"Mix and Shake" Method for Configurational Assignment by NMR: Application to Chiral Amines and Alcohols

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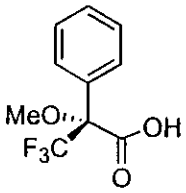
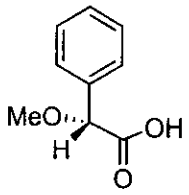
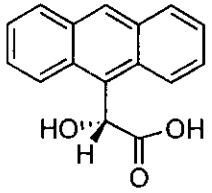
Auxillary Reagents



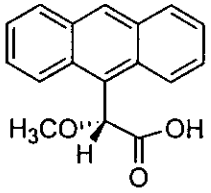
(R)-MTPA



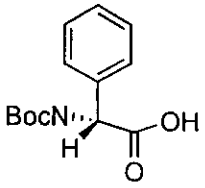
(R)-MPA



(R)-AHA



(R)-AMA

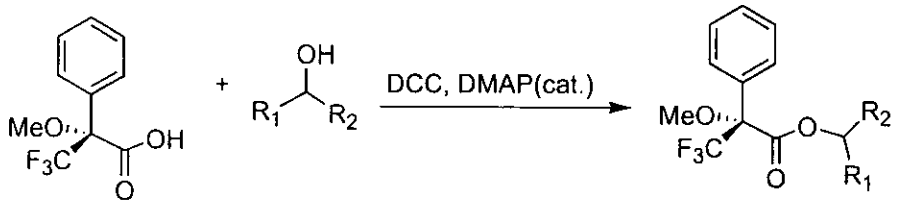


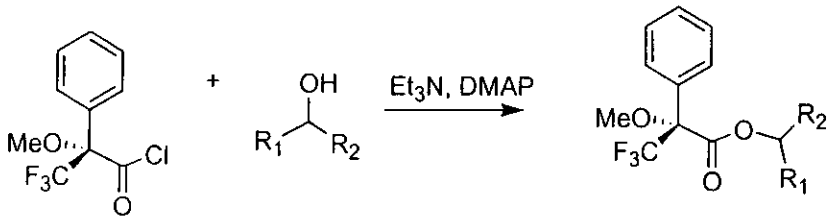
(R)-BPG

- 1°, 2° alcohols, 1° amines, and carboxylic acids

-choice of auxillary reagent for substrate

-choice of derivitization procedure



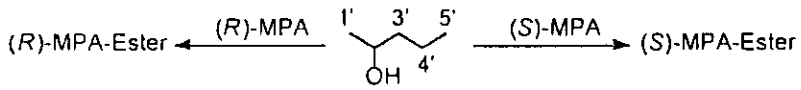


* to produce (R)-MTPA ester or amide----> the (S)-MTPA chloride or the (R)-MTPA acid should be used.

Seco, J.M. et al. Tetrahedron: Asymm. 2001, 12, 2915-2925

Double Derivatization:

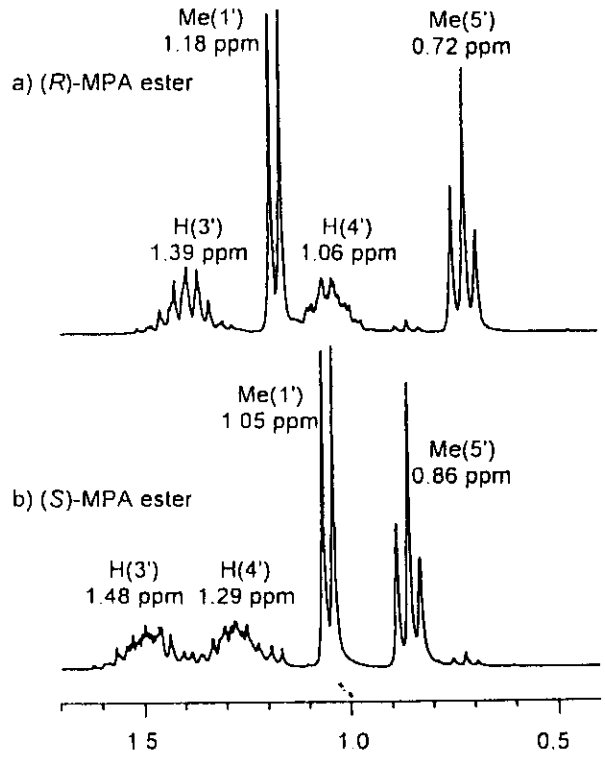
a)



(R)- or (S)-pentanol?

L_1 = Me (1')
L_2 = Me (5'). H(3') and H(4')

b)



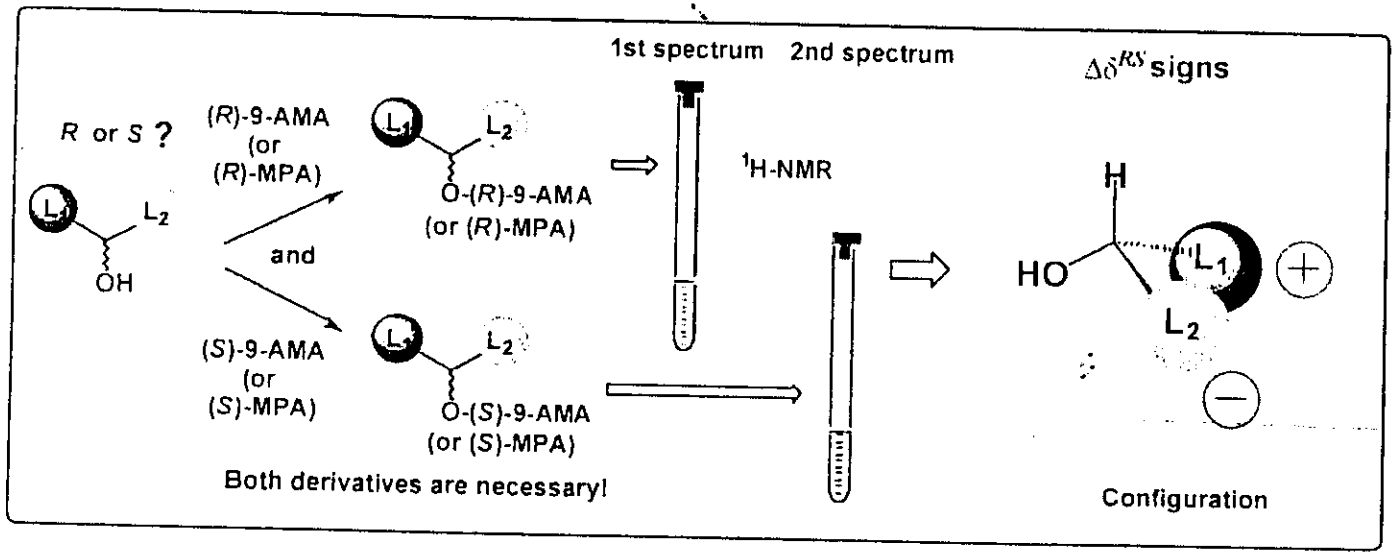
Seco, J.M. et al. Tetrahedron: Asymm. 2001, 12, 2915-2925

a) Derivatization of the substrate with the R and S enantiomers of the selected auxillary reagents.

b) Assignment of the proton NMR signals of the L_1 and L_2 in both derivatives.

Double Derivatization:

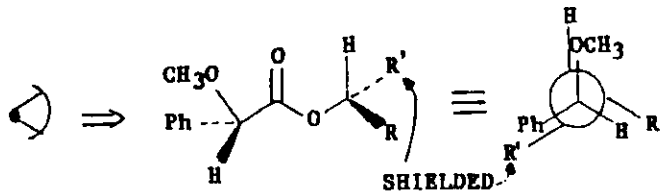
2° Alcohols:



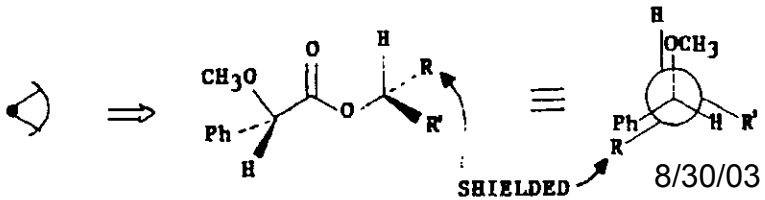
-MTPA sometimes produces very small $\Delta\delta^{RS}$ values and an irregular distribution of sign

-MPA works well

-9-AMA produces the greatest $\Delta\delta^{RS}$ values, suited for substrates with overlapping spectra and long chains.



1



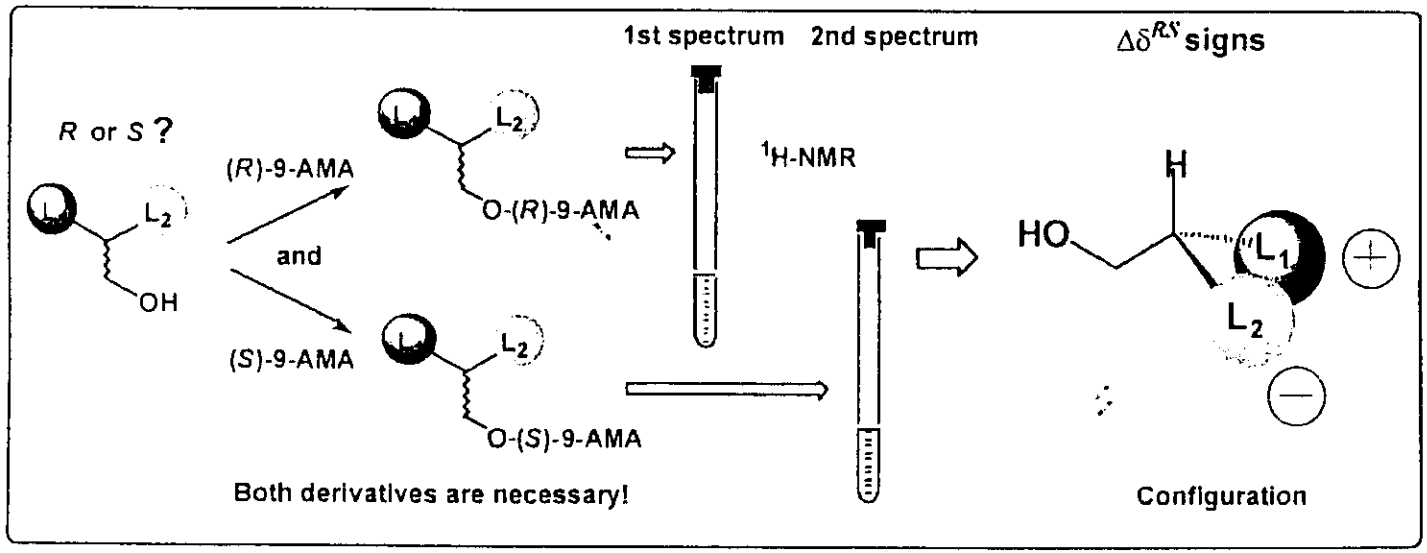
2

Trost, B.M. et al. JOC 1986, 51, 2730-2374

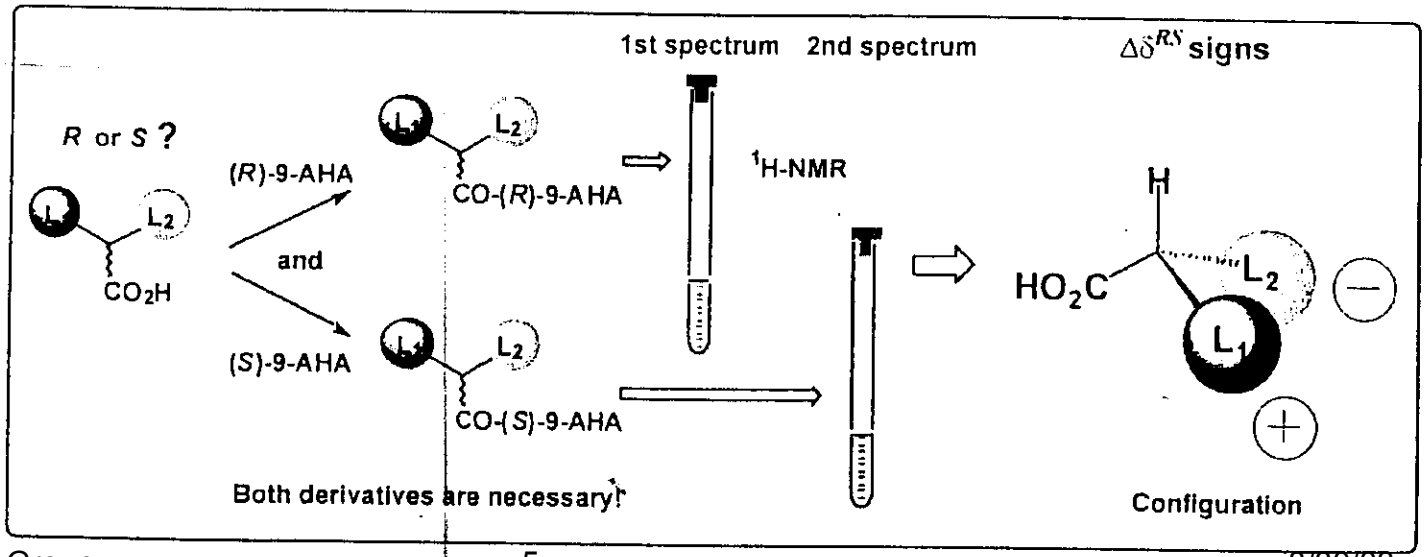
Seco, J.M. et al. Tetrahedron: Asymm. 2001, 12, 2915-2925

Double Derivatization:

1° Alcohols:

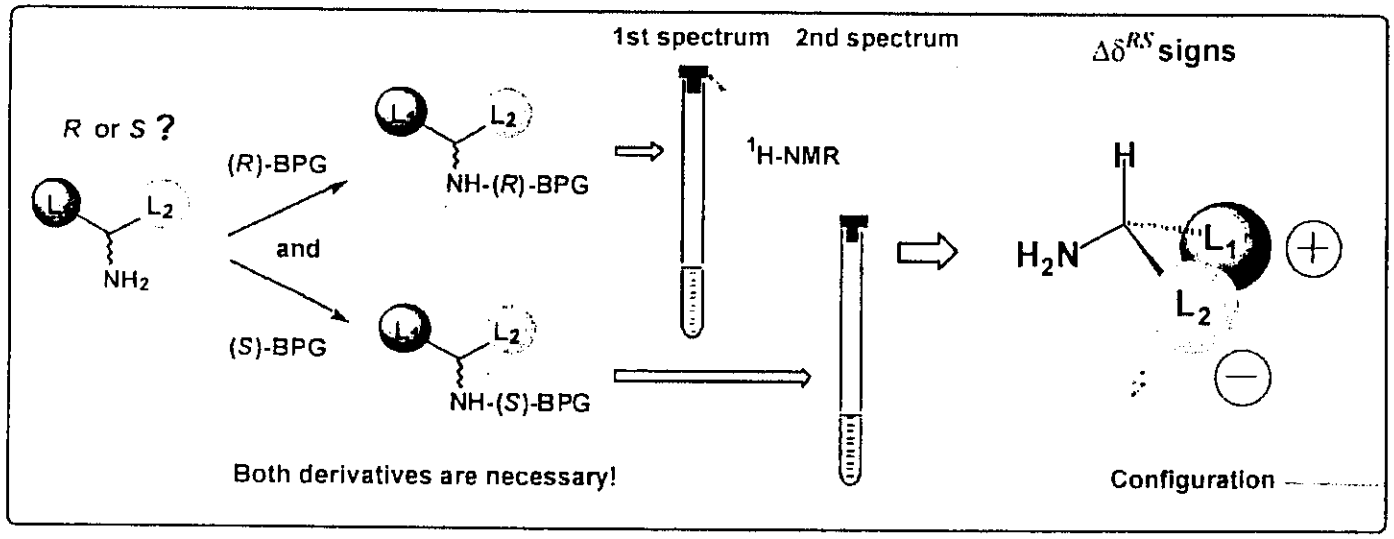


Carboxylic Acids:



Double Derivatization:

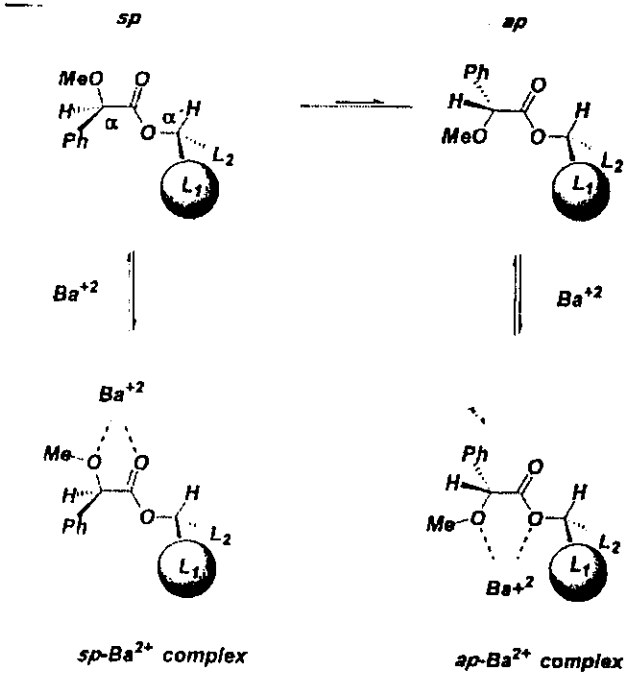
1° Amines:

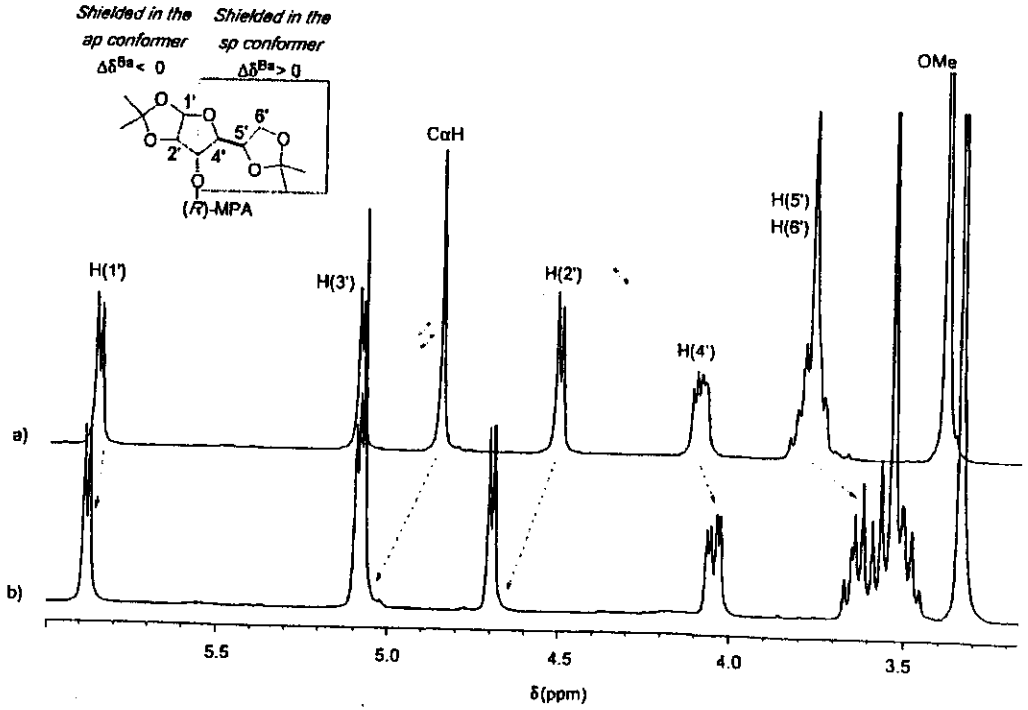


-can use MPA, MTPA, and BPG-- but BPG produces the $\Delta\ \delta$ greatest values and also is the cheapest

Single Derivatization: Primary Amines and Secondary Alcohols

-Complexation with Ba^{2+}

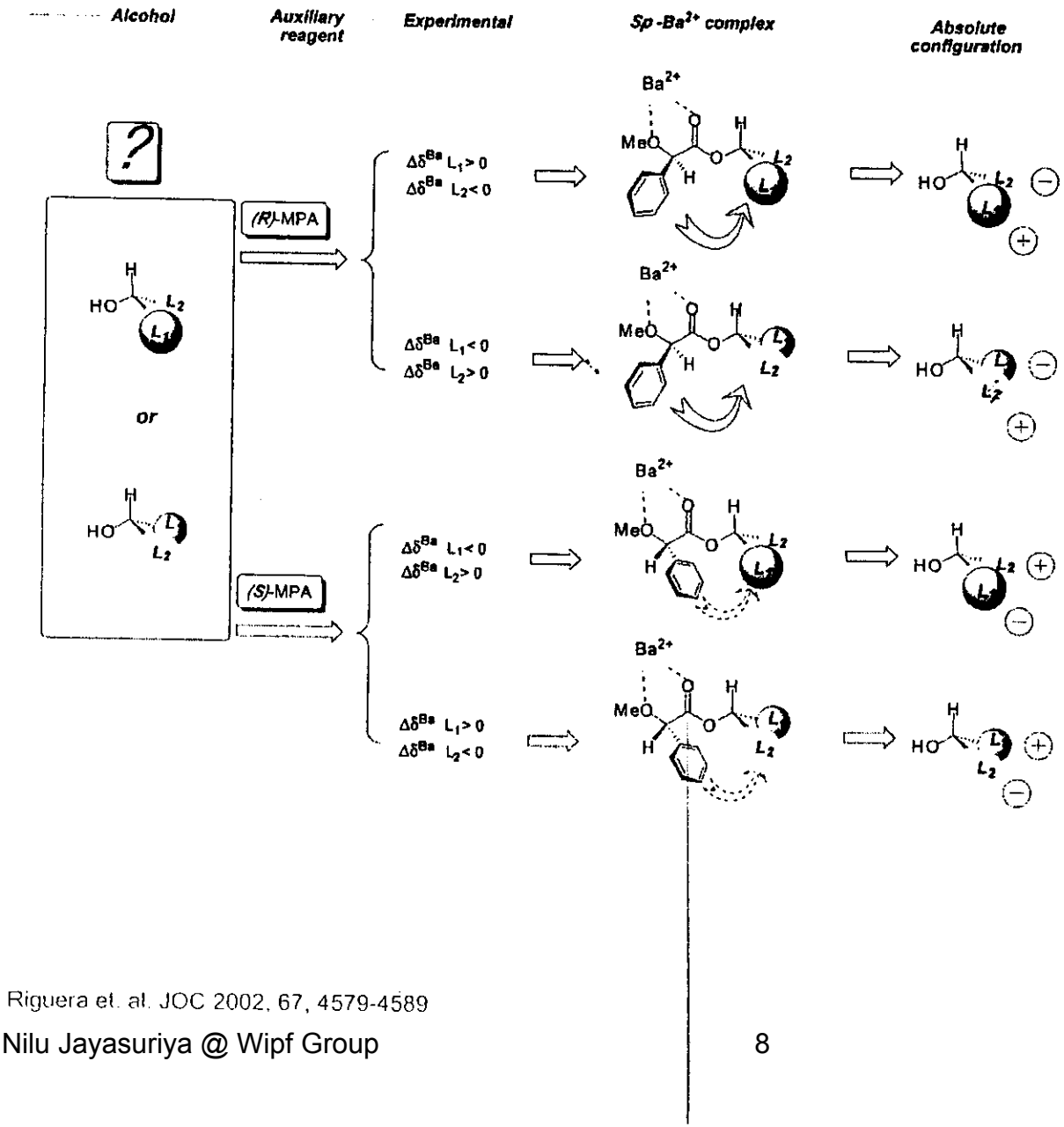




- substrates with stereogenic carbon in the α -position preferably w/o groups that can complex with Ba^{2+}
- substituents on one side of the plane move to a higher field upon addition of Barium, while those on the other plane shift to a lower field, this is due to the preferential chelation of one of the conformers of the MPA esters.
- other metal cations were evaluated (i.e. Li^{+}, Rb^{+}, Cs^{+}, Mg^{2+}, Ca^{2+}, Sc^{3+}, V^{3+}, Zn^{2+})

Riguera et. al. JOC 2002, 67, 4579-4589

Barium Procedure:



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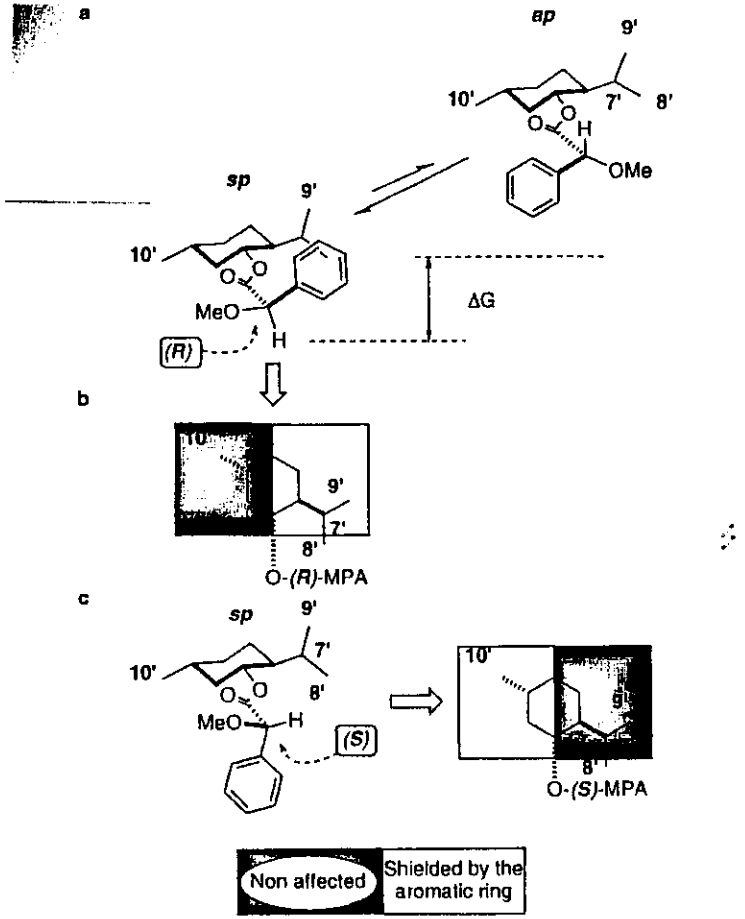
Single Derivatization: Secondary Alcohols

- Low Temperature



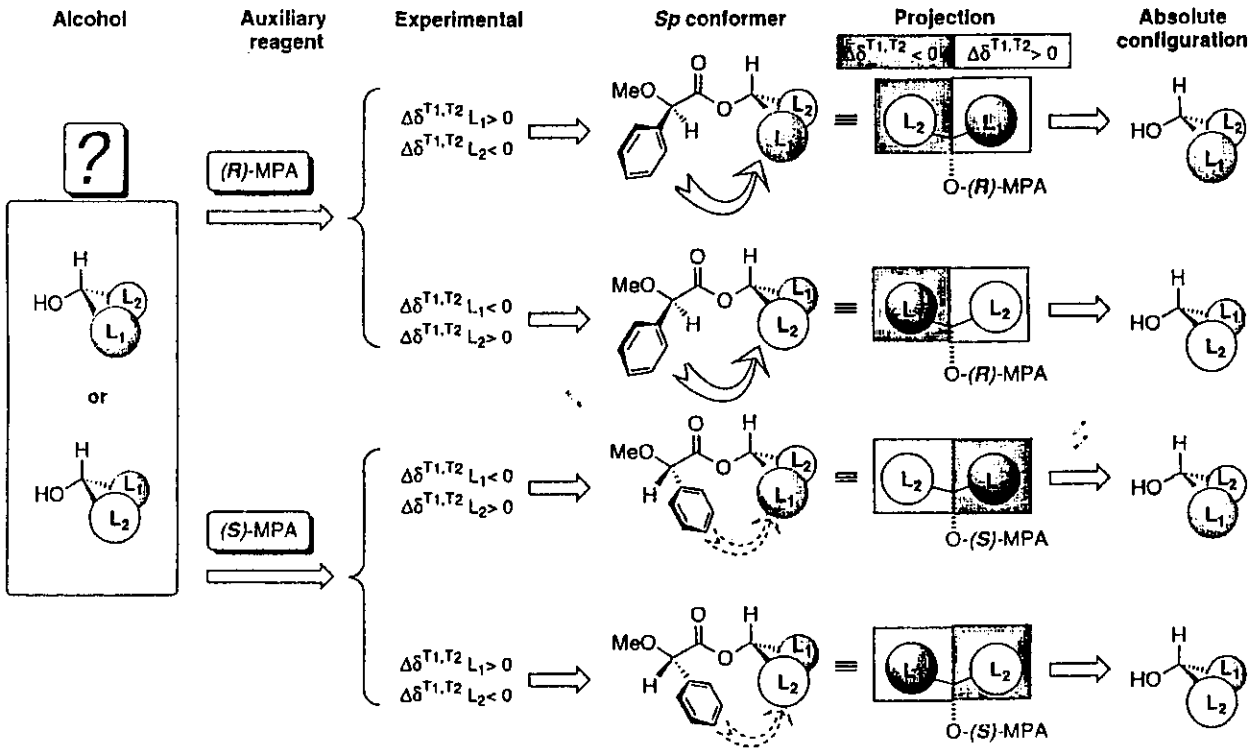
- substrates with stereogenic carbon in the α -position

- variable temperature- eg. rt to -70°C

- based on selective modification of the conformational equilibrium by lowering the temperature of the NMR probe. At low temperature, the relative population of the most staple sp conformer is increased and the resonance of the substituent of the alcohol, located under the shielding done of the pheny ring are shifted upfield.

Riguera et. al. JACS 1998, 120(5), 877-882

Low Temp. Procedure:



- 15 know alcohols of known configuration were tested

- effects are not influenced by association in solution or solvent effects

- NMR spectra recorded at room temperature and low temperature at concentrations ranging from 1 to 8 mg/mL and in solvents of low to high polarity showed no relevant changes.

Riguera et. al. JACS 1998, 120(5), 877-882

"Mix and Shake" Method

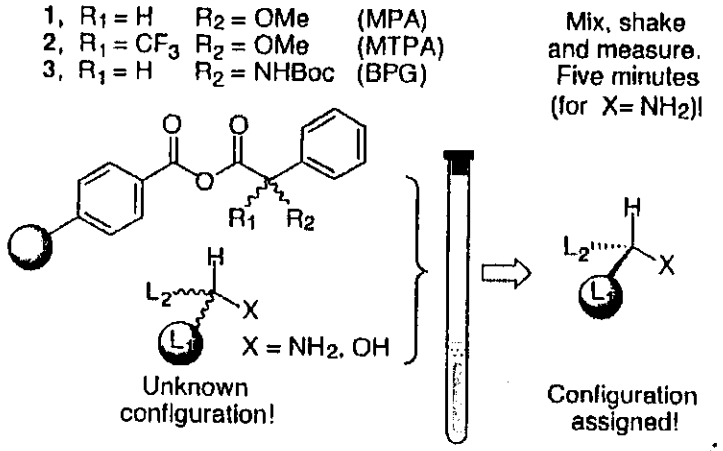
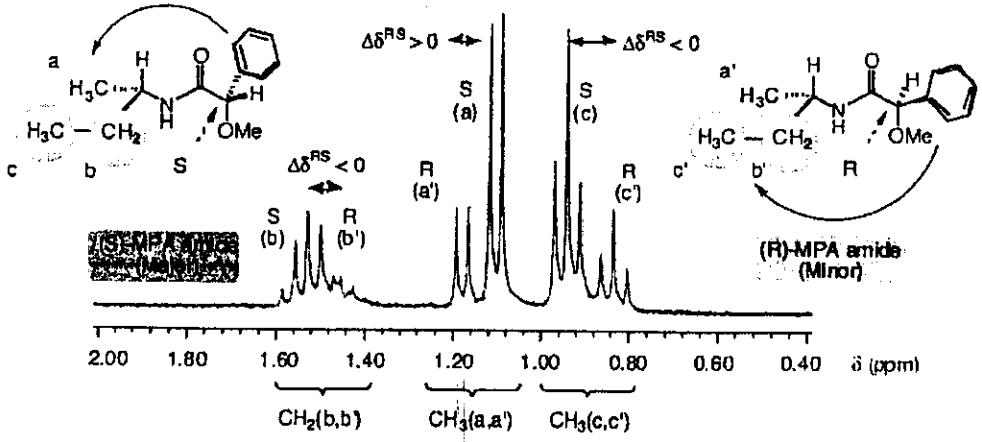


Figure 1. MPA, MTPA, and BPG resins employed in this new methodology.

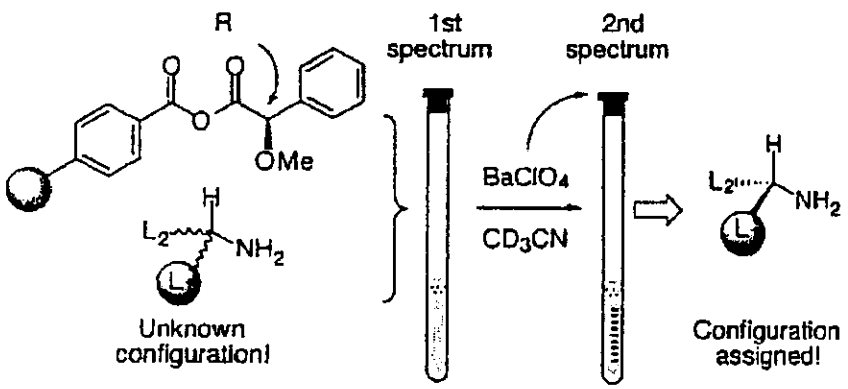
-derivatives are obtained by mixing a solid matrix bound auxillary with a chiral substrate directly in the NMR tube.
-solid resin causes no interference while it floats on top of the $CDCl_3$.
-samples composed of different enantiomeric ratios of MPA(such as 1:2 (R)/(S)-MPA) were prepared and reacted with amine.

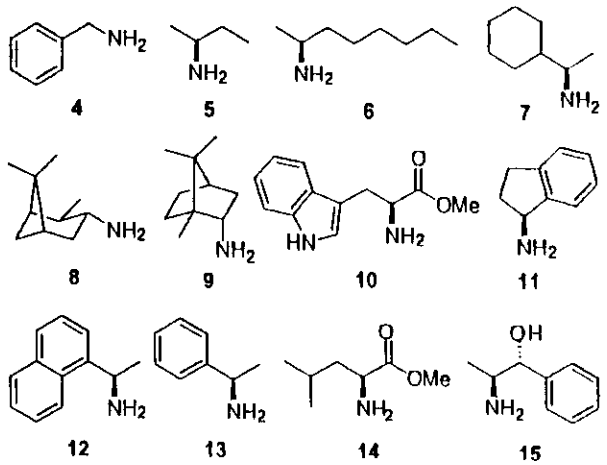


Riguera et. al. OL 2003, 5(17), 2979-2982.

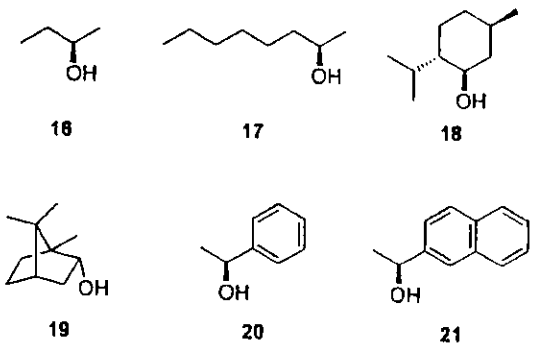
"Mix and Shake" Method

- Ba^{2+}





Advantages:
- No external reaction flasks or manipulations are necessary
- coupling reagents are not necessary(DCC)
- no undesired side products(dicyclohexylurea) are generated
- no filtration or purification is required
- takes 5 minutes @ rm. temp. in a quantitative yield and on a microscale



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