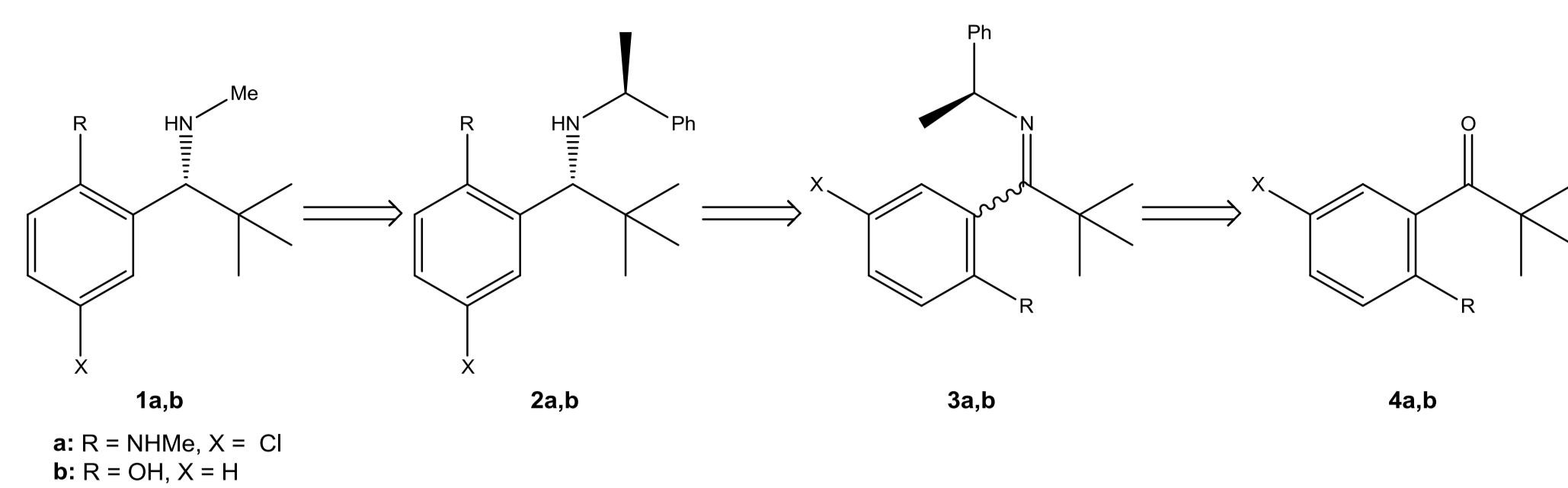
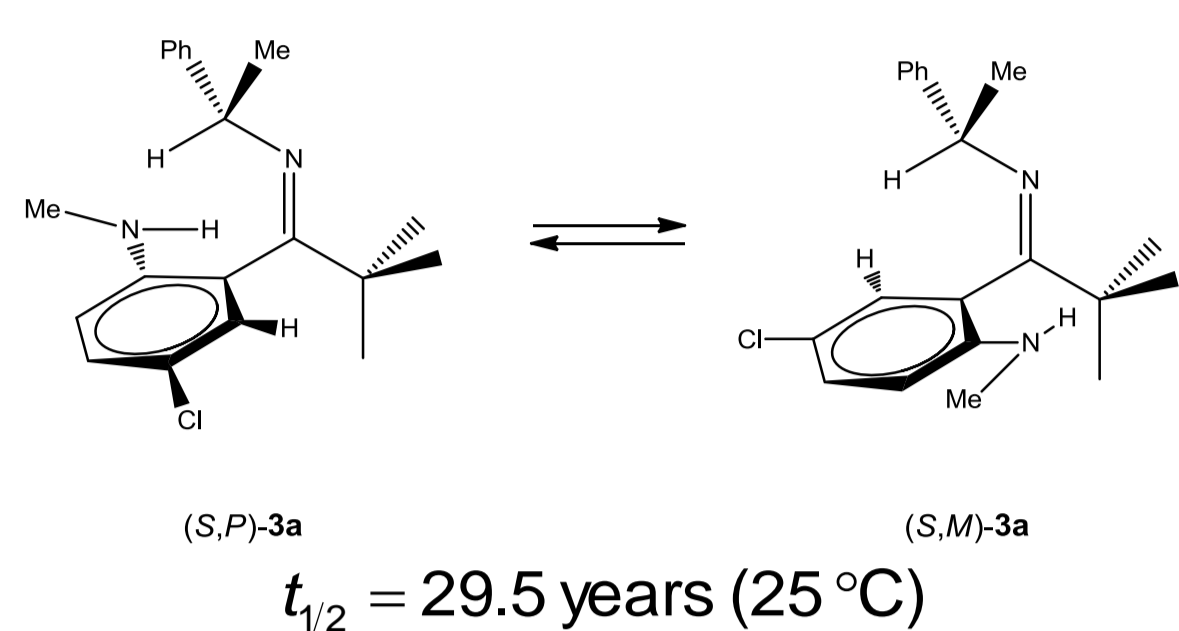




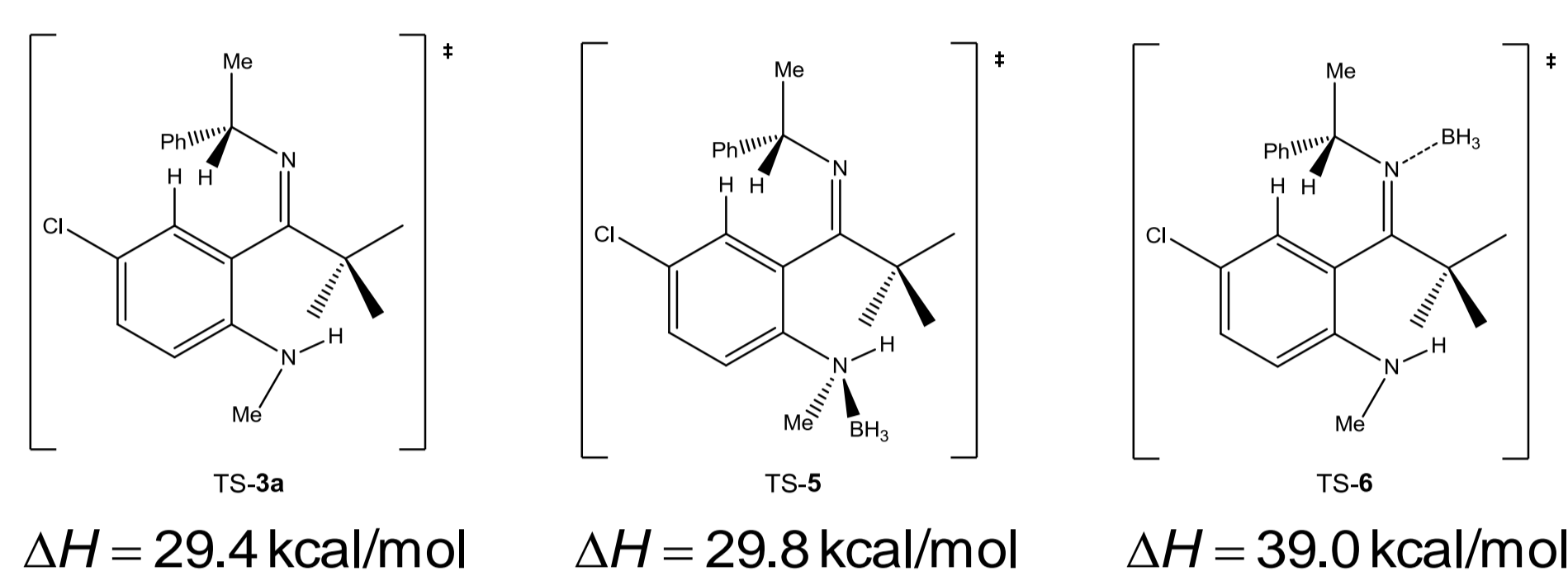
## Retrosynthetic analysis



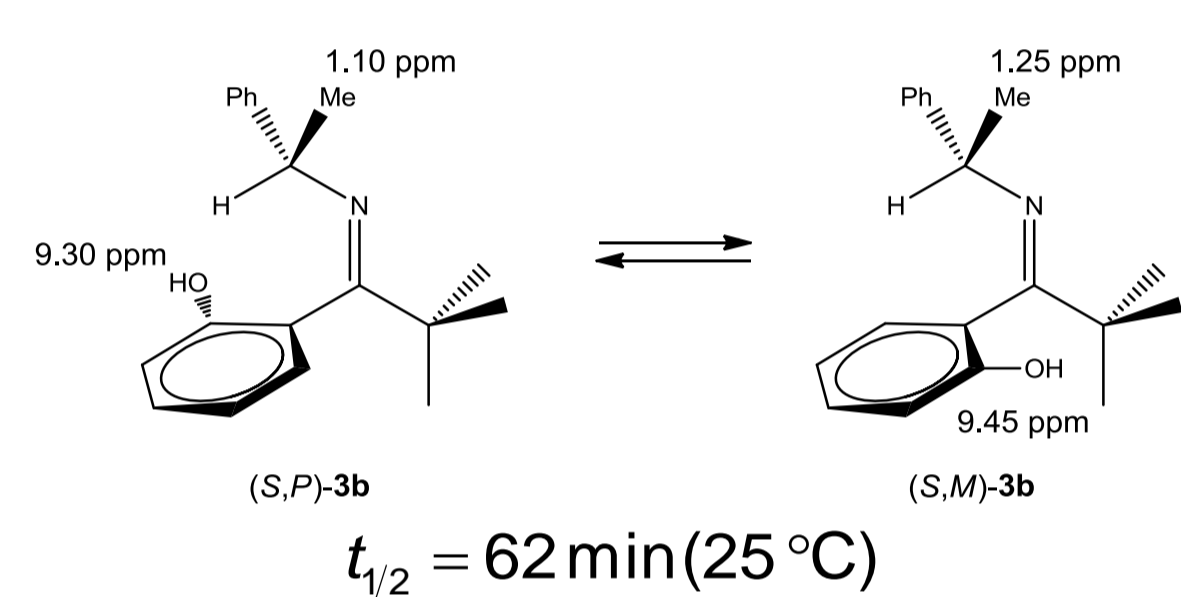
## Atropisomerization barriers



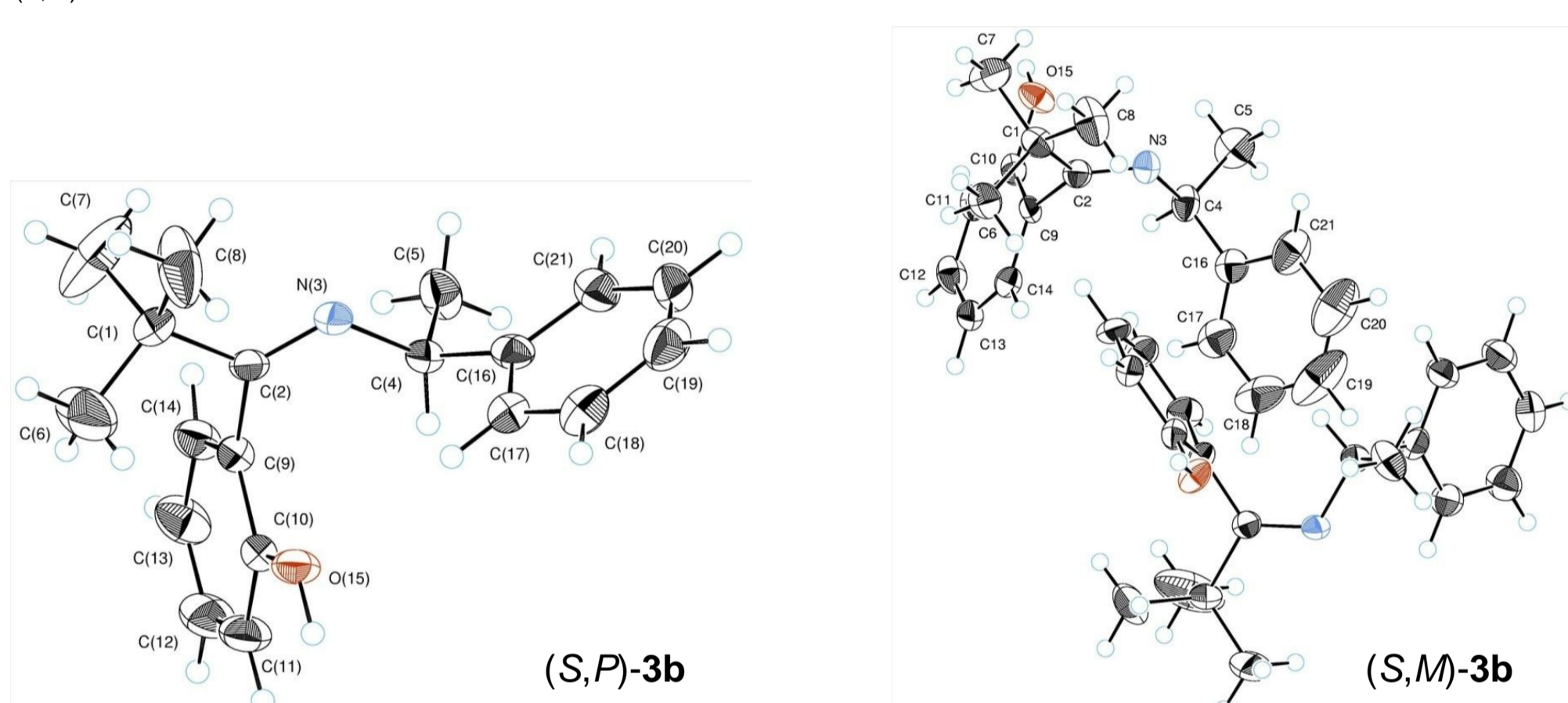
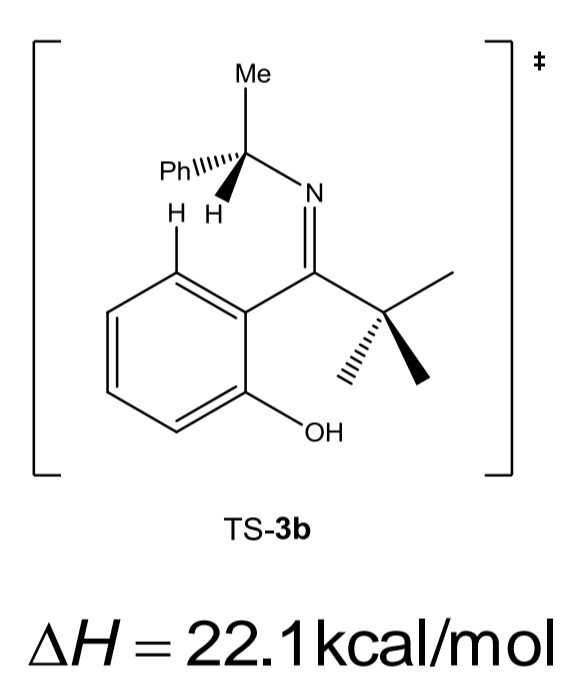
Atropisomers **(S,P)-3a** and **(S,M)-3a** were separated by column chromatography. They are stable at room temperature. *E* isomer of imine **(S,P/M)-3a** was not observed.



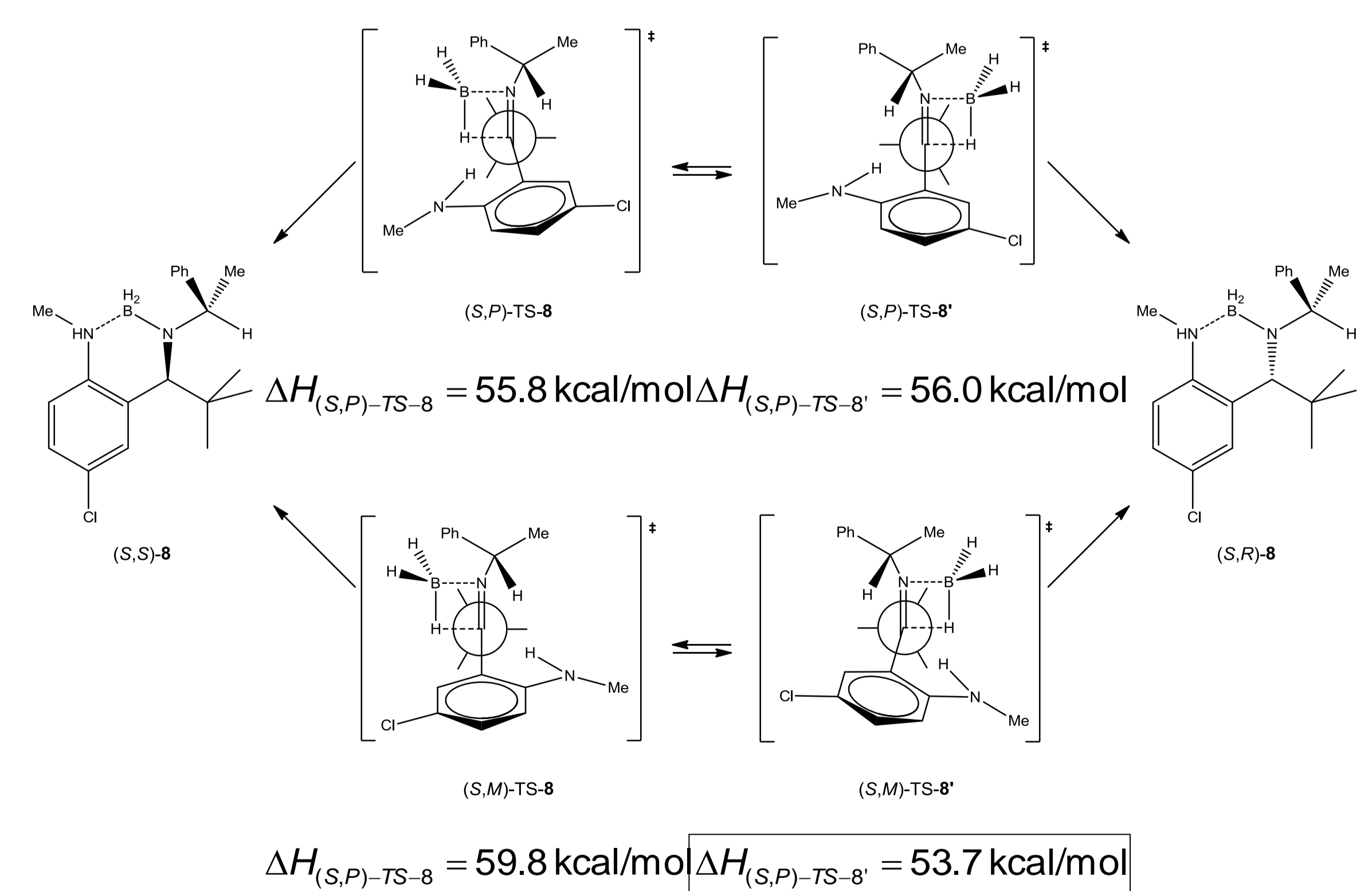
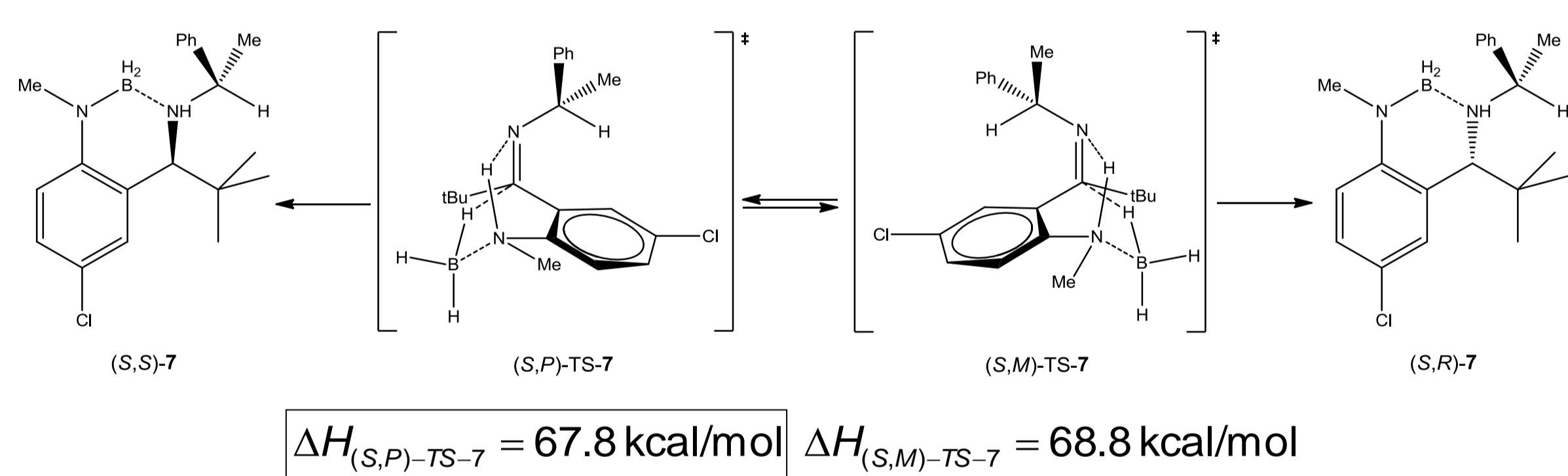
DFT calculations at the b3lyp/6-31g(d,p) level show that complexation with Lewis acid further increases barrier for interconversion of atropisomers.



Atropisomers **(S,P)-3b** and **(S,M)-3b** were separated by HPLC. Atropisomers are stable as solids at -10 °C. While isomerization occurs in solutions at room temperature.

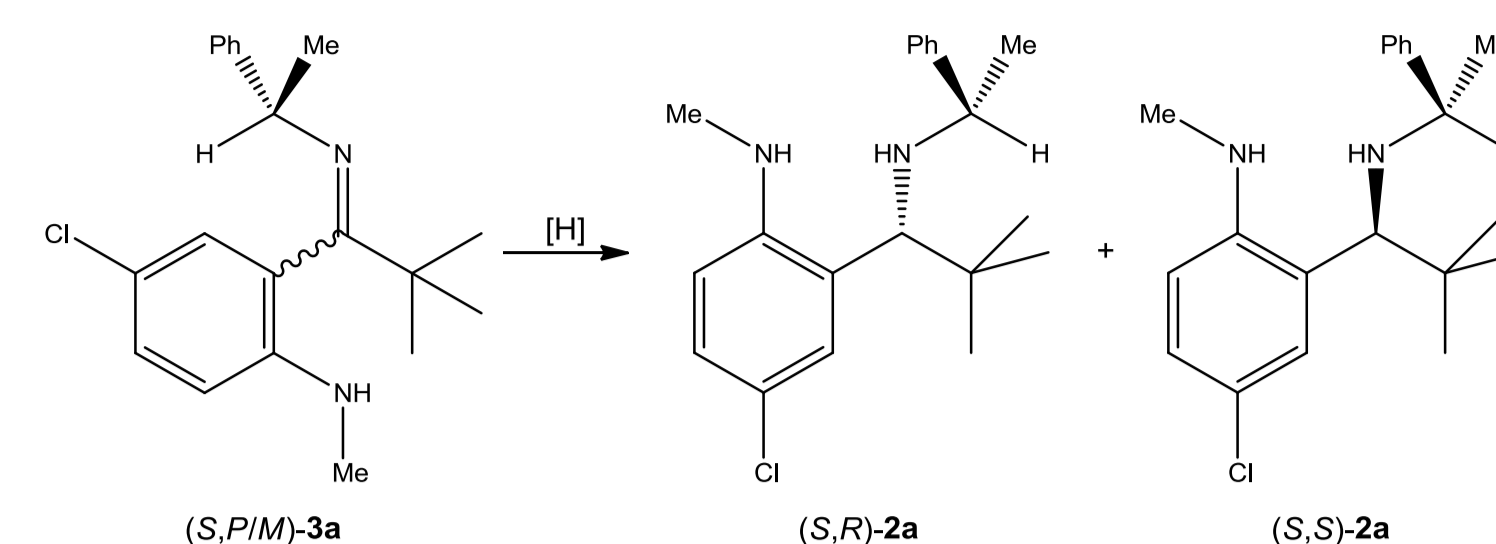


## Calculated transition states for the reduction of 3a



Intramolecular 6-membered transition state **(S,P/M)-TS-7** is higher in energy compared to 4-membered transition state **(S,P/M)-TS-8** ( $\Delta H = 14.1$  kcal/mol). Hence, aniline nitrogen complex with borane does not control reactions diastereoselectivity. Diastereoselectivity of the reaction of **3a** is controlled by the chiral auxiliary.

## Diastereoselective reduction of imines 3a and 3b

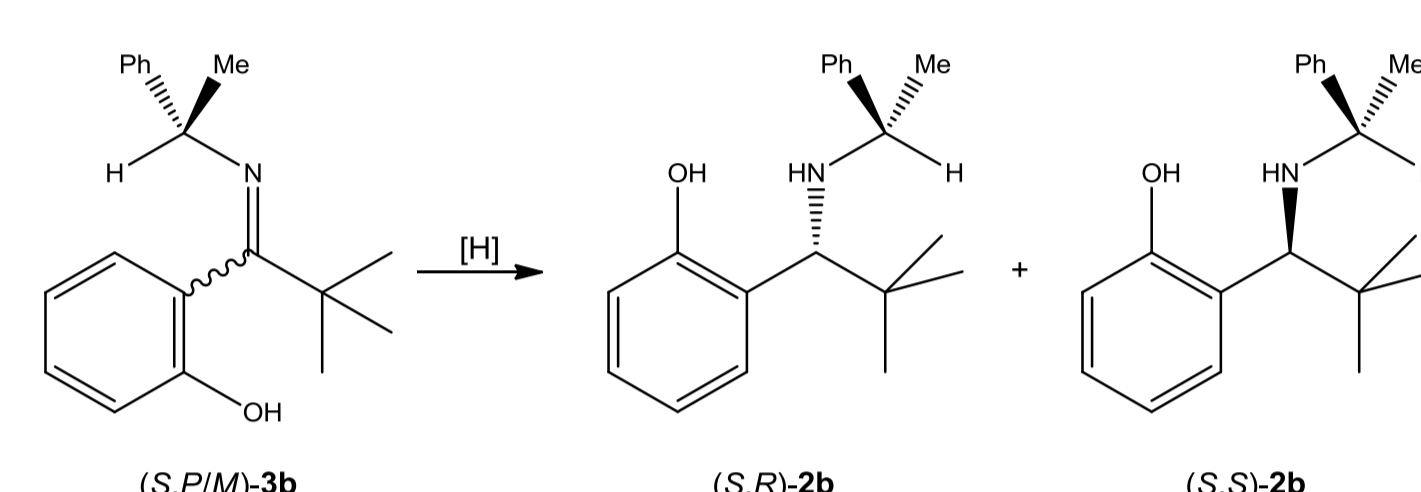


No.	(S,P)-3a:(S,M)-3a	Reaction conditions <sup>a</sup>	(S,R)-2a:(S,S)-2a <sup>b</sup>	Absolute configuration	Yield, %
1	99:1	A	99.5:0.5	R	95
2	1:99	A	96:4	R	76
3	1:1	A	99:1	R	93
4	99:1	B	99:1	R	91
5	1:99	B	99:1	R	90
6	99:1	C	81:19	R	96
7	1:99	C	99:1	R	96

(a) Reaction conditions: A: NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, -78 °C; B: NaBH<sub>4</sub>, Ti(OEt)<sub>4</sub>, MeOH, -78 °C; C: BH<sub>3</sub>·THF, THF, -78 °C.

(b) Determined by chiral HPLC

## Reduction of both (S,P)-3a and (S,M)-3a atropisomers gives diamine (S,R)-2a with R configuration



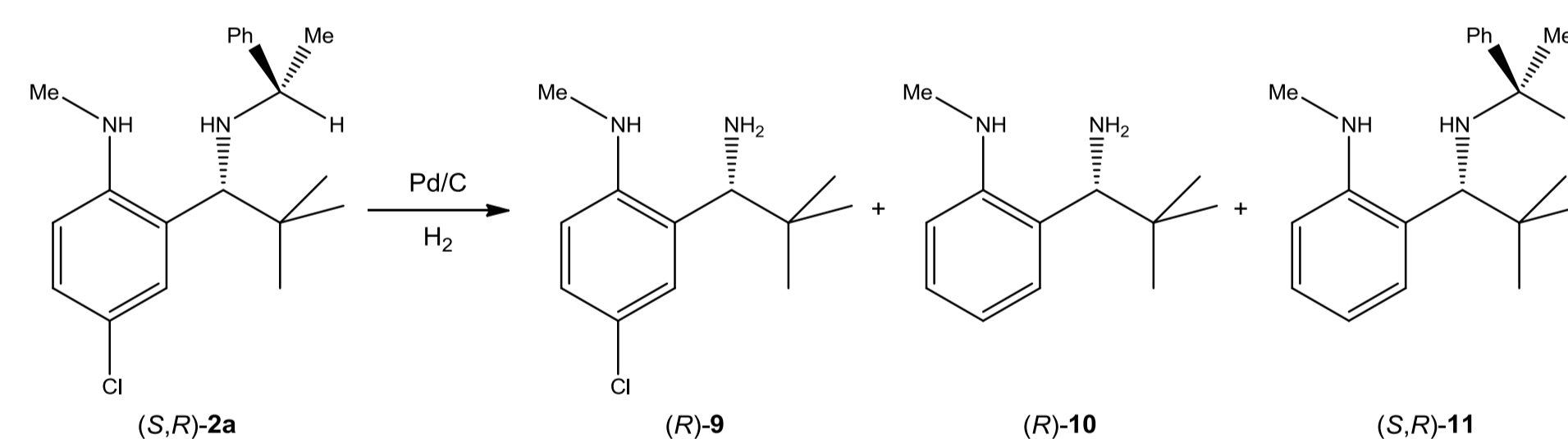
No.	(S,P)-3b:(S,M)-3b	Reaction conditions <sup>a</sup>	(S,R)-2b:(S,S)-2b <sup>b</sup>	Absolute configuration	Yield, %
1	99:1	A	99:1	R	92
2	1:99	A	1:1	-	93
3	99:1	B	97:3	R	96
4	1:99	B	1:1	-	84
5	99:1	C	99:1	R	95
6	1:99	C	93:7	R	93

(a) Reaction conditions: A: NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, -78 °C; B: NaBH<sub>3</sub>CN, AcOH, r.t.; C: BH<sub>3</sub>·THF, THF, -78 °C.

(b) Determined by chiral HPLC

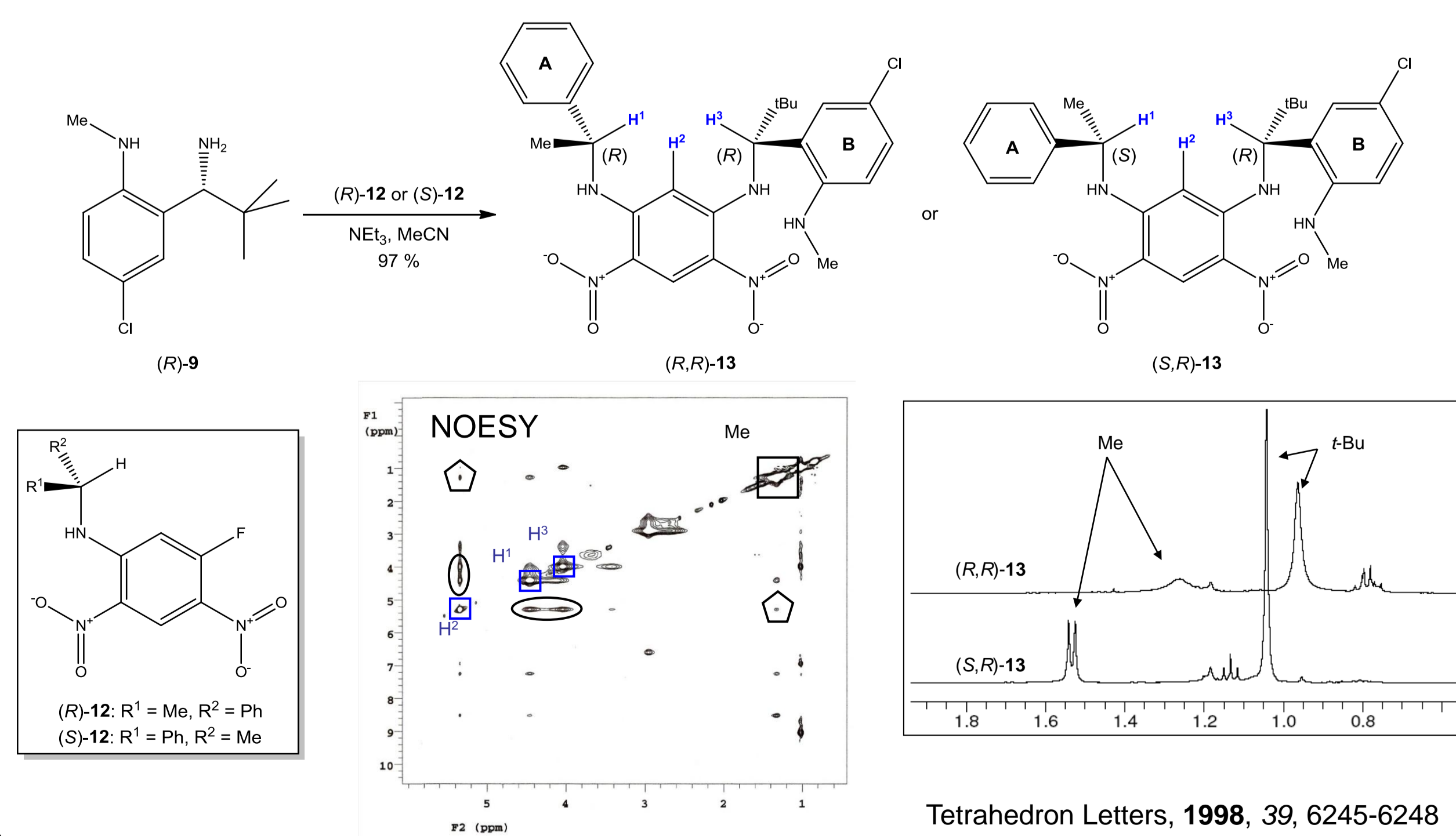
## Reduction of imine (S,P)-3b gives diamine (S,R)-2b with R configuration, but reduction of imine (S,M)-3b gives mixture of diamines (S,R)-2b and (S,S)-2b with ratio 1:1.

## Selective cleavage of chiral auxiliary



No.	Solvent	Pressure, atm	time, h	(S,R)-2a, %	(R)-9, %	(R)-10, %	(S,R)-11, %
1	AcOH/HCl 2N aq (2/1)	70	12	24	32	38	6
2	AcOH/HCl 2N aq (2/1)	8	12	51	41	8	-
3	AcOH/HCl 2N aq (2/1)	4	24	41	50	9	-
4	AcOH/HCl 2N aq (2/1)	1	24	100	-	-	-
5	MeOH/HCl in Et <sub>2</sub> O (1 eq)	4	6	-	-	100	-
6	MeOH/HCl 2N aq (1/1)	4	12	80	10	10	-
7	HCl 0.5N aq	4	6	-	-	100	-
8	HCl 6N aq	4	48	6	81	13	-
9	NH <sub>4</sub> Cl sat.	4	24	-	-	100	-
10	HCl (3N aq) sat. with NH <sub>4</sub> Cl	4	6	-	89	11	-

## Determination of absolute configuration



Tetrahedron Letters, 1998, 39, 6245-6248