

SMOPEX-301TM an effective replacement for Triphenylphosphine

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Introduction:

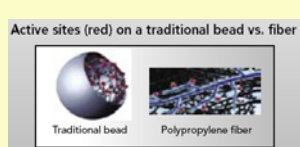
The removal of reagents, by-products and residual catalysts from desired product can be a major challenge in the work-up of chemical reactions. Solid supported reagents have been used for a number of years to ease the work-up process. They present a large surface area for functionalisation, coupled with chemical stability. However, bead type solid supports can suffer from mechanical instability by prolonged stirring and reactants have to diffuse into the porous materials to access the majority of the active sites.

Solid supported triphenylphosphine has been used for many years due to the ease of removing the oxide formed by simple filtration.

SMOPEXTM is a unique solid support based on surface functionalised polypropylene fibres marketed by Johnson Matthey. The fibres were developed as scavengers in metal recovery processes and are produced on multi ton scale.

These fibres offer excellent mechanical stability and the reactant is mainly bound externally, reducing the need for diffusion of reagents to access active sites.

SMOPEXTM fibres are offered with a range of functionalisation. SMOPEX-301TM is functionalised with triphenylphosphine that can be used in reactions as a substitute for other solid supported triphenylphosphines as well as the unsupported phosphine.



Electron microscope photograph of SMOPEX-301 fibers.
Courtesy of Johnson Matthey

Mitsunobu Reaction:

Standard reaction conditions:

For ease of work-up, di-tert-butyl azodicarboxylate was chosen as the resulting di-BOC-hydrazide can be decomposed with acid and the hydrazine extracted in to water during the work-up.

To a reaction vessel containing the corresponding triphenyl phosphine source (1.5eq.) was added 2-methyl tetrahydrofuran (7ml/mmol). Di-tert-butyl azodicarboxylate (1.5eq) was added, followed by the corresponding phenol (1eq). The mixture was stirred for 15 minutes at room temperature before adding the corresponding alcohol (1eq). The reactions were stirred over night at room temperature.

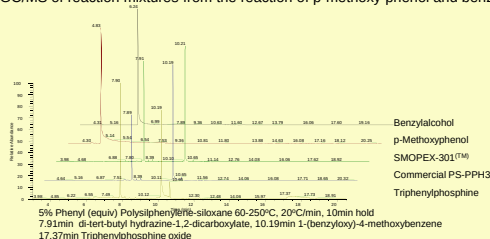
The reactions with solid reagent were filtered off, the solid washed 2x with 2-methyl tetrahydrofuran and the filtrate evaporated to dryness. TFA:dichloromethane:water 50:48:2 was added and the solution stirred for 2h. 2-methyl tetrahydrofuran was added and washed 3x with water. The organic layer was dried and evaporated to dryness to give the crude products.

Phenol	Alcohol	Product	Phosphine source	conversion ^a
			Triphenylphosphine	98%
			PS-PPH ³	98%
			SMOPEX-301 TM	98%
			SMOPEX-301 TM	95%
			SMOPEX-301 TM	40%
			SMOPEX-301 TM	98%

^a GC/MS: 5% Phenyl (equiv) Polysilphenylene-siloxane 60-250°C, 20°C/min, 10min hold

^b Commercial, 2mmol/g loading

GC/MS of reaction mixtures from the reaction of p-methoxy phenol and benzylalcohol:



Halogenation of alcohols:

Triphenylphosphine-halogen adducts are versatile reagents for converting alcohols into halides. For this work, carbon tetrachloride and N-halo succinimides were investigated for the halogenation of alcohols in combination with SMOPEX-301TM.

Standard reaction conditions for using carbon tetrachloride¹:

SMOPEX-301TM (2eq) was suspended in carbon tetrachloride (10ml/mmol) and the corresponding alcohol was added. The suspension was stirred at 60°C for 3h.

Standard reaction conditions for using halo-succinimide²:

SMOPEX-301TM (2eq) was suspended in dichloromethane (7ml/mmol). A solution of the N-halo succinimide (2eq) in dichloromethane was added dropwise at room temperature. Slight exotherm. After 10 minutes of stirring at room temperature, a solution of the alcohol (1eq) in dichloromethane (1ml/mmol) was added and the suspension stirred at room temperature for 3h.

Alcohol	Product	Halogen source	conversion ^a	Alcohol	Product	Halogen source	conversion ^a
		CCl ₄	100%			NBS	95%
		CCl ₄	100%			NS	30%
		NCS	100%			NS	40%
		NCS	100%			NCS	92% ^b
		NBS	95%				

^a GC/MS: 5% Phenyl (equiv) Polysilphenylene-siloxane 60-250°C, 20°C/min, 10min hold

^b LC/MS: Aquity CSH C18; A: water+0.1% Formic acid; B: acetonitrile+0.1% formic acid; 5-98%B 0.2-1.55min

Wittig reaction

Standard reaction conditions:

The phosphonium salts of SMOPEX-301TM can readily be synthesised by reacting the corresponding bromide (3eq) with SMOPEX-301TM in DMF at 50°C for 48h. The suspension was filtered off and washed 3x with 2-methyl tetrahydrofuran. The solid was dried in vacuum at 40°C over night.

The phosphonium salt SMOPEX (2eq) was then suspended in 2-methyl tetrahydrofuran. Sodium hexamethyldisilazide in THF (1.8eq) was added drop wise at room temperature. The coloured suspension was stirred for 1h at room temperature. The corresponding carbonyl compound was added dropwise at room temperature and the suspension stirred at room temperature for 3h. The reaction mixture was filtered off and the solid was washed 3x with 2-methyl tetrahydrofuran. The filtrate was extracted once with water. The organic layer was dried over MgSO₄, filtered off and evaporated to dryness to give the crude product.

Carbonyl compound	Bromide	Product	conversion ^a	cis/trans ^b
			98%	1/1
			95%	trans only
			20%	ND
			0%	ND

^a GC/MS: 5% Phenyl (equiv) Polysilphenylene-siloxane 60-250°C, 20°C/min, 10min hold

^b Determined by NMR of crude product

Tetrazole formation

1,5-di-substituted tetrazole formation from thioamides has been reported in the literature³. With triphenylphosphine, these reactions give good conversion at room temperature. With SMOPEX-301TM some reactions had to be performed at 60°C to achieve conversion to the tetrazole. The scope of this reaction needs further exploration

Standard procedure:

To SMOPEX-301TM (2eq) in 2-methyl tetrahydrofuran (3ml/mmol) was added di-tert-butyl azodicarboxylate (2eq) and the corresponding thioamide (1eq). The suspension was stirred at room temperature for 15 minutes before adding trimethylsilyl azide (2eq). The suspension was heated to 60°C over night. The work-up was the same as for the Mitsunobu reaction.

Thioamide	Product	conversion ^a
		4% ^b
		13% ^c
		65% ^c

^a LC/MS: Aquity CSH C18; A: water+0.1% Formic acid; B: acetonitrile+0.1% formic acid; 5-98%B 0.2-1.55min

^b 60°C/5h

^c room temperature/5h

Summary

- SMOPEX-301TM was used in reactions as a replacement for triphenylphosphine. It provided similar results in the reactions compared to both triphenylphosphine and other polymer supported triphenylphosphines, with the added benefit of easy removal by filtration.
- SMOPEX-301TM is easy to handle and mechanically stable to prolonged stirring at elevated temperatures.
- We recommend washing commercially available technical grade SMOPEX-301TM with 2-methyl tetrahydrofuran and drying under vacuum before use to remove low level of impurities.
- Due to its low density, more solvent is required for the reactions than with unsupported triphenylphosphine.
- Filtration can sometimes be slow.
- SMOPEX-301TM does not require the swell/shrink washing steps required by some polymer supported reagents to elute the product.

Acknowledgments:

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References:

- 1 For a review see: Apple, R; Angewandte Chemie Int. Ed. Eng., 14, p 801-811, 1975
- 2 Hanessian, S et al; Carbohydrate Research, 24, p 45-46, 1972
- 3 Athanassopoulos, C.M. et al; Organic Letters 7, p 561-564, 2005