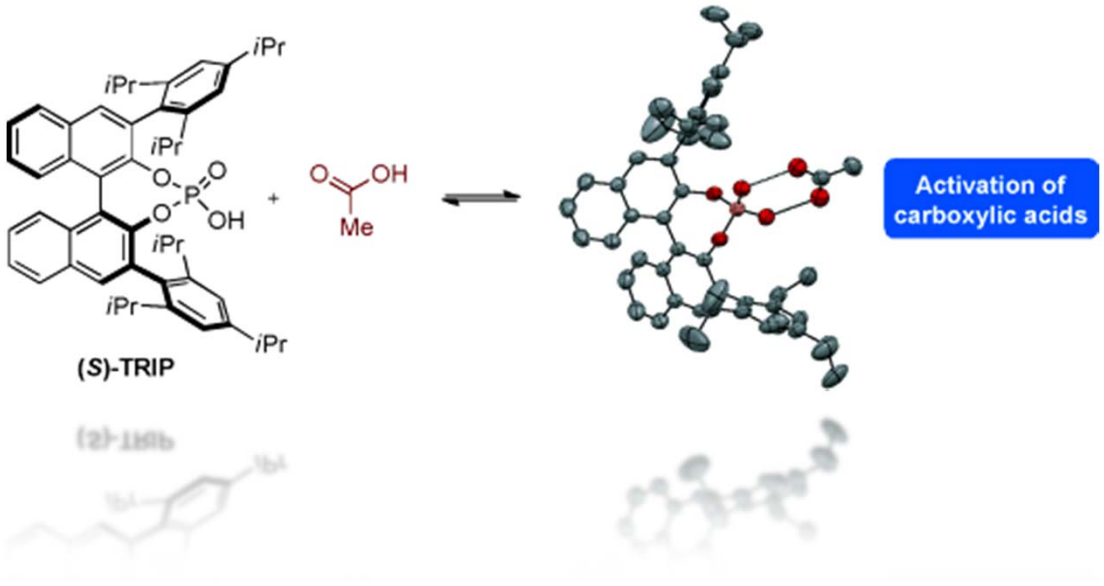
Activation of Carboxylic Acids in Asymmetric Organocatalysis



Mattia Riccardo Monaco, Beln Poladura, Miriam Diaz de Los Bernardos, Markus Leutzsch, Richard Goddard, and Benjamin List*

Angew. Chem. Int. Ed. **2014**, *53*, 7063 –7067

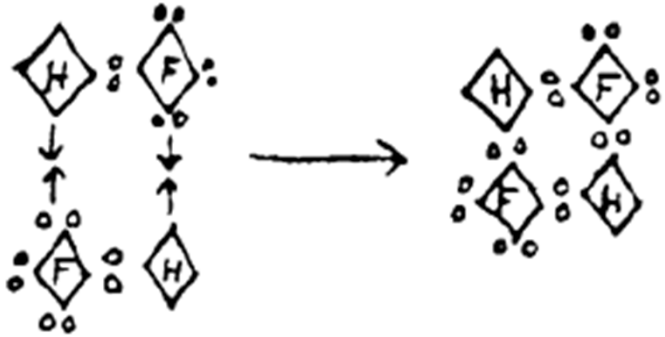
1. Hydrogen Bonding

G. N. Lewis

It seems to me that the most important addition to my theory fo valence lies in the suggestion of what has become known as the **hydrogen bond**

1920

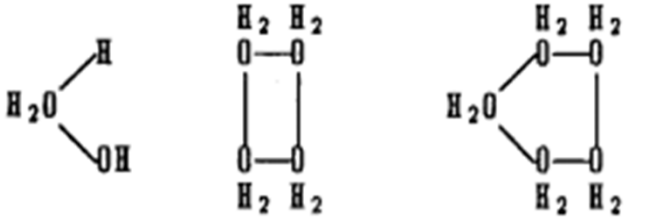
Wendell Latimer, Worth Rodebush and **Maurice Huggins**



The hydrogen nucleus held between two octets constitutes a weak ‘bond’

1923

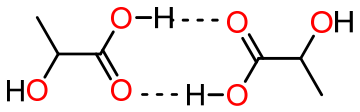
Henry Edward Armstrong



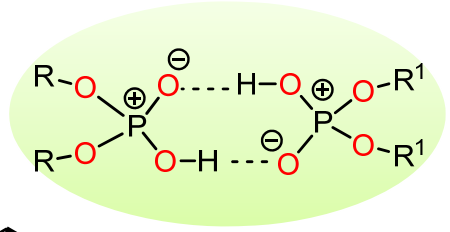
hydranol tetrahydrone pentahydrone

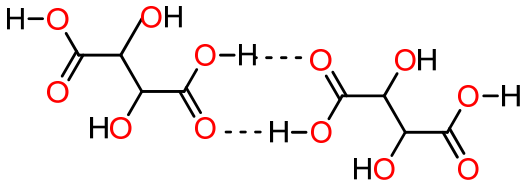
The association is assumed to be by way of O-O bond

1. Hydrogen Bonding

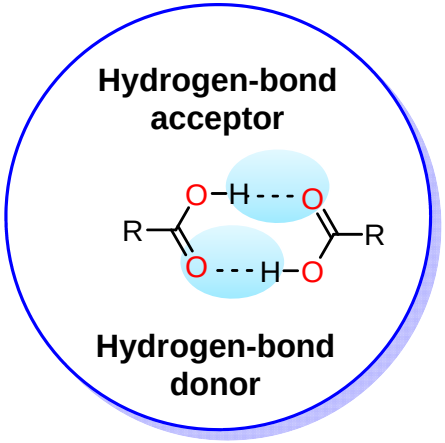


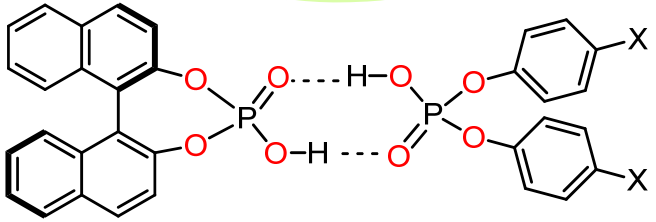
lactic acid





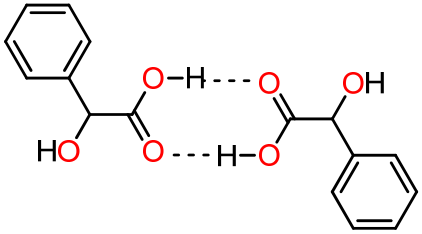
tartaric acid



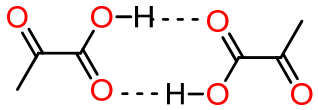


X = H, CH_3, Cl, NO_2

phosphoric acid diesters



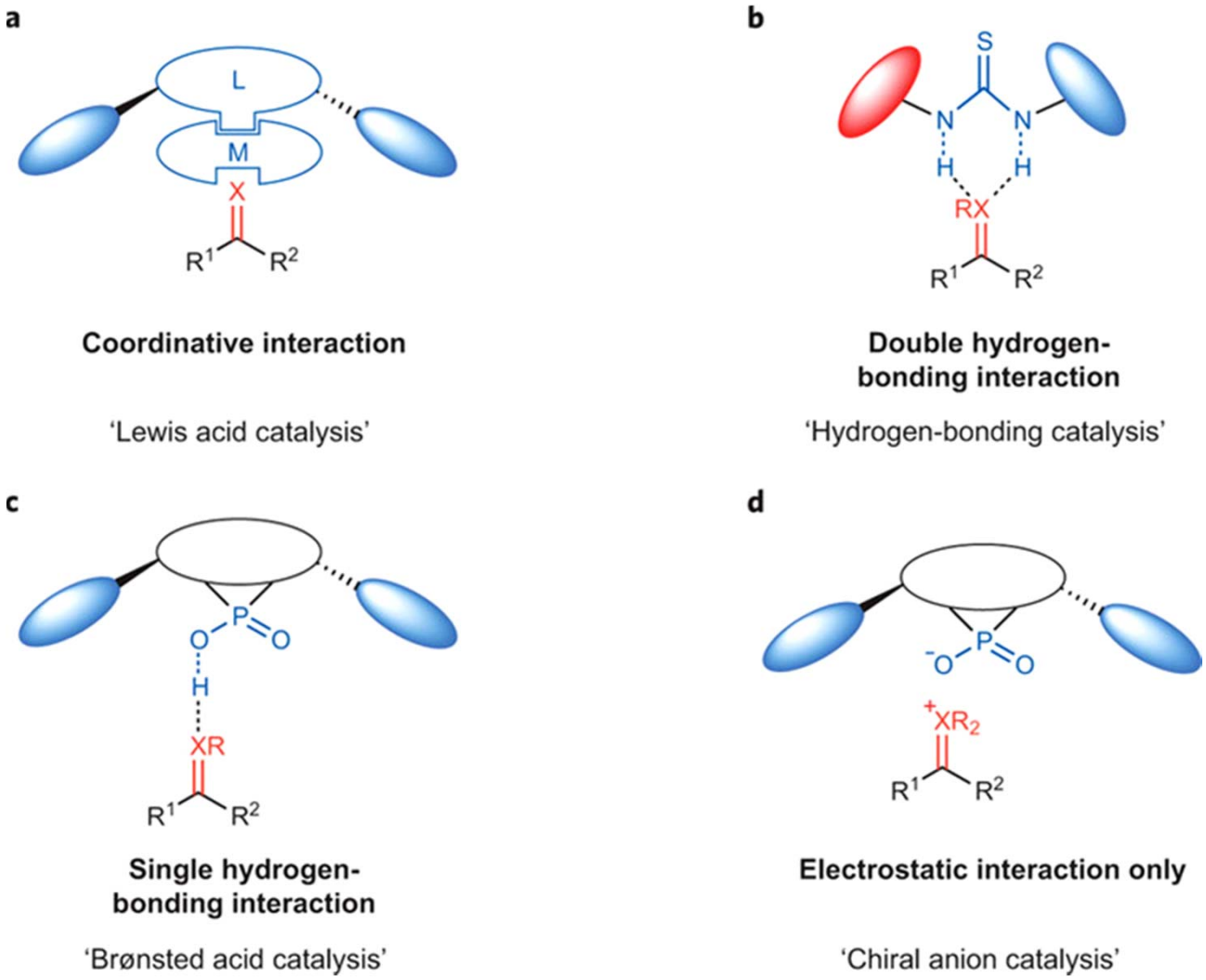
mandelic acid



pyruvic acid

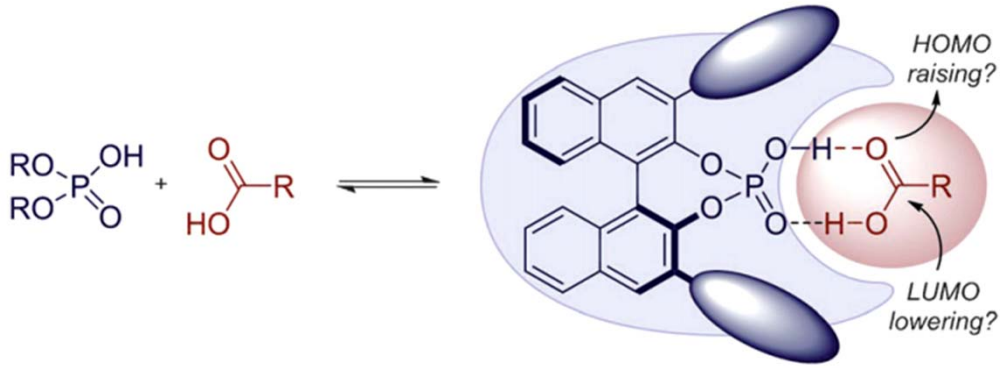
[1] DeFord, J.; Chu, F.; Anslyn, E. V. *Tetrahedron Lett*. **1996**, *37*, 1925–1928

1. Asymmetric activation modes of a carbonyl group or imine



[2] Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nature Chemistry* **2012**, *4*, 603 –614

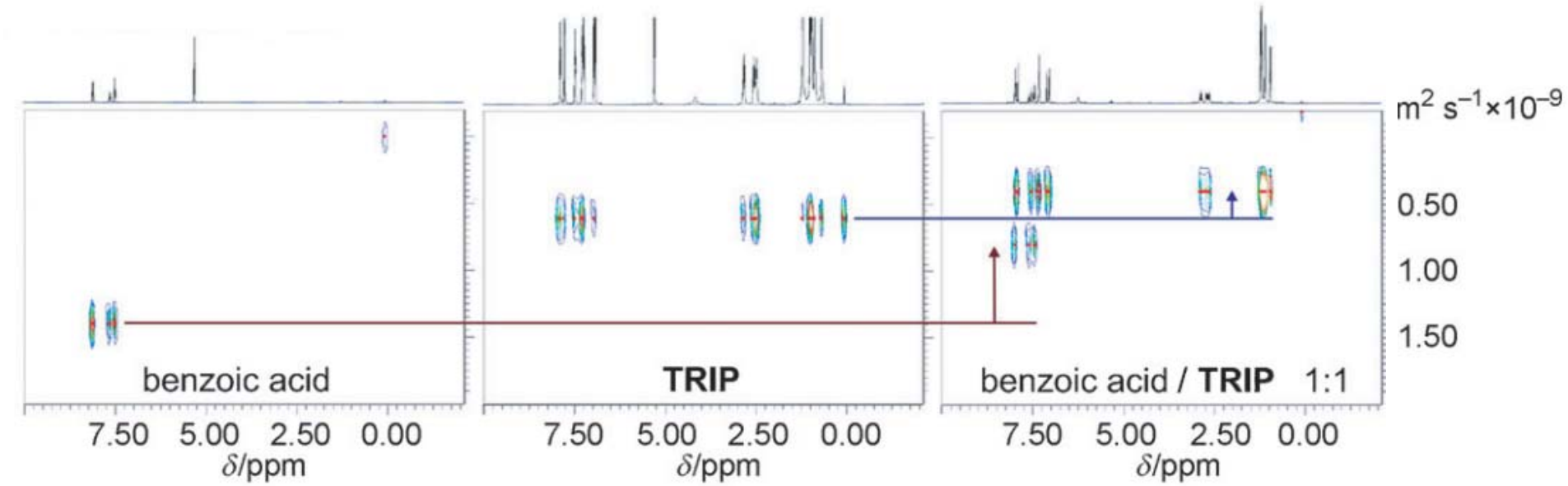
2. Activation of carboxylic acids by heterodimerization with phosphoric acids



partial deprotonation of the RCO_2H

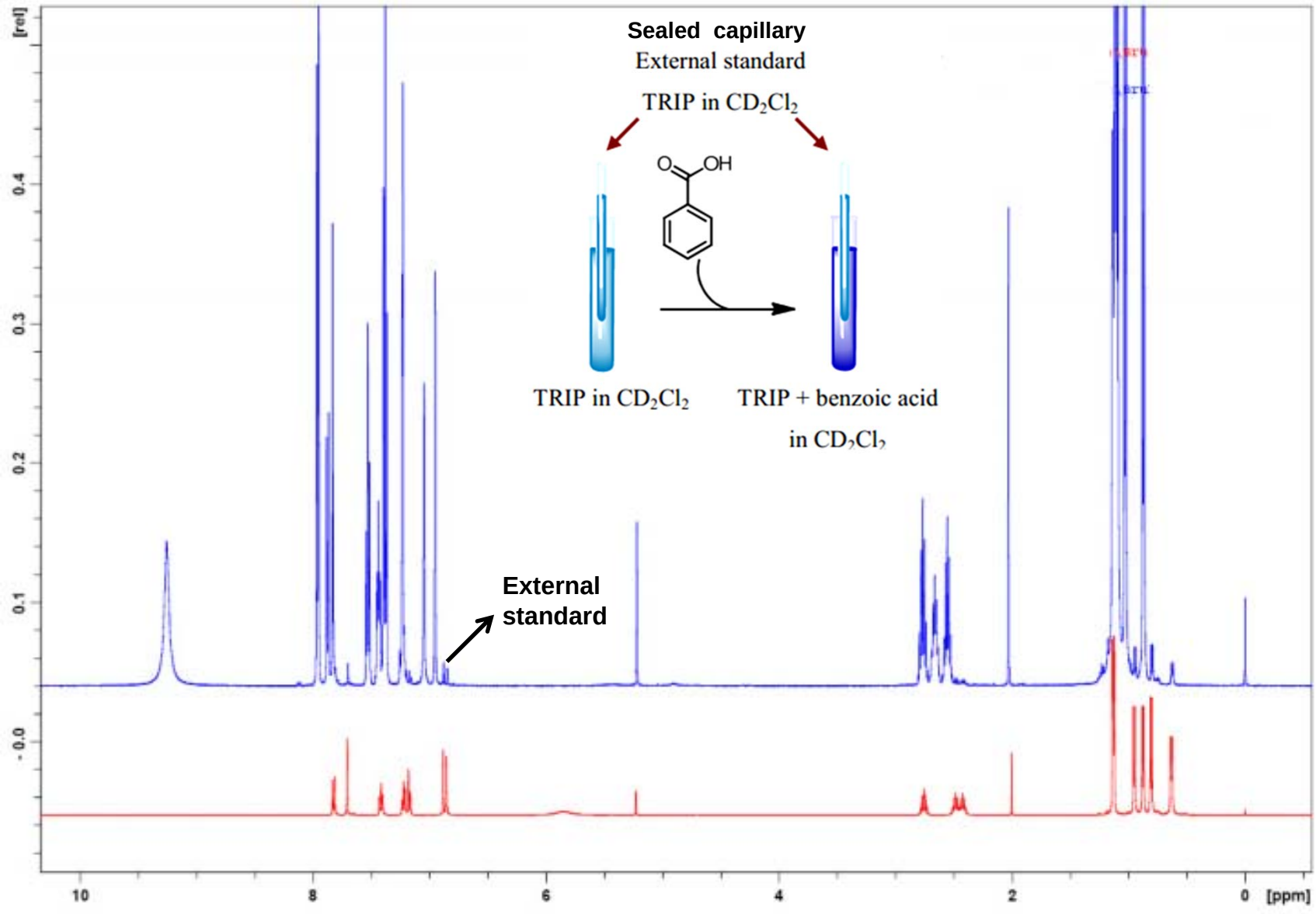
protonation of the RCO_2H

a) 2D-DOSY analysis



2. Activation of carboxylic acids by heterodimerization with phosphoric acids

b) 1D-NMR analysis



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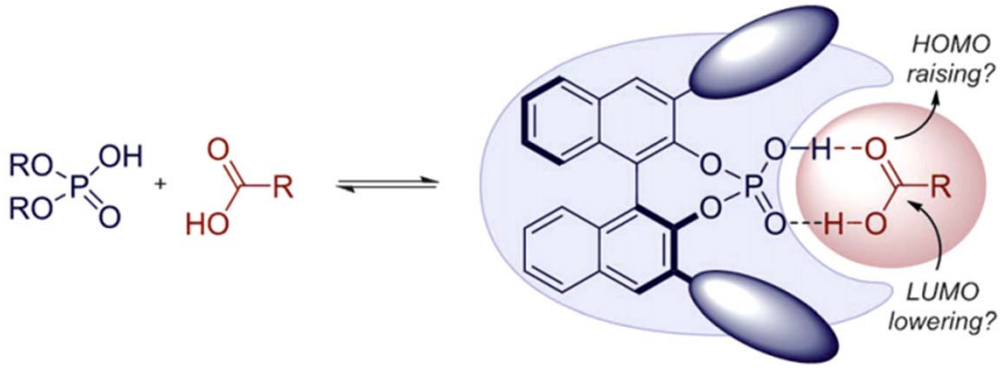
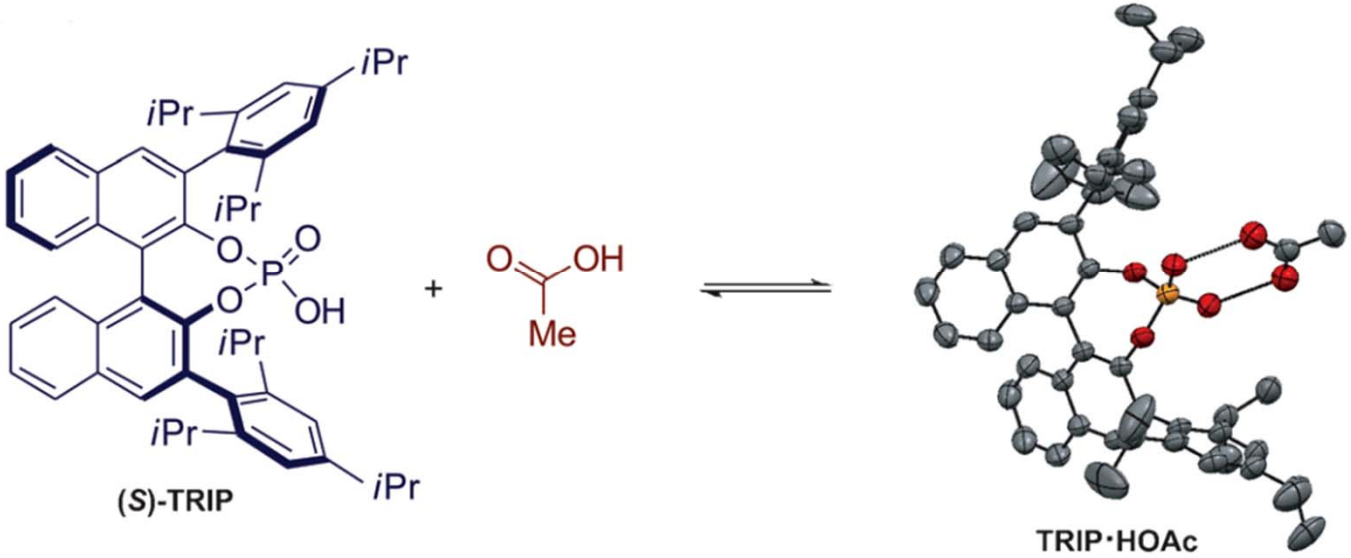
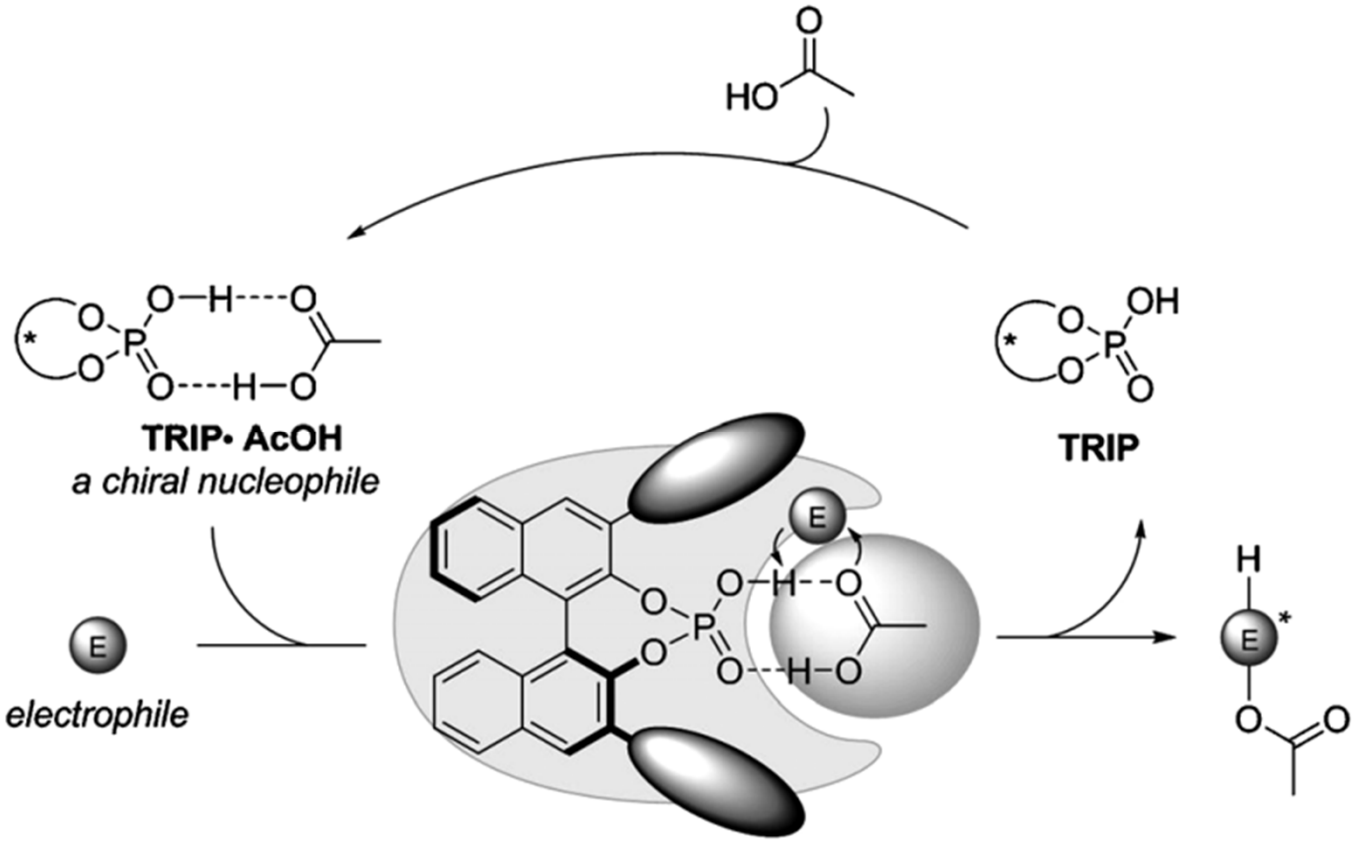


c) Crystallization of TRIP.HOAc



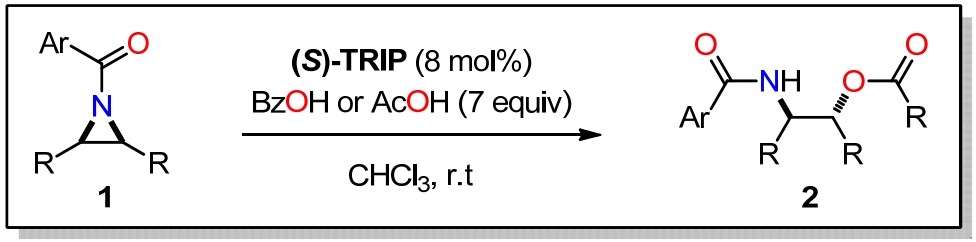
2. Activation of carboxylic acids by heterodimerization with phosphoric acids

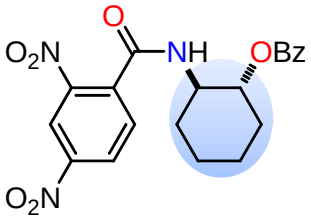


Synergistic Activation

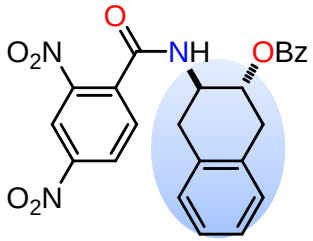
Nucleophilicity of AcOH and acidity of TRIP
INCREASE ¡¡¡¡¡¡

3. Desymmetrization of *meso*-aziridines

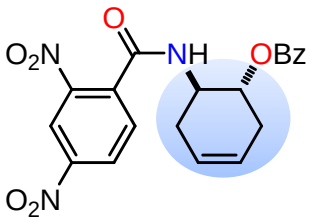




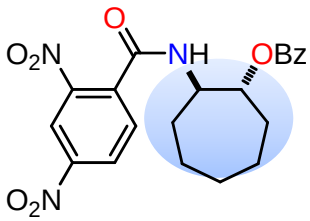
2a
98%, e.r. > 99.5 : 0.5



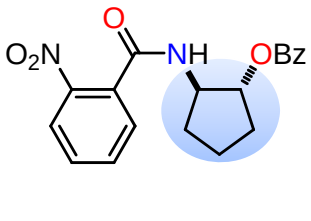
2b
99%, e.r. > 98.5 : 1.5



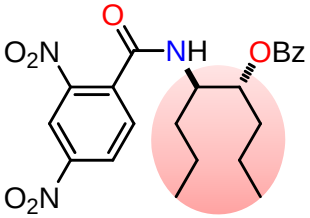
2c
83%, e.r. > 99 : 1



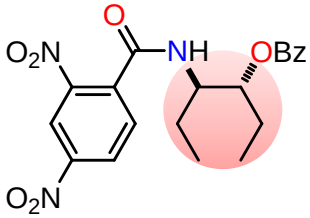
2d
98%, e.r. > 96.5 : 3.5



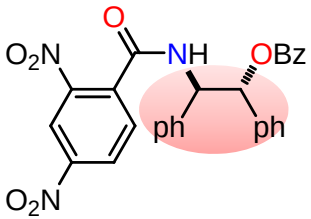
2e
96%, e.r. > 98 : 2



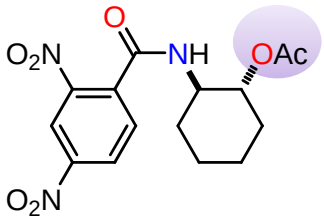
2f
94%, e.r. > 94 : 6



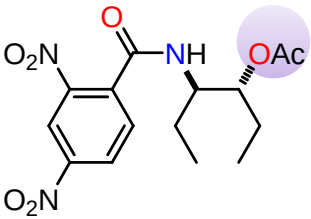
2g
99%, e.r. > 93.5 : 6.5



2h
70%, e.r. > 96 : 4



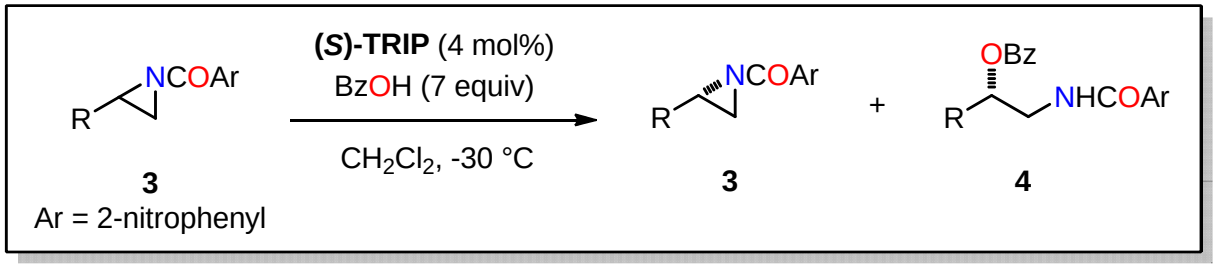
2i
94%, e.r. > 97.5 : 2.5

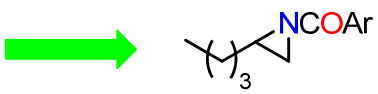
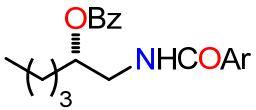
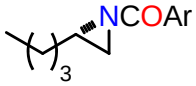
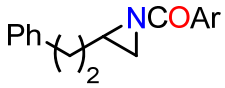
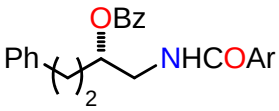
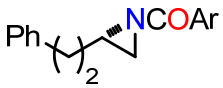
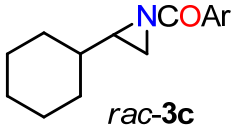
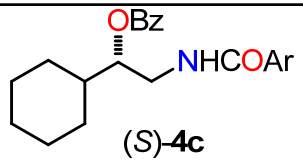
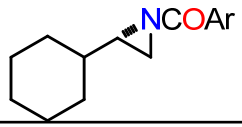


2j
88%, e.r. > 92.5 : 7.5

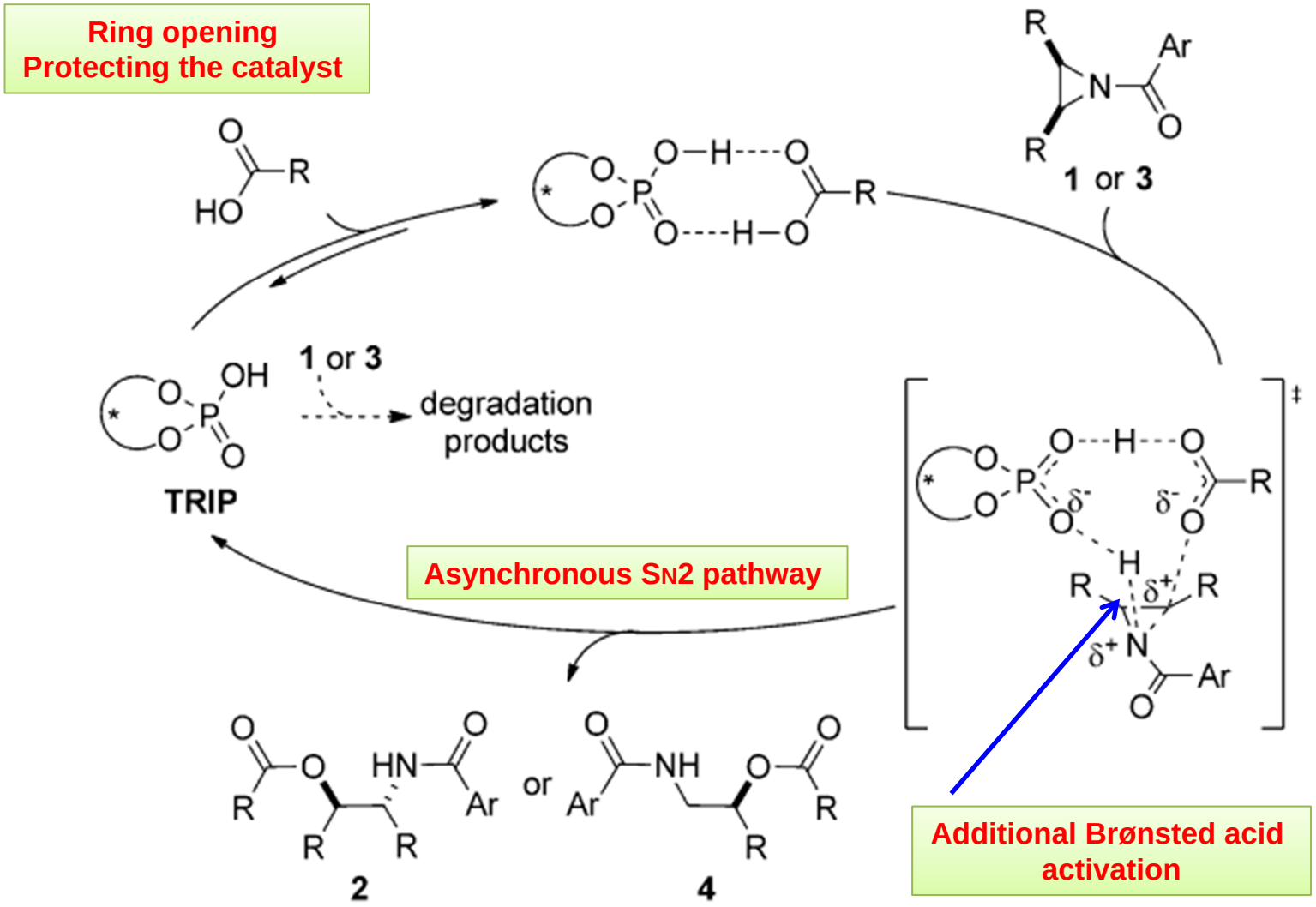
Reactions were performed on a 0.2 mmol scale. The loading of AcOH was increased to 10 equivalents in the reactions to products **2i**,**j**.

4. Kinetic resolution of racemic terminal aziridines



Entry	Aziridine	Product	Yield [%]	e.r.
1	 *rac*-**3a**	 (*S*)-**4a**	49	94 : 6
			46	95.5 : 4.5
2	 *rac*-**3b**	 (*S*)-**4b**	51	92.5 : 7.5
			44	98.5 : 1.5
3	 *rac*-**3c**	 (*S*)-**4c**	28	96 : 4
			58	72 : 28

5. Proposed catalytic cycle for the TRIP·RCO_2H-mediated ring opening of aziridines



6. Conclusions

▪ **NEW CONCEPT FOR THE ACTIVATION OF CARBOXYLIC ACIDS** by heterodimerization with chiral phosphoric acids.