**2a**)	(*R,R*)-**L1**	MeOH	–	93	99
2	H (**2a**)	(*R,R*)-**L2**	MeOH	–	92	98
3	H (**2a**)	(*R,R*)-**L3**	MeOH	–	82	93
4	H (**2a**)	(*R*)-**L4**	MeOH	–	<5	–
5	H (**2a**)	(*R*)-**L5**	MeOH	–	<5	–
6	H (**2a**)	(*R,R*)-**L6**	MeOH	–	97	55
7	H (**2a**)	(*R,S*)-**L7**	MeOH	–	20	73
8	H (**2a**)	(*R,R*)-**L1**	*t*-BuOH	–	92	79
9	H (**2a**)	(*R,R*)-**L1**	PhOH	–	40	55
10[d]	H (**2a**)	(*R,R*)-**L1**	MeOH	–	92	93
11[e]	H (**2a**)	(*R,R*)-**L1**	MeOH	–	96	99
12[f,g]	H (**2a**)	(*R,R*)-**L1**	MeOH	–	91	99
13[h]	Ph (**2b**)	(*R,R*)-**L1**	MeOH	99:1	83	25
14[h]	Ph (**2b**)	(*R*)-**L5**	*t*-BuOH	97:3	94	92







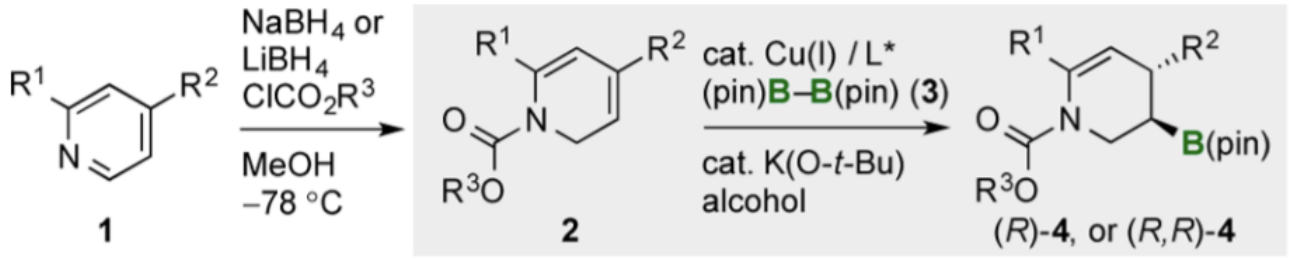


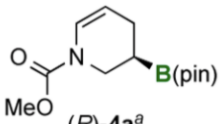


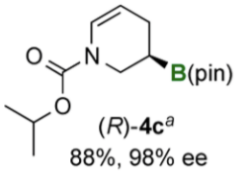
Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), 2 (0.5 mmol), bis(pinacolato)diboron 3 (0.6 mmol), alcohol (1.0 mmol), and K(O-t-Bu) (0.1 mmol) in THF. **B** NMR yield. **C** The ee values of (R)-4a were determined by HPLC analysis of the corresponding benzoate ester. **D** The reaction was carried out at 30 °C. **E** The reaction was carried out on a 5 mmol scale. **F** 1 mol% CuCl and ligand were used. **G** The reaction time was 16 h. **H** The reaction was carried out at 0 °C and the reaction time was 1 h.

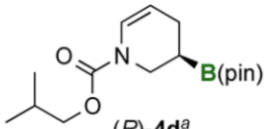
DOI: 10.1021/jacs.6b01375

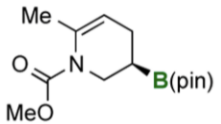
Substrate Scope

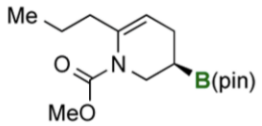


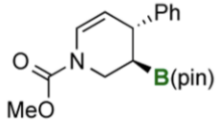

(*R*)-**4a**[a]
90%, 99% ee

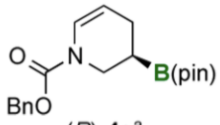

(*R*)-**4c**[a]
88%, 98% ee

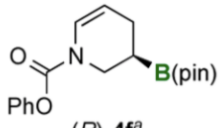

(*R*)-**4d**[a]
90%, 97% ee

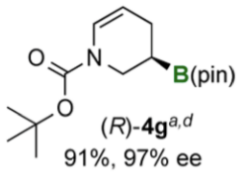

(*R*)-**4h**[a]
86%, 92% ee

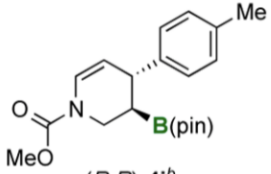

(*R*)-**4i**[a]
67%, 96% ee

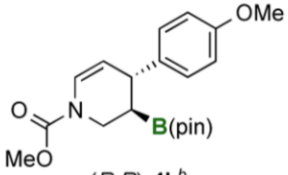

(*R,R*)-**4b**[b]
90%, d.r. 97:3
92% ee

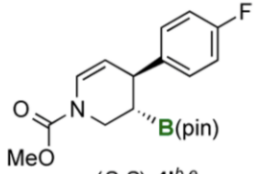

(*R*)-**4e**[a]
76%, 97% ee

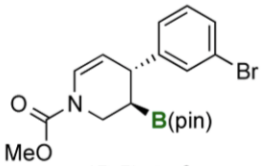

(*R*)-**4f**[a]
84%, 93% ee

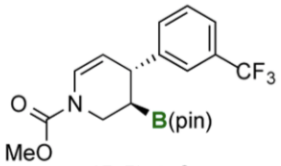

(*R*)-**4g**[a,d]
91%, 97% ee

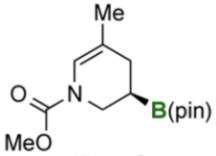

(*R,R*)-**4j**[b]
91%, d.r. 98:2
95% ee


(*R,R*)-**4k**[b]
82%, d.r. 96:4
96% ee


(*S,S*)-**4l**[b,e]
91%, d.r. 97:3
96% ee


(*R,R*)-**4m**[c]
93%, d.r. 90:10
74% ee

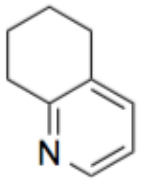

(*R,R*)-**4n**[c]
79%, d.r. 87:13
66% ee


(*R*)-**4o**[a]
no reaction

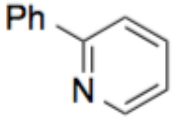
DOI: 10.1021/jacs.6b01375

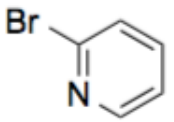
Substrate Scope: Limitations

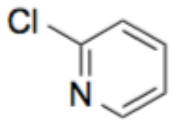
- $NaBH_4$ reduction did not proceed.



steric hinderance around the nitrogen

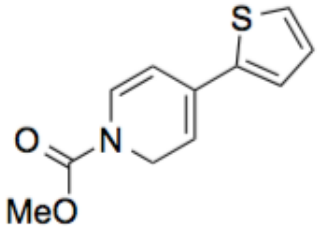




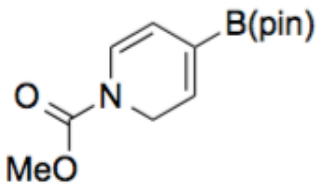


Heteroatom substituent at 2-position

- 1,2-Dihydropyridines are significantly unstable.

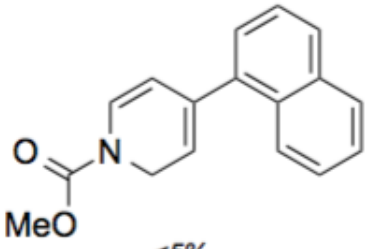


Heteroaromatic substituent



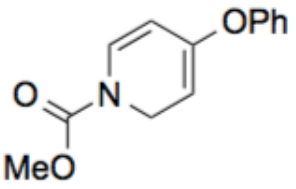
B(pin) group

- Borylation did not proceed.



<5%

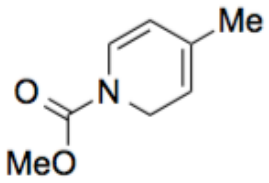
Bulky aryl group at 4-position



complex mixture

Heteroatom substituent at 4-position

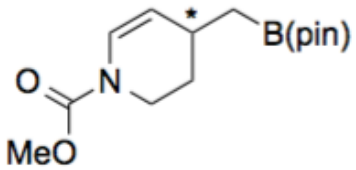
- Other borylation product was formed.



Alkyl substituent at 4-position

CuCl (5 mol %)
(*R*,*R*)-QuinoxP* (5 mol %)
$B_2(pin)_2$ (1.2 equiv)

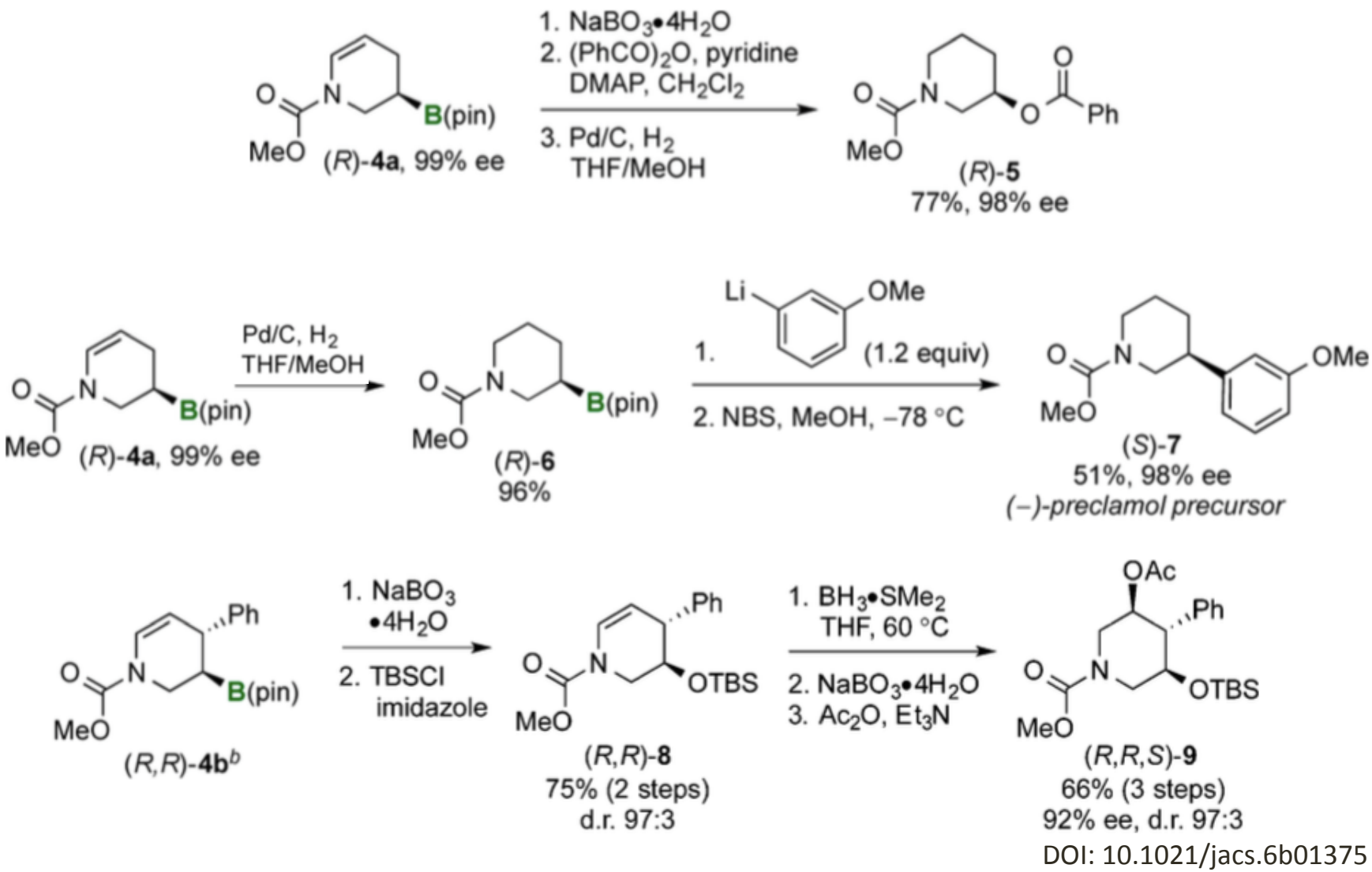
K(O-*t*-Bu) (20 mol %)
t-BuOH (2 equiv)
THF, 0 °C, 12 h



44% yield
71% ee

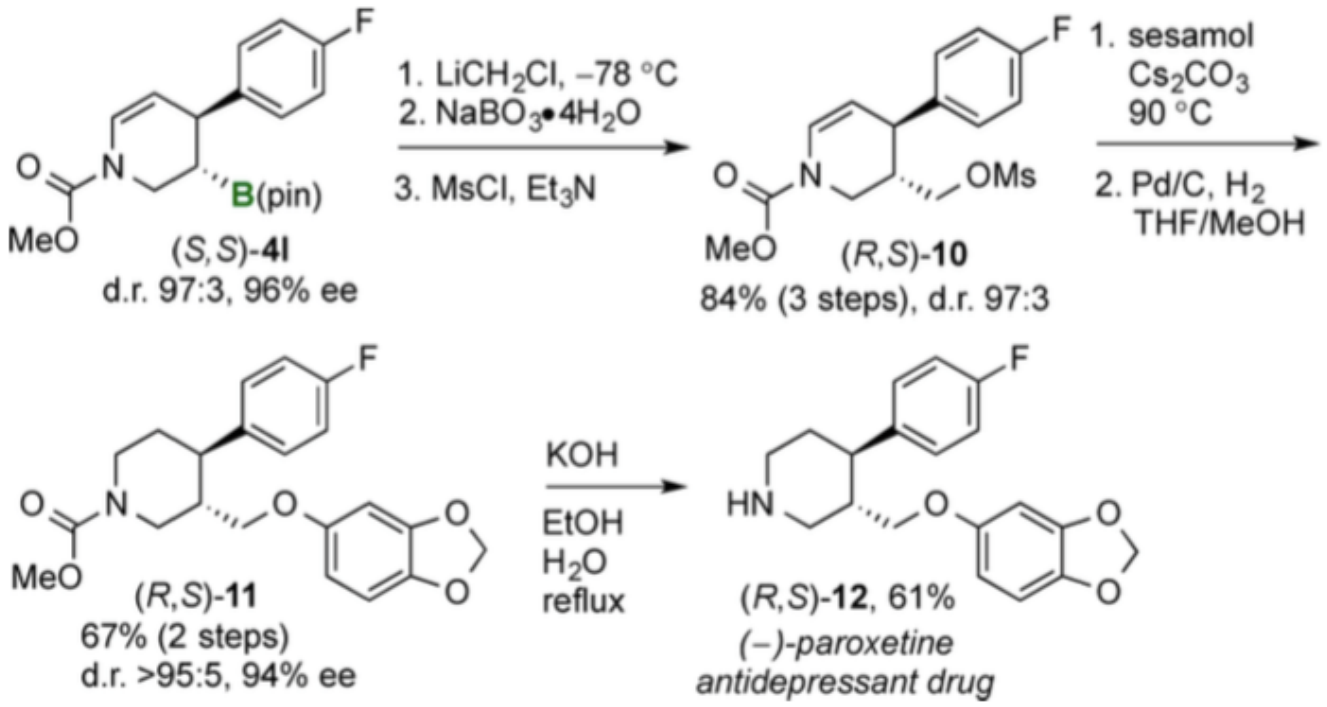
DOI: 10.1021/jacs.6b01375

Derivatization of Tetrahydropyridines



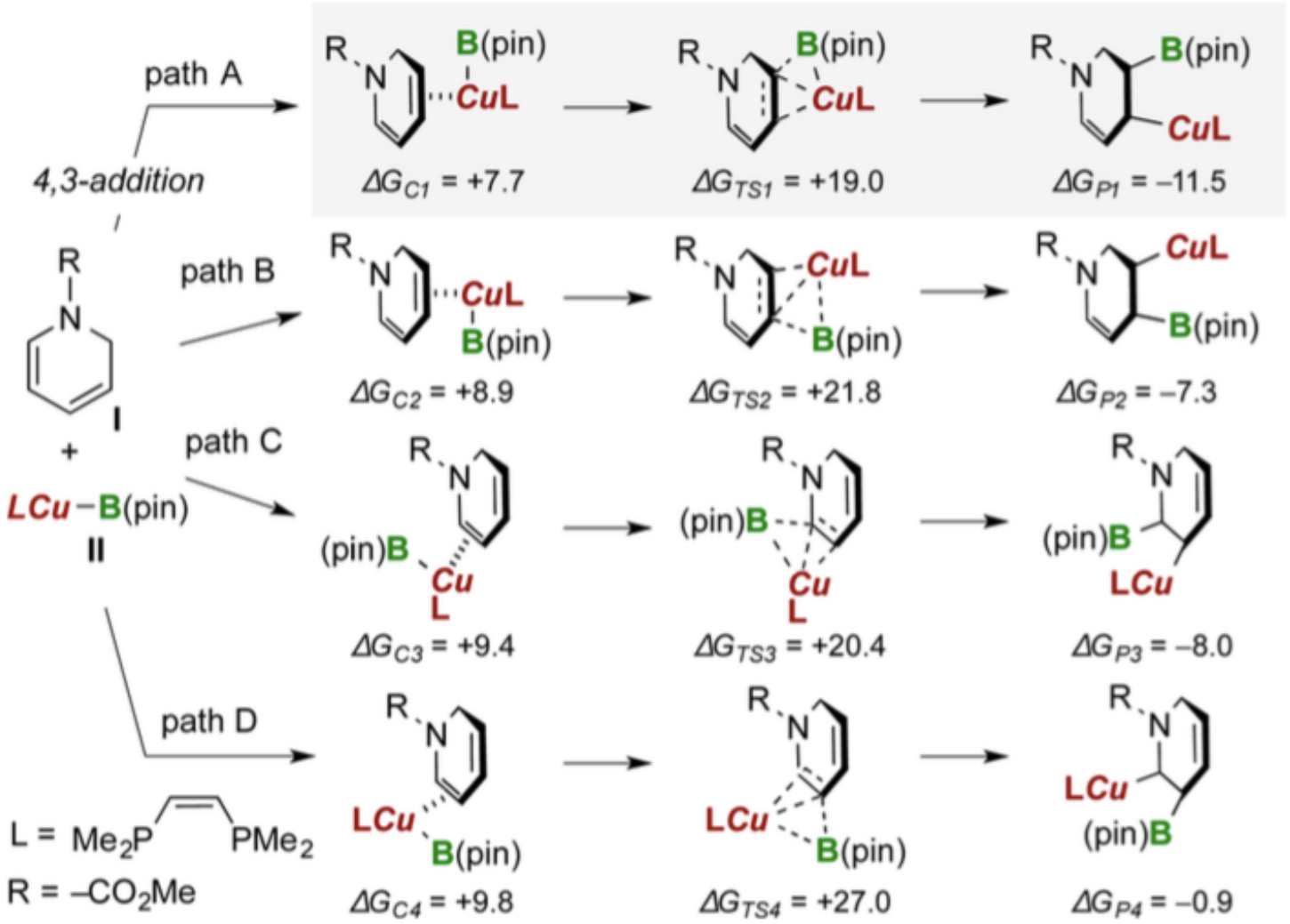
DOI: 10.1021/jacs.6b01375

Synthesis of (-)-Paroxetine



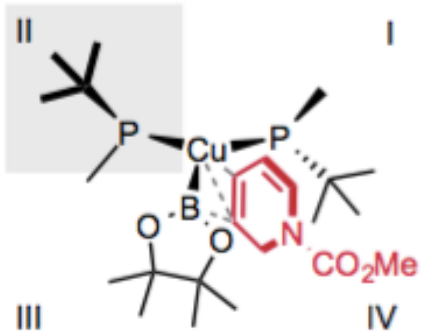
DOI: 10.1021/jacs.6b01375

DFT Calculations for Borylation Pathway

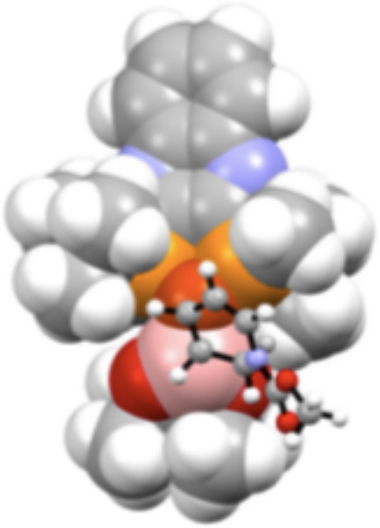


(B3PW91/cc-pVDZ). Relative G values (kcal/mol) at 298 K, 1.0 atom in the gas phase.

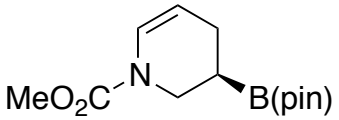
DOI: 10.1021/jacs.6b01375



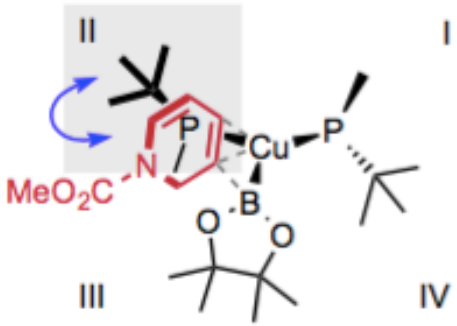
Si-face TS



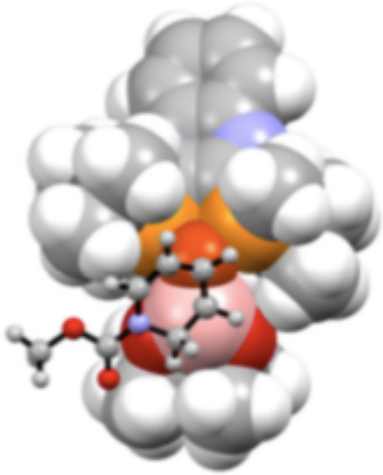
0 kcal/mol



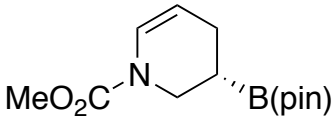
(R)-enantiomer



Re-face TS



+1.81 kcal/mol



(S)-enantiomer

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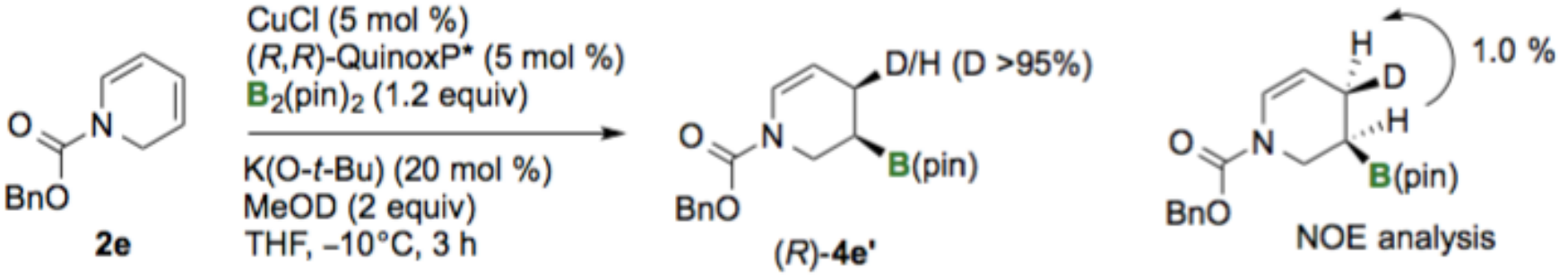
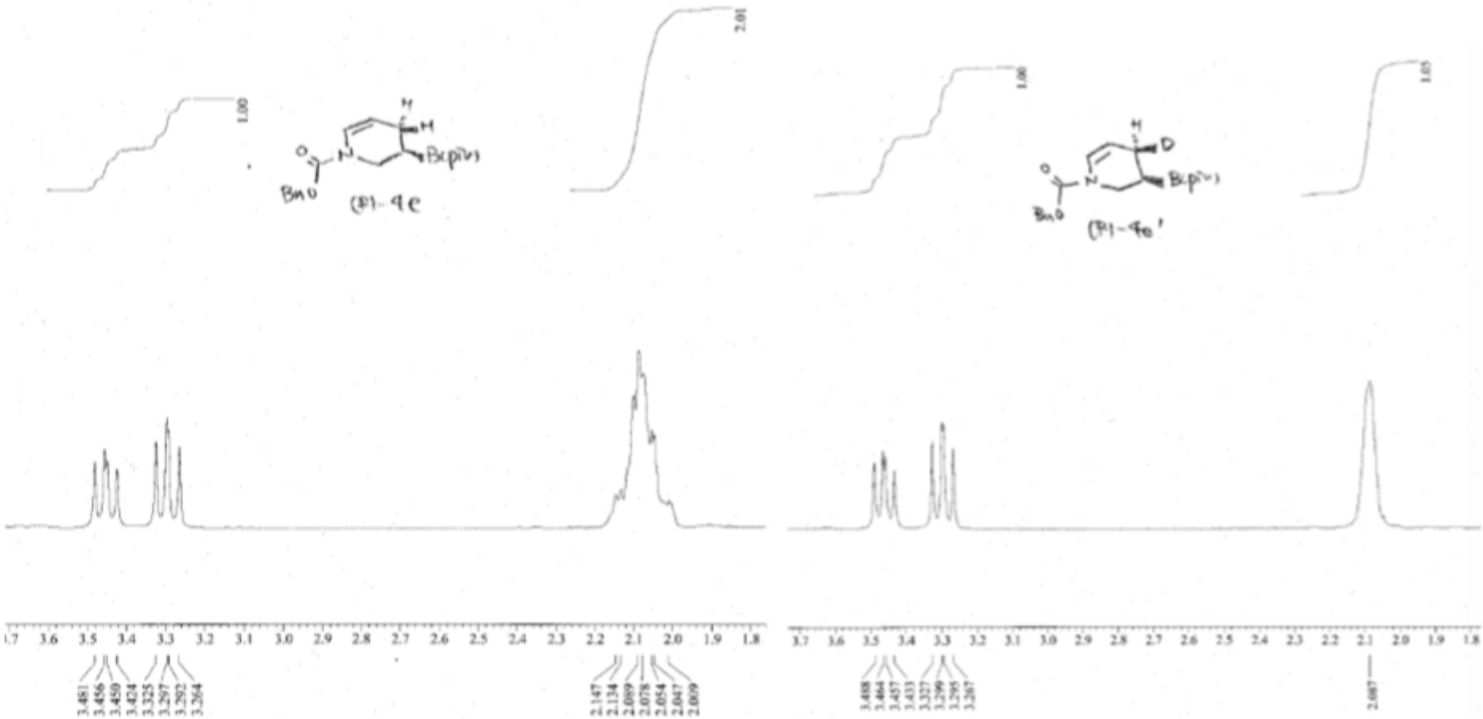
Deuterium Labeling





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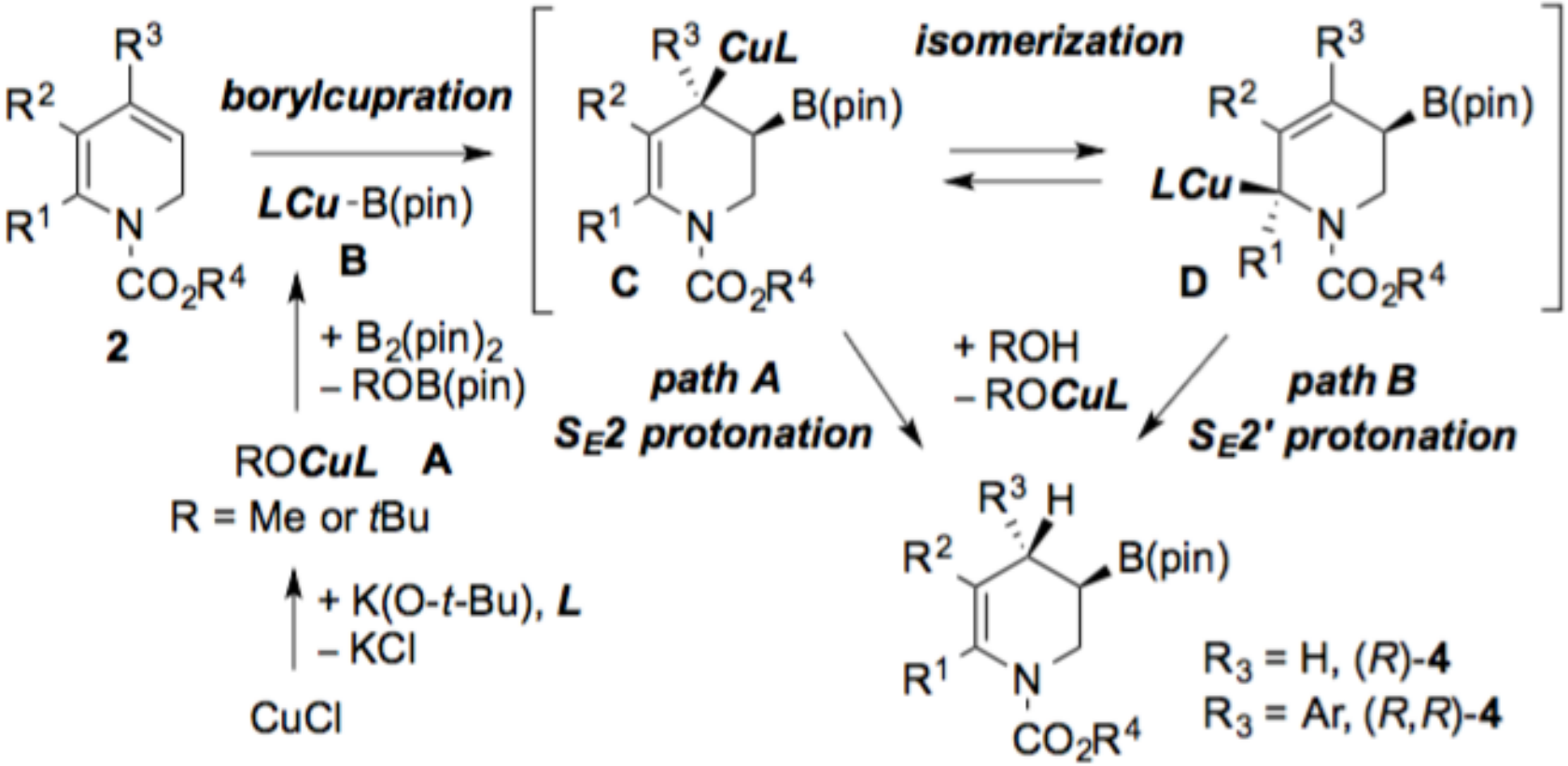
Proposed Mechanism



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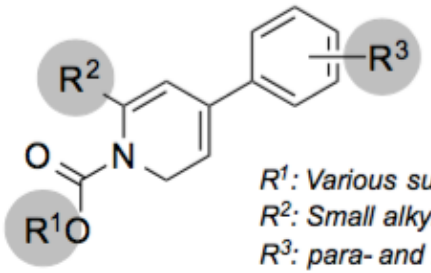
Conclusions

Applicable substrates



R^1: Various substituents
R^2: Small alkyl substituents
R^3: para- and meta-Substituted phenyl group

- Developed a novel dearomatization/enantioselective borylation of dihydropyridines.
- Interesting stereoretentive protonation of the allylcopper(I) intermediate
- Substrate limitations
- Expedited synthesis of chiral 3 substituted piperidines
- Potential Med Chem applications

Thanks

Aggarwal's Cross Coupling