Redox-neutral Organocatalytic Mitsunobu Reactions

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Checker: Yang Zhao
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Beddoe, R. H.; Denton, R. M. *et al*. *Science* **2019**, *365*, 910

Contents

CV of Prof. Ross M. Denton

Background:

- **2001-2004** Ph.D., University of Nottingham
- **2005-2007** Postdoc, The Scripps Research Institute
- **2007-2008** Postdoc, University of Cambridge
- **2008-2016** Lecturer, Lectureship, University of Nottingham
- **2016-Now** Associate Professor, University of Nottingham

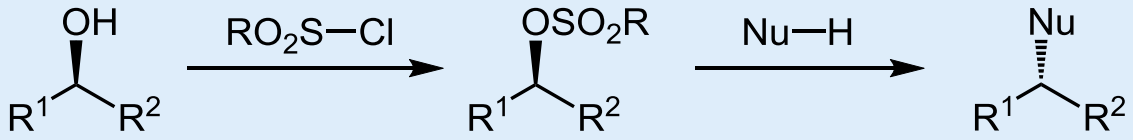
Research Interests:

- ✓ The design and development of new reactions, synthesis methods, and catalysts to make valuable organic molecules more efficiently
- ✓ Organophosphorus and organosilicon chemistry

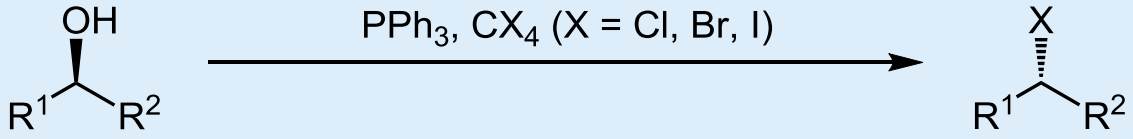
Introduction

Nucleophilic substitution reactions of alcohols

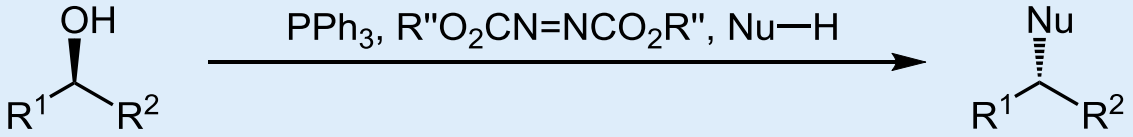
a) Sulfonate approach



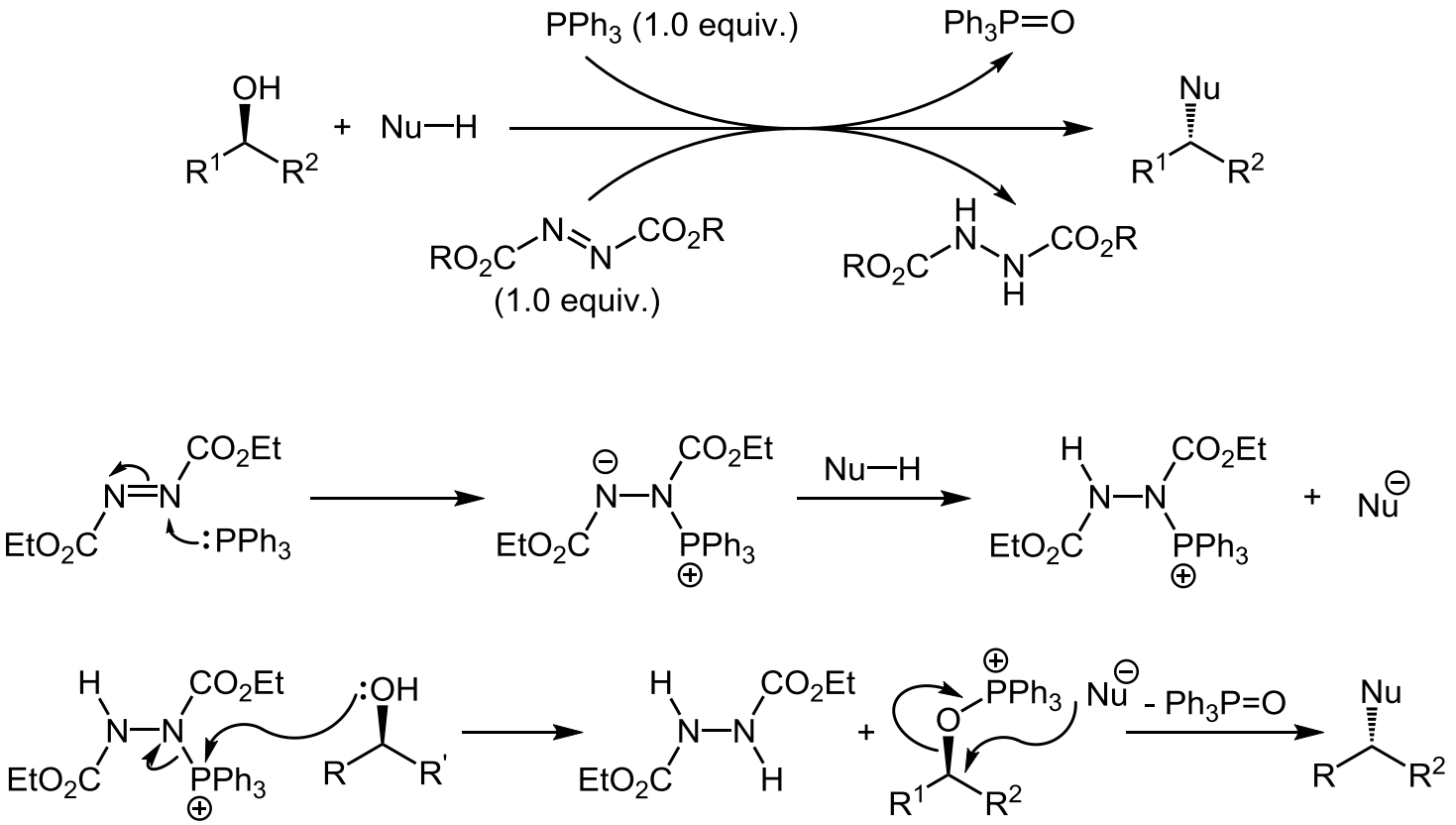
b) Appel reaction



c) Mitsunobu reaction

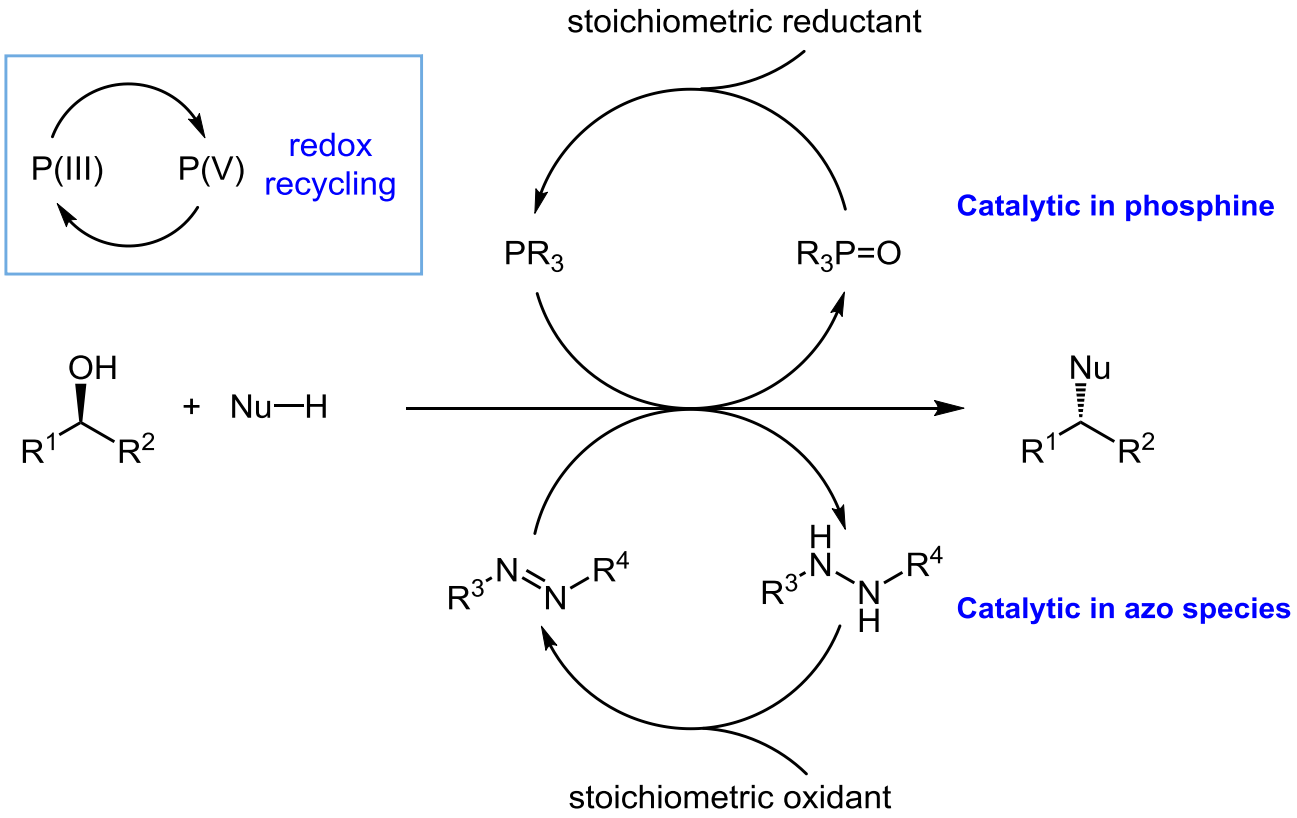


Mitsunobu Reaction

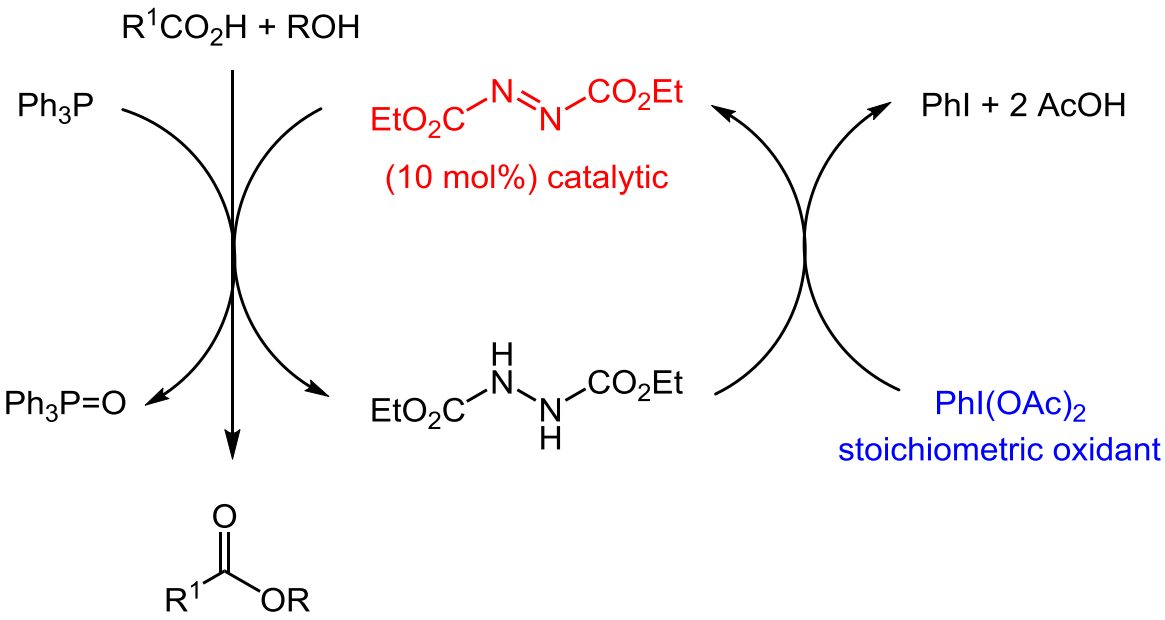


Mitsunobu, O. *et al. Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380

Redox Organocatalytic Mitsunobu Reactions

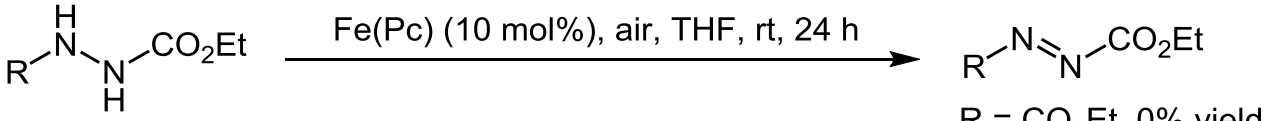


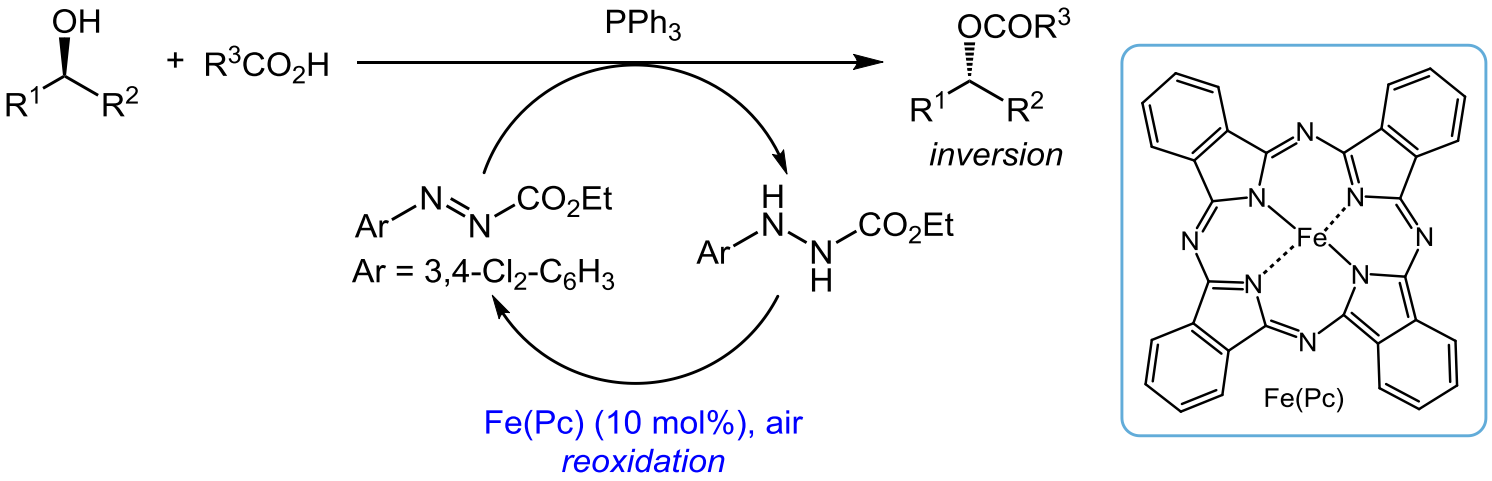
Mitsunobu Reactions with Catalytic Azo Species



Toy, P. H. *et al. J. Am. Chem. Soc.* **2006**, *128*, 9636

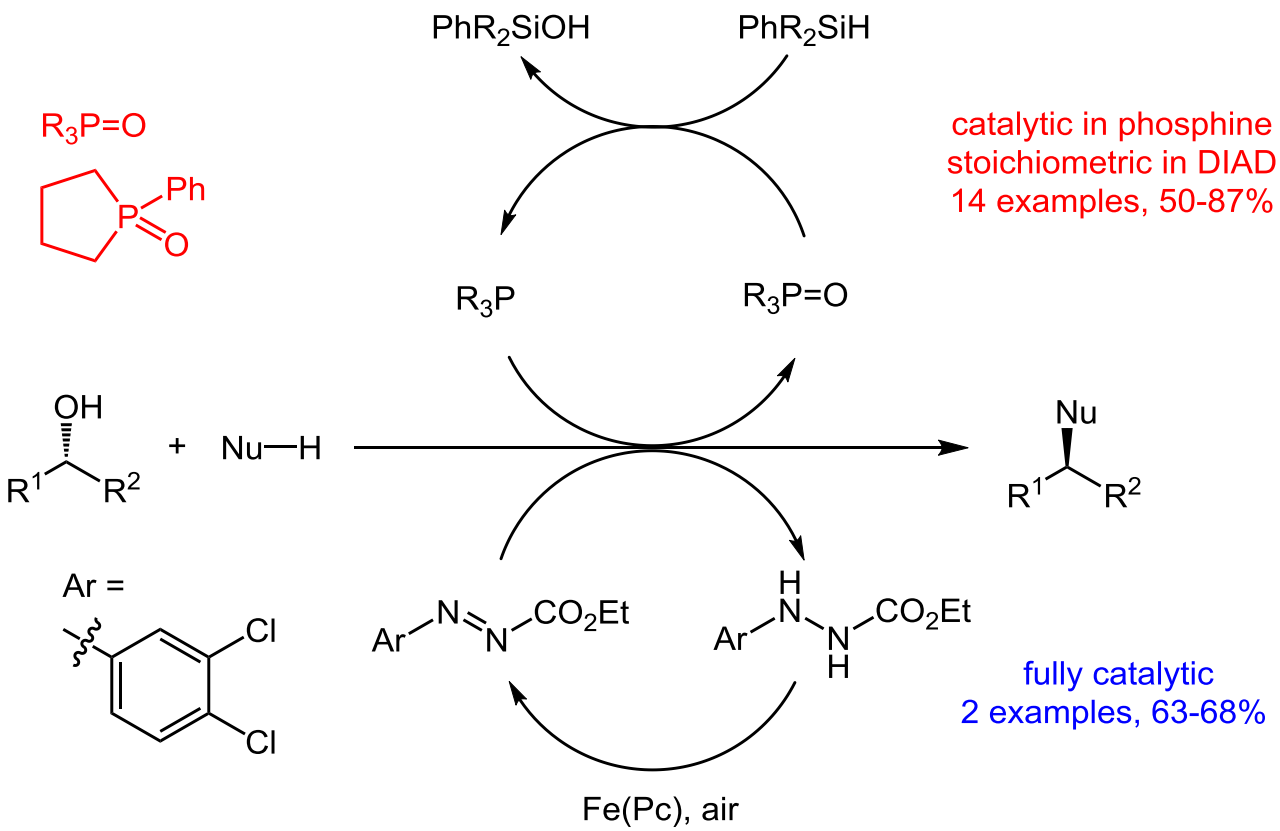
Mitsunobu Reactions with Catalytic Azo Species





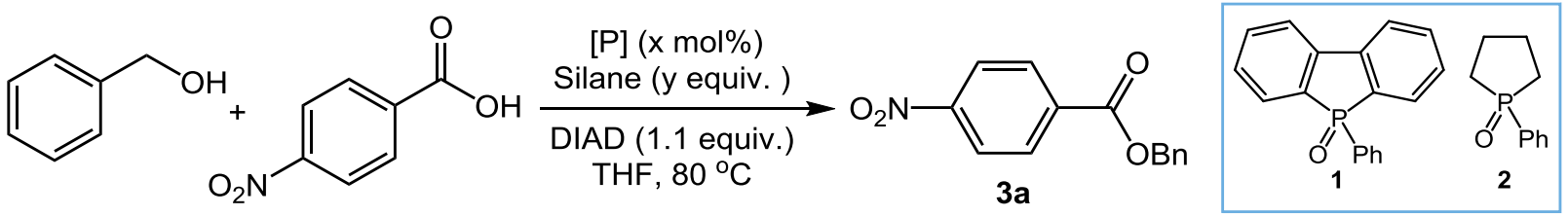
Taniguchi, T. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 4613

Catalytic in Phosphine and Fully Catalytic System



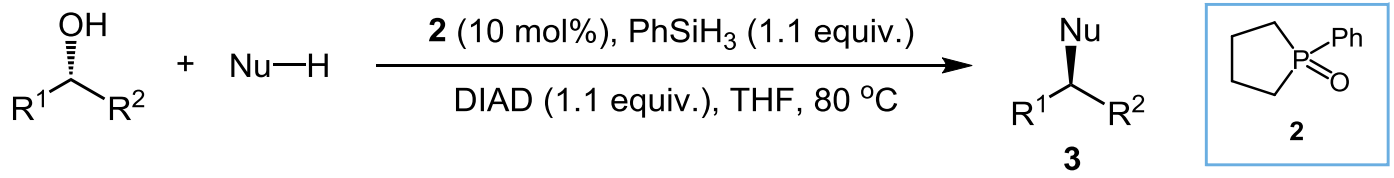
Aldrich, C. C. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 13041

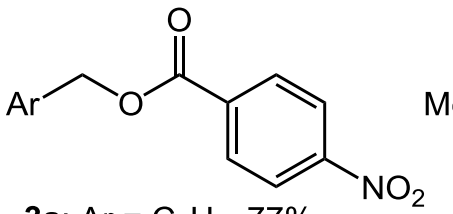
Catalytic in Phosphine



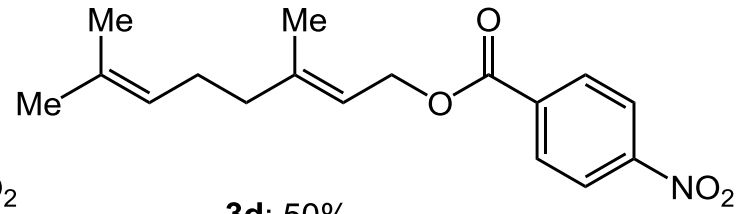
Entry	[P]	x	Silane	y	Yield (%)
1	TPP	110	none		84
2	TPP	110	$PhSiH_3$	1.1	77
3	**1**	10	PHMS	1.5	0
4	**1**	10	Ph_3SiH	2.0	0
5	**1**	10	Ph_2SiH_2	1.1	42
6	**1**	10	$PhSiH_3$	1.1	63
7	**2**	10	$PhSiH_3$	1.1	77
8	**2**	5	$PhSiH_3$	1.1	77
9	**2**	2	$PhSiH_3$	1.1	58
10	**2**	1	$PhSiH_3$	1.1	54

Substrate Scope

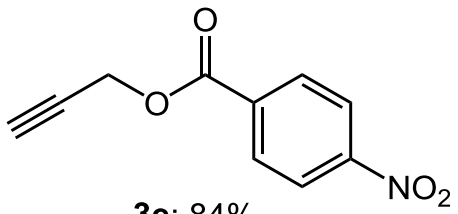




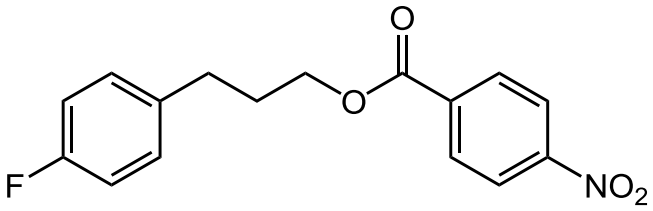
3a: Ar = C_6H_5, 77%
3b: Ar = 4-$F_3CC_6H_4$, 76%
3c: Ar = 4-$MeOC_6H_4$, 61%



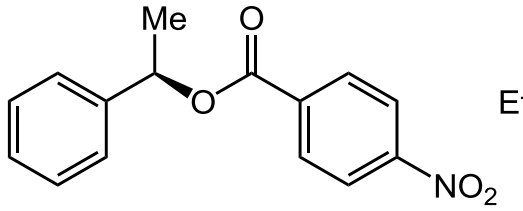
3d: 50%



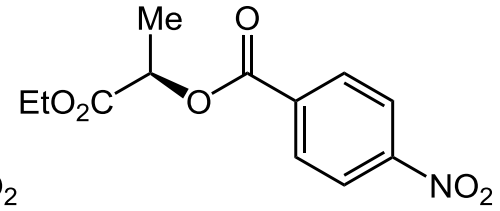
3e: 84%



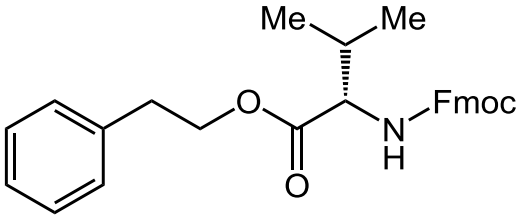
3f: 82%



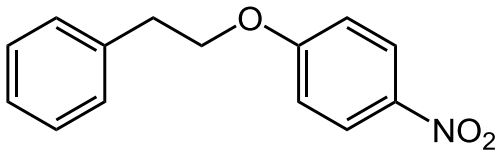
3g: 69%, 88% ee



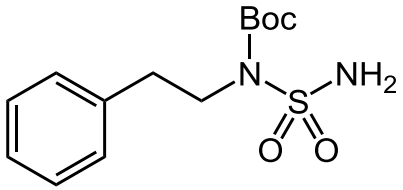
3h: 68%, > 99% ee



3i: 63%

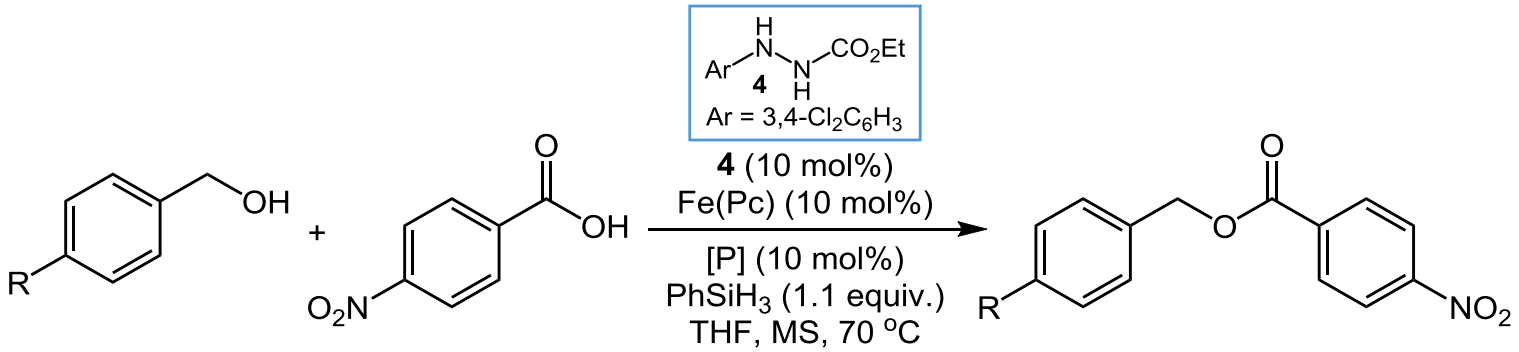


3j: 51%



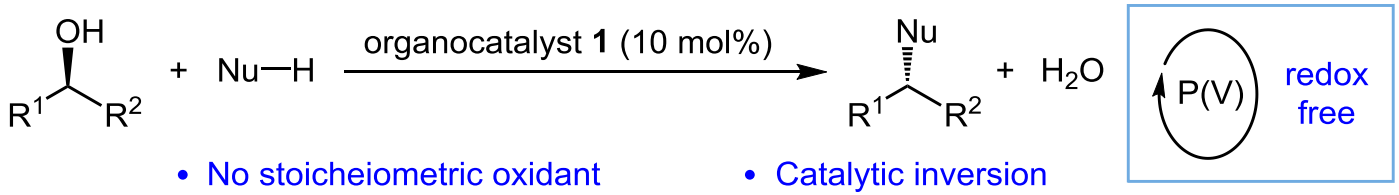
3k: 72%

Fully Catalytic System



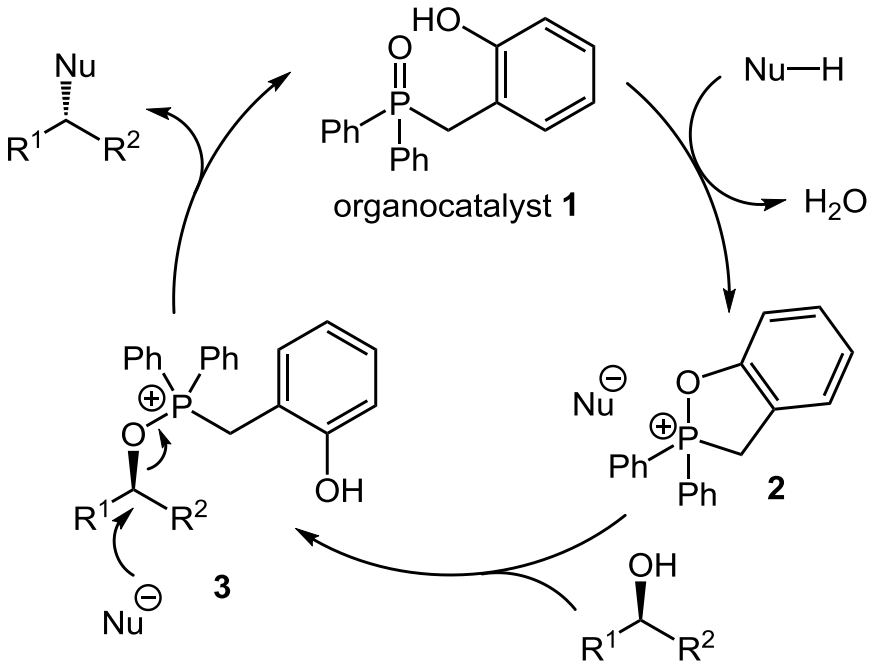
Entry	R	[P]	MS [Å]	Atmosphere	Yield (%)
1	OMe	**1**	4	air	15
2	OMe	**1**	5	air	19
3	OMe	**1**	5	O_2 enriched	35
4	OMe	**2**	5	air	35
5	OMe	**2**	5	O_2 enriched	63
6	H	**2**	5	O_2 enriched	68

Redox-free Catalytic Mitsunobu Reactions



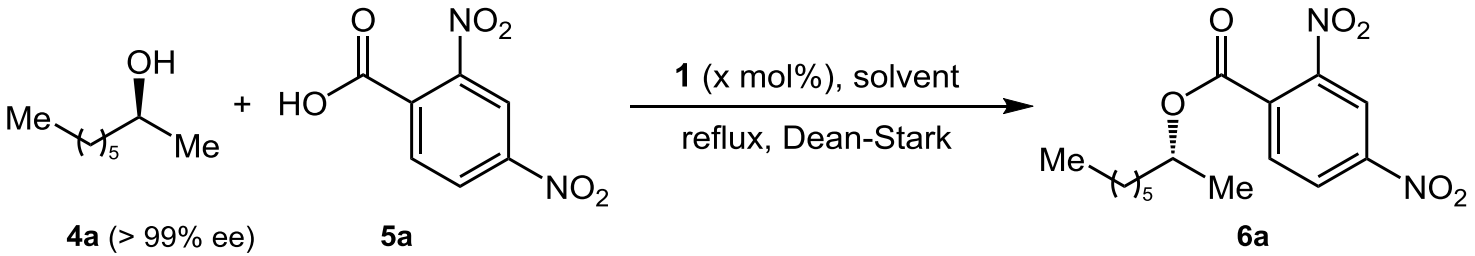
- No stoicheiometric oxidant
- No stoicheiometric reductant
- Catalytic inversion
- H_2O sole by-product

Enabled by a redox-neutral dehydration platform



Denton, R. M. *et al*. *Science* **2019**, *365*, 910

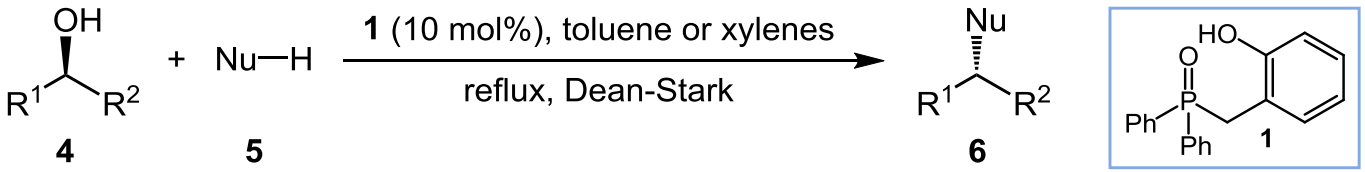
Redox-free Catalytic Mitsunobu Reactions



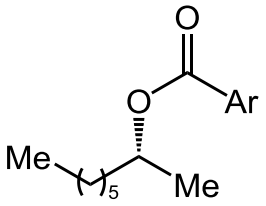
4a (> 99% ee) **5a** **6a**

Entry	Solvent	x	Concentration (M)	t (h)	Yield (%)	Ee (%)
1	toluene	10	0.08	72	56	98
2	toluene	10	0.16	72	54	96
3	toluene	10	0.40	96	72	89
4	toluene	25	0.08	96	75	96
5	toluene	25	0.16	72	77	90
6	**xylenes**	**10**	**0.08**	**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

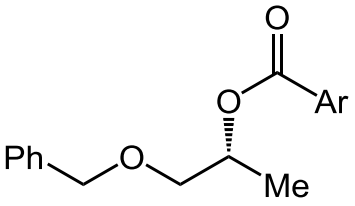
Substrate Scope



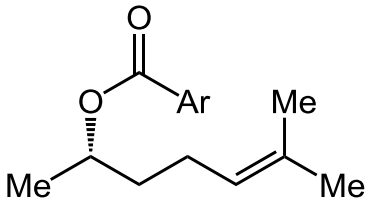
C-O bond formation Ar = 2,4-$(NO_2)_2C_6H_3$



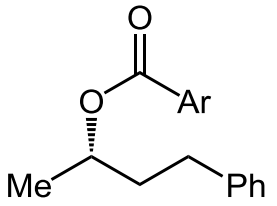
alcohol > 99% ee (*S*)
6a: 84%, 98% ee (*R*)



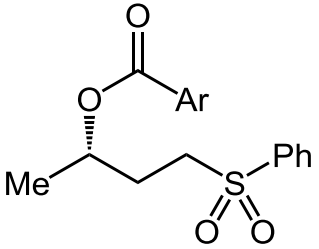
alcohol 97% ee (*S*)
6b: 68%, 91% ee (*R*)



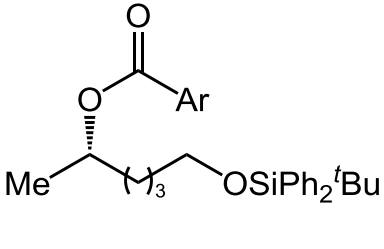
alcohol 93% ee (*R*)
6c: 62%, 89% ee (*S*)



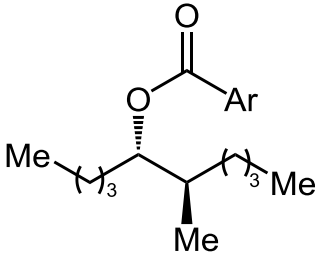
alcohol 92% ee (*R*)
6d: 82%, 91% ee (*S*)



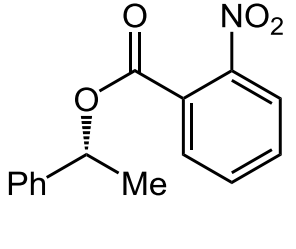
alcohol > 99% ee (*R*)
6e: 77%, 96% ee (*S*)



alcohol > 99% ee (*R*)
6f: 86%, 97% ee (*S*)



alcohol 99% de (*R,R*)
6g: 48%, 91% de (*S,R*)

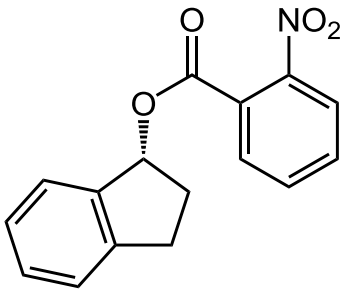


alcohol > 99% ee (*S*)
6h: 92%, 85% ee (*R*)

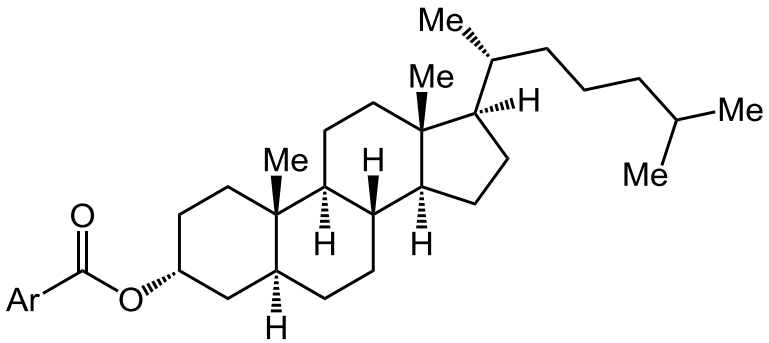
Substrate Scope

C-O bond formation

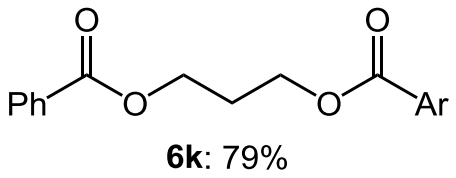
Ar = 2,4-$(NO_2)_2C_6H_3$



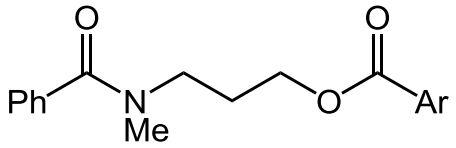
alcohol 99% ee (*S*)
6i: 71%, 67% ee (*R*)



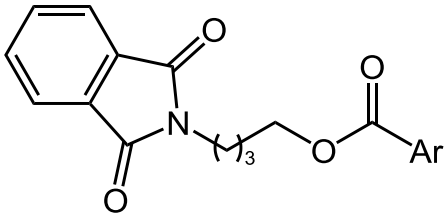
alcohol > 20:1 dr (3β)
6j: 59%, 20:1 dr (3α)



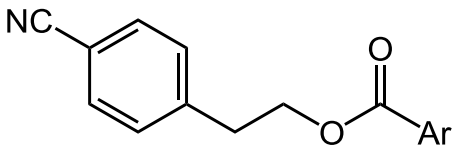
6k: 79%



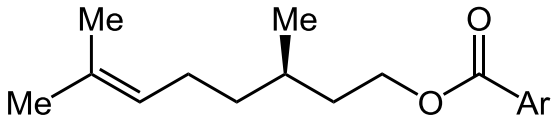
6l: 53%



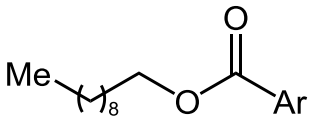
6m: 85%



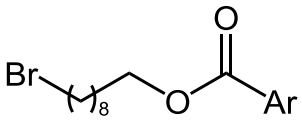
6n: 84%



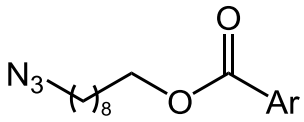
6o: 50%



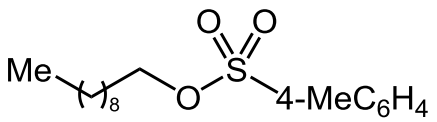
6p: 88%



6q: 59%



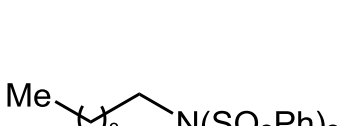
6r: 79%



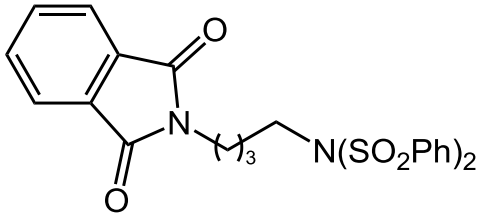
6s: 97%

Substrate Scope

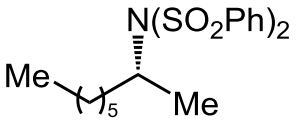
C-N bond formation



6t: 83%

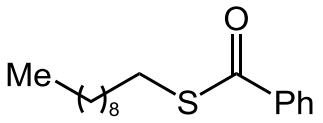


6u: 88%



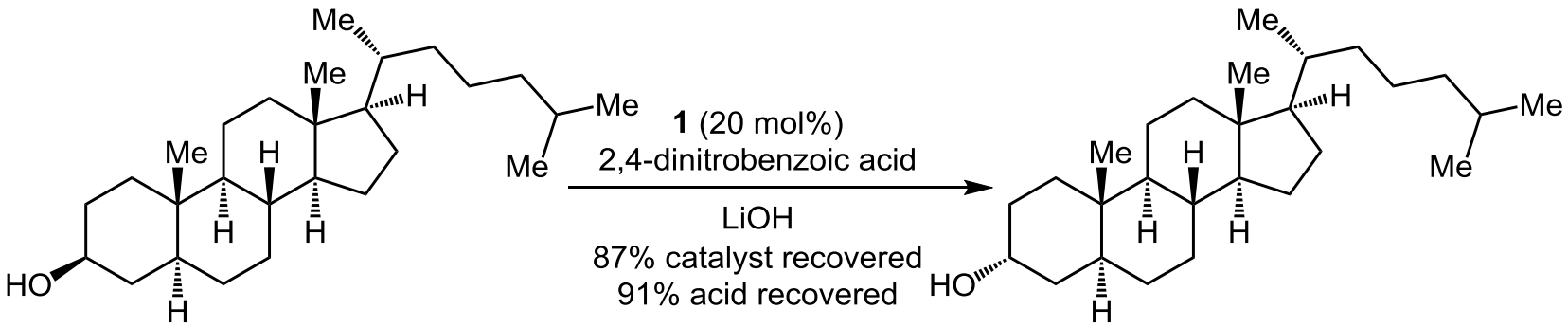
alcohol > 99% ee (*S*)
6v: 42%, 92% ee (*R*)

C-S bond formation



6w: 35%

Stereoinversion with catalyst and acid recovery

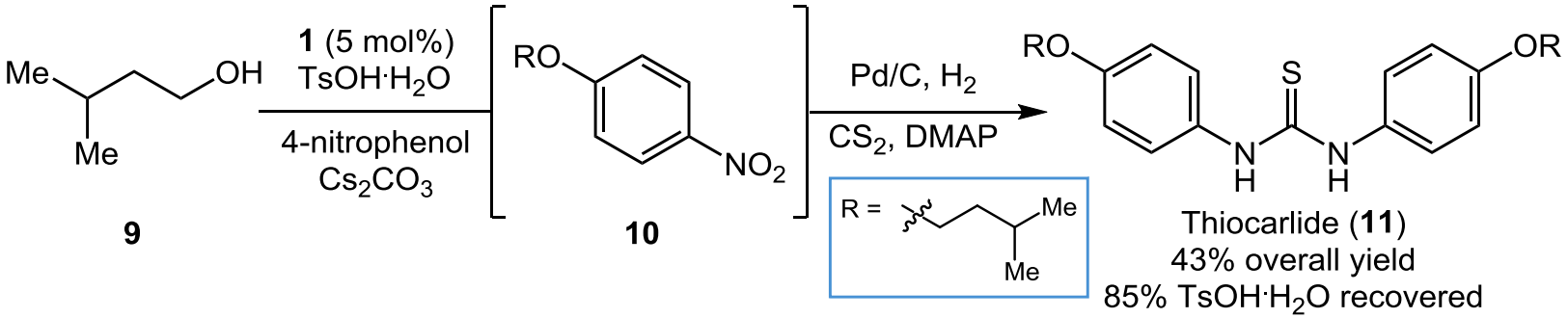


5α-Cholestan-3β-ol (**7**)
20 mmol

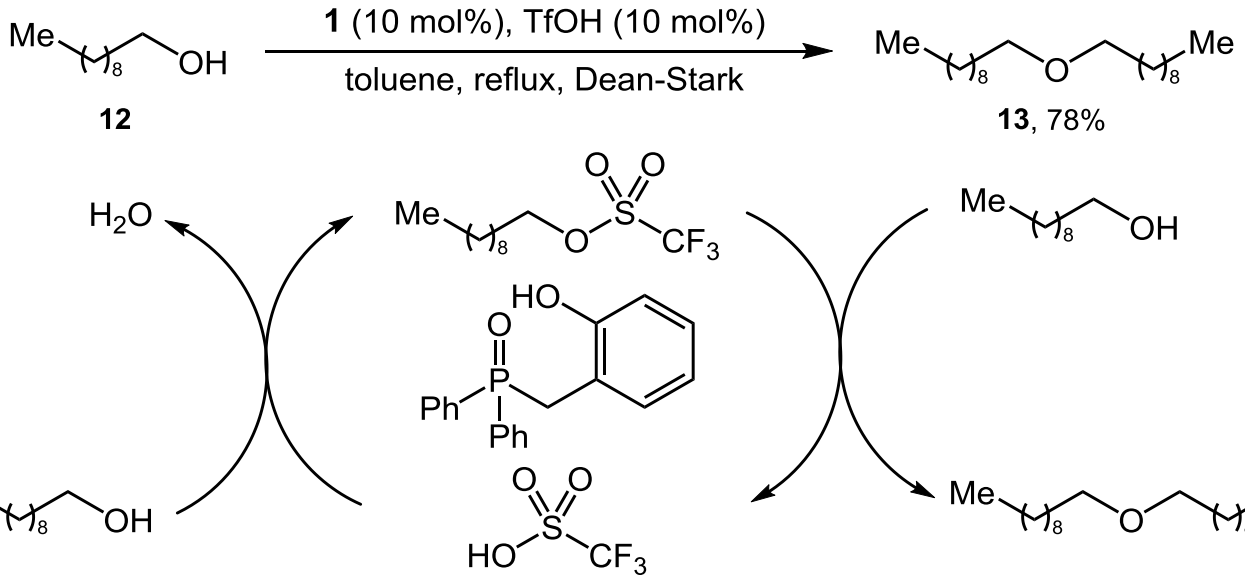
5α-Cholestan-3α-ol (**8**)
4.37 g, 56% yield

Substrate Scope

Active pharmaceutical ingredient synthesis

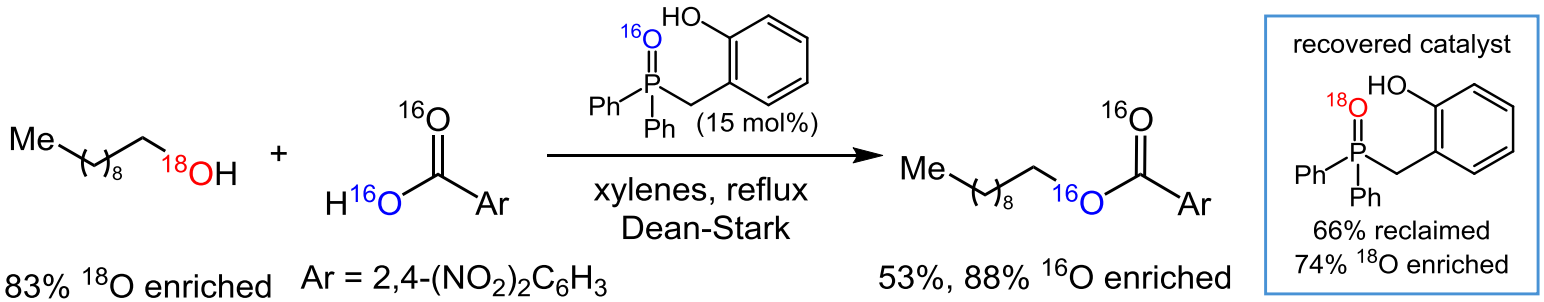


Ether synthesis



Mechanistic Investigation

A: Labelling study demonstrates oxygen transfer from decanol to phosphine oxide

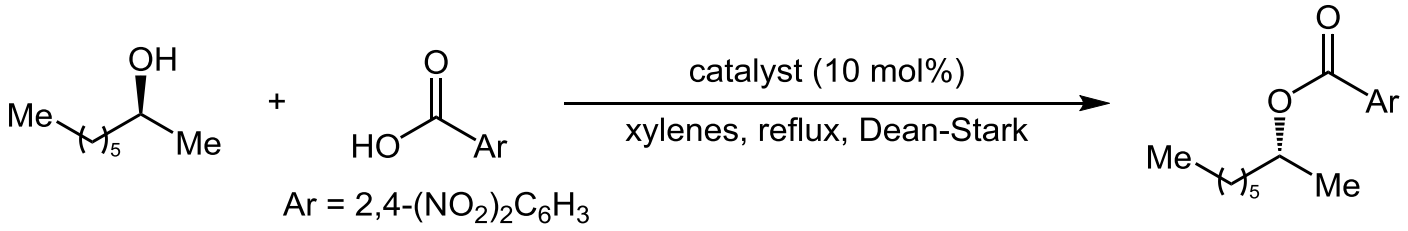


83% ^{18}O enriched

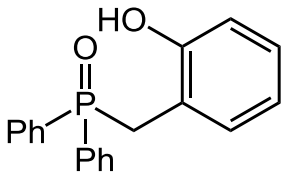
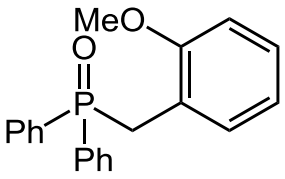
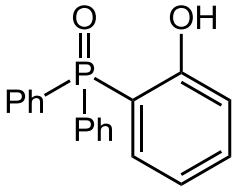
Ar = 2,4-$(NO_2)_2C_6H_3$

53%, 88% ^{16}O enriched

B: Catalyst structure activity relationship

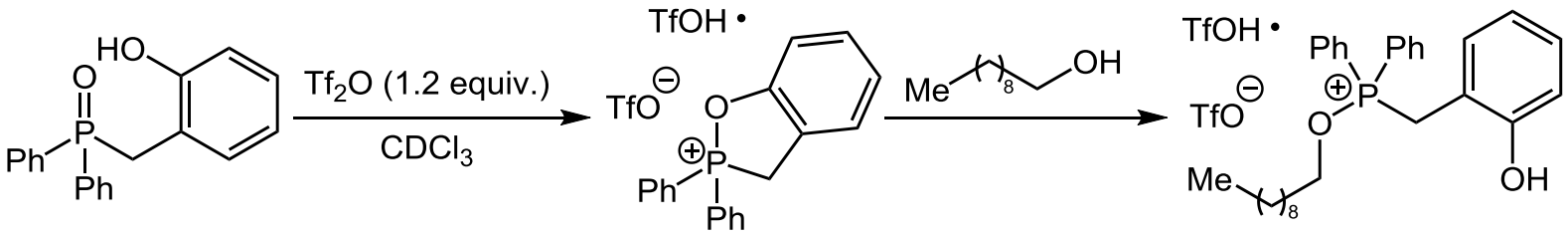


Ar = 2,4-$(NO_2)_2C_6H_3$

catalyst	no catalyst			
yield	10%	84%	8%	10%
ee	19% ee (retention)	98% ee (inversion)	22% ee (retention)	15% ee (retention)

Mechanistic Investigation

C: Possible catalytic intermediates 2 and 3 generated by an alternative activation method

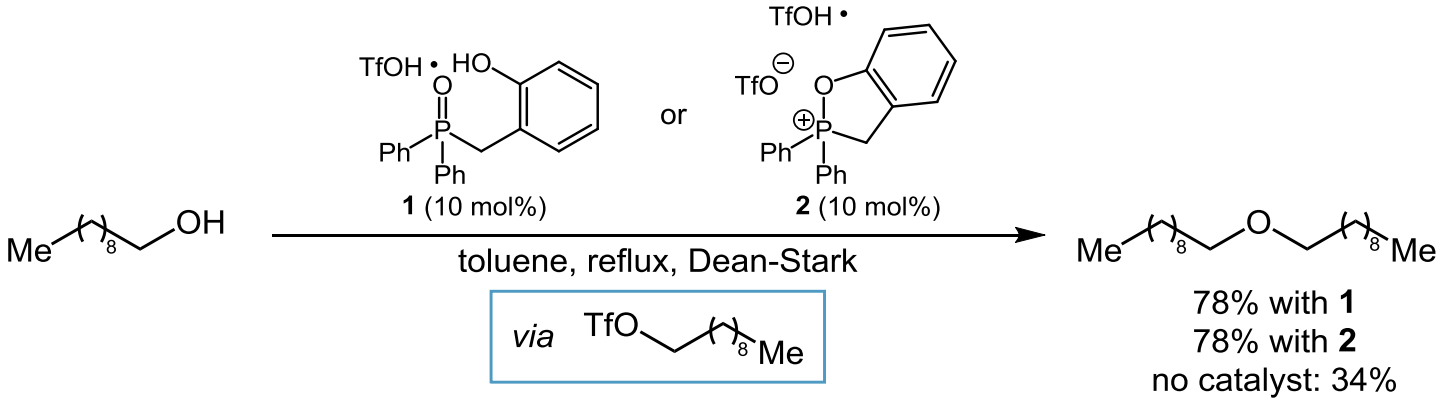


1 ^{31}P δ = 38.3 ppm

2 ^{31}P δ = 92.9 ppm

3 ^{31}P δ = 68.0 ppm

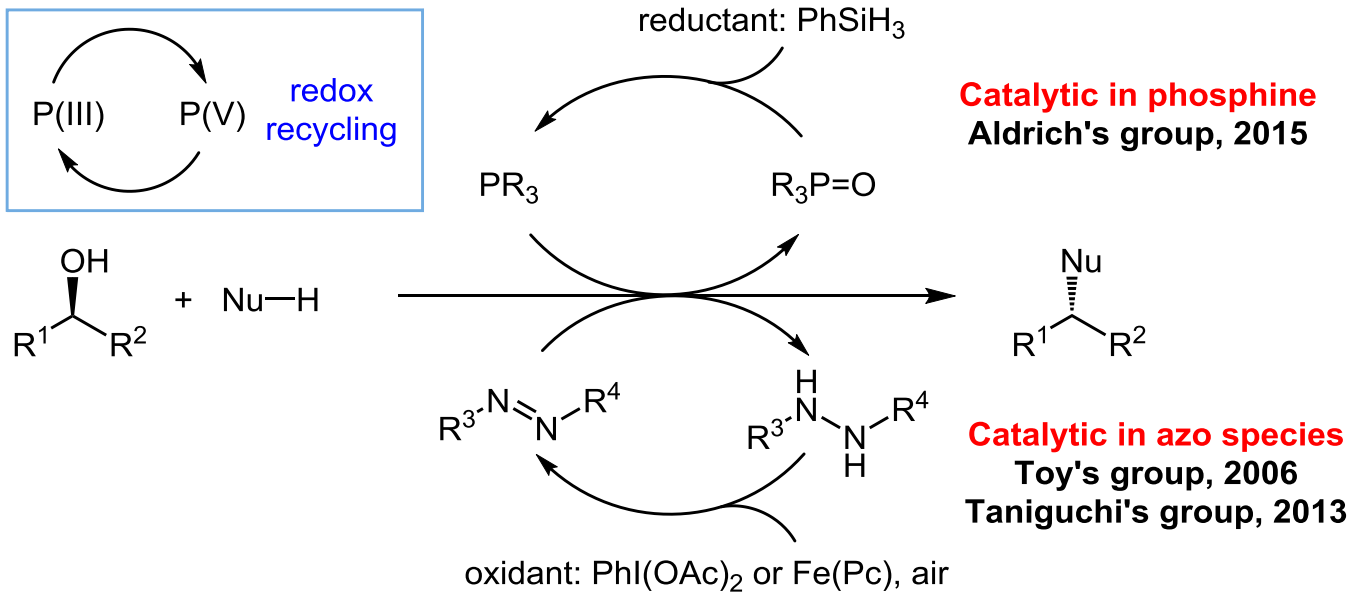
D: Oxide 1 and proposed intermediate 2 perform the catalytic etherification reaction with decanol



78% with **1**
78% with **2**
no catalyst: 34%

Summary

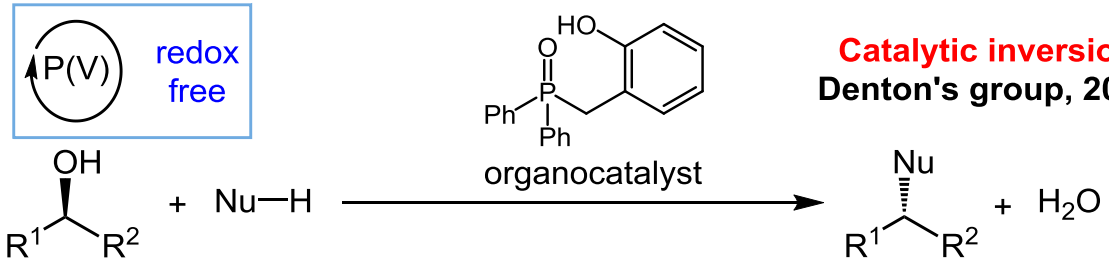
Redox Organocatalytic Mitsunobu Reactions



Catalytic in phosphine
Aldrich's group, 2015

Catalytic in azo species
Toy's group, 2006
Taniguchi's group, 2013

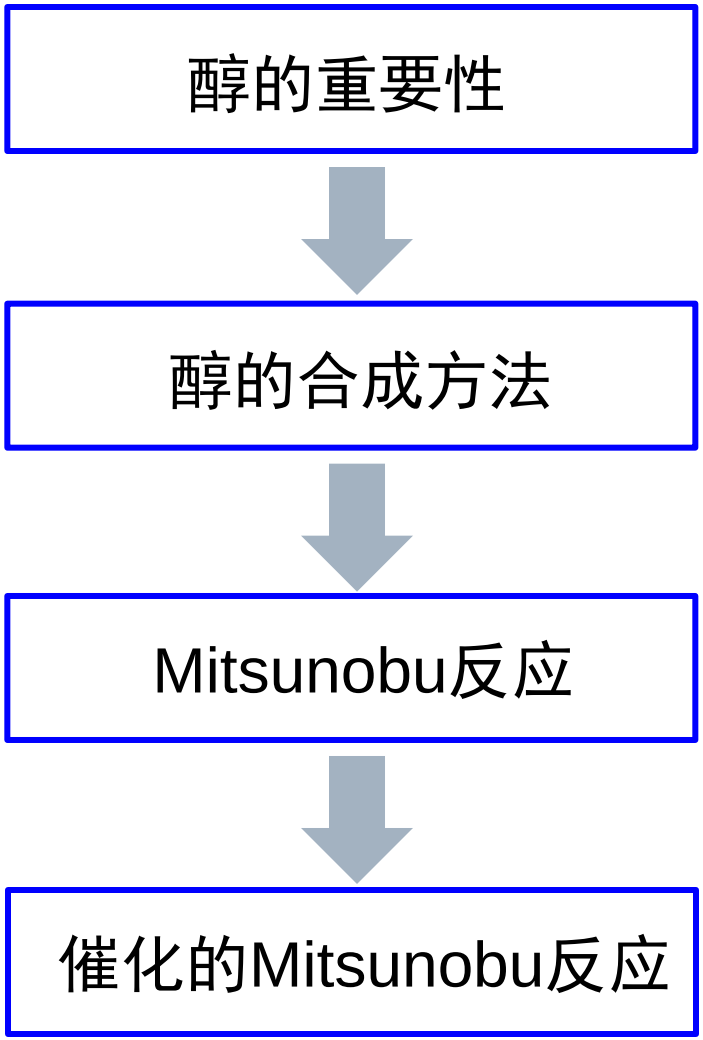
Redox-free Organocatalytic Mitsunobu Reactions



Catalytic inversion
Denton's group, 2019

The First Paragraph

写作思路



The First Paragraph

Alcohols are important feedstocks for chemical synthesis because they are abundant and inexpensive and can be converted into a wide range of additional functional groups by using, among others, nucleophilic substitution reactions. The ideal (hypothetical) nucleophilic substitution would involve direct stereospecific displacement of the hydroxyl group with concomitant elimination of water. In practice, kinetic and thermodynamic barriers prevent direct substitution, and therefore, additional chemical activating agents must be used. However, conventional methods, such as the Mitsunobu protocol, involve hazardous stoichiometric reagents that are incongruous with the principle of atom economy. Nevertheless, this method is used very frequently and remains the state of the art in terms of stereospecific nucleophilic substitution.

The First Paragraph

Therefore, it is clear that alternative catalytic substitution reactions would have a major impact on chemical synthesis and eventually replace the inherently inefficient current methods. To date, a variety of strategies have been devised to enable catalytic coupling of π-activated alcohols and nucleophiles, which include Brønsted or Lewis acid catalysis and transition metal-catalyzed. In many cases, these reactions occur through stabilized carbocation intermediates and, necessarily, generate racemic products. However, there are notable examples in which excellent stereoselectivity has been achieved. A conceptually different approach to catalytic nucleophilic substitution termed “borrowing hydrogen” involves oxidation of the alcohol, condensation with a nucleophile, and then reduction to achieve the product of a direct substitution reaction.

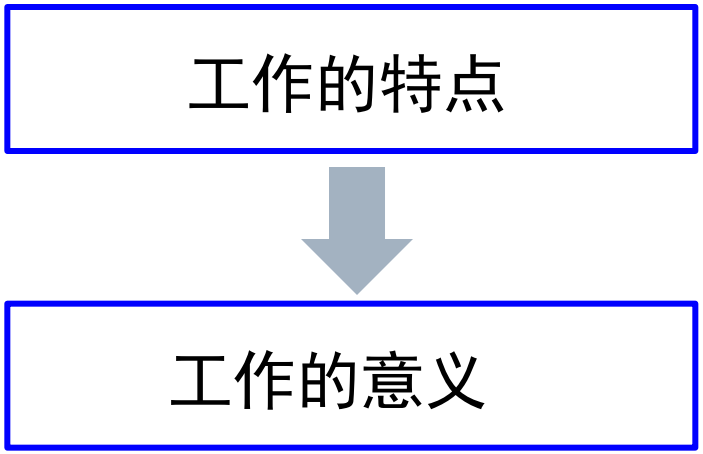
The First Paragraph

Despite these advances, the development of catalytic methods that enable stereospecific bimolecular substitution of nonactivated chiral alcohols remains a major challenge. Although some progress has been made by using cyclopropenone catalysis, most effort to date has been focused on modifying the original Mitsunobu protocol by redox recycling of the stoichiometric reagents. Although this approach is intuitive, implementation is challenging because recycling the phosphine reagent requires a stoichiometric reductant and recycling the azo oxidant requires a mutually compatible stoichiometric oxidant.

The Last Paragraph

The elimination of redox chemistry in our catalytic Mitsunobu protocol obviates the need for terminal oxidants and reductants and results in substantially increased reaction mass efficiency of 65%. The established organophosphorus-catalyzed dehydration manifold has potential applications in a range of other classical phosphorus-mediated transformations.

写作思路



Representative Examples

Alcohols are important feedstocks for chemical synthesis because they are abundant and inexpensive and can be converted into a wide range of additional functional groups by using, among others, nucleophilic substitution reactions.

However, conventional methods, such as the Mitsunobu protocol, involve hazardous stoichiometric reagents that are incongruous with the principle of atom economy.

To date, a variety of strategies have been devised to enable catalytic coupling of π-activated alcohols and nucleophiles.

Conscious of these limitations, we questioned whether an alternative catalysis manifold could be developed in which the oxidation state of phosphorus was invariant.

Furthermore, if this catalytic dehydration system could be validated, it would expand the field of phosphorus-based organocatalysis.

Representative Examples

A hallmark of the Mitsunobu reaction is secondary alcohol inversion.
We next sought to extend the method to encompass carbon-nitrogen and carbon-sulfur bond formations.
To assess the catalytic dehydration platform depicted in Fig. 1D, we carried out mechanistic studies beginning with an isotope labeling experiment.
In summary, the experiments described above and in the supplementary material are congruous with the catalytic cycle depicted in Fig. 1D.
The labeling study and stereochemical inversion are consistent with the carbon-nucleophile bond formation.

Acknowledgement

Thanks
for your attention