Enantioselective Friedel-Crafts Alkylations of Indole and Pyrrole

Literature Presentation by

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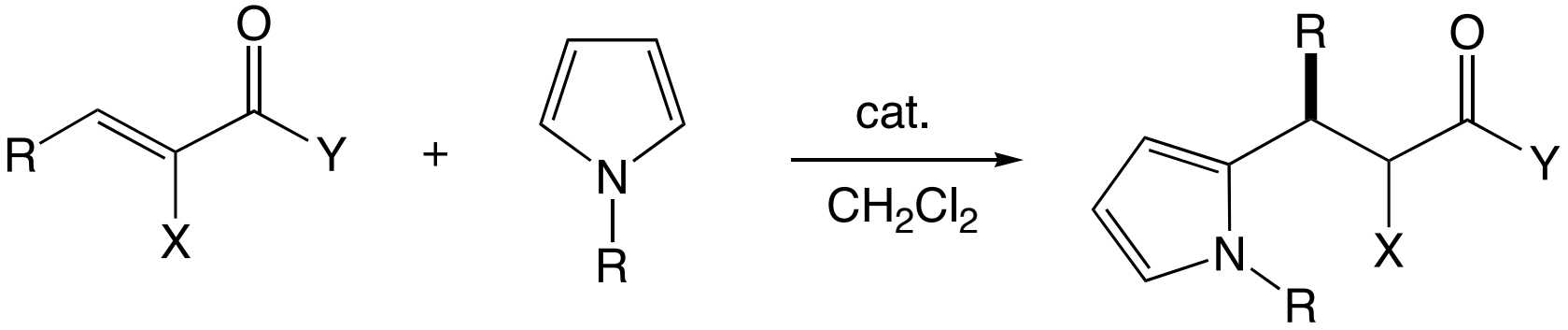
Outline:

- Organocatalytic Reactions (D.W.C.McMillan's research group)
- Metal-Catalyzed Reactions (research groups of K.A.Jorgensen, Y.Tang, and D.A.Evans)

Generalized Alkylation Reaction



X: H Y: H
X: H Y: CO_2R'
X: CO_2R Y: OR'
X: H Y: $P(O)(OMe)_2$
X: H Y: Ar
X: H Y: S-heterocycle

R = H, CH_3

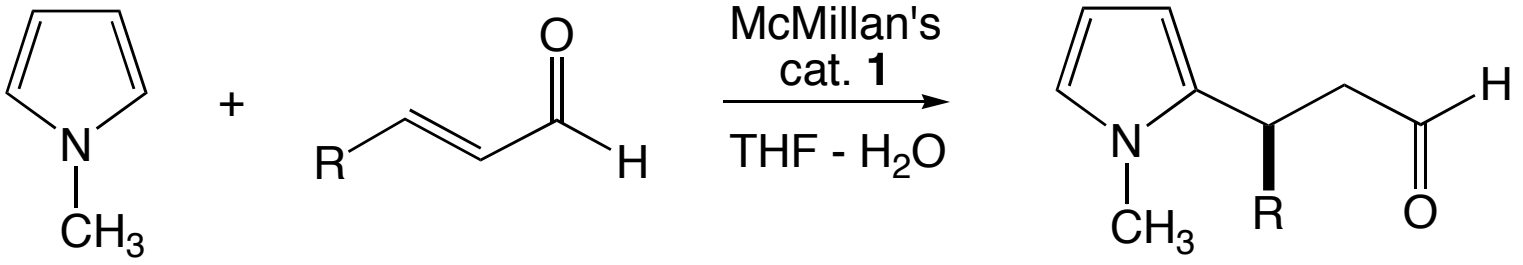
Why This Reaction?

- Friedel-Crafts reaction is a very well studied reaction, catalyzed by Lewis acids. Surprisingly enough, no asymmetric version of this reaction were reported till 2001

- Over 3000 natural isolates and 40 medicinal agents contain indole framework

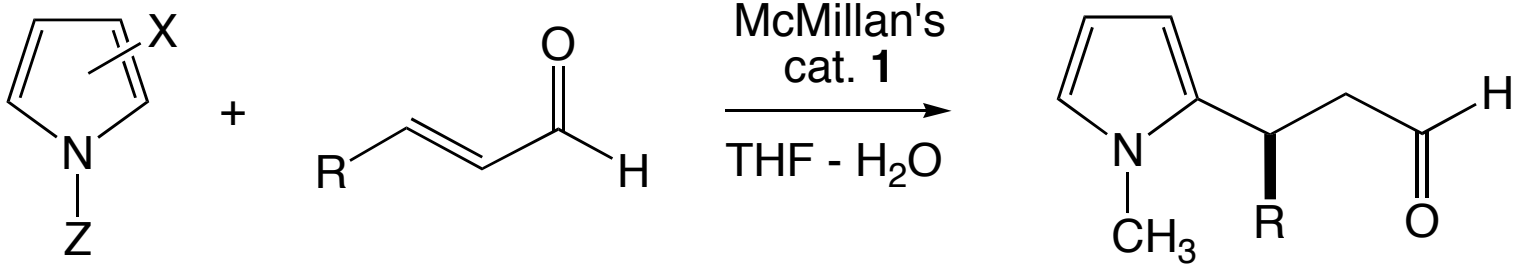
- Over 5000 natural isolates and many therapeutic agents (e.g. Zoloft, Paxil, Detrol) contain benzylic carbon stereocenter

1. First Example - McMillan



R = Me, Pr, iPr, Ph, CH_2OBn, CO_2Me

yield 72-90%, ee 87-93%

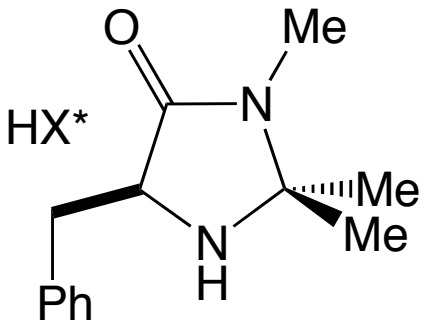


R = Ph, CO_2Me; X = 2-Bu, 3-Pr;
Y = Me, Bn, Allyl, H

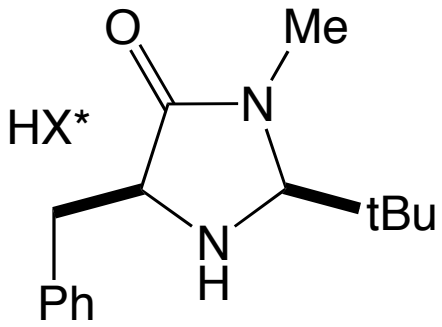
yield 68-87%, ee 90-97%

D.W.C. MacMillan et. al., JACS **2001**, *123*, 4370 - 4371

Structures of Catalysts



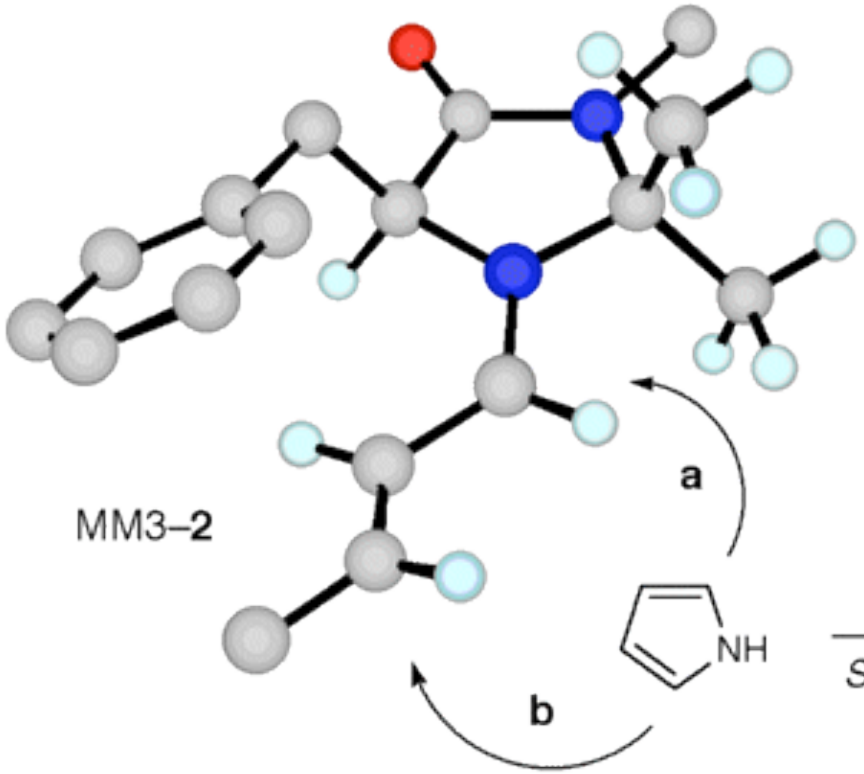
Catalyst **1**

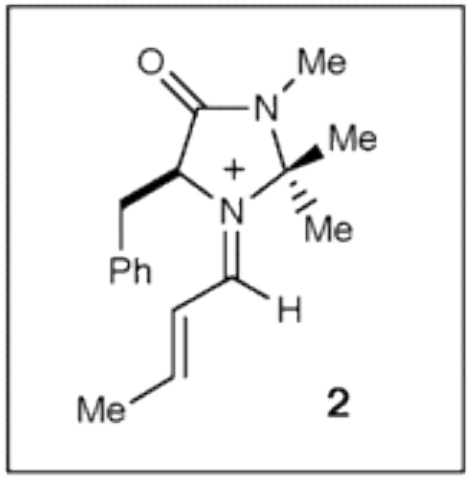


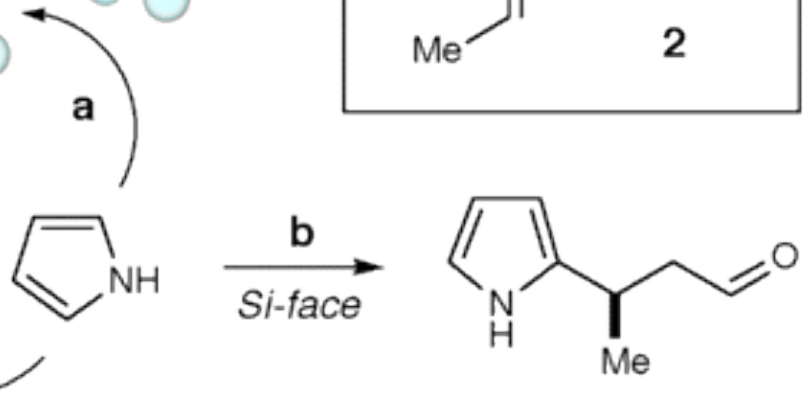
Catalyst **2**

HX checked: $NCCH_2COOH$, $Cl_2CHCOOH$, Cl_3COOH, TFA
Conditions of choise - TFA at low temperatures

Proposed Structure of Catalytic Complex



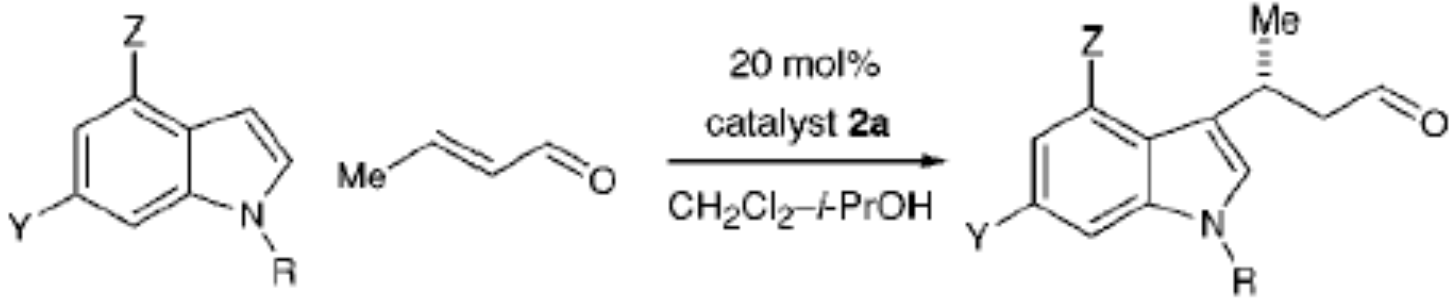




a = conventional acid catalyzed pathway

b = non-conventional 1,4-addition

2. Indoles Alkylation - McMillan

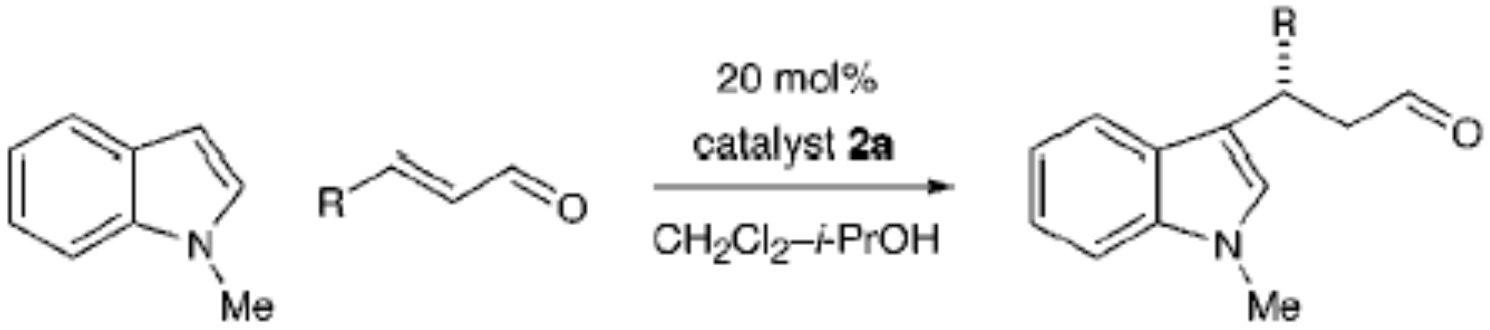


	indole substituents						
entry	R	Y	Z	temp (°C)	time (h)	% yield	% ee[a]
1	Me	H	H	−87	19	82	92[b]
2	H	H	H	−60	22	72	91[b]
3	allyl	H	H	−72	20	70	92
4	CH_2Ph	H	H	−60	120	80	89[b]
5	H	H	Me	−60	3	94	94[c]
6	Me	H	OMe	−87	19	90	96[c]
7	H	Cl	H	−60	13	73	97[c]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by chemical correlation. [c] Reaction conducted with (*E*)-$BzOCH_2CH{=}CHCHO$.

D.W.C. MacMillan et. al., JACS **2002**, *124*, 1172 - 1173

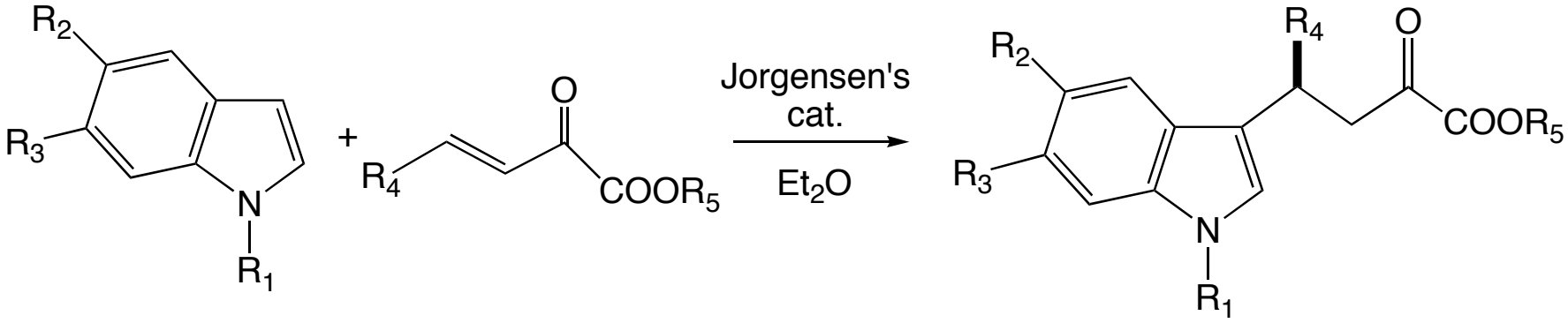
Indoles Alkylation Continued



entry	R	temp °C	time (h)	% yield	% ee[a]
1	Me	−83	19	82	92[b]
2	Pr	−60	6	80	93
3	*i*-Pr	−50	32	74	93
4	CH_2OBz	−83	18	84	96[b]
5	Ph	−55	45	84	90
6	CO_2Me	−83	21	89	91

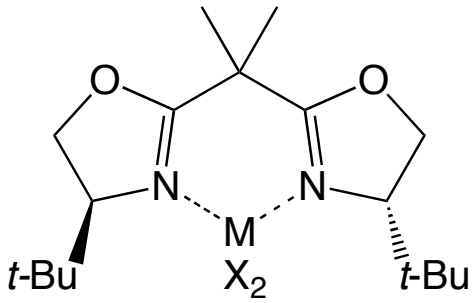
[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by chemical correlation.

3. First Metal Used - Jørgensen



R_1 = H, Me;
R_2 = H, OMe;
R_3 = H, Cl, COOMe;

R_4 = Ph, Me, CH_2OBn;
R_5 = Me, Et.

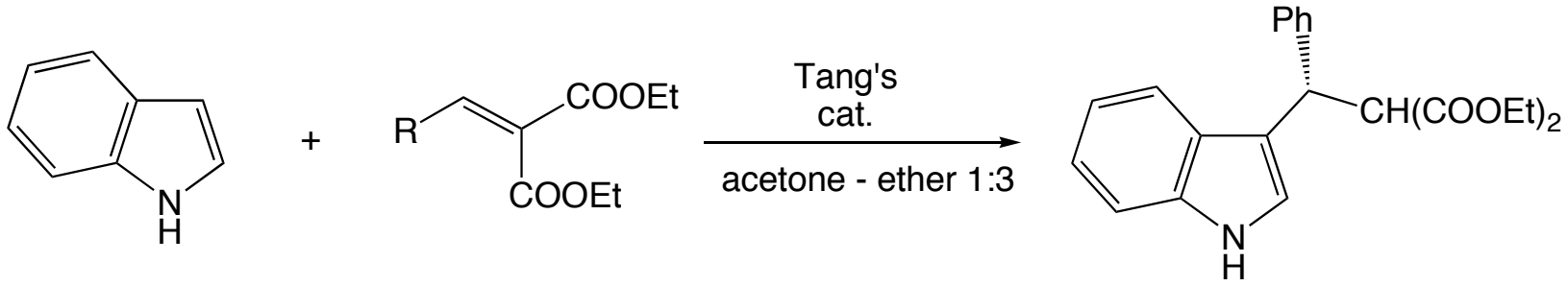


M = Cu, Zn
L = OTf, SbF_6

yields 65 - 98%
ee 88 - 99.5 %

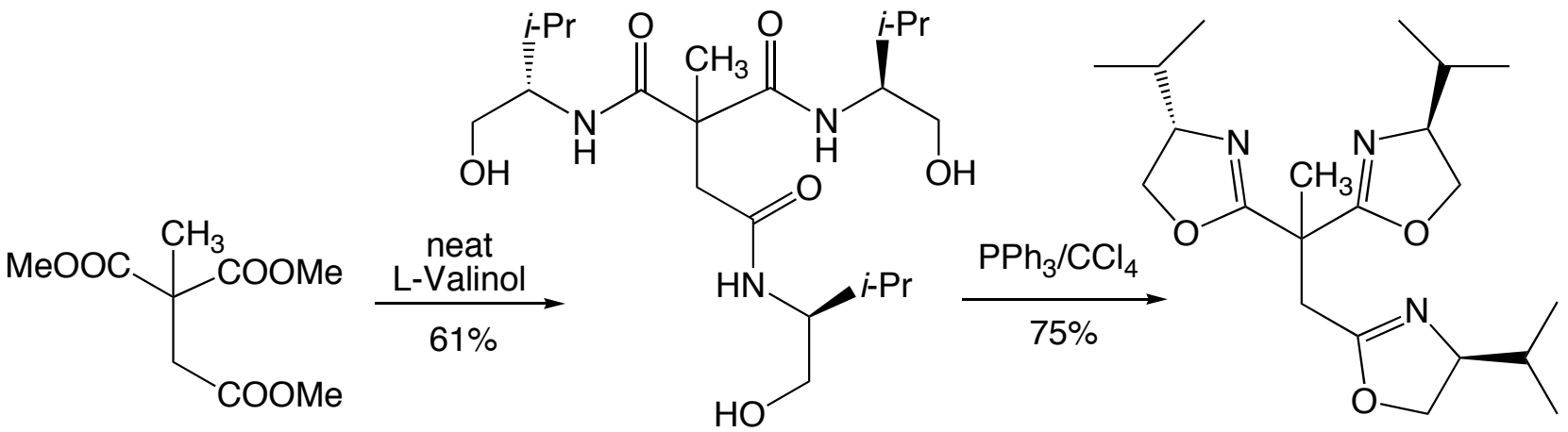
K.A.Jorgensen et. al., Angew. Chem. **2001**, *40*, #1, 160 - 163

4. Malonates Addition - Tang



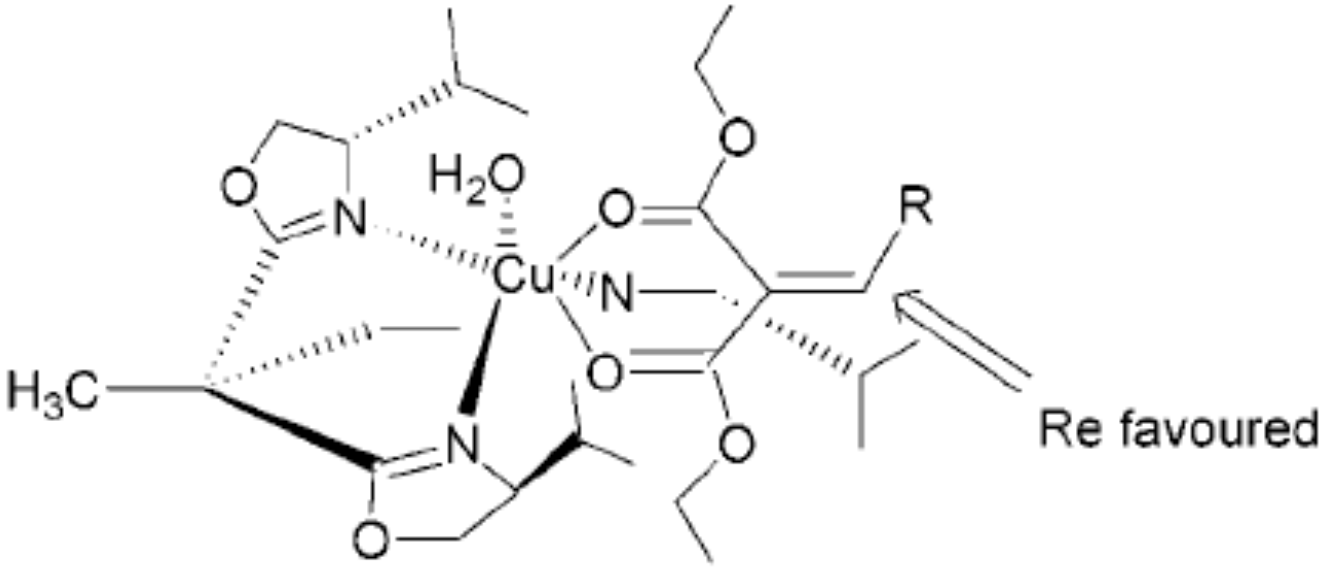
R = Ph, 3-NO_2-Ph, 4-NO_2-Ph, 4-Cl-Ph, 4-Br-Ph, 2-Cl-Ph, Me

yield 73-99%, ee 89-93%
(60% for Me)

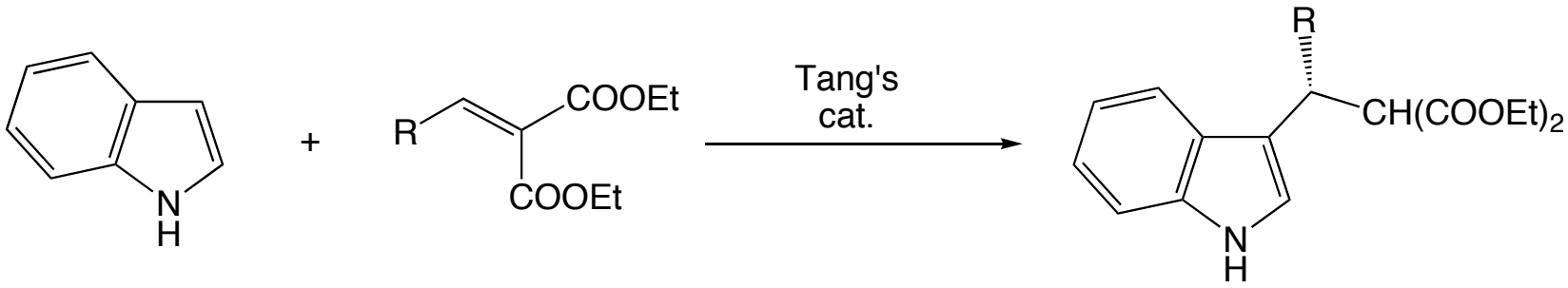


Y.Tang et. al., JACS **2002**, *124*, 9030-9031

Proposed Active Intermediate - Tang's Catalyst

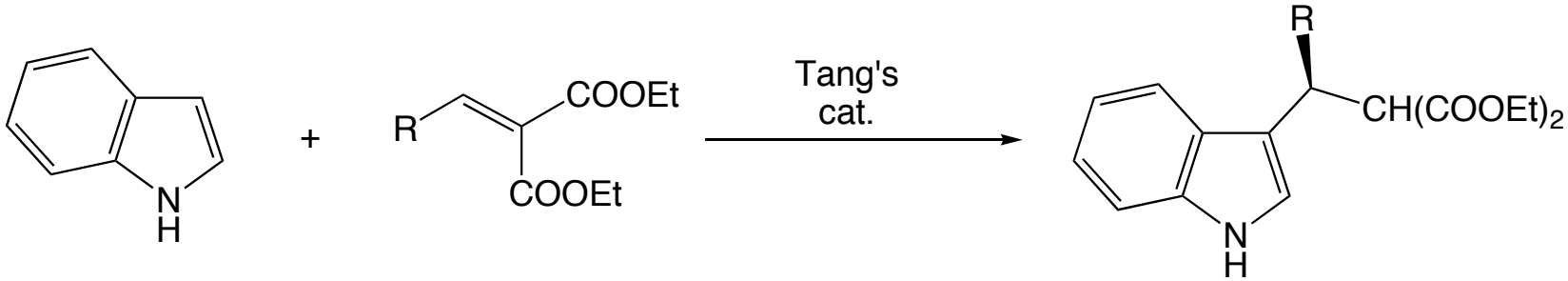


Solvent Controlled Selectivity



acetone - ether 1:3 yield 73-99%, ee 89-93%

isobutanol yield 85-99%, ee 93-99%

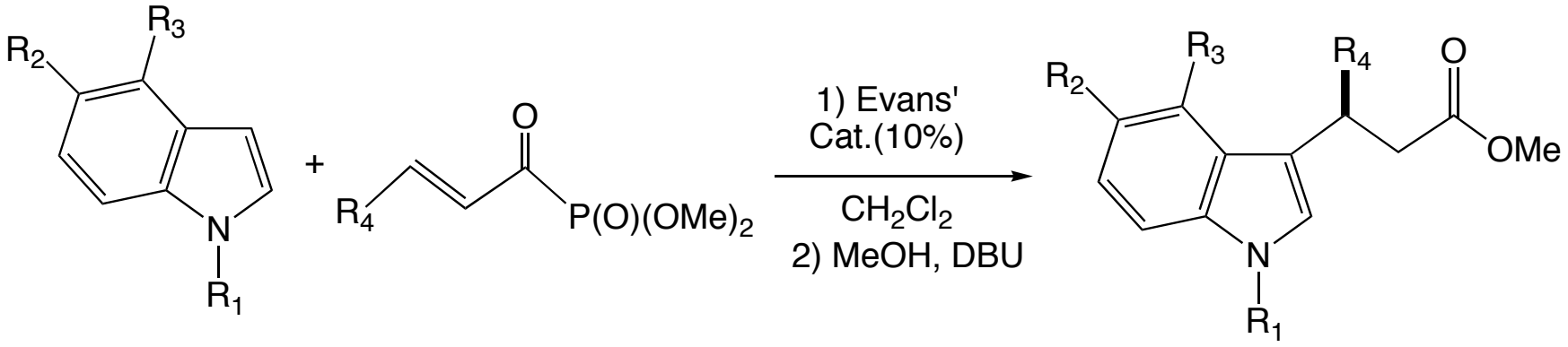


1,1,2,2-tetrachloroethane (TTCE) yield 73-99%, ee 80-89%

R = Ph, 3-NO_2-Ph, 4-NO_2-Ph, 4-Cl-Ph, 4-Br-Ph, 2-Cl-Ph

Y.Tang et. al., JOC **2004**, *69*, 1309-1320

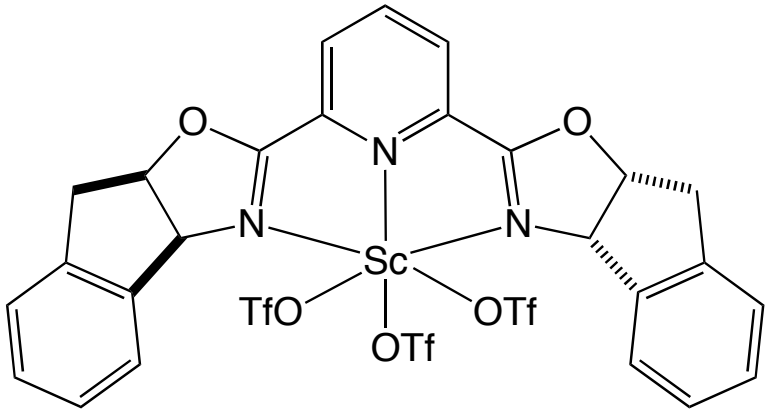
5. Phosphonates Addition - Evans



R_1 = H or Allyl, Bn
R_2 = H, Cl, COOMe, OMe
R_3 = H, Cl
R_4 = Me, Et, *i*-Pr, $CH_2OTBDPS$, Ph

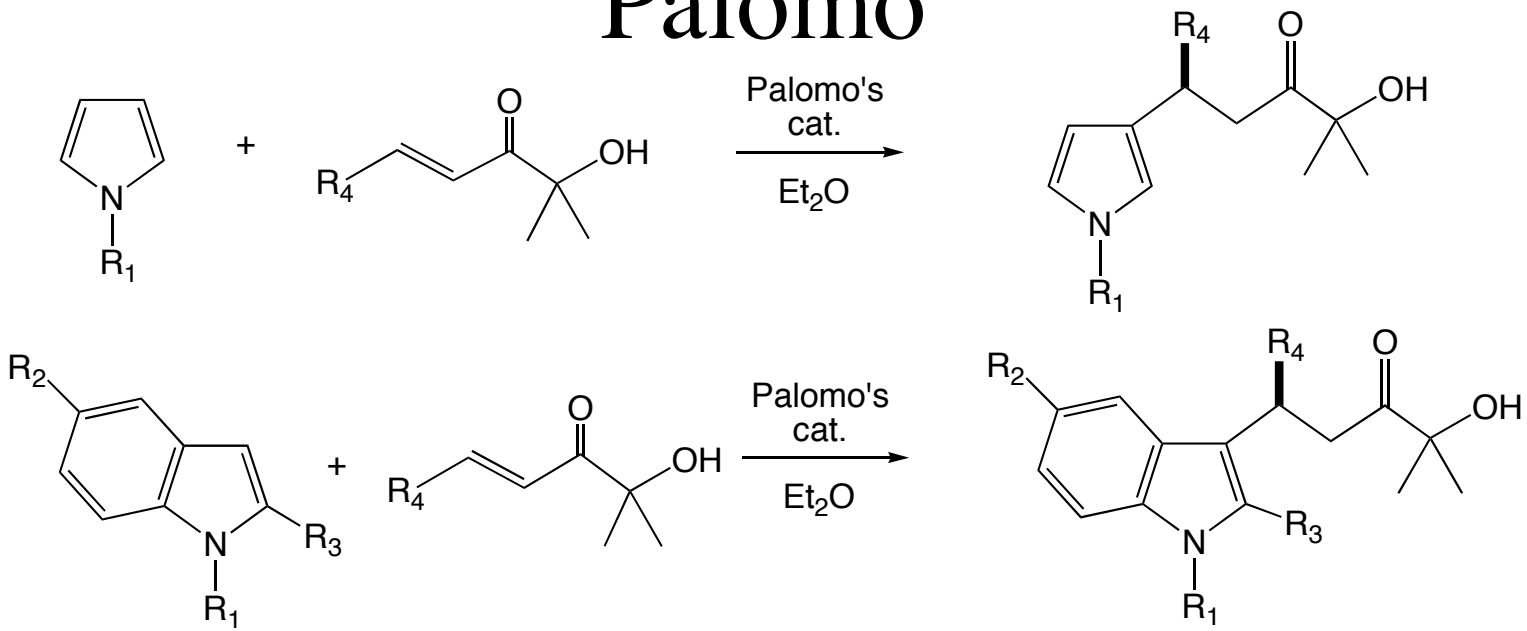
yield 57-88%, ee 93-97%
for R_4 = Ph ee 80%

Evans' catalyst



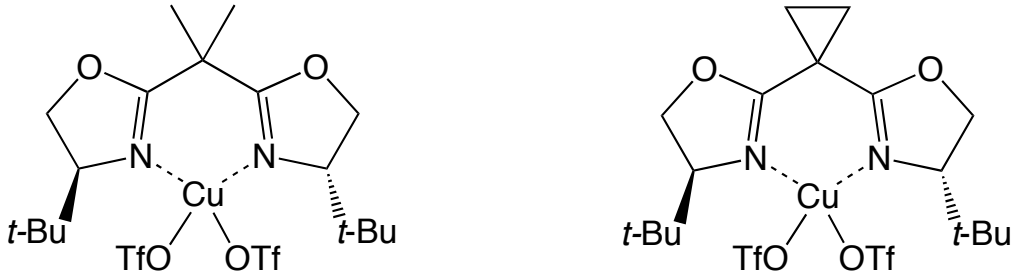
D.A. Evans et. al., JACS **2003**, *125*, 10780 - 10781

6. Hydroxy Enones Addition - Palomo



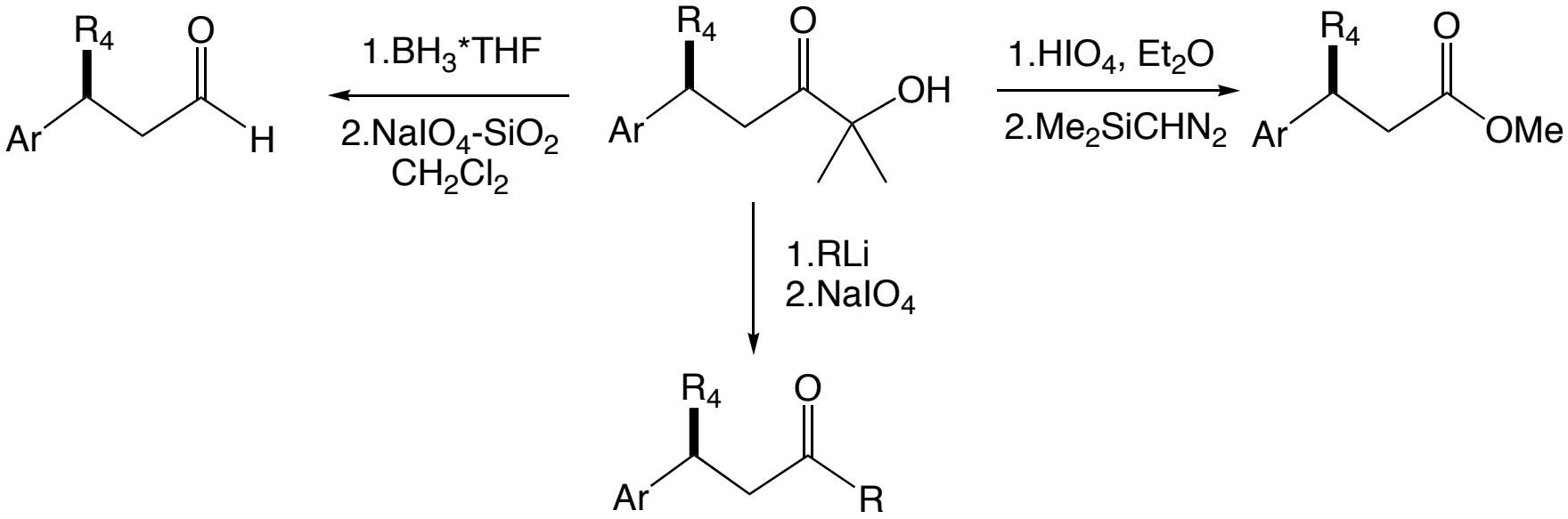
R_1 = H, Me; R_2 = H, OMe; R_3 = H, Me; R_4 = $PhCH_2CH_2$, *n*-Hex, *i*-Pr, Cy, Et, *i*-Bu, Ph

yield 82-95% ee 91-97% (for R_4 = Ph ee 68%, yield 95%)



C.Palomo et. al., JACS **2005**, *127*, 4154-4155

Possible Derivatization



Conclusions

- Friedel-Crafts reaction of indoles and pyrroles can be performed enantioselectively using both metal-based and organic catalysts

- Yields of these reactions are generally high, enantioselectivities are excellent