Solid-Phase Preparation of Dienes

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The Stille reaction has been used to prepare a variety of functionalized dienes on a solid support.

The field of solid-phase combinatorial chemistry has rapidly developed over the past several years.[1] This method is potentially very useful for the synthesis of biologically active peptidomimetic molecules.[2] Given the great synthetic utility of the [4 + 2] cycloaddition reaction in preparing cyclic compounds in solution, it is surprising that only a few reports of solid-phase Diels−Alder reactions have appeared. Both the dienophile[3] and the diene[4] have been used as the resin-linked component. Notably, in only one report have a number of different products been isolated,[4c] and in none of the papers are the dienes synthesized on the solid support. While there are several examples of diene synthesis on the resin[5] (as opposed to attachment of intact dienes), little attention has been paid to this area.

We sought a route to prepare functionalized dienes on a solid support, with the ultimate goal of employing these dienes in Diels−Alder reactions to prepare a library of functionalized bicyclic peptidomimetics. A number of potential synthetic routes to dienes were tested, and the versatility of the most successful approach was demonstrated by the preparation of a variety of dienes. Examination of the diene indicates three possible disconnections (Scheme 1), with two combinations of reagents for each disconnection. Of the six possible routes, we initially explored the four Wittig/Horner−Wadsworth−Emmons-type reactions (paths A, B, E, and F), but these eventually proved to give unsatisfactory results. The two Stille/Suzuki-type couplings (paths C and D) were then examined, and success was ultimately attained using Stille reaction conditions and the path C reagent combination.

Results and Discussion

The development of the polymer-supported chemistry was carried out on PEG-5000 poly(ethylene glycol) monomethyl ether resin, which has recently been used in several combinatorial syntheses.[6] The great advantage of this support is the ability to easily collect useful NMR spectra of the reaction products while they are still attached to the resin, without resorting to magic angle spinning techniques.[6a] The extent of conversion can be easily determined without cleavage of the product from the resin, a benefit which is particularly useful for following the progress of multistep reactions. The primary disadvantage of PEG is that reaction workups are more difficult than with true solid-phase supports, especially during isolation of the final cleaved product, if the product and PEG have similar solubility properties. We hoped that if reaction conditions could be optimized on PEG they would be transferable to more conventional polystyrene-based solid supports.

Initial test reactions employed an Ala-Gly dipeptide linker to the resin. Once successful reaction conditions were established, the C-terminal amino acid was changed to aminocaproic acid (Aca), a flexible extended linker that might eventually allow for enzymatic assay of the final product on the resin.

Wittig/Horner−Wadsworth−Emmons Reactions (paths A, B, E and F). Our initial attempts at diene preparation focused on a Wittig or Horner−Wadsworth−Emmons-type coupling, due to the literature precedent for solid-phase diene synthesis using these reactions.[5] For our purposes, the presence of the ester linkage to the PEG support meant that strongly basic conditions needed to be avoided. For this reason, the mild deprotonation conditions of Et_3N/LiBr reported for the Horner−Wad-

(1) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, (a) 1233−1251, (b) 1385−1401. (c) Terrett, N. K.; Gardner, M. G.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135−8173. (d) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554. (e) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (f) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42. (g) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337.

(2) See entire issue 5 of *Biorg. Med. Chem.* **1996**, *4*, 631−737 for recent examples.

(3) (a) Yedidia, V.; Leznoff, C. C. *Can. J. Chem.* **1980**, *58*, 1144−1150 (acrylic acid on Merrifield resin, react with two dienes and cleave from resin). (b) Keana, J. F. W.; Guzikowski, A. P.; Ward, D. D.; Morat, C.; Van Nice, F. L. *J. Org. Chem.* **1983**, *48*, 2654−2660 (urazole on silica, used to remove several dienes from solution, one prodict−ergosterol adduct−cleaved and isolated). Ritter, H.; Sperber, R. *Macromolecules* **1994**, *27*, 5919−5920 (alkene in poly(vinylformyl) resin, reacted with heterodiene, no product cleaved).

(4) (a) Gavina, F.; Palazon, B. *Tetrahedron Lett.* **1979**, *15*, 1333−1336 (butadienol attached as ester to polystrylacetyl resin, reacted with diimine, cleaved in 18% yield). (b) Guhr, K. I.; Greaves, M. D.; Rotello, V. M. *J. Am. Chem. Soc.* **1994**, *116*, 5997−5998 (cyclopentadiene on Merrifield resin, add buckminsterfullerene, no cleaved product). (c) Sclessinger, R. H.; Bergstrom, C. P. *Tetrahedron Lett.* **1996**, *37*, 2133−2136 (furan on silylated polystyrene resin, several dienophiles, product cleaved and isolated).

(5) (a) Leznoff, C. C.; Wong, J. Y. *Can. J. Chem.* **1973**, *51*, 3756−3764 (1,4-diphenyl *Z* diene by Wittig reaction). (b) Leznoff, C. C.; Greenberg, S. *Can. J. Chem.* **1976**, *54*, 3824−3829 (1,4-diphenyl *E* diene by Wittig reaction). (c) Nieuwstad, TH. J.; Kieboom, A. P. G.; Beijer, A. J.; Van Der Linden, J.; Van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 225−231 (diene on polymer by desulfuration or by Grignard addition/elimination). (d) Leznoff, C. C.; Sywanyk, W. *J. Org. Chem.* **1977**, *42*, 3203−3205 (carotenoid tetra-, hexa-, and heptaenes on polystyrene support). (e) Johnson, C. R.; Zhang, B. *Tetrahedron Lett.* **1995**, *36*, 9253−9256 (Wittig−Horner olefination with cinnamaldehyde).

(6) (a) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5095−5097. (b) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419−6423. (c) Zhu, J.; Hegedus, L. S. *J. Org. Chem.* **1995**, *60*, 5831−5837. (d) Park, W. K. C.; Auer, M.; Jaksche, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 10150−10155.

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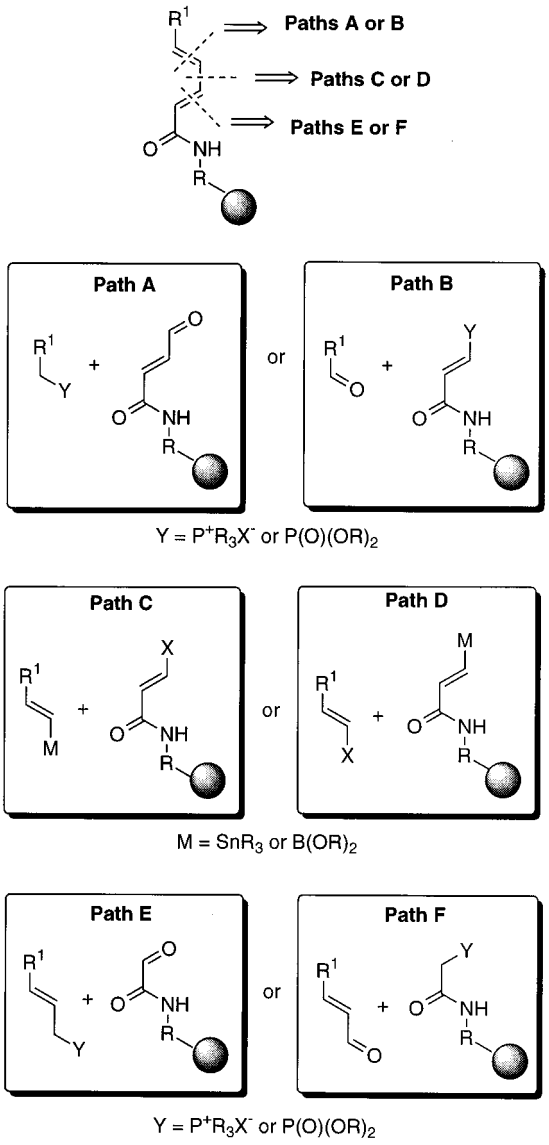
Scheme 1. Possible Disconnections of Diene



sworth−Emmons[5e,7] reactions were employed. Of the four possible paths (A, B, E, and F), path E was discarded due to the difficulty of working with glyoxalic acid derivatives (attempts to couple glyoxalic acid derivatives to the peptide-resin gave mixtures of products).

The Horner−Wadsworth−Emmons reagent **4** needed for path F was prepared by coupling deprotected Ala-Gly-OPEG **3** (prepared by conventional peptide synthesis methods) with diethylphosphonoacetic acid (see Scheme 2). The corresponding Wittig reagent **6** was prepared via the bromoacetic acid adduct **5**. Reaction of both reagents with acetaldehyde using Et_3N/LiBr as base proceeded quantitatively, with **4** giving much better *E*:*Z* selectivity as expected (see Table 1). The Wittig reagent **6** also reacted with α,β-unsaturated aldehydes, giving good yields of the desired diene, but poor *E*:*Z* selectivity was again observed for the bond being formed. The isomer ratio was not improved by variation of the solvent or removal of the LiBr. The identity of the *E*,*E* diene product was confirmed by coupling sorbic acid with **3**. Unfortuntely, when the Horner−Wadsworth−Emmons reagent **4** was reacted with α,β-unsaturated aldehydes, very poor yields (<25%) of the diene were obtained, although the *E* selectivity remained high (see Table 1).

Scheme 2. Diene Synthesis via Wittig-Type Reactions Corresponding to Path F

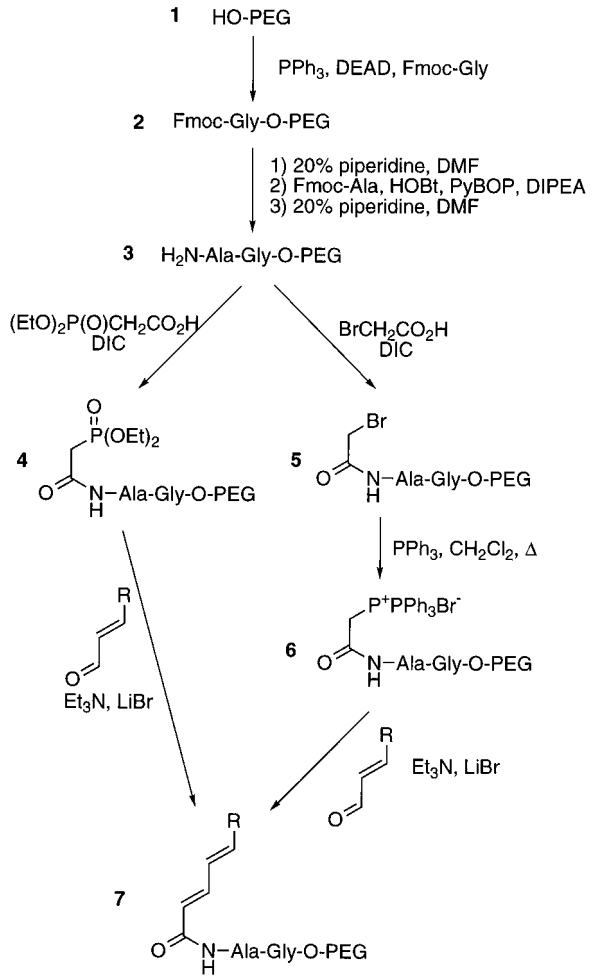


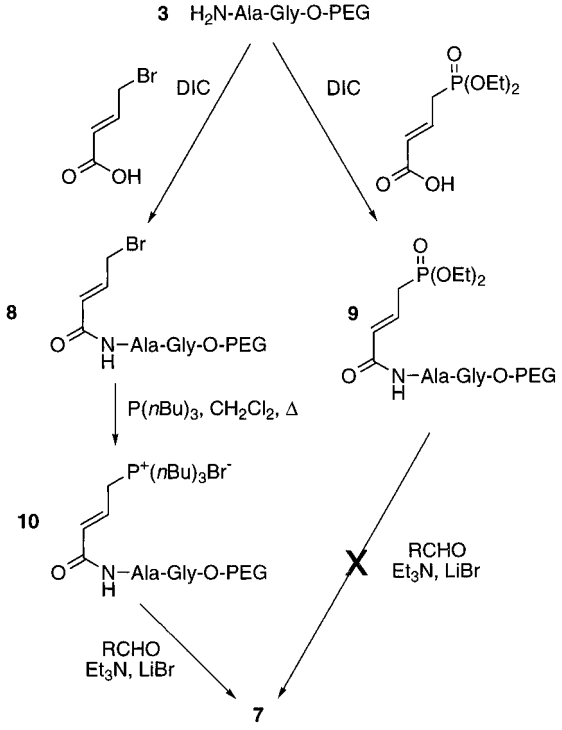
Table 1. Reaction of Wittig/Horner−Wadsworth−Emmons Reagents with Aldehydes

substrate	RCHO	conditions[a]	product:sm[b]	*E*:*Z*[c]
4	Me	standard	100:0	97:3
4	PhCH=CH	standard	16:84	100:0
4	PhCH=CH	standard in DMF	0:100	
4	PhCH=CH	standard in CH_3CN	24:76	100:0
4	PhCH=CH	standard at 60 °C	cleaved	
4	PhCH=CH	*d*	cleaved	
4	PhCH=CH	*e*	18:82	100:0
4	PhCH=CH	K_2CO_3/toluene	11:89	100:0
4	PhCH=CH	5 equiv of NaH/DMSO	cleaved	
4	PhCH=CH	1.2 equiv of NaH/THF	22:78	100:0
4	MeCH=CH	standard	0:100	
4	H_2C=C(Me)	standard	10:90	100:0
6	Me	standard	100:0	74:26
6	PhCH=CH	standard	100:0	70:30
6	PhCH=CH	DMF	100:0	60:40
6	PhCH=CH	no LiBr	100:0	55:45
6	MeCH=CH	standard	100:0	65:35
6	H_2C=C(Me)	standard	100:0	80:20
9	Me	standard	<10:>90	100:0
9	Ph	standard	18:82	100:0
10	Ph	standard	85:15	100:0
10	Me	standard	50:50	

[a] Standard conditions are 11.5 equiv of LiBr, 11 equiv of Et_3N, and 11 equiv of RCHO in dry THF, reacted at rt overnight. [b] As determined by integration of of ^{1}H NMR of PEG attached product. [c] *E*:*Z* ratio of bond formed during reaction, as determined by integration of ^{1}H NMR alkene region. [d] 30 equiv of Et_3N/100 equiv of LiBr/CH_3CN. [e] 10 equiv of DIPEA/10 equiv of LiCl/CH_3CN.

A variety of reaction conditions were examined, with little or no improvement in yield. The reason for the low

Scheme 3. Diene Synthesis via Wittig-Type Reactions Corresponding to Path B



conversion is unclear as under similar conditions a PEG-PS Tentagel resin supported diethylphosphonoacetamide was reported to successfully react with cinnamaldehyde, although the yield was significantly lower compared to reaction with other aldehydes.[5e]

Attention now turned to path B, with the conjugated Horner−Wadsworth−Emmons reagent **9** (see Scheme 3) readily prepared by coupling diethylphosphonocrotonic acid with dipeptide **3**. Reaction of **9** with several aldehydes under a variety of conditions again gave very poor yields of diene (see Table 1). Attempts to prepare the corresponding Wittig reagent **10** by refluxing the bromocrotonic acid intermediate **7** with triphenylphosphine gave mixtures of impure products, but reaction with tri-*n*-butylphosphine gave the desired **10**, although still somewhat impure. Treatment of **10** with benzaldehyde under standard conditions gave surprisingly clean diene with good *E* selectivity. Unfortunately, reaction with acetaldehyde was less successful.

Given the lack of success obtained with the Wittig-type reactions, and the limitations that this type of reaction imposes on substitutions at other positions of the diene, the remaining possible path A was not investigated.

Stille Reactions (Paths C and D). We then focused our research on the possiblities of a Stille or Suzuki coupling, represented by paths C and D in Scheme 1. The Suzuki reaction is useful for diene synthesis,[8] but for solid-phase chemistry it has generally been used to couple aryl halides with alkylboranes, alkenylboranes, or arylboronic acids.[9] In our case, the basic reaction conditions would probably not be compatible with the PEG ester linkage. Stille couplings[10] have also been employed on solid phase for the preparation of aryl[11] and acyl derivatives,[12] but the related diene preparation[13] has not yet been reported. The Stille reaction is tolerant of a variety of functional groups and appeared compatible with our substrate, so the reaction was investigated further.

The organostannane alkenes required for path C were prepared from the corresponding terminal alkynes. Palladium-catalyzed hydrostannylations of bromoalkyne intermediates[14] were used to prepare some of the (*E*)-1-stannylalk-1-enes, but in our hands the *E*:*Z* ratios obtained were often somewhat poor. For polar compounds it was much easier to directly reduce the alkyne with *n*-Bu_4SnH/AIBN and separate the *E* isomer from the mixture of *E*-, *Z*-, and *gem*-substituted products by flash column chromatography. The *Z* isomer could be prepared by $ZrCl_4$-catalyzed anti-hydrostannation.[15]

Initially, the Gly-OPEG linked bromoacrylic acid derivative **14**[16] required for path C (see Scheme 4, left-hand side) was reacted with 1.5 equiv of (*E*)-1-(tributylstannyl)-2-phenylethene (**16**) ($R^2 = R^3 = H$, $R^4 = Ph$) using the modified conditions of Farina et al.[13b] ($AsPh_3$, Pd_2dba_3, NMP), with 0.025 equiv of palladium catalyst. An *all-E* product (**17**) with only 5% starting material **14** remaining was obtained after reaction overnight at room temperature. The next organostannane tested proved to be the most difficult of *all*-(*E*)-1-stannylalk-1-enes to couple. The extremely bulky *t*-Bu-substituted **16** ($R^2 = R^3 = H$, $R^4 =$ *t*-Bu) gave a very poor yield (2% after 1 h, 40% after overnight), and a mixture of predominantly 2*E*,4*E*:2*E*,4*Z*:2*Z*,4*E* isomers (40:50:10) was obtained. When additional catalyst (0.2 equiv of palladium) was employed, the reaction could be forced to completion, but a mixture of isomers was still produced. The desired 2*E*,4*E* product was finally obtained as the predominant isomer (2*E*,4*E*:2*E*,4*Z*:2*Z*,4*E* 87:11:2) by using a large excess of organostannane (10 equiv), with no preactivation of the bromoalkene/palladium complex.

Once suitable reaction conditions were established, the ability of the Stille coupling to produce diene diversity was examined (see Table 2). The potential C-terminus (Xaa_2) of our substrate/inhibitor was varied with alanine

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(8) (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972−980. (b) Uenishi, J.-I.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4765−4758.

(9) (a) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171−11172. (b) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177−9180. (c) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169−5171. (d) Koh, J. S.; Ellman, J. A *J. Org. Chem.* **1996**, *61*, 4494−4495. (e) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742−5743. (f) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331−6332. (g) Han, Y.; Walker, S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *37*, 2703−2706. (h) Chenera, B.; Finkelstein, J. A.; Veber, D. *J. Am. Chem. Soc.* **1995**, *117*, 11999−12000.

(10) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771−1780.

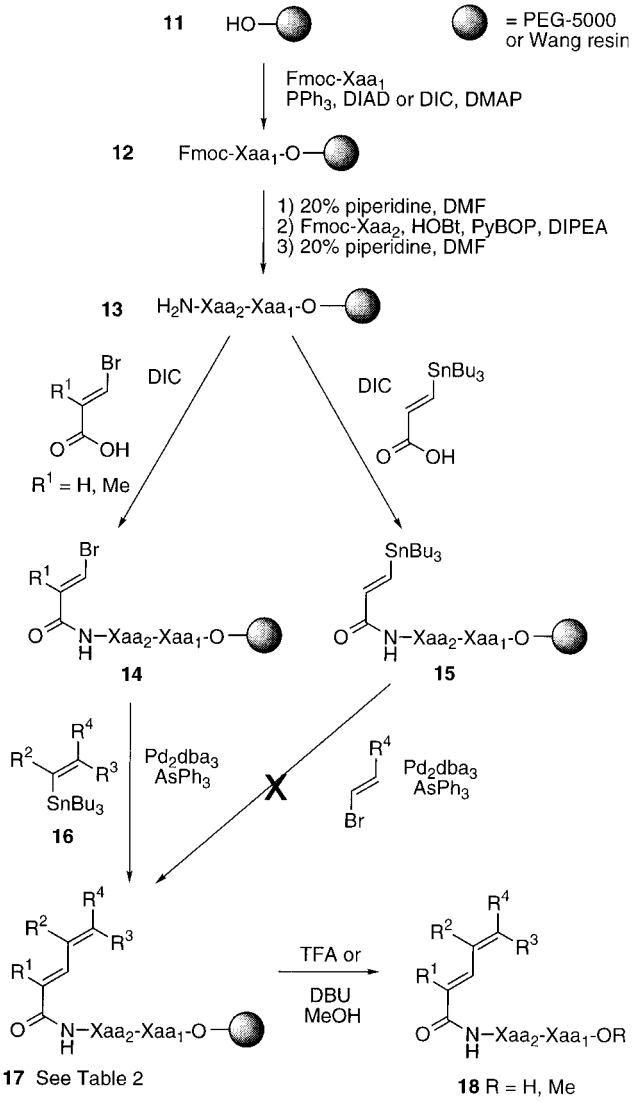
(11) (a) Forman, F. W.; Sucholeiki, I. *J. Org. Chem.* **1995**, *60*, 523−528 (tributylphenyltin or iodobenzene attached by amide bond to Rink amide resin, coupled with aryl halides/triflates or trialkylphenyltin, respectively). (b) Beaver, K. A.; Siegmund, A. C.; Spear, K. L. *Tetrahedron Lett.* **1996**, *37*, 1145−1148 (iodobenzene attached by sulfonamide linker on Rink resin, coupled with 1-(ethoxyvinyl)-tributyltin). (c) Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613−5614 (iodobenzoic acid on Rink or Wang resin, coupled with five organostannanes).

(12) (a) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006−6007 (aryltrimethyltin on (aminomethyl)polystyrene resin, couple with four acid chlorides). (b) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306−3307 (arylstannane on (aminomethyl)polystyrene resin, couple with 15 acid chloride intermediates).

(13) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(14) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417−2419.

Scheme 4. Diene Synthesis via Stille Coupling Corresponding to Paths C and D



or Pbf[18] protected arginine in order to demonstrate the tolerance of the reaction to substitution at this site. No difference in reactivity was noted. A variety of (*E*)-alkenylstannanes were tested, with standard coupling conditions (0.1 equiv palladium catalyst, 1.5−2 equiv of organostannane, reaction at room temperature overnight) generally giving good yields and stereoselectivity. Unsubstituted tributylvinylstannane (**16**, R^4 = H) reacted very quickly (<1 h), but as previously noted, the bulky *t*-Bu-substituted stannane (**16**, R^4 = *t*-Bu) required an excess of reagents. The other exception was an organostannane containing an unprotected amine (**16**, R^4 = CH_2NH_2), which only coupled in 50% yield under the standard conditions. Again, adding additional palladium catalyst (0.2 equiv) and organostannane (3 equiv) allowed for quantitative reaction. ^{1}H NMR spectra of the alkene/amide region of three representative PEG-linked dienes clearly show the purity of the Stille product and demonstrate the advantage of being able to monitor reactions on the PEG resin (Figure 1).

Several (*Z*)-alkenylstannane reagents were examined and found to react sluggishly. Increased catalyst (0.2 equiv of palladium), organostannane (3−5 equiv) and temperature (60 °C) generally allowed for complete reaction, although with one organostannane (**16**, R^3 = CO_2CH_3) mixtures of 2*E*,4*E*:2*E*,4*Z* isomers were obtained at the increased temperature, presumably due to *Z* to *E* isomerization of the alkenylstannane.

A similar decrease in reaction rate was observed when additional steric hindrance was placed on the bromoalkene component. The 2-methyl-substituted acrylic acid derivative **14** (R^1 = Me) gave only a 20% yield of product when reacted with the methoxymethyl stannane reagent **16** (R^4 = CH_2OCH_3) under standard coupling conditions. Increased catalyst (0.2 equiv of palladium), excess organostannane (10 equiv), and elevated reaction temperature (60 °C) were required for complete reaction.

Gem-substituted alkenylstannanes were also examined. Commercially available tributyl(1-ethoxyvinyl)tin (**16**, R^2 = OEt) reacted well under the standard conditions (75% complete after 3.5 h, complete after reaction overnight). However, a more substituted example (**16**, R^2 = Et, R^3 = H, R^4 = Me) reacted slowly and gave a complex mixture of isomers.

Finally, the possibility of carrying out the reverse Stille reaction indicated by path D (see Scheme 4, right-hand side), with the organostannane on the resin, was examined, as only one organostannane would then need to be synthesized. The desired PEG-linked stannane **15** was readily prepared by coupling 3(*E*)-(tributylstannyl)acrylic acid with the deprotected Ala-Aca-PEG dipeptide **13**. Unfortunately, reaction of **15** with alkenylbromides under a variety of conditions was not successful. The reason for this is not clear, although a previous report on Stille couplings has noted reduced yields when the stannane is the resin-linked component instead of the solution component.[11a]

Cleavage from Resin and Confirmation of Product Identity. Several sample dienes were cleaved from the PEG support by treatment with DBU in MeOH. The crude solution was purified by column chromatography to give the pure diene methyl ester in good overall yield (60−80%, six examples), with satisfactory analytical data (NMR, MS for all six samples, elemental analysis for one).

Wang Resin. The reaction sequence was also successfully transferred to a more conventional polystyrene support. Initially, commercially available Fmoc-Phe-Wang resin was elaborated to the bromoalkene-functionalized precursor **14** (R^1 = H), and the Stille coupling conditions were tested. The reactions were successful, so the unfunctionalized Wang resin was converted to the same bromoalkene-derivatized Ala-Aca and Arg(Pbf)-Aca dipeptides **14** (R^1 = H, Me) that were previously prepared using the PEG support. After Stille coupling with a number of organostannanes, each reaction was divided into two portions, with one half treated with TFA to cleave the product from the resin as the free acid and the other half treated with DBU in MeOH to give the cleaved product as a methyl ester. The identity of the

(15) Asao, N.; Liu, J.-X.; Sudoh, T.; Yamamoto, Y. *J Org. Chem.* **1996**, *61*, 4568−4571.

(16) (*E*)-Bromoacrylic acid was prepared from propiolic acid by reaction with aqueous HBr[17] followed by crystallization from $CHCl_3$. Only DIC was used for coupling of the bromoacrylic acid to the resin-bound amino acid, as it was found that other coupling reagents (PyBOP) or the presence of base (DIPEA) resulted in impure product.

(17) Crout, D. H. G.; Corkill, J. A. *Tetrahedron Lett.* **1977**, *49*, 4355−4357.

(18) Carpino, L. A.; Shroff, H.; Triolo, S. A.; Mansour, E.-S. M. E.; Wenschuh, H.; Albericio, F. *Tetrahedron Lett.* **1993**, *34*, 7829−7832.

Table 2. Summary of Compounds Prepared by Stille Couplings

support	Xaa_2-Xaa_1	R^1	R^2, R^3, R^4	cleaved diene **18**
PEG	Gly	H	$R^2 = R^3 = H$, $R^4 = H$, Ph, *t*-Bu	
	Ala-Aca	H	$R^2 = R^3 = h$, $R^4 = H$, $(CH_3)_7CH_3$, Ph, *t*-Bu, CH^- OH, CH_2OCH_3, CH_2NH_2, CH_2NHBoc, CH_2NMe_2, CO_2H, CO_2CH_3	R = Me, $R^2 = R^3 = H$, $R^4 = H$, CO_2H, CO_2CH_3, CH_3OCH_3
			$R^2 = R^4 = H$, $R^3 = CH_2OH$, CO_2CH_3	
			$R^2 = R^4 = H$, $R^3 = OEt$	$R^3 = H$, $R^2 + R^4 =$
			$R^3 = H$, $R^2 + R^4 = -SCH{=}CH-$, $-OCH{=}CH-$	$-SCH{=}CH-$
		Me	$R^2 = R^3 = H$, $R^4 = H$, CH_2OCH_3, CH_2NHBoc	
			$R^2 = R^4 = H$, $R^3 = OEt$	
	Arg(Pbf)-Aca	H	$R^2 = R^3 = H$, $R^4 = H$, $(CH_2)_7CH_3$, Ph, *t*-Bu, CH_2OH, CH_2OCH_3, CH_2NH_2, CH_2NHBoc, CH_2NMe_2, CO_2H, CO_2CH_3	R = Me, $R^2 = R^3 = H$, $R^4 = CH_2NMe_2$
			$R^2 = R^4 = H$, $R^3 = CH_2OH$, CO_2CH_3	$R^3 = H$, $R^2 + R^4 =$
			$R^2 = R^4 = H$, $R^3 = Oet$	$-SCH{=}CH-$
			$R^3 = H$, $R^2 + R^4 = -SCH{=}CH-$, $-OCH{=}CH-$	
		Me	$R^2 = R^3 = H$, $R^4 = CH_2NHBoc$	Me
Wang	Phe	H	$R^2 = R^3 = H$. $R^4 = CH_2OH$, CH_2NMe_2, CH_2NHBoc	R = H: all
				R = Me, $R^2 = R^3 = R^4 = H$
		Me	$R^2 = R^3 = H$, $R^4 = h$, CH_2OH, CH_2NMe_2, CH_2NHBoc	R = H: all
	Ala-Aca	H	$R^2 = R^3 = H$, $R^4 = H$, $(CH_2)_7CH_3$, Ph, CH_2OH, CH_2NMe_2	R = HL all
				R = Me: all
			$R^2 = R^4 = H$, $R^3 = (CH_2)_7CH_3$, Ph, CH_2OH	
			$R^3 = H$, $R^2 + R^4 = -OCH{=}CH-$	
		Me	$R^2 = R^3 = H$, $R^4 = H$, $(CH_2)_7CH_3$, Ph, CH_2NMe_2	R = H: all
			$R^2 = R^4 = H$, $R^3 = (CH_2)_7CH_3$, Ph	R = Me: all
			$R^3 = H$, $R^2 + R^4 = -OCH{=}CH-$	
	Arg(Pbf)-Aca	H	$R^2 = R^3 = H$, CH_2NMe_2	R = H: all
			$R^3 = H$, $R^2 + R^4 = -SCH{=}CH-$	R = Me: all

products was confirmed by mass spectral and ^{1}H NMR analysis. The correct MH^+ ion was observed for all samples.

In summary, the Stille reaction provides a facile method of preparing a diverse range of dienes on solid-phase supports. The reaction can stereoselectively produce 2*E*,4*E* and 2*E*,4*Z* geometry with mono-, di-, and trisubstitution and is very tolerant of functional groups present elsewhere in the molecule, even when unprotected. No special precautions need to be taken to exclude air or moisture from the reaction mixture, and the method has been validated on two very different polymer supports. Preliminary results demonstrate that the dienes can be employed in a subsequent Diels–Alder reaction. Results of Diels–Alder reactions, preparation of a combinatorial library, and biological assay of the bicyclic peptidomimetics will be reported in due course.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 500 at 500 and 125.8 MHz, respectively, referenced to the appropriate solvent signal ($CDCl_3$, 7.26/77.00 ppm; acetone-d_6, 2.05 ppm; CD_3OD, 3.31 ppm; DMSO-d_6, 2.54 ppm; CD_3CN, 1.94 ppm). Mass spectra were obtained by electrospray ionization. Elemental analysis was performed by Galbraith Laboratories, Inc., Knoxville, TN. Where applicable, reactions were monitored by analytical TLC on glass precoated with silica gel $60F_{254}$. Flash chromatography used E. Merck silica gel 60 (230–400 mesh). Solid-phase reactions employing the Wang resin were carried out in plastic disposable syringes of the appropriate size, fitted with a polypropylene frit to retain the resin.

Materials. All reagents were obtained from Aldrich or Fluka, with the exception of the Wang resin which was purchased from Advanced Chemtech. THF and Et_2O were distilled from sodium benzophenone ketyl under a nitrogen atmosphere, CH_2Cl_2 from $CaCl_2$, and MeOH from $Mg(OMe)_2$.

Wittig/Horner–Wadsworth–Emmons Reagents. 2-(Diethylphosphono)ethan-1-amide-Ala-Gly-OPEG-OCH_3 (4). H_2N-Ala-Gly-OPEG-OCH_3 (**3**) (5.14 g, 1.00 mmol), diethylphosphonoacetic acid (0.241 mL, 1.50 mmol, 1.5 equiv), PyBOP (0.781 g, 1.50 mmol, 1.5 equiv), and HOBt·H_2O (0.230, 1.50 mmol, 1.5 equiv) were dissolved in DMF (30 mL), and *N*-methylmorpholine (0.220 mL, 2.00 mmol, 2.0 equiv) was added. After being stirred overnight, the reaction was poured into Et_2O and worked up as usual.

^{1}H NMR ($CDCl_3$): δ 7.24 (t, J = 5.5, 1H), 6.94 (d, J = 7.2, 1H), 4.52 (quint, J = 7.2, 1H), 4.26 (m, 2H), 4.2–4.1 (m, 4H), 4.08 (dd, J = 18.1,5.9, 1H, PEG), 3.95 (dd, J = 18.1,5.5, 1H, PEG), 3.8–3.45 (m, PEG), 3.36 (s, 3H, PEG), 2.88 (d, J = 20.6, 2H) [varies from sample to sample, is often 2.97 (dd, J = 20.6, 14.9, 1H), 2.90 (dd, J = 21.2, 14.7, 1H)], 1.41 (d, J = 7.2, 3H), 1.333 (t, J = 7.1, 3H), 1.326 (t, J = 7.1, 3H).

2-(Triphenylphosphonium bromide)ethan-1-amide-Ala-Gly-OPEG-OCH_3 (6). 2-Bromoethan-1-amide-Ala-Gly-OPEG-OCH_3 (**5**) (4.50 g, 0.855 mmol) and PPh_3 (2.25 g, 8.60 mmol, 10 equiv) were dissolved in CH_2Cl_2 (30 mL) and refluxed overnight. The reaction volume was reduced, and the remainder was poured into Et_2O. The precipitated product was filtered, rinsed with cold EtOH and Et_2O, dried, and then recrystallized from EtOH.

^{1}H NMR ($CDCl_3$): δ 9.63 (d, J = 8.4, 1H), 7.84–7.76 (m, 9H), 7.70–7.62 (m, 6H), 7.50 (t, J = 5.5, 1H), 5.12 (t, J = 14.9, 1H), 4.94 (t, J = 14.9, 1H), 4.34 (quint, J = 7.5, 1H), 4.23 (t, J = 5.0, 2H), 3.96 (dd, J = 17.9,6.1, 1H, PEG), 3.87 (dd, J = 17.9,5.7, 1H, PEG), 3.8–3.45 (m, PEG), 3.37 (s, 3H, PEG), 1.34 (d, J = 7.2, 3H).

4-(Diethylphosphono)but-2(*E*)-en-1-amide-Ala-Gly-OPEG-OCH_3 (9). H_2N-Ala-Gly-OPEG-OCH_3 (**3**) (2.30 g, 0.442 mmol), diethylphosphonocrotonic acid (0.241 mL, 1.50 mmol, 1.5 equiv), PyBOP (0.2345 g, 0.663 mmol, 1.5 equiv), and HOBt·H_2O (0.102, 0.663 mmol, 1.5 equiv) were dissolved in DMF (15 mL) and *N*-methylmorpholine (0.097 mL, 0.88 mmol, 2.0 equiv) was added. After being stirred overnight, the reaction was poured into Et_2O and worked up as usual.

^{1}H NMR ($CDCl_3$): δ 6.95 (t, J = 5.2, 1H), 6.77 (dq, J = 15.4,7.7, 1H), 6.45 (d, J = 7.2, 1H), 6.00 (dd, J = 15.4,5.0, 1H), 4.58 (quint, J = 7.2, 1H), 4.35–4.2 (m, 2H), 4.15–4.07 (m, 4H), 4.07 (dd, J = 18.1,5.9, 1H, PEG), 4.01 (dd, J = 18.1,5.4, 1H, PEG), 3.8–3.45 (m, PEG), 3.37 (s, 3H, PEG), 2.72 (dd, J = 22.6,7.7, 2H), 1.41 (d, J = 7.2, 3H), 1.31 (t, J = 7.2, 6H).

4-(Tri-*n*-butylphosphonium bromide)but-2(*E*)-en-1-amide-Ala-Gly-OPEG-OCH_3 (10). 4-Bromobut-2(*E*)-en-1-

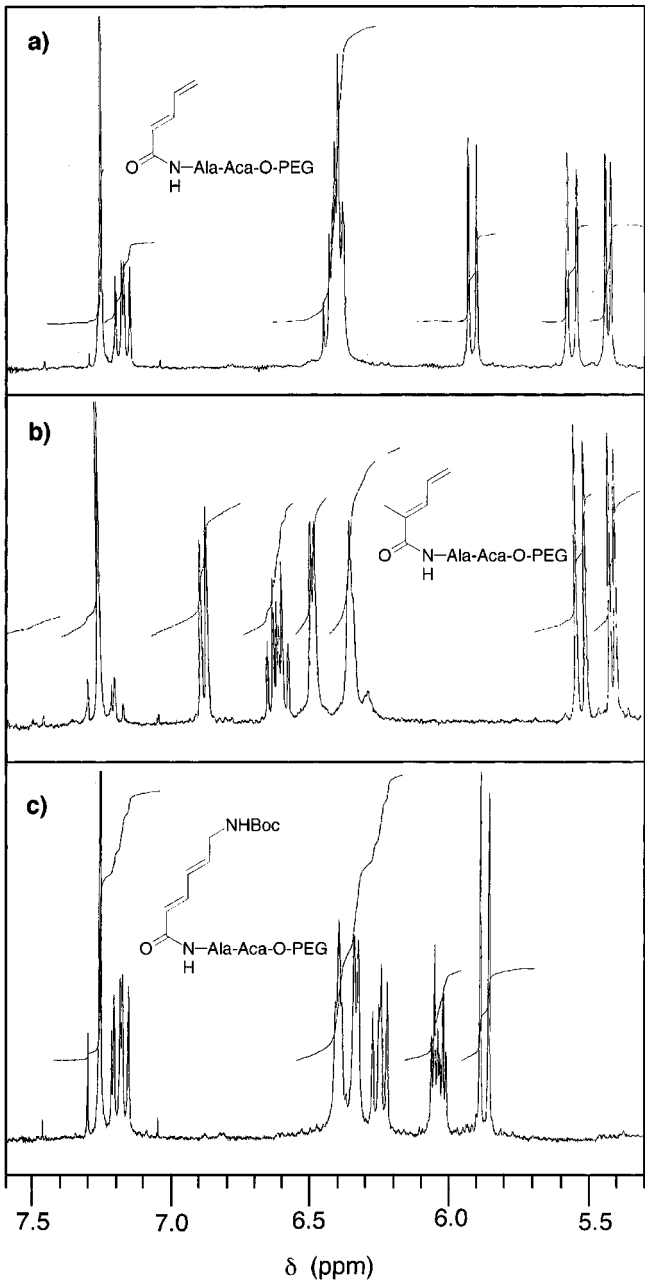


Figure 1. 500 MHz proton NMR spectra of alkene/amide region of $R^4R^3C{=}(R^2)CH{=}CHC(R^1)CONH$-Ala-Aca-OPEG-OMe in $CDCl_3$.

amide-Ala-Gly-OPEG-OCH_3 (**8**) (0.384 g, 0.0726 mmol) and tri-*n*-butylphosphine (0.036 mL, 0.145 mmol, 2 equiv) were refluxed in CH_2Cl_2 (10 mL) for 6 h and then poured into Et_2O and worked up as usual.

^{1}H NMR ($CDCl_3$): δ 7.96 (d, J = 7.2, 1H), 7.43 (t, J = 5.0, 1H), 6.70 (s, 2H), 4.55 (quint, J = 7.2, 1H), 4.3−4.15 (m, 2H), 4.1−3.9 (m, 2H), 3.76 (t, J = 5.0, 2H, PEG), 3.8−3.45 (m, PEG), 3.37 (s, 3H, PEG), 2.45−2.35 (br m, 6H), 1.6−1.45 (br m, 12H), 1.47 (d, J = 7.5, 3H), 0.97 (t, J = 6.9, 9H).

Standard Wittig/Horner−Wadsworth−Emmons Reaction Conditions. 4, **6**, **9**, or **10** (0.40 g, 0.075 mmol), LiBr (0.076 g, 0.875 mmol, 11.5 equiv), and THF (5 mL) were added to a 5 mL flame-dried round-bottom flask under Ar. After 5 min Et_3N (0.12 mL, 0.84 mmol, 11.0 equiv) was added, followed by the aldehyde (0.84 mmol, 11.0 equiv) after an additional 5 min. The reaction was stirred overnight; then H_2O and CH_2Cl_2 were added. The organic phase was separated, evaporated, taken up in acetone, and reevaporated, taken up in a minimum volume of DMF, poured into Et_2O, and worked up as usual.

General Procedure for Organostannane Synthesis. Method A. The heteroatom-containing (*E*)-1-stannylalk-1-enes, as well as the *t*-Bu and Ph-substituted products, were obtained by heating the appropriate alkyne (approximately 20 mmol), tri-*n*-butylstannane (0.95 equiv) and AIBN (0.05 equiv) to 100 °C over 3 h. After 12 h at 100 °C the product, a mixture of *E*-, *Z*-, and gem-substituted alkenylstannane, was purified by flash column chromatography (heteroatom-containing compounds) or distillation. The *Z* isomer generally coeluted with the gem isomer. This procedure was not successful for propiolic acid; the desired free acid was instead obtained by hydrolysis of the stannane derived from methyl propiolate.

Method B. (*E*)-1-(Tri-*n*-butylstannyl)-1-decene and 1-(tri-*n*-butylstannyl)-3-methoxy-1-propene were prepared by the method of Boden et al.[14] via the bromoalkyne.

Method C. (*Z*)-1-(Tri-*n*-butylstannyl)-1-decene was prepared by the method of Asao et al.[15]

Stille Coupling Reagents. 3-Bromoprop-2(*E*)-en-1-amide-Ala-Aca-OPEG-OCH_3 (14 R^1 = H, Xaa = Ala-Aca). H_2N-Ala-Aca-OPEG-OCH_3 (**13**) (11.2 g, 2.16 mmol) was dissolved in DMF (50 mL), and a solution of 3-bromoprop-2-en-1-oic acid (0.652 g, 4.32 mmol, 2.0 equiv) and diisopropylcarbodiimide (0.676 mL, 4.32 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL), preactivated for 10 min and filtered, was added. After reaction overnight the solution was poured into Et_2O and worked up as usual.

^{1}H NMR ($CDCl_3$): δ 7.45 (d, J = 13.7, 1H), 6.66 (d, J = 7.6, 1H), 6.56 (d, J = 13.4, 1H), 6.39 (t, J = 5.5, 1H), 4.44 (quint, J = 7.2, 1H), 4.20 (dd, J = 5.5,4.0, 2H, PEG), 3.8−3.45 (m, PEG), 3.36 (s, 3H, PEG), 3.22 (m, 2H), 2.32 (t, J = 7.2, 2H), 1.62 (br quint, J = 7.4, 2H), 1.49 (br quint, J = 7.3, 2H), 1.36 (d, J = 6.9, 3H), 1.32 (br quint, J = 7.5, 2H).

3-Bromo-2-methylprop-2(*E*)-en-1-amide-Ala-Aca-OPEG-OCH_3 (14, R^1 = Me, Xaa = Ala-Aca). H_2N-Ala-Aca-OPEG-OCH_3 (**13**) was coupled with 3-bromo-2-methylprop-2-en-1-oic acid using DIC as described above.

^{1}H NMR ($CDCl_3$): δ 7.21 (q, J = 1.1, 1H), 6.59 (d, J = 6.9, 1H), 6.24 (t, J = 5.2, 1H), 4.47 (quint, J = 7.1, 1H), 4.20 (t, J = 4.6, 2H, PEG), 3.8−3.45 (m, PEG), 3.36 (s, 3H, PEG), 3.25−3.15 (m, 2H), 2.33 (t, J = 7.4, 2H), 2.01 (d, J = 1.1, 3H), 1.62 (br quint, J = 7.5, 2H), 1.51 (br quint, J = 7.3, 2H), 1.38 (d, J = 6.9, 3H), 1.33 (br quint, J = 7.6, 2H).

3-(Tri-*n*-butylstannyl)prop-2(*E*)-en-1-amide-Ala-Aca-OPEG-OCH_3 (15). H_2N-Ala-Aca-OPEG-OCH_3 (**13**) was coupled with 3-(tri-*n*-butylstannyl)prop-2-en-1-oic acid using DIC as described above.

^{1}H NMR ($CDCl_3$): δ 7.50 (d, J = 19.1, 1H), 6.34 (t, J = 5.5, 1H), 6.26 (d, J = 7.2, 1H), 6.24 (d, J = 19.1, 1H), 4.43 (quint, J = 7.0, 1H), 4.21 (dd, J = 5.5, 4.0, 2H, PEG), 3.8−3.45 (m, PEG), 3.36 (s, 3H, PEG), 3.3−3.2 (m, 2H), 2.31 (t, J = 7.4, 2H), 1.62 (br quint, J = 7.4, 2H), 1.55−1.45 (m, 8H), 1.38 (d, J = 6.9, 3H), 1.35−1.30 (m, 2H), 1.28 (sex, J = 7.4, 6H), 0.93 (dd, J = 8.2, 8.2, 6H), 0.86 (t, J =7.2, 9H).

General Procedure for Stille Coupling: (1) On PEG Resin. Functionalized PEG resin **14** (0.400 g, 0.078 mmol), Pd_2dba_3 (7.2 mg, 0.0078 mmol, 0.1 equiv), and $AsPh_3$ (9.6 mg, 0.031 mol, 0.4 equiv) were dissolved in NMP, and the organostannane **16** (0.156 mmol, 2 equiv) was added by syringe. After being stirred overnight at rt, the reaction was poured into Et_2O and worked up as usual. Hindered reactions required more reagent (5−10 equiv of organostannane) and catalyst (0.2 equiv of palladium) with reaction at 60 °C (see text, Table 3 in Supporting Information).

(2) On Wang resin. A solution of Pd_2dba_3 and $AsPh_3$ in NMP (0.260 mL of a 0.01 mmol/mL of Pd_2dba_3, 0.04 mmol/mL of $AsPh_3$ solution, 0.0026 mmol of Pd_2dba_3, 0.1 equiv and 0.0104 mmol $AsPh_3$, 0.4 equiv; twice as much for hindered reactions) was added to functionalized Wang resin **14** (40 mg, 0.026 mmol), followed by the addition of organostannane **16** (0.052 mmol, 2 equiv; 5 or 10 equiv for hindered reactions) by syringe directly into the reaction solution. After agitation overnight at rt (60 °C for hindered reactions), the solvent was removed, and the resin rinsed with NMP (3×) and, alternately, MeOH and CH_2Cl_2 (3×) and then dried.

General Procedure for Cleavage. (1) From PEG Resin. PEG product **17** (0.040 mmol) was dissolved in 0.25 mL of dry CH_2Cl_2 and 2.0 mL of dry MeOH in a flame-dried flask under Ar. DBU (0.012 mL, 0.080 mmol, 2 equiv) was added, and the reaction was stirred overnight. The solution was evaporated to near dryness, dissolved in CH_2Cl_2, and purified directly by flash column chromatography. Alternatively, the deprotected PEG can be precipitated by addition of the cleavage solution to Et_2O, with column purification of the filtrate after evaporation, but yields were slightly lower.

3-(2′-Thiopheneyl)prop-2(*E*)-ene-1-amide-Arg(Pbf)-OCH$_3$ (18, R^1 = R^3 = H, R^2 = R^4 = -SCH=CH-, Xaa$_2$-Xaa$_1$ = Arg(Pbf)-Aca, R = Me). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, J = 15.3, 1H), 7.30 (br s, 1H), 7.29 (d, J = 5.0, 1H), 7.15 (d, J = 3.0, 1H), 7.00 (dd, J = 5.0, 3.8, 1H), 6.41 (d, J = 15.3, 1H), 6.33 (br s, 3H), 6.25 (vbr s, 1H), 4.62 (br s, 1H), 3.63 (s, 3H), 3.4−3.2 (m, 2H), 3.22 (m, 2H), 2.93 (s, 2H), 2.58 (s, 3H), 2.51 (s, 3H), 2.27 (t, J = 7.4, 2H), 2.08 (s, 3H), 1.89 (br m, 1H), 1.77 (m, 1H), 1.65−1.45 (m, 2H), 1.59 (br quint, J = 7.6, 2H), 1.52 (br quint, J = 7.3, 2H), 1.44 (s, 6H), 1.31 (br quint, J = 7.7, 2H). MS (ES$^+$): 690 (MH^+, 100), 337 ($MH^+ - 353$, 22), 273 ($MH^+ - 417$, 12), 229 ($MH^+ - 461$, 15), 146 ($MH^+ - 544$, 12). Anal. Calcd for CHNOS: C, 57.45; H, 6.87; N, 10.15; S, 9.29. Found: C, 57.52; H, 6.87; N, 9.90; S, 8.80.

(2) From Wang Resin: (a) As Methyl Ester. Wang resin **17** (10 mg, 0.0065 mmol) was treated with a solution of DBU (0.5 mL of 0.05 mmol/mL DBU in 1:1 MeOH:CH_2Cl_2, 0.025 mmol DBU, 4 equiv) overnight. The solution was removed from the resin, and the resin was rinsed with MeOH (1×) and CH_2Cl_2 (2×). The rinses were combined and evaporated to dryness, and the residue was taken up in CH_2Cl_2, which was then loaded on a short silica gel plug (0.5 g). The Ala-containing compounds were eluted with EtOAc and the Arg-(Pbf) compounds with 5:1 EtOAc:MeOH. The eluant was evaporated to dryness.

(b) As Free Acid. Wang resin **17** (10 mg, 0.0065 mmol) was treated with a solution of TFA:CH_2Cl_2:H_2O (0.5 mL of a 80:15:5 solution) for 1 h. The solution was removed from the resin, and the resin was rinsed with TFA solution (1×) and CH_2Cl_2 (2×). The rinses were combined and evaporated to dryness.

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Supporting Information Available: Tabulation of polymer-supported compounds prepared (Table 3), giving Stille coupling conditions and yields of cleaved dienes. Experimental procedures for the preparation of the resin-supported reagents. Lists of ^{1}H NMR data for PEG-supported compounds, ^{1}H and ^{13}C NMR data for organostannane reagents, and ^{1}H NMR and mass spectral data for the cleaved final products. NMR spectra of PEG-supported diene precursors (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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