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Regioselective Palladium Cross-Coupling of 2,4-Dihalooxazoles: Convergent Synthesis of Trisoxazoles

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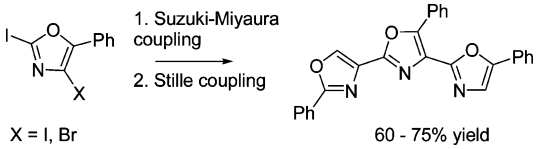


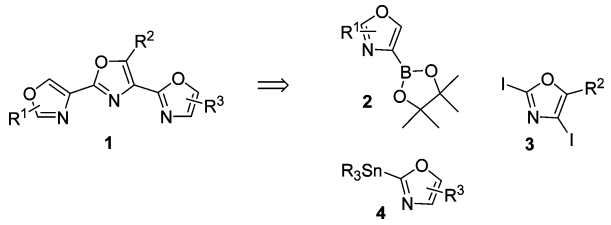
A regioselective Suzuki−Miyaura cross-coupling of 2,4-dihalooxazoles followed by a Stille coupling has been successfully developed. The procedure affords convergent syntheses of trisoxazoles in high yield and in a minimum number of steps.

Naturally occurring polyoxazoles commonly display a 2−4 substitution pattern, a consequence of their biosynthetic assembly from serine residues.[1] In certain natural products, such as telomestatin[2] or ulapualide A,[3] three or more successive C2−C4′ linked polyoxazoles are present rather than single oxazole units. These compounds have fascinating structures, show a wide range of biological properties, and therefore make ideal targets for the synthetic chemist.[4]

A plethora of methods have been developed for the construction of C2−C4′ linked polyoxazoles. Although these methods differ greatly in their synthetic strategy, they share a common linear approach, involving a high number of consecutive steps each time an oxazole ring needs to be introduced.[5,6] An alternative approach is to employ the palladium-catalyzed cross-coupling of appropriately functionalized oxazole units, a challenging reaction that has appeared only rarely in the literature. The first example was reported in 1995 by Barrett, using a Stille coupling to prepare a bisoxazole in an approach to the natural product Hennoxazole A.[7] Since that time, bisoxazole synthesis has been reported by Vedejs using a Negishi coupling[8] and by our own group[9] and that of Inoue[10] using the Suzuki−Miyaura reaction of oxazoyl boronate esters. Inoue has recently extended this work to the production of some challenging pentakis and hexakis polyoxazole structures.[11] However, the linearity of this approach combined with a lengthy preparation of a common boronic ester intermediate necessarily restricts its scope. Given recent developments in azole cross-coupling reactions,[12] we were interested in developing our own method based on a convergent approach to the synthesis of trisoxazoles.

2,4-Diiodooxazoles **3**, known in the literature from work of Vedejs,[8] would be expected to undergo preferential oxidative addition of Pd^0 at the more reactive C2 position, followed by Suzuki−Miyaura cross-coupling with an oxazol-4-ylboronate **2** (Scheme 1). The C4−I bond would be left intact for a second cross-coupling with a 2-metallo-oxazole **4**, forming the trisoxazole **1**. Selective cross-coupling on dihaloazoles is a well precedented strategy but has yet to be applied to polyoxazole synthesis.[13]

SCHEME 1. Cross-Coupling Strategy for the Synthesis of Trisoxazoles



We elected to break down the proposed regioselective trisoxazole synthesis into two parts, examining each C−C bond formation separately on monoiodooxazoles to define the reaction parameters, prior to using the diiodooxazoles **3**. Accordingly, we began by examining a simplified version of the proposed Suzuki−Miyaura reaction, using 2-phenyl-oxazol-4-yl boronate ester **2a** and 2-iodo-5-phenyloxazole **5**, both of which can be prepared in multigram quantities[8,10] (Table 1). Standard Suzuki−Miyaura conditions at 100 °C in DMF produced dioxazole **6** in 49% yield (entry 1). Milder conditions such as those developed by Liebeskind[14] and Fu[15] gave a complex mixture of products that could not be separated (entries 2 and 3 respectively). It

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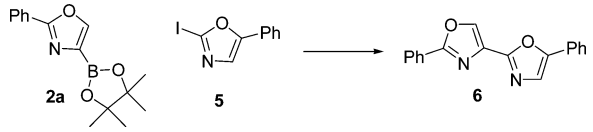
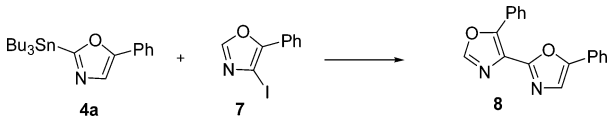
TABLE 1. Suzuki−Miyaura Coupling between Oxazol-4-ylboronate 2a and 2-Iodo-5-phenyloxazole 5[a]



entry	time	solvent	palladium source	base	temperature	additives	yield of **6** (%)[b]
1	2 h	DMF	$Pd(PPh_3)_4$	K_2CO_3	100 °C	none	49
2	4 days	THF	$Pd(PPh_3)_4$	none	rt	CuTC (1.1 equiv)	complex mixture
3	4 days	THF	$Pd_2(dba)_3$	KF	rt	$[(tBu)_3PH]BF_4$ (0.1 equiv)	complex mixture
4	20 min	dioxane/H_2O	$PdCl_2(PPh_3)_2$	Na_2CO_3 2M	150 °C, microwave	none	34
5	20 min	DMF	$Pd(PPh_3)_4$	K_2CO_3	150 °C, microwave	none	79
6	20 min	DMF	$Pd_2(dba)_3$	K_2CO_3	150 °C, microwave	PCy_3 (0.1 equiv)	87

[a] Conditions: 1.1 equiv of **2a**, 1 equiv of **5**, 3 equiv of base, 5 mol % of Pd, 3 mL of solvent. [b] Isolated yields.

TABLE 2. Stille Coupling between Oxazol-2-ylstannane 4a and 4-Iodo-5-phenyloxazole 7[a]



entry	time	solvent	palladium source[a]	base	temperature	additives	yield of **8** (%)[b]
1	2 days	DME	$PdCl_2(PPh_3)_2$	none	reflux	none	42
2	3 h	NMP	$Pd_2(dba)_3$	CsF	rt	$[(tBu)_3PH]BF_4$ (0.12 equiv)	traces
3	5 min	NMP	$Pd_2(dba)_3$	CsF	150 °C, microwave	$[(tBu)_3PH]BF_4$ (0.12 equiv)	complex mixture
4	2 h	NMP	$Pd_2(dba)_3$	none	100 °C	TFP (0.1 equiv) and Cu_2O (1 equiv)	35
5	4 days	NMP	$Pd_2(dba)_3$	KF	rt	$[(tBu)_3PH]BF_4$ (0.2 equiv) and Cu_2O (1 equiv)	traces
6	2 days	NMP	$Pd_2(dba)_3$	none	rt	TPF (0.2 equiv) and $Cu(OAc)_2$ (1 equiv)	26
7	4 days	NMP	None	none	rt	CuTC (1.5 equiv)	traces
8[c]	20 min	DMF	$Pd_2(dba)_3$	none	150 °C, microwave	PCy_3 (0.1 equiv)	54
9[d]	5 min	DMF	$Pd_2(dba)_3$	none	150 °C, microwave	PCy_3 (0.1 equiv)	87

[a] 5 mol % of Pd. [b] Isolated yields. [c] 1.5 equiv of stannane **4a** was used. [d] 3 equiv of stannane **4a** was used.

was quickly found that the use of microwave irradiation not only shortened reaction times but also increased the yields dramatically, a combination of $Pd_2(dba)_3$ (5 mol %) with PCy_3 (10 mol %) in DMF giving the desired product **6** in an excellent 87% isolated yield (entry 6). With a good yield of the Suzuki−Miyaura coupling in hand, we turned out attention to the second cross-coupling. We settled on a Stille coupling as the method of choice,[16] given that oxazol-2-ylstannanes are known nucleophiles in Pd-catalyzed oxazole cross-coupling reactions.[17]

We synthesized oxazol-2-ylstannane **4a** by trapping 5-phenyloxazole with *n*-BuLi at −78 °C and quenching the reaction mixture with Bu_3SnCl. The resulting stannane did not store well and was best used freshly prepared.[18] The optimization results for the Stille reaction are shown in Table 2. Standard conditions provided a moderate yield of **8** after 2 days reflux in DME (entry 1). Milder Stille catalyst systems were not effective for this substrate: Fu's $(tBu)_3PHBF_4$ salt[15] used at room temperature, under microwave irradiation or in combination with Cu_2O, only led to complex mixtures or slow reaction rates (entries 2, 3, 5, and 8). The ligand trifurylphosphine (TFP) in combination with $Pd_2(dba)_3$ and Cu_2O gave a modest 35% of isolated **8**, but a slow reaction rate if combined with $Cu(OAc)_2$ (entries 4 and 6, respectively). Liebeskind's copper-mediated Stille coupling[19] gave a slow reaction rate in our system (entry 7). After considerable optimization, we realized that higher yields could be achieved if higher loadings (3 equiv) of stannane **4a** where used in the reaction. Hence, the best of all combinations appeared to be same catalyst system used for the Suzuki−Miyaura coupling in Table 1: $Pd_2(dba)_3$ (5 mol %) and PCy_3 (10 mol %) in DMF and under microwave irradiation gave an excellent 87% yield of isolated **8** (entry 9).

To merge the two reactions into a trisoxazole synthesis, we synthesized diiodooxazole **3a** according to Vedejs' selective C-4 iodination[8] procedure followed by C2 iodination using 1,2-diiodoethane.[18] As planned, the Suzuki−Miyaura coupling was regioselective for C2 and gave the desired dioxazole **9** in 46% isolated yield when using $Pd_2(dba)_3/PCy_3$ (50% yield if $Pd(PPh_3)_4$ was used) (Scheme 2). Careful analysis of the crude reaction mixture by HPLC and LC-MS revealed the formation of trimer **10** (presumably the Pd-catalyzed product of the reaction between **9** and starting material **2a**), **11** (protodeboronation of **2a**), and **12** (homo-coupled **2a**) as side products.

We sought to reduce the formation of unwanted trisoxazole **10** by modifying the diiodo compound **3a**. Thus, we envisaged that if a Br atom would be selectively placed at C4 instead of I, oxidative addition on newly formed **9** would be diminished and therefore the yield should be improved. No examples exist in the literature of hybrid dihalooxazoles. We successfully managed to selectively brominate 5-phenyloxazole[20] **13** on C-4

(16) In agreement with Inoue (ref 11), attempts at oxazole C2 borylation for potential Suzuki−Miyaura coupling have not been successful.

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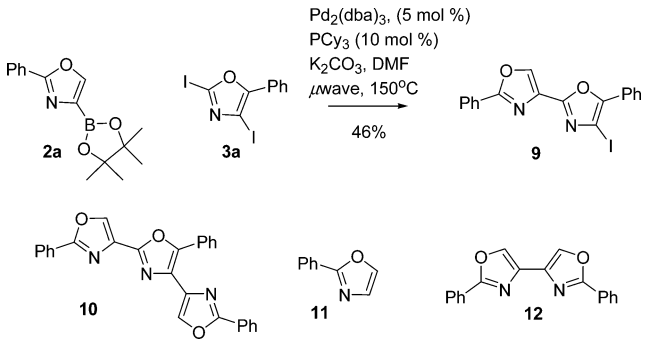
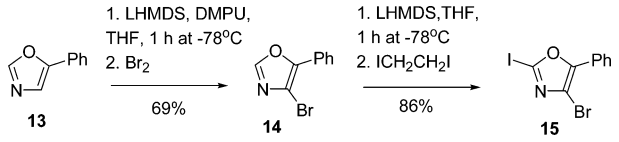
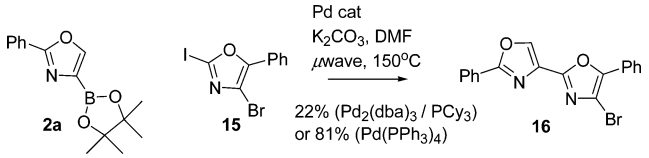
SCHEME 2. Regioselective Coupling between Oxazol-4-yl-boronate 1 and 2,4-Diiodooxazole 2



SCHEME 3. Synthesis of 2-Iodo-4-bromo-5-phenyloxazole 15 via Selective C4 Bromination on 5-Phenyloxazole



SCHEME 4. Regioselective Coupling between Oxazol-4-yl-boronate 2a and 2,4-Dihalooxazole 15



using a modification of Vedejs' procedure,[8] obtaining 4-bromo-5-phenyloxazole **14** in a good 69% yield after column chromatography. Then, iodination using LHMDS and 1,2-diiodoethane gave the desired dihalooxazole **15** in excellent yield (86% after recrystallization) (Scheme 3).

Initial attempts at regioselective Suzuki−Miyaura coupling of **15** with **2a** using $Pd_2(dba)_3/PCy_3$ produced the dioxazole **16** in a disappointing 21% yield. However, a switch to $Pd(PPh_3)_4$ proved effective, producing the bromo dioxazole **16** in a very good 81% yield (Scheme 4). This result points to the ability of the bulkier and electron-rich PCy_3 ligand to facilitate oxidative addition, eroding the selectivity in our system.

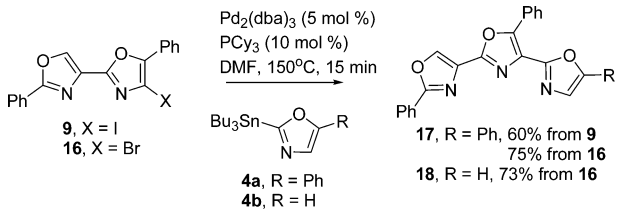
Finally, we were pleased to observe clean formation of the desired trisoxazoles using the optimized Stille coupling conditions developed previously. Trisoxazole **17** was obtained in 60% yield from iodide **9** and stannane **4a** and 75% yield using the bromide **16**. Coupling was also successful for the simple stannane **4b**, producing trisoxazole **18** in 73% yield using the same procedure (Scheme 5).

To conclude, we have developed a novel and regioselective Suzuki−Miyaura reaction for the synthesis of 2,4-bisoxazoles followed by a second palladium-catalyzed Stille coupling, which has produced trisoxazole structures. The method is convergent and avoids the synthesis of complicated precursors giving a high level of complexity in a minimum number of steps.

Experimental Section

4-Bromo-5-phenyloxazole 14. Synthesized using Vedejs protocol[8] with modifications. 5-Phenyloxazole[20] **13** (5.00 g, 34.47 mmol, 1 equiv) was dissolved in 50 mL of dry THF and 40 mL of DMPU and cooled to −78 °C. LHMDS (1 M in THF, 55 mL, 55.0 mmol, 1.6 equiv) was added slowly with a syringe. The reaction mixture was stirred 1 h at −78 °C, and then neat bromine (2.1 mL, 41.37 mmol, 1.2 equiv) was added dropwise to the reaction mixture, which was stirred for an additional 30 min at −78 °C. The reaction mixture was then poured into a mixture of TBME (200 mL) and aqueous $Na_2S_2O_3$ (10%, 200 mL) at room temperature. The two layers were separated, and the organic phase was washed three times with distilled water, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/TBME 10:0.5 to 10:1) and gave the desired bromooxazole **14** (5.32, 69% yield) as a white solid. Mp = 60−61 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37−7.86 (3H, m), 7.86 (1H, s), 7.92−7.95 (2H, m). ^{13}C NMR (90 MHz, $CDCl_3$) δ 110.9 (quat), 125.5 (CH), 126.7 (quat), 128.8 (CH), 129.1 (CH), 146.7 (quat), 149.6 (CH). HRMS (ESI) calculated for C_9H_6BrNO 223.9705, found 223.9709.

SCHEME 5. Stille Couplings for the Formation of Trisoxazoles



2-Iodo-4-bromo-5-phenyloxazole 15. Synthesized using Vedejs' protocol[8] with minor modifications. 4-Bromo-5-phenyloxazole **14** (5.00 g, 22.32 mmol, 1 equiv) was dissolved in 70 mL of dry THF and cooled to −78 °C. LHMDS (1 M in THF, 27 mL, 27 mmol, 1.21 equiv) was added slowly, and the reaction mixture stirred for 1 h at −78 °C. Then, solid 1,2-diiodoethane (7.62 g, 26.78 mmol, 1.2 equiv) was added, and the reaction mixture allowed to warm to room temperature. After 10 min complete consumption of the starting material was observed by HPLC, and the reaction was quenched with a mixture of TBME (200 mL) and aqueous $Na_2S_2O_3$ (10%, 200 mL). The two layers were separated, and the organic phase washed three times with distilled water, dried over magnesium sulfate, and concentrated in vacuo to give an orange solid which was recrystallized from toluene to afford the desired dihalooxazole **15** (6.70 g, 86% yield) as a white solid. Mp = 104−106 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37−7.48 (3H, m), 7.85−7.88 (2H, m). ^{13}C NMR (90 MHz, $CDCl_3$) δ 99.3 (quat), 112.5 (quat), 125.3 (CH), 125.9 (quat), 128.7 (CH), 129.4 (CH), 153.1 (quat). HRMS (ESI) calculated for C_9H_5NOBrI 348.8594, found 348.8597.

4-Bromo-5,2′-diphenyl-[2,4′]bisoxazole 16. A 5 mL microwave vial was charged with oxazol-4-ylboronate **2a**[10] (72 mg, 0.27 mmol, 1.2 equiv), 2-iodo-4-bromo-5-phenyloxazole **15** (77 mg, 0.22 mmol, 1 equiv), $Pd(PPh_3)_4$ (13 mg, 5 mol %), K_2CO_3 (92 mg, 0.66 mmol, 3 equiv), and anhydrous DMF (1 mL). The microwave vial was then sealed, and the resulting mixture was stirred at room temperature for about 5 min before irradiation at a preselected temperature of 150 °C in a Smith synthesizer for 10 min. The vial was then cooled with air jet cooling, opened, and poured into a mixture of Et_2O (20 mL) and brine (20 mL). The organic phase was separated, and the aqueous layer extracted twice with Et_2O. The organic layers were combined, dried over $MgSO_4$, and filtered. The organic solvent was removed in vacuo, and the residue was purified by flash column chromatography (silica, hexane/EtOAc 9:1) to give the coupled product **16** (65 mg, 81% yield) as a white solid. Mp = 149−152 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.36−7.50 (6H, m), 8.00−8.02 (2H, m), 8.13−8.15 (2H, m), 8.31 (1H, s). ^{13}C NMR (90 MHz, $CDCl_3$) δ 112.3 (q), 125.5 (CH), 126.3 (q), 126.5 (q) 126.8 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 130.9 (q), 131.1 (CH), 138.7 (CH), 146.2 (q), 153.7 (q), 162.8 (q). HRMS (ESI) calculated for $C_{18}H_{11}N_2O_2Br$ 365.9998, found 366.0001.

5, 5′, 2″-Triphenyl-[2, 4′, 2′, 4″] teroxazole 17. A 5 mL microwave vial was charged with dioxazole **16** (100 mg, 0.27 mmol,

(20) Prepared according to: Van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *23*, 2369−2372.

1 equiv), oxazol-4-ylstannane **3** (354 mg, 0.82 mmol, 3 equiv), $Pd_2(dba)_3$ (12 mg, 5 mol %), PCy_3 (8 mg, 10 mol %), and anhydrous DMF (1 mL). The microwave vial was then sealed, and the resulting mixture stirred at room temperature for 5 min before irradiation at a preselected temperature of 150 °C in a Smith synthesizer for 15 min. The vial was then cooled with air jet cooling, opened, poured into a mixture of saturated aqueous KF (30 mL) and EtOAc (30 mL), and stirred for 30 min. After this time the organic layer was separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried over Mg_2SO_4, and filtered through celite. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (silica doped with 10% KF, hexane/Et_2O 6:4) to give the coupled product **17** (88 mg, 75% yield) as a yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42−7.54 (10H, m), 7.74 (2H, dd, J_1 = 1.3 Hz, J_2 = 8.4 Hz), 8.17−8.20 (2H, m), 7.74−8.32 (2H, m), 8.47 (1H, s). ^{13}C NMR (90 MHz, $CDCl_3$) δ 123.3 (CH), 124.4 (CH), 125.5 (quat), 126.5 (quat), 126.9 (CH), 127.1 (quat), 127.6 (quat), 127.7 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 128.9 (CH), 129.9 (CH), 131.1 (CH), 138.0 (quat), 139.2 (CH), 150.1 (quat), 151.6 (quat), 154.2 (quat), 155.0 (quat), 162.8 (quat). HRMS (ESI) calculated for $C_{27}H_{17}N_3O_3$ 431.1264, found 431.1266.

5′, 2″,-Diphenyl-[2,4′;2′,4″]teroxazole 18. Prepared as for compound **17** from bisoxazole **16** (100 mg, 0.27 mmol, 1 equiv), 2-(tributylstannyl)oxazole[17] (314 mg, 0.82 mmol, 3 equiv), $Pd_2(dba)_3$ (12 mg, 5 mol %), PCy_3 (8 mg, 10 mol %), and 1 mL of anhydrous DMF. The crude product was purified by flash chromatography (silica, hexane/EtOAc 8:2) to give the desired product **18** (63 mg, 60% yield) as a white solid. Mp = 179−182 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.32 (1H, s), 7.44−7.52 (6H, m), 7.79 (1H, s), 8.14−8.17 (m, 2H), 8.35−8.37 (2H, m), 8.44 (1H, s). ^{13}C NMR (90 MHz, $CDCl_3$) δ 125.4 (quat), 126.4 (quat), 126.8 (CH), 126.9 (quat), 127.5 (CH), 128.3 (CH), 128.5 (CH), 128.8 (CH), 129.8 (CH), 131.1 (CH), 131.1 (quat), 138.8 (CH), 139.1 (CH), 149.9 (quat), 154.0 (quat), 155.8 (quat), 162.7 (quat). HRMS (ESI) calculated for $C_{21}H_{13}N_3O_3$ 355.0951, found 355.0949.

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Supporting Information Available: Full characterization of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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