

Exploiting Poly(ethylene glycol) as a Matrix for Liquid-Phase Organic Synthesis

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Abstract: Soluble polymer-supported chemistry is a technology that allows the blending of the benefits of polymer-supported synthesis and solution-phase chemistry. Herein, we describe our recent efforts in this area targeted at exploring the scope of poly(ethylene glycol) (PEG) as the matrix. Specifically we describe the use of PEG as a support for triphenyl phosphine and for the Stille reaction.

Keywords: soluble polymer, synthesis, poly(ethylene glycol), triphenyl phosphine, Wittig reaction, Stille reaction.

Introduction

For many years solid polymers have been dominant both as supports for organic reagents and in combinatorial synthesis [1,2]. However, there are concerns associated with the use of insoluble polymeric derivatives such as lowered reactivity, site-site interactions, extended reaction times and diffusion-limited reactivity. The use of soluble matrices [3] such as poly(ethylene glycol) [4] circumvents these problems while also allowing for routine monitoring of reaction progress [5,6].

Our efforts in this field have included the development of soluble polymer-supported combinatorial libraries [7], catalysts [8], reagents [9-11], linker strategies [12,13] and synthetic methodology [14,15]. This report details the development and application of a poly(ethylene glycol) bound triarylphosphine reagent and the optimization of a liquid-phase Stille cross-coupling reaction with subsequent generation of a small library of biaryl, heterobiaryl and styryl derivatives in high yields and purity.

Results and Discussion

Development and Application of a Poly(ethylene glycol)-Supported Triarylphosphine Reagent (2)

Our group recently communicated an extension of PEG-supported chemistry into the field of functionalized polymers as reagent supports [16-18]. We prepared a novel triarylphosphine derivative of PEG (**1**) and showed that, when compared to a heterogeneous commercially available counterpart, it possesses favorable reaction kinetics in both the Staudinger and Mitsunobu etherification reactions. The present study expands on those preliminary investigations.

Synthesis of Liquid-Phase Phosphine Reagent (2)

A concern with the original reagent **1** was the carbamate ester moiety incorporated as a linker between the triarylphosphine and the PEG support. The known base and acid sensitivity of the urethane linkage, coupled with worries about its lability in the presence of Lewis acids and metallating reagents, linked any further exploitation of PEG-supported triarylphosphines to an immediate replacement of this carbamate ester group. An aryl-alkyl ether moiety was chosen as the replacement linker, the chemical stability of which is comparable to that of the poly(ethylene oxide) backbone, therefore reagent **2** became the functionalized polymer of choice [19].

The synthetic strategy towards **2** involves an initial concise preparation of the key hydroxyphosphine **3** [20], followed by its attachment to PEG *via* the dimesylate **4** [21]. 4-Bromo-phenol **5** was protected as the TBDMS ether **6**, that was then phosphinylated under standard conditions [22] to give the triarylphosphine **7**. The silyl ether was removed and the resultant hydroxyphosphine **3** was obtained in 87% yield for the three steps. Mesylate **4** was obtained by heating (50°C) a neat solution of PEG₃₄₀₀ **8** in methanesulfonyl chloride. No base was required under these conditions, which had the benefit that the purification of **6** was simplified from its original preparation [21]. Etherification between **4** and **3** was performed in rigorously degassed DMF. Phosphine **2** was then isolated by addition of the reaction mixture into degassed diethyl ether, followed by filtration and sequential washing of the polymeric precipitate with *i*-Pr alcohol (to remove salts) followed by diethyl ether to give reagent **2** in 92% yield, based on the weight of polymer isolated.

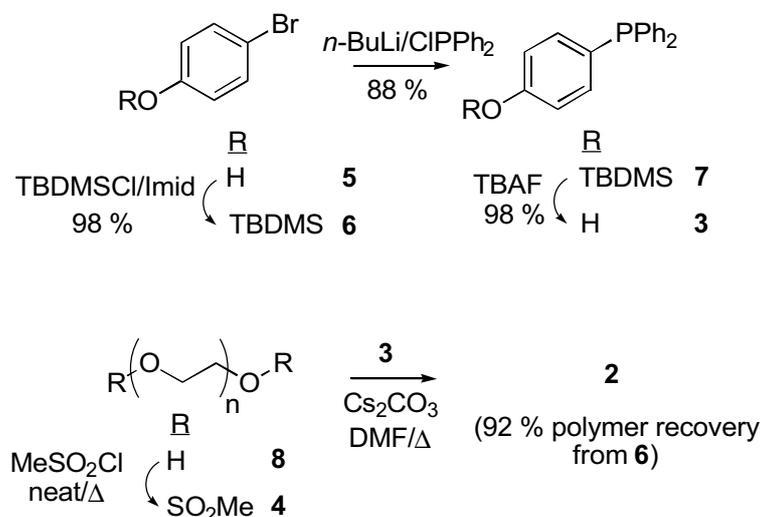


Figure 1.

The oxidation state of the phosphine termini of **2** was routinely quantified by ^{31}P NMR after certain periods of storage. This revealed that even after prolonged exposure to air (2-3 weeks) little oxidation to the phosphine oxide (< 5%) occurs.

The derivatization level of the polymer is also determined by inspection of the ^1H NMR of **2**. The chemical shift of α -methylene protons of PEG and its derivatives is a function of the moiety attached to the termini hydroxyl groups. For underivatized PEG₃₄₀₀, the chemical shift of these α -protons is δ 3.8 ppm, for PEG-mesylate **4**, this changes to δ 4.35 ppm (also detectable are the β -methylene protons δ 3.74 ppm) and for the phosphine terminated polymer **2** this changes to δ 4.16 ppm (β -methylene protons δ 3.64 ppm). Inspection of the ^1H NMR of **2** shows that no mesylate **4** remains. Therefore there is high confidence that the polymeric phosphine **2** is quantitatively substituted with terminal triarylphosphine residues (*ca.* 0.5 mmol g⁻¹). The ease of NMR-characterization of soluble polymer reagent **2** offers a considerable advantage over its solid-phase homologue which, in order to determine the oxidation state of the phosphine center, must involve either gel- or solid-phase NMR, or single-bead FTIR techniques [23].

Liquid-Phase Ozonide Reduction

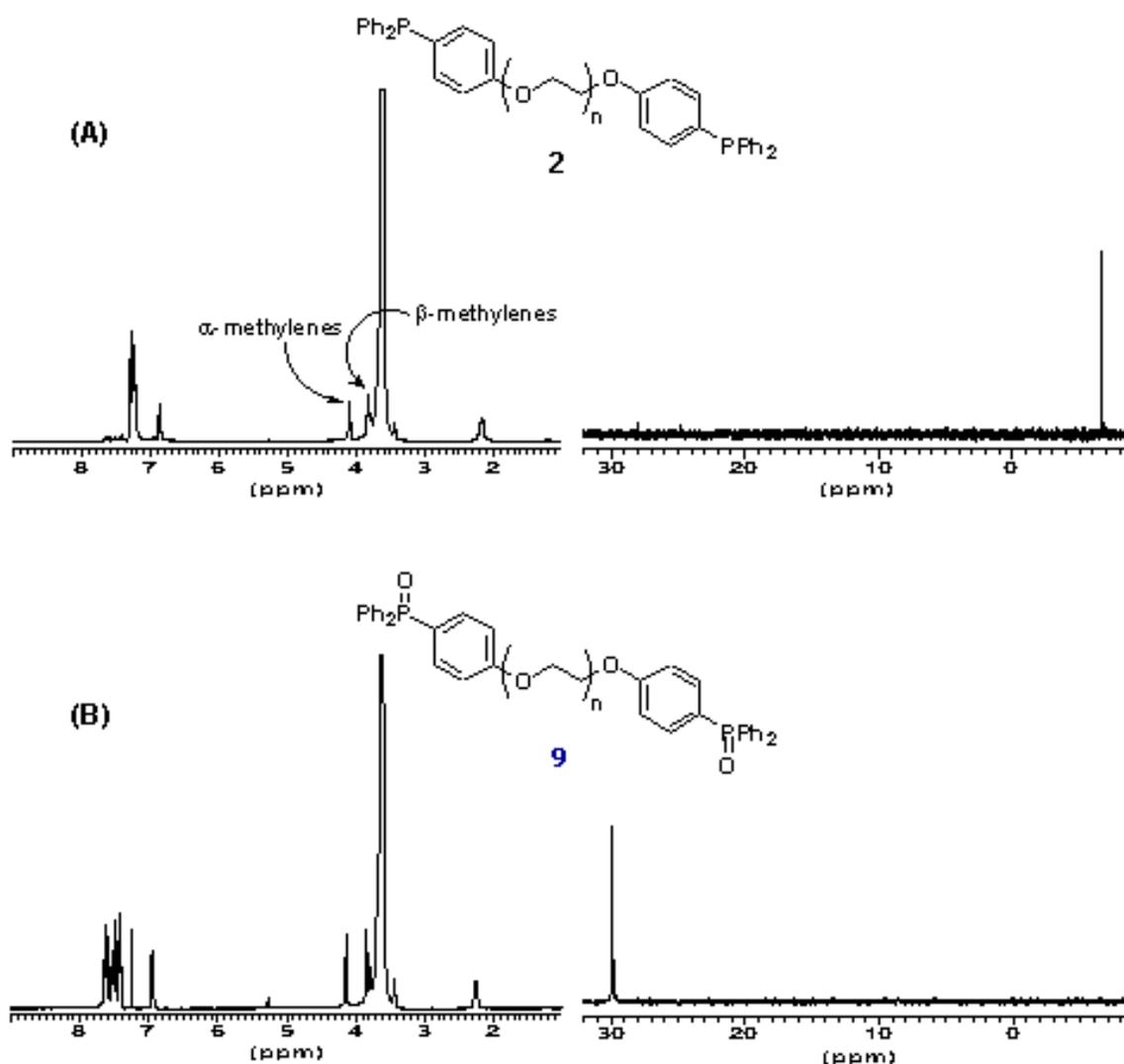
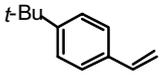
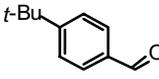
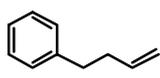
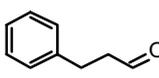
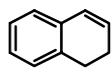
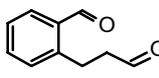
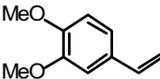
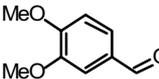
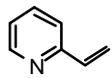
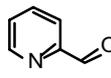


Figure 2. A) ^1H and ^{31}P NMR spectra of PEG-supported triarylphosphine **2**. B) ^1H and ^{31}P NMR spectra of PEG-supported triarylphosphine **9**.

As an entry level into the utility of **2** in organic chemistry, the mild chemical decomposition of ozonides was selected. Ozonolysis of alkenes has a broad scope of application in organic chemistry, and the range of methods for destruction of the intermediary ozonides is equally broad. However, the two major methods of choice: Zn/acetic acid or dimethyl sulfide have limitations, a result of potential chemical substituent sensitivity in the former case, or noxious reagents and high-boiling point byproducts in the latter. For these reasons PPh₃ is an excellent alternative [24]. It has received only limited use in solution-phase chemistry however, because of the problems of removing both the excess PPh₃ and reaction byproduct, triphenylphosphine oxide, from the reaction mixture. The use of polystyrene-supported PPh₃ as a stoichiometric reagent for this reaction has been reported as an alternative and gives good to excellent yields of aldehydes [25]. Therefore an important part of this study was a direct comparison between this new liquid-phase approach with **2**, and a solid-phase approach with commercially available PPh₃.

A range of alkenes **10a-e** were treated with ozone. The incipient ozonides were then decomposed into the product aldehydes (**11a-e**) by addition of one of three reagents: PPh₃, polystyrene-supported PPh₃, or PEG-supported PPh₃ (**2**). The results are shown below (Table 1).

Table 1. Direct comparison of ozonide hydrolysis between solution-phase, solid-phase and liquid-phase triphenylphosphine.

Entry	Alkene	Product	Yield, ^a %		
			PPh ₃ ^b	⊙-PPh ₃ ^c	2
1			94	58	98
	10a	11a			
2			80	73	92
	10b	11b			
3			84 ^d	60 ^d	97 ^d
	10c	11c			
4			51	56	77
	10d	11d			
5			72	62	63
	10e	11e			

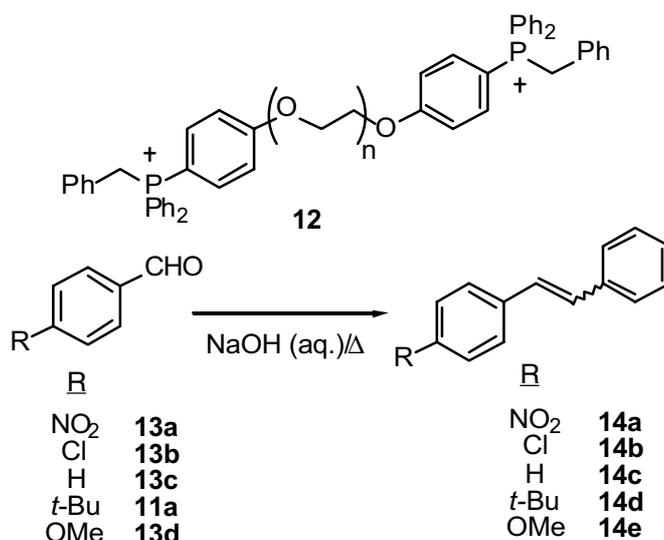
^aReaction conditions: The respective triphenylphosphine (2eq.) was added to the ozonide (1eq.) of the alkene in CH₂Cl₂ and left to stir for 2 h. Yields based on HPLC comparison to authentic product standards; ^bCommercially available PPh₃ (Aldrich Chem. Co.); ^cCommercially available polystyrene-PPh₃ resin (Aldrich Chem. Co.); ^dIsolated yield.

The isolation procedure for the PEG-supported reagent involved a simple precipitation of the spent reagent into ether, and concentration. This consistently removed > 99% of the polymer byproduct. Passage of the ether concentrate through a short silica pad completely removed the remaining polymer traces, giving the product aldehydes in analytically pure form. The solid-phase reagent was separated from the reaction mixture by filtration. The product was isolated by then washing the resin with volumes of CH₂Cl₂. The solution-phase reactions were purified by silica gel chromatography to remove the excess PPh₃ and the byproduct PPh₃O.

In all cases studied, the yields of aldehyde were highest with the soluble polymer-supported reagent **2** and with the exception of **11d** the soluble reagent gave higher yields than the solid-phase reagent. This result may be a composite of three factors; increased reducing power of the soluble polymer-supported phosphine **2** when compared to both the solid- and solution-phase reagents, a result of the *p*-ethoxyether functionality which links the reagent to the soluble polymer support, the homogeneous nature of the ensuing chemical process when compared to the heterogeneous resin reagent and the ease of isolation and purification of the products when compared with solution-phase strategy.

Liquid-Phase Wittig Reactions *in aqua*

Reagent **2** was subsequently transformed into the polymer-supported phosphonium salt **12** suitable for Wittig olefination in aqueous solution. Organic chemistry in water has been the focus of considerable efforts in recent years [26-28]. The Wittig olefination reaction has also been much studied throughout the evolution of crosslinked polymer-supported reagents and considerable success has been achieved [29-34]. Bernard and Ford [34] noted an inverse correlation between the yield of alkene obtained from polymer-supported Wittig reagents with aldehydes and ketones in solution and the degree of divinylbenzene (DVB) cross-linking in the resin. Progressing from 0.5-20% DVB crosslinking, *i.e.* from gel to macroporous resins, can result in a fall of 20% in the yield of alkenes. These results suggested that a soluble polymer-supported phosphonium salt may give excellent yields in the Wittig reaction.



Scheme 2.

The physical properties of the PEG backbone are such that the PEG-supported phosphonium salt **12** is eminently water soluble and offer the tantalizing prospect of facilitating the first soluble polymer-supported Wittig olefination reactions *in aqua*. Treatment of PEG-supported phosphine **2** with benzyl-bromide, followed by precipitation into diethyl ether yielded the soluble polymer-supported benzyl tri-arylphosphonium salt **12** in 81% yield (based on the weight of polymer obtained). This polymeric phosphonium salt **12** is completely soluble in water at pH 7. The reaction of this novel Wittig salt (**12**) was then studied with a range of aldehydes (**11a** and **13a-d**) in aqueous sodium hydroxide solution (Scheme 2, Table 2).

Table 2. Aqueous Wittig reactions phosphonium salt **12** and aldehydes (**11a-13a-d**).

Entry	Aldehyde	Conditions	Yield % ^a (<i>E/Z</i> ratio) ^b
1	13a	1 N NaOH, r.t.	65 (56:44)
2		1 N NaOH, 90°C	62 (75:25)
3	13b	1 N NaOH, r.t.	80 (46:54)
4		1 N NaOH, 90°C	78 (75:25)
5	13c	1 N NaOH, r.t.	95 (48:52)
6	11a	1N NaOH, r.t.	38 (49:51)
7		1 N NaOH, 90°C	49 (47:53)
8	13d	1 N NaOH, r.t.	63 (54:46)

^a Yields of isolated stilbenes (**14a-e**).

^b Measured by ¹H NMR of crude mixture.

The isolated yields of the alkenes **14a-e** by this method were good to excellent, proving that the rate of reaction of the ylide with the substrate aldehydes is indeed much faster than decomposition to **9**. Isolation of the stilbenes (**14a-e**) was achieved by partitioning the reaction mixture with CH₂Cl₂, followed by removal of the water by addition of anhydrous magnesium sulfate, and then precipitation of the polymer supported triphenylphosphine oxide byproduct **9** into diethyl ether and concentration of the etheric solution to dryness.

To explore the scope of this reaction two components were varied: base strength and temperature. Increasing the base-strength (from 1 N to 2 N NaOH) neither affected the yield of stilbenes (**14a-e**) nor the *E:Z* isomer distribution. However, elevating the temperature (up to 90°C) resulted in improved yields of **14d** and as to be expected an increase in the *E:Z* ratio for the stilbene products.

Regeneration of Spent Reagent **9**

A number of standard methods were employed to regenerate the oxidized polymer-supported phosphine **9** (Table 3). Only poor to moderate reduction of **9** to **2** occurred with polymethylhydrosiloxane (PMHS) [35] using various conditions. The reason is perhaps due to unfavorable polymer-polymer-interactions between the polymeric reductant and the PEG-backbone. Trichlorosilane [36,37], while leading to a significant reduction of the phosphine group (56%), completely cleaved the terminal phos-

phine from the polymer. However, quantitative reduction of **9** was achieved with freshly prepared alane (AlH_3) [38] in THF as determined by ^{31}P NMR *vide supra*. The polymer was isolated in 75% yield following the usual precipitation into degassed ether. The incomplete polymer recovery is attributed to problems associated with the byproduct aluminium salts either complexing to the polymer support and thus preventing precipitation or polymer-backbone hydrolysis during the reduction process. Thus, the utility of this reagent was made complete by its facile regeneration by quantitative reduction and reiso-

Table 3. Regeneration of PEG-supported triarylphosphine **2**.

Entry	Reagent	Conditions	P(V) to P(III) ^a /%
1	PMHS ^b , CH_2Cl_2	CH_2Cl_2 / r.t.	20
2	PMHS	Benzene/ reflux 20 h	33
3	PMHS	THF/ reflux 20 h	40
4	HSiCl_3 ^c	Benzene/ reflux 20 h	56
5	$\text{AlH}_3 \bullet \text{THF}$	THF/ r.t. 30 min	100

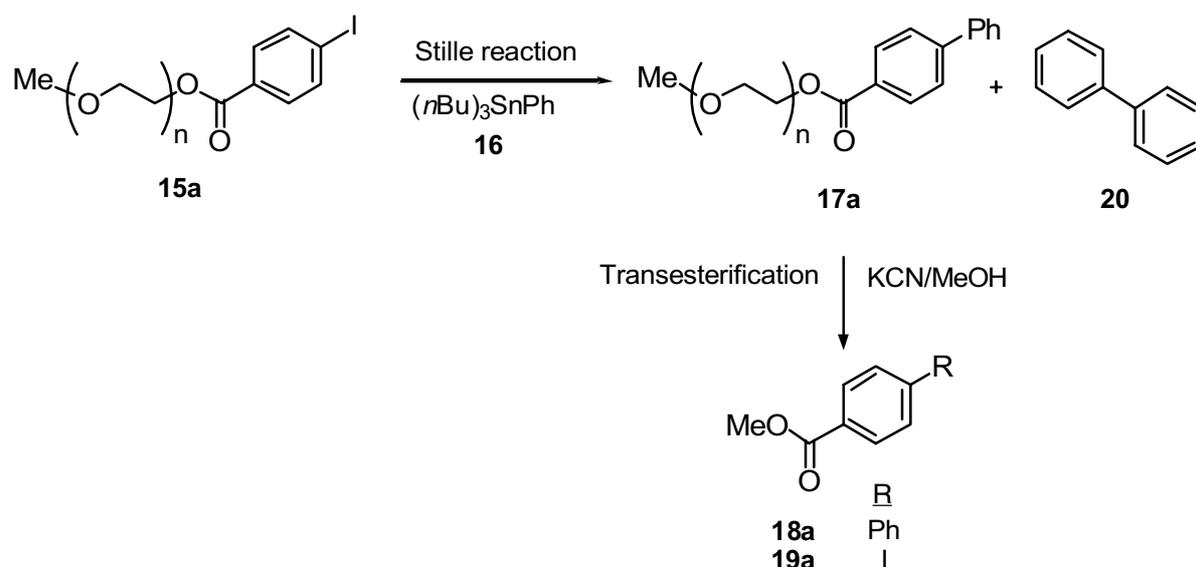
^aMeasured by ^{31}P NMR of the reaction mixtures. ^bPolymethylhydrosiloxane. ^cWith triethylamine.

Poly(ethylene glycol) as a Soluble Polymer Matrix for the Stille Cross Coupling Reaction

The Stille [39,40] cross-coupling reaction possesses wide scope and functional group tolerance. In addition, the requisite tin reagents are easily prepared and relatively stable when compared to most organometallic reagents. These properties make this particular process very attractive as a route to many carbon-carbon bond forming reactions under relatively ambient conditions. The importance of this reaction within the sphere of polymer-supported chemistry has been demonstrated with the recent emergence of solid- [41-43] and fluorous-phase [44,45] approaches.

The defining feature of the Stille coupling is the use of a trialkyltin reagent in a palladium-catalyzed coupling with either a halide or triflate. As with all tin chemistry, the benefits associated with these reagents are to some extent outweighed by the problems associated with their removal after reaction completion. The tri-*n*-butyl derivatives are more difficult to remove from a reaction mixture than the methyl congeners due to their low volatility and poor water solubility. Therefore there is an increasing need for methodologies which facilitate the separation of the side-product tributyltin derivatives from the required adducts following the Stille reaction. Our aim was to study the potential of poly(ethylene glycol) as a soluble matrix for the electrophile component of the reaction. The tributyltin derivative and 'other' components of the reaction being in solution could, theoretically, be separated from the polymer-supported products by a simple precipitation of the support into a suitable solvent and recovery by filtration.

MeO-PEG_{5000} was initially esterified with either *para*- or *ortho*-iodobenzoic acid using DCC and DMAP to give *para*- and *ortho*-polymer-supported iodides, **15a-b** respectively, with polymer recoveries being > 95% [46]. The conversion was quantitative based upon ^1H NMR spectroscopic analysis of **15a-b**.



Scheme 3.

A number of efficient reaction conditions for solution-phase Stille couplings have been developed [39,40,47,48] and initially we utilized a number of these for the reaction between PEG-iodide **15a** and tributyl phenyltin (**16**) to explore the viability of PEG as a soluble polymer support for this reaction and then to identify the optimal conditions necessary for the PEG-supported Stille variant (Scheme 3 and Table 4). Previous work has revealed conflicting evidence regarding the potential for coordination of the PEG polyether backbone to transition metals [49-51]. Initially therefore, we had serious concerns that the PEG-backbone may serve to either retard or completely inhibit the Stille reaction *via* complexation of either the palladium catalyst, the alkali metal halide or the organostannane reagent.

Table 4. Optimization of the Stille cross-coupling reaction parameters between **15a** and **16**.

Entry	Catalyst	Solvent	conc./mM ^a	T/°C	LiCl	Time/h	Yield 18a/% ^b	Yield 19a/% ^b
1	Pd(PPh ₃) ₂ Cl ₂	toluene	20	110	+	24	22	- ^c
2	Pd(PPh ₃) ₂ Cl ₂	THF	20	reflux	+	24	68	- ^c
3	Pd(PPh ₃) ₂ Cl ₂	DMF	20	80	+	24	89	- ^c
4	Pd(PPh ₃) ₄	toluene	20	110	+	24	53	- ^c
5	Pd(PPh ₃) ₄	THF	20	reflux	+	24	7	73
6	Pd(PPh ₃) ₄	DMF	20	80	+	24	10	58
7	Pd(PPh ₃) ₂ Cl ₂	DMF	20	80	-	24	86	12
8	Pd(PPh ₃) ₂ Cl ₂	DMF	20	80	+	48	97	0
9	Pd(PPh ₃) ₂ Cl ₂	DMF	10	80	+	24	98	0

^a Based on the concentration of PEG-bound substrate **15a**.

^b Isolated yields after workup.

^c Not determined.

The efficiency of the initial series of experiments was determined both by ^1H NMR analysis of the PEG-biaryl adduct **17a** and, following transesterification, by the isolated yields of the biaryl methyl ester **18a** and monoaryl ester **19a** (resulting from no cross-coupling with **15a**). Reactions were conducted in toluene, THF or DMF, with either a Pd(0) or Pd(II) catalyst (0.1 equiv.) in the presence or absence of LiCl (10 equiv.). A three-fold excess of tributyl phenylstannane **16** was used relative to the PEG-supported electrophile **15a**. Additional parameters that were modified included temperature, reaction time and reaction concentration. solvent (Table 1, entries 3 and 6-9) under standard conditions of **15a** (20 mM) and 80°C. The results show that DMF is the most superior of the solvents tested for the PEG-supported Stille reaction. Similar to the case with THF, $\text{PdCl}_2(\text{PPh}_3)_2$ is the best catalyst (Table 4, entries 3 and 6) with considerable amounts of the transesterified iodide **19a** being recovered after reaction with Pd(0) (58%). In addition, by leaving the reaction to run for 48 h rather than the preliminary 24 h, a considerable increase in the observed biaryl adduct **18a** is achieved (89 and 97% respectively) (Table 4, entries 3 and 8).

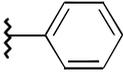
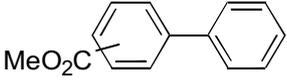
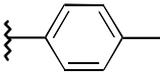
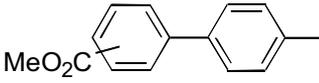
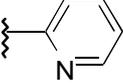
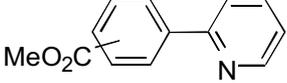
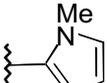
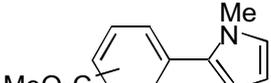
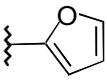
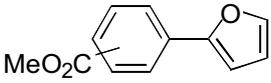
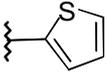
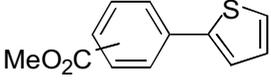
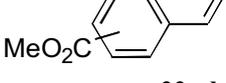
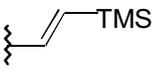
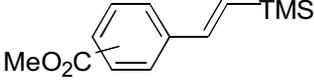
In a recent fluororous-phase approach to the Stille reaction, between aryl tin reagents and aryl halides, it was observed that by using LiCl as an additive that the cross-coupling efficiencies were significantly enhanced [44]. However, the positive effect of LiCl on our PEG-supported Stille variant seems to be only marginal (compare Table 4, entries 3 and 7). This result is more in line with previous reports which found that LiCl does not usually enhance the reaction between trialkyl tin reagents with aryl halides, but is generally more useful with aryl triflate electrophiles [52,53].

The summary of these results is that the use of $\text{PdCl}_2(\text{PPh}_3)_2$ in the presence of LiCl in DMF at a reaction concentration of 20 mM for 48 h, or 10 mM for 24 h, gives excellent yields for the monomethoxy-PEG₅₀₀₀-supported variant of the Stille cross-coupling reaction (97 and 98% respectively).

This liquid-phase approach imparts a number of significant advantages over its solution-phase counterpart. The toxic tributyl tin derivatives are easily separated from the PEG-biaryl adduct **17a** by precipitation of the polymer-support into either *iso*-propyl alcohol or diethyl ether. Polymer recovery was >99% in each case. In addition, the homocoupled biaryl side-product **20**, an incontrovertible product in the solution-phase reaction [39,40], does not contaminate the soluble-polymer supported biaryl product **17a**, because the homocoupling side-reaction takes place in solution and thus the contaminant is removed during the precipitation step. Having optimized the liquid-phase Stille reaction conditions on monomethoxy-PEG₅₀₀₀, we then sought to examine the scope of this cross coupling process in a parallel format. A range of tributyl stannanes, **16** and **21-28**, were reacted with the PEG-supported iodides **15a-b** in a parallel fashion, furnishing the library of biaryl, heterobiaryl and styryl derivatives **18a-b** and **28a-b** to **34a-b** (Table 5).

The isolated yields of all library members were good to excellent (69 - 99%) showing that under our pre-optimized conditions *vide supra*, that the scope of the PEG-supported variant of the Stille reaction is quite broad. Following passage down a short pad of silica gel, the library members (**18a-b**, **28a-b** to **34a-b**) were each isolated in > 95% purity.

Table 5. Parallel liquid-phase Stille couplings of iodides **15a-b** with tributyl stannanes **16** and **21-27^a**.

Entry	Bu ₃ Sn-R	Products ^b	Yield/% ^c	
			a	b
1	 16	 18a-b	98	82
2	 21	 28a-b	99	78
3	 22	 29a-b	94	81
4	 23	 30a-b	71	-- ^d
5	 24	 31a-b	96	78
6	 25	 32a-b	90	69
7	 26	 33a-b	98	90
8	 27	 34a-b	99	82

^aReactions were conducted under the conditions described *vide supra*.

^bCompound descriptors **a** and **b** represent the *para*- and *ortho*-isomers respectively. All the products were characterized by ¹H, ¹³C NMR spectroscopy and HRFABMS and gave satisfactory spectroscopic data when compared to authentic samples or to literature data. See the supporting information for more detail.

^cIsolated yields after the two steps.

^dYields of *ortho*-product **30b** was not determined because instability of the stannanes **23** precluded its efficient synthesis.

In each case (Table 5, entries 1-8) the yield of the *ortho*-isomer was lower than its corresponding *para*-congener. We rationalize that this phenomenon may be a result, at least in part, of the steric effect imparted by the PEG-backbone polymer chain during ligand transfer. However this effect followed no definitive trend related to the size of the moiety being transferred. suggests that the process involved may be more complex than simple steric retardation. While, in this report, no attempt has been made to re-optimize the reaction conditions to improve the yield of the *ortho*-isomers, it is speculated that future studies directed to resolve this issue would involve simply increasing the number of equivalents of the stannane and/or palladium catalyst, whilst perhaps using more dilute reaction conditions.

Experimental

General

Unless otherwise stated, all reactions were performed under an inert atmosphere using dry reagents and solvents and flame-dried glassware. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm pre-coated silica gel Kieselgel 60 F₂₅₄ plates. Visualisation of the chromatogram was by UV absorbance, iodine, dinitrophenylhydrazine, ceric ammonium molybdate, iron(III) chloride or *p*-anisaldehyde as appropriate. Liquid chromatography was performed using compressed air (flash chromatography) with the indicated solvent system and silica gel 60 (230-400 mesh). Preparative and semi-preparative TLC was performed using Merck 1 mm or 0.5 mm coated silica gel Kieselgel 60 F₂₅₄ plates respectively. ¹H-NMR spectra were recorded on a Bruker AMX-600, AMX-500, AMX-400 or AC-250 spectrometers at 600, 500, 400 or 250 MHz respectively. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard. ¹³C NMR spectra were recorded on either a Bruker AMX 500 spectrometer at 125 MHz or a Bruker AMX 400 spectrometer at 100 MHz. ³¹P NMR spectra were recorded on a Bruker AMX 400 spectrometer at 162 MHz. Infra-red spectra were run on a Nicolet 510 FT-IR spectrometer from 4000-600 cm⁻¹. Mass spectra were recorded on a VG ZAB-VSE instrument. Optical rotations were measured using a Perkin-Elmer 241 polarimeter.

Standard Procedure A: Ozonide Reduction With Solution-Phase PPh₃

2-Formylbenzenepropanal (**11c**)

A solution of 1,2-dihydronaphthalene (**10c**) (100 mg, 0.77 mmol) in CH₂Cl₂ (30 mL) was cooled to -78°C. A stream of ozone-enriched oxygen was introduced until a blue color persisted. After 5 min a stream of dry nitrogen or argon was bubbled through the reaction mixture until the blue color disappeared. PPh₃ (403 mg, 1.54 mmol) was added in one portion and the resulting solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then concentrated *in vacuo* and the crude residue was purified by silica gel chromatography, using 25% hexanes-ethyl ether as the eluant, to give the aldehyde **11c** (105 mg, 84%) as a colorless oil. R_f (Et₂O / hexane 9:1) = 0.56; R_T 4.4 min; ¹H NMR (250 MHz, CDCl₃) δ 10.16 (s, 1H), 9.82 (d, *J* = 1.0 Hz, 1H, Ar-H), 7.82 (dd, *J* = 7.4 Hz, 1H, Ar-H), 7.56-7.25 (m, 3H, Ar-H), 3.35 (t, *J* = 7.5 Hz, 2H), 2.79 (dt, 2H); ¹³C (101 MHz, CDCl₃) δ 201.3, 192.9, 147.9, 142.7, 135.4, 134.5, 131.3, 127.0, 102.0, 45.2, 25.6; FABHRMS calcd. for C₁₀H₁₀O₂ (M⁺) 162.1852, found 162.1854.

Standard Procedure B: Ozonide Reduction With Liquid-Phase PPh₃ reagent **2***2-Formylbenzenepropanal (11c)*

A solution of the ozonide of 1,2-dihydronaphthalene (**10c**) (100 mg, 0.77 mmol) in CH₂Cl₂ (30 mL) was prepared as described in standard procedure A. PEG-PPh₃ **2** (3.08 g, 1.54 mmol) was added in one portion and the resulting solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then concentrated (to 5 mL) *in vacuo* and added dropwise to vigorously stirring diethyl ether (200 mL). The precipitate was removed by filtration and washed with diethyl ether (50 mL). The filtrate and washings were then concentrated (10 mL) *in vacuo* and passed through a pad of silica gel (1cm × 2cm). The eluant was evaporated to dryness to give the dialdehyde **11c** (121 mg, 97%) as a colorless oil.

Standard Procedure C: Ozonide Reduction With Solid-Phase PPh₃ reagent*2-Formylbenzenepropanal (11c)*

A solution of the ozonide of 1,2-dihydronaphthalene (**10c**) (100 mg, 0.77 mmol) in CH₂Cl₂ (30 mL) was prepared as described in standard procedure A. Resin-bound PPh₃ (513 mg, 1.54 mmol) was added in one portion and the resulting solution was allowed to warm to room temperature and stirred for 2 h. The resin was removed by filtration and washed with CH₂Cl₂ (250 mL). The filtrate and washings were then concentrated (10 mL) *in vacuo* and passed through a pad of silica gel (1cm × 2cm). The eluant was evaporated to dryness to give the dialdehyde **11c** (75 mg, 60%) as a colorless oil.

Standard Procedure D: Wittig reactions in aqua with Liquid-Phase Phosphonium Salt **3***4-Nitrostilbene (14a)*

Wittig salt **12** (200 mg, 0.10 mmol) and **13a** (70 mg, 0.46 mmol) were dissolved in a solution of 1 N NaOH (4.6 mL) and water (1 mL). The reaction mixture was then stirred at either room temperature (Table 2, entry 1) or 90°C (Table 2, entry 2). The reaction mixture was then diluted with CH₂Cl₂ (100 mL) and anhydrous MgSO₄ was added with vigorous stirring. The desiccant was then removed by filtration and washed with CH₂Cl₂. The combined filtrate and washings were concentrated *in vacuo* (to 3 mL) and then added dropwise to vigorously stirring diethyl ether (100 mL). The precipitate was removed by filtration and washed with diethyl ether (20 mL). The filtrate and washings were then concentrated (2 mL) *in vacuo* and passed through a pad of silica gel (1cm × 2cm). The eluant was evaporated to dryness to give a mixture of the *E:Z* stilbenes **14a** (Table 2, entry 1; 45 mg, 65%. Table 2, entry 2; 43 mg, 62%) as a pale yellow oil.

Regeneration of PEG-(OPhPPh₂)₂ (2)

PEG-phosphine oxide **9** (200 mg, 0.1 mmol) was dissolved in THF (2.5 mL) and cooled (0°C). Freshly prepared alane [44] 0.5 M in THF (0.25 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 30 min. The reaction mixture was then

cooled (0°C) and quenched with MeOH (0.3 mL). The crude mixture was filtered through a short pad of Celite, the clear filtrate was then concentrated *in vacuo* (to 4 mL) and added dropwise into vigorously stirring degassed diethyl ether (50 mL). The precipitate was collected by filtration, washed with diethyl ether (30 mL) and dried *in vacuo* to give reagent **2** (150 mg, 75%) as an ivory solid.

Standard Procedure E: Stille Coupling of PEG-bound iodo benzoate and Transesterification with KCN/MeOH

Stille Coupling

In a typical procedure MeO-PEG₅₀₀₀ bound *para*-iodobenzoate **15a** (1.0 g, 191 μmol) was dissolved in a degassed anhydrous solution of LiCl (79 mg, 1.91 mmol) in DMF (5 mL). Dichlorobis(triphenyl phosphine)-palladium(II) (13 mg, 19 μmol) and tributyl-phenylstannane (187 μL, 574 μmol) were then added. The reaction mixture was stirred under nitrogen at 80°C for 24 h. The dark suspension was cooled to room temperature, diluted with CH₂Cl₂, filtered through a glass fritted funnel and concentrated *in vacuo* to 8 mL. This clear solution was added into vigorously stirred diethyl ether (120 mL). The precipitate was isolated by filtration and washed with *i*-Pr alcohol and diethyl ether to give the polymeric biaryl product **3a** as a white solid (980 mg, 99%).

MeO-PEG₅₀₀₀-(4-phenylbenzoate) (**18a**). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 8.1 Hz, 2 H), 7.65-7.59 (m, 4 H), 7.44 (t, *J* = 7.56 Hz, 2 H), 7.37 (t, *J* = 7.28 Hz, 1 H), 4.47 (t, *J* = 4.56 Hz, 2 H, PEG-α-methylenes), 3.81 (m, PEG-β-methylenes), 3.62 (m, PEG-methylenes).

Transesterification

The PEG-bound biphenyl **3a** (980 mg, 189 μmol) and potassium cyanide (100 mg, 1.5 mmol) were dried at room temperature under high vacuum for 1 h. Anhydrous methanol (10 mL) was added under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h and then added to diethyl ether (150 mL). The precipitate was collected by filtration and washed twice with diethyl ether. The filtrate was concentrated *in vacuo* and the crude residue was purified by passage through a short column of silica gel (CH₂Cl₂ or hexane-10% diethyl ether as the eluant), to give the methyl ester **18a** as a white solid (40 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 8.1 Hz, 2 H), 7.67-7.61 (m, 4 H), 7.44 (t, *J* = 7.56 Hz, 2 H), 7.39 (t, *J* = 7.32 Hz, 1 H), 3.94 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.94, 145.55, 139.90, 133.81, 130.04, 128.87, 128.09, 127.21, 126.97, 52.07; FABHRMS calcd. for C₁₄H₁₃O₂ (MH⁺) 213.0916, found 213.0922.

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