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Exploring the Scope of Poly(ethylene glycol) (PEG) as a Soluble Polymer Matrix for the Stille Cross-Coupling Reaction

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The optimization and efficient parallel synthesis and purification of a library of biaryl, heterobiaryl, and styryl derivatives, via the first reported poly(ethylene glycol)-supported palladium-catalyzed Stille procedure, are described. Preliminary investigations into the reaction between monomethoxy poly(ethylene glycol)$_{5000}$-supported iodide **1a** with tributylphenyltin **2** revealed that the optimal "liquid-phase" conditions employ $PdCl_2(PPh_3)_2$ (0.1 equiv) catalysis with LiCl (10 equiv) in DMF at 80 °C for either 48 h (at 20 mM concentration of **1a**) or 24 h (at 10 mM concentration of **1a**). The soluble polymer-supported reaction is superior to its solution-phase counterpart because the tributyltin side products and excess reagents are easily separated from the product intermediate **3a** by precipitation of **3a** into diethyl ether followed by recovery of the polymer by filtration in >99%. In addition, the homocoupled byproduct **6** is also removed during this precipitation step. Under these conditions the transesterified biaryl adduct **4a** can be isolated in 97−98% yield. The scope of this reaction was probed in a parallel format with the PEG-supported electrophiles **1a**−**b** and a range of tributyl stannanes **2** and **7**−**13** under the optimized conditions vide supra. Subsequent cleavage of the polymer-supported adducts, by transesterification, and short column chromatography yielded a library of substituted methyl benzoates **4a**−**b** and **14a**−**b** to **20a**−**b** in high yield (69−99%) and purity (>95%).

Introduction

Soluble polymer-supported organic chemistry, dubbed "liquid-phase" synthesis, is developing as an increasingly useful adjunct to the more classical heterogeneous resin-supported approaches across the broad spectrum of polymer-supported chemical methodology and combinatorial chemistry.[1,2] Our efforts in this field have included the development of soluble polymer-supported combinatorial libraries,[3] catalysts,[4] reagents,[5−7] linker strategies,[8,9] and synthetic methodology.[10,11] This latest report details the development and application of the first liquid-phase Stille cross-coupling reaction with the subsequent generation of a parallel library of biaryl, heterobiaryl, and styryl derivatives in high yields and purity.

The Stille[12,13] 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-[14−16] and fluorous-phase[17,18] 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. The alkyl groups, generally methyl or *n*-butyl, are "nontransferable" ligands, whereas the fourth tin ligand is coupled with a suitable electrophile. The tributyltin derivatives are more synthetically useful for two reasons: they are not as toxic as their trimethyl congeners and butyl transfer occurs much slower than methyl transfer. 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 butyl derivatives are more difficult to remove from a reaction mixture than the methyl homologues 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. It is with these problems in mind that we attempted to develop a soluble polymer-supported approach to the Stille cross-coupling 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.

Results and Discussion

Optimization of the PEG-Supported Stille Reaction. When selecting a soluble polymer for liquid-phase synthesis a balance always has to be made between loading capacity

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Scheme 1. Liquid-Phase Stille Reaction

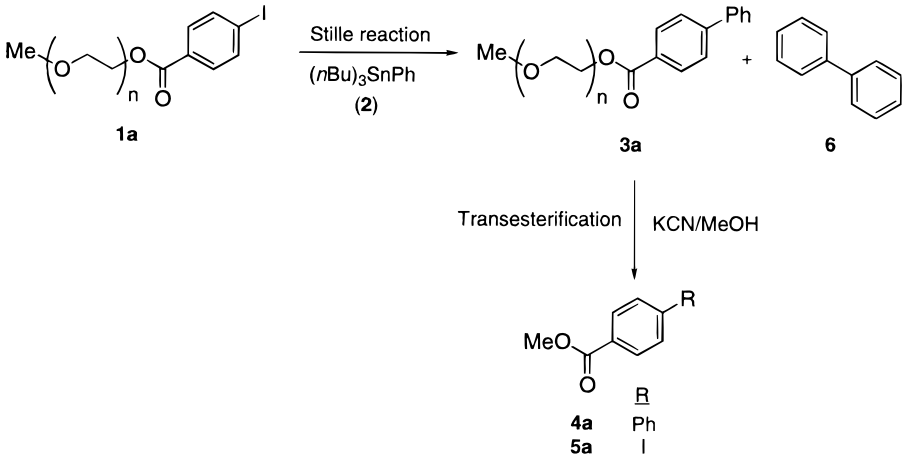


Table 1. Optimization of the Stille Cross-Coupling Reaction Parameters between **1a** and **2**

entry	catalyst	solvent	conc./mM[a]	*T*/°C	LiCl	time/h	yield **4a**/%[b]	yield **5a**/%[b]
1	$Pd(PPh_3)_2Cl_2$	toluene	20	110	+	24	22	-[c]
2	$Pd(PPh_3)_2Cl_2$	THF	20	reflux	+	24	68	-[c]
3	$Pd(PPh_3)_2Cl_2$	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	$Pd(PPh_3)_2Cl_2$	DMF	20	80	−	24	86	12
8	$Pd(PPh_3)_2Cl_2$	DMF	20	80	+	48	97	0
9	$Pd(PPh_3)_2Cl_2$	DMF	10	80	+	24	98	0

[a] Based on the concentration of PEG-bound substrate **1a**. [b] Isolated yields after workup. [c] Not determined.

and polymer recovery. For this study, where the loading of the polymer is not a critical factor to the overall success of the strategy, MeO-PEG (5000 molecular weight, equivalent to a loading of 0.2 mmol g^{-1}) was selected as the soluble polymer of choice. Its excellent crystallization properties and high recoveries from a number of organic solvents is well documented.[2,19] 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, **1a** and **1b**, respectively, with polymer recoveries being >95%.[20] The conversion was quantitative based upon ^{1}H NMR spectroscopic analysis of **1a**−**b**.

A number of efficient reaction conditions for solution-phase Stille couplings have been developed,[12,13,21,22] and initially we utilized a number of these for the reaction between PEG-iodide **1a** and tributylphenyltin (**2**) 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 1 and Table 1). Previous work has revealed conflicting evidence regarding the potential for coordination of the PEG polyether backbone to transition metals.[20,23] 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.

The efficiency of the initial series of experiments was determined both by ^{1}H NMR analysis of the PEG-biaryl adduct **3a** and, following transesterification, by the isolated yields of the biaryl methyl ester **4a** and monoaryl ester **5a** (resulting from no cross-coupling with **1a**). 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 3-fold excess of tributyl phenylstannane **2** was used relative to the PEG-supported electrophile **1a**. Additional parameters that were modified included temperature, reaction time, and reaction concentration.

Toluene was the first solvent tried because it is an excellent solvent for both the tributylphenyltin (**2**) and the PEG-supported iodide **1a.** However, the reaction in toluene even at 110 °C, in the presence of LiCl, was incomplete after 24 h (Table 1, entries 1 and 4). Also, in contrast to the reactivity observed in both DMF and THF, $Pd(PPh_3)_4$ is a better catalyst than $PdCl_2(PPh_3)_2$ (compare Table 1, entries 1−3 with 4−6).

The next solvent studied was THF which, while a poor solvent for PEG at low temperatures, is excellent at elevated temperatures. However, even though the reaction was completely homogeneous, it was found to be incomplete after heating for 24 h under reflux. In addition, there is a clear disparity between the effects of the palladium catalysts (Table 1, entries 2 and 5). Pd(II) is a far more efficient catalyst than Pd(0), the required biaryl adduct **4a** being isolated in 68% and 7% yield, respectively. The unreacted electrophile, in the $Pd(PPh_3)_4$-catalyzed reaction, was recovered as its transesterified iodide **5a** in 73% yield (Table 1, entry 5).

DMF was then studied as a solvent (Table 1, entries 3 and 6−9) under standard conditions of **1a** (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, $PdCl_2(PPh_3)_2$ is the best catalyst (Table 1, entries 3 and 6) with considerable amounts of the trans-

esterified iodide **5a** 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 **4a** is achieved (89% and 97%, respectively) (Table 1, entries 3 and 8).

In a recent fluorous-phase approach to the Stille reaction, between aryltin reagents and aryl halides, it was observed that by using LiCl as an additive the cross-coupling efficiencies were significantly enhanced.[17] However, the positive effect of LiCl on our PEG-supported Stille variant seems to be only marginal (compare Table 1, entries 3 and 7). This result is more in line with previous reports which found that LiCl does not usually enhance the reaction between trialkyltin reagents with aryl halides but is generally more useful with aryl triflate electrophiles.[24,25]

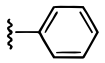
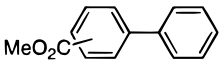
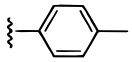
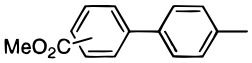
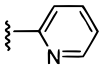
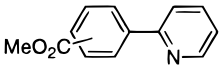
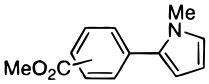
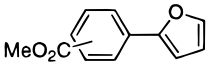
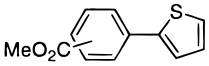
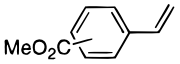
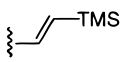
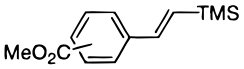
Dilution of the reaction mixture by a factor of 2 in DMF resulted in a marked increase in the yield of **4a** after 24 h [(Table 1, entries 3 and 9) (89% and 98%, respectively)]. When performing liquid-phase chemistry above a "critical" polymer concentration, the soluble polymer, as a result of its molecular weight, can cause an increase in the solution viscosity thereby inhibiting the "free" flow of reactants. This effect is both polymer and solvent specific. The observed retardation in reaction rate at the higher PEG-**1a** concentration (20 mM) is rationalized as being a potential result of this phenomenon.

The summary of these results is that the use of $PdCl_2(PPh_3)_2$ 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-PEG_{5000}-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 tributyltin derivatives are easily separated from the PEG-biaryl adduct **3a** by precipitation of the polymer support into either isopropyl alcohol or diethyl ether. Polymer recovery was >99% in each case. In addition, the homocoupled biaryl side product **6**, an incontrovertible product in the solution-phase reaction,[12,13] does not contaminate the soluble polymer-supported biaryl product **3a** because the homocoupling side reaction takes place in solution and thus the contaminant is removed during the precipitation step. An additional concern when developing this polymer-supported variant of the Stille reaction was that the relative accessibility and reactivity of the terminal aryl iodide on the PEG support may be reduced relative to the solution-phase process such that the competing homocoupling reaction, which takes place in solution, could contribute significantly to the product distribution. Normally this side reaction accounts for only 5% of the total isolated yield of products. While the absolute amount of **6** generated in this liquid-phase reaction was not determined, the fact that under the optimal conditions vide supra 98% yield of the biaryl ester **4a** was obtained strongly supports the notion that the competing side reaction is still only a minor problem and that the reactivity of the terminal PEG-supported iodide **1a** is not adversely affected.

Parallel Library Synthesis. Having optimized the liquid-phase Stille reaction conditions on monomethoxy-PEG_{5000}, we then sought to examine the scope of this cross-coupling process in a parallel format. A range of tributyl stannanes, **2** and **7**−**13**, were reacted with the PEG-supported iodides **1a**−**b** in a parallel fashion, furnishing the library of biaryl, heterobiaryl, and styryl derivatives **4a**−**b** and **14a**−**b** to **20a**−**b** (Table 2).

Table 2. Parallel Liquid-Phase Stille Couplings of Iodides **1a**−**b** with Tributyl Stannanes **2** and **7**−**13**[a]

Entry	Bu_3Sn-R	Products[b]	Yield/%[c] a	Yield/%[c] b
1	 **2**	 **4a-b**	98	82
2	 **7**	 **14a-b**	99	78
3	 **8**	 **15a-b**	94	81
4	 **9**	 **16a-b**	71	--[d]
5	 **10**	 **17a-b**	96	78
6	 **11**	 **18a-b**	90	69
7	 **12**	 **19a-b**	98	90
8	 **13**	 **20a-b**	99	82

[a] Reactions were conducted under the conditions described vide supra. [b] Compound descriptors **a** and **b** represent the *para*- and *ortho*-isomers, respectively. All of the products were characterized by ^1H and ^{13}C 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. [c] Isolated yields after the two steps. [d] Yield of *ortho*-product **16b** was not determined because instability of the stannane **9** precluded its efficient synthesis.

The isolated yields of all library members were good to excellent (69−99%), showing that under our preoptimized conditions vide supra 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 (**4a**−**b**, **14a**−**b** to **20a**−**b**) were each isolated in >95% purity.

In each case (Table 2, entries 1−8) the yield of the *ortho*-isomer (**4b** and **14b** to **20b**) was lower than its corresponding *para*-congener (**4a** and **14a** to **20a**). This effect ranged from a difference of 21% for the furan containing heterobiaryls **18a**−**b** to 8% for the styryl derivatives **19a**−**b**. 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. The smallest ligand, the vinyl group of stannane **12**, gave an 8% difference between the isolated yields of the *para*- and *ortho*-methyl esters **19a** and **19b** [Table 2, entry 7 (98% and 90%, respectively)]. This difference jumped to 17% with the vinylsilyl stannane **13** (Table 2, entry 8), supporting the steric crowding hypothesis. However the five-membered heterocyclic ligand containing stannanes **10**−**11** gave the highest differences in the isolated yields of *para*- and *ortho*-esters **17a**−**b** and **18a**−**b** (18% and 21%, respectively). This difference is greater than, or equal to, that observed with the bulkier six-membered ring containing stannanes **2** and **7**−**8** (Table 2, entries 1−3), which suggests that the process involved may be more complex than simple steric retardation. While no attempt has been made to reoptimize the reaction conditions to improve the yield of the *ortho*-isomers, it is speculated that future studies directed to resolve this issue would involve increasing the number of equivalents of the stannane and/or palladium catalyst while perhaps using more dilute reaction conditions.

Conclusion

This study has shown that the synthetically useful Stille cross-coupling reaction can be performed facilely and in high yield in a liquid-phase format. The scope of the process has been probed by the parallel synthesis of a small library of biaryl, heterobiaryl, and styryl derivatives, the members of which were all produced in good to excellent yields and purities. The soluble polymer approach offers the potential of being as broad in its scope as its solution-phase counterpart but with the added advantages that the contaminating tributyl stannane side products and excess reagents are easily removed by precipitation of the polymer-supported products into diethyl ether followed by efficient polymer isolation by filtration. In addition, the homocoupling byproducts are easily separated during the precipitation step. This report further highlights the increasing applicability of liquid-phase organic chemistry within the sphere of polymer-supported chemistry.

Experimental Section

Unless otherwise stated, all reactions were performed under an inert atmosphere with dry solvents and flame-dried glassware. All reagents were purchased from Aldrich Chemical Co. except for compounds **9** and **13** which were purchased from Frontier Scientific Inc. Product **4a** was obtained from Sigma Chemical Co., and products **5a** and **5b** were obtained from Pfaltz and Bauer and were used as authentic samples for spectroscopic comparison. Liquid chromatography was performed using compressed air (flash chromatography) with the indicated solvent systems and stationary phases. NMR spectra were recorded on either a Bruker AM-300 or a Bruker AMX-400 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale relative to an internal standard. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-VSE mass spectrometer.

Standard Procedure A: Esterification of Iodobenzoic Acids with MeO-PEG$_{5000}$. MeO-PEG$_{5000}$-(4-iodobenzoate) (1a). MeO-PEG$_{5000}$ (10 g, 2 mmol) was dissolved in anhydrous CH_2Cl_2. 4-Iodobenzoic acid (2.04 g, 10 mmol) and DCC (2.06 g, 10 mmol) were added, and the resulting suspension was stirred for 45 min at room temperature. DMAP (1.22 g, 10 mmol) was then added in one portion, and the reaction mixture was stirred at room temperature overnight. Filtration of the solution through Celite yielded a clear yellow solution. This solution was added to *i*-Pr alcohol (900 mL), and all CH_2Cl_2 was evaporated. The resulting precipitate was isolated by filtration and washed with *i*-Pr alcohol (1 × 100 mL) and diethyl ether (2 × 150 mL) to give the polymeric iodobenzoate **1a** as a white solid (9.98 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2 H), 7.68 (d, J = 4 Hz, 2 H), 4.38 (t, J = 4.6 Hz, 2 H, PEG-α-methylenes), 3.74 (m, PEG-β-methylenes), 3.59 (m, PEG-methylenes); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.48, 130.93, 87.07, 71.70, 70.70, 70.34, 68.88, 64.13, 58.83.

MeO-PEG$_{5000}$-(2-iodobenzoate) (1b). The reaction was carried out according to standard procedure A and gave the PEG-bound iodobenzoate **1b** as a white solid (10.2 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.8 Hz, 1 H), 7.76 (dd, J = 1.6 Hz, J = 7.8 Hz, 1 H), 7.34 (t, J = 7.3 Hz, 1 H), 7.09 (dt, J = 1.6 Hz, J = 7.6 Hz, 1 H), 4.42 (t, J = 4.6 Hz, 2 H, PEG-α-methylenes), 3.76 (m, PEG-β-methylenes), 3.58 (m, PEG-methylenes); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.10, 132.54, 130.96, 127.74, 90.43, 71.74, 70.44, 68.78, 64.48, 59.99.

Tributyl (4-methylphenyl)stannane (7).[26] *n*-Butyllithium (2.5 M in hexane, 1.59 mL, 4.0 mmol) was added to a solution of 4-bromotoluene (490 μL, 681 mg, 4.0 mmol) in anhydrous diethyl ether (40 mL) at 0 °C and stirred for 1 h at room temperature. Tributyltin chloride (770 μL, 924 mg, 3.2 mmol) was added dropwise, and the reaction was refluxed for further 4 h. The crude mixture was quenched with saturated aqueous NH_4Cl solution and extracted twice with hexanes. The organic fractions were dried ($MgSO_4$), the desiccant was removed by filtration, and the solvent was removed in vacuo. Purification by chromatography on silica (hexanes) gave stannane **7** as a colorless liquid (1.0 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.84 Hz, 2 H), 7.15 (d, J = 7.32 Hz, 2 H), 2.33 (s, 3 H), 1.60−1.46 (m, 6 H), 1.37−1.26 (m, 6 H), 1.12−0.95 (m, 6 H), 0.90−0.86 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.82, 137.59, 136.59, 136.44, 136.28, 129.04, 128.84, 128.79, 128.62, 29.21, 29.11, 29.00, 27.40, 13.68, 9.49.

2-(1,1,1-Tributylstannyl)pyridine (8).[27] A Grignard reagent was prepared from 2-bromopyridine (496 μL, 822 mg, 5.2 mmol) and magnesium (146 mg, 6.2 mmol) in anhydrous diethyl ether (30 mL) under reflux for 1 h. Tributyltin chloride (2.48 g, 2.0 mmol) was added to the dark suspension, and the reaction mixture was refluxed for 30 min and then stirred at room temperature overnight. The crude mixture was quenched with saturated aqueous NH_4Cl solution and extracted twice with hexanes. The organic fractions were dried ($MgSO_4$), the desiccant was removed by filtration, and the solvent was removed in vacuo. Purification by chromatography on neutral alumina (hexane) gave stannane **8** as a pale yellow liquid (861 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 4.8 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 1

H), 7.40 (d, $J = 7.28$ Hz, 1 H), 7.11 (t, $J = 6.48$ Hz, 1 H), 1.62−1.52 (m, 6 H), 1.43−1.28 (m, 6 H), 1.17−1.04 (m, 6 H), 0.93−0.86 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.49, 133.23, 132.33, 121.96, 29.05, 27.31, 13.65, 9.72.

Standard Procedure B: Stille Coupling of PEG-Bound Iodobenzoate and Transesterification with KCN/MeOH. (a) Stille Coupling. In a typical procedure MeO-PEG_{5000}-bound *para*-iodobenzoate **1a** (1.0 g, 191 μmol) was dissolved in a degassed anhydrous solution of LiCl (79 mg, 1.91 mmol) in DMF (5 mL). Dichlorobis(triphenylphosphine)palladium(II) (13 mg, 19 μmol) and tributylphenylstannane (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 CH_2Cl_2, 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-PEG_{5000}-(4-phenylbenzoate) (3a): ^{1}H NMR (400 MHz, $CDCl_3$) 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).

(b) 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 (CH_2Cl_2 or hexane−10% diethyl ether as the eluant) to give the methyl ester **4a** as a white solid (40 mg, 98%).

Methyl 4-phenylbenzoate (4a): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.94, 145.55, 139.90, 133.81, 130.04, 128.87, 128.09, 127.21, 126.97, 52.07; FABHRMS calcd for $C_{14}H_{13}O_2$ (MH^+) 213.0916, found 213.0922.

Methyl 2-phenylbenzoate (4b).[28] The reaction was carried out according to standard procedure B to give **4b** as a colorless oil (82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, $J = 1.1$ Hz, $J = 7.8$ Hz, 1H), 7.53 (dt, $J = 1.4$ Hz, $J = 7.6$ Hz, 1 H), 7.42−7.30 (m, 7 H), 3.63 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.41, 141.24, 131.23, 130.67, 129.73, 128.26, 128.22, 128.01, 127.19, 127.16, 127.13, 51.93; FABHRMS calcd for $C_{14}H_{12}O_2$ (M^+) 212.0837, found 212.0844.

Methyl 4-(4-methylphenyl)benzoate (14a).[29] The reaction was carried out according to standard procedure B to give **14a** as a white solid (99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, $J = 8.4$ Hz, 2 H), 7.63 (d, $J = 8.4$ Hz, 2 H), 7.51 (d, $J = 8.1$ Hz, 2 H), 7.26 (d, $J = 7.8$ Hz, 2 H), 3.93 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.04, 145.55, 138.09, 137.04, 130.06, 130.04, 129.65, 128.55, 127.09, 126.77, 52.36, 21.16; FABHRMS calcd for $C_{15}H_{15}O_2$ (MH^+) 227.1672, found 227.1077.

Methyl 2-(4-methylphenyl)benzoate (14b).[30] The reaction was carried out according to standard procedure B to give **14b** as a colorless oil (78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, $J = 8.1$ Hz, 2 H), 7.51 (dt, $J = 1.4$ Hz, $J = 7.6$ Hz, 2 H), 7.46−7.31 (m, 4 H), 3.66 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.43, 138.30, 136.92, 131.22, 130.74, 129.70, 128.82, 128.17, 126.93, 51.98, 21.22; FABHRMS calcd for $C_{15}H_{14}O_2$ (M^+) 226.0994, found 226.0988.

Methyl 4-(2-pyridyl)benzoate (15a).[31] The reaction was carried out according to standard procedure B to give **15a** as a white solid (94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, $J = 4.8$ Hz, 1 H), 8.14 (d, $J = 8.4$ Hz, 2 H), 8.06 (d, $J = 8.4$ Hz, 2 H), 7.77 (d, $J = 3.5$ Hz, 2 H), 7.27 (dd, $J = 4.6$ Hz, $J = 8.6$ Hz, 1 H), 3.94 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.89, 156.16, 149.87, 143.50, 136.92, 130.04, 126.83, 122.89, 121.01, 52.18; FABHRMS calcd for $C_{13}H_{12}NO_2$ (MH^+) 214.0868, found 214.0873.

Methyl 2-(2-pyridyl)benzoate (15b).[31] The reaction was carried out according to standard procedure B to give **15b** as a colorless oil (81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, $J = 4.6$ Hz, 1 H), 7.82 (d, $J = 7.6$ Hz, 1 H), 7.74 (t, $J = 7.8$ Hz, 1 H), 7.57 (d, $J = 4.1$ Hz, 2 H), 7.47 (ddd, $J = 0.8$ Hz, $J = 3.2$ Hz, $J = 7.5$ Hz, 2 H), 7.26 (dt, $J = 0.8$ Hz, $J = 3.4$ Hz, 1 H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.50, 149.01, 136.23, 131.12, 129.72, 129.68, 128.29, 122.67, 122.03, 52.01; FABHRMS calcd for $C_{13}H_{12}NO_2$ (MH^+) 214.0868, found 214.0862.

Methyl 4-(1-methyl-2-pyrrolyl)benzoate (16a). The reaction was carried out according to standard procedure B to give **16a** as a white solid (71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.6$ Hz, 2 H), 7.47 (d, $J = 8.4$ Hz, 2 H), 6.76 (bs, 1 H), 6.34 (d, $J = 1.9$ Hz, 1 H), 6.23 (d, $J = 2.7$ Hz, 1 H), 3.93 (s, 3 H), 3.71 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.69, 129.70, 127.86, 127.81, 127.78, 125.08, 109.99, 108.23, 52.07, 35.36; FABHRMS calcd for $C_{13}H_{14}NO_2$ (MH^+) 216.1024, found 216.1023.

Methyl 4-(2-furyl)benzoate (17a).[32] The reaction was carried out according to standard procedure B to give **17a** as a white solid (96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, $J = 1.9$ Hz, $J = 6.8$ Hz, 2 H), 7.72 (dd, $J = 1.8$ Hz, $J = 6.8$ Hz, 2 H), 7.52 (d, $J = 1.3$ Hz, 1 H), 6.78 (d, $J = 3.2$ Hz, 1 H), 6.51 (dd, $J = 1.3$ Hz, $J = 3.2$ Hz, 1 H), 3.92 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.78, 152.87, 143.09, 134.73, 130.07, 128.48, 123.36, 111.99, 107.20, 52.07; FABHRMS calcd for $C_{12}H_{11}O_3$ (MH^+) 203.0708, found 203.0713.

Methyl 2-(2-furyl)benzoate (17b).[33] The reaction was carried out according to standard procedure B to give **17b** as a colorless oil (81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, $J = 1.0$ Hz, $J = 7.7$ Hz, 1 H), 7.61 (dd, $J = 0.5$ Hz, $J = 7.8$ Hz, 1 H), 7.51−7.47 (m, 2 H), 7.36 (dt, $J = 1.1$ Hz, $J = 7.6$ Hz, 1 H), 6.58 (d, $J = 3.2$ Hz, 1 H), 6.48 (dd, $J = 1.9$ Hz, $J = 3.2$ Hz, 1 H), 3.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.72, 130.89, 129.76, 129.14, 128.07,

127.62, 111.53, 107.91, 52.34; FABHRMS calcd for $C_{12}H_{10}O_3$ (M^+) 202.0630, found 202.0634.

Methyl 4-(2-thienyl)benzoate (18a).[29] The reaction was carried out according to standard procedure B to give **18a** as a white solid (90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.4 Hz, 2 H), 7.42 (dd, J = 0.8 Hz, J = 2.7 Hz, 1 H), 7.36 (dd, J = 0.8 Hz, J = 3.5 Hz, 1 H), 7.11 (dd, J = 3.8 Hz, J = 4.9 Hz, 1 H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.76, 143.05, 138.61, 130.27, 130.24, 128.75, 128.32, 126.28, 125.50, 125.47, 124.49, 124.45, 52.14; FABHRMS calcd for $C_{12}H_{10}O_2S$ (M^+) 218.0402, found 218.0408.

Methyl 2-(2-thienyl)benzoate (18b).[34] The reaction was carried out according to standard procedure B to give **18b** as a colorless oil (69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.42−7.38 (m, 1 H), 7.35 (dd, J = 1.1 Hz, J = 4.8 Hz, 1 H), 7.07−7.03 (m, 2 H), 3.74 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.58, 141.39, 131.16, 131.00, 129.42, 127.71, 127.22, 126.25, 125.88, 101.58, 52.23; FABHRMS calcd for $C_{12}H_{11}O_2S$ (MH^+) 219.0480, found 219.0407.

Methyl 4-vinylbenzoate (19a).[35] The reaction was carried out according to standard procedure B to give **19a** as a colorless liquid (98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2 H), 7.45 (d, J = 8.4 Hz, 2 H), 6.75 (dd, J = 17.7 Hz, J = 10.9 Hz, 1 H), 5.86 (d, J = 17.5 Hz, 1 H), 5.38 (d, J = 10.8 Hz, 1 H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.88, 141.91, 136.01, 129.89, 129.26, 126.18, 126.15, 126.12, 116.49, 52.08.

Methyl 2-vinylbenzoate (19b).[36] The reaction was carried out according to standard procedure B to give **19b** as a colorless oil (90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 1.3 Hz, J = 7.8 Hz, 1 H), 7.59 (d, J = 7.3 Hz, 1 H), 7.50−7.43 (m, 2 H), 7.32 (dt, J = 1.1 Hz, J = 7.8 Hz, 1 H), 5.65 (dd, J = 1.2 Hz, J = 17.4 Hz, 1 H), 5.35 (dd, J = 1.1 Hz, J = 11.1 Hz, 1 H), 3.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.86, 139.57, 135.86, 132.13, 130.31, 127.39, 127.22, 116.49, 52.11.

Methyl [(*E*)-4-(1,1,1-trimethylsilyl)-1-ethenyl]benzoate (20a).[37] The reaction was carried out according to standard procedure B to give **19a** as a colorless liquid (99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.9 Hz, 2 H), 7.50 (d, J = 7.9 Hz, 2 H), 6.92 (d, J = 19.3 Hz, 1 H), 6.64 (d, J = 19.3 Hz, 1 H), 3.92 (s, 3 H), 0.19 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.88, 142.45, 133.12, 129.85, 126.19, 52.05.

Methyl [(*E*)-2-(1,1,1-trimethylsilyl)-1-ethenyl]benzoate (20b).[37] The reaction was carried out according to standard procedure B to give **20b** as a colorless oil (82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 7.5 Hz, 1 H), 7.92−7.85 (m, 2 H), 7.74 (t, J = 7.5 Hz, 1 H), 7.56 (t, J = 7.5 Hz, 1 H), 6.66 (d, J = 19.3 Hz, 1 H), 4.17 (s, 3 H), 0.45 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.54, 141.96, 139.93, 132.66, 131.50, 129.77, 126.88, 126.65, 51.58.

Methyl 4-iodobenzoate (5a). The reaction was carried out according to standard procedure B (transesterification) using PEG-bound iodide **1a** as a substrate and gave **5a** as a white solid (99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2 H), 7.73 (d, J = 8.4 Hz, 2 H), 3.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.56, 137.69, 131.00, 129.54, 100.74, 52.30; FABHRMS calcd for $C_8H_8O_2$ (M^+) 262.9569, found 262.9577.

Methyl 2-iodobenzoate (5b). The reaction was carried out according to standard procedure B (transesterification) using PEG-bound iodide **1b** as a substrate and gave **5b** as a white solid (98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.1 Hz, 1 H), 7.80 (dd, J = 1.6 Hz, J = 7.6 Hz, 1 H), 7.40 (dd, J = 1.1 Hz, J = 7.6 Hz, 1 H), 7.15 (dt, J = 1.6 Hz, J = 7.6 Hz, 1 H), 3.93 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.93, 141.27, 135.01, 132.62, 130.90, 127.86, 94.04, 52.46.

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Supporting Information Available. Spectroscopic data for the PEG-supported iodides **1a**−**b**, the PEG-supported biaryl **3a**, and the pyrrole methyl ester **16a**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Wentworth, P., Jr.; Janda, K. D. Liquid-phase chemistry: recent advances in soluble polymer-supported catalysts, reagents and synthesis. *Chem. Commun.* **1999**, 1917−1924.
(2) Gravert, D. J.; Janda, K. D. Organic synthesis on soluble polymer supports: liquid-phase methodologies. *Chem. Rev.* **1997**, *97*, 489−509.
(3) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. Liquid-phase combinatorial synthesis. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419−6423.
(4) Han, H.; Janda, K. D. Soluble polymer-bound ligand-accelerated catalysis: asymmetric dihydroxylation. *J. Am. Chem. Soc.* **1996**, *118*, 7632−7633.
(5) Sieber, F.; Wentworth, P., Jr.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. Development and application of a poly(ethylene glycol)-supported triarylphosphine reagent: expanding the sphere of liquid-phase organic synthesis. *J. Org. Chem.* **1999**, *64*, 5188−5192.
(6) Wentworth, P., Jr.; Vandersteen, A. M.; Janda, K. D. Poly(ethylene glycol) (PEG) as a reagent support: the preparation and utility of a PEG-triarylphosphine conjugate in liquid-phase organic synthesis (LPOS). *Chem. Commun.* **1997**, 759−760.
(7) Hori, M.; Janda, K. D. A soluble polymer approach to the "fishing out" principle: synthesis and purification of β-aminoalcohols. *J. Org. Chem.* **1998**, *63*, 889−894.
(8) Zhao, X.-Y.; Janda, K. D. Syntheses of alkylated malonates on a traceless linker derived soluble polymer support. *Tetrahedron Lett.* **1997**, *38*, 5437−5440.
(9) Zhao, X.-Y.; Janda, K. D. Soluble polymer traceless linker investigations: Solvent effects on the desulfonylation of poly(ethylene glycol) (PEG) substituted aryl alkyl sulfones with sodium amalgam. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2439−2442.
(10) Chen, S.; Janda, K. D. Synthesis of prostaglandin E2 methyl ester on a soluble-polymer support for the construction of prostanoid libraries. *J. Am. Chem. Soc.* **1997**, *119*, 8724−8725.
(11) Chen, S.; Janda, K. D. Total synthesis of naturally occurring prostaglandin F2α on a non-cross-linked polystyrene support. *Tetrahedron Lett.* **1998**, *39*, 3943−3946.
(12) Stille, J. K. Palladium catalyzed coupling of organotin reagents with organic electrophiles. *Pure Appl. Chem.* **1985**, *57*, 1771−1780.
(13) Stille, J. K. The palladium-catalyzed cross-coupling reactions of organotin reagents with organic electrophiles. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.
(14) Deshpande, M. S. Formation of carbon−carbon bond on solid support: application of the Stille reaction. *Tetrahedron Lett.* **1994**, *35*, 5613−5614.
(15) Forman, F. W.; Sucholeiki, I. Solid-phase synthesis of biaryls via the Stille reaction. *J. Org. Chem.* **1995**, *60*, 523−528.
(16) Plunkett, M. J.; Ellman, J. A. Solid-phase synthesis of structurally diverse 1,4-benzodiazepine derivatives using the Stille coupling reaction. *J. Am. Chem. Soc.* **1995**, *117*, 3306−3307.

(17) Hoshino, M.; Degenkolb, P.; Curran, D. P. Palladium-catalyzed Stille couplings with fluorous tin reactants. *J. Org. Chem.* **1997**, *62*, 8341−8349.
(18) Curran, D. P.; Hoshino, M. Stille couplings with fluorous tin reactants: Attractive features for preparative organic synthesis and liquid-phase combinatorial synthesis. *J. Org. Chem.* **1996**, *61*, 6480−6481.
(19) Zhao, X.-Y.; Metz, W. A.; Sieber, F.; Janda, K. D. Expanding on the purification methodology of poly(ethylene glycol) (PEG) bound molecules: The synthesis of 3,5-pyrazolidinediones. *Tetrahedron Lett.* **1998**, *39*, 8433−8436.
(20) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. Poly(ethylene glycol) supported liquid-phase synthesis of biaryls. *Synlett* **1998**, 295−297.
(21) Mitchell, T. N. Palladium-catalyzed reactions of organotin compounds. *Synthesis* **1992**, 803−815.
(22) Farina, V. New perspectives in the cross-coupling reactions of organostannanes. *Pure Appl. Chem.* **1996**, *68*, 73−78.
(23) Bergbreiter, D. E.; Liu, Y.-S. Amphoteric, water-soluble polymer-bound hydrogenation catalysts. *Tetrahedron Lett.* **1997**, *38*, 3703−3706.
(24) Scott, W. J.; Stille, J. K. Palladium-catalyzed coupling of vinyl triflates with organostannanes. Synthetic and mechanistic studies. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.
(25) Scott, W. J.; Crisp, G. T.; Stille, J. K. Palladium-catalyzed coupling of vinyl triflates with organostannanes: 4-*tert*-butyl-1-vinylcyclohexene and 1-(4-*tert*-butylcyclohexen-1-yl)-2-propene-1-one. *Org. Synth.* **1990**, *68*, 116−129.
(26) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 41−48.
(27) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. Enantioselective synthesis of optically active pyridine derivatives and C_2-symmetric 2,2′-bipyridines. *Chem. Ber.* **1992**, *125*, 1169−1190.
(28) Saito, S.; Oh-Tani, S.; Miyaura, N. Synthesis of biaryls via a nickel(0)-catalyzed cross-coupling reaction of chloroarenes with arylboronic acids. *J. Org. Chem.* **1997**, *62*, 8024−8030.
(29) Matsushita, Y.; Sakamoto, K.; Murakami, T.; Matsui, T. A convenient synthesis of methyl 4-substituted benzoates via Diels−Alder reaction in the presence of palladium on activated carbon. *Synth. Commun.* **1994**, *24*, 3307−3313.
(30) Kageyama, H.; Miyazaki, T.; Kimura, Y. Nickel-catalyzed cross-coupling reaction of aryl halides in pyridine. A practical synthesis of 4′-methylbiphenyl-2-carbonitrile as a key intermediate of angiotensine II receptor antagonists. *Synlett* **1994**, 371−372.
(31) Terashima, M.; Seki, K.; Yoshida, C.; Ohkura, K.; Kanaoka, Y. Photo-arylation. IV. Synthesis of 2-arylpyridines by photo-reaction of 2-iodopyridine with substituted benzenes. *Chem. Pharm. Bull.* **1985**, *33*, 1009−1015.
(32) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. Palladium-catalyzed arylation of furan, thiophene, benzo[*b*]furan and benzo[*b*]thiophene. *Heterocycles* **1990**, *31*, 1951−1958.
(33) Fisera, L.; Kovac, J.; Komanova, E.; Lesko, J. Furan derivatives. LX. Convenient new method of arylation of furan. Reaction of diazoaminobenzenes with furan and isopentyl nitrite. *Tetrahedron* **1974**, *30*, 4123−4127.
(34) Mataka, S.; Oshima, T.; Tashiro, M. Reaction of diazoindenothiophenes with acetylenic esters and the thermal behavior of the adducts. *J. Org. Chem.* **1981**, *46*, 3960−3964.
(35) Kikukawa, K.; Nagira, K.; Terao, N.; Wada, F.; Matsudo, T. Reaction of diazonium salts with transition metals. II. Palladium-catalyzed arylation of ethylene with arenediazonium salts. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2609−2610.
(36) Howe, R. K.; Schleppnik, F. M. Nitrile oxide cycloaddition route to 2-(isoxazolyl)benzoates and 2-(1,2,4-oxadiazol-3-yl)benzoates. *J. Heterocycl. Chem.* **1982**, *19*, 721−726.
(37) Karabelas, K.; Hallberg, A. Synthesis of (*E*)-(2-arylethenyl)silanes by palladium-catalyzed arylation of vinylsilanes in the presence of silver nitrate. *J. Org. Chem.* **1986**, *51*, 5286−5290.

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