Combinatorial Approaches in Homogeneous Catalysis Development: Case Studies

Min Xie

June 17, 2008

Combinatorial Mathematics

3 building blocks

$A_{1,2,..,10}$, $B_{1, 2,..,10}$, $C_{1, 2,..,10}$

2-step synthesis

A + B then + C

→ # of different compounds A-B-C ?

A small number of building blocks can generate a large number of different compounds.

Combinatorial Chemistry

- a branch of applied chemistry concerned with the rapid **synthesis** and **screening** of large numbers of different but related chemical compounds generated from a mixture of known building blocks in order to recover new substances optimally suited for a specific function

For a historical review:

- Handbook of Combinatorial Chemistry. Drugs, Catalysts, Materials.
  Edited by K. C. Nicolaou, R. Hanko, and W. Hartwig
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Unique Aspects of Combinatorial Approach in Homogeneous Catalytic System

Neccessity:

- Development of a new catalytic system.
- Optimization of a known catalyzed reaction for specific substrates.

Aspects:

Ligand library

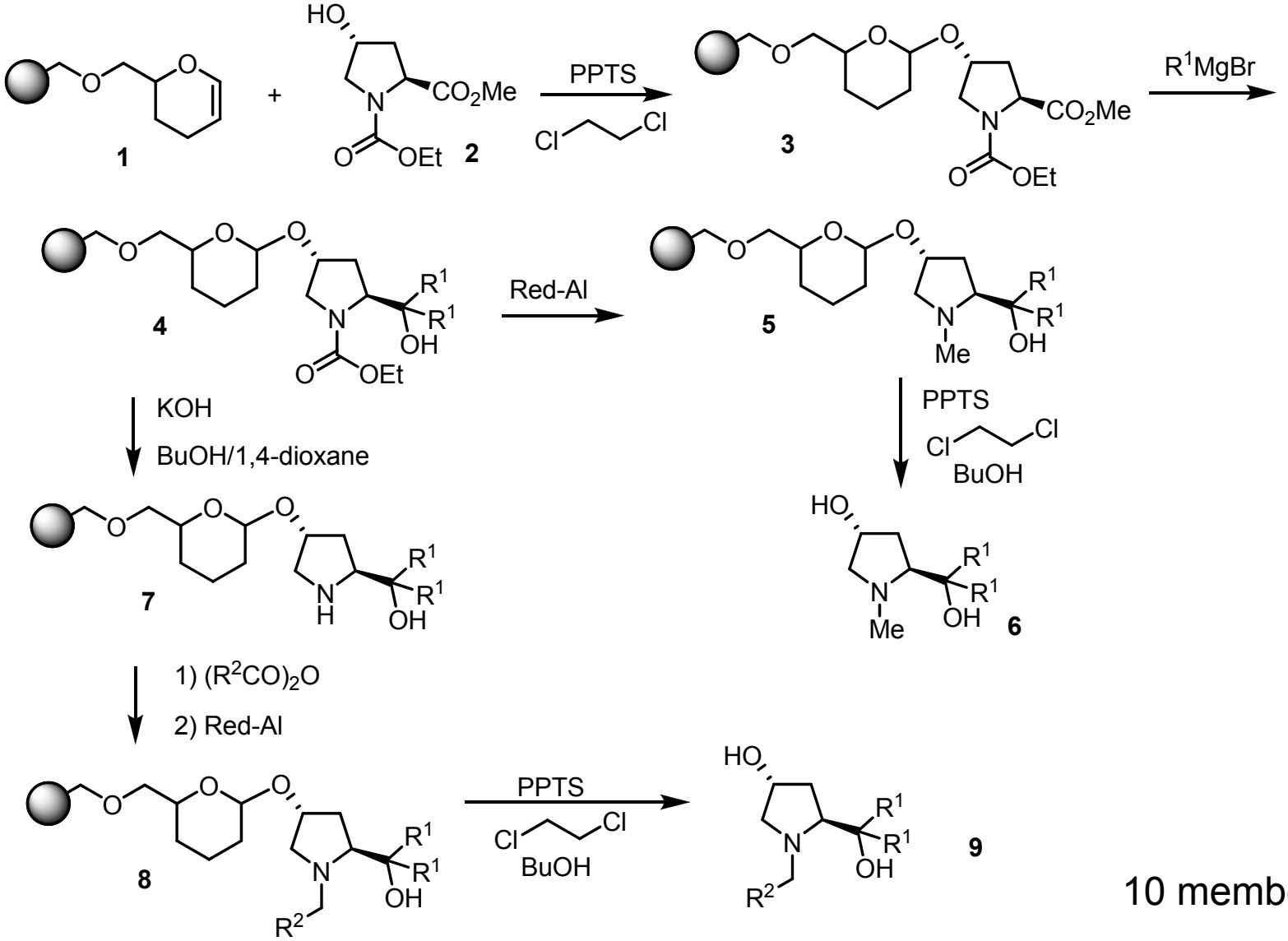
- Rapid, modular, parallel synthesis

Reaction conditions

Reactivity, Selectivity

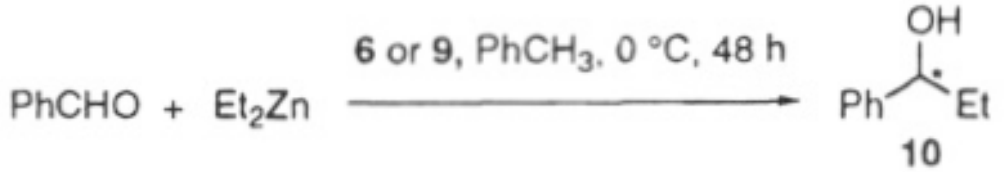
- High-throughput screening

Pyrrolidinemethanol Ligands via Solid State Synthesis



10 members

Ellman, JOC, 1995, 60, 7712



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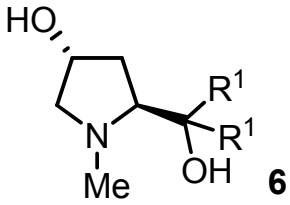

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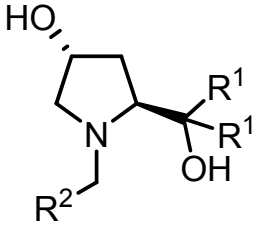


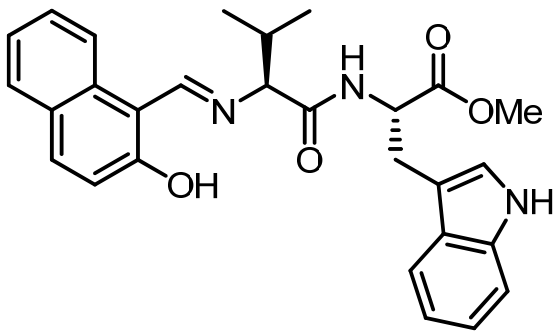
9

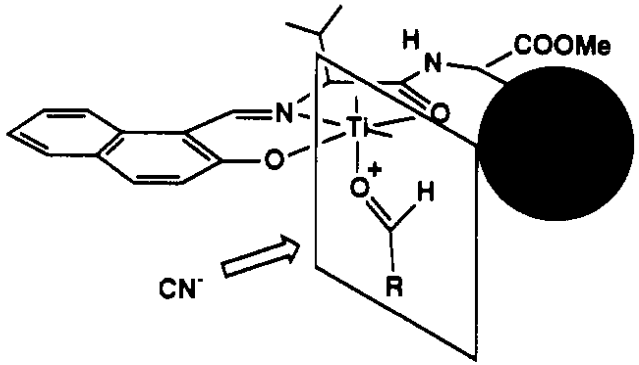
entry	R^1	R^2	source 1 (% ee)[a]	source 2 (% ee)[b]
6a	phenyl		93 (*S*)	94 (*S*)
9a	phenyl	methyl	83 (*S*)	84 (*S*)
9b	phenyl	phenyl	89 (*S*)	85 (*S*)
9c	ethyl	methyl	0	0
9d	ethyl	phenyl	30 (*R*)	45 (*R*)

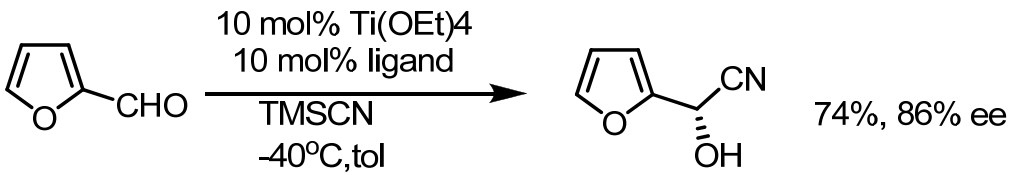
Source1: Synthesized on support and isolated by **extraction** after cleavage.
Source 2: Synthesized in solution and purified by **chromatography** and **recrystallization.**

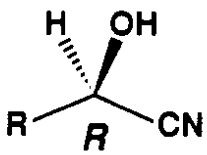
Combinatorial strategies may be useful for the development of asymmetric catalysts.

Peptide-derived Ligands







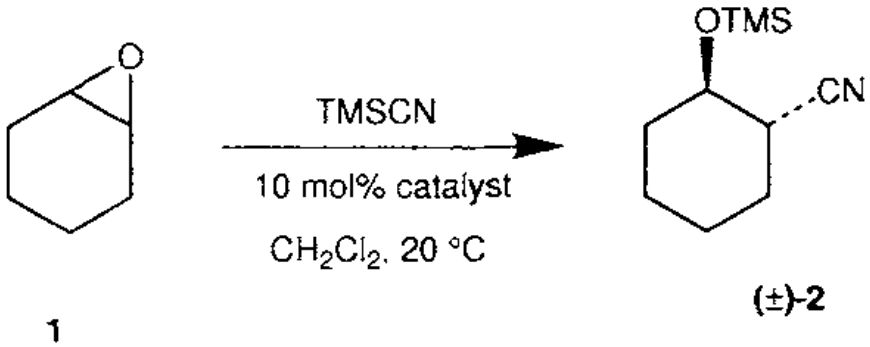


Potential opportunities for the establishment of a combinatorial catalyst library:

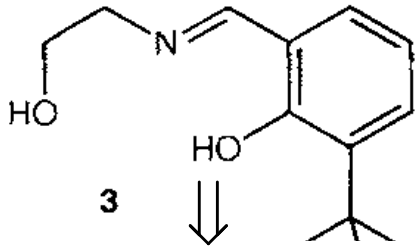
- Ease of Schiff base and petptide synthesis
- Readily available building blocks

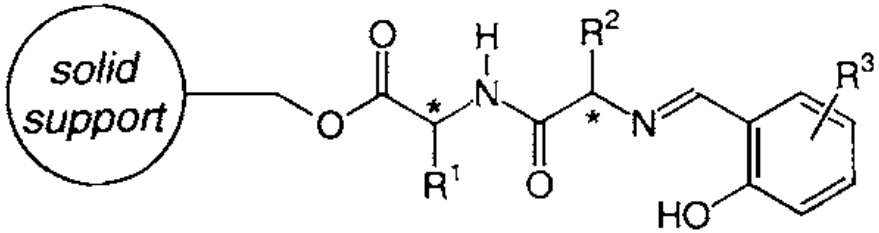
Inoue, JACS,1992,114,7969

Potential Catalytic System for Cyanide Opening of Epoxide



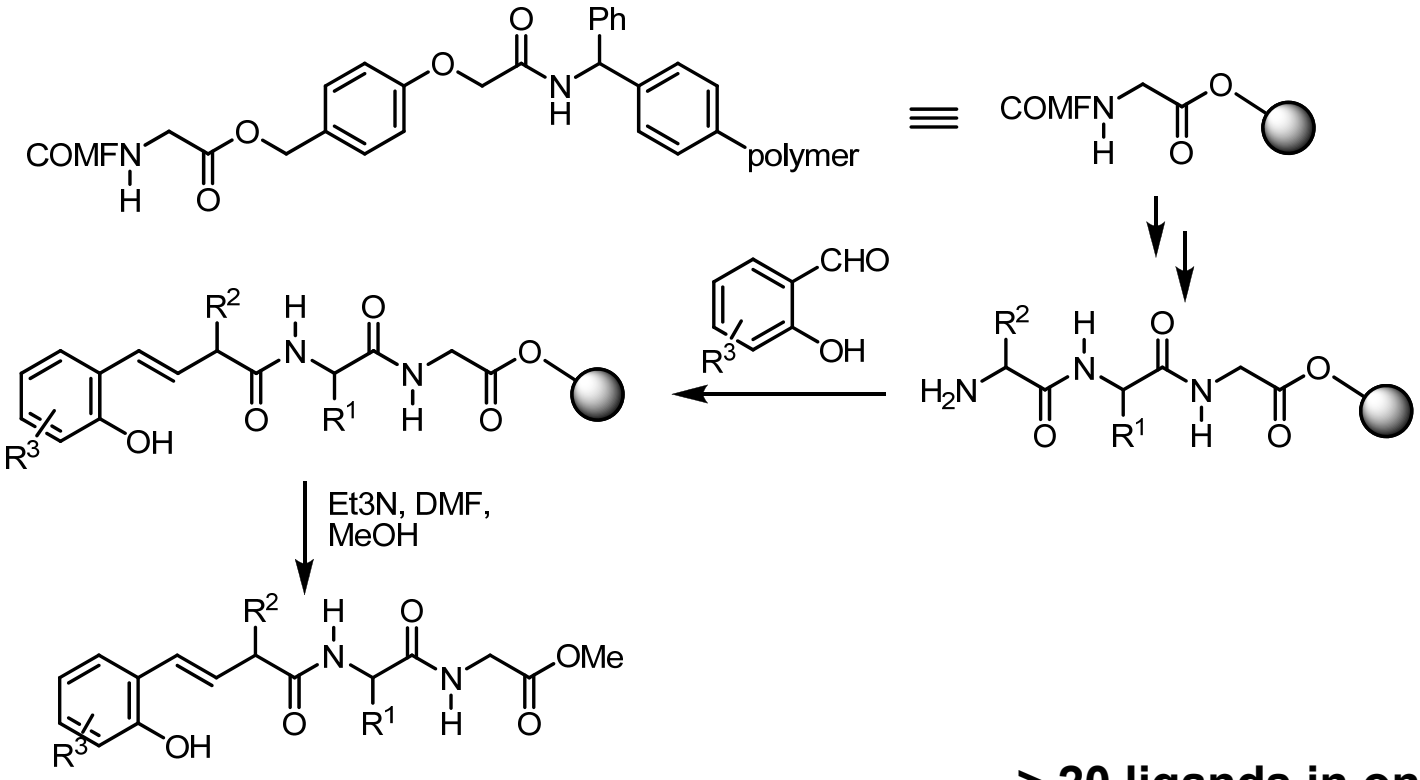
catalyst: $Ti(O\mathit{i}Pr)_4$	12%
catalyst: $Ti(O\mathit{i}Pr)_4$ + **3**	80%





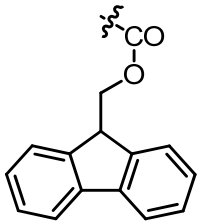
Hoveyda, ACIEE,1996, 35,1668

Peptidic Schiff Base Ligands



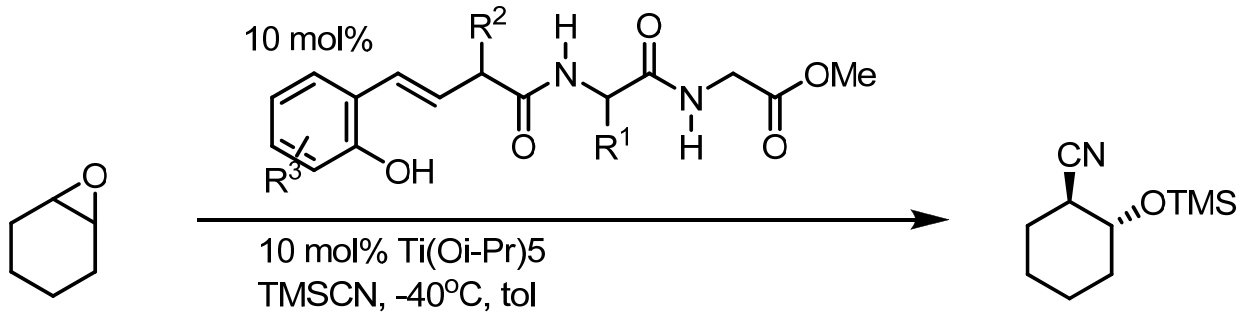
> 20 ligands in one day

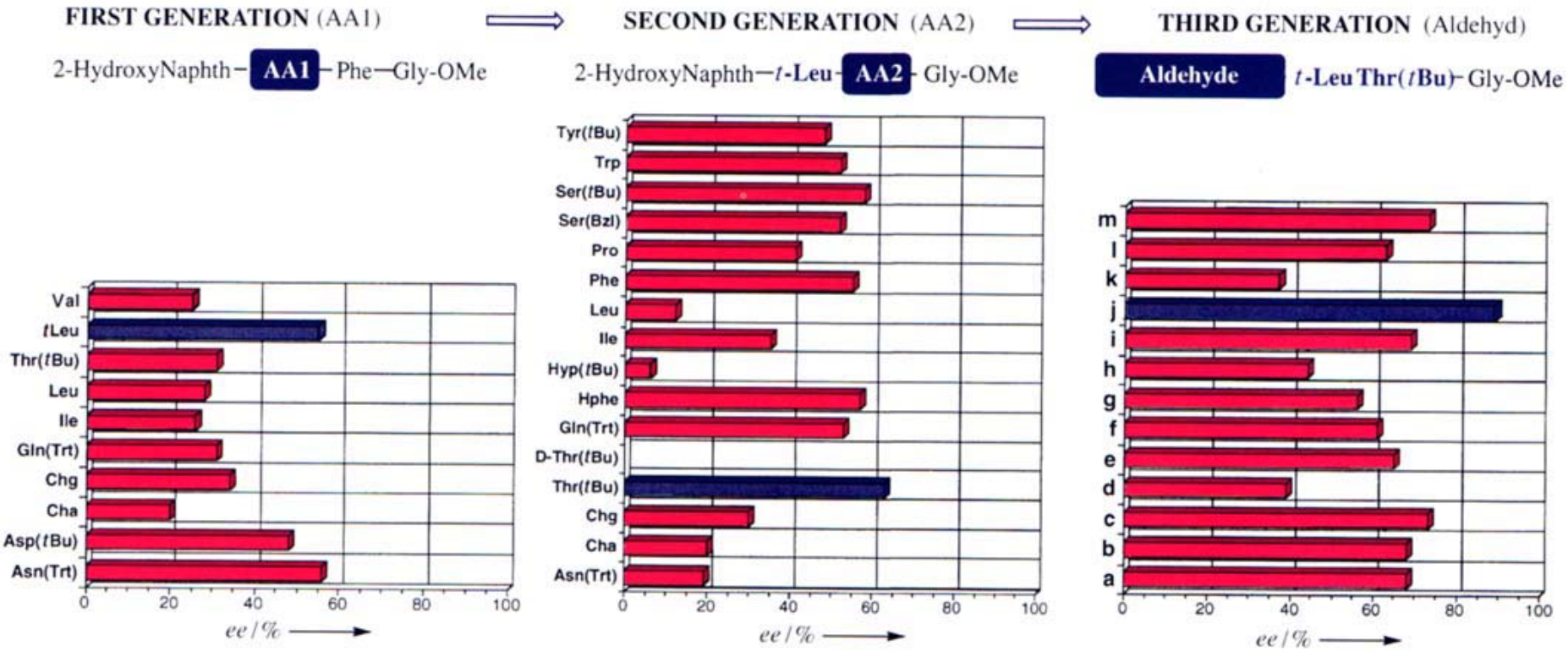
FMOC = **9-fluorenylmethyloxycarbonyl**



Hoveyda, ACIEE,1996, 35,1668

Optimization of Ligand via Position Screening

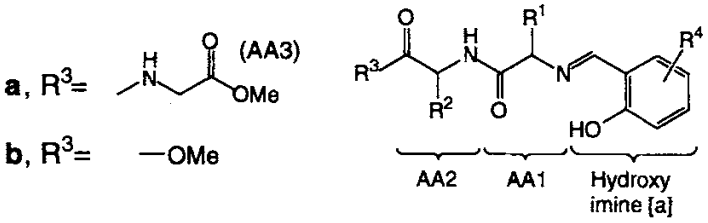




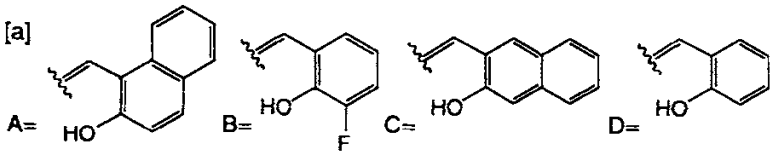
tert-Leucine O-tert-butyl-threonine 3-fluorosalicylaldehyde

Hoveyda, ACIEE,1996, 35,1668

Optimized Ligands for Specific Substrates



Ligand	R^2 (AA2)	R^1 (AA1)	Hydroxy imine
1	Ph		A
2	tBuO		A
3	Ph		A
4	tBuO		B
5	tBuO		C
6	tBuO		D
7	N(H)Trt		A



Entry	Substrate	Ligand	Product	*ee* [%][b]	Yield [%][c]	Conversion [%][d]
1	**10**	**2a (2b)**	**11**	83 (63)	72	83
2	**12**	**4a (4b)**	**13**	87 (86)	65	80
3	**8**	**5a (5b)**	**9**	84 (69)	68	79
4	**14**	**6a (6b)**	**15**	78 (58)	69	81

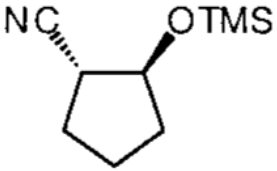
Hoveyda, ACIEE,1997, 36,1704

Unexpected Structure-Selectivity Relation

7

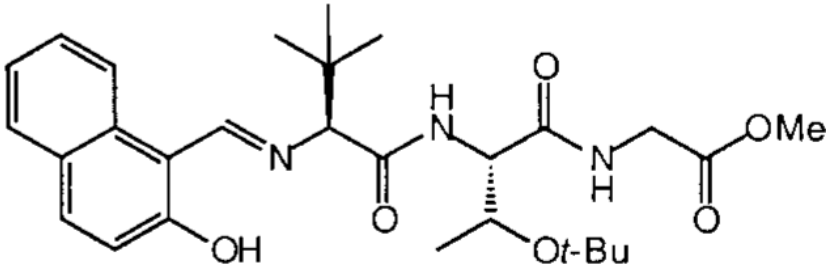
10-20 mol % Ligand,
10-20 mol % $Ti(OiPr)_4$

TMSCN, 4 °C, tol



8

9	83% *ee*
17	-58% *ee*



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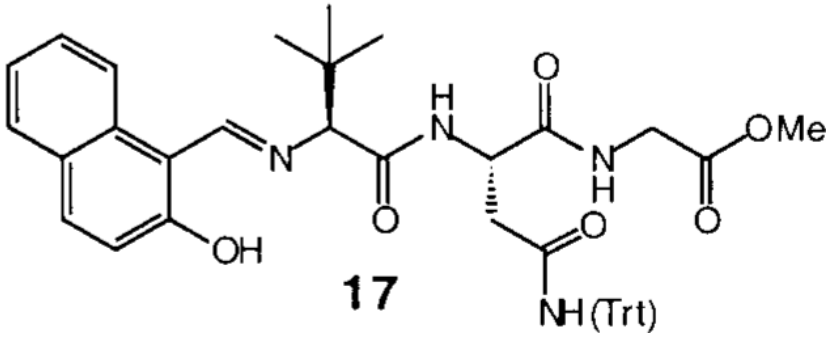

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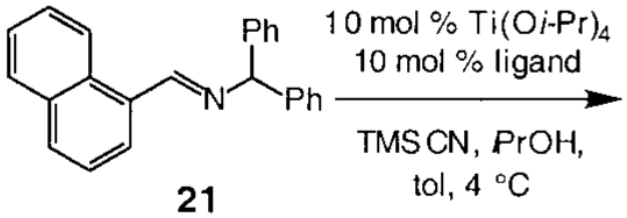
N-β-trityl-L-asparagine

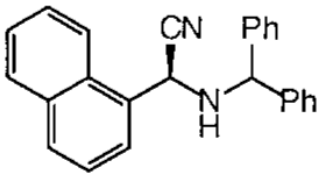
Hoveyda, ACIEE,1997, 36,1704

Peptidic Ligands for Enantioselective Cyanide Addition to Imines



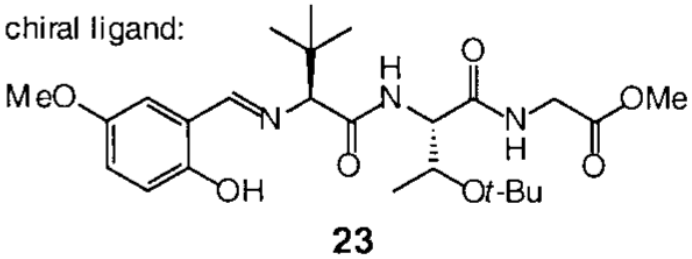
10 mol % Ti(O*i*-Pr)$_4$
10 mol % ligand

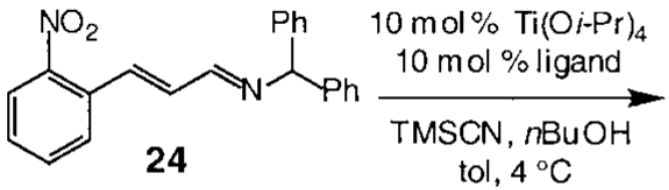
TMSCN, *i*PrOH,
tol, 4 °C



90% *ee*, 87%
(>99% *ee* after purification)

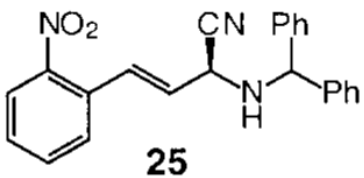
chiral ligand:





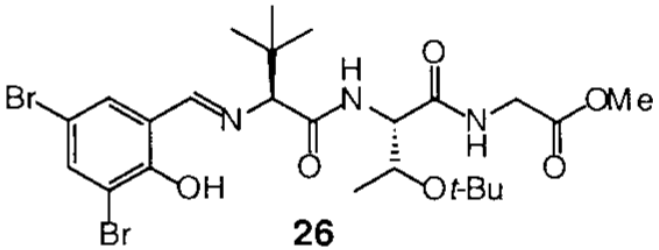
10 mol % Ti(O*i*-Pr)$_4$
10 mol % ligand

TMSCN, *n*BuOH
tol, 4 °C



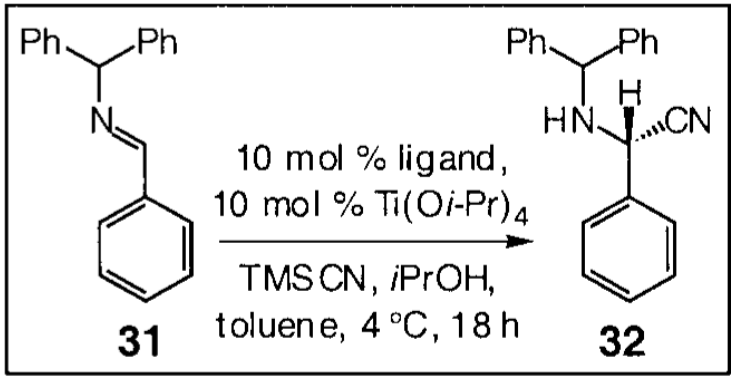
90% *ee*, 87%
(97% *ee* after purification)

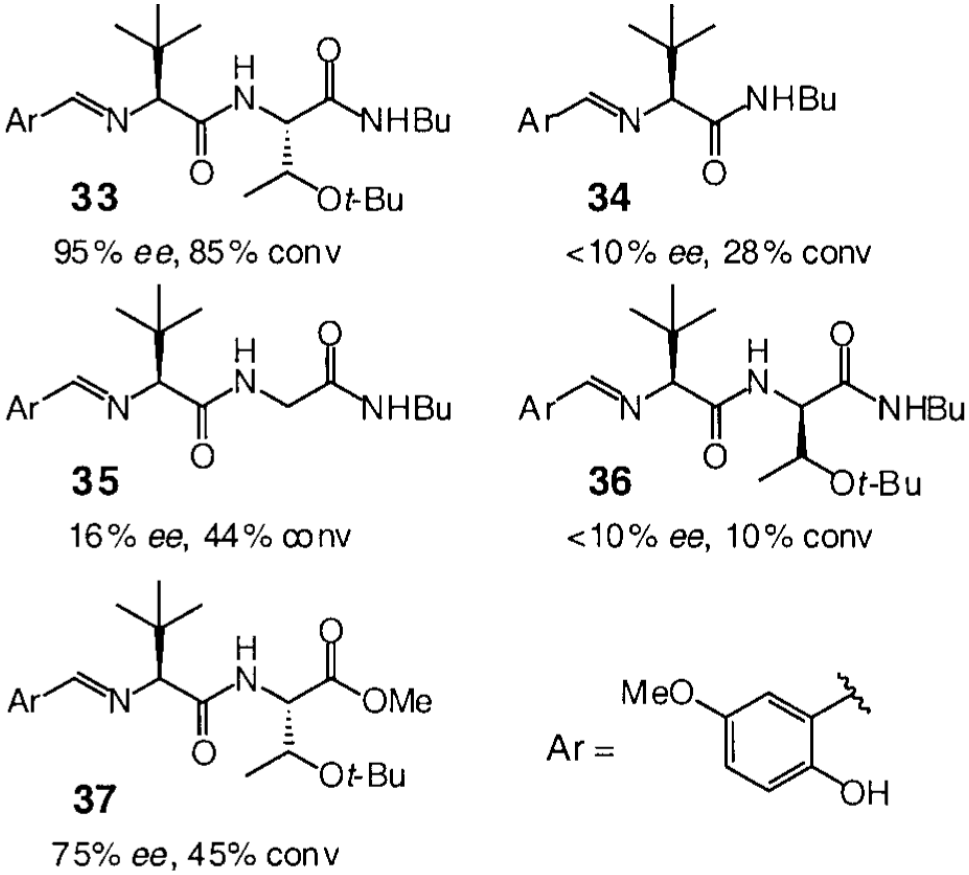
chiral ligand:



Hoveyda, JACS,1999, 121,4284
Hoveyda, JACS,2000, 122,2657

Mechanistic Insights from SAR Studies



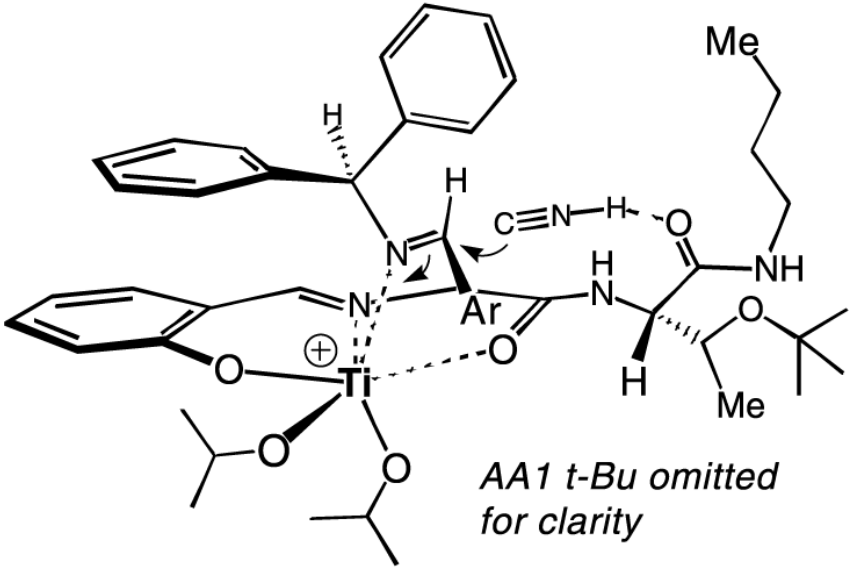


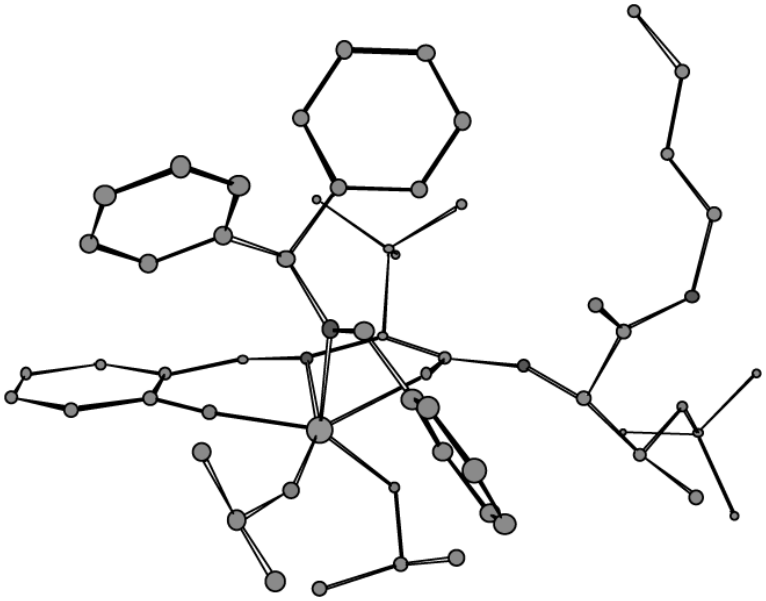
Scheme 33.7. Effect of the AA2 moiety on reactivity and

Terminal amide participates in the stereo-determining step.

Hoveyda, JACS,1999, 121,4284
Hoveyda, JACS,2000, 122,2657

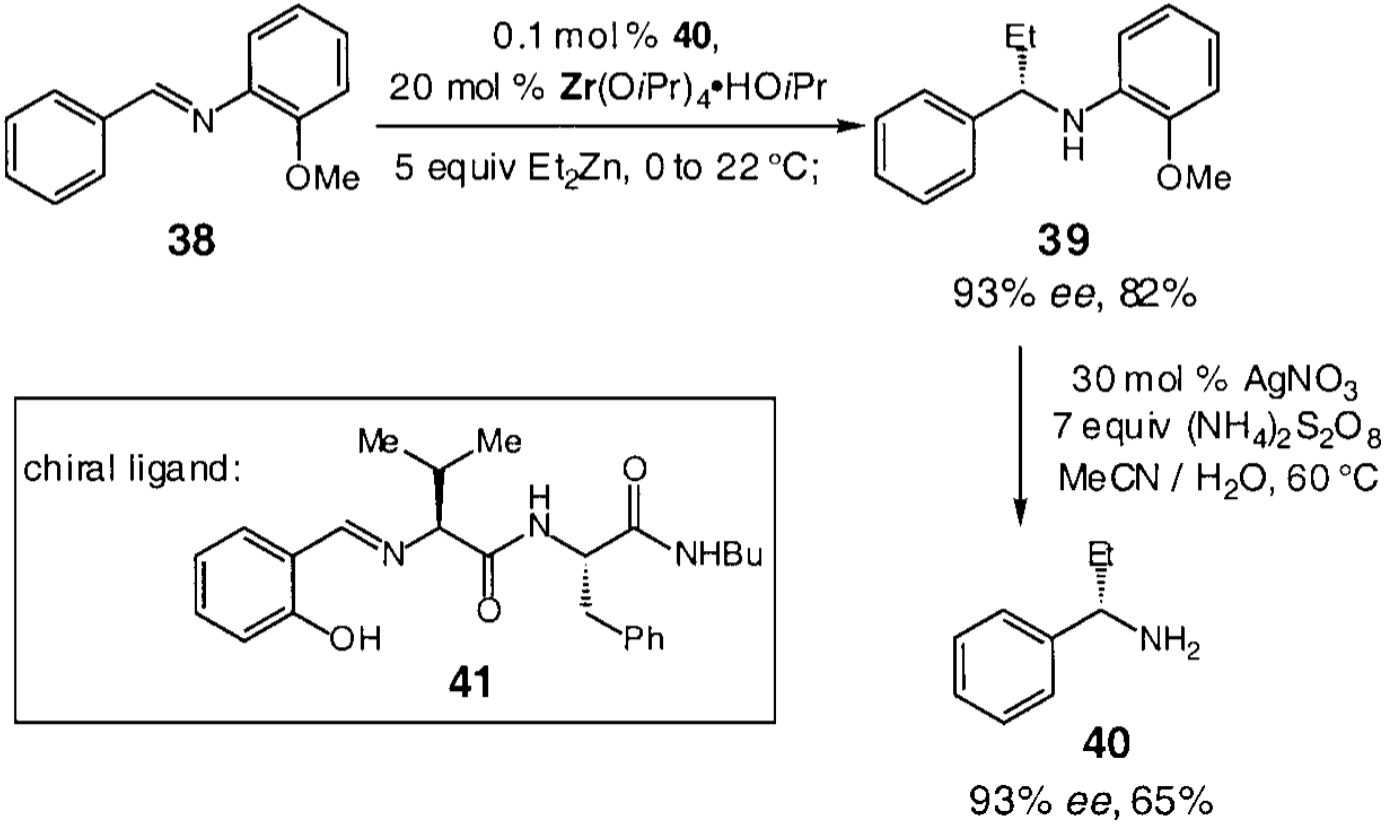
Proposed Model



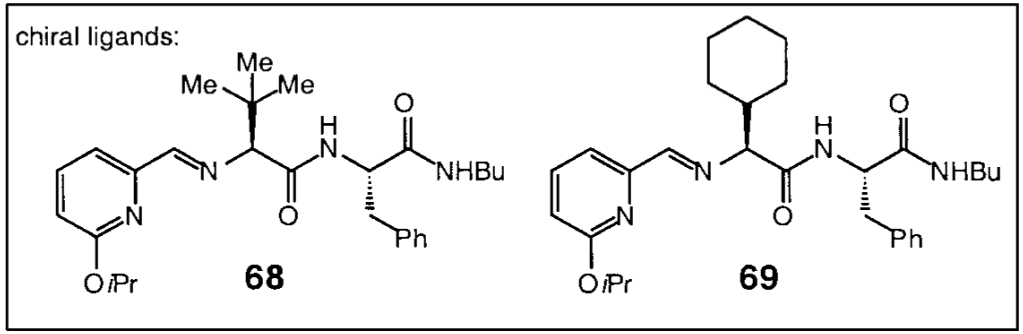


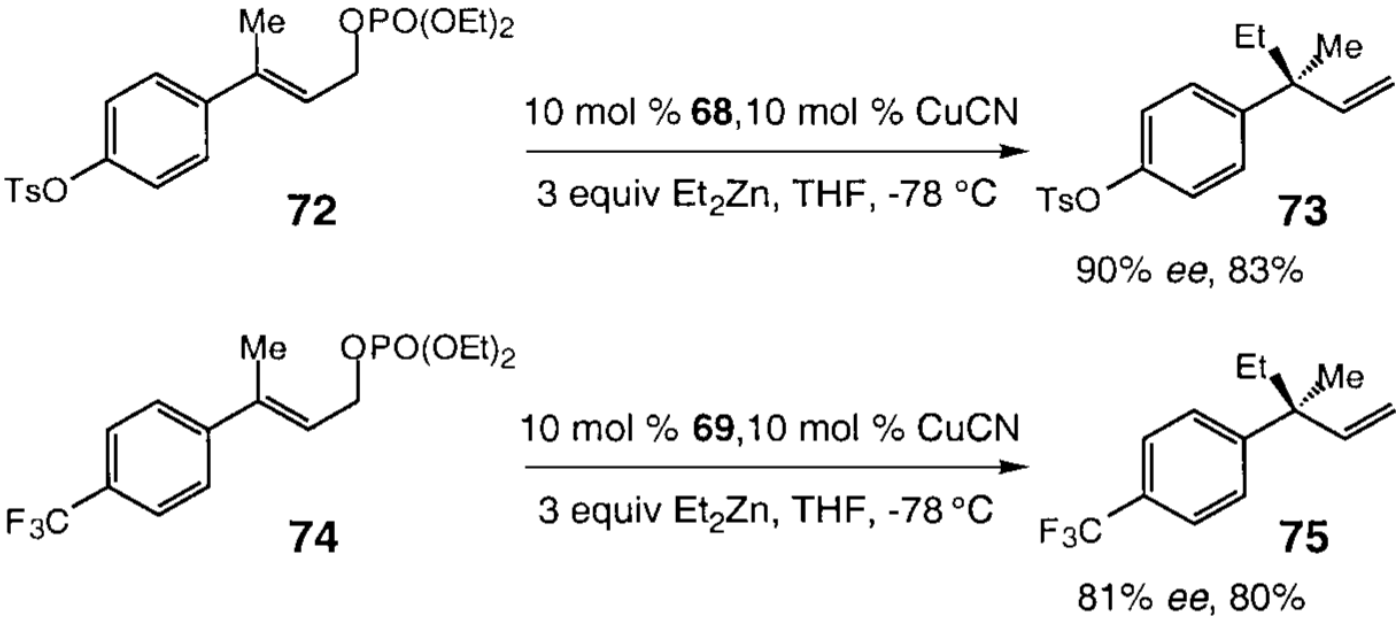
Kelation control may be utilized to deliver other nucleophilic RM.

Zr Catalyzed Enantioselective Addition of Dialkylzinc to Imines

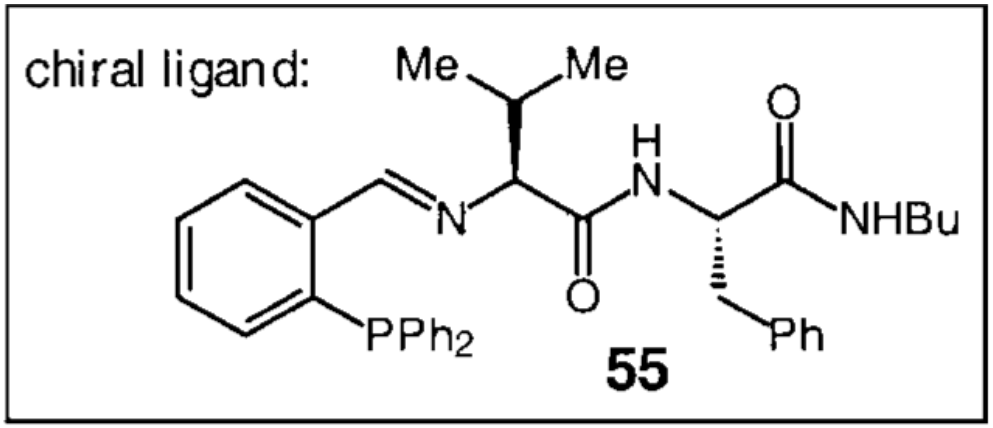


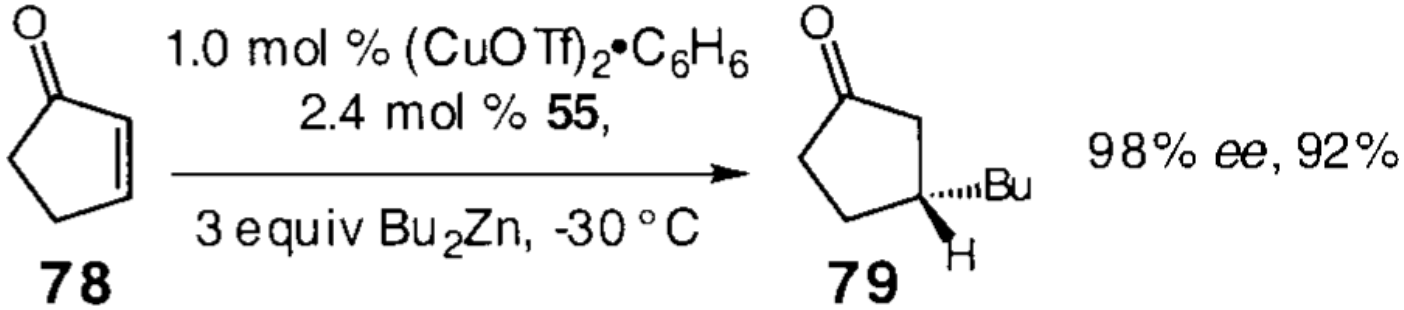
Cu Catalyzed Enantioselective SN2' of Allylic Phosphates



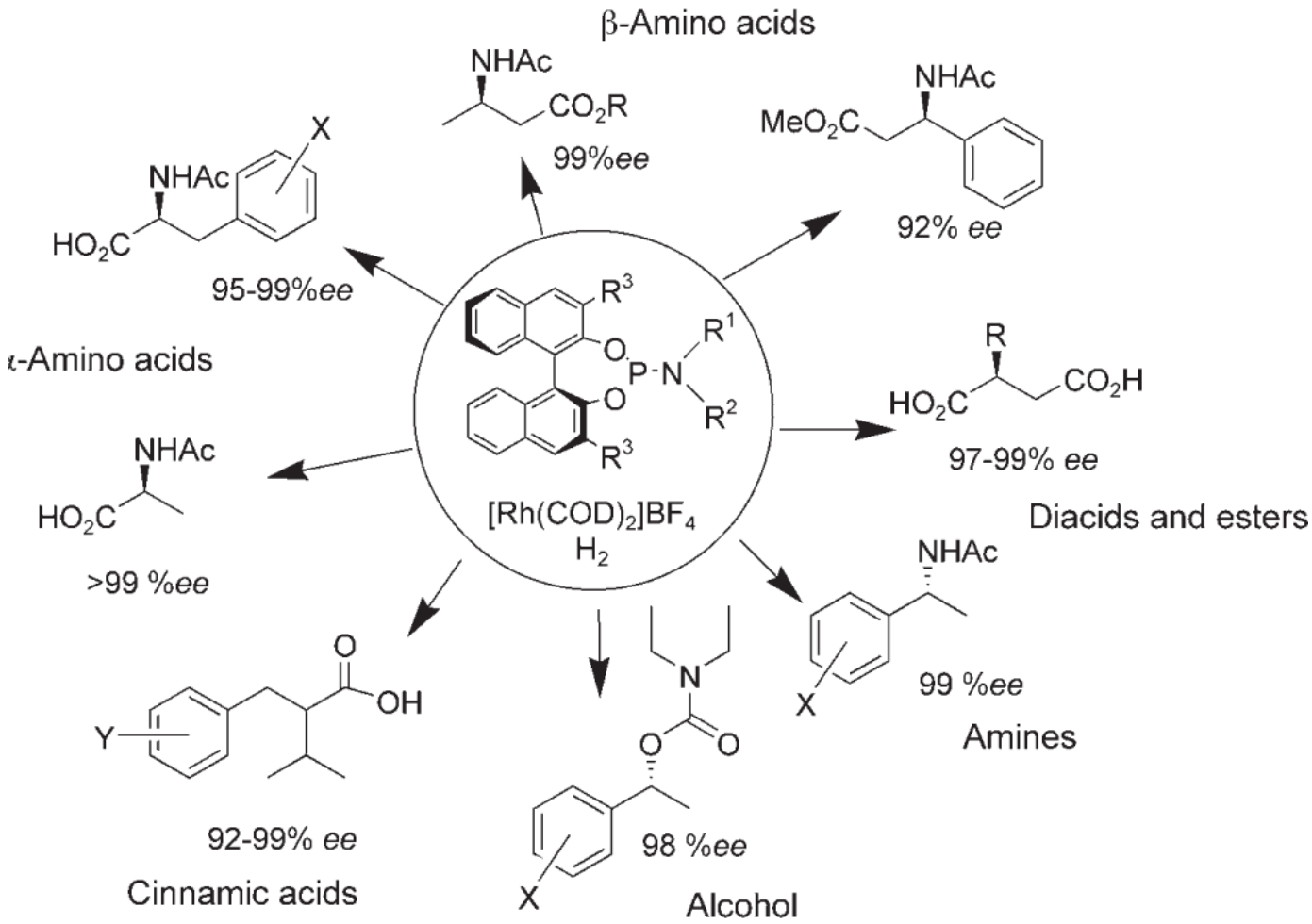


Cu Catalyzed Enantioselective Conjugate Additions



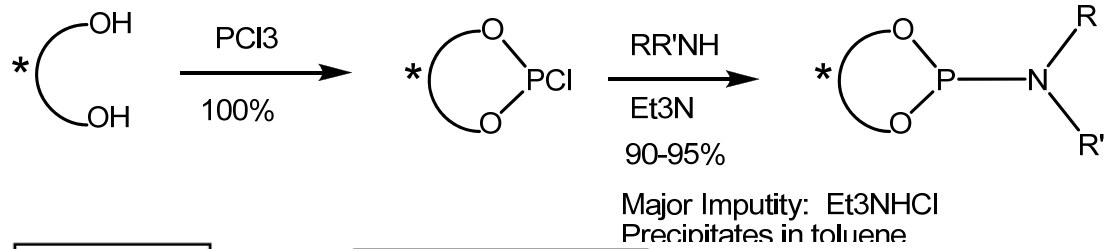


Established MonoPhos Ligands in Catalytic Asymmetric Hydrogenation

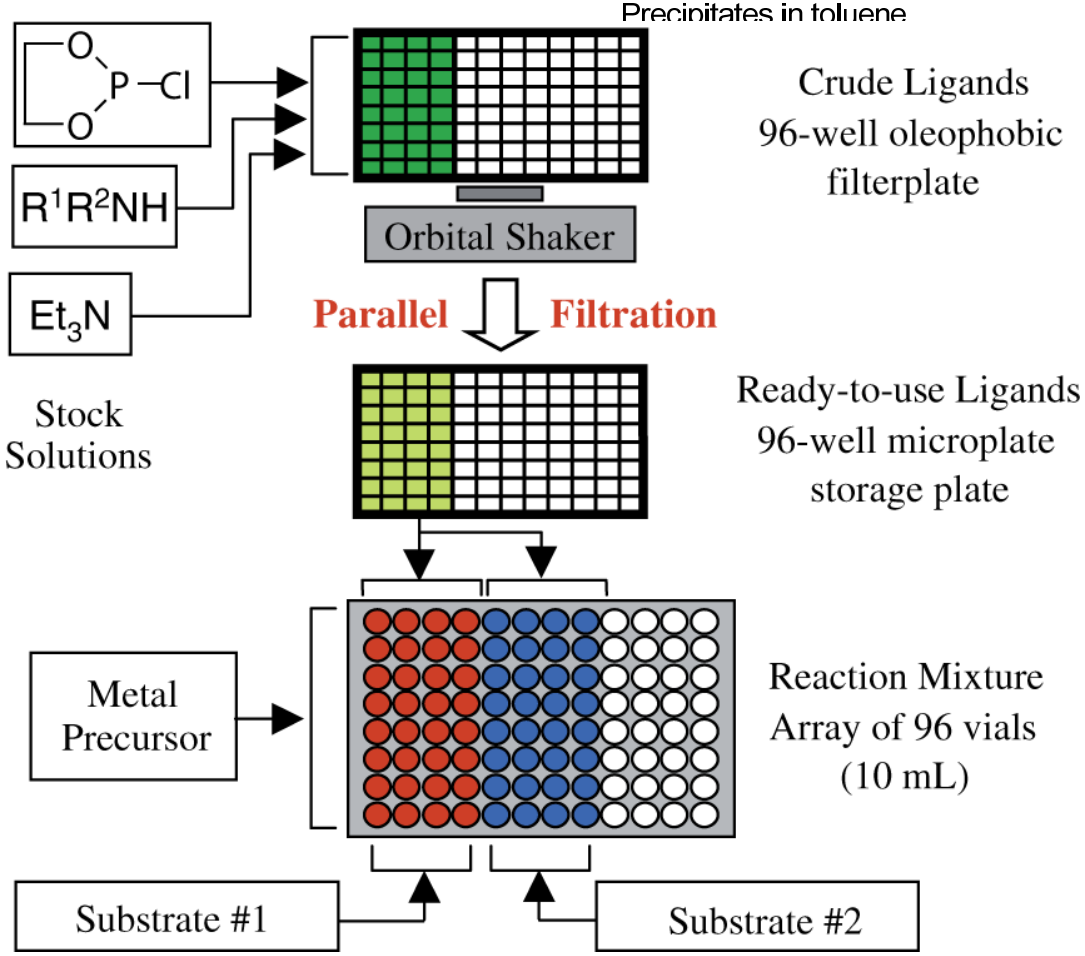


Review:
Berg, Feringa, Minnaard
Handbook of Homogeneous Hydrogenation (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, 2006

Synthesis of Phosphoamidite Ligands



Major Imputity: Et3NHCl
Precipitates in toluene



Vries, Chem. Eur. J. ,2006, 12,4722

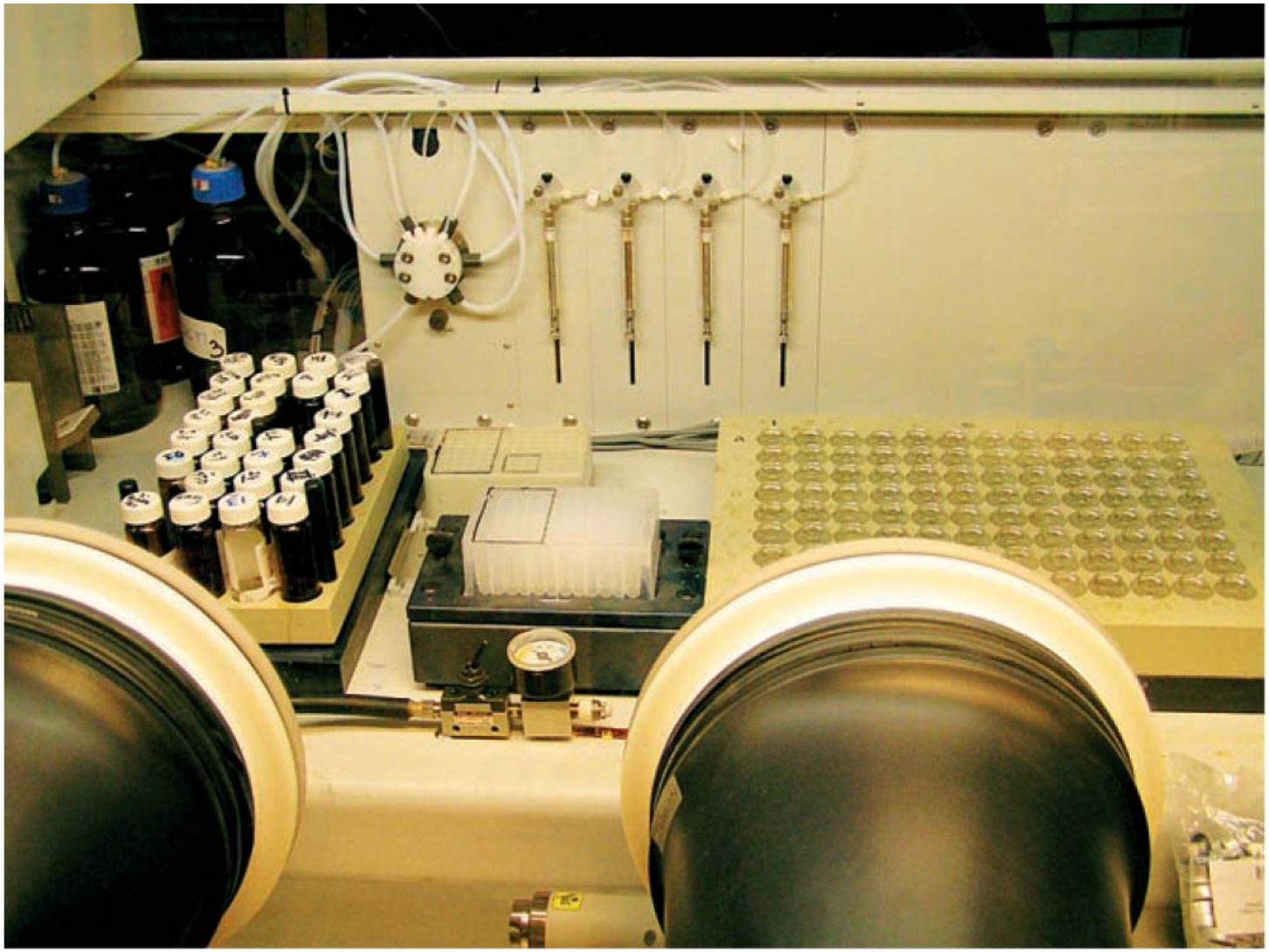


Figure 2. Liquid handling robot in glove box. (Stock solutions on the left. In the middle, the oleophobic filter on a vacuum manifold. On the right the tray with vials in which ligands, metals and substrates are mixed.)

Table 1. Comparison of library ligands with purified ligands.

	Purified ligands		Library ligands	
	Conv. [%]	*ee* [%]	Conv. [%]	*ee* [%]
1b	8	46	11	41
1d	11	55	7	43
1i	96	94	51	88
1m	100	95	95	92

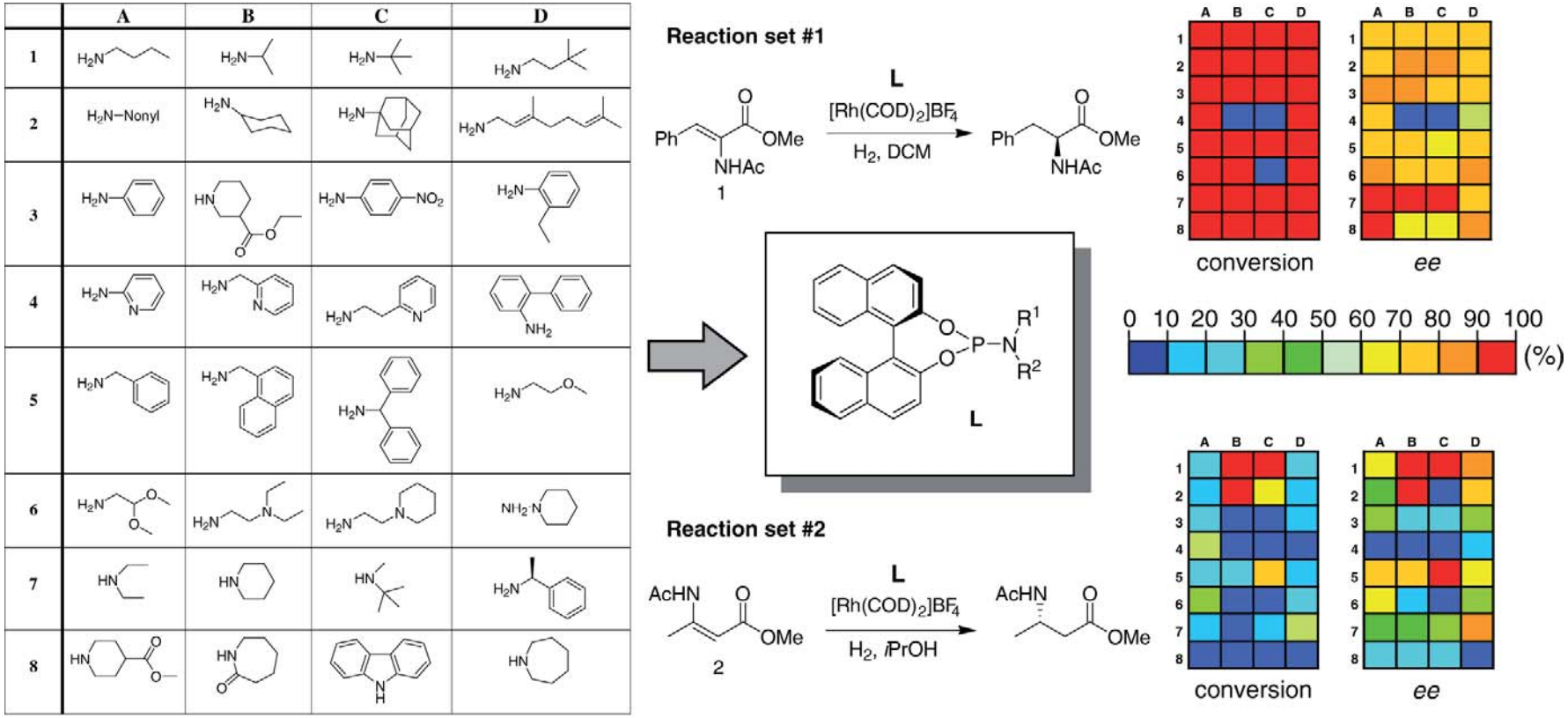


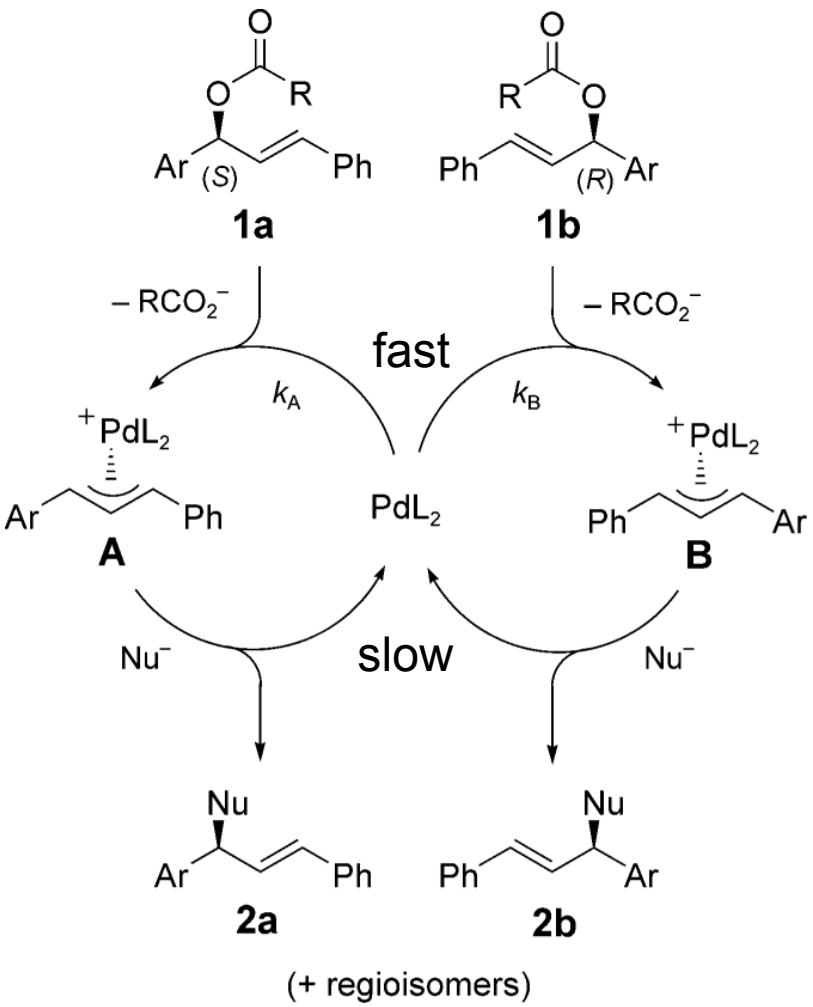
Figure 4. Parallel synthesis and screening of monodentate phosphoramidites in asymmetric hydrogenation.

Mass Spec Screening

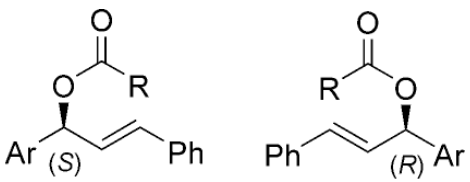
Advantages:

- High sensitivity.
- Minimal requirements on sample quality.
- Mild ionization method (electrospray) preserves structural information.
- Ideal for the detection of charged intermediates.

Pd Catalyzed Kinetic Resolution of Allylic Esters

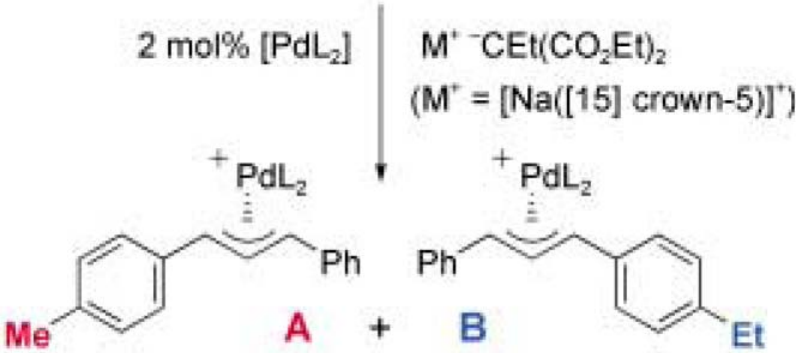


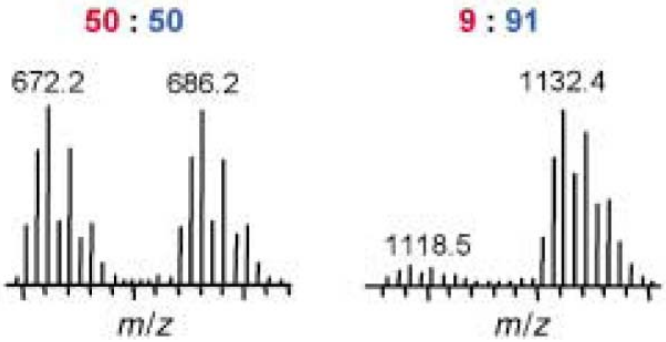
A/B ratio directly reflects the selectivity of the catalyst.
How to differentiate A vs B with MassSpec?
- Pseudo racemates.

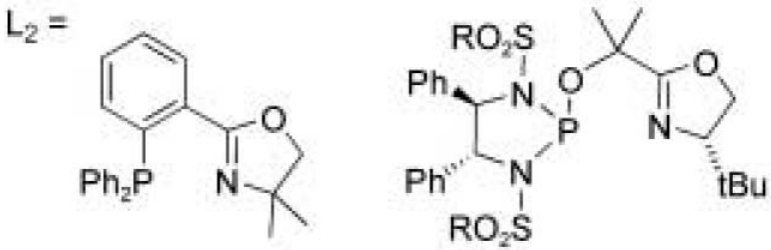


1a + 1b

1a: Ar = 4-methylphenyl
1b: Ar = 4-ethylphenyl

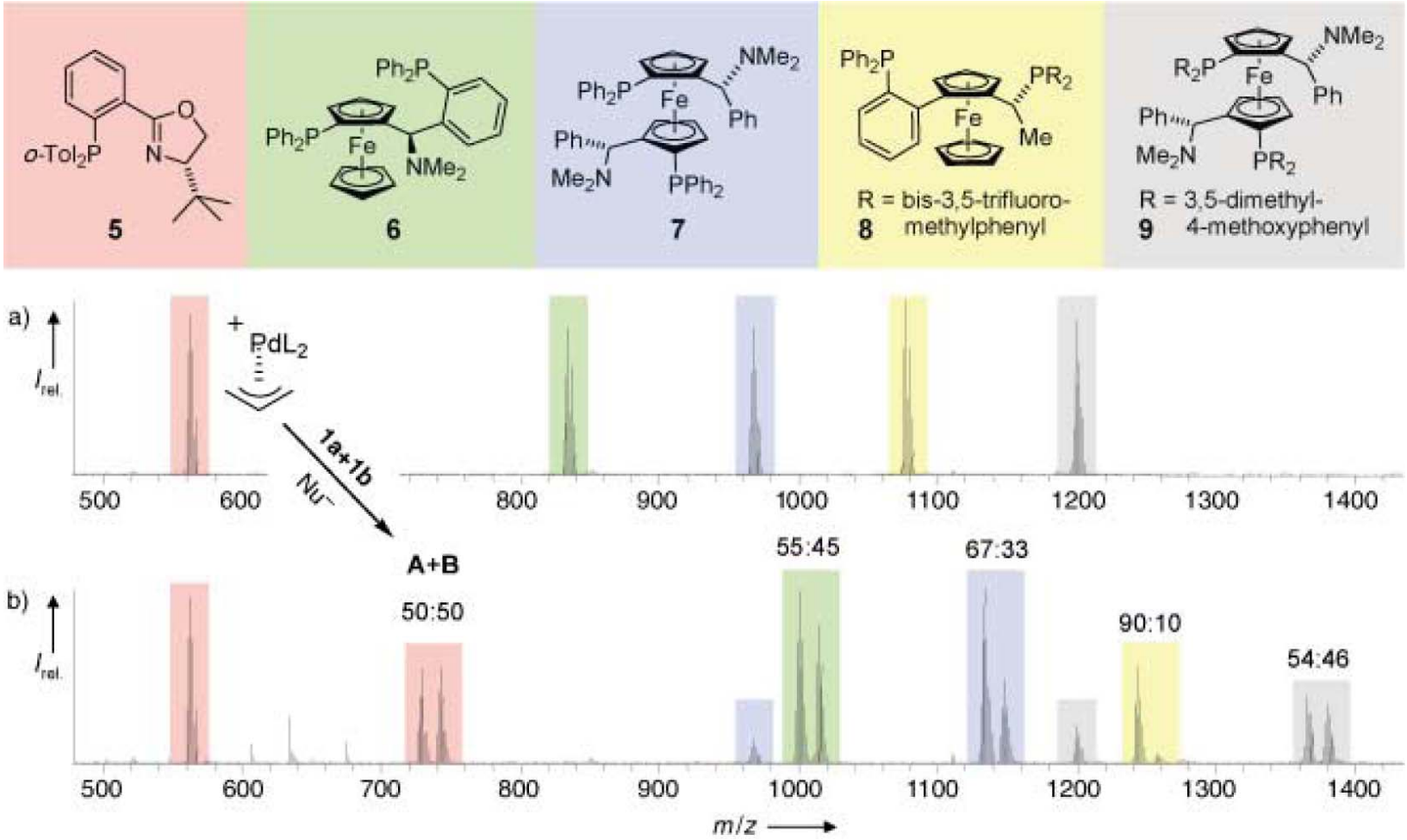






3: R = 2-naphthyl

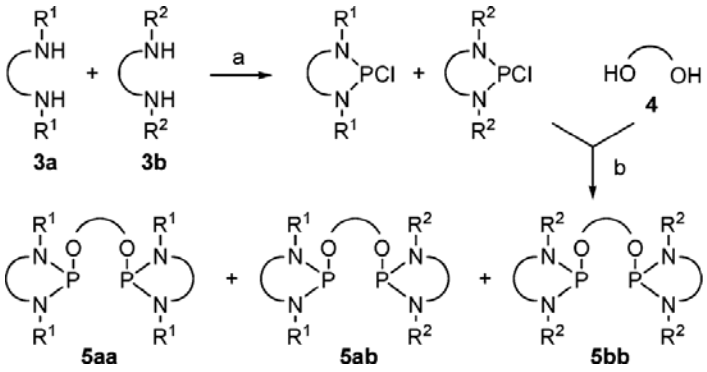
Screening a Mixture of Catalysts

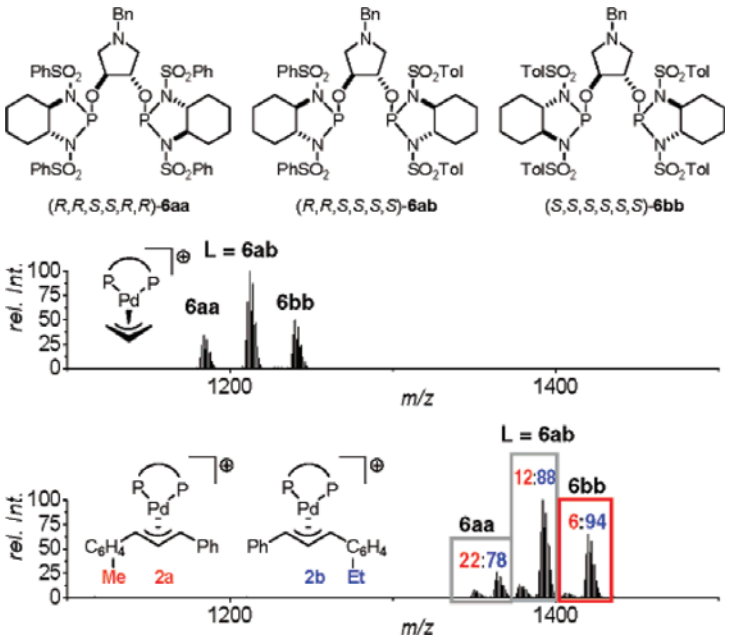


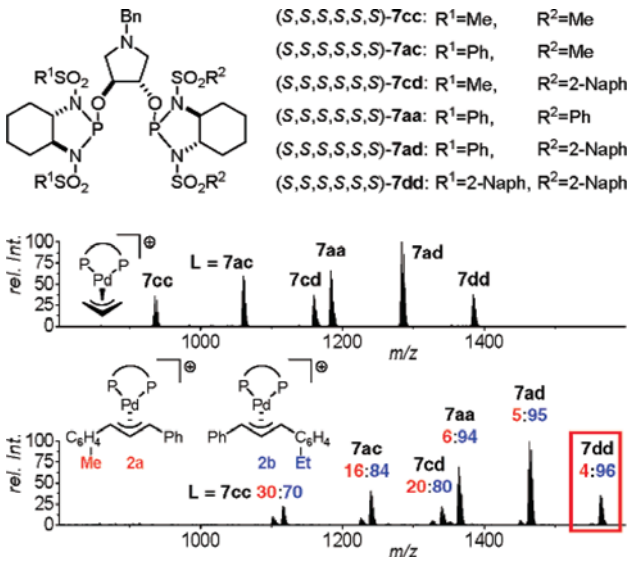
S factors calculated closely match with ESI-MS data (<10 % deviation).

Pfaltz, ACIEE,2007, 43, 2498

Preparation and Screening a Mixture of Quasi-diastereomeric Catalysts







Pfaltz, JACS,2008, 130, 3234

Conclusion

- Combinatorial approach in the development of catalytic system is still developing, in terms of new types of ligands, libraries of ligands, and screening methods.

  - Facile synthesis of ligands is still the bottleneck.

- Ideally, combinatorial libraries of catalysts will resolve the dilema of “high generality” and “high effectiveness”.

  - Screen for the optimum in a large toolkit for a specific transformation.