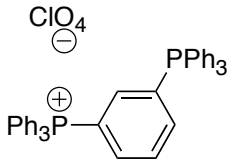
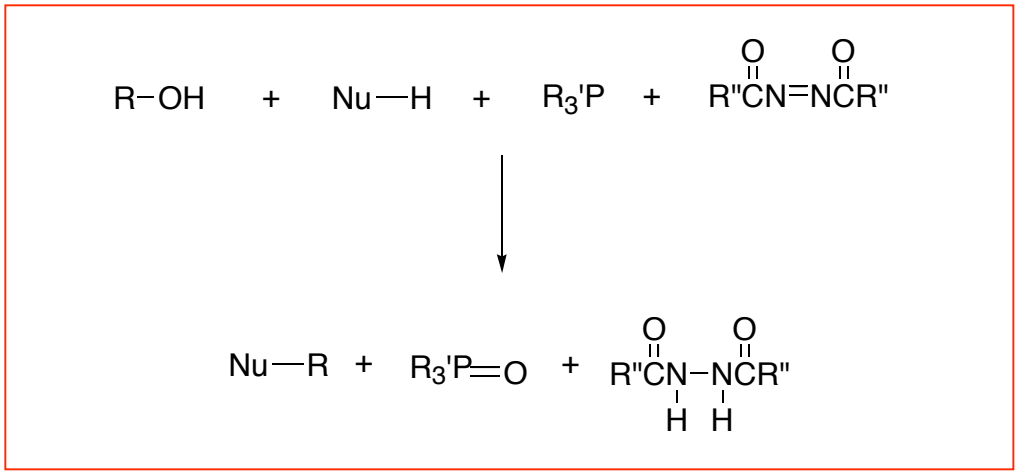
Tetraarylphosphonium Salts as Solubility-Control Groups: Phosphonium-Supported Triphenylphosphine and Azodicarboxylate Reagents

Poupon, J-C.; Boezio, A.; Charette, A. B.

Angew. Chem. Int. Ed. **2006**, *45*, 1415.



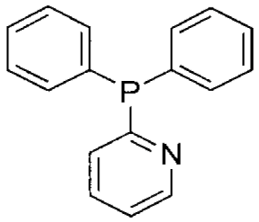
Mitsunobu Reaction



- Widely used reaction
- Stereoselective, compatible with variety of fuctional groups, mild conditions
- Problematic:
  - Separation of products from spent and excess reagent
  - Applications towards combinatorial chemistry

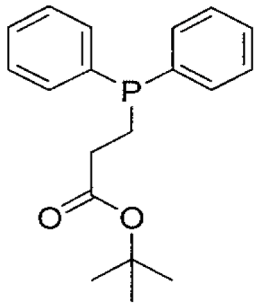
Modified Reagents

- Phosphanes



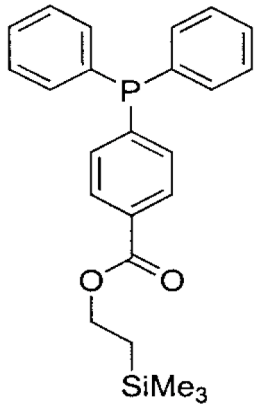
3a

4M HCl;
acidc aq. wash



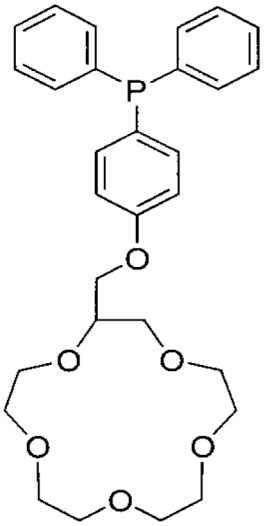
3b

TFA, resin



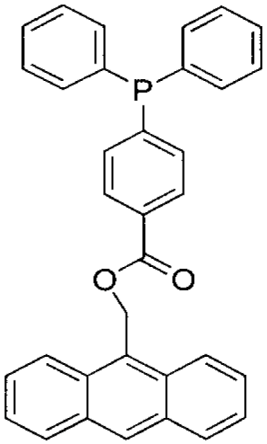
3c

TBAF;
base wash



3d

Ammonium-functionalized solid phase



3e

Diels-Alder

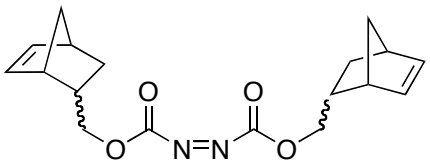
- Drawback:

  Additional reactions are necessary to affect separation

Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763.

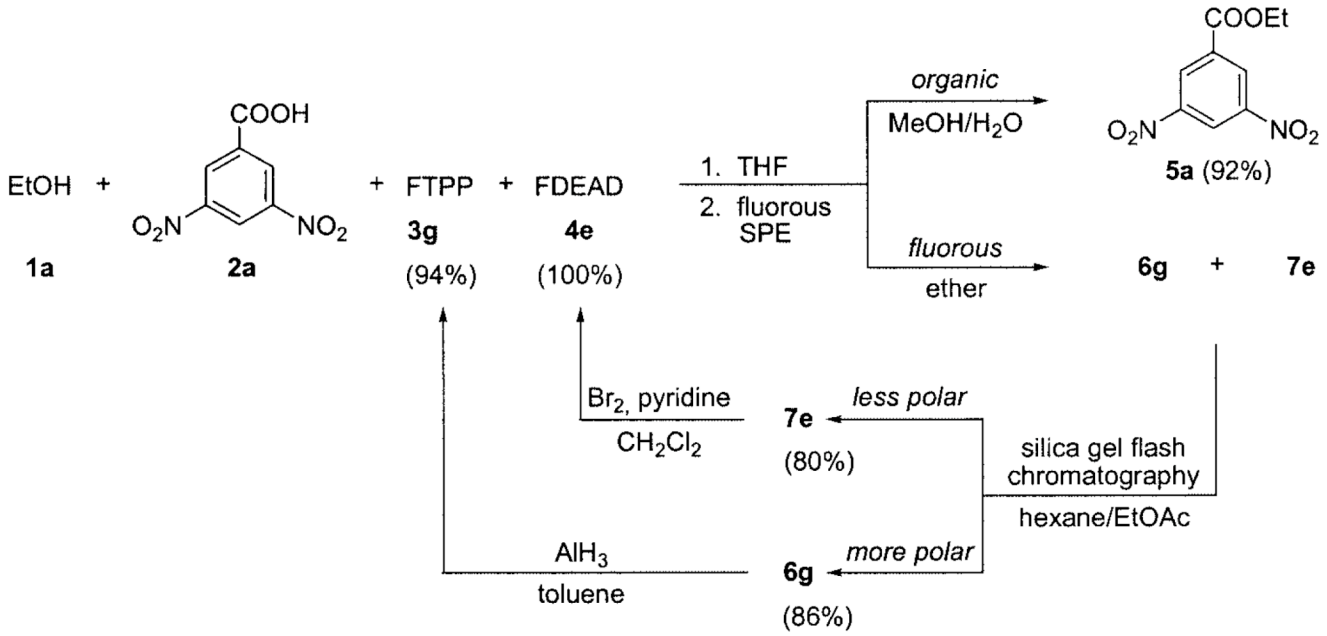
Modified Reagents

- Azodicarboxylates



Drawback: funtional group compatibility

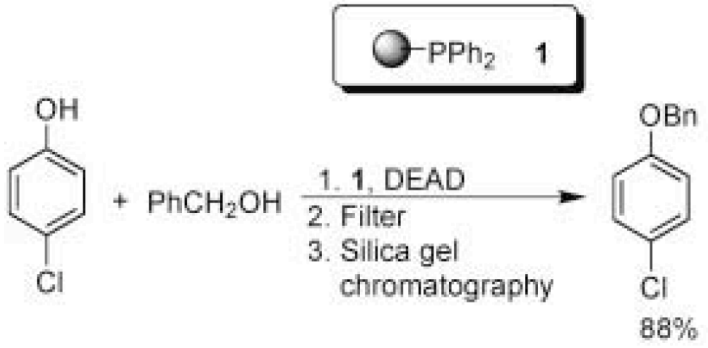
- Fluorous Reagents



Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763.

➢ Insoluble Polymer bound reagents-

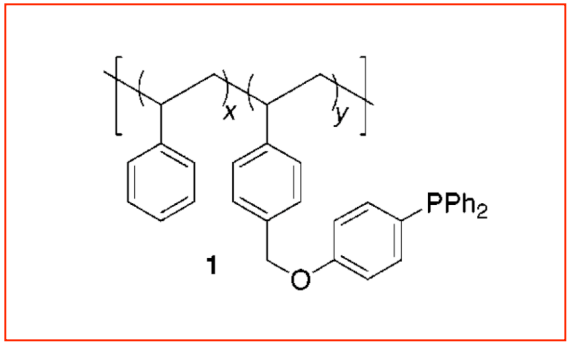
easy filtration; longer reactions times; large excess required

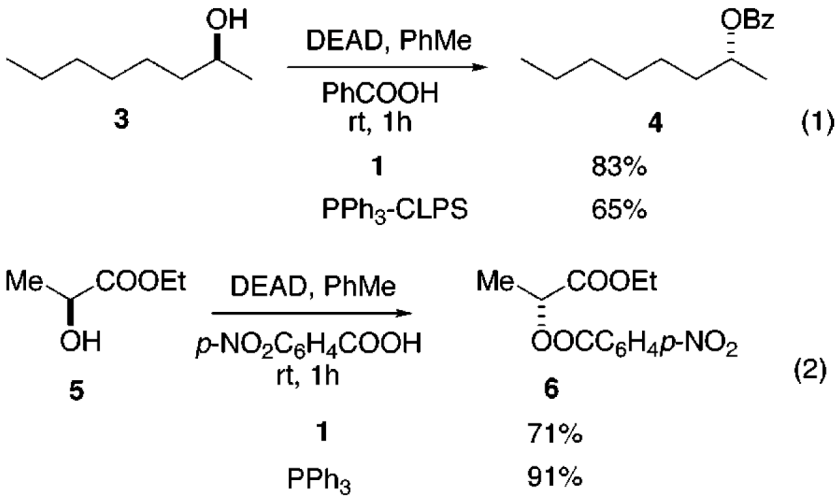


Curran, D. P.; Dandapani, S. *Chem. Eur. J.* **2004**, *10*, 3130.

Charette

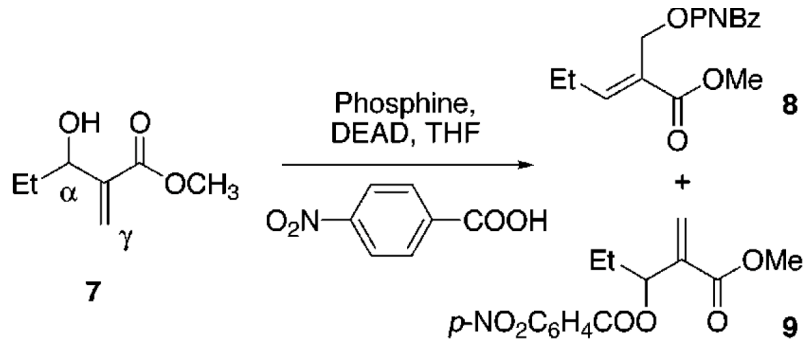
➢ Soluble polymer support





-Lower yields due to trapping of product in polymer

-Available in 3 steps from commercially available polystyrene
-Can be recovered after reaction
-Additional of MeOH to precipitate



entry	temp (°C)	ratio (**9**:**8**)[a]	phosphine	yield (%)[b]
1	rt	1:6	PPh_3	90
2	rt	1:20	**1**	88
3	0	1:10	PPh_3	86
4	0	1:>90	**1**	81
5	−40	1:25	PPh_3	85
6	−40	1:>90	**1**	65[c]

[a] The ratios were determined by ^1H NMR of the crude reaction mixture. [b] Isolated yield of **8** + **9**. [c] In this case, the remaining was the starting alcohol **7**.

Charette, A. B.; Janes, M. K.; Boezio, A. *J. Org. Chem.* **2001**, *66*, 2178.

Solubility of Phosphonium Salts

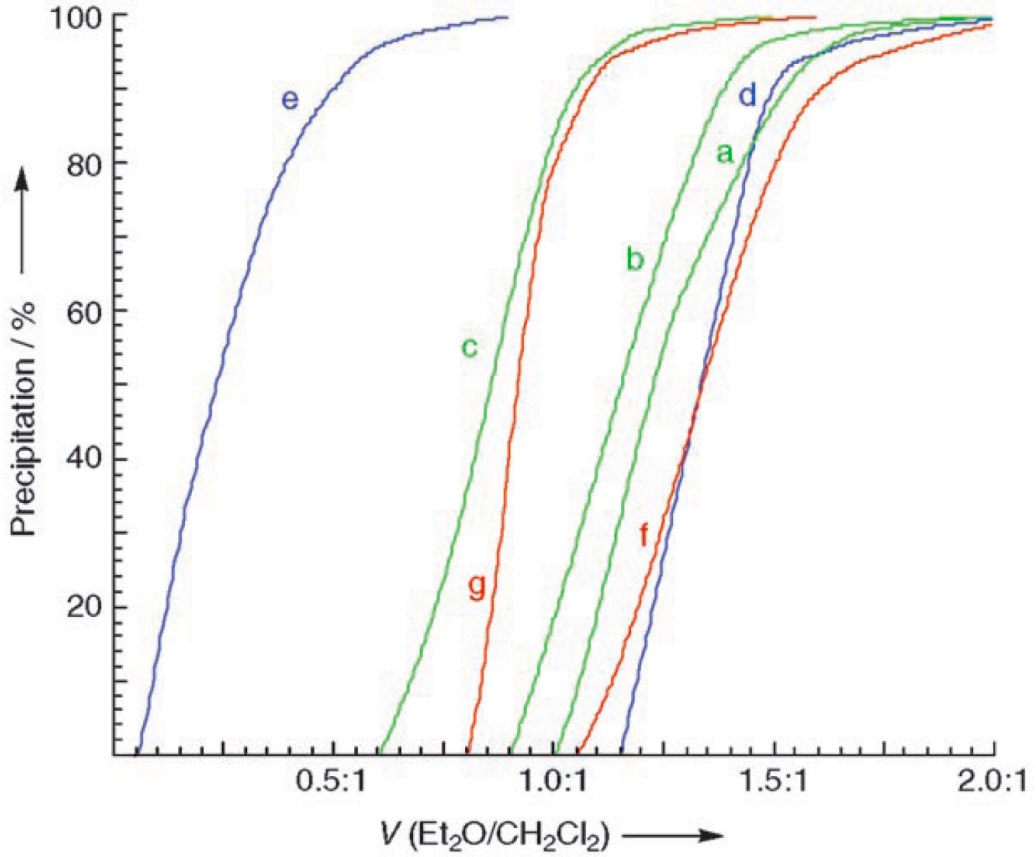
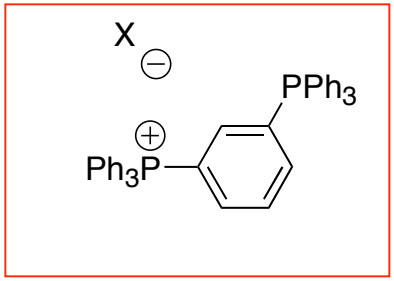


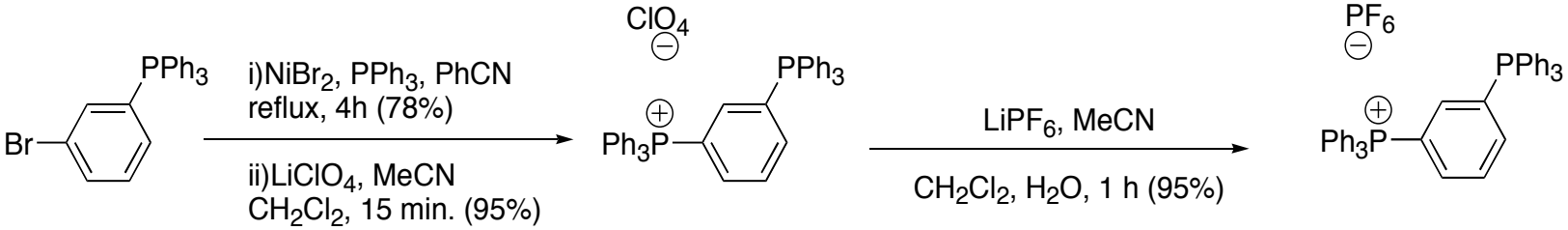
Figure 1. Relative solubility of arylphosphonium salts in Et_2O/CH_2Cl_2. Ph_3PMe; a) Ph_4PX, X = Br; b) Ph_4PX, X = ClO_4; c) Ph_4PX, X = PF_6; d) Ph_4PX, X = Br; e) Ph_4PX, X = ClO_4, X = PF_6 (insoluble); f) **3**; g) **5**.

- Amount of Et_2O required is counterion dependent
  Br > ClO_4 > PF_6

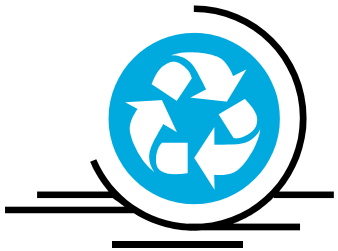
- Amount of Et_2O required is less for Ph_4PX than for Ph_3PMeX for the same counterion

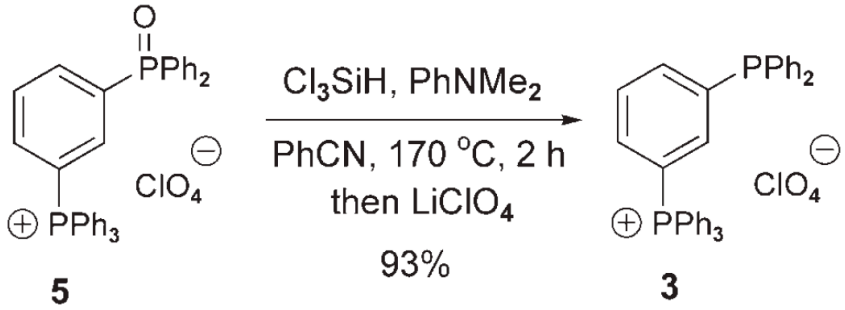


Tetraarylphosphonium salts



- Soluble in solvents of medium polarity--> CH_3CN, DMSO, DMF, CH_2Cl_2
- Insoluble in solvents of low polarity--> Et_2O, PhMe, hexanes
- No extra equivalents needed-- all reactive sites are available





5 **3**

➢Little propensity to trap organic molecules

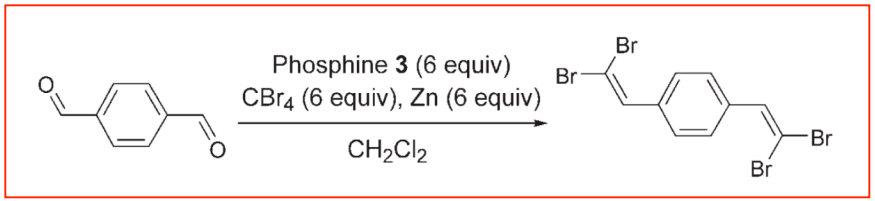
Et_2O
(3 mL)

Filter

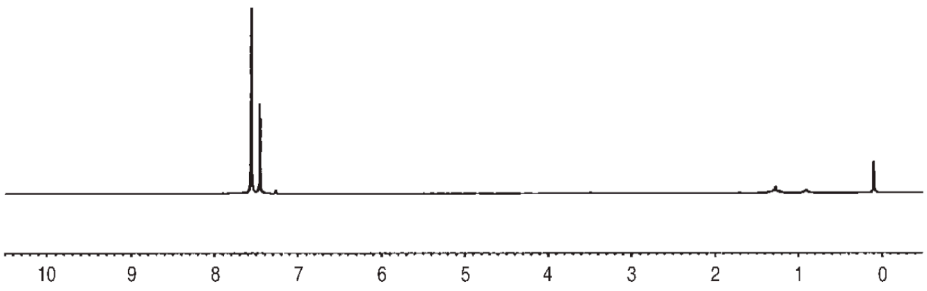
Phosphonium Salt(247 mg)

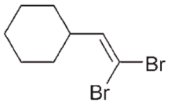
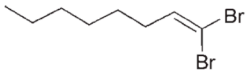
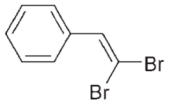
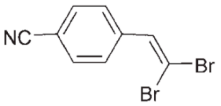
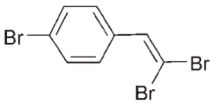
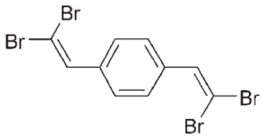
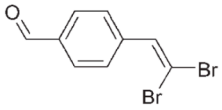
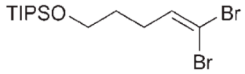
Ph_4PBr(250 mg) and
sudan red 7B(5 mg)
CH_2Cl_2(1 mL)

Corey-Fuchs



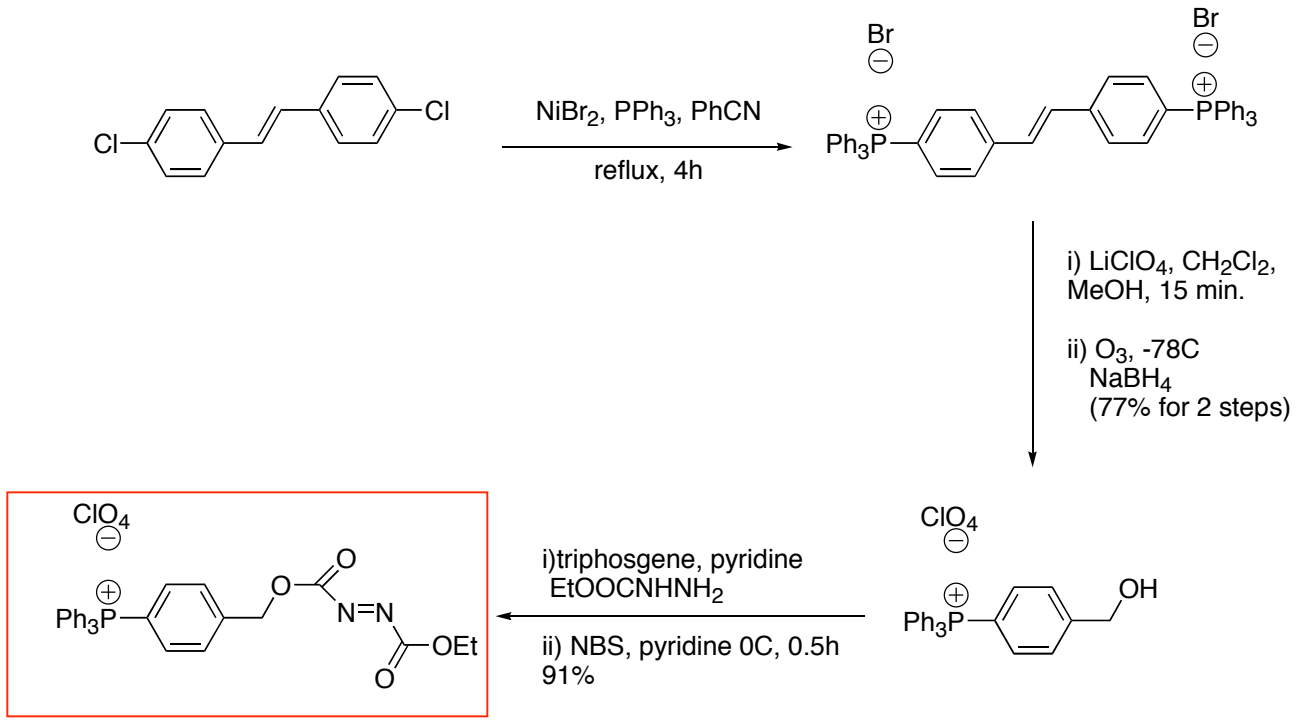
- Substantial amounts of Ph_3PO produced
- Yields comparable to Ph_3P



Entry			Yield [%][a]
1		**6**	94[b]
2		**7**	90[b]
3		**8**	90[b]
4		**9**	96[b]
5		**10**	96[b]
6		**11**	98[c]
7		**12**	95[d]
8		**13**	85[b]
9		**14**	96[b]

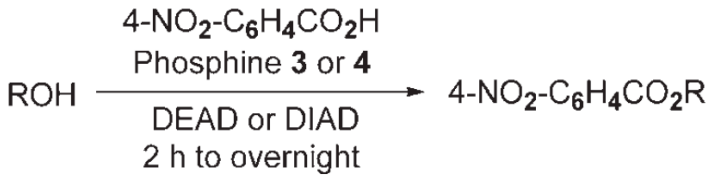
[a] After flash chromatography. [b] Phosphine **3** (2.5 equiv), CBr_4 (2.5 equiv), Zn dust (2.5 equiv), CH_2Cl_2 (0.2 M), reflux (0.5 h); then addition of aldehyde, RT, 3 h. [c] Three equivalents of all reagents, RT, 6 h. [d] Six equivalents of all reagents, RT, 6 h.

DEAD Reagent

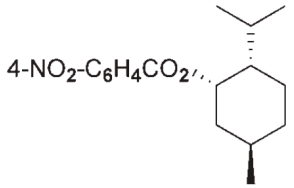
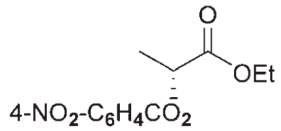
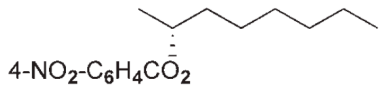
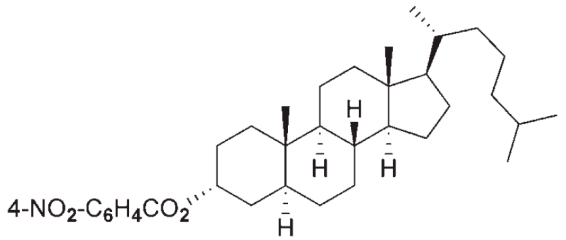
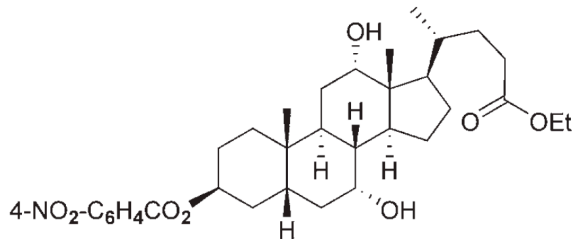


- 60% overall yield

Mitsunobu



- Comparable Yields to PPh_3
- Phosphorous free product
- Less than 2% of product is evident in ^{31}P NMR of recovered phosphonium salt
- 2 supported reagents were used

Entry	ROH		Yield [%][a]	Yield [%][f]
1		**15**	79[b] 84[c]	65–84
2		**16**	83[b]	71–91
3		**17**	91[b] 84[d]	83
4		**18**	78[b]	70–89
5		**19**	89[e]	–

[a] After flash chromatography. [b] Phosphine **3** and DEAD reagent. [c] Phosphine **4** and DEAD reagent. [d] Phosphine **3** and azodicarboxylate **24** at −10 °C. [e] Phosphine **3** and DIAD reagent. [f] PPh_3 or other supported systems.[18,27,29]

Summary

- Developed a novel solubility control group-low molecular weight
- Both PPh_3 and DEAD reagents are reactive on this support
- Convenient to precipitate out using Et_2O
- Reagents display comparable reactivity to their parent compounds
- Extra equivalents or longer reaction times are not needed
- Salts are easy to handle and can be recycled

- Application towards other reactions, reagents, and catalyst
- Applications towards Combinatorial Chemistry