Stille Coupling Reactions of 4-Substituted-2,5-Diphenyloxazoles†

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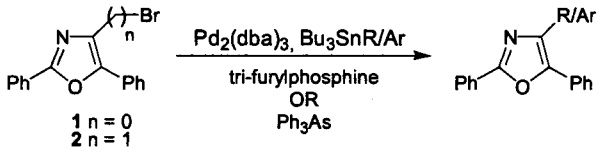
Introduction

Many naturally occurring biologically active compounds contain one or more oxazole heterocyclic units, and recently, there has been considerable interest in the synthesis of such oxazole-containing natural products.[1] In addition, certain oxazole derivatives, most notably, 2,5-diphenyloxazole, scintillate or emit light in the presence of ionizing radiation. Our interest in these heterocycles derives from this latter activity. Previously, we have synthesized a variety of 4-functionalized-2,5-diphenyloxazoles and evaluated their scintillation efficiencies for use as reporter tags in molecular recognition systems.[2] More recently, we have developed a series of scintillant-containing chemically functionalized polystyrene resin beads for application in combinatorial chemistry.[3] These "scintillating" polymers can serve as supports for both solid-phase synthesis and subsequent on-bead scintillation proximity assay (SPA) of library compounds. Among other reagents, the preparation of these resins requires the "scintillant monomer" 2,5-diphenyl-4-vinyloxazole **3**, which was synthesized previously in six steps from ethyl benzoyl acetate.[3,4] To enable scale-up production and the development of new resins, more efficient routes to 2,5-diphenyl-4-vinyloxazole (**3**) and related oxazole-containing monomers were required.

The mild conditions employed in the Stille reaction[5] made it an ideal method for introducing polymerizable groups directly onto the 2,5-diphenyloxazole skeleton via robust C−C bonds. Although Stille couplings of oxazole-containing molecules are known, most employ couplings remote from the oxazole center. In contrast, reactions that involve coupling directly onto the oxazole ring are comparatively rare, and therefore, little is known about their efficiency.[6,7] Because of our interest in the production of polymerizable scintillants, we wished to develop optimal conditions for Stille couplings at the 4-position of the oxazole ring in the presence of bulky neighboring groups. Using 2,5-diphenyloxazole as the electrophile in a Stille coupling, we generated two of the required scintillant monomers in excellent yield. Unfortunately, other monomers proved inaccessible via this route. However, by reversing the Stille strategy and using the oxazole as the stannane, in conjunction with stoichiometric quantities of copper(II) oxide, these other monomers were obtained in good yield. Moreover, the success of a variety of further coupling reactions suggests that this latter approach has general applicability. Herein, we report the first examples of 4-stannyl-2,5-bifunctional oxazoles and their efficiencies in Stille coupling reactions with a variety of electrophiles.

Scheme 1



Results and Discussion

To establish optimal Stille coupling conditions for use of 2,5-diphenyloxazole as the electrophile, model coupling reactions of 4-bromo-2,5-diphenyloxazole (**1**) and 4-bromomethyl-2,5-diphenyloxazole (**2**) with a range of commercially available tributyltin reagents were investigated. Preliminary investigations determined that the highly active catalytic systems described by Farina, prepared conveniently in situ by mixing a palladium source with an appropriate ligand, gave higher yields than traditional triphenylphosphine-derived catalytic systems (Scheme 1).

When triphenylarsine was used in conjunction with tris(dibenzylidineacetone)dipalladium(0) ($Pd_2(dba)_3$) (palladium/ligand = 1/4), the desired products were isolated in modest yields. In each case, recovery of starting materials led us to believe that the relatively weak coordinating nature of the triphenylarsine ligand was responsible for premature catalyst decomposition, which, in turn, was responsible for reduced product yields. Substitution of triphenylarsine with the tri-2-furylphosphine ligand (palladium/ligand = 1/4) gave a good compromise between reaction rate and catalytic stability and resulted in higher yields of cross-coupled products in each case (Table 1).

These findings consolidate existing literature precedent[6,7a] and demonstrate that Stille coupling proce-

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† Dedicated to Professor Ian O. Sutherland on the occasion of his 70th birthday.

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(1) For illustrative examples, see: (a) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533. (b) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536. (c) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301. (d) Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Reader, M.; Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, *15*, 2415. (e) Chattopadhyay, S. K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, *15*, 2429. (f) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Duan, J. J.-W.; Hull, K. G.; Iwashima, M. Qiu, Y.; Spoors, P. G.; Salvatore, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 10478. (g) Mulder, R. J.; Shafer, C. M.; Molinski, T. F *J. Org. Chem.* **1999**, *64*, 4995. (h) Williams, D. R.; Brooks, D..A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924.

(2) Clapham, B.; Richards, A.; Wood, M.; Sutherland, A. J. *Tetrahedron Lett.* **1997**, 38, 9061.

(3) (a) Clapham, B.; Sutherland, A. J. *Tetrahedron Lett.* **2000**, *41*, 2253. (b) Clapham, B.; Sutherland, A. J. *Tetrahedron Lett.* **2000**, *41*, 2257. (c) Clapham, B.; Sutherland, A. J. International Patent WO 00/20475, 2000.

(4) Tanaka C.; Saito, N. *Chem. Abstr.* **1963**, *58*, 3407f.

(5) For reviews of the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. Stille, J. K. *Angew. Chem., Int Ed. Engl.* **1986**, *25*, 508.

(6) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469.

(7) (a) Liu, C.-M.; Chen, B.-H.; Liu, W.-Y.; Wu, X.-L.; Ma, Y.-X. *J. Organomet. Chem.* **2000**, *598*, 348. (b) For the synthesis of 4-bromo-2,5-diphenyloxazole (**1**), see: Gilchrist, T. L.; Pearson, D. P. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 989.

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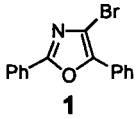
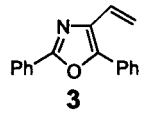
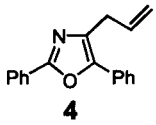
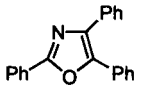
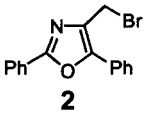
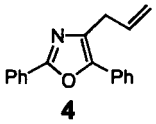
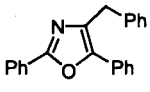
Table 1. Tri-2-furylphosphine/$Pd_2(dba)_3$-Catalyzed Stille Coupling Reactions of 4-Bromo-2,5-diphenyloxazole (1) and 4-Bromomethyl-2,5-diphenyloxazole (2) with Various Stannanes

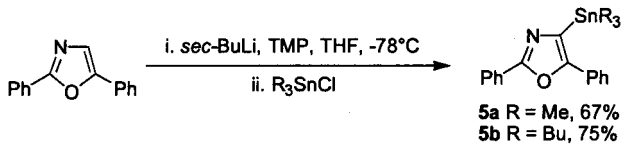
entry	electrophile	stannane and conditions[a]	product	isolated yield[b]
1	 **1**	vinyltributyltin 65°C, 16h	 **3**	98%
2	"	allyltributyltin 65°C, 16h	 **4**	49%
3	"	phenyltributyltin 90°C, 8h		85%
4	 **2**	vinyltributyltin 65°C, 16h	 **4**	98%
5	"	phenyltributyltin 100°C, 8h		84%

[a] All reactions were carried out on a 1 mmol scale in dry 1-methyl-2-pyrrolidinone in the presence of 2.5 mol % $Pd_2(dba)_3$, 20 mol % tri-2-furylphosphine, and 1.2 mmol of stannane. [b] Based on pure material after purification by flash chromatography on SiO_2.

dures involving 4-bromo-2,5-diphenyloxazole (**1**) and 4-bromomethyl-2,5-diphenyloxazole (**2**) are viable methods for introducing substituents at the 4-position of a 2,5-di-functionalized oxazole system either directly or via a methylene linker. This Stille coupling strategy also provided an efficient two-step route to 2,5-diphenyl-4-vinyloxazole (**3**) from commercially available 2,5-diphenyloxazole in overall 82% yield. In addition, a route to 4-allyl-2,5-diphenyloxazole (**4**), required for comparative polymerization studies, has been established. Notably, the optimum route to this compound utilized 4-bromomethyl-2,5-diphenyloxazole (**2**) rather than 4-bromo-2,5-diphenyloxazole (**1**) as the electrophile. Unfortunately, it did not prove possible to construct styrene-containing 2,5-diphenyloxazoles in this manner. Because these monomers were needed for comparative polymerization studies, an alternative coupling strategy was required.

A reversal of the Stille coupling approach, i.e., coupling a 2,5-diphenyl-4-trialkylstannanyloxazole with an electrophile, was viewed as an attractive alternative. If successful, this approach would constitute a new and synthetically flexible method for constructing trisubstituted oxazole ring systems from 2,5-disubstituted oxazole precursors. We wished to evaluate whether steric factors would preclude this alternative route. Accordingly, 2,5-diphenyl-4-trimethylstannanyloxazole (**5a**) and 2,5-diphenyl-4-tributylstannanyloxazole (**5b**) were synthesized. Although Barrett had previously reported difficulties

Scheme 2



in preparing a 2-oxazolylstannane via direct metal exchange,[8] we were delighted to find that treatment of 4-lithio-2,5-diphenyloxazole[9] with the appropriate trialkylstannyl chloride gave good yields of both 2,5-diphenyl-4-trialkylstannanyloxazoles (**5**) (Scheme 2).

It has been reported that tributyl tin compounds give greater aryl/alkyl selectivity than the corresponding trimethyl tin compounds.[10] Consequently, Stille coupling reactions involving 2,5-diphenyl-4-tributylstannanyloxazole (**5b**) were selected primarily for study. Unfortunately, attempts to couple stannane **5b** with a variety of electrophiles under standard reaction conditions gave disappointing results. Although it was possible to synthesize 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**), the reaction proved capricious, and the best yield obtained for oxazole **6** was 57% after a reaction time of 20 h.

The use of cocatalytic copper(I) salts in conjunction with palladium catalysts in Stille reactions has been widely reported.[11] In particular, these systems have given superior results for cross-couplings of sterically hindered reaction partners.[11a,d] Unfortunately, when cocatalytic copper(I) iodide was added to Stille coupling reactions employing stannane **5b**, no enhancement of either reaction rate or yield was observed.

The addition of copper(II) oxide has also been reported to enhance Stille coupling reactions. For example, reactions involving 2-pyridyltin compounds have been improved by the addition of CuO under both traditional[12] and microwave-promoted fluorous phase[13] conditions. However, only one instance of a CuO-enhanced Stille coupling reaction involving an oxazole heterocycle has been reported.[7a] Moreover, in this case, which involved the $Pd(PPh_3)_4$-mediated coupling of tributylstannylferrocene to 4-bromo-2,5-diphenyloxazole (**1**), the oxazole was the electrophile, rather than the stannane.

We were delighted, therefore, to find that, when a stoichiometric quantity of CuO was added to Stille coupling reactions involving 2,5-diphenyl-4-tributylstannanyloxazole (**5b**), a dramatic increase in both reaction rates and product yields was observed (Scheme 3). For example, in the case of monomer 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**), the rate of reaction was shortened dramatically from 20 to 4 h, and the yield of product increased from 57 to 95%.

To determine whether this novel coupling strategy might have generic applicability, we examined the cou-

(8) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415.
(9) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058.
(10) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.
(11) (a) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 7600. (b) Nicoloau, K. C.; Sato, M.; Miller, N. D.; Gunzer, J. L.; Renaud, J.; Untersteller, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 889. (c) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. (d) Saa, J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963. (e) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408. (f) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.
(12) Gronowitz, S.; Björk, P.; Malm, J.; Hörnfeldt, A. B. *J. Organomet. Chem.* **1993**, *460*, 127.
(13) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583.

Scheme 3

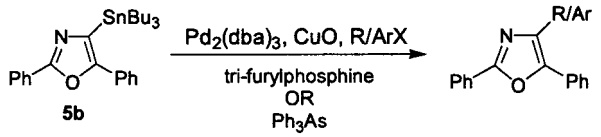
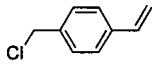
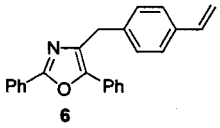
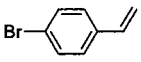
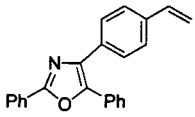
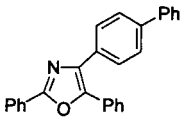
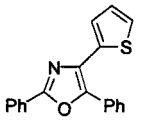
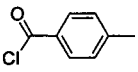
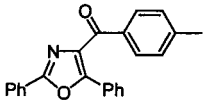
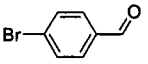
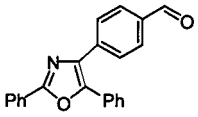


Table 2. Copper(II) Oxide-Enhanced Palladium-Catalyzed Stille Coupling Reactions of 2,5-Diphenyl-4-tributylstannanyloxazole (5b) with Various Electrophiles

entry	electrophile	conditions[a]	product	isolated yield[b]
1		Ph_3As, 65°C, 4h	 **6**	95%
2		$(2\text{-furyl})_3P$, 65°C, 16h		58%
3		$(2\text{-furyl})_3P$, 65°C, 24h		51%
4		$(2\text{-furyl})_3P$, 80°C, 24h		42%
5		Ph_3As, 65°C, 4h		69%
6		$(2\text{-furyl})_3P$, 65°C, 16h		82%

[a] All reactions were carried out on a 1 mmol scale in dry 1-methyl-2-pyrrolidinone in the presence of 2.5 mol % $Pd_2(dba)_3$, 20 mol % ligand, 1 mmol of CuO, and 1.2 mmol of stannane. [b] Based on pure material after purification by flash chromatography on SiO_2.

pling of a diverse selection of electrophiles with 2,5-diphenyl-4-tributylstannanyloxazole (**5b**). Table 2 demonstrates that this variety of electrophiles, which includes benzyl halide, aryl halides, and acid chlorides, undergoes successful Stille couplings in generally good yield. It should be noted that the more stubborn couplings, involving the introduction of an aryl group directly adjacent to another aryl group on the oxazole ring, required the use of the more robust tri-2-furylphosphine-based catalytic system. Using this new protocol, it also proved possible to construct monomer 2,5-diphenyl-4-(4′-vinylphenyl)oxazole (Table 2, entry 2), which had previously been inaccessible. The copper-mediated reaction is also readily amenable to scale-up and has enabled the routine production of multigram quantities of 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**) in our laboratories. Finally, 4-trimethylstannyl-2,5-diphenyloxazole (**5a)** also proved to be an excellent coupling partner in this reaction, giving a similarly high yield of 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**). We are unaware of any previous reports involving either the synthesis or the use of such 2,5-di-substituted-4-stannanyloxazoles.

Conclusion

In summary, we have developed a mild and synthetically flexible Stille coupling procedure that exploits 2,5-diphenyl-4-trialkylstannanyloxazoles (**5**) to provide an attractive synthetic route for introducing the oxazole heterocycle into target molecules. This straightforward, clean, and high-yielding procedure should be of use in natural product synthesis, combinatorial library generation, and the construction of scintillant-containing materials.

Experimental Section

General. Reactions were carried out in oven-dried glassware under nitrogen atmosphere. All commercial reagents were used without purification, and all solvents were reaction grade. THF was freshly distilled from sodium/benzophenone under nitrogen. All reaction mixtures were stirred magnetically and were monitored by thin-layer chromatography using Merck silica gel 60 F_{254} precoated glass plates, which were visualized with UV light and then developed using either iodine, a solution of 10% phosphomolybdic acid in ethanol, or an aqueous solution of potassium permanganate. Flash column chromatography was carried out using Fluka silica gel 60 (0.035−0.070 μm, 220−440 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AC300 spectrometer. Deuterated chloroform was used as the solvent, and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C). ^{13}C NMR spectra were recorded using the PENDANT program.[14] Low-resolution mass spectra were recorded using a Finnigan LCQ ion-trap spectrometer using atmospheric pressure chemical ionization (APCI). High-resolution mass spectra were recorded by Mr. Peter Ashton (School of Chemistry, Birmingham University) using a Micromass LCT mass spectrometer in the electrospray mode using a mobile phase of methanol (200 μL min^{-1}) and lock mass to correct the mass scale. Elemental analyses were performed by Medac Ltd., Brunel Science Center, Cooper's Hill Lane, Engelfield Green, Egham, Surrey, U.K. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer as either a thin film pressed between two sodium chloride plates or as a solid suspended in a potassium bromide disk.

2,5-Diphenyl-4-vinyloxazole (3). 4-Bromo-2,5-diphenyloxazole (**1**) (300 mg, 1.00 mmol), tris(dibenzylidineacetone)dipalladium(0) [23 mg, 25 μmol (5 mol % Pd)], and tri-2-furylphosphine [46 mg, 200 μmol (20 mol % ligand)] were stirred in 1-methyl-2-pyrrolidinone (20 mL) for 15 min. Tributyl(vinyl) tin (351 μL; 381 mg, 1.20 mmol) was added, and the resultant mixture was heated to 65 °C and stirred for 16 h, after which time blackening of the mixture had occurred. The reaction mixture was then stirred with a 10% aqueous solution of potassium fluoride (75 mL) and diethyl ether (25 mL) for 1 h before being filtered through a pad of Celite. The pad of Celite was rinsed with a further portion of diethyl ether (25 mL). The aqueous phase was separated and extracted with a further portion of diethyl ether (25 mL). The combined organic extracts were washed with a saturated aqueous solution of ammonium chloride (4 × 25 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give a yellow solid. Flash chromatography (4% diethyl ether in hexanes) gave 2,5-diphenyl-4-vinyloxazole (**3**) as a white solid (244 mg, 98%), mp 70−71 °C. IR (KBr) ν_{max}/cm^{-1} 3053, 2925, and 1637; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.47 (1H, dd, J = 10.9, 2.0 Hz), 6.28 (1H, dd, J = 17.0, 2.0 Hz), 6.79 (1H, dd, J = 17.0, 10.9 Hz), 7.30−7.48 (6H, m), 7.64−7.69 (2H, m), and 8.09−8.14 (2H, m); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 117.65, 125.8, 126.4, 126.6, 127.2, 128.4, 128.6, 128.7, 128.8, 130.4, 135.2, 146.1, and 160.2; LRMS (APCI) m/z 248 (M + H$^+$); Found C, 82.8; H, 5.3; N, 5.7; $C_{17}H_{13}NO$ requires C, 82.6; H, 5.3; N, 5.7.

4-Allyl-2,5-diphenyloxazole (4). Using the same procedure as described for the preparation of 2,5-diphenyl-4-vinyloxazole

(14) Homer, J.; Perry, M. C. *J. Chem. Soc., Chem. Commun.* **1994**, 373.

(**3**), 4-bromomethyl-2,5-diphenyloxazole (**1**) (314 mg, 1.00 mmol) and tributyl(vinyl)tin (351 μL; 381 mg, 1.20 mmol) were coupled together to form 4-allyl-2,5-diphenyloxazole (**4**), after flash column chromatography (10% diethyl ether in hexanes), as a white solid (257 mg, 98%), mp 60−62 °C. IR (KBr) ν_{max}/cm^{-1} 3058, 2956, 2922, 2853, and 1638; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.64 (2H, dt, J = 6, 2 Hz), 5.29−5.21 (2H, m), 6.10−6.23 (1H, m), 7.32−7.51 (6H, m), 7.68−7.72 (2H, m), and 8.12−8.17 (2H, m); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 31.5, 116.3, 125.4, 126.2, 127.3, 127.7, 128.5, 128.6, 130.0, 134.4, 135.0, 144.9, 145.9, and 159.6; LRMS (APCI) m/z 262 (M + H$^+$).

4-Benzyl-2,5-diphenyloxazole (Table 1, Entry 5). Using the same procedure as described for the preparation of 2,5-diphenyl-4-vinyloxazole (**3**), 4-bromomethyl-2,5-diphenyloxazole (**1**) (314 mg, 1.00 mmol) and tributylphenyltin (392 μL; 441 mg, 1.20 mmol) were coupled together at 100 °C for 3 h to form 4-benzyl-2,5-diphenyloxazole, after flash column chromatography (7.5% diethyl ether in hexanes), as a white solid (262 mg, 84%), mp 90−92 °C. IR (KBr) ν_{max}/cm^{-1} 3059, 3023, and 2921; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.32 (2H, s), 7.31−7.56 (11H, m), 7.75−7.78 (2H, m), and 8.20−8.24 (2H, m); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 33.2, 125.6, 126.4, 127.5, 128.0, 128.5, 128.6, 128.7, 128.9, 130.2, 135.8, 138.6, 146.5, and 159.9; LRMS (APCI) m/z 312 (M + H$^+$).

2,5-Diphenyl-4-trimethylstannanyloxazole (5a). To a solution of 2,5-diphenyloxazole (8.21 g, 37.1 mmol) and 2,2,6,6-tetramethylpiperidine (0.63 mL; 0.53 g, 3.73 mmol) in tetrahydrofuran (150 mL) cooled to −78 °C was added *sec*-butyllithium (1.3 M solution in cyclohexane, 31.5 mL, 40.1 mmol) over 30 min. The mixture was allowed to warm to 0 °C over 30 min, and the resultant solution, containing 2,5-diphenyl-4-lithio-oxazole, was added via cannula to a solution, cooled to −78 °C, of trimethyltin chloride (7.40 g, 37.1 mmol) in tetrahydrofuran (50 mL). After the mixture was warmed to room temperature, the reaction was quenched cautiously by the addition of a saturated aqueous solution of ammonium chloride (100 mL). The organic layer was separated, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark red solid. Recrystallization from methanol gave 2,5-diphenyl-4-trimethylstannanyloxazole (**5a**) (9.50 g, 67%) as a white solid; mp 80−82 °C. IR (KBr) ν_{max}/cm^{-1} 3057, 2981, and 2906; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.50 (9H, s), 7.37−7.54 (6H, m), 7.71−7.75 (2H, m), and 8.18−8.22 (2H, m); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C −8.7, 125.7, 126.3, 127.8, 128.1, 128.5, 128.6, 129.7, 129.8, 136.0, 157.5, and 161.7; LRMS (APCI) m/z 386 (M + H$^+$).

2,5-Diphenyl-4-tributylstannanyloxazole (5b). Using the same procedure as described for the preparation of 2,5-diphenyl-4-trimethylstannanyloxazole (**5a**), the lithiated anion of 2,5-diphenyloxazole (8.84 g, 40.0 mmol) and tributyltin chloride (10.9 mL, 13.1 g, 40.2 mmol) were reacted together to give 2,5-diphenyl-4-tributylstannanyloxazole (**5b**), after flash column chromatography (gradient elution with 0−3% diethyl ether in hexanes), as a colorless oil (15.4 g, 75%). IR (film) ν_{max}/cm^{-1} 3032, 2955, 2924, and 2851; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.85−1.60 (27H, m), 7.34−7.48 (6H, m), 7.66−7.69 (2H, m), and 8.14 (2H, dd, J = 8.3, 1.8 Hz); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 10.4, 13.7, 27.2, 29.0, 125.8, 126.4, 128.1, 128.6, 128.65, 129.7, 130.2, 132.0, 136.4, 157.8, 161.7; LRMS (APCI) m/z 512 (M + H$^+$); HRMS (EI) m/z 512.1967 (M + H$^+$) (calcd for $C_{27}H_{38}NO^{120}Sn$, 512.1975).

2,5-Diphenyl-4-(4′-vinylbenzyl)oxazole (6). Tris(dibenzylidineacetone)dipalladium(0) [23 mg, 25 μmol (5 mol % Pd)], triphenylarsine [61 mg, 200 μmol (20 mol % ligand)], and copper(II) oxide [79 mg, 1.00 mmol (1 equiv)] were stirred at room temperature in 1-methyl-2-pyrrolidinone (10 mL) for 15 min. 4-Vinylbenzyl chloride (157 μL; 170 mg, 1.00 mmol as 90%) was added, and the resultant mixture stirred for a further 15 min before a solution of 2,5-diphenyl-4-tributylstannanyloxazole (**5b**) (612 mg, 1.20 mmol) in 1-methyl-2-pyrrolidinone (10 mL) was added. The resultant mixture was heated to 65 °C and stirred for 4 h, after which time blackening of the mixture had occurred. The reaction mixture was then stirred with a 10% aqueous solution of potassium fluoride (75 mL) and diethyl ether (25 mL) for 1 h before being filtered through a pad of Celite. The pad of Celite was subsequently rinsed with a further portion of diethyl ether (25 mL). The aqueous phase was separated and extracted with a further portion of diethyl ether (25 mL). The combined organic extracts were washed with a saturated aqueous solution of ammonium chloride (4 × 25 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give a yellow solid. Flash chromatography (10% diethyl ether in hexanes) gave 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**) as a white solid (321 mg, 95%), mp 106−108 °C. IR (KBr) ν_{max}/cm^{-1} 3057, 2925, and 1654; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.28 (2H, s), 5.27 (1H, d, J = 10.9 Hz), 5.78 (1H, d, J = 17.6 Hz), 6.77 (1H, dd, J = 17.6, 10.9 Hz), 7.35−7.54 (10H, m), 7.74−7.77 (2H, m), and 8.21 (2H, dd, J = 7.9, 1.8 Hz); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 32.8, 113.1, 125.4, 125.8, 126.2, 126.3, 127.3, 127.8, 128.4, 128.5, 128.7, 130.0, 135.5, 135.7, 136.4, 138.1, 146.3, and 159.7; LRMS (APCI) m/z 338 (M + H$^+$). Found C, 85.2; H, 5.6; N, 4.1; $C_{24}H_{19}NO$ requires C, 85.4; H, 5.6; N, 4.1.

2,5-Diphenyl-4-(4′-vinylphenyl)oxazole (Table 2, Entry 2). Using the same procedure as described for the preparation of 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**), 2,5-diphenyl-4-tributylstannanyloxazole (**5b**) (612 mg, 1.20 mmol) was coupled to 4-bromostyrene (131 μL, 183 mg, 1.0 mmol). Tri-2-furylphosphine (46 mg, 200 μmol) was used as the ligand, and a reaction time of 16 h at 65 °C and purification by flash column chromatography (4% diethyl ether in hexanes) gave 2,5-diphenyl-4-(4′-vinylphenyl)oxazole as a white solid (187 mg, 58%), mp 76−78 °C. IR (KBr) ν_{max}/cm^{-1} 3054, 2925, and 1654; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.33 (1H, d, J = 10.9 Hz), 5.84 (1H, d, J = 17.6 Hz), 6.78 (1H, dd, J = 17.6, 10.9 Hz), 7.38−7.53 (8H, m), 7.71−7.78 (4H, m), and 8.18−8.22 (2H, m); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 114.1, 126.4, 126.5, 126.6, 127.3, 128.1, 128.5, 128.6, 128.64, 128.9, 129.1, 130.2, 131.9, 136.4, 137.3, 145.5, and 160.1; LRMS (APCI) m/z 324 (M + H$^+$).

4-Biphenyl-4-yl-2,5-diphenyloxazole (Table 2, Entry 3). Using the same procedure as described for the preparation of 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**), 2,5-diphenyl-4-tributylstannanyloxazole (**5b**) (612 mg, 1.20 mmol) was coupled to 4-bromobiphenyl (233 mg, 1.0 mmol). Tri-2-furylphosphine (46 mg, 200 μmol) was used as the ligand, and a reaction time of 24 h at 65 °C and purification by flash column chromatography (5% diethyl ether in hexanes) gave 4-biphenyl-4-yl-2,5-diphenyloxazole as a white solid (190 mg, 51%), mp 79−81 °C. IR (KBr) ν_{max}/cm^{-1} 3056 and 1697; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.37−7.56 (9H, m), 7.67−7.71 (4H, m), 7.76−7.79 (2H, m), 7.85−7.89 (2H, m), and 8.19−8.22 (2H, m); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 126.4, 126.6, 127.0, 127.2, 127.4, 128.4, 128.6, 128.65, 128.7, 128.75, 129.0, 130.3, 131.5, 136.4, 140.6, 140.8, 145.6, and 160.1; LRMS (APCI) m/z 374 (M + H$^+$).

2,5-Diphenyl-4-thiophen-2-yloxazole (Table 2, Entry 4). Using the same procedure as described for the preparation of 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**), 2,5-diphenyl-4-tributylstannanyloxazole (**5b**) (612 mg, 1.20 mmol) was coupled to 2-iodothiophene (110 μL, 209 mg, 1.0 mmol). Tri-2-furylphosphine (46 mg, 200 μmol) was used as the ligand, and a reaction time of 24 h at 80 °C and purification by flash column chromatography (3% diethyl ether in hexanes) gave 2,5-diphenyl-4-thiophen-2-yloxazole as a white solid (127 mg, 42%), mp 66−68 °C. IR (KBr) ν_{max}/cm^{-1} 3053, 2923, 2853, and 1560; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.09 (1H, dd, J = 5.3, 4.6 Hz), 7.37−7.54 (8H, m), 7.79−7.82 (2H, m), and 8.15−8.20 (2H, m); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 125.8, 126.0, 126.5, 126.8, 127.0, 127.4, 127.7, 128.5, 128.66, 128.8, 130.4, 131.3, 134.6, 145.1, and 160.0; LRMS (APCI) m/z 304 (M + H$^+$).

(2,5-Diphenyloxazol-4-yl)-*p*-tolylmethanone (Table 2, Entry 5). Using the same procedure as described for the preparation of 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**), 2,5-diphenyl-4-tributylstannanyloxazole (**5b**) (612 mg, 1.20 mmol) was coupled to *p*-toluoyl chloride (132 μL, 154 mg, 1.0 mmol). Triphenylarsine (61 mg, 200 μmol) was used as the ligand, and a reaction time of 4 h at 65 °C and purification by flash column chromatography (10% diethyl ether in hexanes) gave (2,5-diphenyloxazol-4-yl)-*p*-tolylmethanone as a white solid (234 mg, 69%), mp 110−112 °C. IR (KBr) ν_{max}/cm^{-1} 3058, 2921, and 1652; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.44 (3H, s), 7.30 (2H, d J 7.9), 7.43−7.51 (6H, m), and 8.07−8.19 (6H, m); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 21.6, 126.6, 127.4, 127.6, 128.4, 128.7, 128.8, 130.0, 130.6, 130.8, 132.1, 134.8, 135.1, 143.8, 154.0, 158.8, and 188.3; LRMS (APCI) m/z 340 (M + H$^+$).

(2,5-Diphenyloxazol-4-yl)benzaldehyde (Table 2, Entry 6). Using the same procedure as described for the preparation

of 2,5-diphenyl-4-(4′-vinylbenzyl)oxazole (**6**), 2,5-diphenyl-4-tributylstannanyloxazole (**5b**) (612 mg, 1.20 mmol) was coupled to 4-bromobenzaldehyde (185 mg, 1.0 mmol). Tri-2-furylphosphine (46 mg, 200 μmol) was used as the ligand, and a reaction time of 16 h at 65 °C and purification by flash column chromatography (15% diethyl ether in hexanes) gave (2,5-diphenyloxazol-4-yl)benzaldehyde as a white solid (267 mg, 82%), mp 126−128 °C. IR (KBr) ν_{max}/cm^{-1} 3056, 2923, 2818, 2732, 1697; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.38−7.49 (6H, m), 7.62−7.67 (2H, m), 7.86−7.93 (4H, m), 8.12−8.15 (2H, m), and 10.0 (1H, s); ^{13}C NMR (75 MHz, PENDANT, $CDCl_3$) δ_C 126.3, 126.9, 126.95,128.1, 128.4, 128.7, 128.75, 129.1, 129.8, 130.5, 135.2, 135.6, 138.4, 146.9, 160.4, and 191.5; LRMS (APCI) *m*/*z* 326 (M + H$^+$).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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