

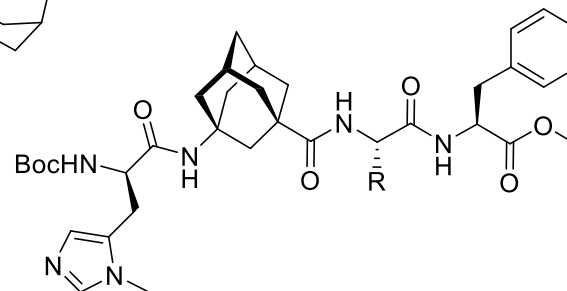
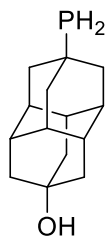
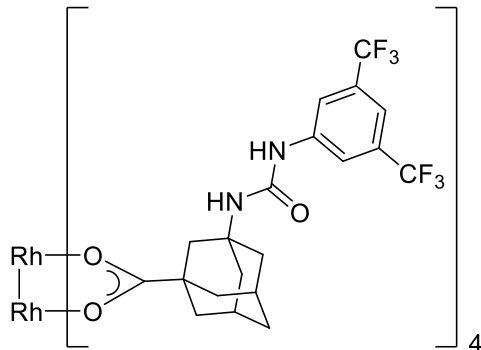
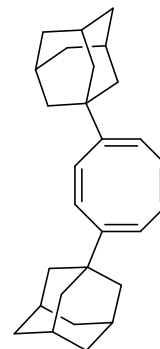
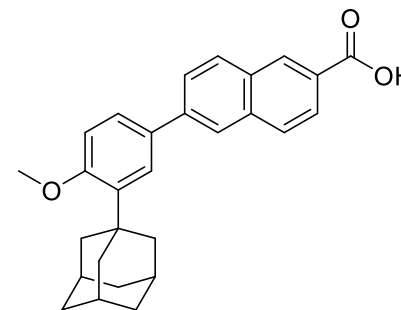
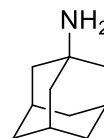
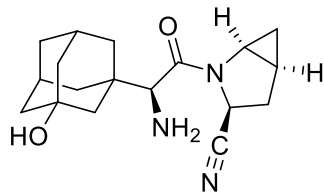
New Perspectives in Diamondoid Chemistry

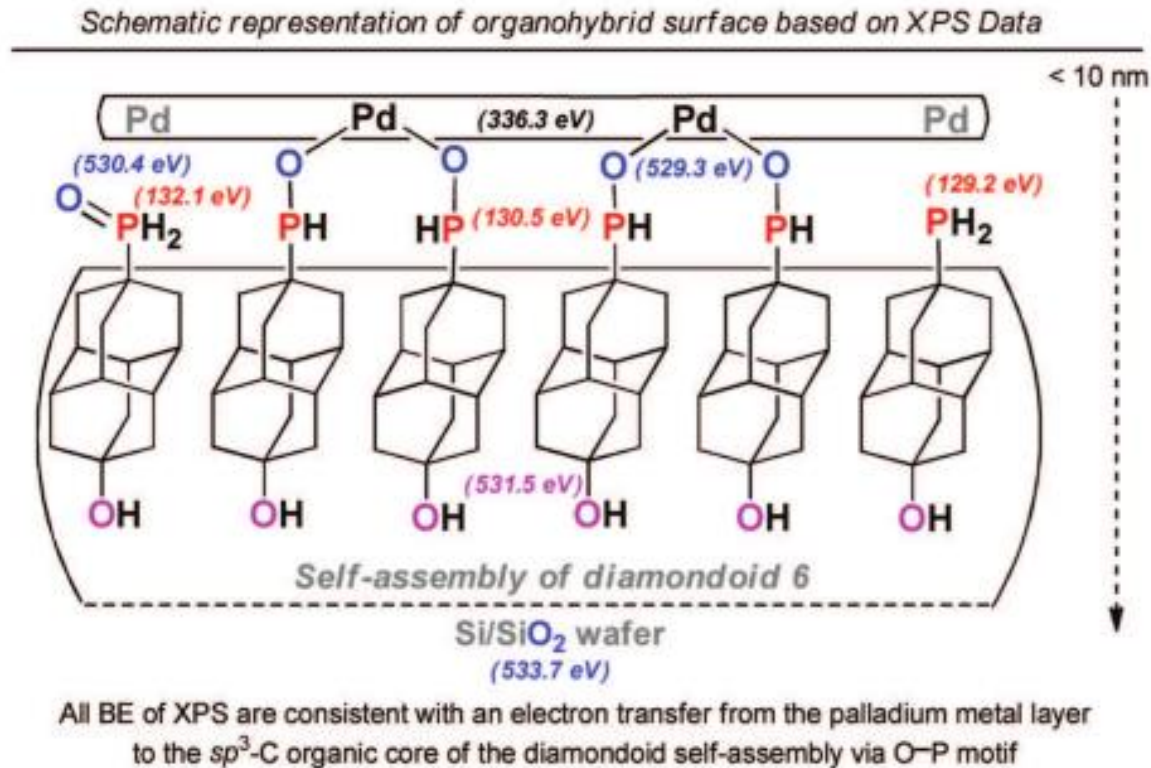
Group Seminar

March 8th 2019

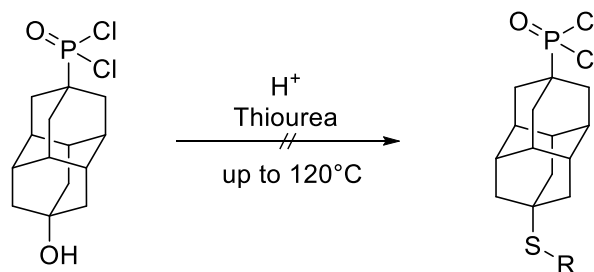
by Lukas Ochmann

*Institute of Organic Chemistry
Justus-Liebig-University*

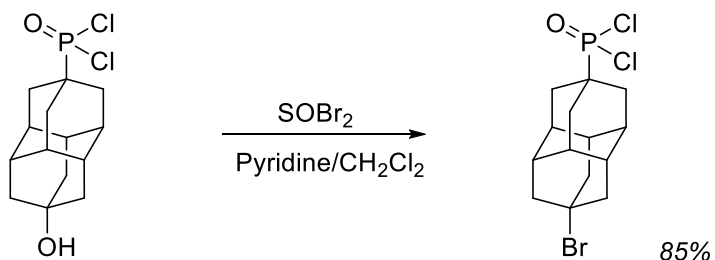




How can we make well defined monolayers of our organohybrid
which show basically the same properties?

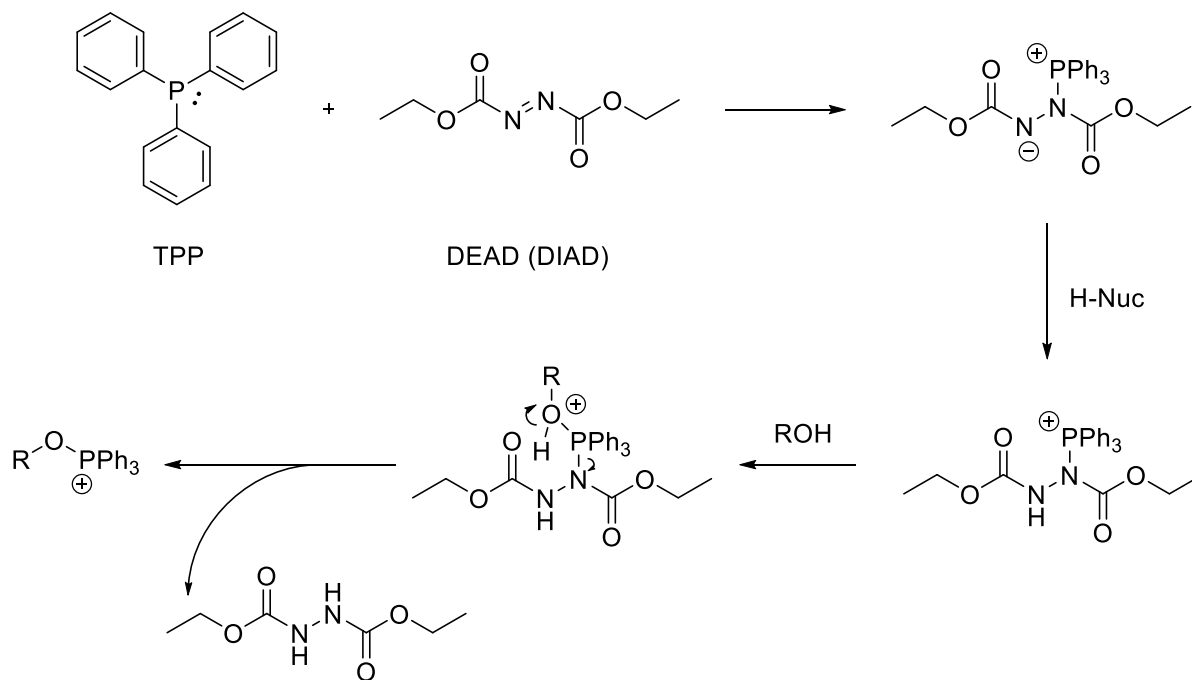


H_2SO_4 , HBr , HOAc , TfOH , CF_3COOH , HCl

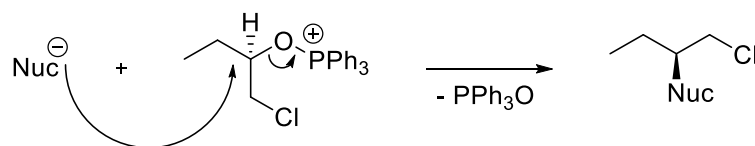


➔ Possible *in situ* activation of the alcohol (Appel, Mitsunobu)?

Mitsunobu Reaction



Clean inversion of the configuration for chiral alcohols! (S_N2)





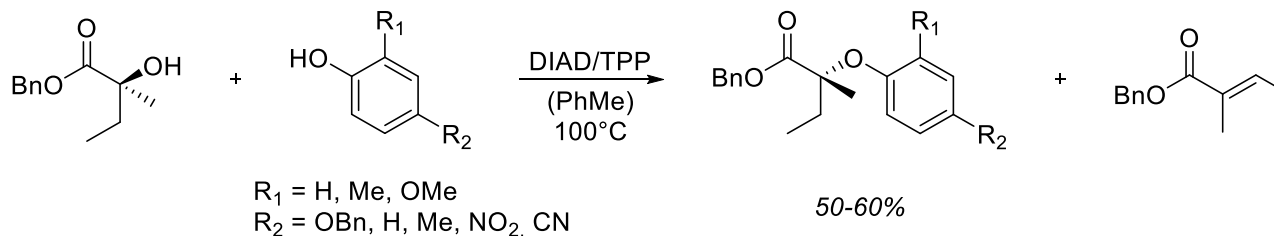
Stereospecific synthesis of chiral tertiary alkyl-aryl ethers via Mitsunobu reaction with complete inversion of configuration

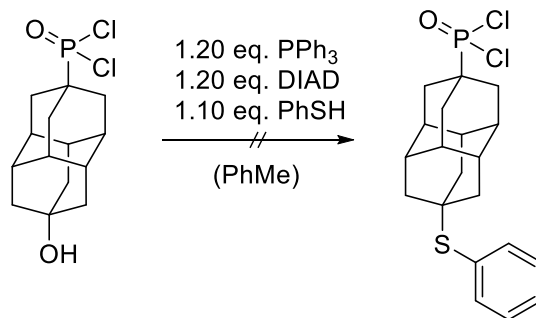
Yao-Jun Shi,* David L. Hughes and James M. McNamara

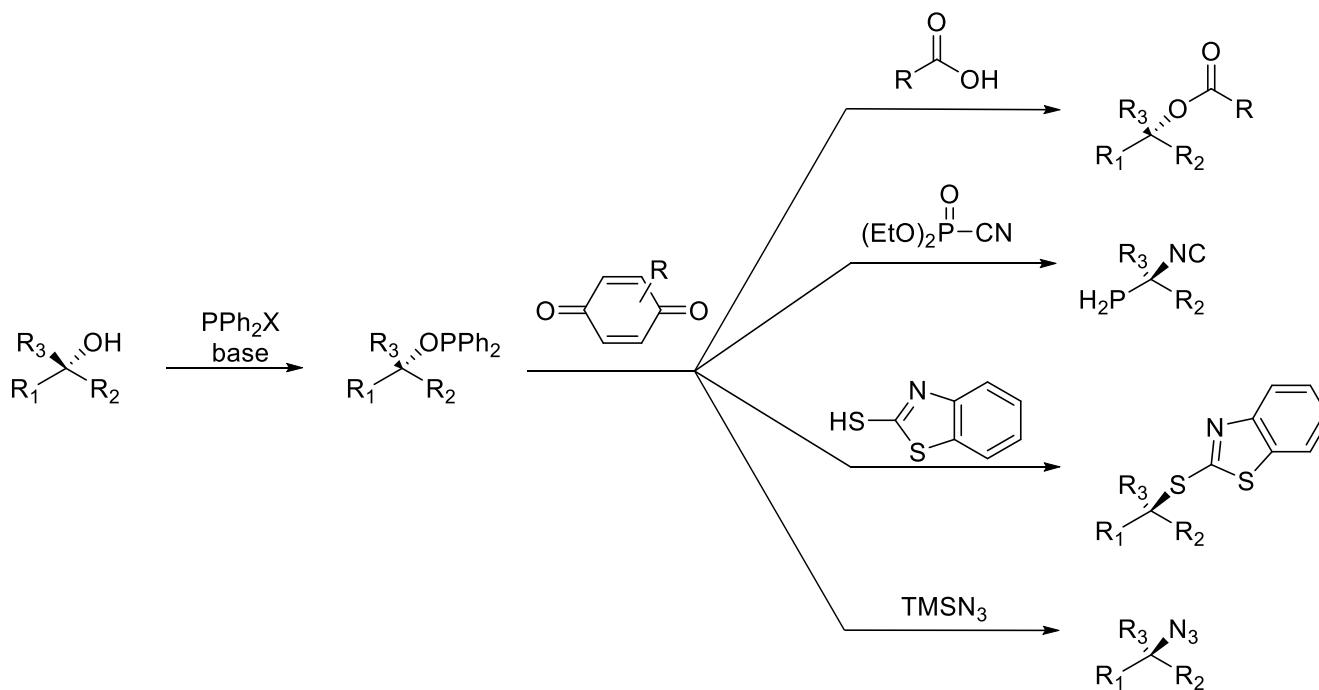
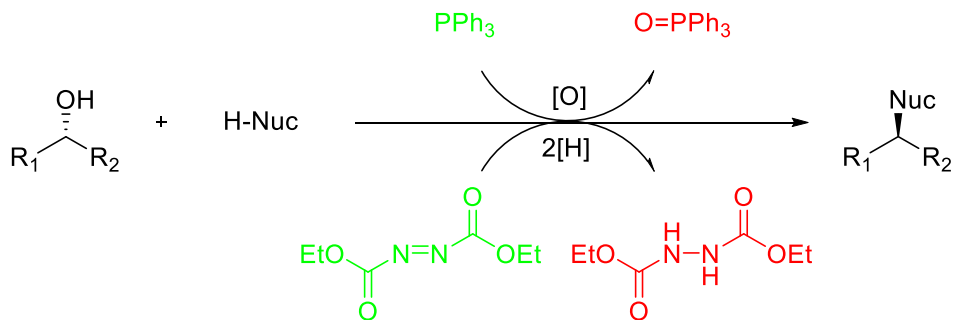
Department of Process Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065 USA

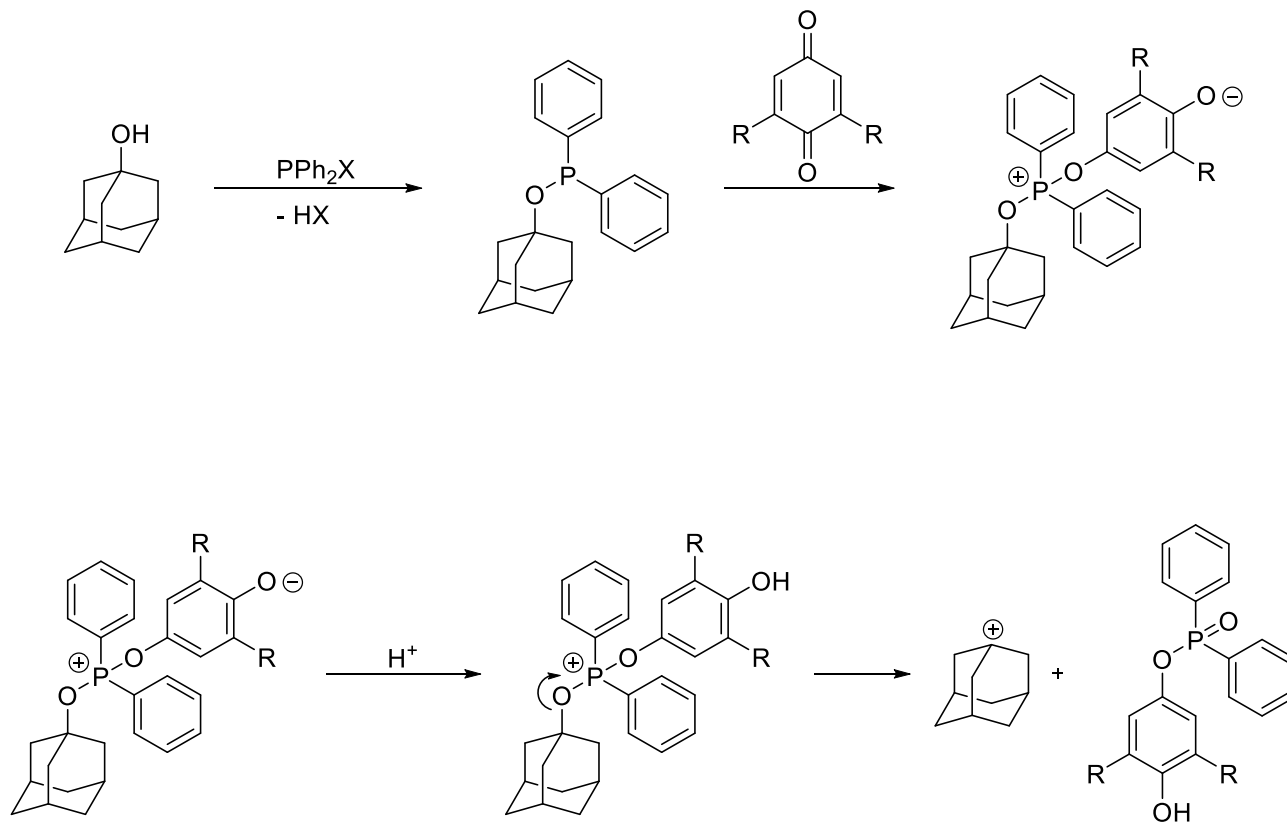
Received 3 January 2003; revised 14 March 2003; accepted 18 March 2003

Abstract—Mitsunobu reaction of chiral tertiary alcohol (*S*)-**2** with phenol **3** provides the desired ether (*R*)-**1** in moderate yields at elevated temperatures (80–100°C). The S_N2 displacement pathway is evident by complete inversion of the (*S*)-alcohol to (*R*)-ether. © 2003 Elsevier Science Ltd. All rights reserved.

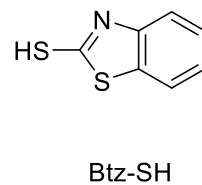
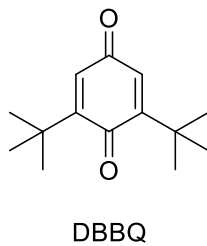
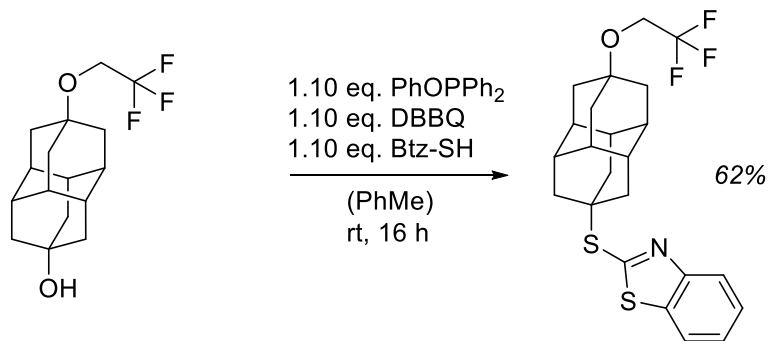
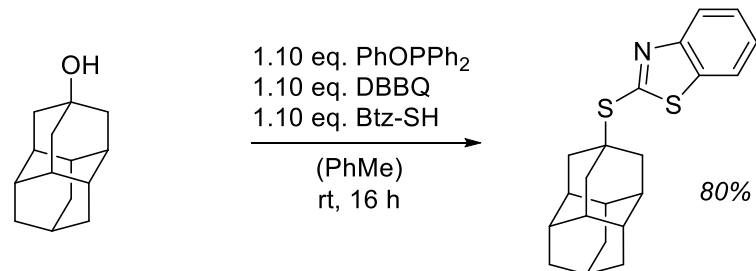
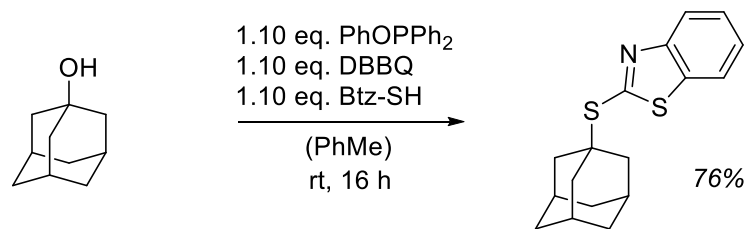


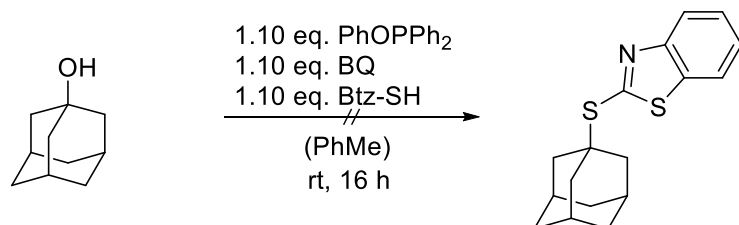




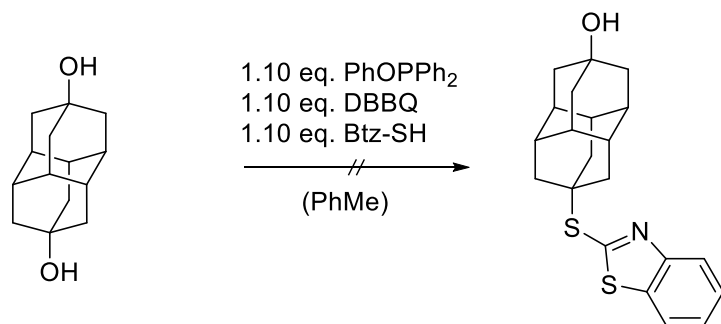


Suitable Substrates

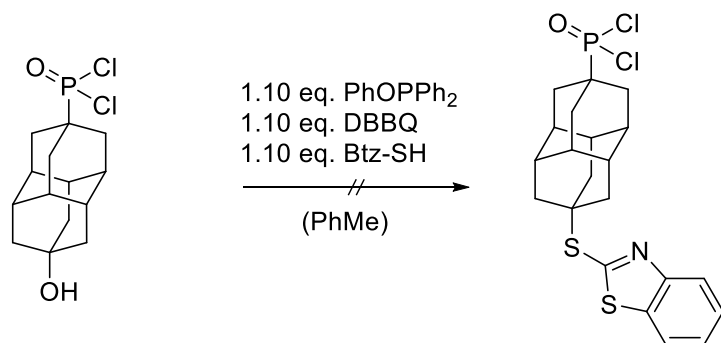




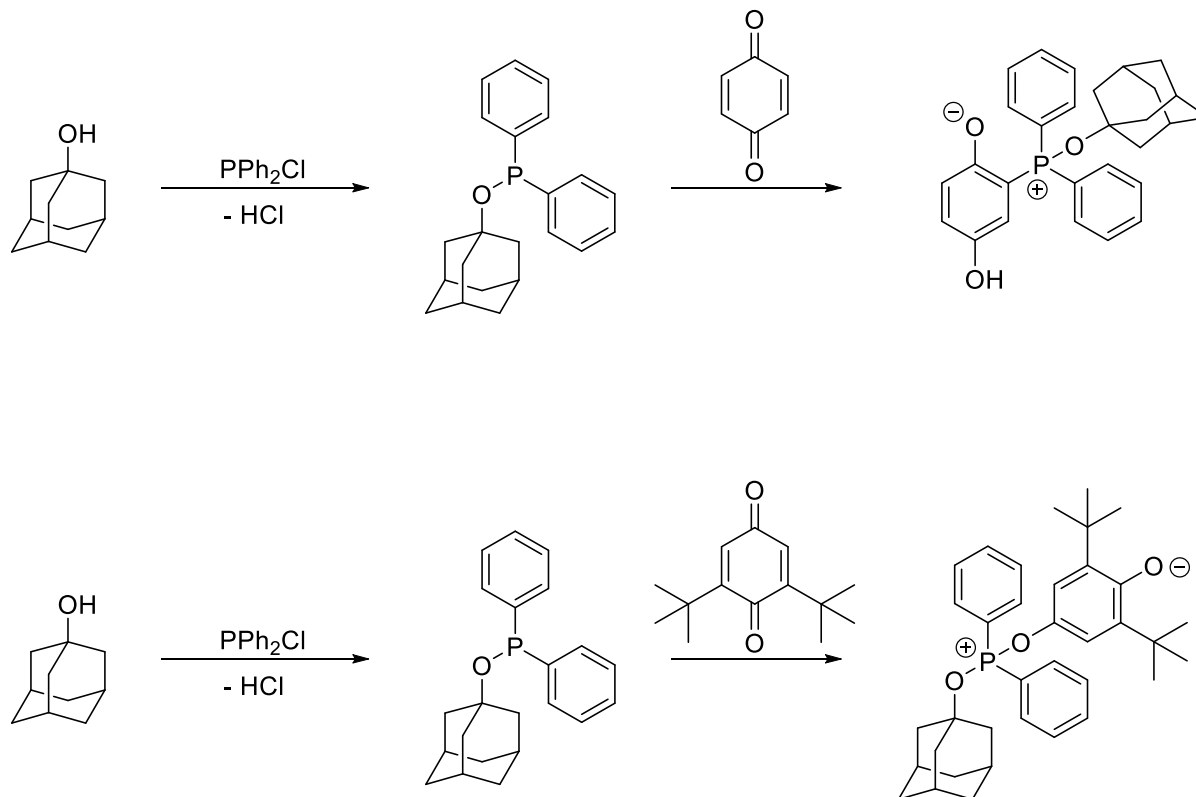
Side reaction of benzoquinone?

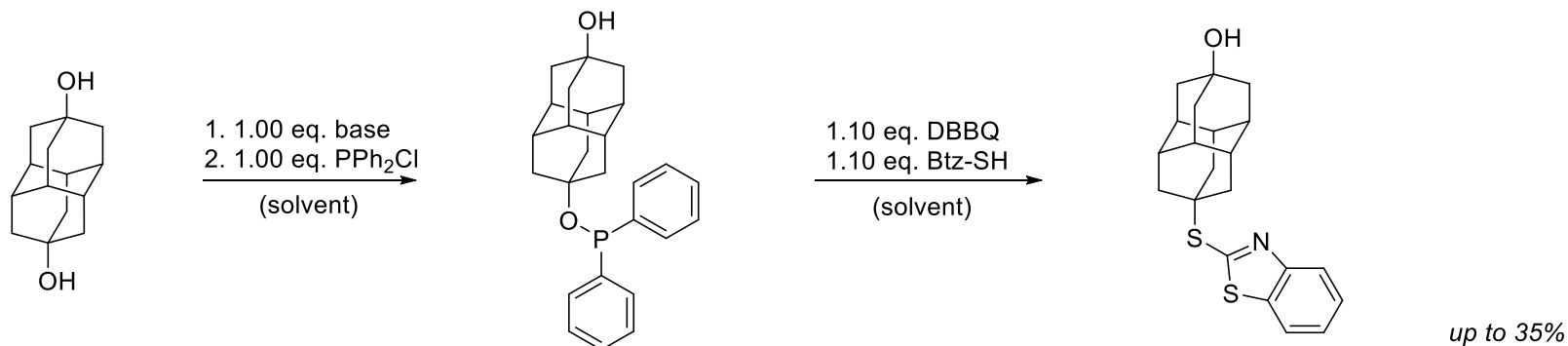


Decreased nucleophilicity
by additional substituents?



Side Reaction of 1,4-Benzoquinone





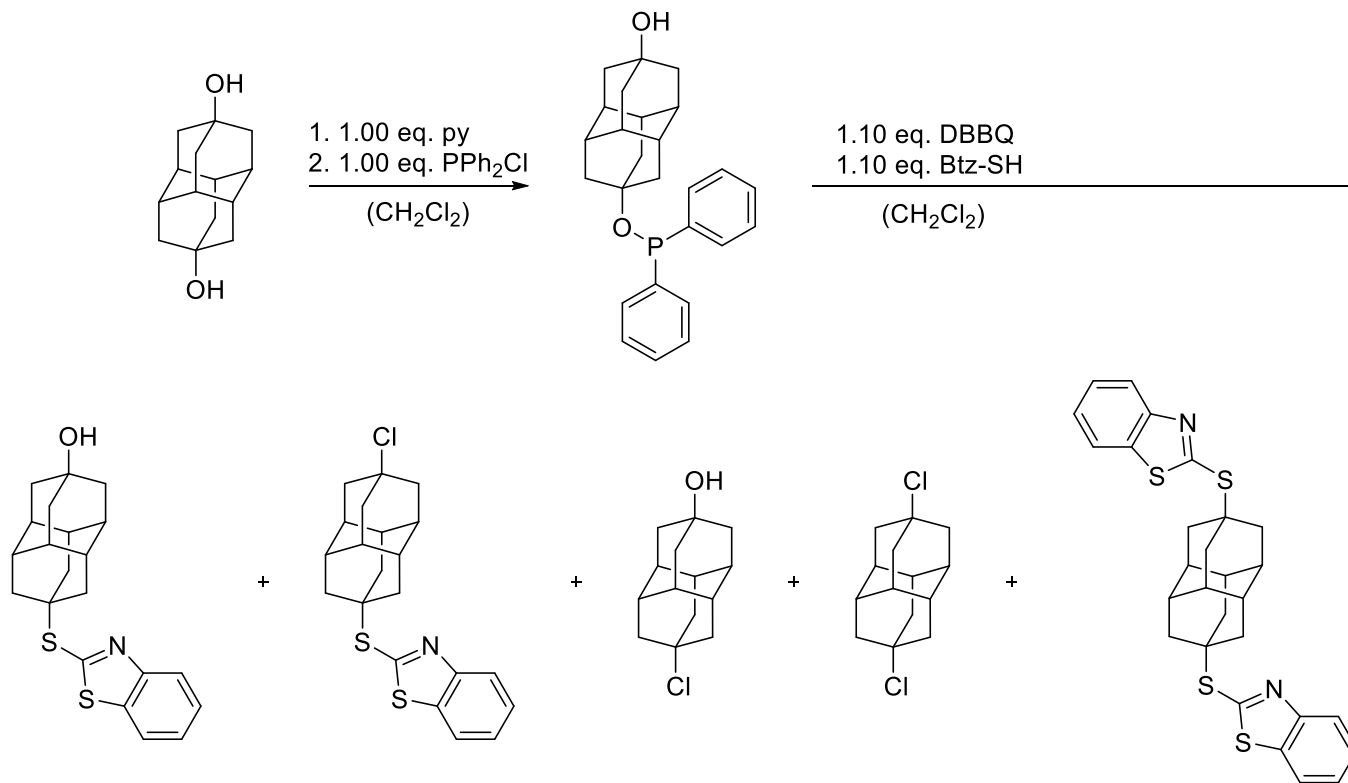
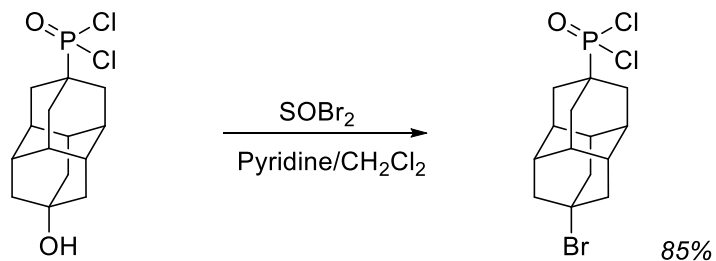
Bases: NaH, n-BuLi, TEA, Li₂CO₃.....

Additives: 18-Crown-6, DMAP, KI, TBAB.....

Solvents: CHCl₃, PhMe, DMF, THF, Et₂O.....

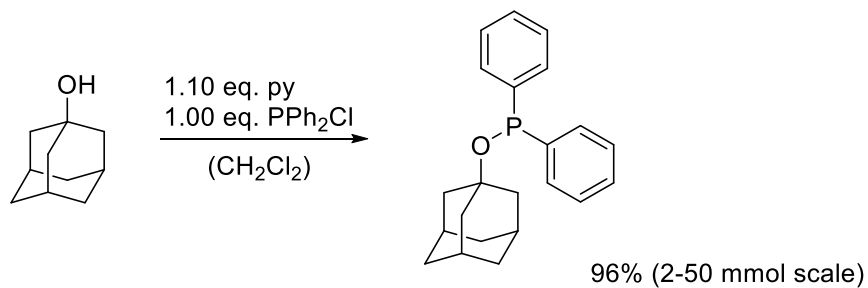
Magic combination:

DCM + Pyridine

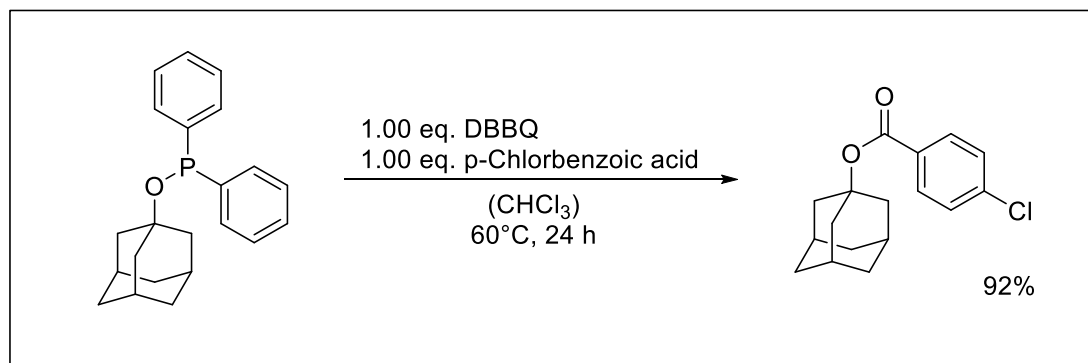
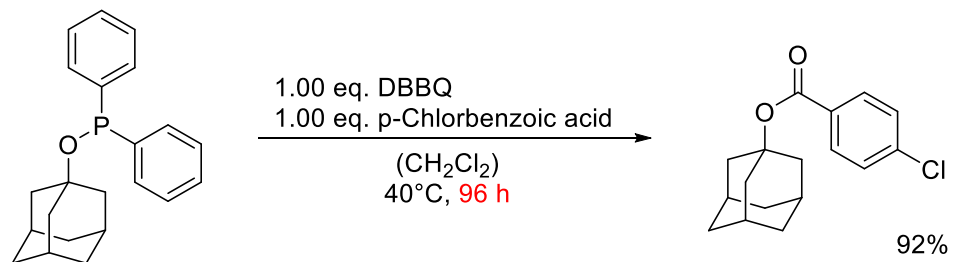




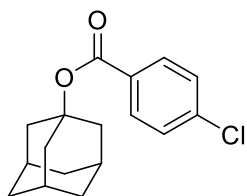
Precursor synthesis:



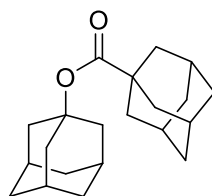
Reaction optimization:



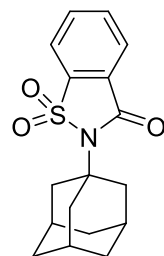
Substrate Scope



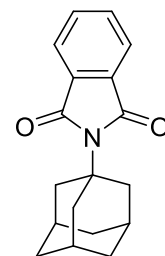
92%



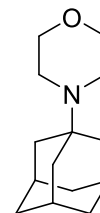
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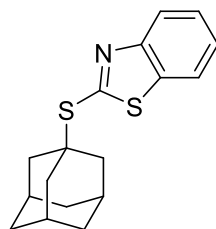
81%



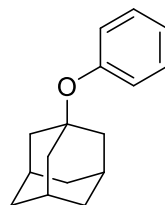
56%



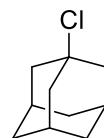
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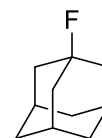
76%



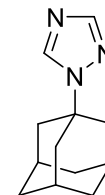
28%



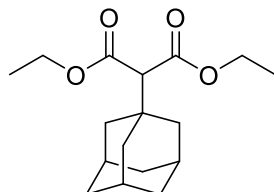
TMSCl: 65%
NH₄Cl: 48%



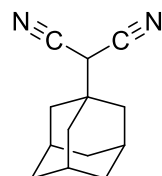
traces



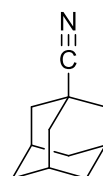
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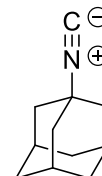
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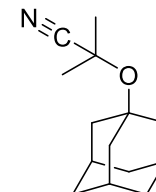
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45%



34%



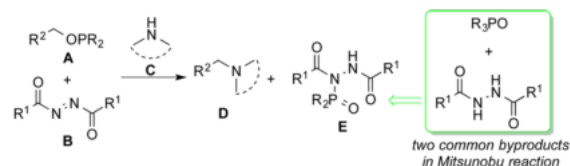
5%



Organic Letters

Letter

Scheme 1. Design of Oxidation–Reduction Condensation Reaction Employing Alkyl Phosphinites and Azo Compounds



hypothesized that the highly nucleophilic phosphinite **A** with azo compound **B** would generate a strongly basic hydrazo anion intermediate that can deprotonate nonacidic nucleophiles **C**. The resulting anionic nucleophile undergoes a substitution reaction with alkoxyphosphonium intermediates to afford alkylated amines **D** and phosphonohydrazines **E** as the sole byproducts, which also have been utilized as potential candidates for novel insecticides and for the synthesis of pharmaceutical compounds containing a P(=O)–N bond.²⁰ This synthetic transformation would avoid the phosphine oxide and hydrazine byproduct formation common in the traditional Mitsunobu reaction.

To test our hypothesis, we began with a control experiment employing (benzyloxy)diphenylphosphine **1a**, diisopropyl azodicarboxylate (DIAD) as a weak oxidant, and morpholine **2a** as an amine nucleophile, which provided **3a** with 30% NMR yield (Scheme 2). With this intriguing result as well as the

Scheme 2. Control Experiment for Evaluating Phosphinite and Diazaphosphite

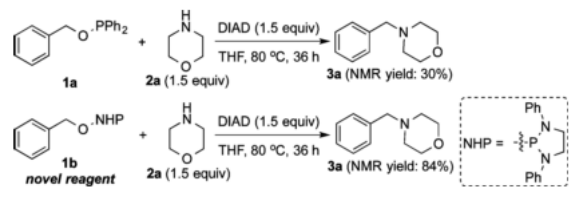


Table 1. Optimization of the Reaction Conditions^a

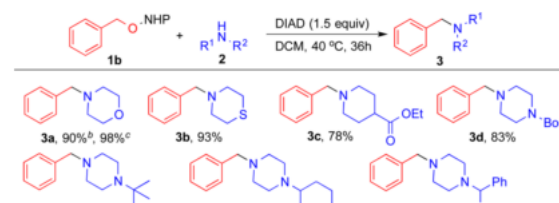
entry	azo reagents	solvent	ratio of 1a/2a/azo	temp (°C)	yield ^b (%)
1	ADDP	THF	1/1.5/1.1	80	64
2	DEAD	THF	1/1.5/1.1	80	74
3	DIAD	THF	1/1.5/1.1	80	84
4	DIAD	THF	1/2.0/1.1	80	72
5	DIAD	THF	1/1.5/1.5	80	88
6	DIAD	THF	1/1.5/2.0	80	78
7		THF	1/1.5/0	80	0
8	DIAD	DCM	1/1.5/1.5	40	96(90 ^c)
9	DIAD	DCE	1/1.5/1.5	83	99(90 ^c)
10	DIAD	CHCl ₃	1/1.5/1.5	61	81
11	DIAD	ether	1/1.5/1.5	35	61
12	DIAD	CH ₃ CN	1/1.5/1.5	81	93
13	DIAD	ethanol	1/1.5/1.5	78	60

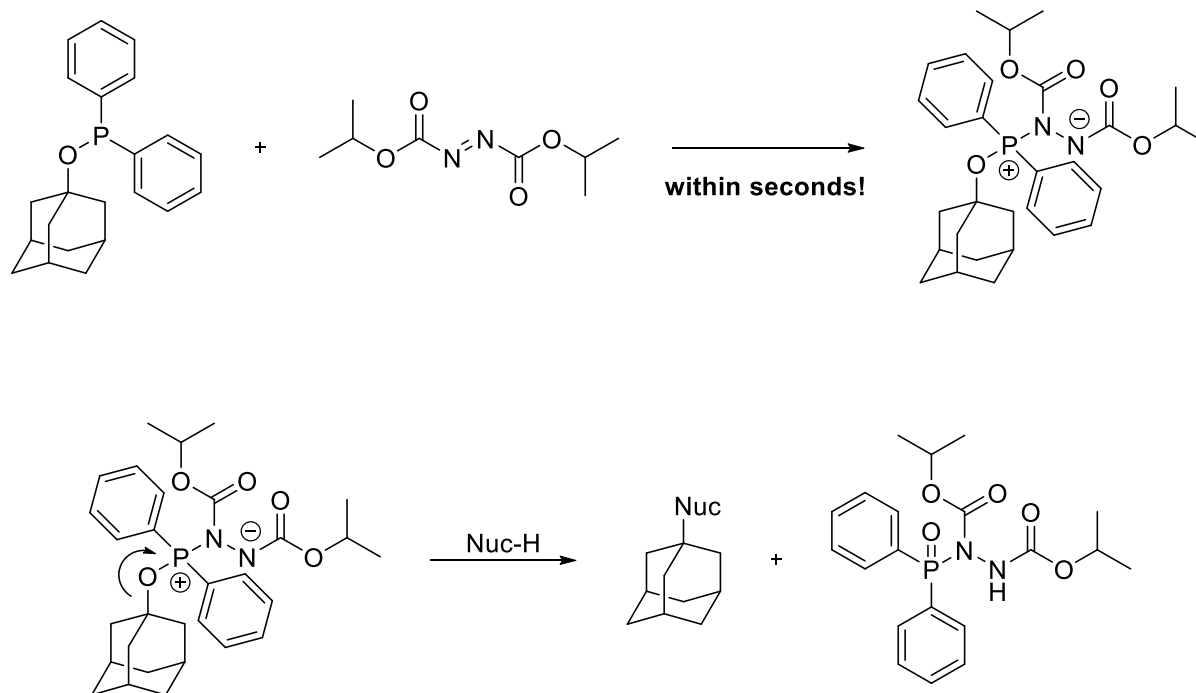
^aReaction conditions: **1b** (0.1 mmol), **2a** (0.15 mmol), and DIAD (0.15 mmol) in solvent (0.5 mL) for 36 h. ^bYield was determined by crude NMR using 1,3,5-trimethylbenzene as internal standard. ^cIsolated yield (%).

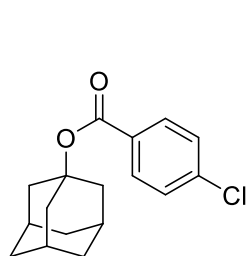
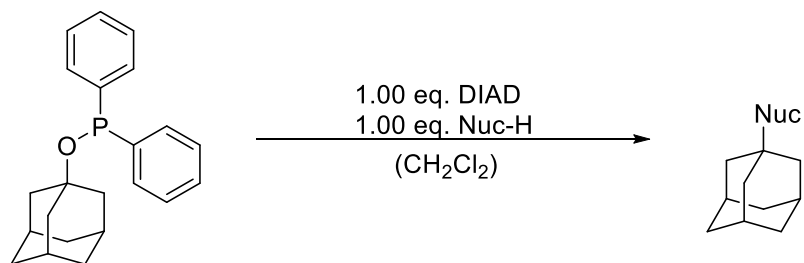
superior to other solvents, providing **3a** in 90% isolated yield (entries 8 and 9).

With the optimized reaction conditions established, we first explored the scope of this reaction by treating different amine nucleophiles (Scheme 3). Employing thiomorpholine instead of

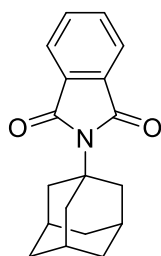
Scheme 3. Scope of Amines^a





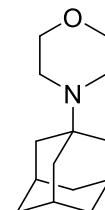


93%
rt, 1 h

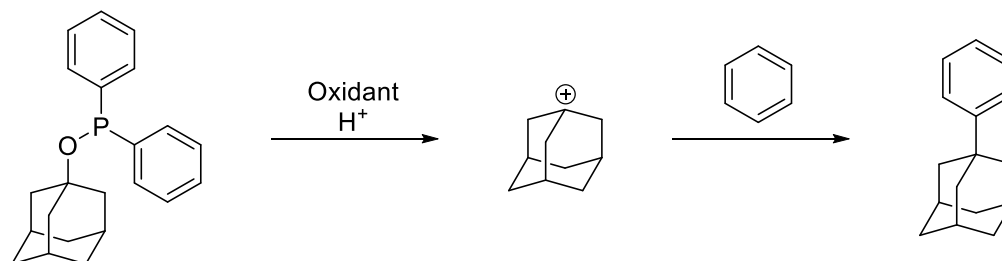


45%
rt, 2 h

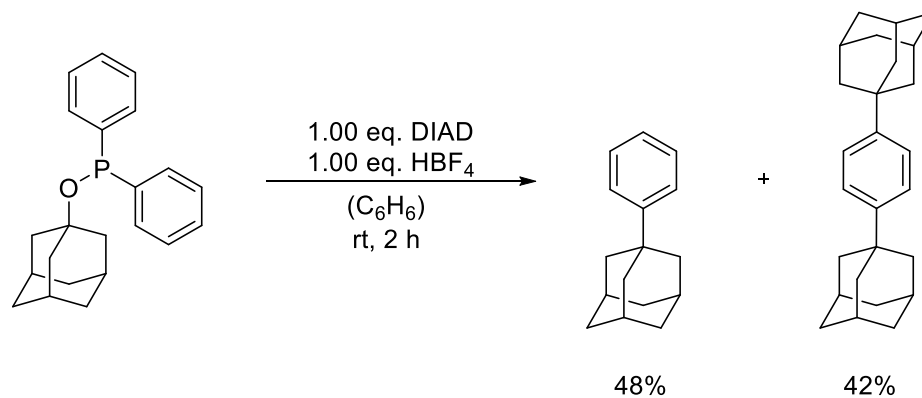
Why using DIAD?

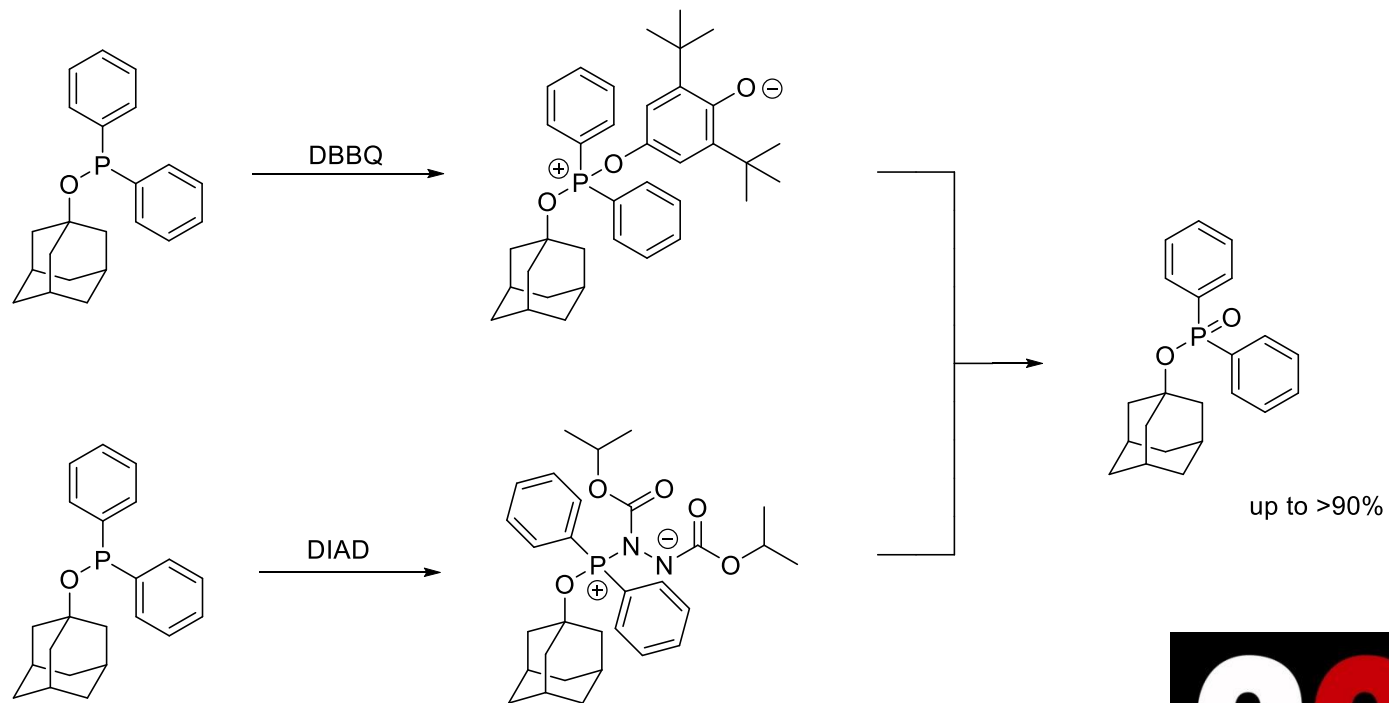


4%
(GC yield)
rt, 24 h



Is Friedel-Crafts alkylation possible?







- New tests for the substrate scope with DIAD as a mild oxidant
- Reveal the secret about side product formation
- Apply this reaction to higher diamondoids
- Selectivities for phosphinite formation of diamondoid diols (i.e. 4,9-Diamantanediol)



Prof. Peter R. Schreiner

B204 and B205 (Alex, Markus, Freddy, Dominik, Jan, Eschi, Berndt, Topp, Friedhelm)

Raffi

The whole PRS group!

