ORGANIC CHEMISTRY

Redox-neutral organocatalytic Mitsunobu reactions

Rhydian H. Beddoe[1], Keith G. Andrews[1], Valentin Magné[1], James D. Cuthbertson[1], Jan Saska[1], Andrew L. Shannon-Little[1], Stephen E. Shanahan[2], Helen F. Sneddon[3], Ross M. Denton[1]*

Oyo Mitsunobu (1934-2003)

BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 40 2380—2382 (1967)

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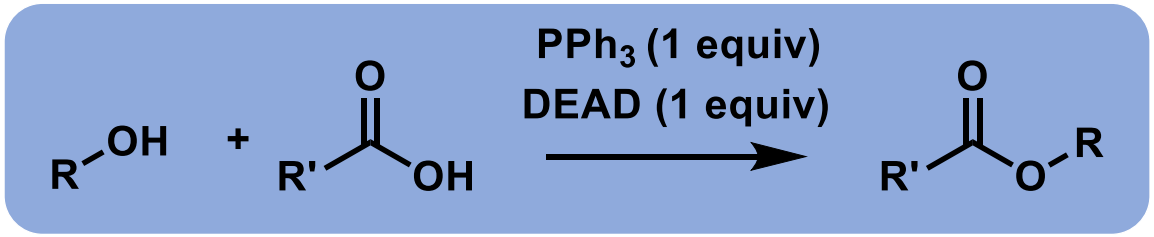

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n-C_4H_9	C_2H_5	*n*-C_4H_9	C_2H_5	34	60—63/28—33
n-C_4H_9	*iso*-C_3H_7	*n*-C_4H_9	*iso*-C_3H_7	43	
C_6H_5	CH_2=$CHCH_2$	C_6H_5	CH_2=$CHCH_2$	85	102—105/12
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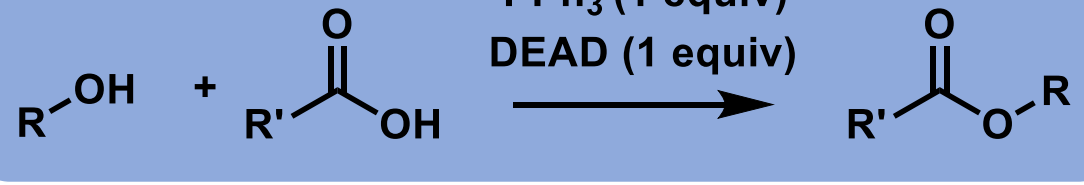
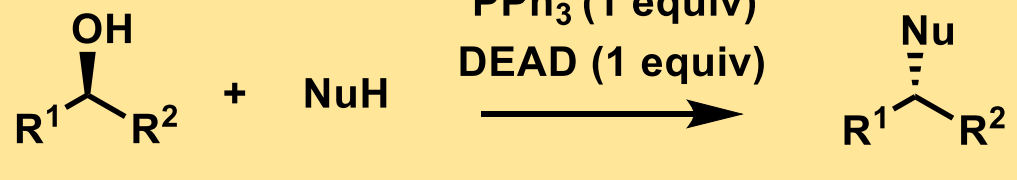


general reaction



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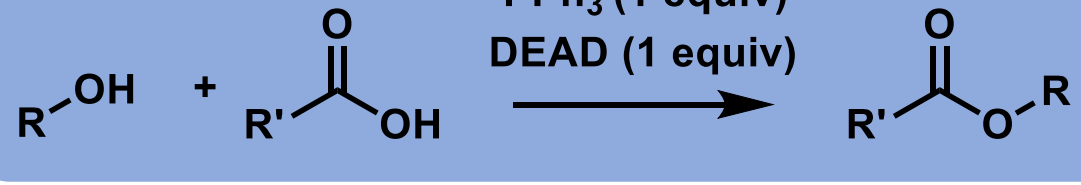

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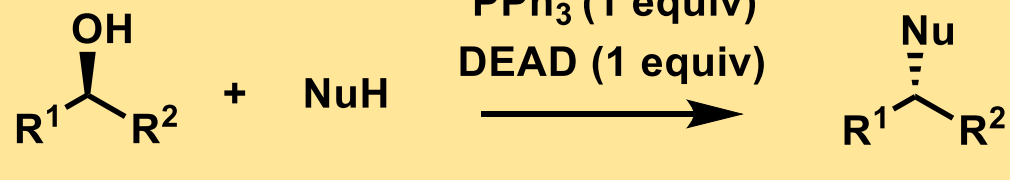

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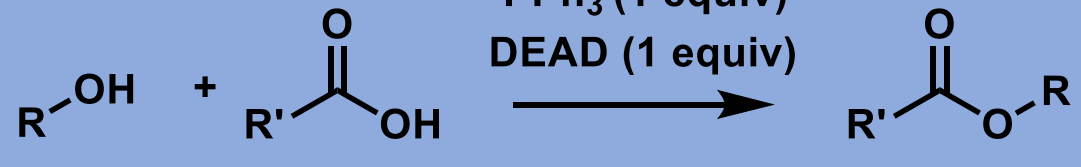

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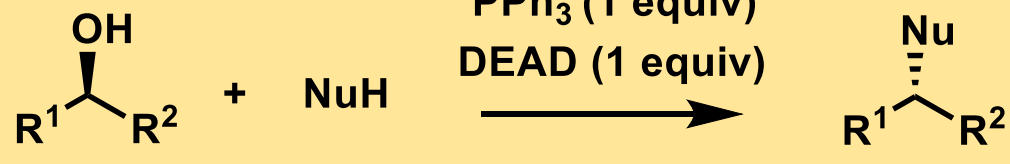

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→ Used very frequently :

Synthesis 1981; 1981(1): 1-28 :

Use of Mitsunobu reaction : +20 examples

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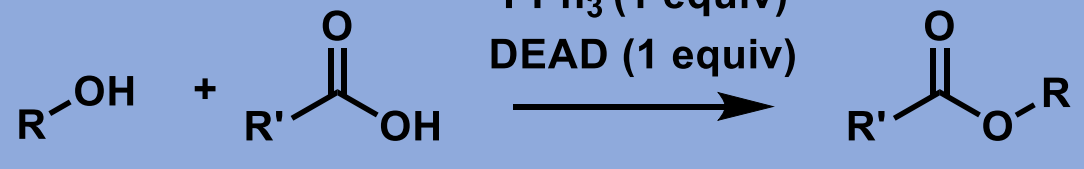

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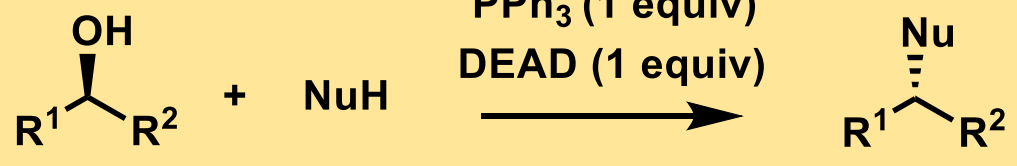

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→ involve hazardous stoichiometric reagents

Interest of developping Mitsunobu reaction ?

Table 1 Reactions companies use now but would strongly prefer better reagents

Research Area	Number of Roundtable companies voting for this research area as a priority area
Amide formation avoiding poor atom economy reagents	**6 votes**
OH activation for nucleophilic substitution	**5 votes**
Reduction of a mides without hydride reagents	**4 votes**
Oxidation/Epoxidation methods without the use of chlorinated solvents	**4 votes**
Safer and more environmentally friendly Mitsunobu reactions	**3 votes**
Friedel–Crafts reaction on unactivated systems	2 votes
Nitrations	2 votes

D. J. C. Constable et al., Green Chem. 9, 411–420 (2007).

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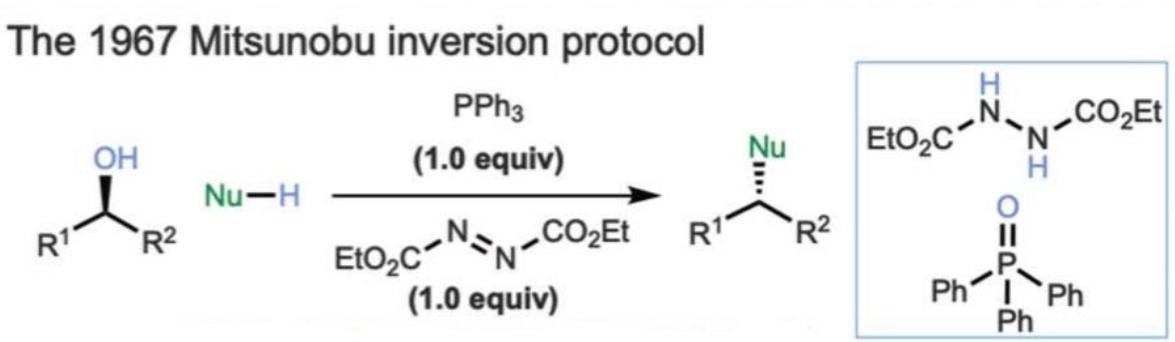

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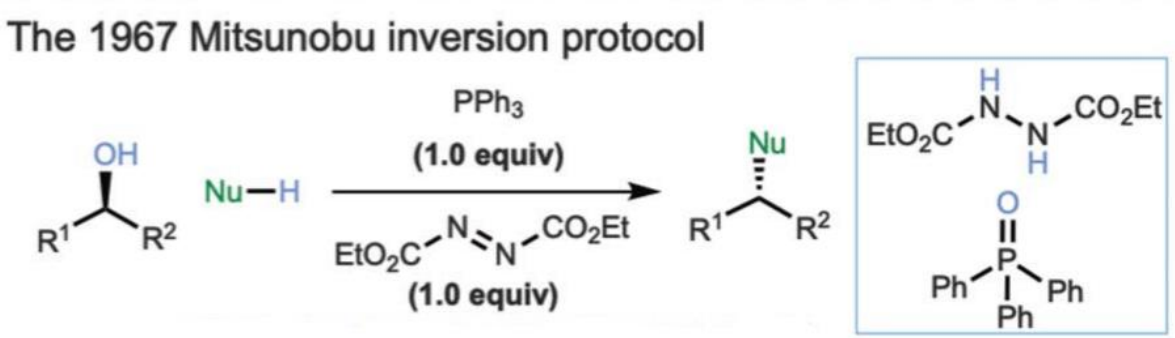
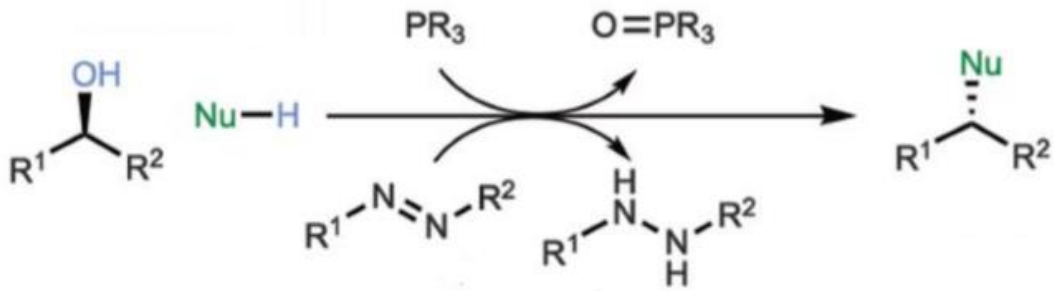


Catalytic amount of phosphine or azo species ?



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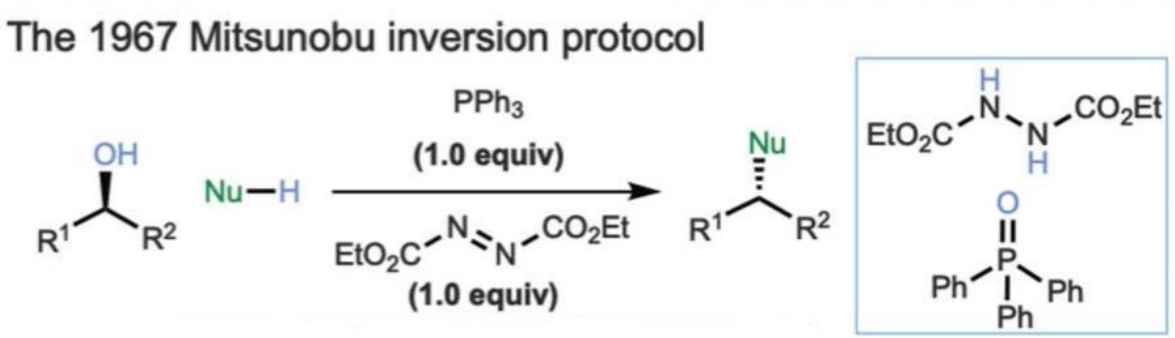

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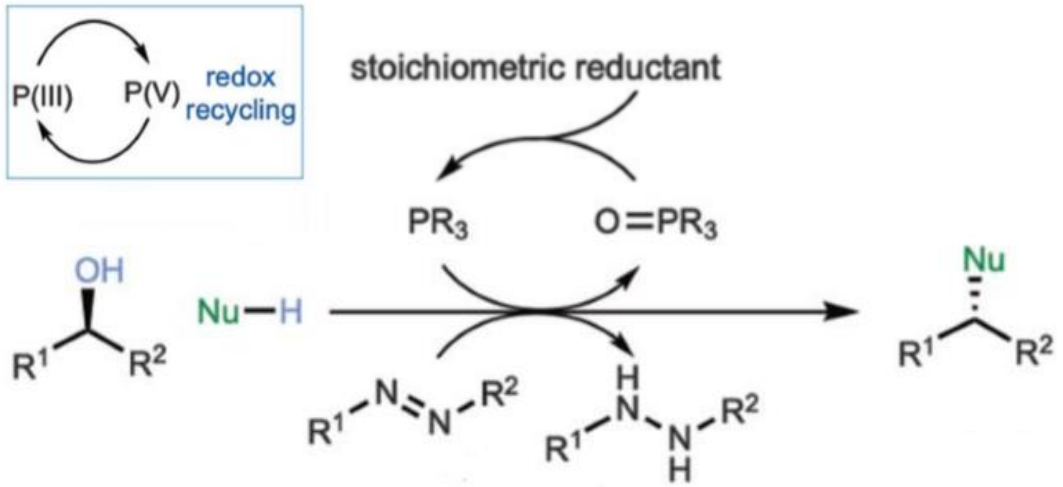

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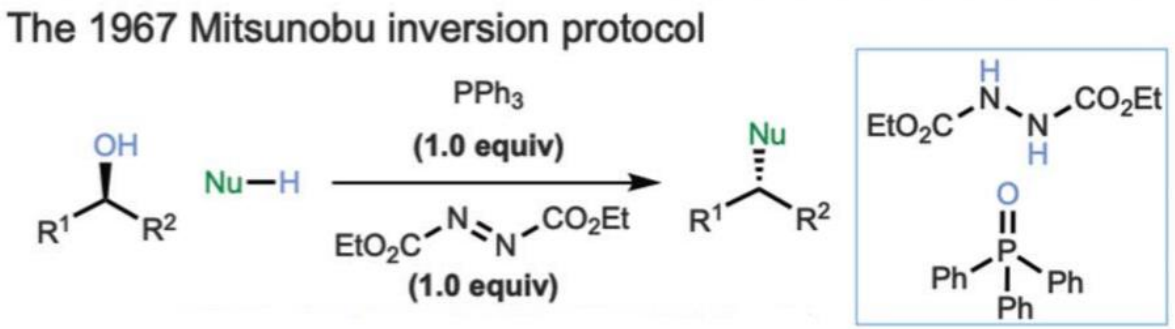

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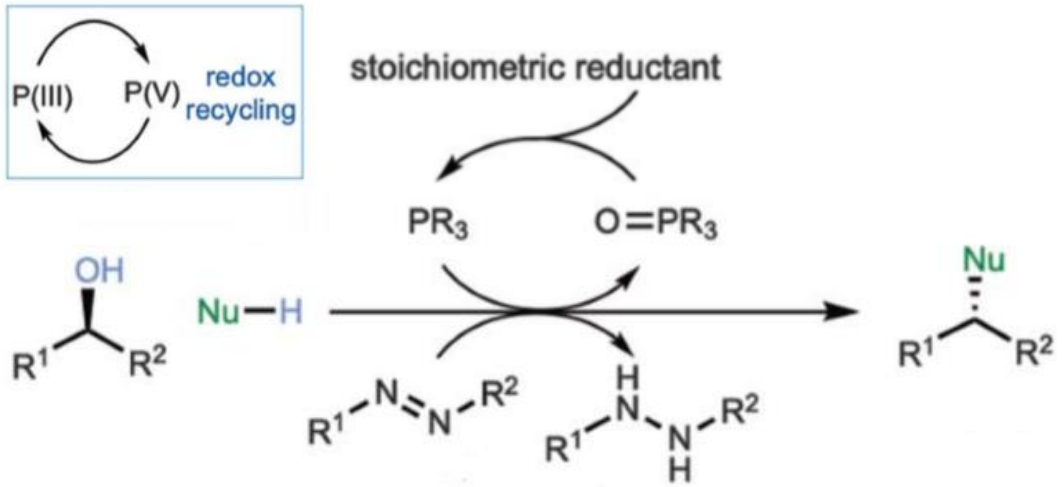

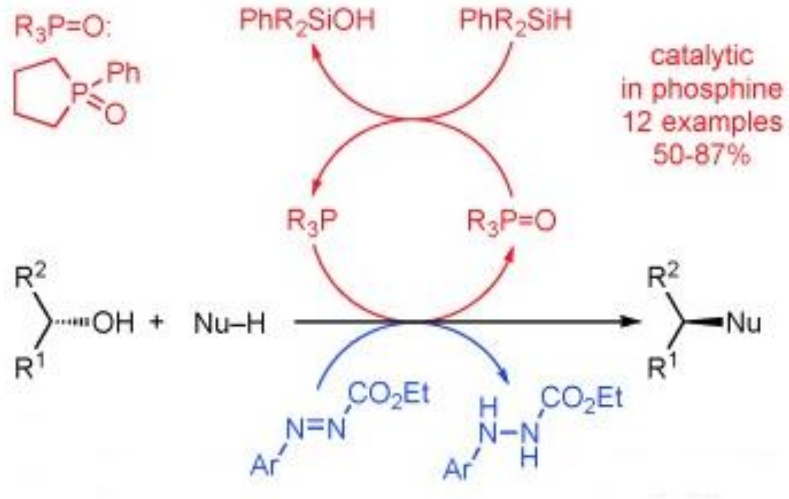

J. A. Buonomo, C. C. Aldrich, Angew. Chem. Int. Ed. 54, 13041–13044 (2015).

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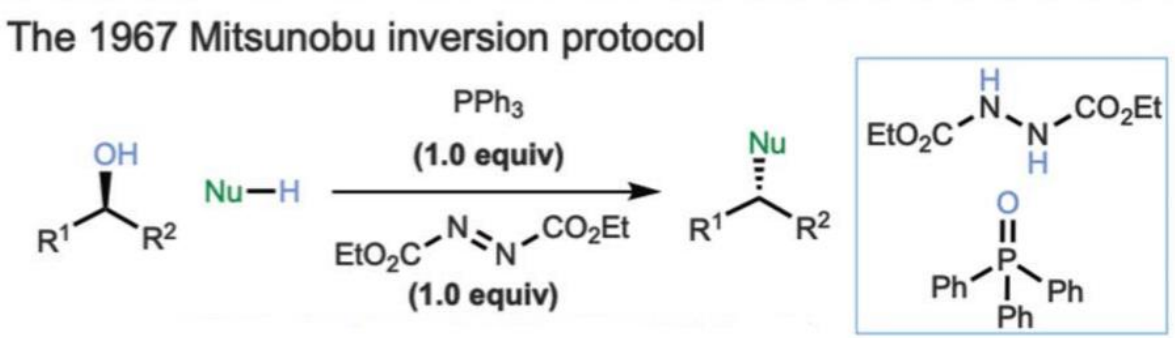

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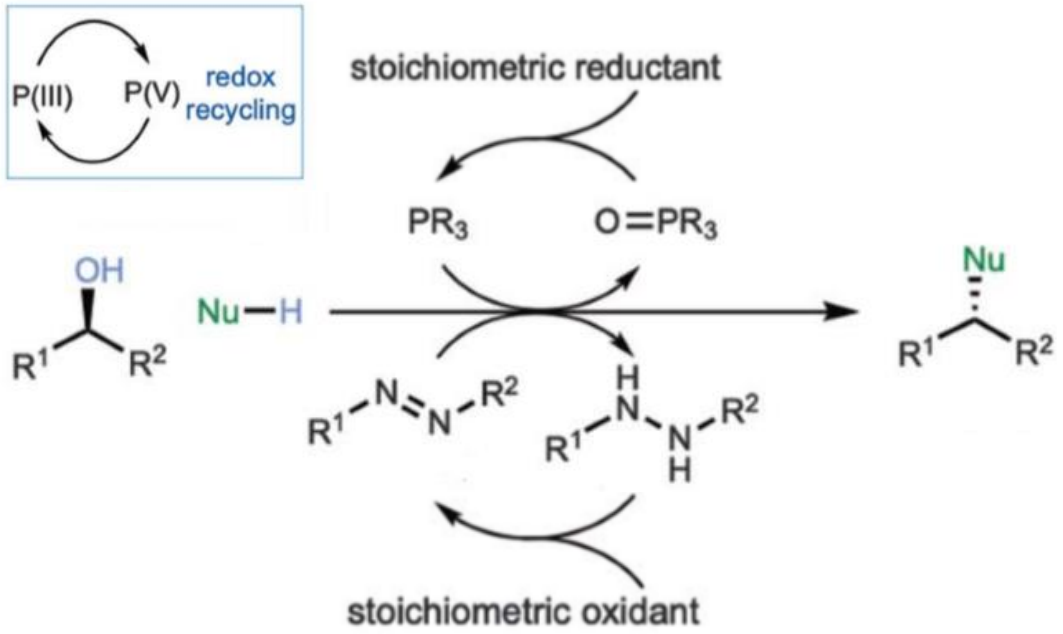

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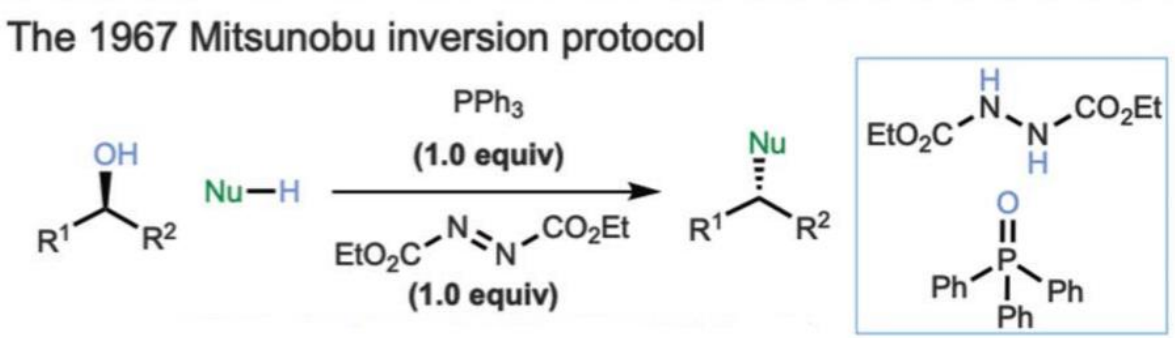

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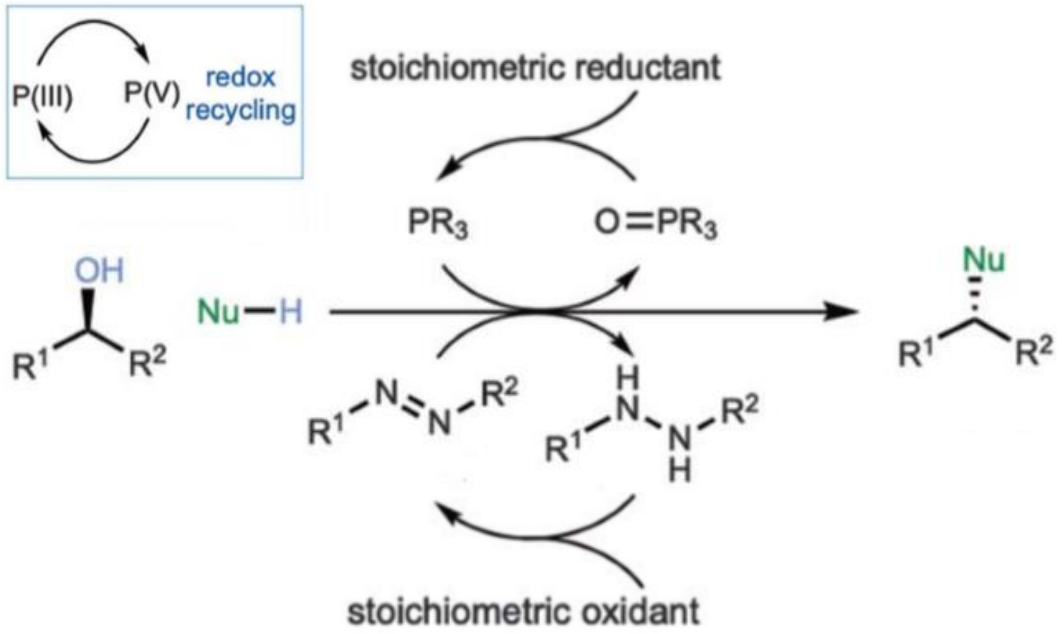

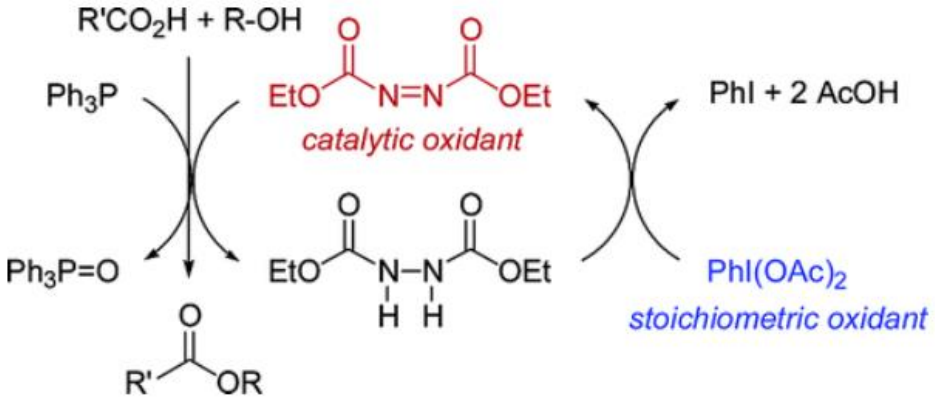

T. Y. S. But, P. H. Toy, J. Am. Chem. Soc. 128, 9636–9637 (2006).

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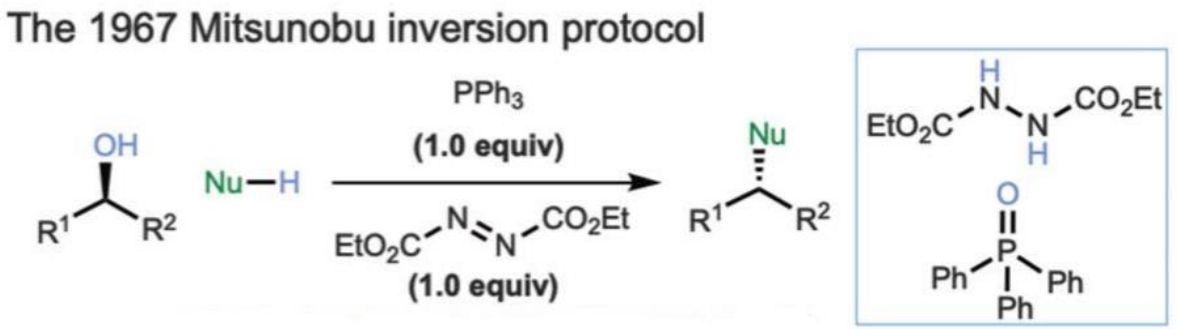

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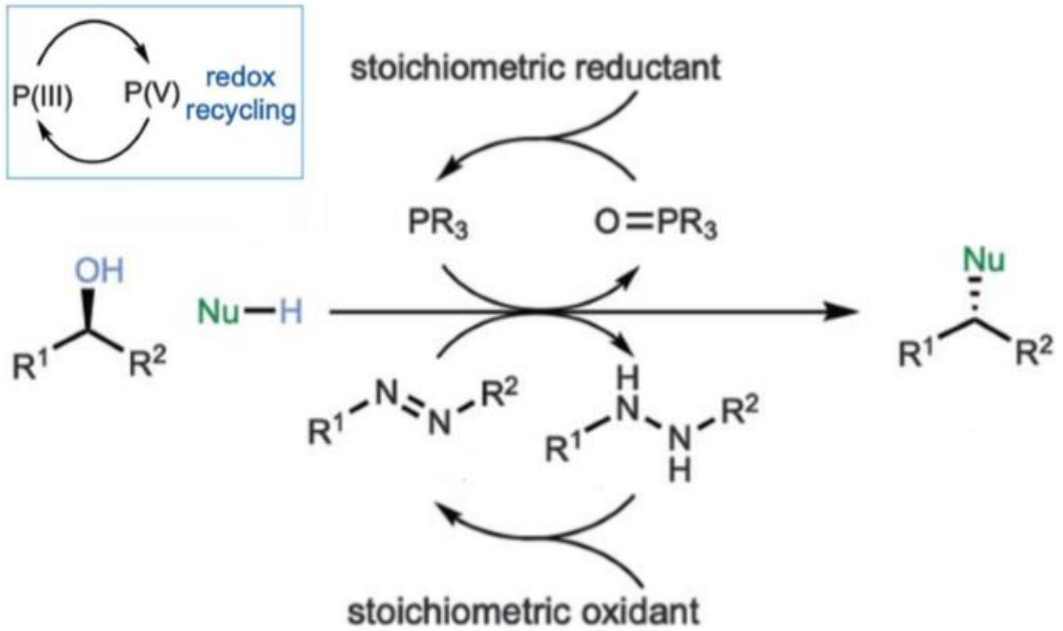

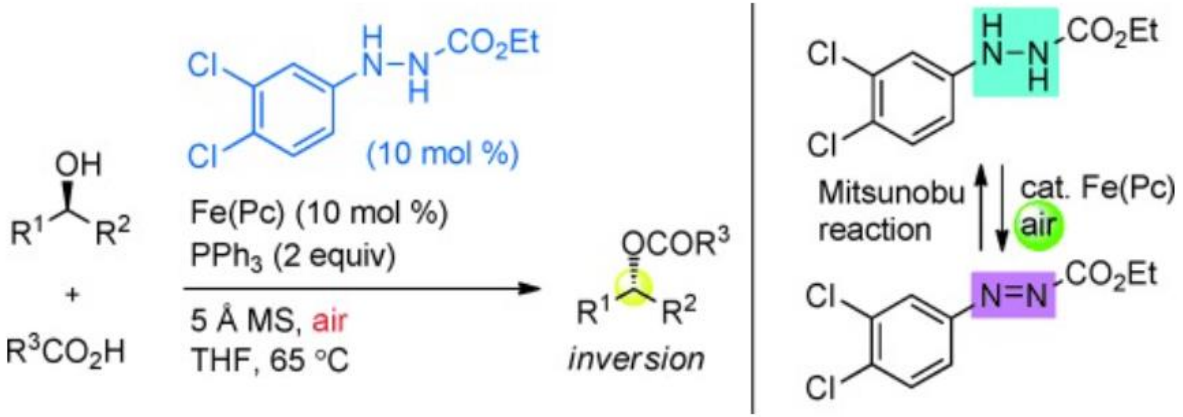

D. Hirose, T. Taniguchi, H. Ishibashi, Angew. Chem. Int. Ed. 52, 4613–4617 (2013).

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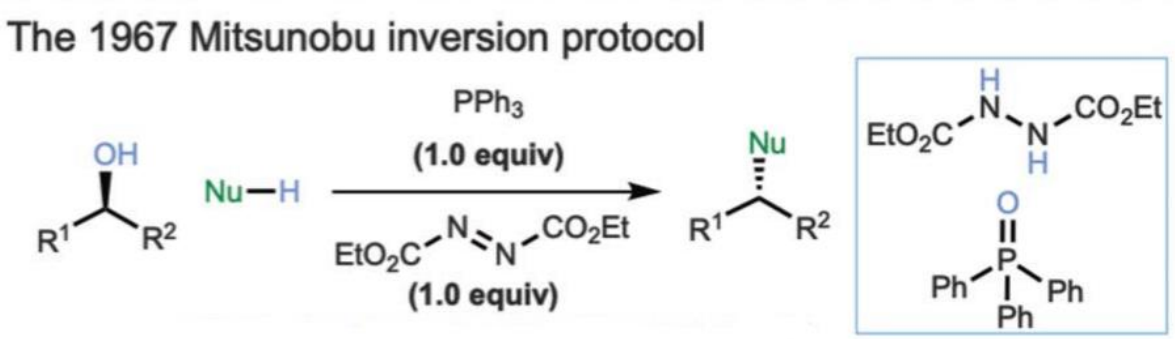

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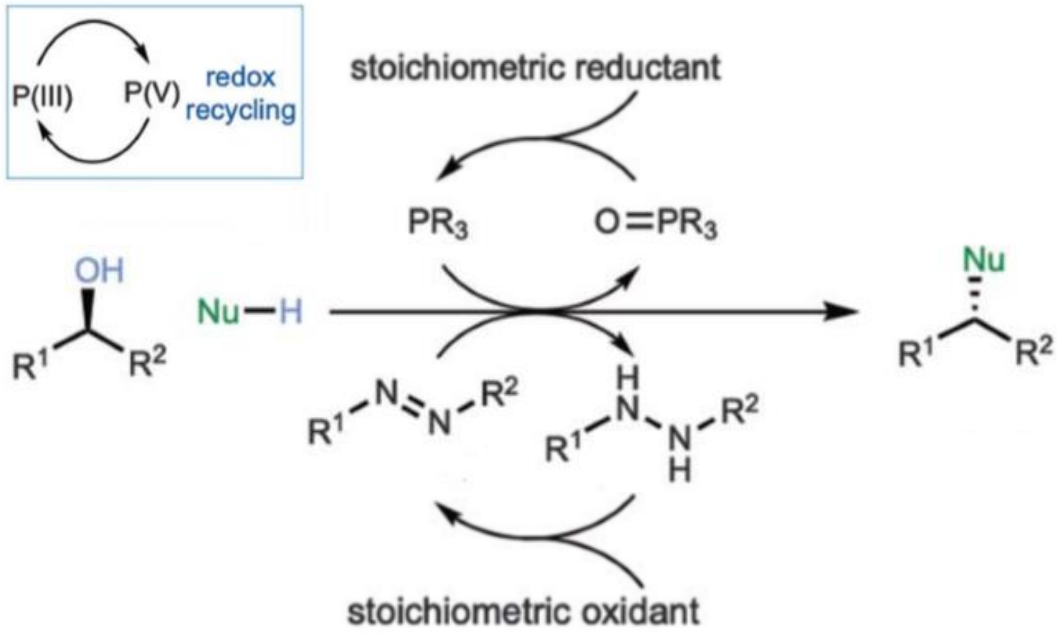

Atom economy ?

Ideal Mitsunobu reaction ?

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→ No stochiometric Oxydant

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→ Non-Hazardeous by-product

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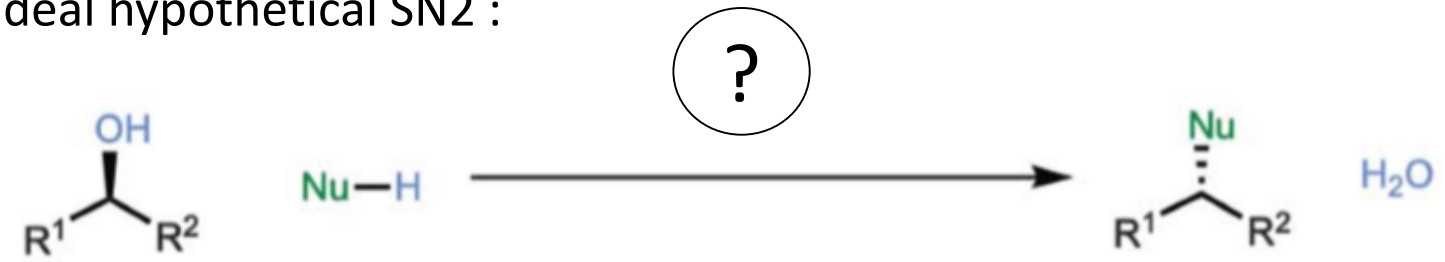
Ideal hypothetical SN2 :



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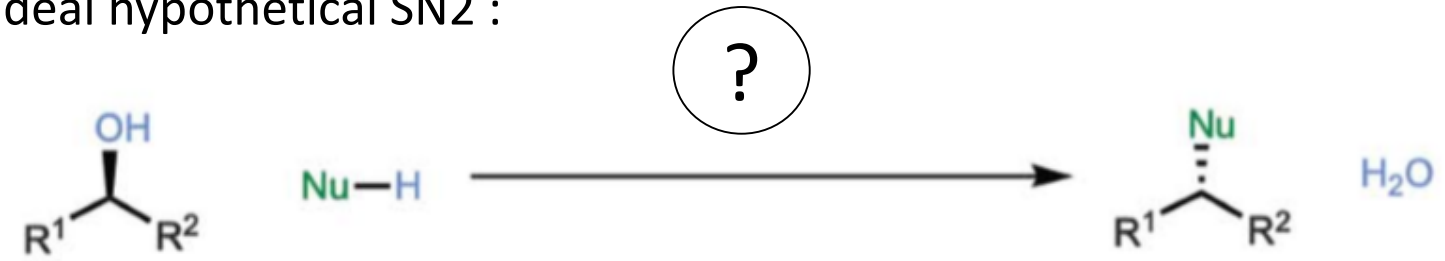

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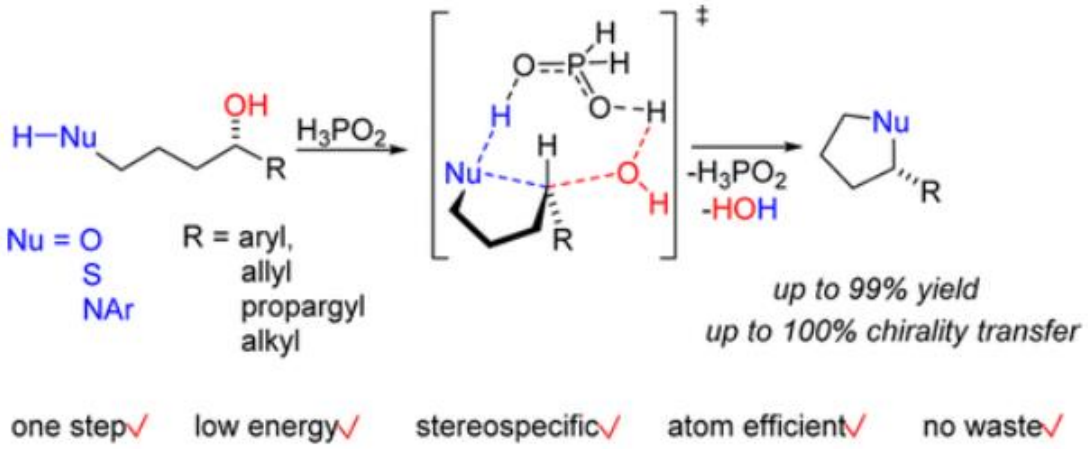

A. Bunrit et al., J. Am. Chem. Soc. 137, 4646–4649 (2015).

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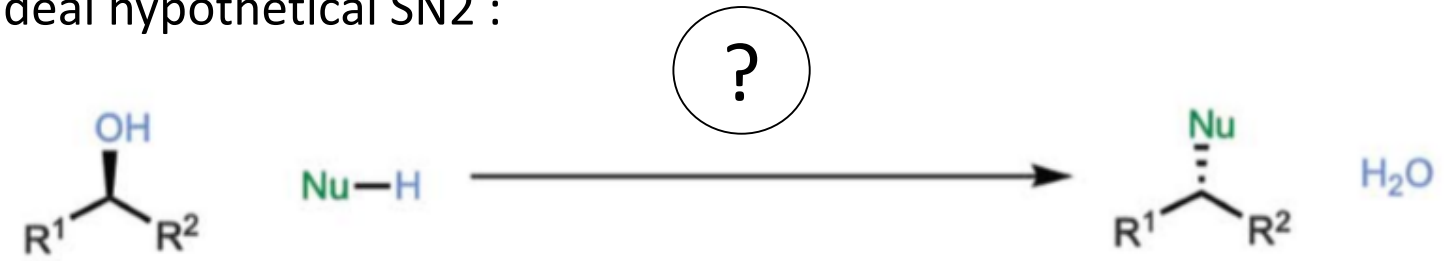

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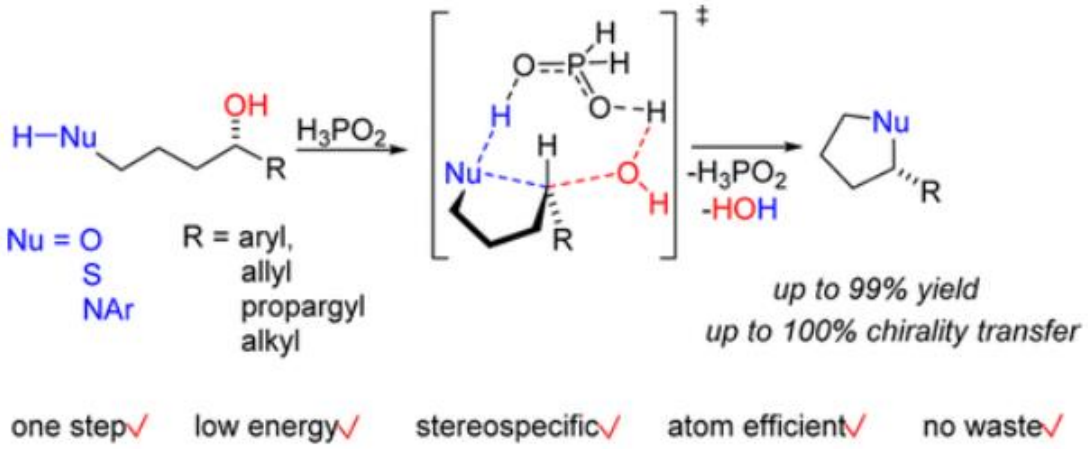

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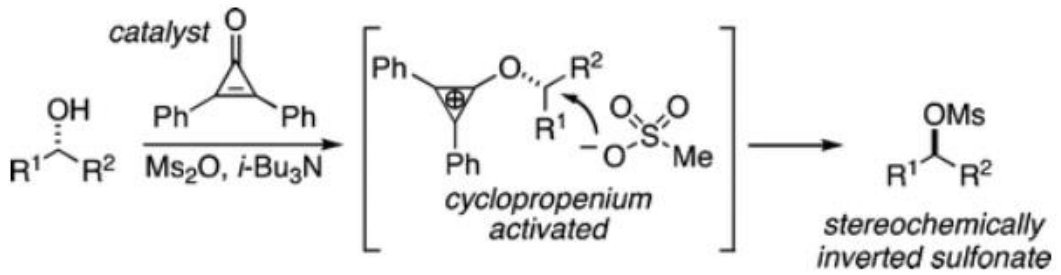
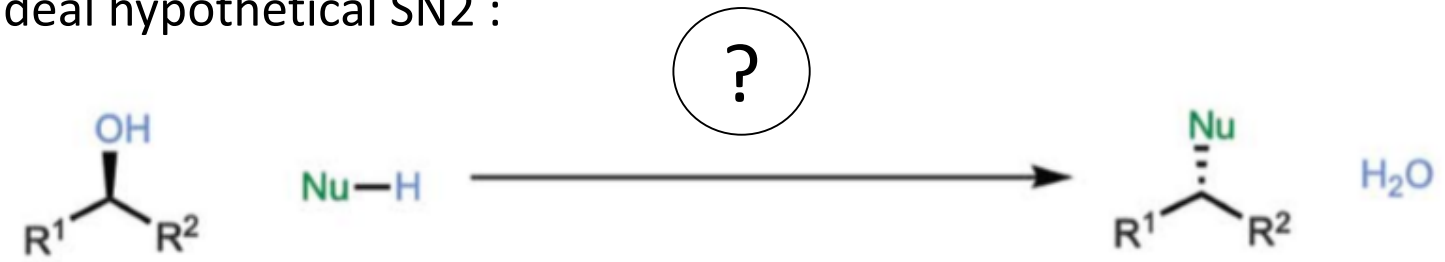


E. D. Nacsa, T. H. Lambert, Org. Lett. 15, 38 –41 (2013).

Ideal Mitsunobu reaction ?

→ No stochiometric Oxydant
→ No stochiometric Reductant
→ Catalytic Inversion
→ Non-Hazardeous by-product

Ideal hypothetical SN2 :



Other catalytic systems :

Review :

M. Dryzhakov, E. Richmond, J. Moran,
Synthesis 48, 935–959 (2016).

Ideal Mitsunobu reaction ?

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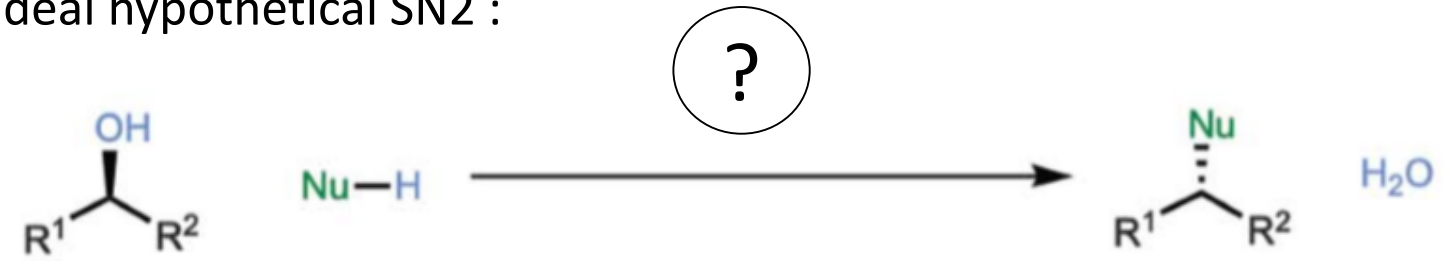
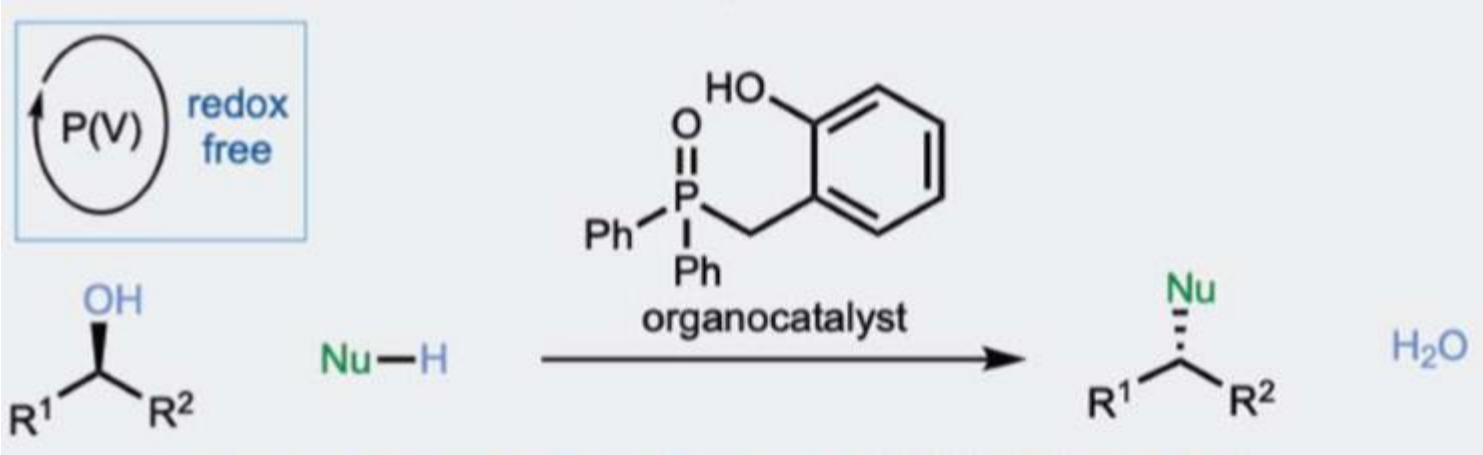


This work :



Redox-free catalytic Mitsunobu reaction enabled by a redox-neutral dehydration platform

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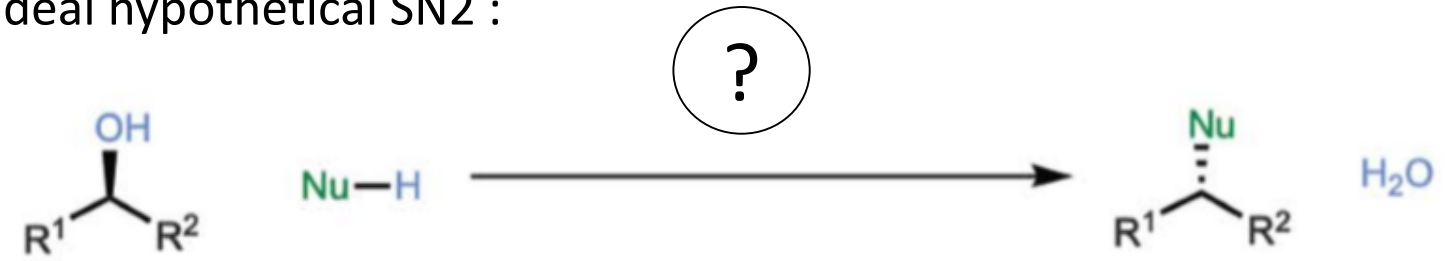
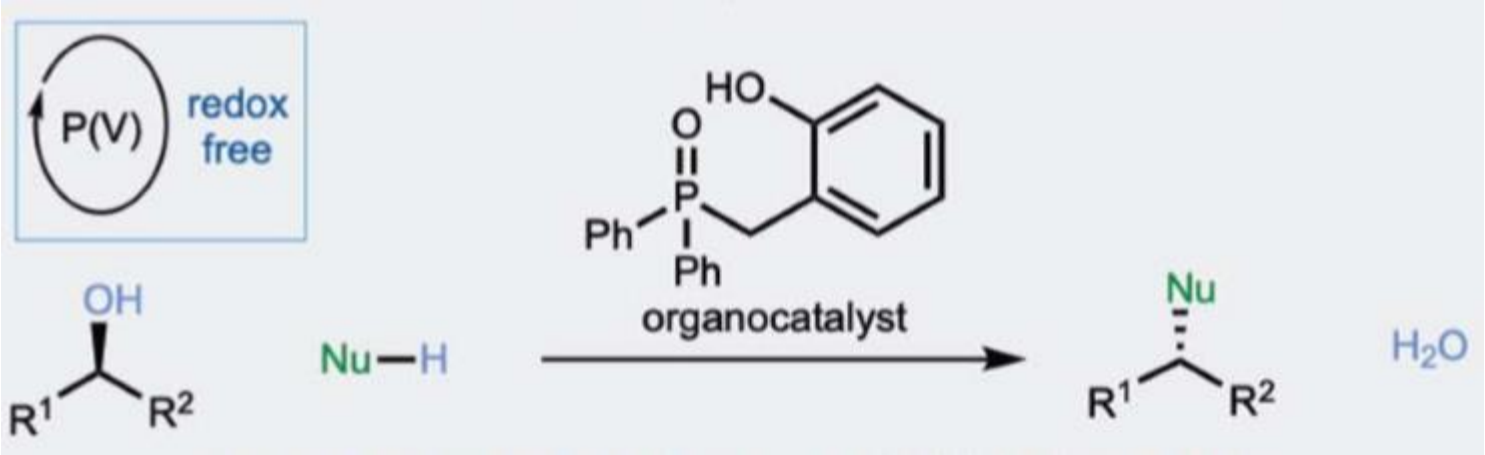
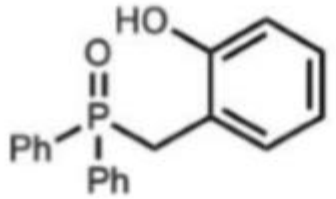
→ No stochiometric Oxydant
→ No stochiometric Reductant
→ Catalytic Inversion
→ Non-Hazardeous by-product

Ideal hypothetical SN2 :



This work :

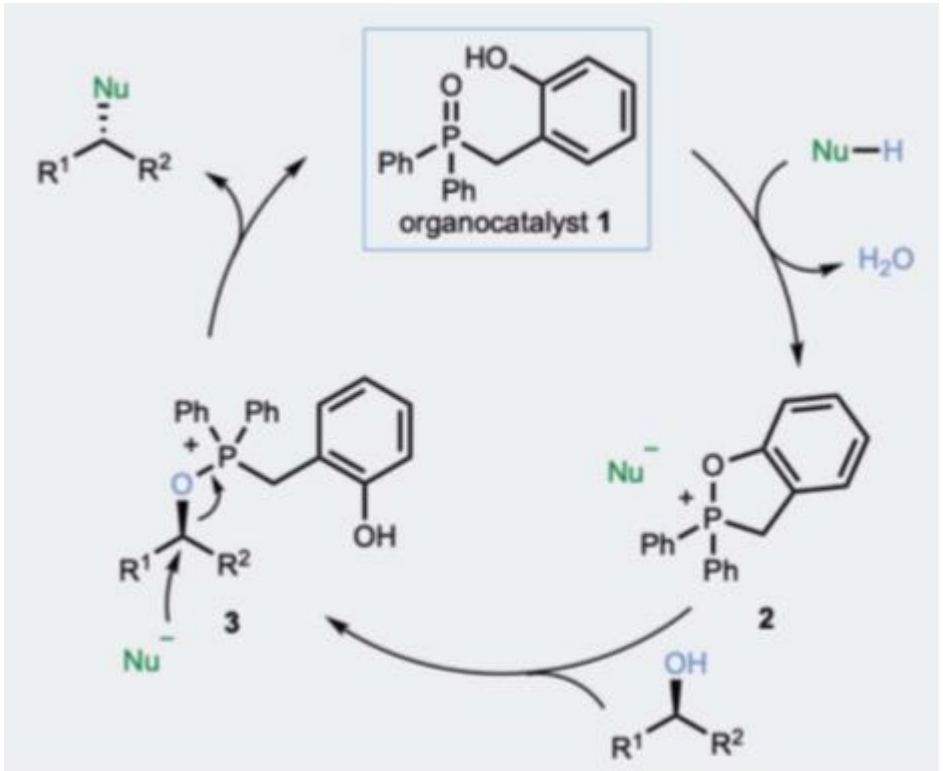




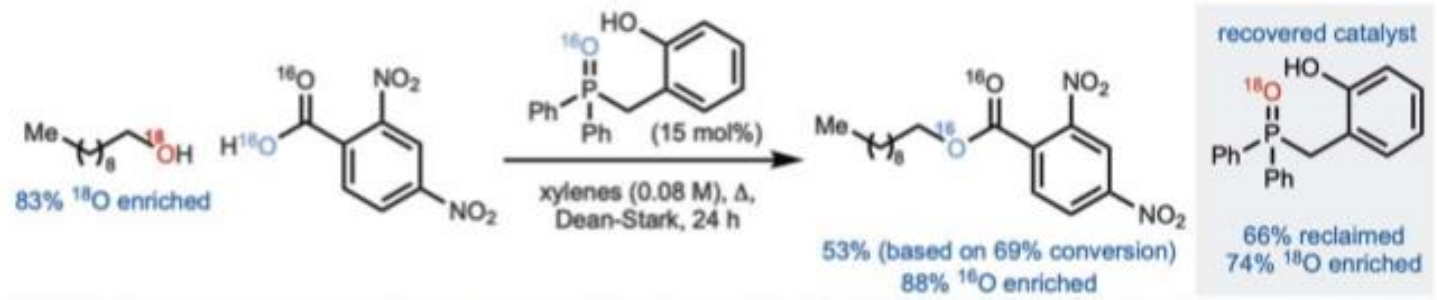
- **68% 2 steps (10 g scale)**
- **no chromatography**
- **air and moisture stable, m.p. 167 °C**

Redox-free catalytic Mitsunobu reaction enabled by a redox-neutral dehydration platform

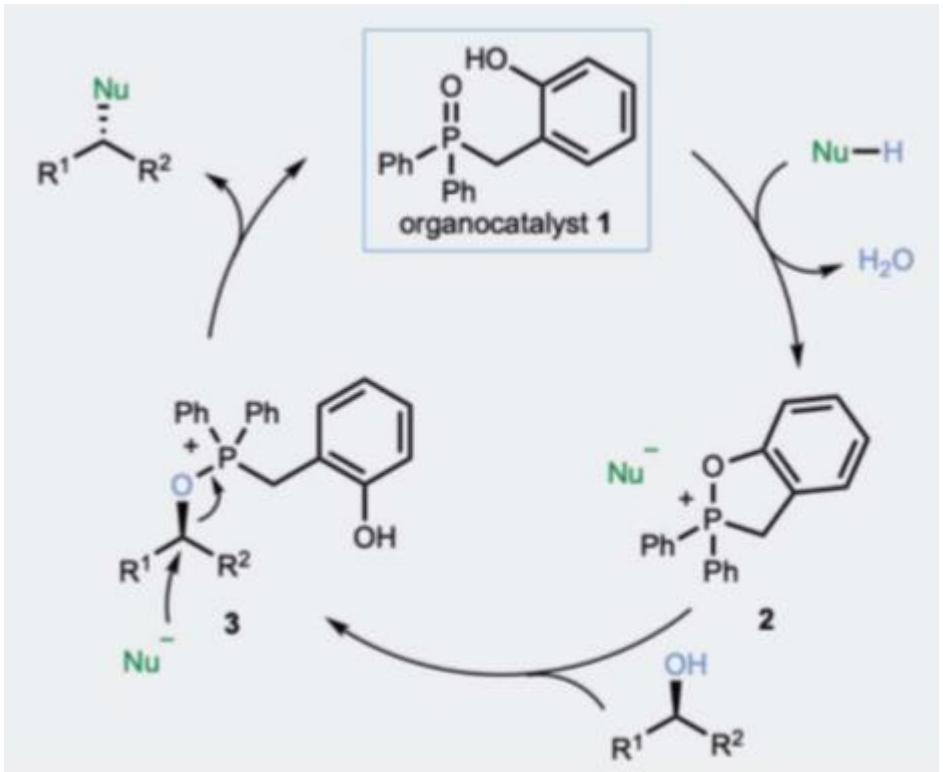
Mechanism :


Nu
R1
R2
HO
O
P
Ph
Ph
organocatalyst 1
Nu—H
H2O
Ph
Ph
P
O
OH
R1
R2
3
Nu
Nu
O
P
Ph
Ph
2
OH
R1
R2

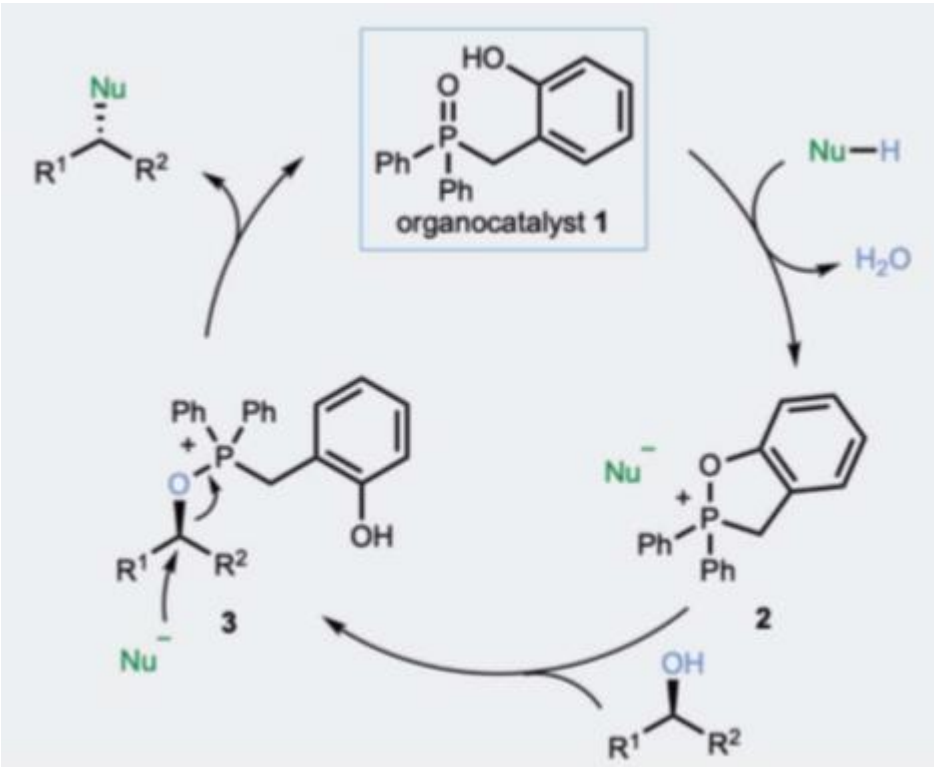
O-Labelling study :



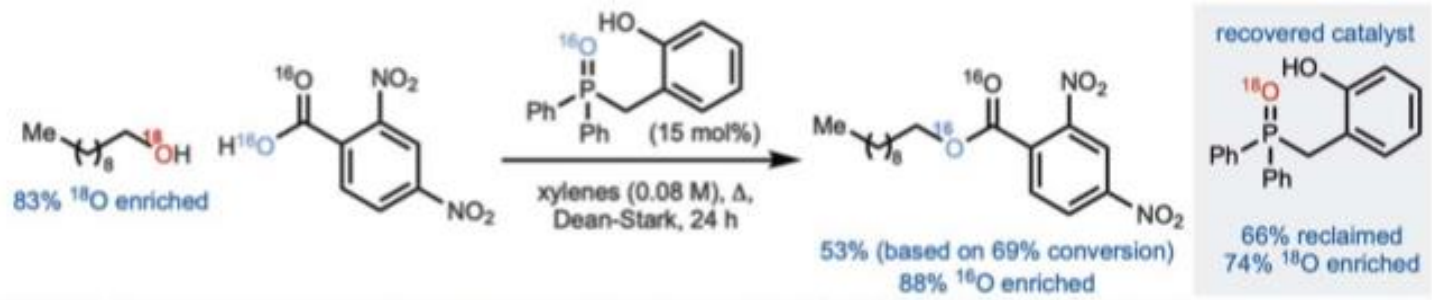
Mechanism :



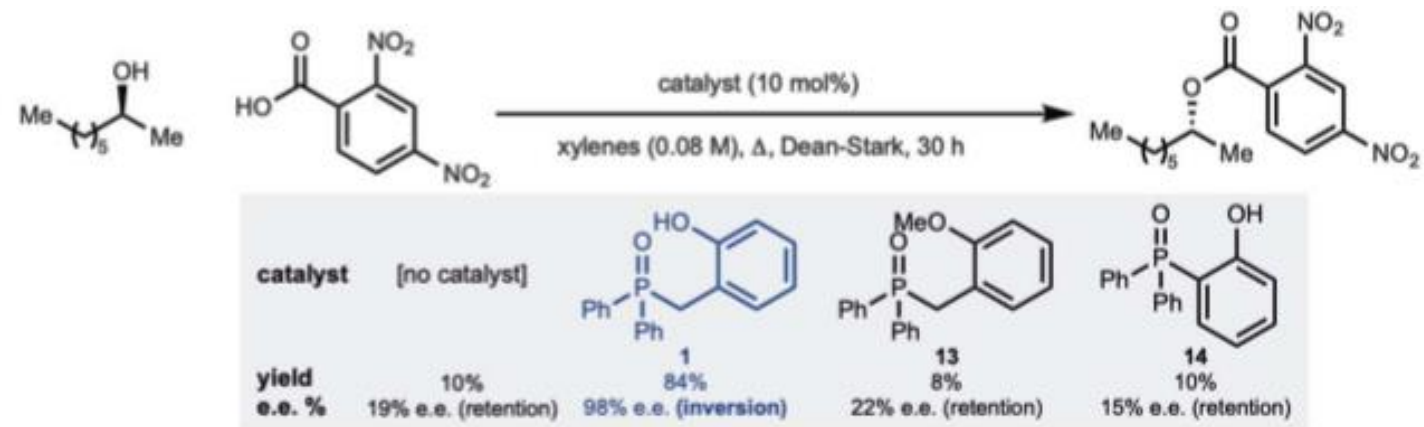
Mechanism :



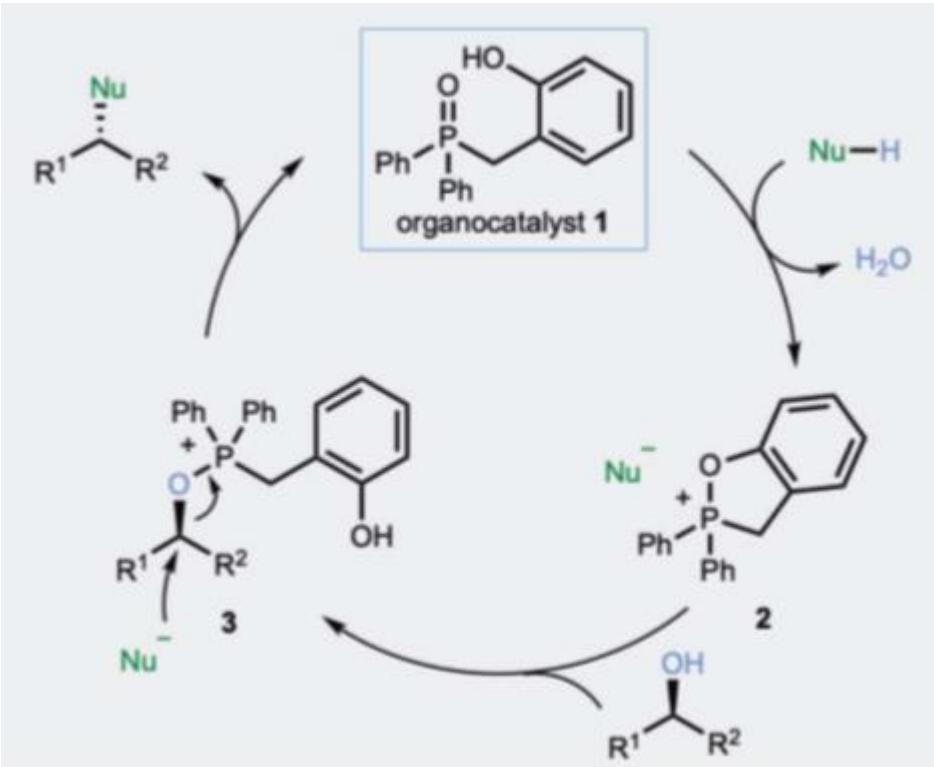
O-Labelling study :



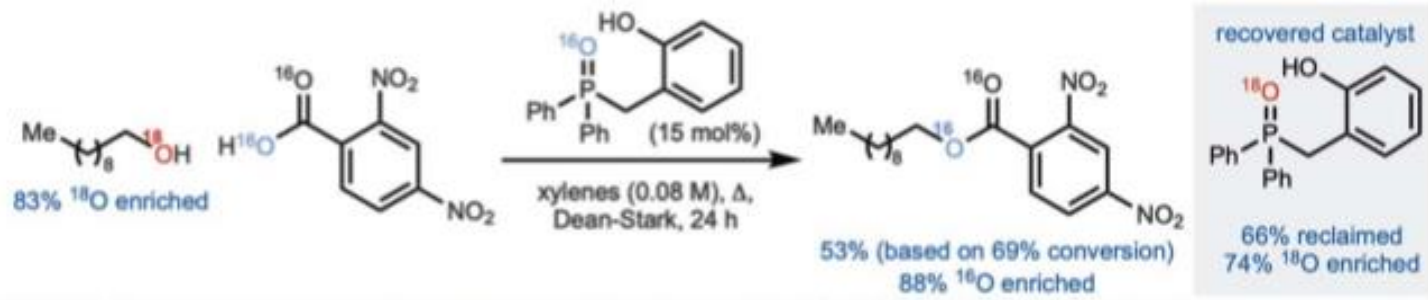
Structure – activity relationship :



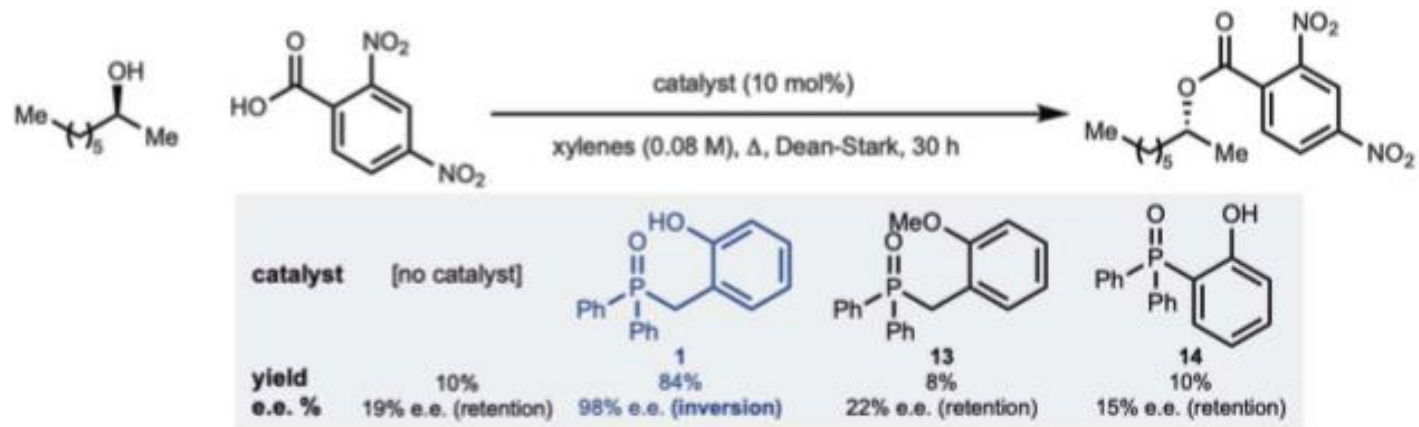
Mechanism :



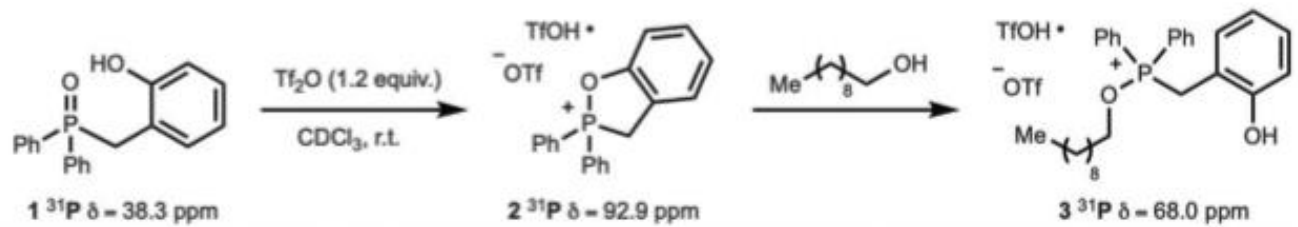
O-Labelling study :

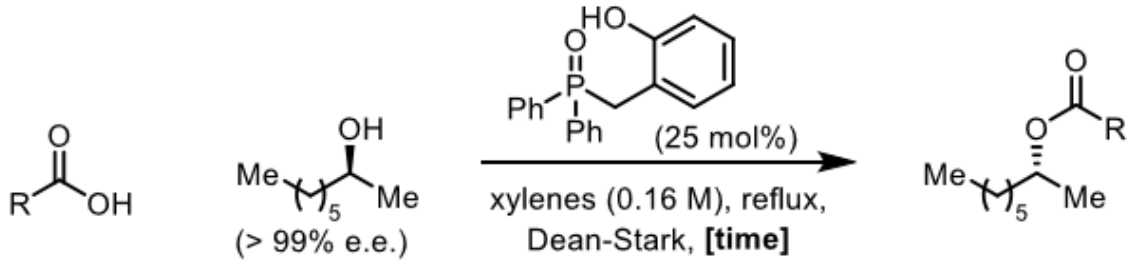


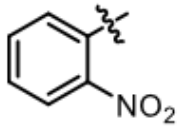
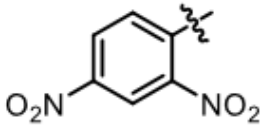
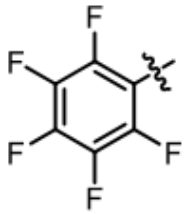
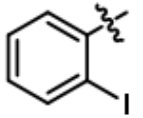
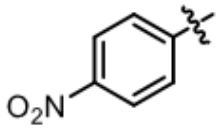
Structure – activity relationship :

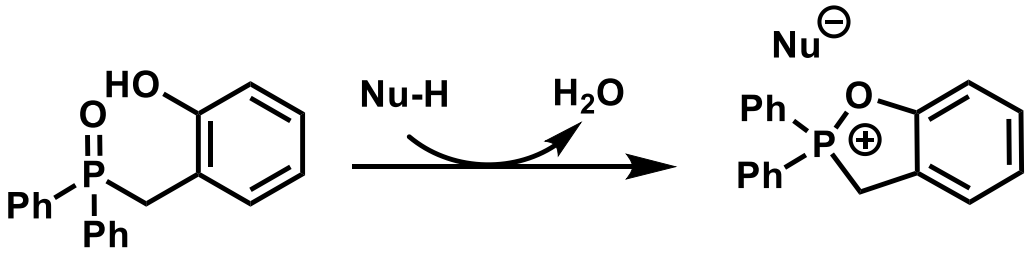


Phosphorus NMR monitoring using triflic anhydride :





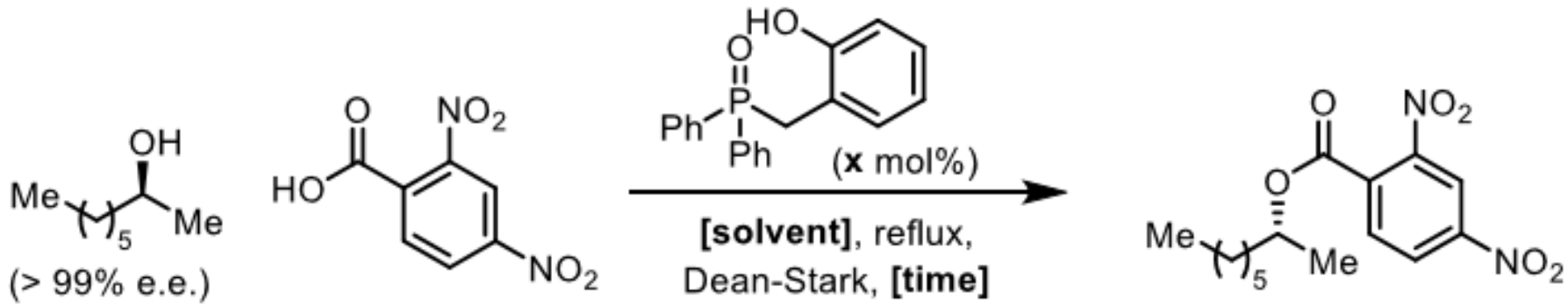
Entry	R	Isolated Yield (%)	Reaction time (hours)	Product e.e. (%)
1		74	48	94
2		76	20	96
3		68	20	89
4		25 (based on 33% conversion)	20	90
5		24 (based on 50% conversion)	48	91



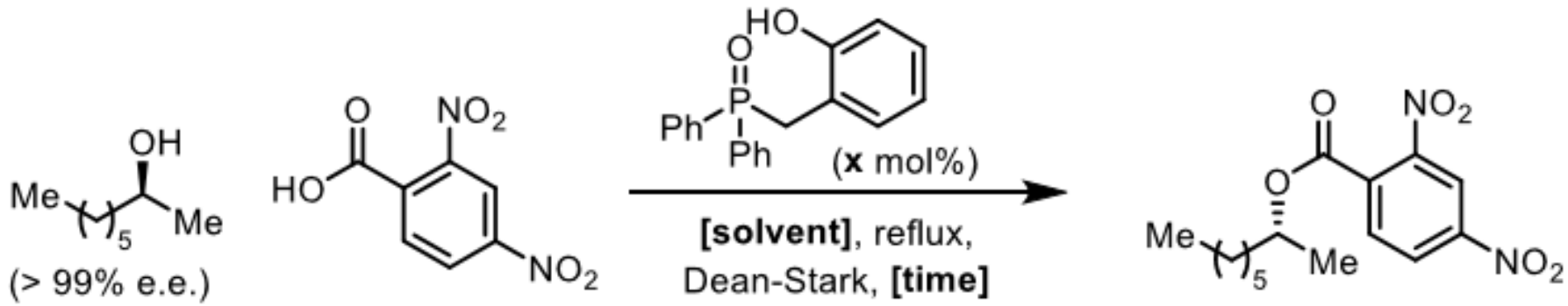
→ Reaction did not work with unsubstituted benzoic acid

→ Pronucleophile needs to be acidic enough to promote dehydration step

Pronucleophile	Pka (H2O)
Benzoic acid	4,2
p-Nitro benzoic acid	3,4
o-Iodo benzoic acid	3,0
o-Nitro benzoic acid	2,2
Pentafluoro benzoic acid	1,5
Dinitro benzoic acid	1,4



Entry	Solvent	Catalyst loading / (mol%)	Concentration / (M)	Reaction duration / (hours)	Isolated yield / (%)	Product e.e. / (%)
1	toluene	10	0.080	72	56	98
2	toluene	10	0.16	72	54	96
3	toluene	10	0.40	96	72	89
4	toluene	25	0.080	96	75	96
5	toluene	25	0.16	72	77	90
6	xylenes	10	0.080	30	84	98
7	xylenes	10	0.16	24	74	96
8	xylenes	10	0.40	24	65	91
9	xylenes	25	0.16	20	76	97



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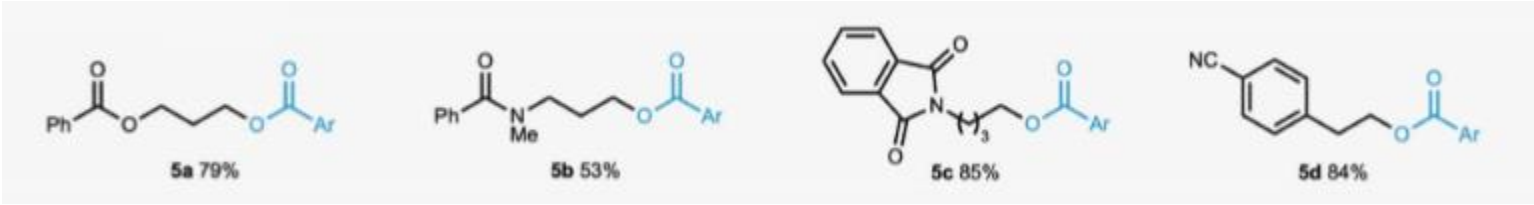
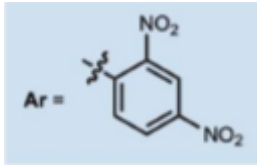
5	toluene	25	0.16	72	77	90
6	xylenes	10	0.080	30	84	98
7	xylenes	10	0.16	24	74	96
8	xylenes	10	0.40	24	65	91
9	xylenes	25	0.16	20	76	97

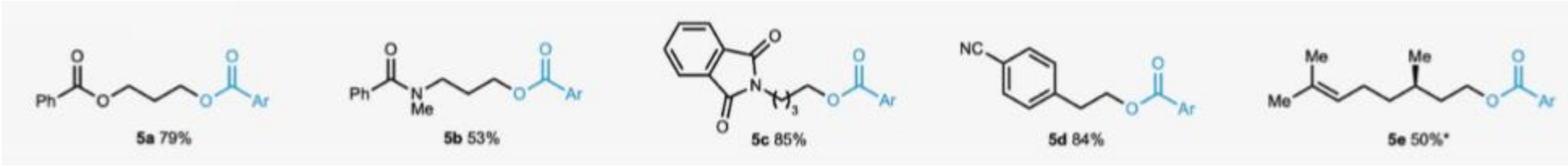
C-O bond formation :





I alcohols

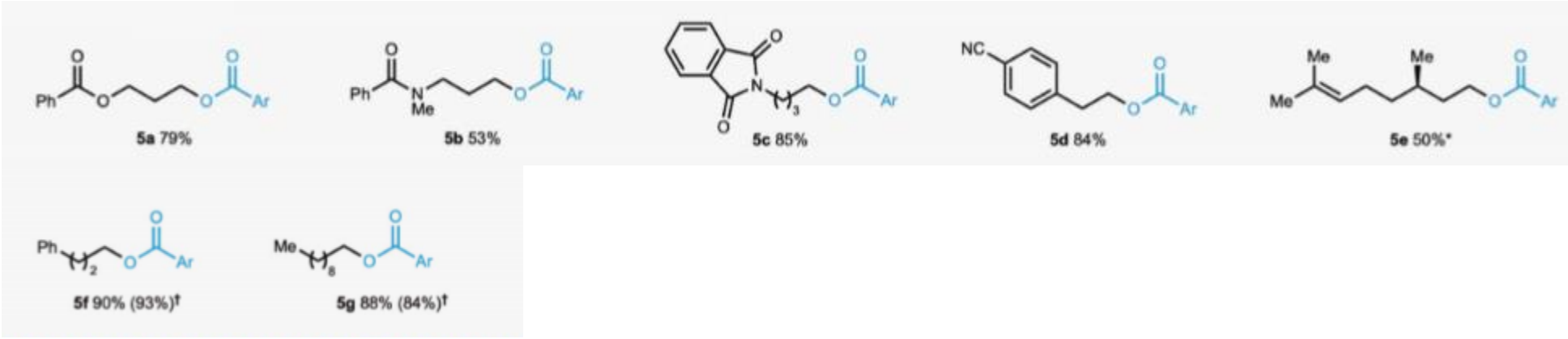
C-O bond formation :



I alcohols

C-O bond formation :

I alcohols



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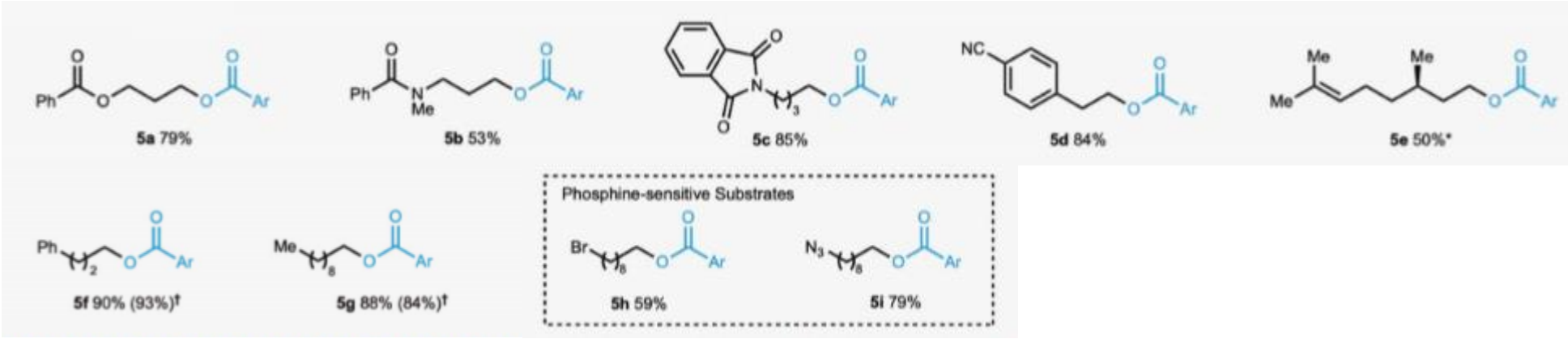
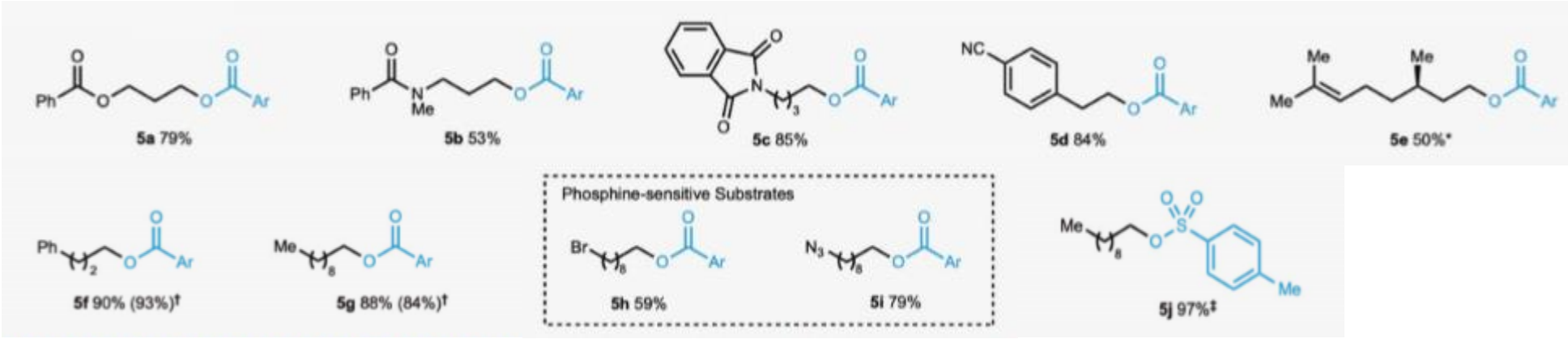
I alcohols



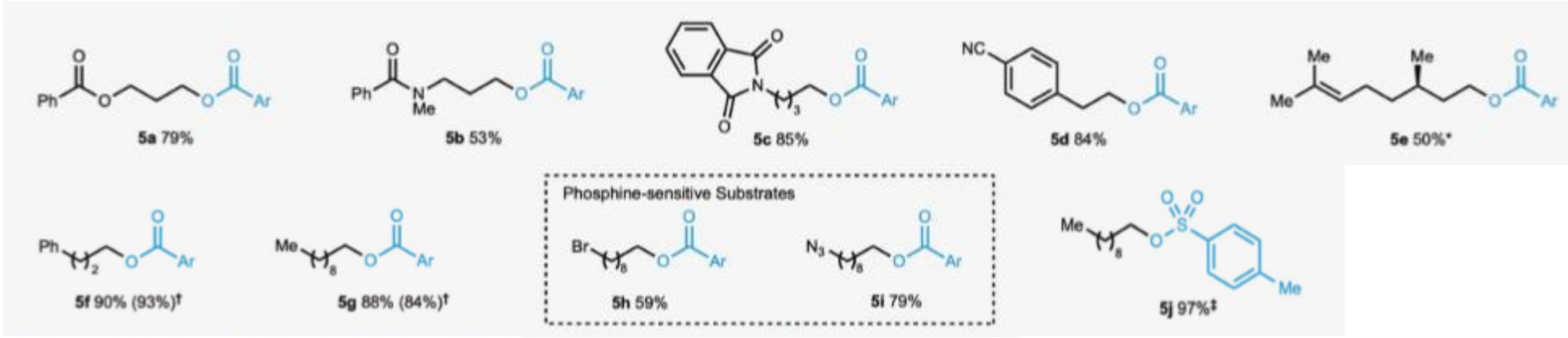
C-O bond formation :

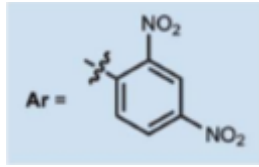
I alcohols



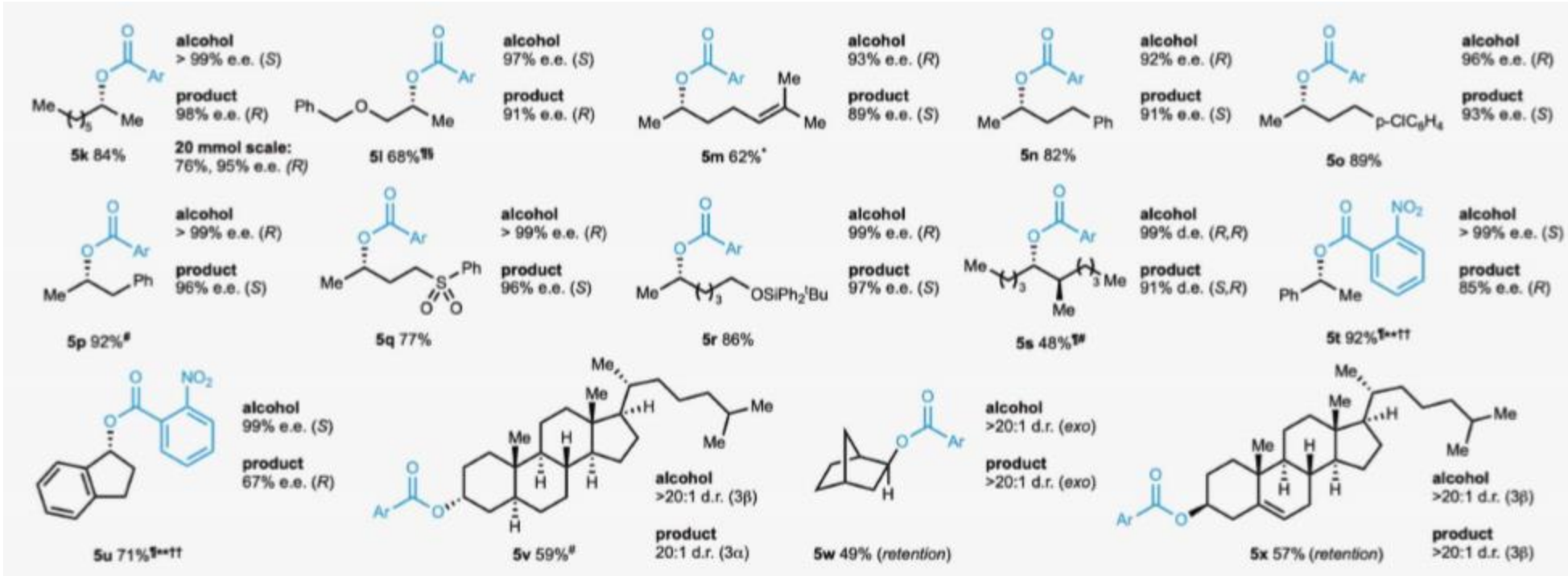
C-O bond formation :

I alcohols

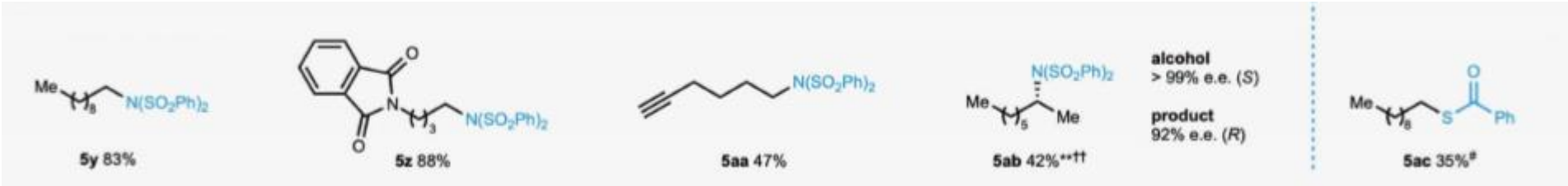




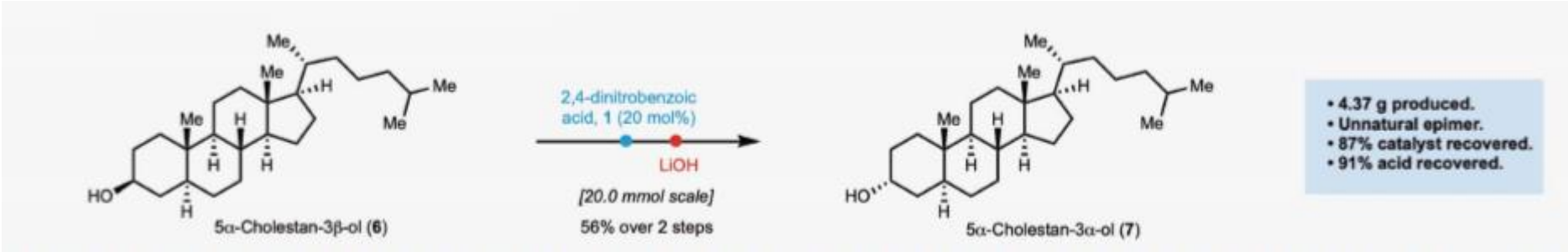
II alcohols



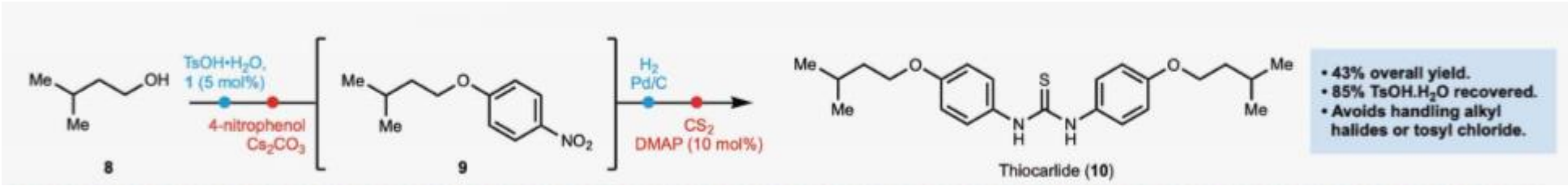
C-N and C-S bond formation :



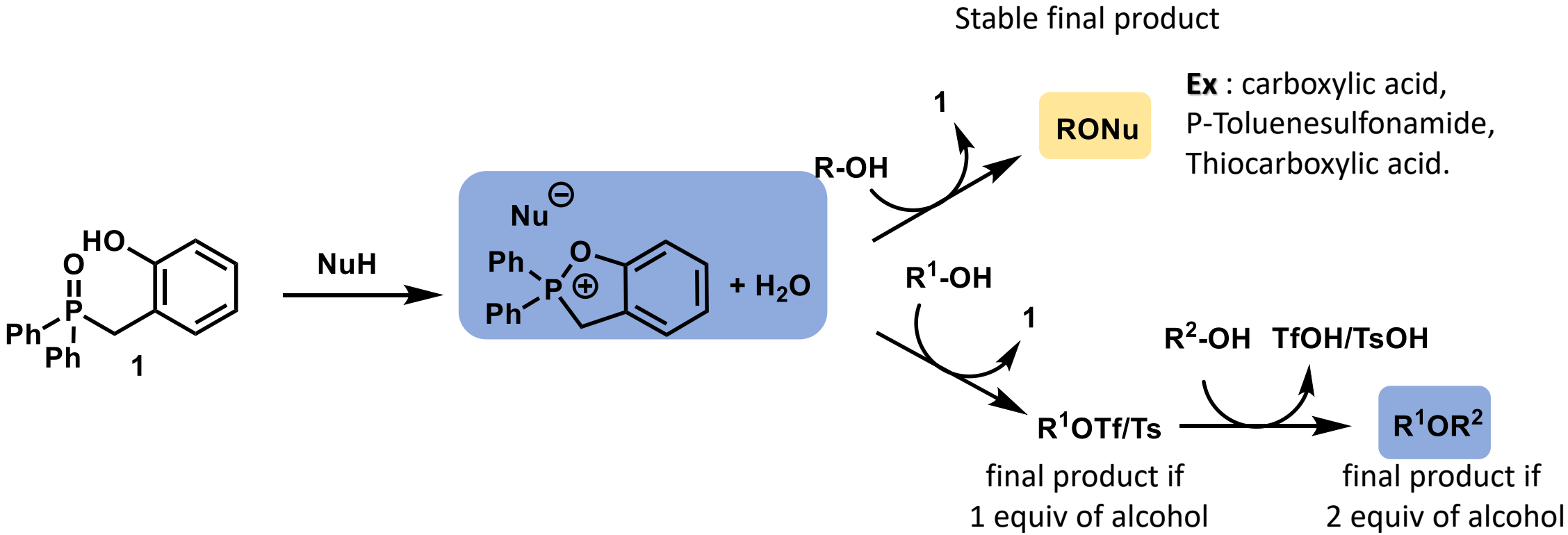
Application on steroid derivative :



Synthesis of active pharmaceutical ingredients:



Synthesis of ether using Triflic/Tosylic acid:

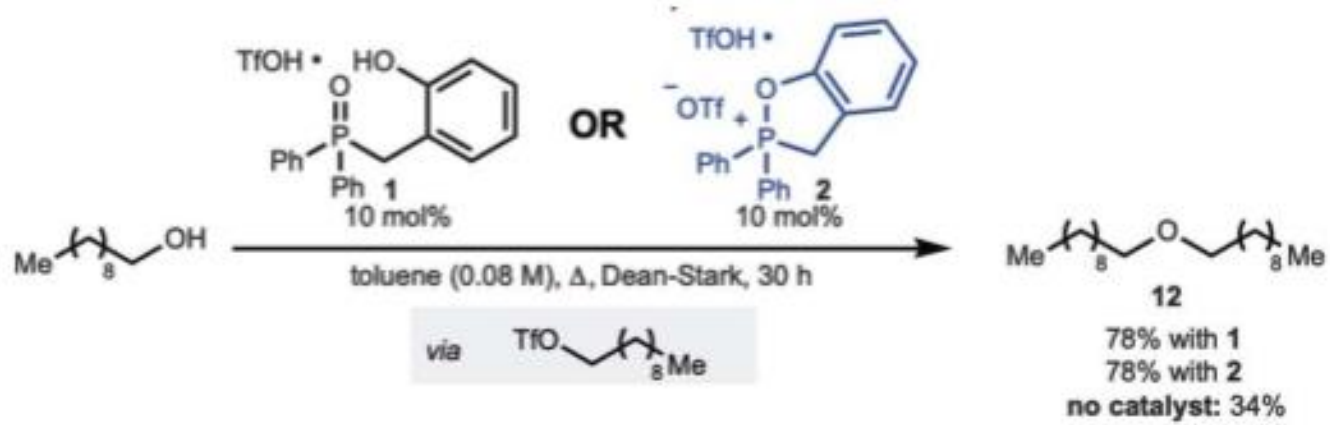


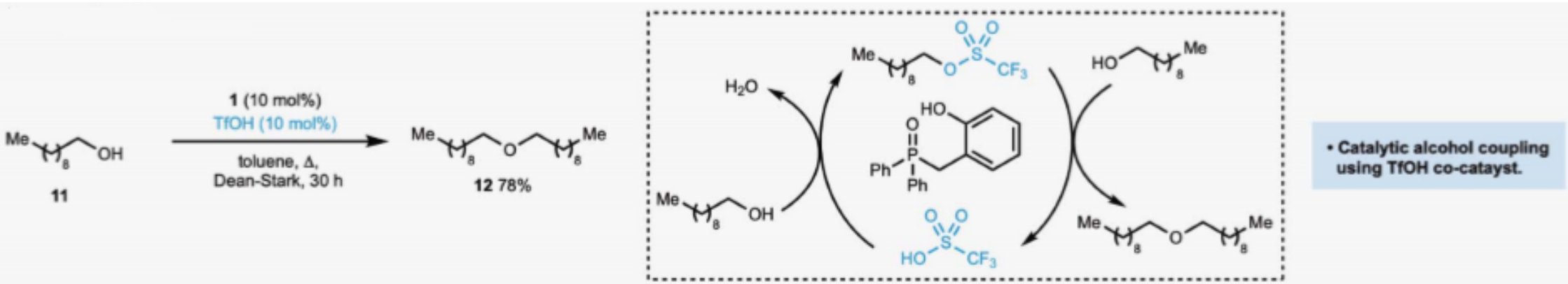
Using Triflic/tosylic acid :

→ good leaving group
→ Product can undergo another SN
→ Catalytic amount of acid if synthesis of ether

Using carbocylic Acids :

→ Synthesis of stable ester product

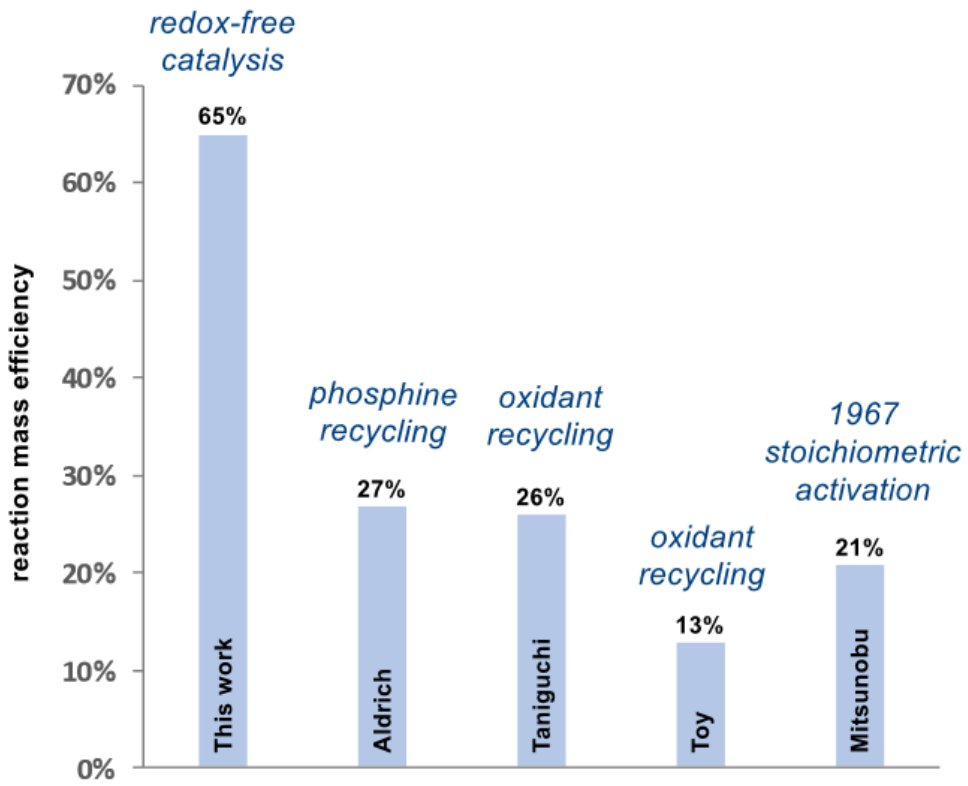

TfOH •
HO
O
P
Ph
Ph 1
10 mol%
OR
TfOH •
OTf
O
P
Ph
Ph 2
10 mol%
Me
8
OH
toluene (0.08 M), Δ, Dean-Stark, 30 h
via
TfO
8
Me
Me
8
O
8
Me
12
78% with 1
78% with 2
no catalyst: 34%


Me
8
OH
11
1 (10 mol%)
TfOH (10 mol%)
toluene, Δ,
Dean-Stark, 30 h
Me
8
O
8
Me
12 78%
H2O
Me
8
OH
Me
8
O
S
O
O
CF3
HO
O
P
Ph
Ph
HO
S
O
O
CF3
HO
8
Me
Me
8
O
8
Me
• Catalytic alcohol coupling using TfOH co-catayst.

Conclusion :

→Better AE

→Better RME



→No stochiometric oxidant

→No stochiometric reductant

→Catalytic Inversion

→Water sole by-product

→Air and moisture stable catalyst

→Catalyst : 2 steps synthesis

→Allows formation of C-O, C-N and C-S bonds

→Allows formation of ethers

→ Atom economy