Solid-Phase Synthesis of Biaryls via the Stille Reaction

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The solid-phase synthesis of biphenyls by heterogenous cross-coupling of trialkylphenylstannanes with aryl electrophiles is described. Tributylphenyltin attached by an amide bond to the Rink amide resin undergoes palladium-catalyzed coupling with aryl triflates and aryl iodides to produce after acid cleavage 4-biphenylacetamide in 3–15% yield. 4-Iodophenylacetic acid attached to the Rink amide resin by an amide bond also undergoes heterogeneous palladium-catalyzed coupling with trialkylphenyltins to give after acid cleavage of the support 4-biphenylacetamide in 21–33% yield. 4-Iodobenzylbromide was then attached to the photocleavable (±)-2-methoxy-5-[2-[(2-nitrophenyl)dithio]-1-oxopropyl]phenylacetamide (NpSSMpact) resin through the formation of a thioether bond. Both substituted and unsubstituted trimethylphenyltins were shown to undergo palladium-catalyzed Stille coupling with the resin bound aryl iodide to give after photolytic cleavage biphenyls containing no residual amide, carboxylic acid, or alcohol appendages.

Introduction

The construction of biphenyls has been of interest due, in part, to their presence in many important natural products which exhibit both antitumor and antiviral activity.[1] Recently, some imidazole substituted biphenyls have been shown to act as angiotensin II receptor antagonists.[2a–e] We were interested in producing combinatorial libraries based on the biphenyl structure.[3a–e] Although there have been many groups attempting to produce heterocyclic structures by combinatorial schemes, we felt that for it to have a long term and cost effective advantage over classic modes of production certain requirements must be met. The chemistry should be amenable to the running of hundreds of multiple simultaneous reactions and most importantly, should be fully automatable. With present robotic technology, it is easier to meet such requirements by having the chemistries run at room temperature and under atmospheric conditions. Although many synthetic strategies have been used to make biphenyls, the palladium-catalyzed cross-coupling reaction between aryl electrophiles and arylstannanes (Stille reaction) has been one of the most useful.[4a–i] These reactions are reported to go in high yield, although in almost every instance prolonged heating as well as an inert atmosphere are required. We were interested in exploring the application of the Stille reaction to the solid-phase, room temperature synthesis of biaryls. Such an application would substantially reduce the amount of time and effort required for purifying the biaryl product, since any unreacted starting material could easily be washed off the support. This would make the simultanous synthesis and purification of hundreds of biphenyl compounds easier to automate.

In a typical Stille biaryl formation, one combines the aryl electrophile with the arylstannane in the presence of palladium, a phosphine ligand, and lithium chloride. While the reaction conditions have been optimized for conventional solution coupling, they are just starting to be explored on heterogeneous systems.[4j] The basic approach can be conceived of in two ways (Scheme 1); treating a solid-phase arylstannane **1** (X = SnR'_3, R' = methyl, butyl) with the electrophile in solution or conversely, starting with the aryl electrophile **1** (X = Br, I, triflate) and treating it with the arylstannane in solution. Additionally, since one can easily separate the reagents from the support by filtration, large excesses can be employed to help offset the expected decrease in coupling rate due to the heterogeneous nature of the system. The type of linker used must also be considered since typical linkers leave a vestigial functional group (R'') as an artifact of cleavage.

Results and Discussion

Our initial experiments began by attaching an arylstannane on the Rink amide resin.[5] The first support that was chosen was the Rink amide resin because of the stability of the resulting amide linkage. 4-Tri-n-butylstannylphenylacetic acid (**6**) was coupled to the Rink amide resin (**5**) using diisopropylcarbodiimide (DIC) in dimethylformamide (DMF) to give the resulting resin bound stannane **7** (Scheme 2).[6] The substitution (0.3 mmol aryl tin/g of resin) of support **7** was measured by tin elemental analysis, as well as quantitative ninhydrin of the free amines remaining after amide formation.[7]

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1995.

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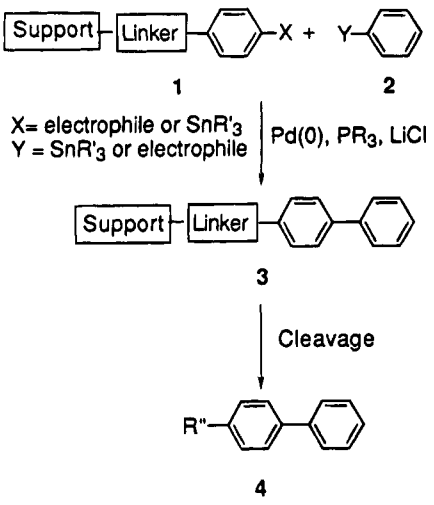
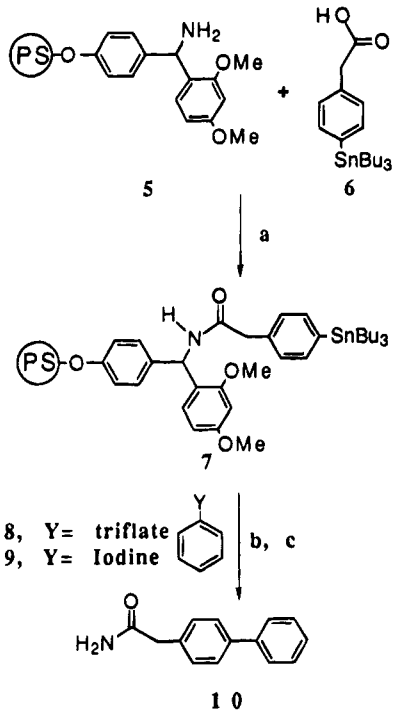
Scheme 1



Scheme 2[a]



[a] (a) DIC, CH_2Cl_2; (b) biaryl coupling; (c) 5%TFA–CH_2Cl_2.

In addition, gel-phase ^{13}C NMR of support **7** was used to characterize the resin bound phenylstannane (Figure 1).[8] The initial biaryl coupling conditions were adapted from the published work of Stille, Saá, and Farina.[4b,e-h] The conditions were subsequently varied. The resulting products were then cleaved from the support with 5% TFA–CH_2Cl_2 and analyzed using reversed-phase HPLC, ^1H NMR spectroscopy, and GC mass spectrometry. The yield of biaryl **10** was determined using reversed-phase HPLC and an internal standard.[9]

The results (Table 1) show that the typical Stille conditions in which triphenylphosphine (TPP) and $PdCl_2$-TPP_2 are used fail to produce the desired biphenyl product **10** (entries 1–3). ^1H NMR spectroscopy of the cleaved product indicate the existence of only phenylacetamide and some tri-n-butyltin byproducts.

However, the desired biphenyl **10** can be produced when utilizing the Farina conditions of tri-2-furylphosphine (TFP) and tris(dibenzylideneacetone)dipalladium (Pd_2dba_3). The results also corroborate what is known in the literature, that an iodine leaving group is more reactive than a triflate (entries 4 and 5).[10]

We next were interested in determining what effect switching the reactivities of the rings would have on the formation of the biphenyl **10**. 4-Iodophenylacetic acid (**11**) was coupled to the Rink amide resin (**5**) using DIC in DMF to give the resin-bound phenyl iodide **12**. The level of substitution of the resin-bound phenylacetamide was determined by iodine elemental analysis (0.3 mmol of iodine/g of resin). The results show that when the Farina conditions were applied in conjunction with trimethylphenyltin, we obtained a 21% yield of the desired biphenyl **10** after acid cleavage (Scheme 3). It is not clear why better biaryl coupling yields are achieved when coupling a trialkylphenyltin to a support containing an aryl electrophile in comparison to the reverse situation. It is possible that resin bound tin changes the expansion and contraction properties of the cross-linked polystrene, restricting the access of the reagents to the interior of the support. When tributylphenyltin was used in place of the trimethylphenyltin we were able to increase the isolated yield to 33% (Scheme 3). In both cases, roughly 3 equiv of the trialkylphenyltin were required. A possible reason for the increase in yield is the lower rate of alkyl transfer in the tributylphenyltin case versus the trimethylphenyltin. This is in accordance with work by Farina that showed that methyl transfer was 10 times faster than butyl transfer in biaryl coupling reactions.[4h] Farina also showed that the rate of biaryl product formation was slower with tributylphenyltin than with trimethylphenyltin.

We were next interested in transferring the best of our biaryl coupling conditions from the Rink amide resin to a support that does not leave an amide appendage on the biphenyl after cleavage. The NpSSMpact resin is a photoactive support recently developed in our laboratory which upon photochemical cleavage leaves no amide or carboxylic acid appendage on the molecule.[11] The free thiol of the NpSSMpact support (**17**) was treated with 4-iodobenzyl bromide (**18**) in the presence of an excess of diisoproplyethylamine (DIEA) in DMF to give the resulting benzyl thioether **19** (Scheme 4). The level of substitution of the resin bound thioether was measured by iodine elemental analysis. The support (0.2 mmol iodine/g of resin) was then treated with various quantities

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(9) The yield of biphenyl product was determined using reversed-phase HPLC and 254 nm detection. First, a known concentration of the desired biphenyl (which was synthesized by solution coupling methods) was injected with a known concentration of 4-amino-3-nitrophenol. A constant was obtained correlating the absorbance of the pure biphenyl with 4-amino-3-nitrophenol. A new constant was derived for a every different biphenyl used. In a typical photolytic cleavage experiment, a measured volume of the reaction mixture containing an unknown amount of the cleaved biphenyl and a solution of 4-amino-3-nitrophenol (used as an internal standard) were injected into the HPLC and the chromatogram peak areas recorded. The earlier derived constant was then used in determining the amount of biphenyl produced after photolytic cleavage.

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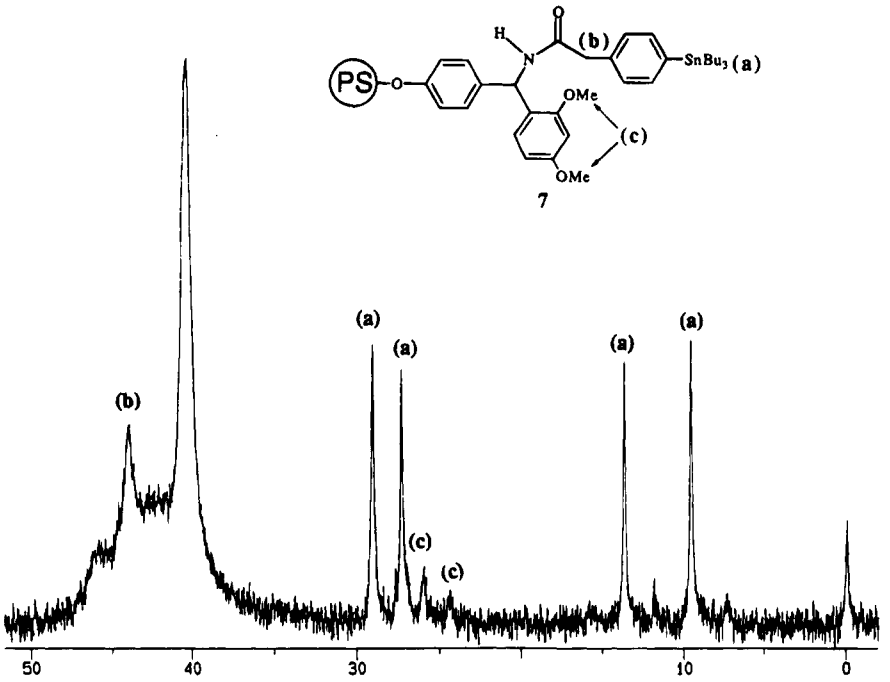


Figure 1. Gel-phase ^{13}C NMR spectra of support **7** showing the presence of the tri-n-butyl (a) and benzylic (b) groups.

Table 1. Percent Yield[a] of Biphenyl (10) after Biaryl Coupling and Acid Cleavage[b] from Solid Support

entry	Ph–Y, equiv	ligand, equiv	catalyst, equiv	LiCl, equiv	temp (°C)	time, h	solvent	% yield of **10**[a]
1	Y = triflate, 6	TPP, 1.2	$PdCl_2(TPP)_2$, 0.2	17	25	24	THF	0
2	Y = triflate, 6	TPP, 1.2	$PdCl_2(TPP)_2$, 0.2	17	100	24	dioxane	0
3	Y = iodine, 3	TPP, 0.4	$PdCl_2(TPP)_2$, 0.15	7	25	12	DMF	0
4	Y = iodine, 3	TFP, 0.1	Pd_2dba_3, 0.1	2	25	12	NMP	15
5	Y = triflate, 4	TFP, 0.1	Pd_2dba_3, 0.1	2	25	12	NMP	3

[a] HPLC yield using an internal standard, ref 9. [b] 5% TFA–CH_2Cl_2; TPP = triphenylphosphine, TFP = trifurylphosphine, Pd_2dba_3 = tris(dibenzylideneacetone)dipalladium, NMP = 1-methyl-2-pyrrolidinone.

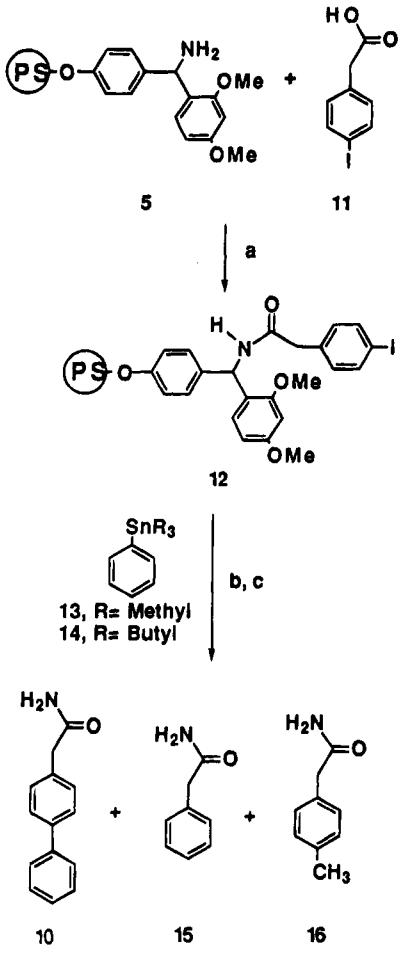
of TFP, LiCl, Pd_2dba_3, and trialkylphenylstannane and subsequently irradiated with 350 nm light to cleave the product from the support. By using deuterated acetonitrile during the photolytic cleavage reaction one is able to determine the ratio of cleaved products in-situ using ^1H NMR spectroscopy. The products were also analyzed using reversed-phase HPLC and GC mass spectrometry.[9]

When the Rink amide coupling conditions were applied to support **19**, only a very small amount of the corresponding biaryls **20** and **21** were isolated (Table 2).[12] Interestingly, beside the expected biaryls **20**, **21**, and unreacted phenyl iodide ring **23**, trifurylphosphine sulfide was also produced (entry 1 and 2). It was possible to eliminate this sulfide byproduct by simply reducing the number of equivalents of TFP used. The results also showed that the quantities of palladium catalyst and trimethylphenylstannane needed were much higher than in the previous biaryl coupling experiments with the Rink amide resin. Three times as much palladium catalyst (0.23 equiv versus 0.07 equiv) and four times as much trimethylstannane (12 equiv versus 3 equiv) were needed to reach comparative biaryl coupling yields. One proposed cause for the disparity is that unreacted free thiols chelated some of the palladium catalyst as well as the phenylstannane. In addition, unlike the earlier results that used Rink amide resin (Scheme 3), the use of tributylphenyltin gave comparatively lower yields than trimethylphenyltin (entries 4 and 5, Table 2). Also unlike the Rink amide results, no evidence of the formation of a methyl transfer product was seen. A possible reason for this is that the photochemical cleavage rate for a methylated monoaryl ring is lower than for a biphenyl. This lower cleavage rate would produce substantially lower amounts of the monoaryl product during a finite photocleavage reaction time. Fortunately, it was possible to adjust the number of equivalents of each of the various reagents to give exculsively biaryl product in modest yield (entry 6, Table 2). Because of our interest in running the biaryl coupling reaction at room temperature, a larger number of equivalents of the trimethylphenyltin was required to overcome the slower rate of reaction due to the rotational restrictions the support imparts on the bound aryl iodide.

We were next interested in determining the extent of heterogeneous biaryl coupling with a functionalized trialkylphenyltin. Although ether functionalized trialkylphenyltins have been widely reported to successfully undergo Stille couplings with aryl electrophiles, incorporation of an ester functional group was of interest since they are more easily capable of undergoing further conversion after biaryl coupling. Farina reports the compatability of phenylacetates to the standard Stille coupling conditions.[4f] (3-Acetoxyphenyl)trimethyltin (**24**) was then coupled to support **19** using Pd_2dba_3, LiCl, and TFP in NMP to isolate after photolytic cleavage a 21% yield of biphenyl **25** (Scheme 5).[9]

(12) Irradiation with 350 nm light causes the C–S bond to break homolytically resulting in biaryl **20** and in the presence of molecular oxygen the formation of biaryl **21** (see ref 11).

Scheme 3[a]



	Product Ratios[a]			% Yield of 10[b]
R=Methyl	1	0.08	0.2	21
R=Butyl	1	0.1	0	33

[a] Obtained by ^{1}H NMR; [b] Ref. 9

[a] (a) DIC, CH_2Cl_2; (b) Pd_2dba_3, LiCl, TFP, NMP, 25 °C; (c) 5% TFA–CH_2Cl_2.

Conclusion

Although the direct utilization of the classic Stille or Saá reagents such as triphenylphosphine and $(PPh_3)_2PdCl_2$ fail to produce biaryl product on solid support, a modified form of the Farina conditions involving trifurylphosphine and Pd_2dba_3 does succeed in assisting biaryl formation. In addition, when coupling aryl electrophiles to a resin bound phenyltin, one observes a higher yield of biaryl product when iodine is the electrophile versus triflate. Higher yields are also obtained when coupling trialkylphenyltin to a support containing an aryl electrophile compared to the reverse case in which a trialkylphenyltin is bound to the support. Because there are some advantages to having the tin on the support, work is continuing on enhancing the biaryl coupling yields with resin bound tin.[13]

(13) The major advantage of having tin on the support as opposed to the aryl electrophile is one of economics. By having the trialkylphenyltin on the support one can treat it as the limiting reagent. Another advantage is the possibility of quantifying the resin bound aryltin substitution level by gel-phase tin NMR.

When the best Rink amide coupling conditions were applied to the photoactive NpSSMpact support (**17**) it was found that much more palladium catalyst as well as trialkylphenyltin was required to reach comparable product yields. It was also shown that one obtains higher yields of isolated product when trimethylphenytin is used in place of tributylphenyltin, a result that is reverse to the results obtained on the Rink amide resin. Most importantly, it was shown that one can reach purities of as high as 90% of biphenyl **20** upon heterogeneous biaryl coupling followed by photolytic cleavage of the support in acetonitrile. The ability to produce and release the desired biphenyl at room temperature and under atmospheric conditions is a major advance toward automating the biaryl coupling process following a multiple reaction well format. The heterogeneous production of such a biphenyl is also a major advance in solid-phase synthesis since there are no amide, carboxylic acid, or alcohol appendages on the molecule. Lastly, the versatility of combining the Stille coupling methodology with the photoactive NpSSMpact support was shown in the successful production of the acetoxybiphenyl **25**. Work is currently underway to transfer this methodology to the automated production of more highly functionalized biphenyls, in addition to other types of Stille reactions.

Experimental Section

Materials. Diisopropylethylamine (DIEA) was distilled from ninhydrin under reduced pressure. TentaGel resin having a substitution of 0.29 mmol/g and the Rink amide resin having a substitution of 0.39 mmol/g were both obtained from Novabiochem. HPLC grade acetonitrile was obtained from EM Science. Flash chromatography was conducted using Kieselgel 60 silica gel. Analytical reversed-phase HPLC was carried out using a Waters 600E and Waters radial compression C-18 reversed-phase columns. UV spectrophotometry was carried out using a Milton Roy 1001+ spectrophotometer. GC mass spectrometry was carried out using an HP 5890 GC equipped with an HP 5971 mass selective detector. ^{1}H NMR was carried out using a Bruker AMX300 spectrometer.

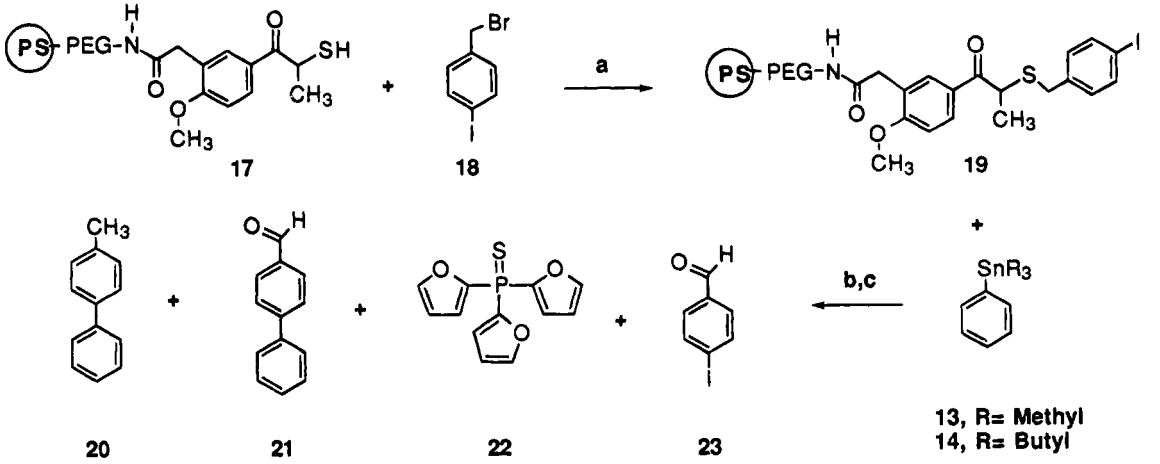
Because of both the volatile nature of many of the biphenyl compounds and the use of acetonitrile during the cleavage reaction, the solution syntheses of the biphenyl compounds were also done for verification purposes.

Phenyl trifluoromethanesulfonate (8) was prepared by the published literature procedure[4g] to isolate after chromatography (SiO_2, first with hexane, then 19/1, hexane/EtOAc) a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.48–7.33 (m, 3H), 7.29–7.23 (m, 2H); HRMS calcd for $C_7H_5O_3SF_3$ *m/z* 225.9911, measured 225.9916.

Solution Synthesis of 4-Biphenylacetamide (10). 4-Biphenylacetic acid (1.0 g, 4.7 mmol) was dissolved and refluxed in thionyl chloride (5 mL) for 0.5 h. The solution was poured into cold 30% aqueous NH_4OH. The liquid was removed by filtration, leaving a yellow solid. The solid was suspended in a large volume of CH_2Cl_2 and washed with 10% NaOH. The organic layer was removed under reduced pressure to give 320 mg (32%) of a white solid: IR (Nujol mull) 3345, 3168, 1634, 1488, 1416, 1294, 1178 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.63–7.52 (m, 5H), 7.46–7.38 (m, 2H), 7.38–7.31 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 183.1, 172.2, 140.0, 138.2, 129.6, 128.9, 127.2, 126.5, 126.4, 41.8; HRMS calcd for $C_{14}H_{13}ON$ *m/z* 211.0997, measured 211.1006.

4-(Tri-n-butylstannyl)phenylacetic Acid (6). A flask containing a solution of methyl 4-bromophenylacetate (3.0 g, 13.1 mmol) in toluene (40 mL) was degassed by bubbling argon through the solution. Hexabutylditin (13 mL, 27 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (140 mg, 0.12 mmol). The mixture was refluxed for 12 h. The reaction was allowed to cool and then filtered through a plug of silica gel. The solvent was removed under reduced pressure

Scheme 4[a]



[a] (a) DIEA, DMF; (b) Pd_2dba_3, LiCl, TFP, NMP, 25 °C; (c) 350 nm light, acetonitrile.

Table 2. Product Distribution[a] and Percent Yield[b] of Biphenyl (20) after Biaryl Coupling at 25 °C for 24 h in NMP Followed by Photolytic Cleavage of Solid Support[c]

					equiv				
entry	R, equiv	TFP, equiv	Pd_2dba_3, equiv	LiCl, equiv	20	21	22	23	% yield of **20**
1	CH_3, 1.5	0.21	0.11	1.4	1	0.25	1.67	0.29	3
2	CH_3, 2.9	0.43	0.23	1.4	1	0.20	0.57	0	10
3	CH_3, 2.9	0.12	0.21	1.4	1	0.7	0	0	4.5
4	CH_3, 4.9	0.22	0.29	2.6	1	0.1	0.12	0	10
5	butyl, 4.3	0.23	0.28	2.8	1	0.7	<0.05	0	3
6	CH_3, 12	0.18	0.23	2.0	1	0.1	0	0	27

[a] Product distribution obtained by ^1H NMR. [b] HPLC yield using an internal standard, ref 9. [c] 350 nm light in acetonitrile, ref 11. TFP = trifurylphosphine, Pd_2dba_3 = tris(dibenzylideneacetone)dipalladium, NMP = 1-methyl-2-pyrrolidinone.

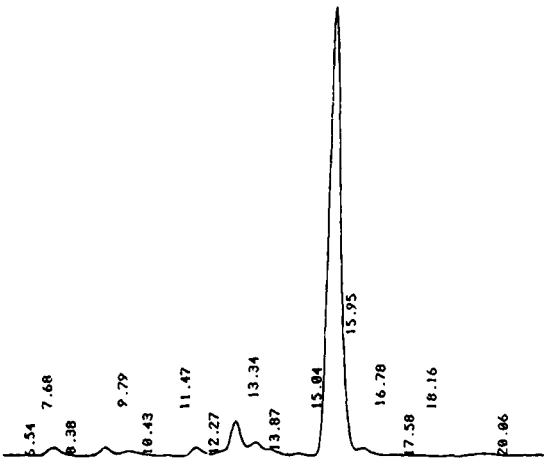
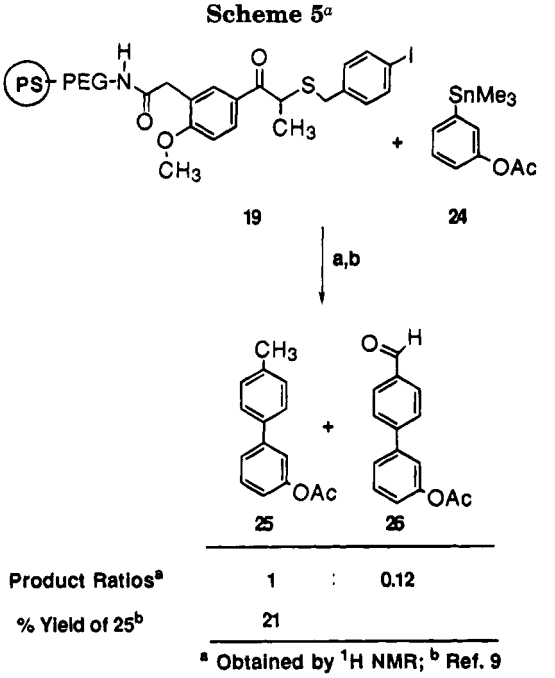


Figure 2. Reversed-phase HPLC chromatogram of crude biphenyl product obtained after photolytic cleavage from support (entry 6, Table 2). HPLC analytical conditions: 2 mL/min 95/5 H_2O/CH_3CN (0.1% TFA), linear gradient to 5/95; 254 nm detection.

to give an oil which was chromatographed (SiO_2, 19/1, hexanes/EtOAc) to isolate a colorless oil. The oil was dissolved in a solution of 1.2 g KOH in 50% EtOH (400 mL) and refluxed for 1 h. The cooled reaction mixture was poured into water (300 mL) containing 5 mL AcOH. The product was extracted with ether that was then washed with brine and dried over Na_2SO_4. The ether was removed under reduced pressure to give a colorless oil, 2.5 g (44%): IR (neat film) 2955, 1708, 1651, 1574, 1491, 1377, 1075, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49–7.32 (m, 2H), 7.24–7.21 (d, J = 7.9 Hz, 2H), 3.61 (s, 2H), 1.50 (m, 6H), 1.33 (m, 6H), 1.20 (m, 6H), 0.87 (t, J = 7.9 Hz, 9H); ^{13}C NMR ($CDCl_3$) δ 136.7, 128.9, 29.1, 27.8, 27.4, 26.9, 13.6, 9.6; HRMS calcd for $C_{20}H_{34}SnO_2$ (M − H + 2Na) m/z 471.1302, measured 471.1310.

Scheme 5[a]



[a] (a) 15 equiv of phenyltin **24**, 0.29 equiv of Pd_2dba_3, 2.5 equiv of LiCl, 0.35 equiv of TFP, NMP, 25 °C; (b) 350 nm light, acetonitrile.

General Method for Attachment of Para-Substituted Phenylacetic Acids on Rink Amide Resin. In a peptide synthesis vessel, the Fmoc protected resin (3.5 g, 0.39 mmol/g) is suspended in DMF/piperidine (40 mL of a 1/1 solution). The mixture is shaken for 20 min to give the resulting free amine **5**. The resin is thoroughly washed by shaking with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×) in that order. To the deprotected resin is added CH_2Cl_2 (40 mL) followed by the

desired para-substituted phenylacetic acid (2 equiv) and diisopropylcarbodiimide (2 equiv). The reaction is shaken for 3 h followed by the above resin washing procedure and drying under vacuum. The amount of resin-bound amine after derivitization was measured by quantitative ninhydrin.[7]

Example of Coupling and Cleavage Procedure on Rink Amide Resin: Resin-Bound 4-Iodophenylacetamide Coupled with Trimethylphenyltin To Give 4-Biphenylacetamide (10). To 0.3 g (0.3 mmol/g subst based on quantitative ninhydrin[7]) of resin-bound 4-iodophenylacetamide (**12**) in a 10 mL round bottom flask containing a stir bar were added TFP (1 mg, 0.005 mmol), LiCl (8 mg, 0.2 mmol), Pd_2dba_3 (4 mg, 0.004 mmol), and *N*-methylpyrrolidinone (5 mL). The mixture was stirred under closed atmosphere for 10 min. Trimethylphenyltin (**13**) (30 mL, 0.16 mmol) was then added by syringe. The reaction was then stirred under closed atmosphere for 24 h at room temperature after which the contents of the flask were filtered through a medium porosity fritted glass funnel. The resin was washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×) in that order and then dried under pump vacuum. Cleavage was affected with three 5 min acid washings (19/1, CH_2Cl_2/TFA). The washes were combined, and volitile components were removed under reduced pressure to give biphenyl **10** in 21% crude yield by reversed-phase HPLC.[9]

4-Iodobenzyl Bromide (18). Ethyl 4-iodobenzoate was reduced to the corresponding benzyl alcohol by published literature procedure.[14] The resulting benzyl alcohol (1.3 g, 5.6 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled in an ice-water bath. To the cooled solution was added carbon tetrabromide (2.4 g, 7.2 mmol) followed by the slow addition of triphenylphosphine (2.2 g, 8.3 mmol). After 10 min, the solvent was removed under reduced pressure, leaving a solid residue which was purified by flash chromatography (SiO_2, hexanes) affording 1.1 g (67%) of **18** as a white solid: IR (neat fim) 2366, 1580, 1479, 1440, 1396, 1274, 1221 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67–7.64 (d, J = 8.4 Hz, 2H), 7.13–7.10 (d, J = 8.4 Hz, 2H), 4.40 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 137.8, 137.3, 130.7, 94.1, 32.4; HRMS calculated for C_7H_6BrI *m/z* 295.8698, measured 295.8709.

Example of Biaryl Coupling and Cleavage Procedure on NpSSMpact Resin.[11] In a peptide synthesis vessel containing 3.3 g of the NpSSMpact resin was added 2-mercaptoethanol (2 mL), DIEA (3 mL), and DMF (15 mL) and the mixture shaken for 1 min followed by a similar 10 min washing. The resin was then washed by shaking with DMF (3×), MeOH (3×), and then DMF (10×) in that order. DMF (15 mL) was again added followed by the benzyl bromide (**18**) (730 mg, 2.5 mmol) and DIEA (1.5 mL, 8.6 mmol). The mixture was shaken in the dark for 12 h, after which the resin was thoroughly washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×) and finally placed under vacuum for 24 h. Iodine elemental analysis gave a resin-bound aryl iodide substitution level of 0.22 mmol/g.

A portion of the resin bound aryl iodide resin (**19**) (300 mg, 0.066 mmol) was added to a 10 mL flask followed by LiCl (5.5 mg, 0.13 mmol), Pd_2dba_3 (13.5 mg, 0.015 mmol), TFP (2.8 mg, 0.012 mmol), and NMP (3 mL). Stirring in the dark was started and trimethylphenyltin (150 mL, 0.81 mmol) was added by syringe. Stirring continued for 12 h under closed atmosphere. The resin was then filtered through a medium porosity fritted glass funnel and then washed thoroughly with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×) in that order. The resin was then placed under pump vacuum for 24 h.

The dry resin was then transferred to a quartz test tube (15.5 × 1.5 cm) containing a stir bar, and CD_3CN (5 mL) was added. The mixture was irradiated while stirring using a Rayonet photochemical reactor (consisting of 16 black phosphor bulbs having a maximum wavelength intensity at 350 nm) for 4.5 h to give 4-phenyltoluene (**20**) in 25% crude yield by quantitative HPLC using an internal standard.[9]

(3-Acetoxyphenyl)trimethyltin (24) was prepared from 3-acetoxyiodobenzene by a procedure similar to that for **6**. The crude stannane was purified by flash chromatography (SiO_2, hexanes and then 19/1, hexanes/EtOAc) to afford **24** as a colorless oil: IR (neat film) 2982, 2912, 1766, 1573, 1471, 1407, 1368, 1214, 1187 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.26 (m, 2H), 7.17–7.16 (d, J = 2 Hz, 1H), 7.03–6.99 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 168.0, 150.4, 144.2, 133.2, 128.9, 128.5, 128.3, 121.4, 21.1; HRMS calcd for $C_{11}H_{16}O_2Sn$ *m/z* 300.0172, measured 300.0183.

Solution Synthesis of 4-(3-Acetoxyphenyl)toluene (25). (3-Acetoxyphenyl)trimethyltin (**24**) (330 mg, 1.1 mmol) was added to a 10 mL round bottom flask followed by 4-iodotoluene (220 mg, 1.0 mmol), LiCl (85 mg, 2.0 mmol), TFP (9.5 mg, 0.04 mmol), Pd_2dba_3 (18 mg, 0.02 mmol), and NMP (3 mL). The reaction mixture was then stirred for 18 h under a nitrogen atmosphere at room temperature. The mixture was then taken up in diethyl ether and filtered through Celite. The filtrate was washed with saturated NH_4Cl, 50% KF, and brine and then dried over $MgSO_4$. The volatile components of the reaction mixture were then removed under reduced pressure to give a brown oil which was purified by flash chromatography (SiO_2, 9/1, hexanes/EtOAc) to isolate 160 mg (71%) of **25** as a white solid: IR (neat film) 2922, 1760, 1586, 1368, 1223, 1174 cm^{-1}; ^1H NMR (CD_3CN) δ 7.54–7.48 (m, 2H), 7.48–7.42 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 2.0 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.08–7.04 (m, 1H), 2.37 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.1, 154.2, 142.0, 137.7, 129.5, 127.0, 124.4, 120.1, 21.1; HRMS calcd for $C_{15}H_{14}O_2$ *m/z* 226.0994, measured 226.0988.

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