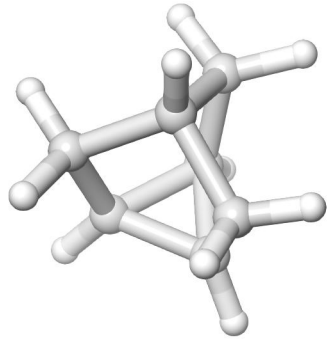
Catalytic Asymmetric Synthesis of Meta Benzene Isosteres—Nortricyclane

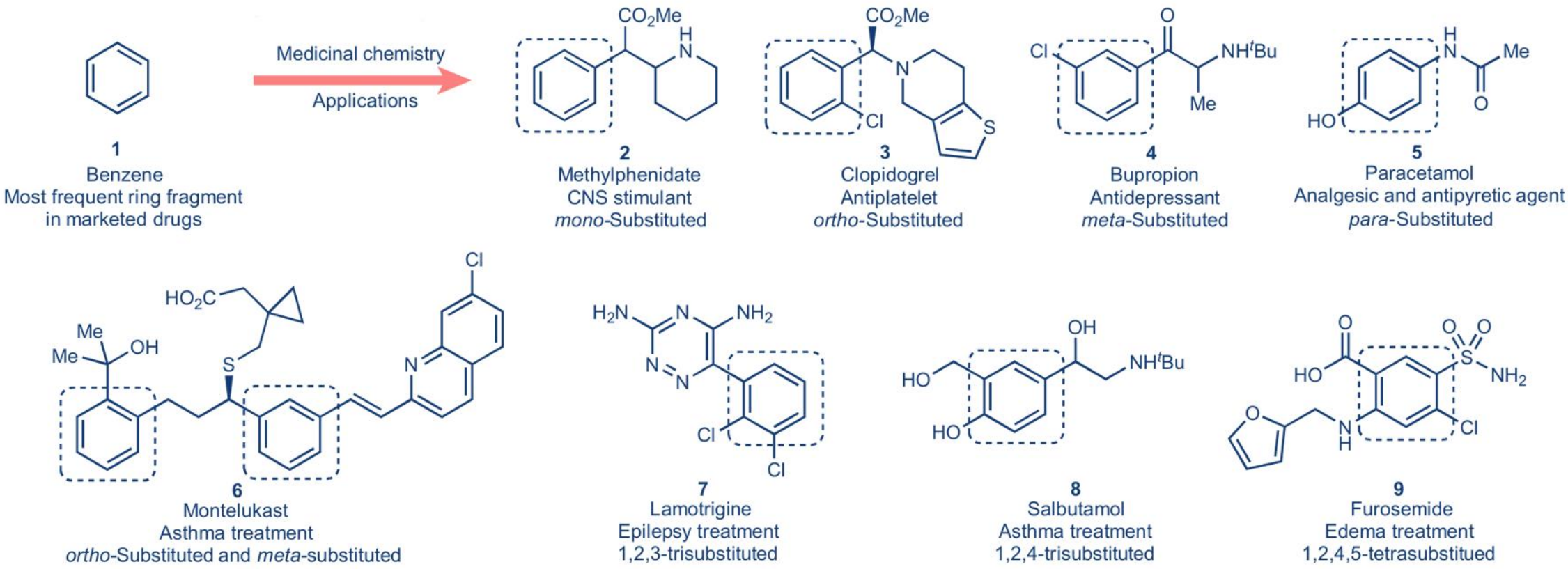
Reporter: Zefang Jin

2025/01/18



Nature. **2024**, 633: 90-95.

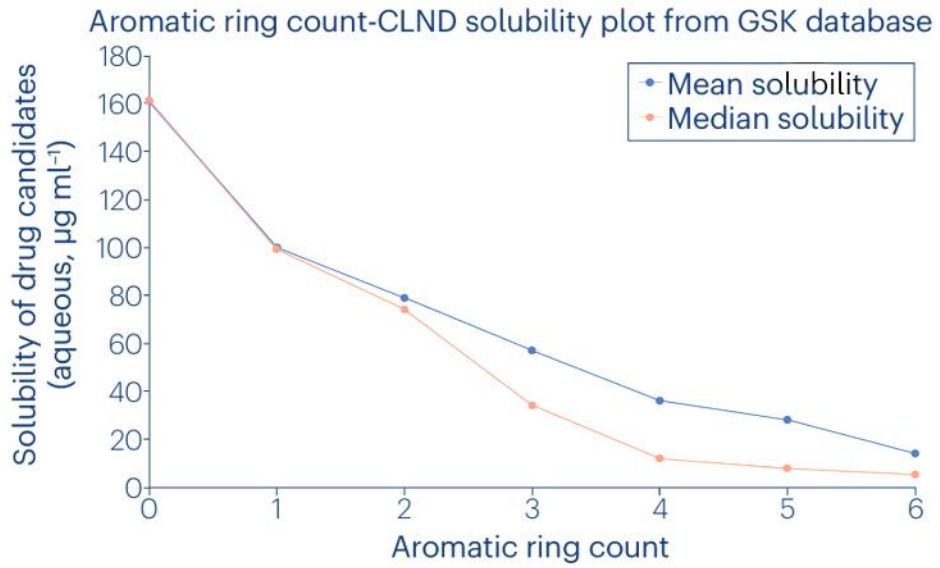
Benzene Ring in Medicinal Chemistry



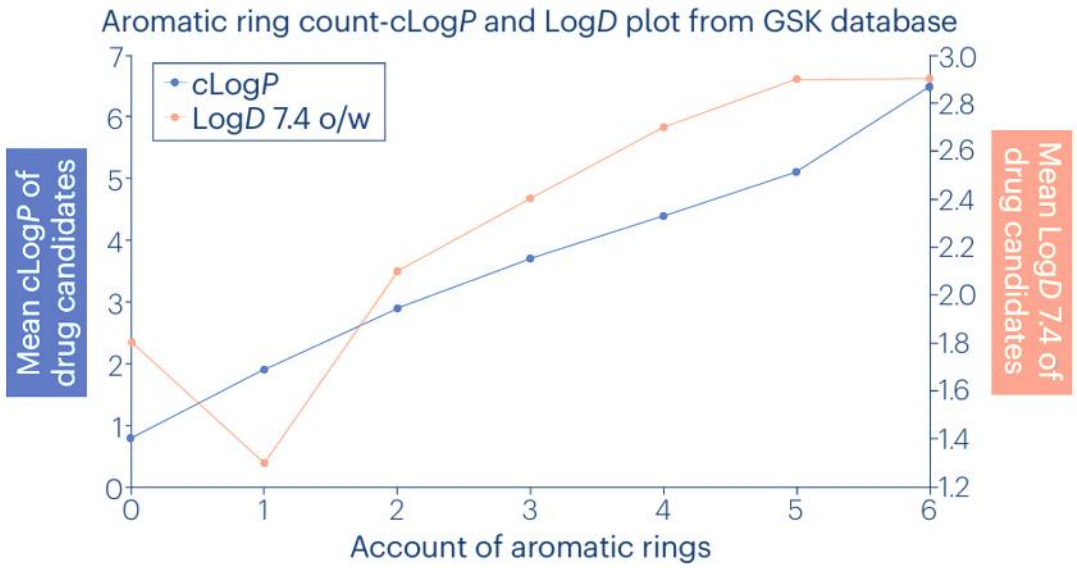
Nat. Rev. Chem. **2024**, 8: 605-627.

Benzene Ring in Medicinal Chemistry

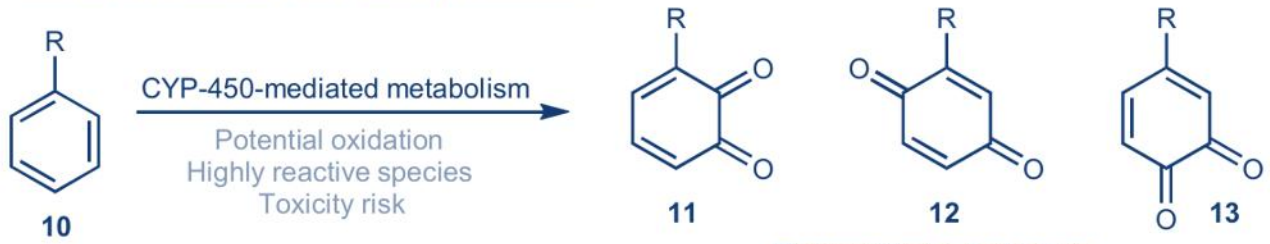
Solubility concern:

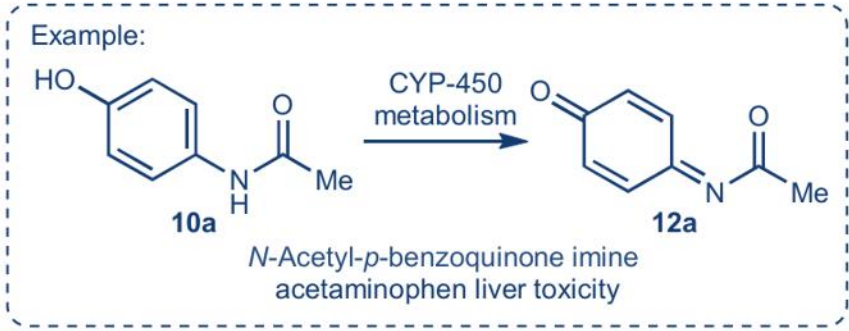


Lipophicility concern:



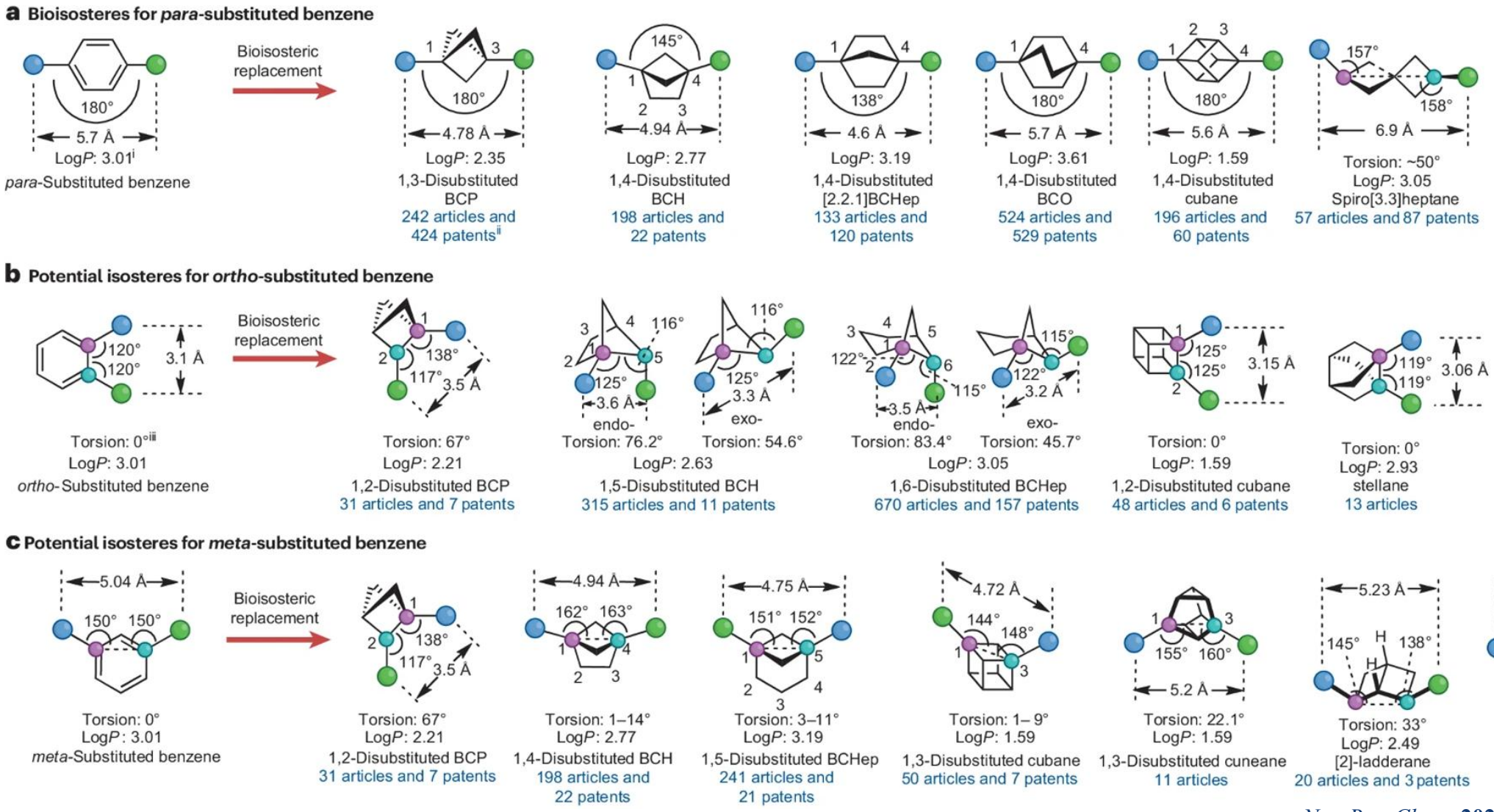
Metabolic stability and safety concern:





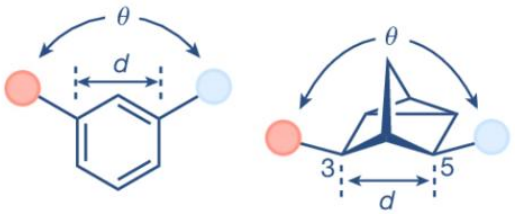
Nat. Rev. Chem. **2024**, 8: 605-627.

Benzene Ring in Medicinal Chemistry

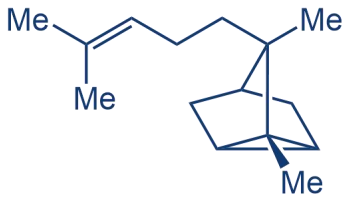


Nat. Rev. Chem. **2024**, 8: 605-627.

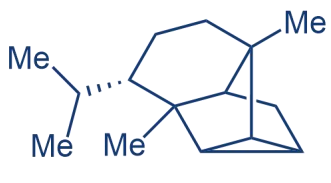
Tricyclo[2.2.1.0^{2,6}]Heptane (Nortricyclane)



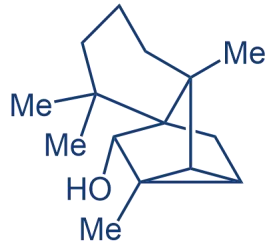
	Meta arene	Nortricyclane
Atom distance (*d*)	2.4 Å	2.4 Å
Exit vector angle (*θ*)	120°	127°
Dihedral angle	0°	2°



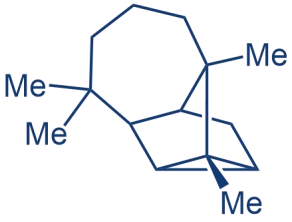
13, (+)-α-santlene



14, cyclosinularane

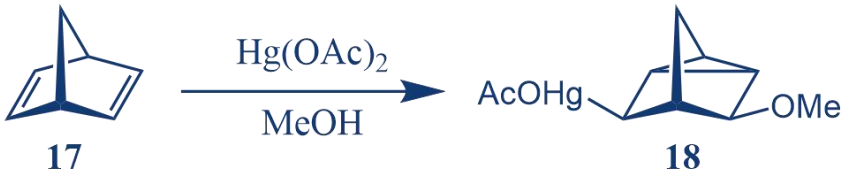


15, cyclomyltaylan-5α-ol



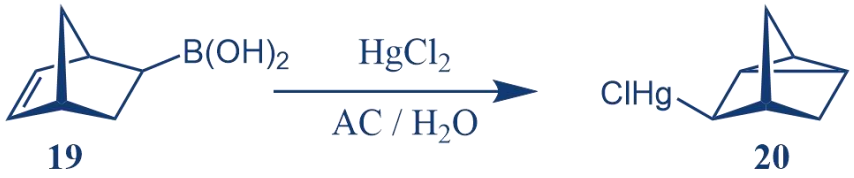
16, longicyclene

Org. Biomol. Chem. **2019**, 17(18): 4456-4459.



17 **18**

Chem. Ind. **1956**: 56–57.



19 **20**

*J. Am. Chem. Soc.***1963**, 85: 1019–1020.

James P. Morken

- Professor of Chemistry
- Louise and Jim Vanderslice and Family Chair

Experience

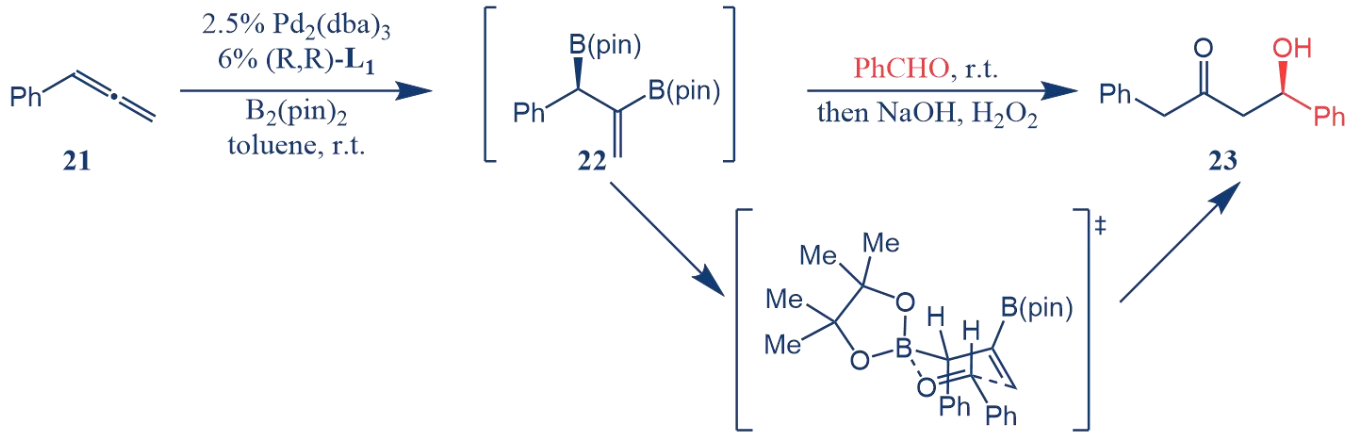
- 1985—1989, B.S., University of California at Santa Barbara (Advisor: Bruce Rickborn)
- 1990—1995, Ph.D., Boston College, (Advisor: Amir H. Hoveyda)
- 1995—1997, Postdoc, Harvard University, (Advisor: Stuart L. Schreiber)
- 1997—2002, University of North Carolina at Chapel Hill, Assistant Professor
- 2002—2006, University of North Carolina at Chapel Hill, Associate Professor;
- 200687, Boston College, Professor of Chemistry;

Selected Honors and Awards

- Arthur C. Cope Scholar Award, 2018
- Sloan Foundation Fellow, 2004-2006
- David and Lucile Packard Foundation Fellow, 1998-2003
- Bristol-Myers Squibb Award, 2002

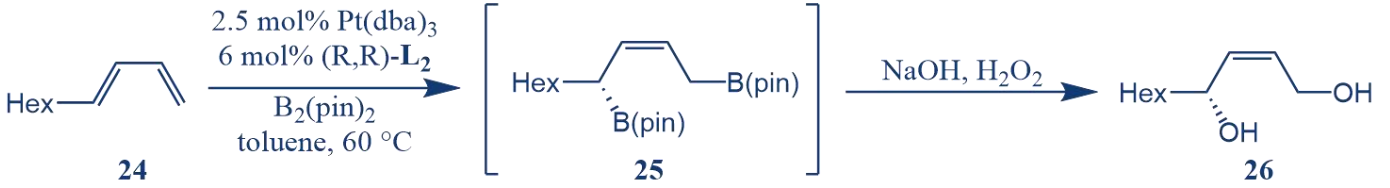
Diboration of Alkenes

1. Diboration of Allene



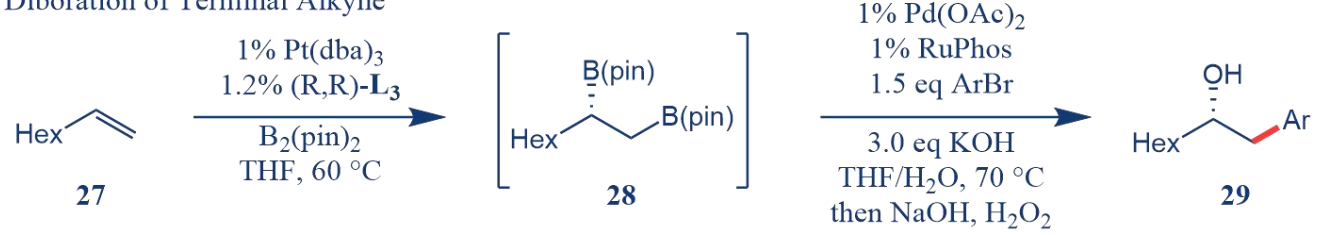
J. Am. Chem. Soc. **2004**, 126, 50: 16328-16329.

2. Diboration of Conjugated-Dienes



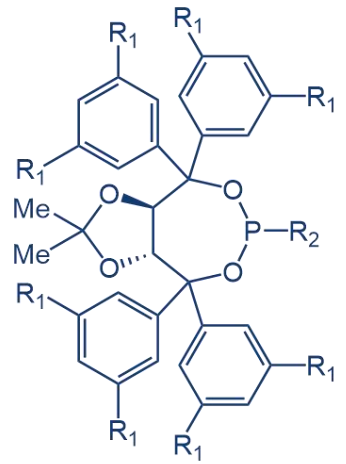
J. Am. Chem. Soc. **2009**, 131, 26: 9134-9135.

3. Diboration of Terminal Alkyne



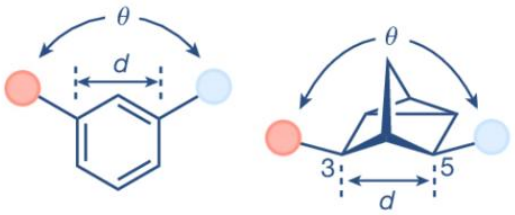
Nature, **2014**, 505: 386-390.

L =

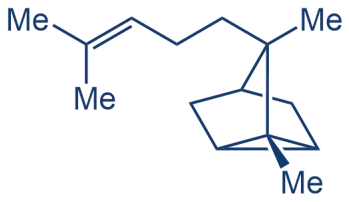


L_1: R_1 = H, R_2 = NMe_2
L_2: R_1 = Me, R_2 = Ph
L_3: R_1 = i-Pr, R_2 = Ph

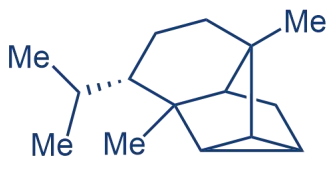
Tricyclo[2.2.1.0^{2,6}]Heptane (Nortricyclane)



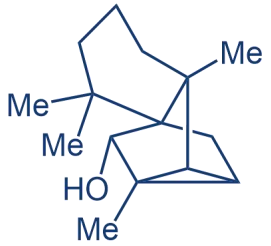
	Meta arene	Nortricyclane
Atom distance (*d*)	2.4 Å	2.4 Å
Exit vector angle (*θ*)	120°	127°
Dihedral angle	0°	2°



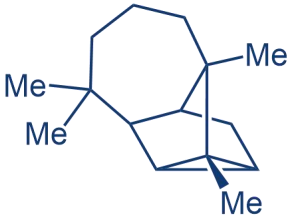
13, (+)-α-santlene



14, cyclosinularane

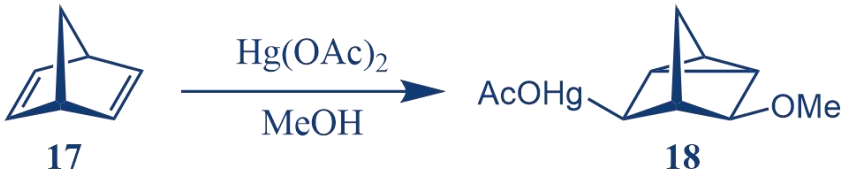


15, cyclomyltaylan-5α-ol



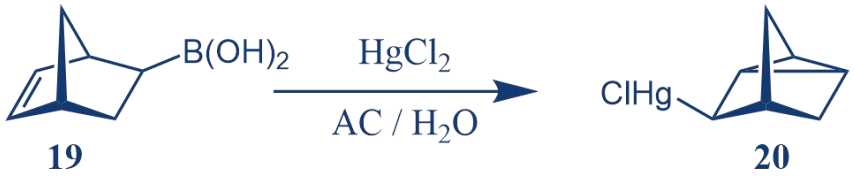
16, longicyclene

Org. Biomol. Chem. **2019**, 17(18): 4456-4459.



17 **18**

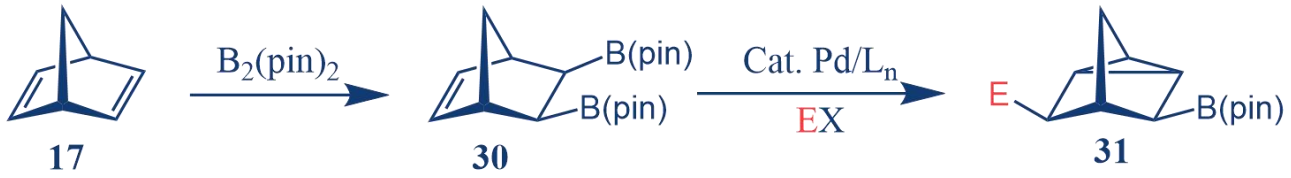
Chem. Ind. **1956**: 56–57.



19 **20**

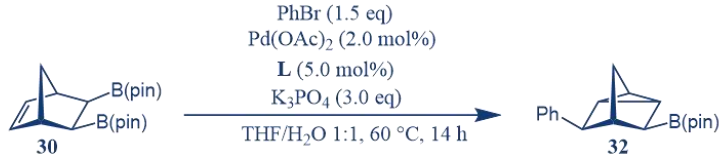
*J. Am. Chem. Soc.***1963**, 85: 1019–1020.

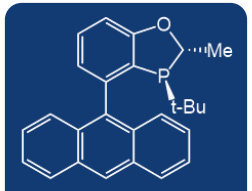
This work



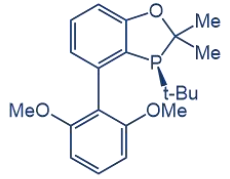
17 **30** **31**

Ligand Screening

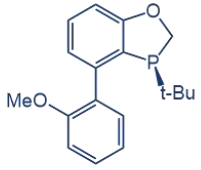




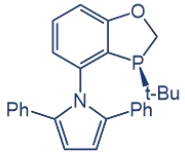
L1
89.6% NMR y.
94:6 er



L2
101.6% NMR y.
62:38 er

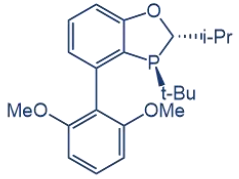


L3
102.8% NMR y.
41:59 er

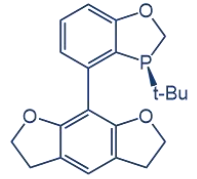


L4
90.2% NMR y.
14:86 er

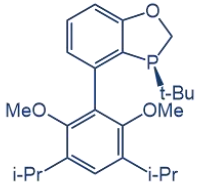
L5
96.3% NMR y.
36:64 er



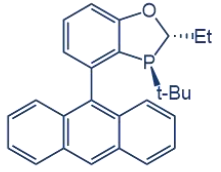
L6
98.6% NMR y.
65:35 er



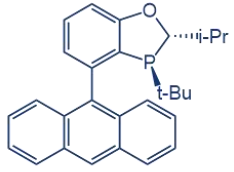
L7
93.4% NMR y.
15:85 er



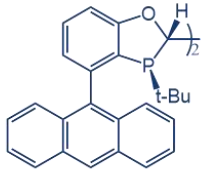
L8
97.5% NMR y.
32:68 er



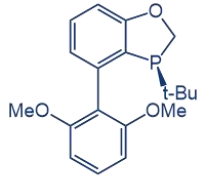
L9
88.9% NMR y.
93:7 er



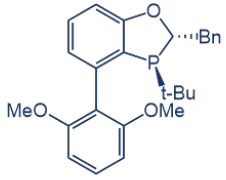
L10
73.2% NMR y.
87:13 er



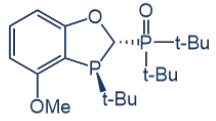
L11
53.8% NMR y.
51:49 er
17.9% SM



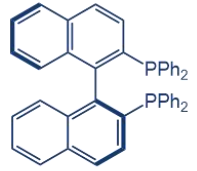
L12
92.0% NMR y.
27:73 er



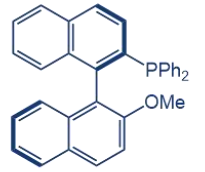
L13
94.7% NMR y.
49:51 er



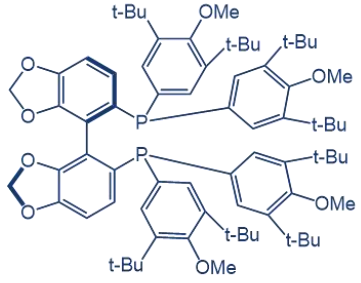
L14
93.4% NMR y.
49:51 er



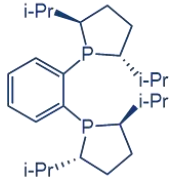
L15
82.0% NMR y.
30:70 er



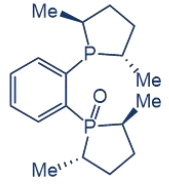
L16
94.8% NMR y.
50:50 er



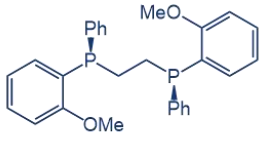
L17
47.2% NMR y.
68:32 er
14.1% SM



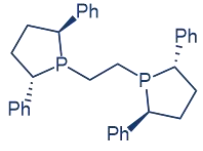
L18
62.0% NMR y.
50:50 er



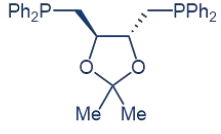
L19
22.3% NMR y.
43:57 er
17.2% SM



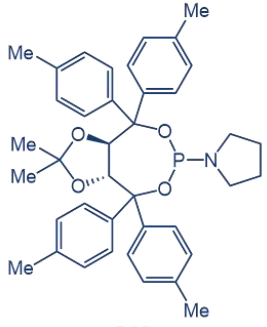
L20
51.0% NMR y.
51:49 er
5.5% SM



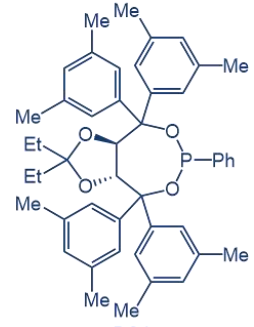
L21
5.8% NMR y.
er nd
53.4% SM



L22
80.0% NMR y.
54:46 er

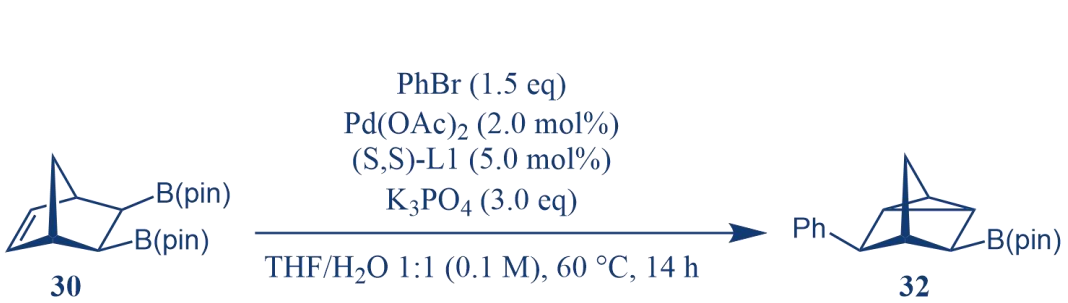


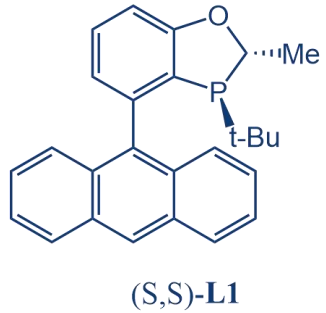
L23
77.6% NMR y.
57:43 er



L24
63.8% NMR y.
50:50 er

Conditions Screening

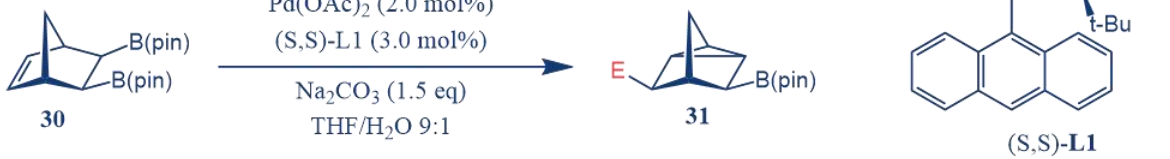




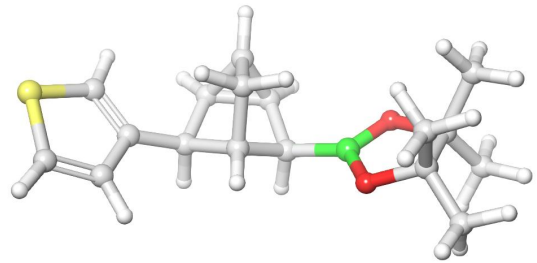
(S,S)-**L1**

entry	variants	NMR y.(%)	er	RSM(%)	entry	variants	NMR y.(%)	er	RSM(%)
1	none	89.6	94:6	-	13	Na_2CO_3, 3% (S,S)-**L1**, dioxane, rt	71.2	90:10	-
2	KF	90.8	93:7	-	14	Na_2CO_3, 3% (S,S)-**L1**, MTBE, rt	< 5	nd	94.2
3	KOH	91.4	89:11	-	15	$PdCl_2$, Na_2CO_3, 3% (S,S)-**L1**, rt	55.9	96.4:3.6	28.0
4	K_2CO_3	93.3	96:4	-	16	$Pd_2(dba)_3$, Na_2CO_3, 3% (S,S)-**L1**, rt	81.3	96.7:3.3	-
5	KOAc	84.2	91:9	-	17	Pd-G3, Na_2CO_3, 3% (S,S)-**L1**, rt	94.2	96.6:3.4	-
6	K_2CO_3, rt	88.6	96.1:3.9	-	18	1.5 eq. Na_2CO_3, 3% (S,S)-**L1**, rt	79.3	96.9:3.1	-
7	Na_2CO_3, rt	87.4	96.4:3.6	-	19	3 eq. Na_2CO_3, 3% (S,S)-**L1**, rt	83.9	96.3:3.7	-
8	Cs_2CO_3, rt	88.9	95.7:4.3	-	20	5 eq. Na_2CO_3, 3% (S,S)-**L1**, rt	78.8	96.2:3.8	-
9	K_2CO_3, 3% (S,S)-**L1**, rt	79.2	96.8:3.2	-	21	1.5 eq. Na_2CO_3, 3% (S,S)-**L1**, 9:1 THF/H_2O, rt	99.5	97.1:2.9	-
10	Na_2CO_3, 3% (S,S)-**L1**, ACN, rt	66.3	87:13	21.9	22	1.5 eq. Na_2CO_3, 3% (S,S)-**L1**, 1:2 THF/H_2O, rt	70.3	95:5	-
11	Na_2CO_3, 3% (S,S)-**L1**, toluene, rt	39.1	95:5	53.7	23	1.5 eq. Na_2CO_3, 3% (S,S)-**L1**, no H_2O, rt	< 5	nd	101.1
12	Na_2CO_3, 3% (S,S)-**L1**, 2-MeTHF, rt	67.5	97.6:2.4	37.9					

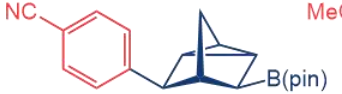
Substrate Expansion



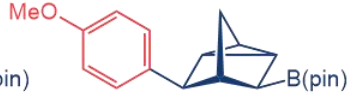
(S,S)-**L1**



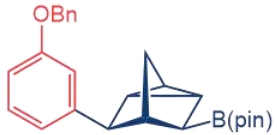
32, (r.t., 14 h)
97% y., 97:3 er



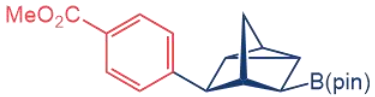
33, (r.t., 14 h)
96% y., 85:15 er



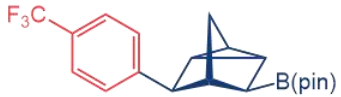
34, (60°C, 14 h)
95% y., 96:4 er



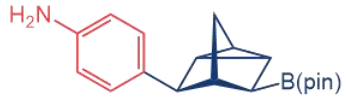
35, (60°C, 14 h)
94% y., 94:6 er



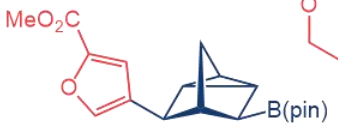
36, (r.t., 14 h)
95% y., 95:5 er



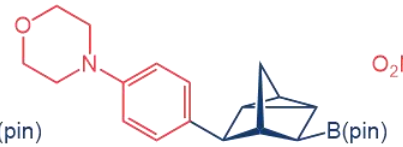
37, (60°C, 14 h)
92% y., 90:10 er



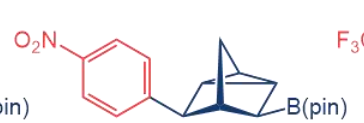
38, (60°C, 14 h)
95% y., 98:2 er



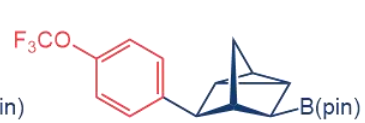
39, (60°C, 14 h)
56% y., 70:30 er



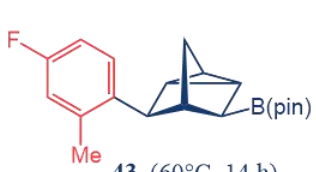
40, (60°C, 14 h)
93% y., 97:3 er



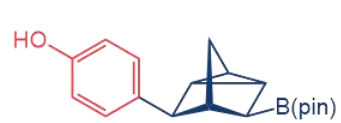
41, (0°C, 14 h)
96% y., 75:25 er



42, (r.t., 14 h)
96% y., 93:7 er

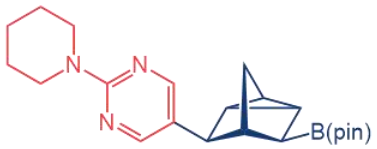


43, (60°C, 14 h)
62% y., 89:11 er

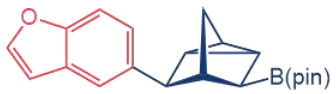


44, (r.t., 14 h)
83% y., 97:3 er

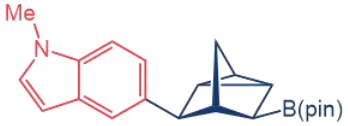
45, (60°C, 14 h)
94% y., 95:5 er



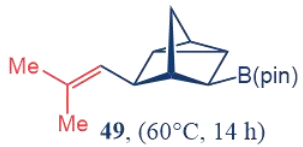
46, (r.t., 24 h)
77% y., 87:13 er



47, (60°C, 14 h)
84% y., 96:4 er



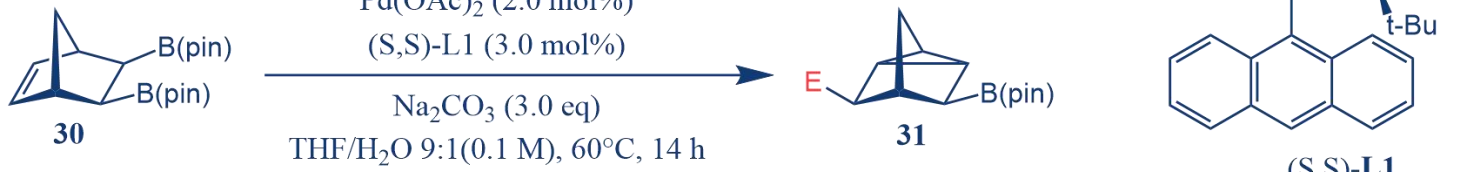
48, (60°C, 24 h)
94% y., 98:2 er



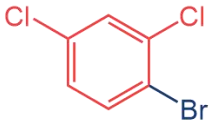
49, (60°C, 14 h)
72% y., 69:31 er

50, (60°C, 14 h)
56% y., 66:34 er

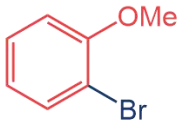
Challenging Substrates Expansion



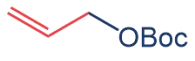
(S,S)-**L1**



51, 70% y.
50:50 er

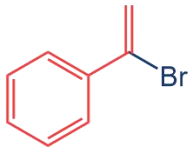


52, 81% y.
67:33 er

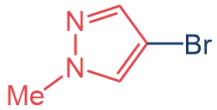


53, 60% y.
70:30 er
46% NMR RSM

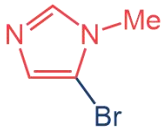
54, <5% NMR y.
63% NMR RSM



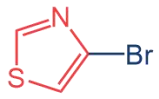
55, <5% NMR y.
80% NMR RSM



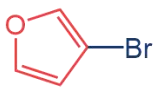
56, <5% NMR y.
71% NMR RSM



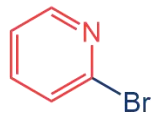
57, <5% NMR y.
77% NMR RSM



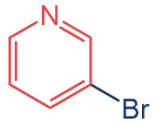
58, <5% NMR y.
77% NMR RSM



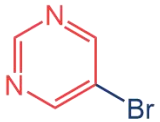
59, <5% NMR y.
77% NMR RSM



60, <5% NMR y.
87% NMR RSM

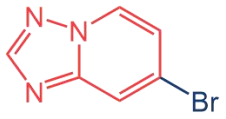


61, <5% NMR y.
78% NMR RSM

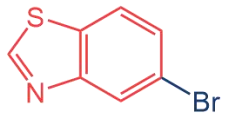


62, <5% NMR y.
71% NMR RSM

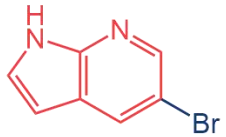
63, 48% NMR y.
er nd
60% NMR RSM



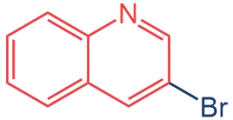
64, <5% NMR y.
85% NMR RSM



65, <5% NMR y.
73% NMR RSM

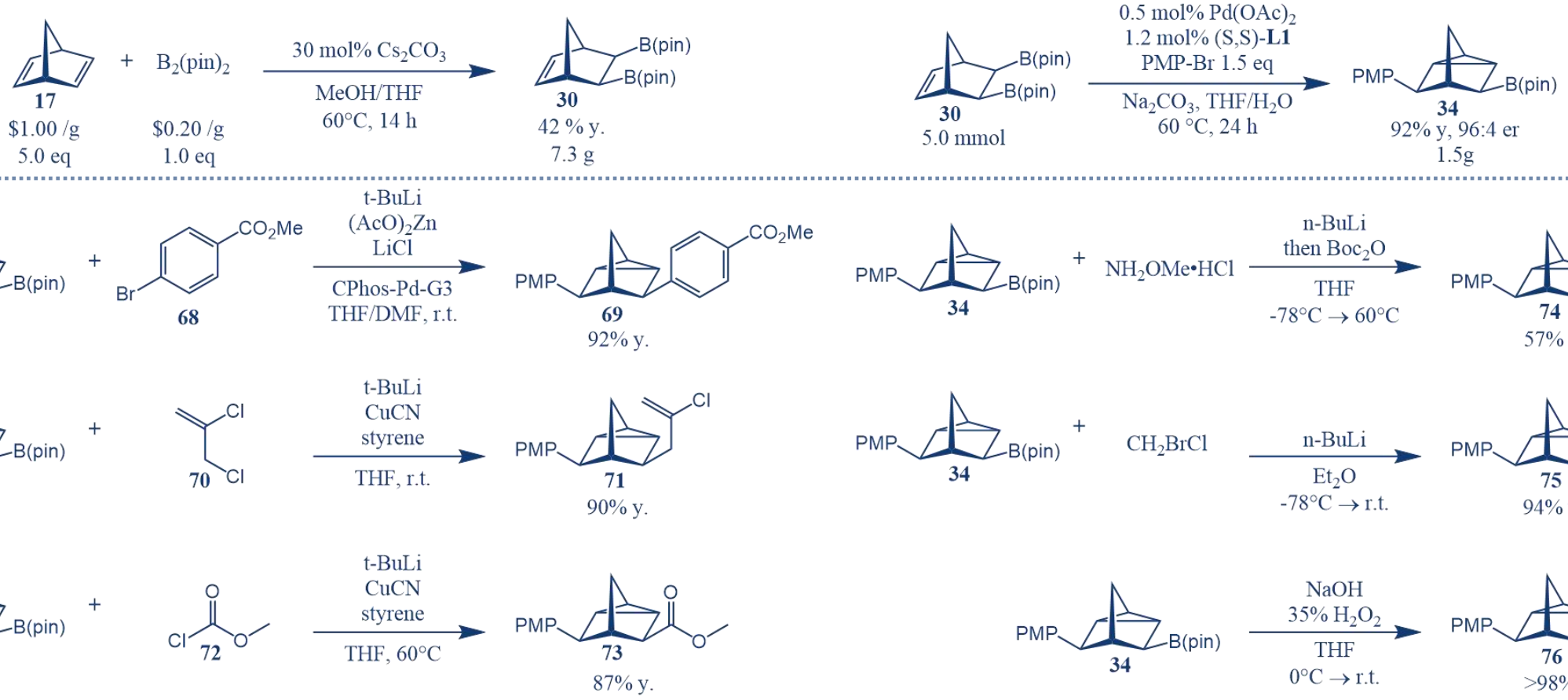


66, <5% NMR y.
79% NMR RSM



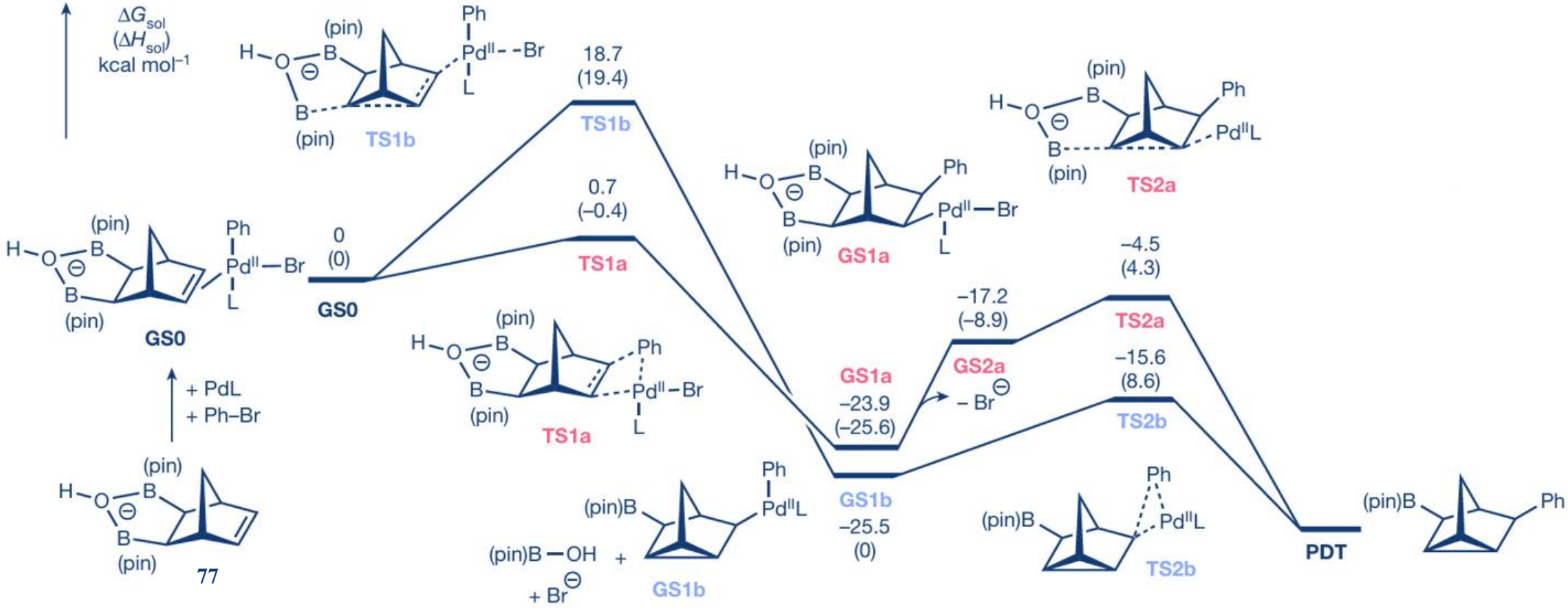
67, 50% NMR y.
er nd
41% NMR RSM

Substrate Synthesis and Subsequent Derivatization



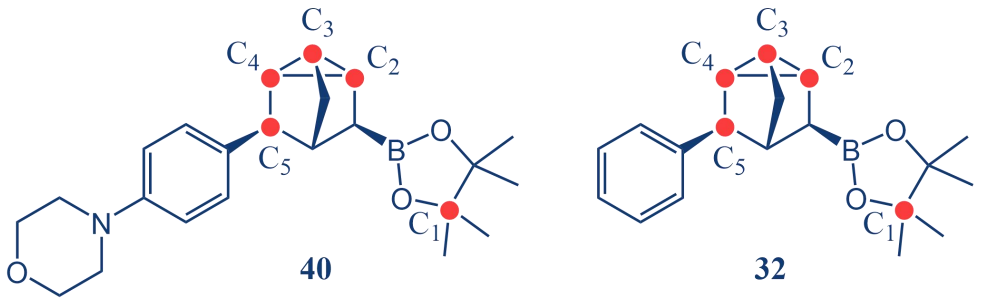
Mechanism Study

DFT Calculation



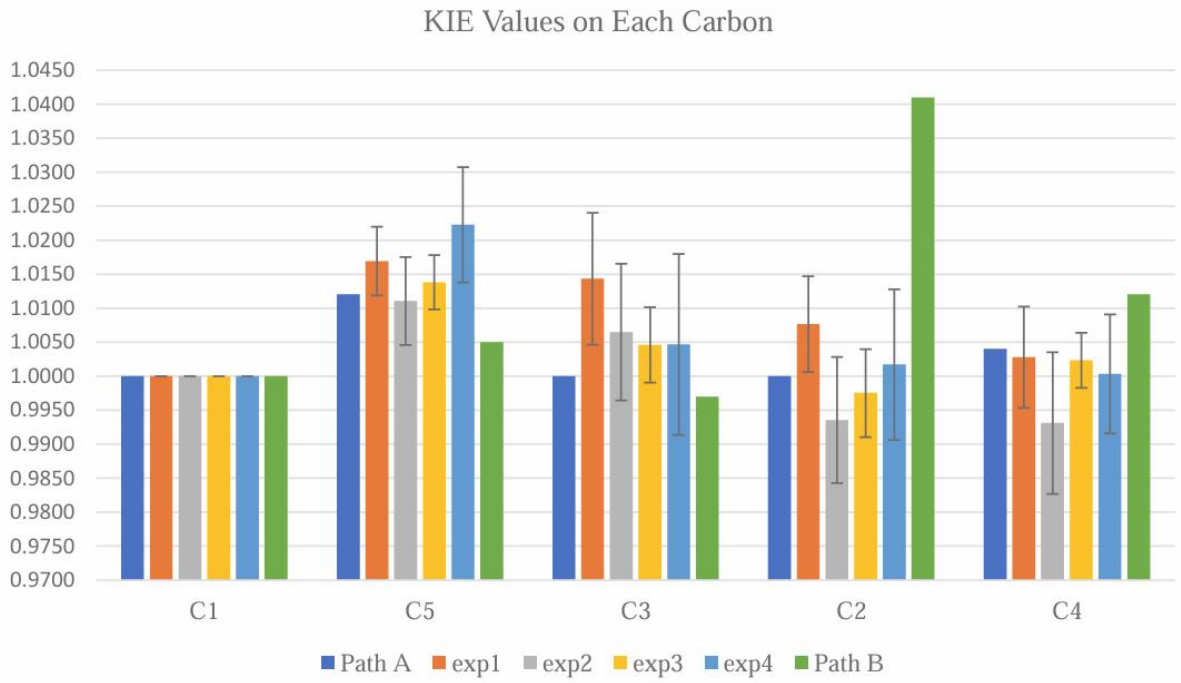
Mechanism Study

^{13}C Kinetic Isotope Effects

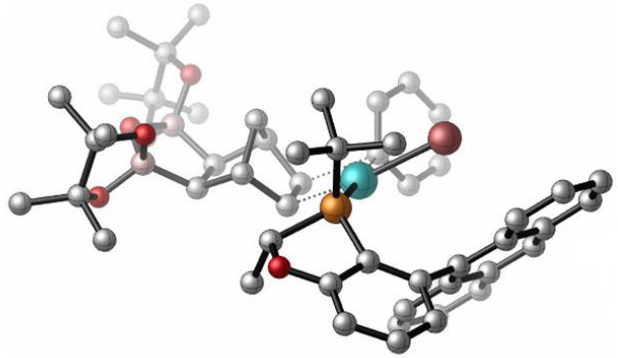


40

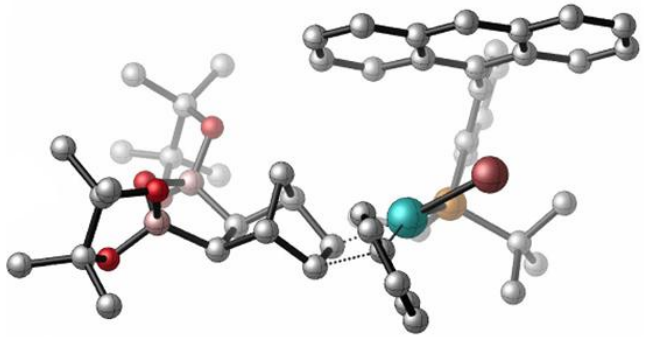
32



Calculated Stereochemistry-Determining Transition States

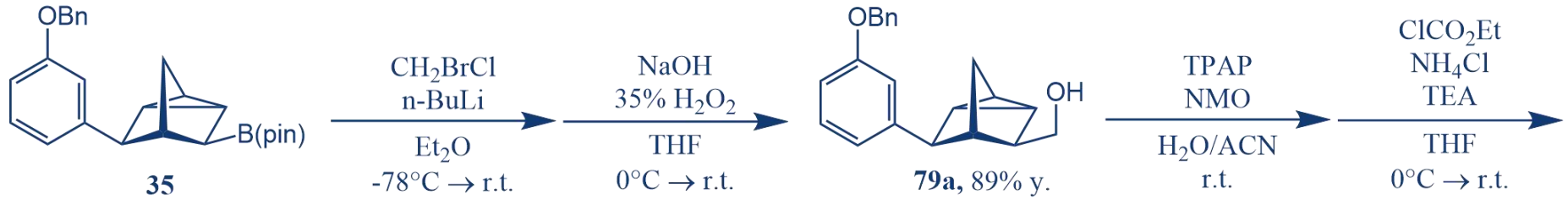


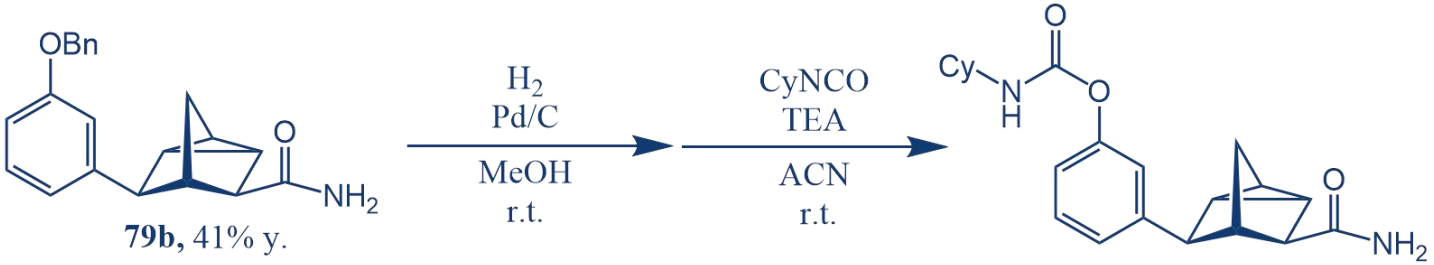
TS1a
Favoured
$\Delta G^{\ddagger}$ = 0.7 kcal mol^{-1}

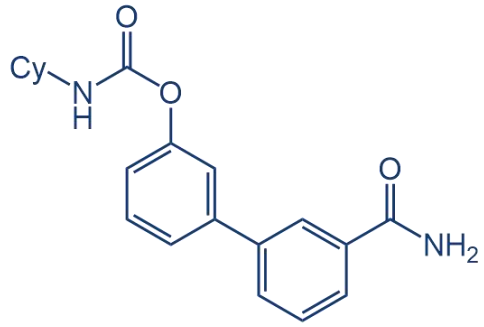


TS1a′
Disfavoured
$\Delta G^{\ddagger}$ = 3.7 kcal mol^{-1}

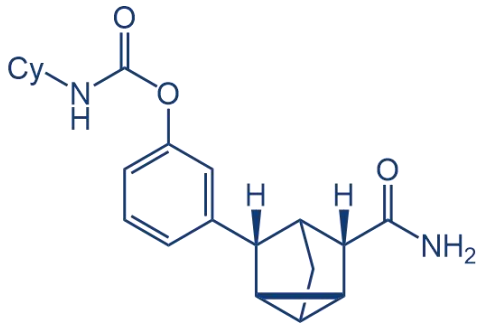
Biophysical and Biochemical Properties



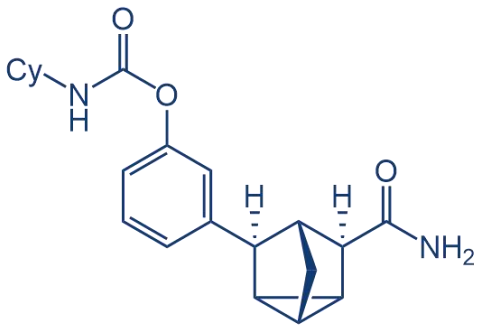




URB597, 78



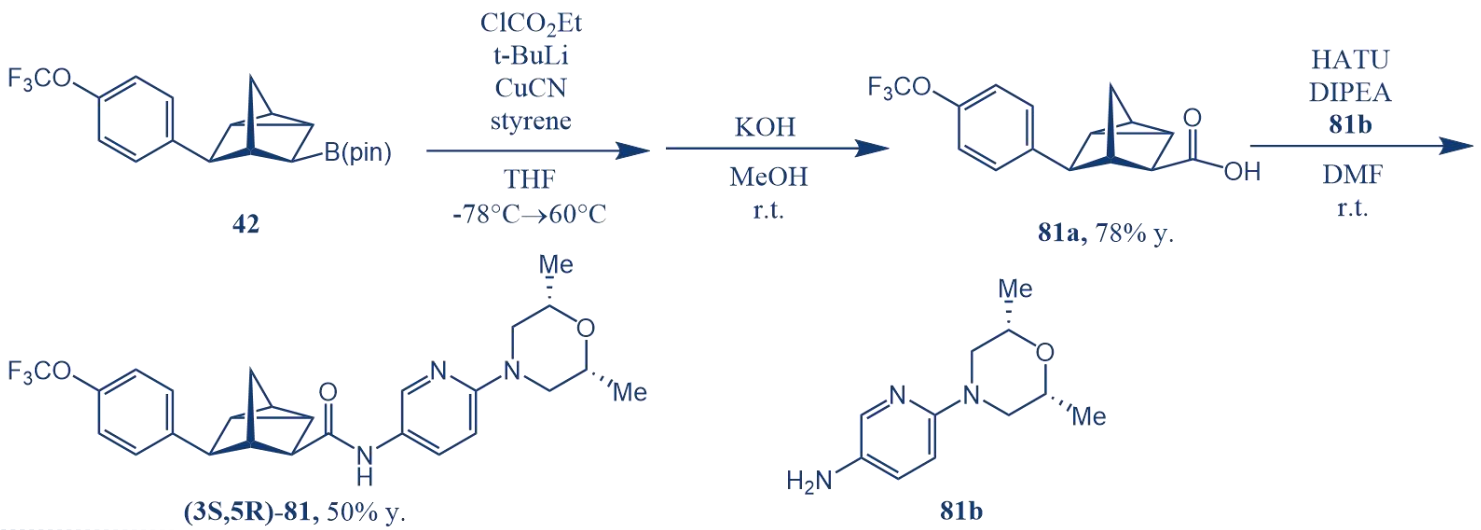
(3R,5S)-79



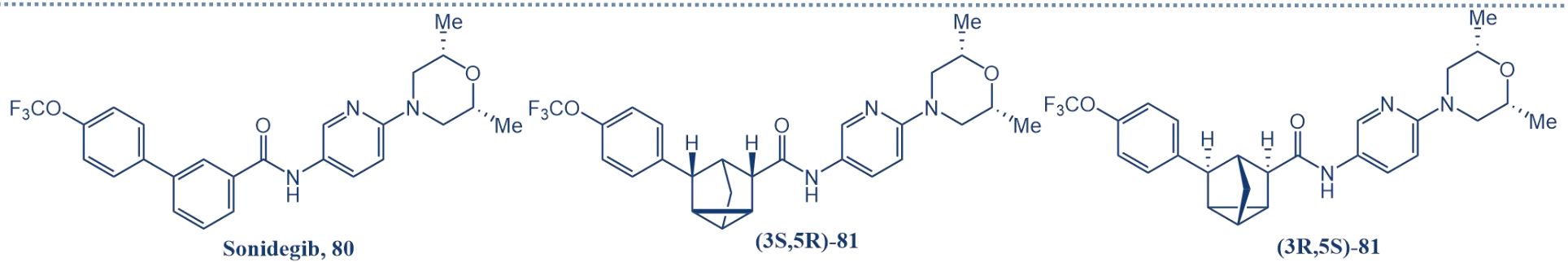
(3S,5R)-79

	URB597	(3S,5R)-79	(3R,5S)-79
MW (g/mol)	338.4	354.4	354.4
Kinetic solubility (μM)	1.01	12.66	10.16
α log D	3.69	3.57	3.56
Microsomal stability(% remaining)	37	67	75
IC_{50} FAAH (μM)	0.0114	0.5	> 4

Biophysical and Biochemical Properties

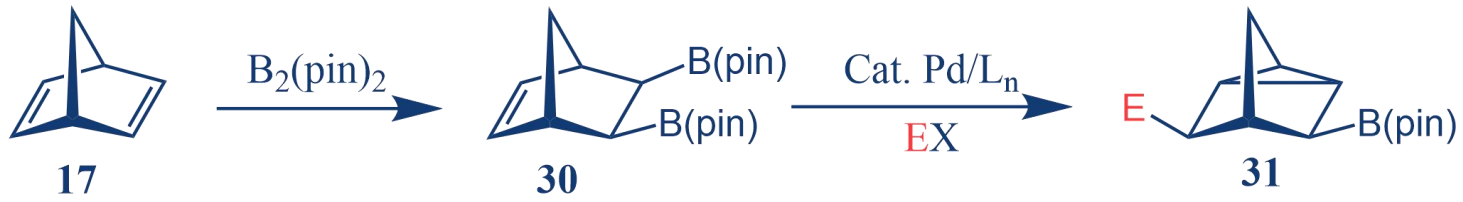


	Sonidegib	(3S,5R)-81	(3R,5S)-81
MW (g/mol)	485.5	487.5	487.5
Kinetic solubility (μM)	0.02	1.04	0.86
α log D	5.74	5.62	5.61
Microsomal stability(% remaining)	78	31	50
IC_{50} Hh (μM)	0.0036	0.5	0.2

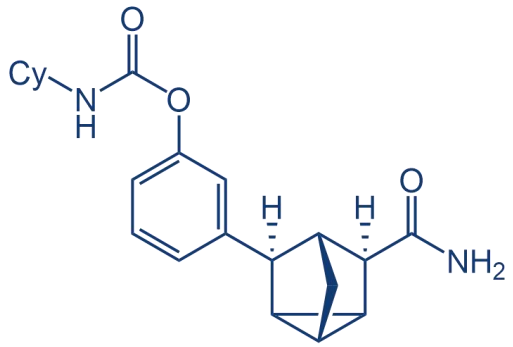


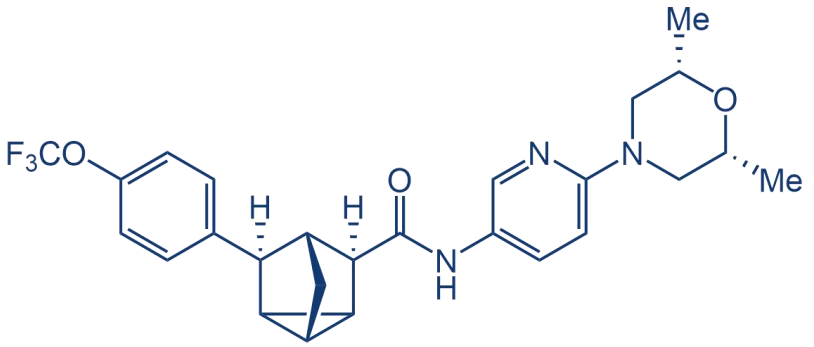
Summary

1. Efficient, enantioselective, catalytic synthesis of Neotricyclane



2. Significant improvement in drug solubility





Thanks for your attention!