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Stille Coupling of an Aziridinyl Stannatrane

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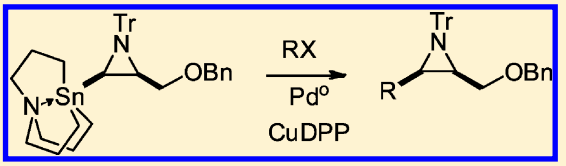
Supporting Information

ABSTRACT: An aziridinyl stannatrane **8** couples with aryl or alkenyl halides RX under modified Stille conditions to afford substituted aziridines. Efficient coupling at room temperature is possible in the best examples in the presence of $(^tBu_3P)_2Pd$ and $CuOP(O)Ph_2$ (CuDPP).



Recent reports have described the first examples of palladium-catalyzed cross-coupling of aziridine derivatives using modified Negishi activation procedures.[1] Since these advances were partly the result of exploiting re-optimized ligands for the palladium catalyst,[2] we were interested to know whether similar improvements are possible using the readily accessible 2-tributylstannyl aziridine **1**,[1a] thereby avoiding conversion to **2** and **3** as required for Negishi coupling (Figure 1). We also expected that a Stille procedure would provide a

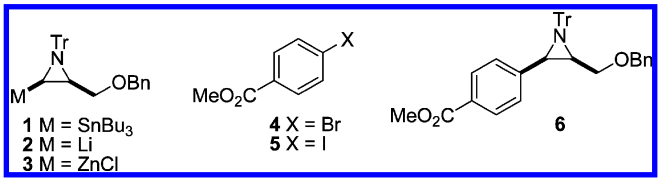


Figure 1. Metalated aziridines as potential coupling partners.

greater safety margin with respect to aziridine decomposition compared to the Negishi method. A preliminary survey of improved Stille conditions gave no hint of coupling between **1** and iodobenzene.[3−5] However, with the more reactive halo esters **4** and **5**, we did see low yields of the coupled product **6** in the presence of Cu salts (Table 1).[6−8] Attempts to improve the above experiments were not promising, but we were encouraged to see that aziridine transfer is possible from **1**, suggesting that the key transmetalation step involving the aziridinyl C−Sn bond is not beyond reach when copper salts are used along with the palladium source. Accordingly, we investigated a modified Stille coupling using a more strongly polarized stannatrane (more precisely, a trideoxastannatrane) derivative in place of **1** to improve C−Sn reactivity.[9] As outlined below, several cases were found where this approach allows efficient Stille cross-coupling to give substituted aziridines under mild conditions. We have also encountered cases where the substrates display unexpected reactivity.

Table 1. Attempted Coupling of 1 with 4 or 5

entry	ArX	conditions	yield of **6**
1	**4**	$Pd_2(dba)_3$/Sphos THF, reflux, 16 h	ND[a]
2	**4**	$Pd(^tBu_3P)_2$ (5%) PhMe, 100 °C, 20 h	trace[b]
3	**4**	$Pd(^tBu_3P)_2$ (5%) CuCN (10%)[3,6] PhMe, 100 °C, 20 h	21%[c]
4	**5**	$Pd(^tBu_3P)_2$ (5%) CuTC[e] (1 equiv)[4,5] DMF, rt, 16 h	trace[d]
5	**5**	$Pd(^tBu_3P)_2$ (5%) CuTC[e] (1 equiv)[5,7] THF, 50 °C, 16 h	10%[d]
6	**5**	$Pd(^tBu_3P)_2$ (5%) CuDPP[g] (1.5 equiv)[8] THF, 50 °C, 16 h	ND[f]

[a]Coupling product not detected by NMR assay. [b]31% $C_6H_5CO_2Me$ isolated. [c]54% of $C_6H_5CO_2Me$ isolated. [d]10% $C_6H_5CO_2Me$ isolated. [e]CuTC = Cu(I) thiophenecarboxylate. [f]90% of aziridine **1** recovered. [g]CuDPP = $CuOP(O)Ph_2$.

Preparation of the key stannatrane **8** began with standard tin−lithium exchange from **1** to the lithioaziridine **2**,[1,10] followed by reaction with the chlorodeoxastannatrane **7** (Scheme 1).[9] According to characteristic NMR signals due to the aziridine CH adjacent to Sn (^1H δ 0.63 ppm, doublet, J = 7.0 Hz), this procedure gave **8** *in situ*. However, attempts to purify **8** by chromatography on silica gel were not successful due to conversion into **9** by protodestannylation. This behavior was somewhat unexpected because analogous stannatranes containing an exocyclic sp^3 hybridized Sn−C bond survive chromatography.[9] Evidently, the increased *s*-character in the Sn−C bond due to the strained ring together with the adjacent nitrogen electron pair are responsible for the relatively greater polarization in the Sn−C bond of **8**. At the extreme, such an effect might induce carbenoid generation by α-elimination and/or conversion to dimeric alkenes as observed by Hodgson et al. in the case of lithiated aziridines at −78 to 0 °C.[11] However, crude **8** was quite stable under inert conditions and survived refluxing toluene over 2 days. None of the unusual decomposition products previously encountered in Negishi coupling using the chlorozinc derivative **3** were observed in the course of the present study.

Undesired protodestannylation during attempted purification of **8** raised concerns about Stille applications because the crude reagent contains Bu_4Sn as the byproduct of tin−lithium exchange. However, **8** was expected to have considerably higher metal exchange reactivity compared to that of Bu_4Sn due to the effect of transannular nitrogen lone pairs,[9] the same

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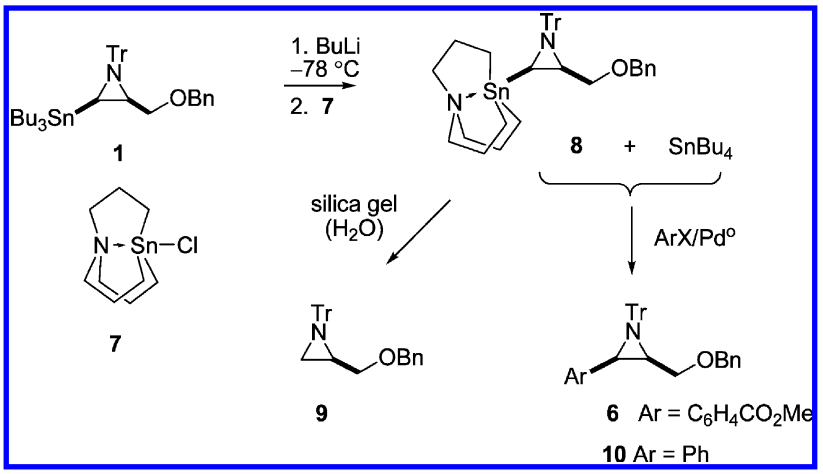
Scheme 1.



effect that is partly responsible for the surprisingly facile protodestannylation of **8**. Modified Stille cross-coupling reactions were therefore conducted using unpurified **8**, prepared from 1.5 equiv of **1** for each equivalent of the intended halide coupling substrate. For purposes of characterization, **8** could be separated from nearly all of the byproducts by thin layer chromatography on neutral alumina, but fortunately, this level of purity was not necessary for successful Stille coupling.

Procedures were initially evaluated with aryl halides **4** and **5** and conventional palladium sources. However, 5 mol % $Pd(PPh_3)_2Cl_2$ or $Pd(CH_3CN)_2Cl_2$ in DMF at room temperature or $Pd_2(dba)_3$/RuPhos in DMF at 80 °C gave no detectable coupling product **6**. On the other hand, heating **5** and **8** in DMF with 5 mol % $Pd(PPh_3)_2Cl_2$ did afford substantial coupling product **6** (Table 2, entry 1), and

Table 2. Modified Stille Coupling of 8 with ArX[a]

entry	Ar-X	reagents	*T*, *t*	product
1	**5**	$Pd(PPh_3)_2Cl_2$ (5%) DMF	100 °C, 16 h	**6** (40%)
2	**5**	$(allyl\text{-}PdCl)_2$ (5%) CH_3CN	rt, 20 h	**6** (10%)
3	**4**	$Pd(dppf)Cl_2$ (5%) PhMe	110 °C, 10 h	**6** (15%)
4	**5**	$Pd(^tBu_3P)_2$ (5%)[12] PhMe	100 °C, 16 h	**6** (20%)
5	**5**	$Pd(^tBu_3P)_2$ (5%) CuI (10%) DMF	rt, 20 h	**6** (46%)
6	**5**	$Pd(^tBu_3P)_2$ (5%)CuDPP (150%)[8] THF	rt, 24 h	**6** (50%)
7	**5**	$Pd(^tBu_3P)_2$ (5%) CuDPP (150%)[8] DMF	rt, 4 h	**6** (90%)
8	**4**	$Pd(^tBu_3P)_2$ (5%) CuDPP (150%)[8] DMF	rt, 4 h	**6** (85%)
9	PhI	$Pd_2(dba)_3$ (5%) $(2\text{-Furyl})_3P$ (10%)[13] DMF	80 °C, 20 h	**10** (20%)
10	PhI	$Pd(^tBu_3P)_2$ (5%) CuDPP (150%)[8] DMF	rt, 4 h	**10** (90%)

[a]Exploratory experiments using 50 mg crude **8** and aryl halide as limiting reagent.

indications of aziridine coupling at room temperature were observed with allylpalladium chloride in acetonitrile (entry 2). Further optimization revealed that experiments conducted in the presence of copper additives were more promising (entry 4 vs entries 5−7), and the best results were seen with Cu(I) diphenylphosphinite (CuDPP) in DMF (entries 7, 8, 10).[8] Although this copper additive was introduced by Liebeskind et al. primarily for palladium-catalyzed cross-coupling reactions with thioesters,[8a] it was also shown to be effective in palladium-free coupling applications between allylic phosphinites and Bu_3SnR (R = sp^2-hybridized carbon) in an earlier thesis from the same group.[8b] Metal exchange (Sn to Cu) as well as a tin scavenging role were invoked for the CuDPP additive.[8b,c] In our aziridine system, CuDPP proved to be an excellent copper source in modified Stille reactions of the aziridinyl stannatrane **8** with aryl halides as coupling partners in the presence of palladium. Thus, a ca. 10−20% increase in product yields was observed in the optimized simple examples of Table 2 (entries 7, 8, 10) versus our prior study using the Negishi coupling of **3** with the same aryl halides. Most of the data points in Table 2 were obtained using 50 mg of crude **8**, but entry 7 was also tested on a ca. 0.5 g scale, resulting in similar yields of **6** (80% with iodide **5** as limiting reagent; 85% with **8** as limiting reagent). Also important, the best CuDPP/DMF conditions allowed cross-coupling at room temperature, a key feature for synthetic applications involving potentially sensitive functional environments.

The $Pd(^tBu_3P)_2$/CuDPP conditions were applied to several more highly functionalized substrates with surprising results (Scheme 2). The coupling of **8** with the *Z*-iodoacrylate ester **11** proceeded smoothly to give **12** (85%). However, the same conditions applied to vinyl bromide afforded a second product in addition to the expected **13**. Based on the HRMS and NMR data, the second product was assigned the alkene structure **14**, corresponding to dimerization of the aziridine subunit. We did not investigate the dimerization pathway at the mechanistic level, but control experiments established that formation of **14** is independent of palladium. Thus, reaction of **8** with CuDPP (1 equiv, DMF, 16 h) in the absence of halide substrate or palladium source gave the same alkene **14**, a finding that implicates metal exchange between **8** and CuDPP as the initiating event leading to **14**.[11] The undesired dimerization did not interfere in the case of the iodoacrylate coupling to **12**, presumably because the Stille pathway is relatively fast. On the other hand, **14** was detected in the crude product mixture obtained from the Stille coupling of the iodobenzoate **5** with **8** and may also be formed as a minor byproduct in some of the other examples of Table 2.

Given the modest yield of vinyl aziridine **13** obtained using CuDPP, we also explored an alternative procedure using CuI/CsF[4] as the copper source (conditions B, Scheme 2). This

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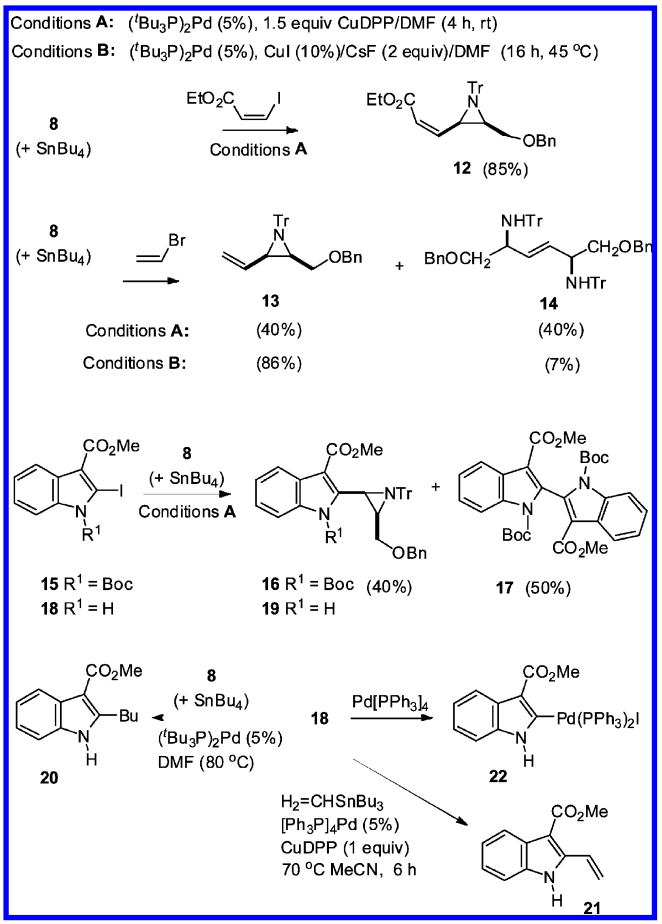
Scheme 2



alternative is less desirable for applications of interest in our laboratory where survival of silicon-based protecting groups is essential. However, the procedure worked very well in the case of the simple Stille coupling of **8** with vinyl bromide, resulting in 86% of the vinylated product **13**.

Complications were also encountered with the iodoindole substrate **15**, which reacted with **8** to afford the expected **16** as the minor product (40%) along with the bis-indole **17** (50%; Table 3, entry 4). In this case, the palladium-free control experiment gave 40% conversion to **17** upon treatment of **15** with CuDPP (1 equiv) in DMF at rt (16 h), along with 55% of recovered **15**. Thus, copper–iodide exchange appears to trigger the formation of the bis-indole **17** from **15**.[14] Therefore, we attempted to couple **15** with **8** using a copper-free procedure at 60 °C in toluene with $(^tBu_3P)_2Pd$ (conditions C). However, this gave no more than traces of coupling product **16**, recovery of unreacted **8**, and slow conversion to deiodo indole (**15** with H in place of I; entry 5). Significant dimerization was not observed.

Table 3. Scheme 2 and Scheme 3 Coupling Summary

entry	halide	conditions	products
1	$EtO_2CCHCHI$	A[a]	**12** (85%)
2	CH_2CHBr	A[a]	**13** (40%), **14** (40%)
3	CH_2CHBr	B[b]	**13** (86%)
4	**15**	A[a]	**16** (40%), **17** (50%)
5	**15**	C[c]	reductive deiodination
6	**18**	A[a]	**9** (10%), **14** (75%)[d]
7	**18**	A[a,e]	**20** (85%)
8	**18**	C[c]	**19** (30%)
9	**23**	A[a]	**25** (33%), **14** (60%)
10	**23**	B[b]	**24** (63%), **14** (20%)
11	**23**	C[c]	**24** (63%)[f]

[a]Conditions A: $Pd(^tBu_3P)_2$ (5%), CuDPP (150%), rt, DMF. [b]Conditions B: $Pd(^tBu_3P)_2$ (5%), CuI (10%)/CsF (200%), 45 °C, DMF. [c]Conditions C: $Pd(^tBu_3P)_2$ (5%), 60–65 °C, PhMe. [d]90% of **18** recovered. [e]Reaction at 80 °C. [f]Unreacted **8** (35%) was also recovered.

In view of the unexpected dimer formation from the *N*-Boc-iodoindole **15**, the standard $Pd(^tBu_3P)_2$/CuDPP cross-coupling procedure was attempted with the simpler N–H substrate **18**. However, the desired **19** was not detected, and nearly all of **18** was recovered (90%), along with the protodestannylated aziridine **9** (10%) as well as the dimeric alkene **14** (75%). Accordingly, we tested the coupling of **8** with **18** in the absence of the copper additive CuDPP in DMF at 80 °C, but the only coupling product proved to be the butylated indole **20** (ca. 85%),[15] resulting from Stille coupling by the Bu_4Sn byproduct present in solutions of **8** (entry 7). This experiment also returned ca. 90% of **9** from protodestannylation of **8**. Eventually, it was found that the desired coupling product **19** does form under copper-free conditions at 60 °C in the presence of 5 mol % of $(^tBu_3P)_2Pd$ in anhydrous toluene (conditions C; entry 8). Although **19** was the major product, 10–20% of **9** was still formed along with other products,[16] suggesting that the indole NH is partly responsible for conversion of **8** to **9**.

The reasons for lack of cross-coupling reactivity between N–H indole **18** and **8** were initially puzzling. We therefore tested the reactivity of **18** in a more conventional Stille reaction with $Bu_3SnCH{=}CH_2$ in the presence of 5 mol % $Pd[PPh_3]_4$ and CuDPP at 70 °C. No lack of reactivity was found, and the expected vinylation product **21** was isolated in 90% yield. During the coupling experiment, precipitation of an intermediate palladium complex was observed. To obtain larger quantities of the complex, **18** was reacted with 1.15 equiv of $Pd[PPh_3]_4$ at 70 °C in the absence of CuDPP or stannane. This gave an intermediate complex identified as the novel indolylpalladium iodide **22** (97%).[17] Evidently, this species reacts normally in the Stille coupling with $Bu_3SnCH{=}CH_2$. However, attempts to couple **22** with the aziridinyl stannatrane **8** resulted in destruction of **8** and recovery of **22** but gave no products of cross-coupling. Taken together, the above experiments suggest that small differences in the substrate-dependent rates of Stille coupling versus the rates of competing side reactions are important factors in the indole series. However, coupling does occur under conditions C, and the dependence of yield on substrate and procedure offers broad opportunities for optimization.

With a better understanding of the empirical parameters and possibilities, the one additional substrate **23** was explored to evaluate survival of a silyl ether protecting group in various coupling procedures. As expected, coupling of **8** with **23** under conditions B gave desilylated product **24** (63%) along with ca. 20% of the dimeric alkene **14** (Scheme 3, eq 1; Table 3, entry 10). Conditions A did afford the desired silyl ether **25** (33%), but the major product (60%) was **14**. Apparently, the Stille coupling with the relatively electron-rich substrate **23** is slower compared to the copper-mediated dimerization pathway from **8**. Fortunately, this complication could be minimized by using the copper-free method (conditions C) to give **25** in 63% yield (eq 2; Table 3, entry 11).

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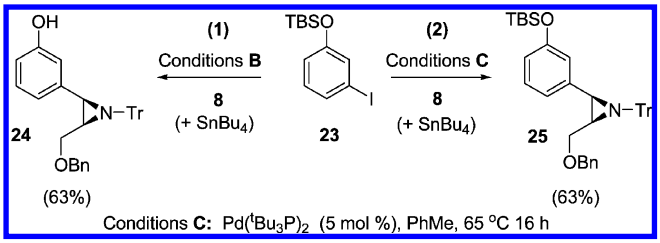
Scheme 3



Overall, the combination of aziridine **8** and the CuDPP method (conditions A) works over a range of substrates and holds promise for coupling applications of aziridines with valuable halides. The combined effects of stannatrane and copper salt activation allow coupling at room temperature. However, the stannatrane effect alone is sufficient in cases where the reactants and products are sensitive to Cu additives but can tolerate heating to ca. 60–80 °C. For substrates containing silicon protecting groups, it would be advisable to evaluate the copper-free procedure at 60 °C (conditions C) as well as conditions A. The alternative procedure using CuI/CsF as the copper source was not tested extensively (conditions B) but is available for those applications where dimerization of the aziridine subunit interferes due to marginal halide reactivity. All of these procedures benefit from the unique Stille coupling reactivity of the deoxastannatrane substituent in an aziridine environment.[18]

EXPERIMENTAL SECTION

Unless otherwise noted, all reagents were used as received. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl, and toluene was distilled over CaH_2 prior to use in the reactions. Commercial copper diphenylphosphinate (CuDPP) was used as received. All reactions were performed under an N_2 atmosphere and in oven-dried glassware unless otherwise stated. TLC analysis was performed on Whatman 0.25 mm K6F silica gel 60 Å plates, visualized with the aid of UV light or an appropriate stain ($KMnO_4$ or I_2). Flash chromatography was accomplished using Silicycle Silica Gel: SiliaFlash P60, 40–63 μm, 60 Å. High-resolution mass spectra were recorded on a mass spectrometer with a time-of-flight (TOF) mass analyzer.

[(2*R*,3*R*)-2-(Benzyloxymethyl)-1-tritylaziridin-2-yl]deoxastannatrane (8). *n*-BuLi (0.48 M in hexanes, 2.25 mL, 1.07 mmol) was added dropwise to the solution of (2*S*,3*R*)-2-(benzyloxymethyl)-3-(tributylstannyl)-1-tritylaziridine[1a] (0.68 g, 0.98 mmol) in dry THF (15 mL) at −60 °C. This reaction mixture was slowly warmed to −30 °C over a period of 30 min (an initial clear solution becomes a red solution). At this time, the reaction mixture was cooled to −78 °C, and a solution of chlorodeoxastannatrane **7**[9] (0.32 g, 1.04 mmol) in THF (5 mL) was added to it via cannula. After 10 min of stirring at −78 °C the acetone–dry ice bath was removed, and the solution warmed to room temperature. After stirring at rt for 1 h, the reaction mixture was concentrated, and the residue obtained was dissolved in ethyl acetate (50 mL). This solution was washed with water, and the organic layer was dried ($MgSO_4$) and concentrated to give 0.95 g (96%) of viscous material containing an equimolar mixture of tetrabutyltin and aziridinyl stannatrane **8** according to NMR assay. For characterization purposes, a small amount of crude product was purified by analytical TLC on neutral alumina, 5% ethyl acetate in hexanes, R_f = 0.8 and 0.5 for tetrabutyltin and aziridinyl stannatrane **8**, respectively. $[\alpha]^{20}_D$ = −16.4 (*c* 1.6, $CHCl_3$); HRMS-ES$^+$ (*m*/*z*) [M + H] calcd for $C_{38}H_{45}N_2OSn$, 665.2554, found 665.2550; IR (film, cm^{-1}) 2925, 1490; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.53 (bd, *J* = 7.5 Hz, 6H), 7.38–7.19 (m, 14H), 4.50 (s, 2H), 3.76 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.46 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.49–2.36 (m, 6H), 1.75–1.63 (m, 6H), 1.45–1.41 (m, 1H), 0.86–0.82 (m, 3H), 0.71–0.67 (m, 3H), 0.63 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 145.0, 138.5, 129.7, 128.2, 127.9, 127.4, 126.9, 126.1, 75.1, 74.4, 73.2, 55.0, 35.2, 29.5, 23.4, 7.8.

Methyl 4-[(2*R*,3*R*)-3-(benzyloxymethyl)-1-tritylaziridin-2-yl]-benzoate (6). *Aryl Halide As Limiting Reagent, Preparative Scale.* In a 100 mL, oven-dried, single-neck round bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed crude aziridinyl stannatrane **8** (0.56 g, 0.85 mmol estimated by NMR assay), methyl 4-iodobenzoate (**5**, 0.147 g, 0.563 mmol), CuDPP (0.24 g, 0.85 mmol), and Pd(^{t}Bu$_3$P)$_2$ (0.014 g, 0.003 mmol) inside the glovebox. This mixture was flushed with a stream of N_2 and dissolved in dry DMF (50 mL). The resulting solution was stirred at rt with monitoring for completion of reaction (4 h). The reaction mixture was diluted with ethyl acetate (100 mL) and water (100 mL). The layers were separated, and the organic layer was washed with water (3 × 20 mL), dried ($MgSO_4$), and concentrated. Silica gel chromatography (10% ethyl acetate in hexanes) afforded 0.24 g (80%) of **6** as clear oil, identified by NMR comparison with the reported data.[1a] $[\alpha]^{20}_D$ = −70.0 (*c* 1.1, $CHCl_3$); HRMS-ES$^+$ (*m*/*z*) [M + H] calcd for $C_{37}H_{34}NO_3$, 540.2539, found 540.2535; IR (neat, cm^{-1}) 3020, 1725; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 7.0 Hz, 6H), 7.29–7.16 (m, 13H), 6.90 (dd, *J* = 7.5 Hz, 2.5 Hz, 2H), 4.18 (d, *J* = 12.0 Hz, 1H), 4.11 (d, *J* = 12.0 Hz, 1H), 3.96 (s, 3H), 3.85 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.36 (dd, *J* = 10.2, 8.0 Hz, 1H), 2.54 (d, *J* = 6.4 Hz, 1H), 1.95 (ddd, *J* = 7.7, 6.5, 4.3 Hz, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 167.1, 143.9, 142.8, 137.8, 129.5, 129.3, 128.2, 128.0, 127.9, 127.5, 127.3, 126.8, 75.4, 72.8, 66.9, 52.1, 39.1, 38.9.

*Aziridinyl Stannatrane **8** as Limiting Reagent, Preparative Scale.* In a similar procedure, aziridinyl stannatrane **8** (0.56 g, 0.85 mmol), methyl 4-iodobenzoate (**5**, 0.33 g, 1.27 mmol), CuDPP (0.24 g, 0.85 mmol), and Pd(^{t}Bu$_3$P)$_2$ (0.032 g, 0.063 mmol) were combined as before and stirred at rt (4 h). The same workup and purification afforded 0.39 g (85%) of **6** as clear oil having the same spectroscopic characteristics.

General Procedure for Small Scale Coupling (Scheme 2 and Table 3); Preparation of 6 Using Conditions A. In a 25 mL, oven-dried, single-neck round bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed aziridinyl stannatrane **8** (0.05 g, 0.05 mmol), methyl 4-bromobenzoate (0.007 g, 0.033 mmol), CuDPP (0.014 g, 0.05 mmol), and Pd(^{t}Bu$_3$P)$_2$ (0.001 g, 0.002 mmol) inside the glovebox. This mixture was flushed with a stream of N_2 and dissolved in dry DMF (3 mL). The resultant solution was stirred at rt while monitoring for completion of reaction (typically 4 h). The reaction mixture was diluted with ethyl acetate (20 mL) and water (15 mL). The layers were separated and the organic layer was washed with water (3 × 10 mL), dried ($MgSO_4$), and concentrated. Silica gel chromatography (10% ethyl acetate in hexanes) afforded 0.015 g (85%) of **6** as clear oil, identical to the material described above.

(2*R*,3*R*)-2-(Benzyloxymethyl)-3-phenyl-1-tritylaziridine (10). Conditions A with **8** (0.055 g, 0.054 mmol) and PhI (0.007 g, 0.036 mmol); silica gel chromatography afforded 0.015 g (90%) of **10**.[1a]

(*Z*)-Ethyl 3-[(2*R*,3*R*)-3-(Benzyloxymethyl)-1-tritylaziridin-2-yl]acrylate (12). Conditions A with **8** (0.053 g, 0.050 mmol) and ethyl (Z)-3-iodoacrylate (0.007 g, 0.033 mmol); silica gel chromatography afforded 0.013 g (85%) of **12**.[1a]

(2*R*,3*R*)-2-(Benzyloxymethyl)-1-trityl-3-vinylaziridine (13) and Dimeric Byproduct 14. Conditions A with **8** (0.100 g, 0.099 mmol) and vinyl bromide (1.0 M solution in THF, 0.066 mL, 0.066 mmol); silica gel chromatography afforded 0.011 g (40%) of **13** and 0.011 g (40%) of **14** as a white solid. Analytical TLC, 5% ethyl acetate in hexanes, R_f = 0.6 and 0.3 for compounds **13**[1a] and **14** respectively; (2*R*,5*S*,*E*)-1,6-bis(benzyloxy)-N^2,N^5-ditritylhex-3-ene-2,5-diamine (**14**), mp 132–134 °C; $[\alpha]^{20}_D$ = −97.13 (*c* 1.1, $CHCl_3$); HRMS-ES$^+$ (*m*/*z*) [M + H] calcd for $C_{58}H_{55}N_2O_2$, 811.4264, found 811.4254; IR (neat, cm^{-1}) 3332, 3028, 2925, 1492, 1448; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.54 (bd, *J* = 7.5 Hz, 10H), 7.29–7.13 (m, 30 H), 5.53 (dd, *J* = 3.5, 1.5 Hz, 2H), 4.17, 4.13 (ABq, *J* = 12.0 Hz, 4H), 3.16–3.12 (m, 2H), 2.89 (dd, *J* = 9.0, 5.0 Hz, 2H), 2.35 (dd, *J* = 9.5, 5.5 Hz, 2H), 2.19 (bs, exchangeable, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ

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147.0, 138.5, 132.0, 128.9, 128.2, 127.6, 127.5, 127.4, 126.1, 73.2, 72.6, 71.1, 54.0; sample contaminated with benzene (128.3).

Preparation of 13 Using Scheme 2 Conditions B. In a 25 mL, oven-dried, single-neck round bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed aziridinyl stannatrane **8** (0.070 g, 0.069 mmol), vinyl bromide (1.0 M solution in THF, 0.14 mL, 0.14 mmol), CuI (0.001 g, 0.007 mmol), CsF (0.021 g, 0.14 mmol), and $Pd(^tBu_3P)_2$ (0.002 g, 0.003 mmol) inside the glovebox. This mixture was flushed with a stream of N_2 and dissolved in dry DMF (5.0 mL). The resultant solution was stirred at 45 °C in an oil bath with monitoring for completion of reaction (ca. 16 h). The reaction mixture was worked up as describe for conditions A, and silica gel chromatography (10% diethyl ether in hexanes) afforded 0.026 g (86%) of **13**.[1a]

Methyl 1-(*tert*-Butoxycarbonyl)-2-[(2*S*,3*R*)-3-(benzyloxymethyl)-1-tritylaziridine-2-yl]-indole-3-carboxylate (16) and Dimeric Indole 17. Conditions A were used with aziridinyl stannatrane **8** (0.050 g, 0.050 mmol) and 2-iodoindole **15**[1a] (0.013 g, 0.033 mmol). Silica gel chromatography (10% ethyl acetate in hexanes) afforded 0.008 g (40%) of coupled product **16**[1a] as an oil and 0.004 g (50%) of dimer **17** as a white solid, analytical TLC, 10% ethyl acetate in hexanes, R_f = 0.5 and 0.3 for compounds **16** and **17**, respectively; 1,1′-di-*tert*-butyl 3,3′-dimethyl 1*H*,1′*H*-[2,2′-biindole]-1,1′,3,3′-tetracarboxylate (**17**): mp 182−184 °C; HRMS-ES$^+$ (*m*/*z*) [M + H] calcd for $C_{30}H_{33}N_2O_8$, 549.2237, found 549.2226; IR (film, cm^{-1}) 1741, 1711; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33 (bd, *J* = 7.5 Hz, 2H), 8.20 (bd, *J* = 7.6 Hz, 2H), 7.44−7.35 (m, 4H), 3.65 (s, 6H), 1.17 (s, 18H); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 164.2, 148.9, 136.1, 135.7, 126.7, 125.5, 123.9, 121.7, 115.4, 112.5, 84.3, 51.5, 27.4.

Control Experiment; Indole 15 Dimerization. In a 25 mL, oven-dried, single-neck round bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 2-iodoindole **15** (0.057 g, 0.142 mmol) and CuDPP (0.040 g, 0.142 mmol) in dry DMF (4.0 mL) under nitrogen, and the mixture was stirred at rt for 16 h. Workup and chromatography as usual afforded 0.016 g (41%) of **17** as white solid and 0.031 g (55%) of unreacted 2-iodoindole **15**; analytical TLC, 10% ethyl acetate in hexanes, R_f = 0.5 and 0.4 for **15** and **17**, respectively.

Methyl 2-((2*S*,3*R*)-3-((Benzyloxy)methyl)-1-tritylaziridin-2-yl)-1*H*-indole-3-carboxylate (19) [Conditions C]. In a 25 mL, oven-dried, single-neck round bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 2-iodoindole **18**[19] (0.012 g, 0.040 mmol), aziridinyl stannatrane **8** (0.100 g, 0.100 mmol), and $Pd(^tBu_3P)_2$ (0.001 g, 0.002 mmol) inside the glovebox. This flask was connected to a reflux condenser and flushed with a stream of N_2 for 5 min. Anhydrous toluene (5.0 mL) was added to the above mixture via syringe, and the resultant brown solution was heated at 60 °C in an oil bath for 16 h. The reaction mixture was cooled to rt and filtered over a small pad of Celite, and the filtrate was concentrated to give a dark residue. Silica gel chromatography (20% ethyl acetate in hexanes) afforded 0.007 g (30%) of **19** as clear oil. Analytical TLC, 20% ethyl acetate in hexanes, R_f = 0.6; $[\alpha]^{20}_D$ = −89.43 (*c* 0.6, $CHCl_3$); HRMS-ES$^+$ (*m*/*z*) [M + H] calcd for $C_{39}H_{35}N_2O_3$, 579.2648, found 579.2639; IR (neat, cm^{-1}) 3332, 3035, 2918, 1693, 1669, 1450; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.46 (bs, exchangeable, 1H), 8.17−8.12 (m, 1H), 7.50−7.47 (m, 6H), 7.29−7.16 (m, 15H), 7.12−7.06 (m, 2H), 4.37, 4.31 (ABq, J_{AB} = 11.9 Hz, 2H), 3.77 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.76 (s, 3H), 3.62 (d, *J* = 6.5 Hz, 1H), 3.56 (dd, *J* = 10.9, 5.9 Hz, 1H), 2.13 (ddd, *J* = 8.0, 6.2, 4.1 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 165.8, 143.6, 143.2, 137.5, 134.3, 129.5, 128.4, 128.3, 127.7, 127.5, 127.1, 122.7, 121.7, 121.3, 111.1, 106.5, 75.4, 72.9, 67.7, 50.7, 40.1, 33.5; one carbon signal is not resolved between 130 −125 ppm due to overlapping chemical shifts.

Attempted Coupling of 18 with 8; Methyl 2-*n*-Butyl-1*H*-indole-3-carboxylate (20) and Protodestannylated Aziridine 9. In a 25 mL, oven-dried, single-neck round bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 2-iodoindole **18**[19] (0.011 g, 0.037 mmol), aziridinyl stannatrane **8** (0.054 g, 0.054 mmol), and $Pd(^tBu_3P)_2$ (0.001 g, 0.002 mmol) inside the glovebox. This flask was connected to a reflux condenser and flushed with a stream of N_2 for 5 min. Anhydrous DMF (4.0 mL) was added to above mixture via syringe, and the resultant clear solution was heated at 80 °C in an oil bath for 16 h. At this time, the reaction mixture was cooled to rt and diluted with ethyl acetate (30 mL) and water (20 mL). The layers were separated, and the organic phase was washed with water (3 × 10 mL), dried ($MgSO_4$), and concentrated. Silica gel chromatography (20% ethyl acetate in hexanes) afforded 0.007 g (85%) of **20** as a solid and 0.019 g (90%) of **9** as clear oil. Analytical TLC, 20% ethyl acetate in hexanes, R_f = 0.8, 0.6 for compounds **9** and **20**, respectively. Product **20** was identified by NMR comparison with reported data.[20] (*S*)-2-[(Benzyloxy)methyl]-1-tritylaziridine (**9**): $[\alpha]^{20}_D$ = −31.95 (*c* 1.1, $CHCl_3$); HRMS-ES$^+$ (*m*/*z*) [M + H] calcd for $C_{29}H_{28}NO$, 406.2171, found 406.2167; IR (film, cm^{-1}) 3020, 1580, 1495; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.36 (bd, *J* = 7.5 Hz, 5H), 7.34−7.20 (m, 15H), 4.53 (s, 2H), 3.86 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.54 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.74 (bd, *J* = 3.0 Hz, 1H), 1.58−1.54 (m, 1H), 1.20 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 144.5, 138.3, 129.5, 128.3, 127.7, 127.5, 127.4, 126.6, 73.7, 73.1, 72.9, 31.9, 25.7.

Methyl 2-Vinyl-1*H*-indole-3-carboxylate (21); Conventional Stille Coupling from 18. In a 25 mL, oven-dried, single-neck round bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 2-iodoindole **18**[19] (0.015 g, 0.050 mmol), tributyl(vinyl)tin (0.032 g, 0.100 mmol), tetrakis(triphenylphosphine) palladium (0.004 g, 0.003 mmol), and CuDPP (0.014 g, 0.050 mmol) inside the glovebox. This flask was connected to a reflux condenser and flushed with a stream of N_2 for 5 min. Anhydrous acetonitrile (5.0 mL) was added to above mixture via syringe, and the resultant green solution was heated at 70 °C in an oil bath for 6 h. The reaction mixture was cooled to rt and filtered over a small pad of Celite, and the filtrate was concentrated to give a green residue. Silica gel chromatography (20% ethyl acetate in hexanes) afforded 0.009 g (90%) of **21** as clear oil, identified by NMR comparison with the reported data.[21]

Bis(triphenylphosphine)(methyl 1-*H* indole-3-carboxylate-2-yl)palladium(II)iodide (22). In a 25 mL, oven-dried, single-neck round bottomed flask equipped with a magnetic stirring bar and a rubber septum were placed 2-iodoindole **18** (0.010 g, 0.033 mmol) and tetrakis(triphenylphosphine)palladium (0.044 g, 0.038 mmol) inside the glovebox. This flask was connected to a reflux condenser and flushed with a stream of N_2 for 5 min. Anhydrous acetonitrile (5.0 mL) was added to above mixture via syringe, and the resultant green solution was heated at 70 °C in an oil bath for 6 h. The suspension was allowed to cool to rt and removal (aspirator) of solvent gave a green solid. Chromatography (25% ethyl acetate in hexanes) gave 0.030 g (97%) of **22** as a bright yellow solid; analytical TLC, 25% ethyl acetate in hexanes, R_f = 0.4; mp >200 °C (decomposition); HRMS-ES$^+$ (*m*/*z*) [M − I] calcd for $C_{46}H_{38}NO_2P_2Pd$, 804.1413, found 804.1419; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.58−7.53 (m, 12H), 7.47 (bs, 1H), 7.44 (bd, *J* = 8.0 Hz, 1H), 7.28−7.21 (m, 6H), 7.17−7.13 (m, 12H), 6.80 (ddd, *J* = 8.0, 8.4, 0.8 Hz, 1H), 6.70 (ddd, *J* = 7.5, 8.0, 0.8 Hz, 1H), 6.60 (bd, *J* = 7.7 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 166.5, 139.5, 134.6 (t, $^2J_{C-P}$ = 6.5 Hz), 131.4 (t, $^2J_{C-P}$ = 23.9 Hz), 130.2, 130.1, 129.6, 127.7 (t, $^2J_{C-P}$ = 5.3 Hz), 119.1, 118.7, 111.1, 108.3, 50.1; ^{31}P NMR (161.7 MHz, $CDCl_3$, ppm) δ 20.3.

3-[(2*R*,3*R*)-3-((Benzyloxy)methyl)-1-tritylaziridin-2-yl]phenol (24). Following conditions B, aziridinyl stannatrane **8** (0.068 g, 0.067 mmol), *tert*-butyl(3-iodophenoxy)dimethylsilane **23**[22] (0.015 g, 0.045 mmol), CuI (0.001 g, 0.004 mmol), CsF (0.014 g, 0.089 mmol), and $Pd(^tBu_3P)_2$ (0.001 g, 0.002 mmol) were combined and dissolved in dry DMF (4 mL). After 16 h at 45 °C, the standard workup and chromatography (12% ethyl acetate in hexanes) afforded 0.005 g (20%) of **14** as a white solid and 0.014 g (63%) of **24** as clear oil; analytical TLC, 10% ethyl acetate in hexanes, R_f = 0.5, 0.2 for **14** and **24**, respectively. Data for **24**: $[\alpha]^{20}_D$ = −53.09 (*c* 0.61, $CHCl_3$); HRMS-ES$^+$ (*m*/*z*) [M + H] calcd for $C_{35}H_{32}NO_2$, 498.2428, found 498.2416; IR (neat, cm^{-1}) 3410, 2950, 1610, 1445; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.52−7.47 (m, 6H), 7.28−7.19 (m, 14H), 7.02

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(bd, J = 7.9 Hz, 1H), 6.97−6.91 (m, 2H), 6.74 (ddd, J = 8.2, 2.7, 0.9 Hz, 1H), 4.80 (bs, exchangeable, 1H), 4.20, 4.15 (ABq, J = 12.1 Hz, 2H), 3.84 (dd, J = 10.3, 4.3 Hz, 1H), 3.41 (dd, J = 10.2, 7.5 Hz, 1H), 2.43 (d, J = 6.4 Hz, 1H), 1.87 (ddd, J = 7.8, 6.5, 4.8 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 155.4, 144.1, 139.2, 138.1, 129.6, 129.3, 128.2, 127.5, 127.4, 127.3, 126.7, 120.6, 114.6, 113.7, 75.4, 72.7, 67.2, 38.8, 38.5.

(2*R*,3*R*)-2-((Benzyloxy)methyl)-3-(3-((*tert*-butyldimethylsilyl)-oxy)phenyl)-1-tritylaziridine (25). According to conditions C, aziridinyl stannatrane **8** (0.068 g, 0.067 mmol), *tert*-butyl(3-iodophenoxy)dimethylsilane **23**[22] (0.015 g, 0.045 mmol), and $Pd(^tBu_3P)_2$ (0.001 g, 0.002 mmol) were combined in anhydrous toluene (4 mL). The resultant solution was stirred at 65 °C in an oil bath for 16 h, and the standard workup gave a dark residue. Chromatography (neutral alumina plates, 5% ethyl acetate in hexanes) afforded 0.017 g (63%) of **25** as clear oil and 0.016 g (35%) of unreacted aziridinyl stannatrane **8**. Analytical TLC (neutral alumina plate, 10% diethyl ether in hexanes, R_f = 0.7 and 0.4 for **8** and **25**. Data for **25**, $[\alpha]^{20}_D$ = −56.81 (c 0.7, $CHCl_3$); HRMS-ES$^+$ (m/z) [M + H] calcd for $C_{41}H_{46}NO_2Si$, 612.3292, found 612.3294; IR (neat, cm^{-1}) 3050, 2920, 1615, 1455; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.53−7.50 (m, 6H), 7.27−7.17 (m, 14H), 7.10−7.00 (m, 2H), 6.94 (dd, J = 7.1, 2.1 Hz, 1H), 6.76 (ddd, J = 8.1, 2.4, 1.1 Hz, 1H), 4.17, 4.13 (ABq, J = 12.5 Hz, 2H), 3.85 (dd, J = 10.3, 4.3 Hz, 1H), 3.41 (dd, J = 10.2, 7.7 Hz, 1H), 2.43 (d, J = 6.4 Hz, 1H), 1.86 (ddd, J = 7.6, 6.4, 4.6 Hz, 1H), 1.00 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 155.5, 144.2, 138.8, 138.1, 129.6, 129.0, 128.2, 127.5, 127.3, 127.2, 126.7, 121.3, 119.3, 118.6, 75.4, 72.7, 67.3, 38.9, 38.4, 25.7, 18.2, −4.3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new substances and X-ray crystallographic data tables for **22** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Nelson, J. M.; Vedejs, E. *Org. Lett.* **2010**, *12*, 5085. (b) Hughes, M.; Boultwood, T.; Zepetelli, G.; Bull, J. A. *J. Org. Chem.* **2013**, *78*, 844.

(2) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555.

(3) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411. (b) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119.

(4) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.

(5) (a) Catalyst generation: Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505. (b) Li, H.; He, A.; Falck, J. R.; Liebeskind, L. S. *Org. Lett.* **2011**, *13*, 3682.

(6) (a) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1. (b) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666.

(7) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

(8) (a) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033. (b) Allred, G. D., Ph. D. Dissertation, Emory University, 1997. (c) For the use of CuDPP as a tin scavenger, see: Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.

(9) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556.

(10) Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607.

(11) (a) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153. (b) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009. (c) For reviews covering aziridine metallation, see: Florio, S.; Luisi, R. *Chem. Rev.* **2010**, *110*, 5128. Florio, S. *Synthesis* **2012**, *44*, 2872.

(12) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(13) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(14) For the formation of dimeric indoles via organocopper intermediates, see: Bergman, J.; Eklund, L. *Tetrahedron* **1980**, *36*, 1439.

(15) Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Costa, M. *Eur. J. Org. Chem.* **2012**, *13*, 2549.

(16) Using 1.5 equiv of **8** with **18** gave a 2:1 mixture of **19**:**20**, while a larger excess (2.5 equiv) of **8** afforded an improved ratio of 6.7:1 along with recovered **8** and deiodo indole (**18** with I replaced by H). Both experiments also produced **9**, but the relative amount could not be established due to overlapping NMR signals. This result suggests that the NH group of **18** is involved in the destruction of an equivalent amount of **8**.

(17) The structure of **22** was established by X-ray crystallography (see Supporting Information).

(18) (a) For an interesting application in a β-lactam environment, see: Jensen, M. S.; Yang, C.; Hsiao, Y.; Rivera, N.; Wells, K. M.; Chung, J. Y. L.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2000**, *2*, 1081. (b) For a systematic study of palladium-catalyzed coupling of sec-alkyl substituted stannatranes, see: Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R.; *Nature Chem.* **2013**, *5*, in press.

(19) Beccalli, E. M.; Broggini, G.; Marchesini, A.; Rossi, E. *Tetrahedron* **2002**, *58*, 6673.

(20) Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Costa, M. *E. J. Org. Chem.* **2012**, *13*, 2549.

(21) Laronze, M.; Laronze, J.-Y.; Nemes, C.; Sapi, J. *Eur. J. Org. Chem.* **1999**, 2285.

(22) Pelter, A.; Hussain, A.; Smith, G.; Ward, R. S. *Tetrahedron* **1997**, *53*, 3879.