A Method for Iodination of Oxazoles at C-4 via 2-Lithiooxazoles

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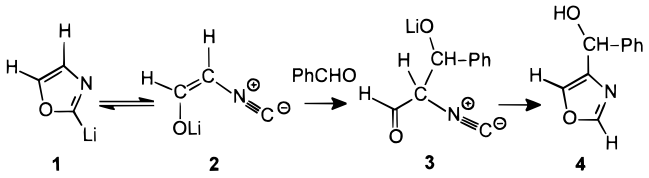
Received July 14, 1998

In connection with a synthesis project, we were interested in testing the palladium-mediated coupling reaction of a 2-unsubstituted 4-halooxazole. However, no prior example of this specific structural type could be found in the literature. Electrophilic halogen sources do react with oxazoles at C-4, but this option is limited by functional group compatibility issues and by competing attack at C-2 and C-5.[1] An alternative approach was sought that would allow functionalization at C-4 without the need to block C-2. A solution to this problem has now been found that exploits the equilibrium between cyclic (**1**) and acyclic (**2**) valence bond tautomers of 2-lithiated oxazoles as described below.

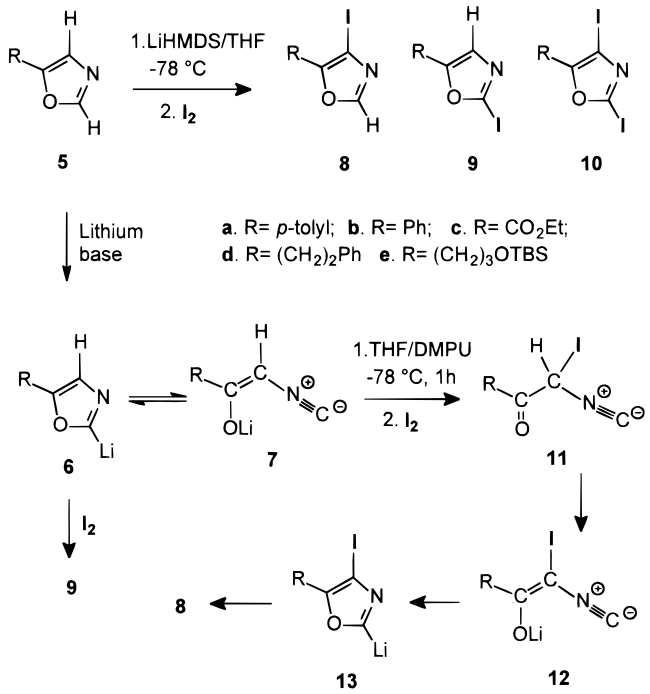
Earlier workers have established that the regiochemistry of lithiooxazole trapping depends on oxazole substituents as well as on the nature of the electrophile.[2−4] In a relevant study, it was shown that the major product of reaction between lithiated oxazole (**1** + **2**) and benzaldehyde is the C-4 substituted oxazole **4**, resulting from



reaction of the dominant acyclic valence bond tautomer **2** via the initial aldol adduct **3** followed by proton transfer and recyclization.[4] On the basis of this precedent, it seemed possible that direct halogenation of a 2-lithiated oxazole might produce a C-4 halogenated oxazole if the halogen source selects for the acyclic valence bond tautomer. The prospects were evaluated starting with 5-(*p*-tolyl)oxazole **5a**[2a,5] as a substrate that contains convenient ^{1}H NMR signals to simplify product assay.

Conversion of **5a** to the lithiated **6a** + **7a** was readily achieved with a variety of bases including LiHMDS and *n*-butyllithium. According to recent studies,[3] the acyclic enolate **7a** should be the dominant if not exclusive species present in THF solution. Nevertheless, addition of iodine to the anion gave mixtures of cyclic products including

Scheme 1



the 4-iodo- and 2-iodooxazoles **8a** and **9a** as well as a diiodooxazole **10a** (Scheme 1). The desired **8a** was the major product using LiHMDS in THF (ca. 3:1 **8a**:**9a**), but the product ratio was inverted with *n*-butyllithium as the base. Some improvement in the ratio was obtained by adding acetonitrile after anion generation with *n*-butyllithium (ca. 5−6:1 **8a**:**9a**). However, this procedure gave increased amounts of the diiodide **10a** (up to ca. 40%, vs 10−15% in THF alone).

All of the experiments were difficult to reproduce until it was found that addition of DMPU to the anion solution causes a larger increase in the **8a**:**9a** ratio (to ca. 10−15:1). When this procedure was modified to include 40−50 volume % of DMPU *prior* to the addition of base (LiHMDS), then a ratio of 97:3 **8a**:**9a** (73% isolated) was consistently obtained, together with 5% of the diiodo derivative **10a**. Alternatively, if the THF experiment was modified by using 1,2-diiodoethane as the electrophile (no DMPU added), then the 2-iodo isomer **9a** was obtained exclusively (>90% yield). High selectivity for a 2-iodooxazole has also been reported by Barrett et al. with iodine as the electrophile reacting with a 4-substituted 2-lithiooxazole.[6] In this case, formation of a 4-iodooxazole is blocked by the presence of a 4-alkyl group.

The same optimized procedure for 4-iodination was effective with 5-phenyloxazole (**5b**)[2a,5] (Table 1, entry 6). Both the yield and isomer ratio were lower in the case of 5-carbethoxyoxazole (**5c**)[7] (entry 7), but the 4-iodo isomer **8c** was obtained as the dominant product. On the other hand, when the optimized procedure was applied to 5-alkyloxazoles (entries 8−11),[8] the ratio of **8**:**9** increased to >49:1, but the proportion of the diiodides **10d** and **10e** increased as well. Fortunately, it was found that the

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(3) (a) Crowe, E.; Hossner, F.; Hughes, M. J. *Tetrahedron* **1995**, *51*, 8889. (b) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber./Recl.* **1997**, *130*, 1213.

(4) (a) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449. For related observations, see: Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058.

(5) Maquestiau, A.; Puk, E.; Flammang, R. *Tetrahedron Lett.* **1986**, *27*, 4023.

(6) Barrett, A. G. M.; Kohrt, J. T. *Synlett.* **1995**, 415.

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10.1021/jo981367d CCC: $18.00
Published on Web 12/30/1998

Table 1. Iodination of Lithiated Oxazoles (6 + 7)[a]

no.	substr	base	solvent	yield **8** + **9**, %	ratio **8**:**9**	ratio (**8** + **9**):**10**
1	**5a**	*n*-BuLi	THF	NA	1:3.3	8:1
2	**5a**	*n*-BuLi	THF/CH_3CN	NA	5.7:1	1.5:1
3	**5a**	KHMDS	THF	NA	1:1.5	1:1
4	**5a**	LiHMDS	THF	NA	3:1	6.7:1
5	**5a**	LiHMDS	THF/DMPU	73[b]	32:1	15:1
6	**5b**	LiHMDS	THF/DMPU	67[b]	32:1[c]	52:1[d]
7	**5c**	LiHMDS	THF/DMPU	44[e]	5.3:1[d]	6.3:1[d]
8	**5d**	LiHMDS	THF/DMPU	43	>49:1[c]	4:1[f]
9	**5d**	(1) LiHMDS (2) *n*-BuLi	THF/DMPU	64[g]	>49:1[c]	99:1[f]
10	**5e**	LiHMDS	THF/DMPU	34	>49:1[c]	1:1[f]
11	**5e**	(1) LiHMDS (2) *n*-BuLi	THF/DMPU	63[g]	>49:1[c]	99:1[f]

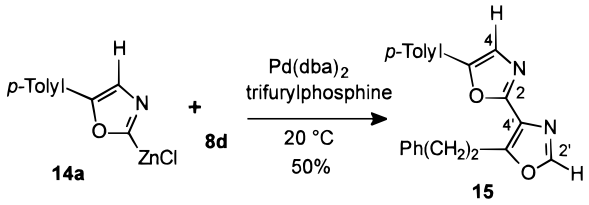
[a] Oxazole lithiation was performed at −78 °C for entries 1−6 and at −40 °C for entries 7−11. Reaction with iodine was performed at −78 °C. [b] Difficult separation; combined yield. [c] Minor isomer not isolated; ratio estimated by ^{1}H NMR C_4−H chemical shift analogy to entry 5 and integration. [d] Ratio based on isolated products. [e] Combined yield of isomers after separation by flash chromatography. [f] The 2,4-diiodo product was not completely purified or fully characterized; the ratio is estimated from NMR integration and the yield of **8**. [g] After iodine addition, the crude product was treated with *n*-butyllithium at −78 °C until a phenanthroline endpoint was detected.

initial mixture of **8** + **10** in these examples could be upgraded by selectively reducing the diiodides **10d** or **10e** in situ to **8d** or **8e**. It was sufficient to add *n*-butyllithium directly to the mixture of **8**, **9**, and **10** at −78 °C in THF/DMPU until a phenanthroline endpoint[9] was reached. Subsequent aqueous workup produced the desired **8d** (entry 9) and **8e** (entry 11) in >60% yield (>49:1 isomer ratio of **8**:**9**). The stoichiometry of *n*-butyllithium needed to reach the phenanthroline endpoint was ca. 2−2.3 equiv based on the substrate, suggesting that the residual hexamethyldisilazane consumes 1 equiv of the *n*-butyllithium and that reduction of the 2-iodo substituent of **10e** or **10d** occurs subsequently via lithium−iodine exchange.

In view of the complex product mixtures that were initially obtained, spectroscopic criteria were evaluated that would help to confirm the regiochemical assignments. Several useful correlations were found. Thus, all 2-unsubstituted oxazoles were readily identified by a singlet in the ^{1}H NMR spectrum in the range of δ 7.7−8.0 and by a distinct infrared absorption at ca. 3100 cm^{-1}. Introduction of iodine at C-2 resulted in the disappearance of these characteristic signals and also caused a striking upfield shift of the ^{13}C-2 NMR signal from ca. 150 ppm to ca. 100 ppm. The analogous heavy atom effect[10] was also seen for the 4-iodooxazoles **8** (C-4: ca. 77−91 ppm) and for the diiodooxazoles **10**. In the latter, two carbons experienced upfield shifts (for **10a**, C-2 or C-4 at 100.2 or 78.8 ppm). The combination of ^{1}H NMR, ^{13}C NMR, and infrared criteria allowed unambiguous assignment of structures for **8**−**10**.

The origins of the DMPU effect on iodination regioselectivity are not understood at this time. We are also uncertain about the pathway leading to the diiodide **10**. Enolization of **11** and eventual reprotonation of **13** are required to produce **8**, and the same intermediate **13** is a likely precursor of **10**. However, the enolate **12** might also react with a second equivalent of iodine. If iodination occurs at the isocyanide carbon, then intermediates would be generated that might be converted to **10** under the reaction conditions. We have no basis to choose between these possibilities.

With a route to 4-iodo-5-alkyloxazoles established, the feasibility of palladium-catalyzed coupling could be tested in a representative case. Barrett et al. had already shown that it is possible to prepare bis-oxazoles by coupling a 2-halooxazole with 2-phenyl-4-(tributylstannyl)oxazole.[6] We were interested in the alternative strategy that would exploit the easily accessible chlorozinc derivative **14a** (from **5a** + *n*-butyllithium, followed by $ZnCl_2$)[3a,11] as the activated organometallic component and **8d** as a representative 4-iodo-5-alkyloxazole coupling partner.[12] The desired coupling proceeded at room temperature using modified $Pd(dba)_2$/trifuranylphosphine conditions similar to those reported by Knochel et al. with 2-halozincated oxazoles made in a different way.[13] The procedure was modified to use a larger excess (2 equiv) of **14a** because the latter was found to decompose competitively with the coupling process. At room temperature (22 h, THF), this procedure gave the bis-oxazole **15** in 50% yield together with unreacted iodide (38% recovered; 88% material balance). No homocoupling products derived from either



14a or **8d** were detected, and 48% of **5a** was recovered (49% material balance based on a 2-fold excess of **14a**). This experiment demonstrates the feasibility of C-2:C′-4 coupling to form a C′-2 unsubstituted bis-oxazole **15** having the potential for subsequent bond formation at C′-2 via metalation chemistry.[3a,11,14]

Experimental Section

General. All reactions were carried out using flame-dried glassware under a nitrogen atmosphere. Solvents were dried as follows: THF was distilled from sodium/benzophenone; DMPU was distilled from CaH_2 and stored over 4 Å sieves.

5-(*p*-Tolyl)oxazole (5a).[2,5] The method of Van Leusen et al.[8b] was used. To a solution of tosylmethyl isocyanide (TosMIC, 4.90 g, 25.1 mmol, Aldrich) in 36 mL of freshly distilled methanol were added *p*-tolualdehyde (2.90 mL, 24.6 mmol, Aldrich) and K_2CO_3 (4.27 g, 30.9 mmol). The suspension was heated to reflux for 18.5 h, cooled to room temperature, and concentrated (aspirator). H_2O (ca. 15−20 mL) was added, the resulting oil was extracted with ether (4 × 100 mL), and the combined organic layer was dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on EM silica gel 60 (26 × 6 cm), 4:1 hexane/ether eluent; fraction volume of 60 mL after an initial fraction of 100 mL. Fractions 23−41 contained 2.49 g (64%) of **5a** as an off-white solid. Analytical

(8) Prepared according to literature precedents: (a) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065. (b) Van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *23*, 2369.

(9) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

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(12) Coupling of 2,5-disubstituted 4-bromooxazoles with alkynes or alkenes has been reported. Sakamoto, T.; Nagata, H.; Kondo, Y.; Shiraiwa, M.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 823.

(13) Prasad, A. S. B.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237.

(14) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192.

TLC on silica gel, 2.1:1 hexane/EtOAc, $R_f = 0.30$. Pure material was obtained by crystallization from hexane, mp 65−65.4 °C, light yellow plates: molecular ion calcd for $C_{10}H_9NO$ 159.06840, found $m/e = 159.0679$, error = 3 ppm; base peak = 159 amu; IR (KBr, cm^{-1}) 3124, =C−H; 1106, C−O; 300 MHz NMR ($CDCl_3$, ppm) δ 7.88 (1H, s), 7.54 (2H, d, $J = 8.1$ Hz), 7.29 (1H, s), 7.23 (2H, d, $J = 8.1$ Hz), 2.38 (3H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 151.7, 150.1, 138.6, 129.6, 125.0, 124.3, 120.8, 21.3.

5-Carbethoxyoxazole (5c). The method of Schöllkopf et al. was used with modifications.[7] To a solution of methyl isocyanide (8.0 mL, 146 mmol) in 150 mL of THF at −78 °C was added *n*-BuLi (154 mmol, 1.54 M in hexanes) dropwise over 20 min. The pale yellow suspension was stirred for 1 h and then transferred via a thick cannula (cooled with dry ice wrapped in aluminum foil) to a vigorously stirred solution of diethyl oxalate (22 mL, 162 mmol) in 50 mL of THF at −78 °C over 5 min. The cooling bath was removed, the yellow solution was allowed to warm to room temperature over 2 h, and 12 mL of AcOH was added. After concentration (aspirator), 100 mL of aqueous $NaHCO_3$ was added to the residue, and the mixture was extracted with 3 × 100 mL of ether and dried (Na_2SO_4). After removal of solvent (aspirator) the residue was purified by flash chromatography on silica gel (4.5 × 20 cm), 500 mL of 3:1 hexane/ether followed by 500 mL of 2:1 hexane/ether, followed by 400 mL of 1:1 hexane/ether eluent, 20 mL fractions. Fractions 37−70 contained 14.6 g (71%) of **5c** as colorless liquid. Analytical TLC on silica gel, 2.1:1 hexane/EtOAc, $R_f = 0.35$. **5c**: molecular ion calcd for $C_6H_7NO_3$ 141.04260, found $m/e = 141.0423$, error = 2 ppm; base peak = 113 amu; IR (neat, cm^{-1}) 3132, =C−H; 1734, C=O; 300 MHz NMR ($CDCl_3$, ppm) 8.03 (1H, s), 7.78 (1H, s), 4.41 (2H, q, $J = 7.1$ Hz), 1.40 (3H, t, $J = 7.1$ Hz);. ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 157.5, 153.2, 142.7, 133.2, 61.6, 14.2.

5-(2-Phenylethyl)oxazole (5d). The method of Schöllkopf et al. was used with modifications.[7] To a solution of methyl isocyanide (1.1 mL, 20 mmol) in 20 mL of THF at −78 °C was added *n*-BuLi (21 mmol, 1.60 M in hexanes) dropwise over 5 min. The pale yellow suspension was stirred for 10 min. A solution of ethyl hydrocinnamate (3.22 g, 18.1 mmol) in 15 mL of THF was added dropwise via cannula over 5 min. The cooling bath was removed, and the tan solution was allowed to warm to room temperature over 3 h. The reaction was quenched with 50 mL of brine, extracted with ether (2 × 50 mL), and dried (Na_2SO_4). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (2.5 × 20 cm), 1:1 hexane/ether eluent, 15 mL flash fractions. Fractions 7−12 contained 2.36 g (75%) of **5d** as a colorless liquid. Analytical TLC on silica gel, 2.1:1 hexane/EtOAc, $R_f = 0.35$. **5d**: molecular ion calcd for $C_{11}H_{11}NO$ 173.08410, found $m/e = 173.0842$, error = 1 ppm; IR (neat, cm^{-1}) 3128, =C−H; 1510, C=C; 300 MHz NMR ($CDCl_3$, ppm) 7.74 (1H, s) 7.30−7.14 (5H, m) 6.71 (1H, s) 2.94 (4H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 151.9, 149.9, 140.2, 128.3, 128.1, 126.1, 122.1, 33.6, 27.1.

5-(*tert*-Butyldimethylsilyloxypropyl)oxazole (5e). The method of Jacobi et al. was used.[8a] To a solution of methyl isocyanide (1.0 mL, 19 mmol) in 130 mL of THF at −78 °C was added *n*-BuLi (21 mmol, 1.54 M in hexanes) dropwise, and the solution was stirred for 40 min. A solution of γ-butyrolactone (1.3 mL, 16.9 mmol) in 10 mL of THF was added dropwise via cannula. The cooling bath was removed, and the tan solution was allowed to warm to room temperature over 3 h. DMF (30 mL) was added to the suspension. After ca. 16 h, glacial acetic acid (1.6 mL) was added, and the mixture was allowed to stir for an additional hour. The mixture was concentrated (aspirator), combined with concd $NaHCO_3$ (80 mL), and extracted with CH_2Cl_2 (6 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated, and the crude alcohol was dissolved in 30 mL of CH_2Cl_2. A solution of DMAP (58 mg, 0.46 mmol) in 10 mL of CH_2Cl_2 was added, followed by *i*-Pr_2NEt (4.42 mL, 25.4 mmol). The solution was cooled to 0 °C, and TBSCl (3.26 g, 20.3 mmol) in 10 mL of CH_2Cl_2 was added. After 30 min, the ice bath was removed and the reaction mixture was warmed to room temperature for 2.5 h. The mixture was poured onto H_2O (30 mL), extracted with CH_2Cl_2 (3 × 10 mL), and dried ($MgSO_4$). After removal of solvent (aspirator) the residue was purified by flash chromatography on silica gel, 8:1 hexane/EtOAc eluent, fraction volume of 15 mL after an initial fraction of 60 mL; fractions 12−27 contained 2.54 g (62%) of **5e** as yellow liquid. Analytical TLC on silica gel, 4:1 hexane/EtOAc, $R_f = 0.37$. **5e**: molecular ion calcd for $C_{12}H_{24}NO_2Si$ 242.1576, found m/e = 242.1570 (M + 1), error = 2 ppm; base peak = 184 amu; IR (neat, cm^{-1}) 3124, =C−H; 2929, C−H; 300 MHz NMR ($CDCl_3$, ppm) 7.76 (1H, s), 6.77 (1H, t, $J = 1.2$ Hz), 3.65 (2H, t, $J = 6.2$ Hz), 2.75 (2H, dt, $J = 1.2$, 7.5 Hz), 1.90−1.81 (2H, m), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 152.8, 149.9, 121.9, 61.7, 30.5, 25.8, 21.7, 18.2, −5.4.

General Procedure for the Synthesis of 4-Iodooxazole Derivatives 8a−c. Method A. To a solution of hexamethyldisilazane (HMDS, 0.16 mL, 0.758 mmol, Aldrich, distilled from CaH_2) in 0.50 mL of THF cooled to 0 °C was added *n*-BuLi (0.50 mL, 1.49 M in hexane, Aldrich). The solution was stirred for 10 min at 0 °C and then warmed to room temperature for an additional 20 min. In a separate flask, the oxazole substrate **5a−c** (ca. 0.627 mmol) was dissolved in a mixture of 1.6 mL of THF/1.25 mL of DMPU, cooled to −78 °C, and the LiHMDS solution was added via cannula. After 1 h, a solution of I_2 (182 mg, 0.716 mmol, Mallinckrodt) in 2.1 mL of THF was added dropwise by syringe over a 15 min period. The mixture was stirred for 1 h at −78 °C and then poured onto a mixture of ether (50 mL) and 10% $Na_2S_2O_3$ (10 mL). The organic layer was washed with H_2O (2 × 25 mL), dried ($MgSO_4$), and purified as described for specific examples.

4-Iodo-5-(*p*-tolyl)oxazole (8a). Reactants (general method A): 5-(*p*-tolyl)oxazole (**5a**) (100 mg, 0.627 mmol), I_2 (182 mg, 0.716 mmol, Mallinckrodt), and 0.75 mmol of LiHMDS. After removal of solvent (aspirator), the residue was purified by flash chromatography on EM silica gel 60 (20 × 2 cm), 4:1 hexane/ether eluent; 15 mL fractions with an initial fraction of 30 mL. Fractions 2−4 contained 13 mg (5%) of 2,4-diiodooxazole **10a**; fractions 5−10 contained 131 mg (73%) of a mixture of **8a**:**9a**, 97:3 by ^1H NMR analysis; fractions 17−23 contained 14 mg of recovered oxazole **5a**. **8a**: TLC on silica gel, 2.1:1 hexane/EtOAc, $R_f = 0.46$. Pure material was obtained by crystallization from hexane: mp 40.0−41 °C, light yellow rods; molecular ion calcd for $C_{10}H_8INO$ 284.96530, found $m/e = 284.9656$, error = 1 ppm; base peak = 285 amu; IR (KBr, cm^{-1}) 3093, =C−H; 1491, C=C; 300 MHz NMR ($CDCl_3$, ppm) 7.87 (1H, s), 7.85 (2H, d, $J = 8.1$ Hz), 7.27 (2H, d, $J = 8.1$ Hz), 2.40 (3H, s); ^{13}C NMR (75.4 MHz, CD_2Cl_2, ppm) 151.5, 150.9, 139.9, 129.7, 126.3, 124.5, 77.3, 21.5. 2-Iodo-5-(*p*-tolyl)oxazole **(9a)**: TLC on silica gel, 2.1:1 hexane/EtOAc, $R_f = 0.46$. Pure material was obtained by crystallization from hexane: mp 112−112.5 °C, light yellow needles; molecular ion calcd for $C_{10}H_8INO$ 284.96530; found $m/e = 284.9647$, error = 2 ppm; base peak = 285 amu; IR (KBr, cm^{-1}) 3024, =C−H; 1506, C=C; 300 MHz NMR ($CDCl_3$, ppm) 7.50 (2H, d, $J = 8.3$ Hz), 7.25−7.22 (3H, m), 2.39 (3H, s); ^{13}C NMR (75.4 MHz, CD_2Cl_2, ppm) 158.0, 139.6, 129.9, 124.7, 124.5, 124.4, 99.8, 21.5. 2,4-Diiodo-5-(*p*-tolyl)oxazole (**10a**): TLC on silica gel, 2.1:1 hexane/EtOAc, $R_f = 0.59$. Pure material was obtained by crystallization from ether/hexane: mp 147−148 °C, light yellow rods; molecular ion calcd for $C_{10}H_7I_2NO$ 410.86220, found $m/e = 410.8606$, error = 4 ppm; base peak = 411 amu; IR (KBr, cm^{-1}) 3024, =C−H; 1456, C=C; 1170, C−O; 300 MHz NMR ($CDCl_3$, ppm) 7.79 (2H, d, $J = 8.1$ Hz), 7.27 (2H, d, $J = 8.1$ Hz), 2.41 (3H, s); ^{13}C NMR (125.7 MHz, CD_2Cl_2, ppm) δ 157.7, 140.5, 129.7, 126.3, 123.7, 100.7, 78.8, 21.5.

4-Iodo-5-phenyloxazole (8b). Reactants (general method A): 5-phenyloxazole (**5b**) (90 mg, 0.623 mmol), I_2 (181 mg, 0.714 mmol, Mallinckrodt), and 0.75 mmol of LiHMDS. After removal of solvent (aspirator), the residue was purified by flash chromatography on EM silica gel 60 (20 × 2 cm), 4:1 hexane/ether eluent; 15 mL fractions with an initial fraction of 30 mL. Fractions 1−3 contained 3 mg (1%) of 2,4-diiodooxazole **10b**; fractions 4−10 contained 114 mg (67%) of **8b**:**9b**, 97:3 ratio by ^1H NMR analysis; fractions 13−20 contained 4 mg of recovered oxazole **5b**. **8b**: TLC on silica gel, 2.1:1 hexane/EtOAc, $R_f = 0.47$. Pure material was obtained by crystallization from ether/hexane: mp 103−104 °C, light yellow hexagonal rods; molecular ion calcd for C_9H_6INO 270.94960, found $m/e = 270.9489$, error = 3 ppm; base peak = 271 amu; IR (KBr, cm^{-1}) 3124, =C−H; 1495, C=C; 300 MHz NMR ($CDCl_3$, ppm) 7.96 (2H, d, $J = 7.7$ Hz), 7.89 (1H, s), 7.48−7.35 (3H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) δ 151.3, 150.4, 129.2, 128.6, 126.9, 126.1, 77.6. 2,4-Diiodo-5-phenyloxazole (**10b**): TLC on silica gel, 2.1:1 hexane/EtOAc, $R_f = 0.54$. Pure material was obtained by crystallization from

ether/hexane: mp 110−111 °C, white needles; molecular ion calcd for $C_9H_5I_2NO$ 396.84650, found *m/e* = 396.8455, error = 3 ppm; base peak = 397 amu; IR (KBr, cm^{-1}) 3057, =C−H; 1454, C=C; 300 MHz NMR ($CDCl_3$, ppm) 7.91 (2H, d, *J* = 7.4 Hz), 7.47−7.43 (3H, m); ^{13}C NMR (125.7 MHz, CD_2Cl_2, ppm) 130.0, 129.1, 126.7, 126.3, 101.3, 79.6 (one signal unaccounted for due to signal/noise limitations).

4-Iodo-5-carbethoxyoxazole (8c). Reactants (general method A): 5-carbethoxyoxazole (**5c**) (89 mg, 0.628 mmol), I_2 (182 mg, 0.716 mmol, Mallinckrodt), and 0.75 mmol of LiHMDS. The general procedure was modified by performing the addition of LiHMDS to a solution of the oxazole at −40 °C. After addition of I_2, the solution was immediately cooled to −78 °C. After removal of solvent (aspirator), the residue was purified by flash chromatography on EM silica gel 60 (20 × 2 cm), 5.7:1 hexane/ether eluent; fraction volumes of 15 mL with an initial fraction of 30 mL. Fractions 12−13 contained 17 mg (7%) of 2,4-diiodooxazole **10c**; fractions 15−18 contained 12 mg (7%) of 2-iodooxazole **9c**; fractions 20−25 contained 62 mg (37%) of 4-iodooxazole **8c**; fractions 33−40 contained 3 mg of recovered oxazole **5c**. **8c**: TLC on silica gel, 2.1:1 hexane/EtOAc, R_f = 0.42. Pure material was obtained by crystallization from hexane: mp 56.5−57 °C, white cubes; molecular ion calcd for $C_6H_6INO_3$ 266.93950, found *m/e* = 266.9403, error = 3 ppm; base peak = 239 amu; IR (KBr, cm^{-1}) 3109, =C−H; 1711, C=O; 300 MHz NMR ($CDCl_3$, ppm) 7.96 (1H, s), 4.43 (2H, q, *J* = 7.2 Hz), 1.43 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 157.1, 153.7, 143.4, 90.9, 62.0, 14.1. 2-Iodo-5-carbethoxyoxazole **(9c)**: TLC on silica gel, 2.1:1 hexane/EtOAc, R_f = 0.45. Pure material was obtained by crystallization from hexane: mp 75−75.5 °C, white needles; molecular ion calcd for $C_6H_6INO_3$ 266.93950, found *m/e* = 266.9415, error = 8 ppm; base peak = 112 amu; IR (KBr, cm^{-1}) 3105, =C−H; 1720, C=O; 300 MHz NMR ($CDCl_3$, ppm) 7.65 (1H, s), 4.40 (2H, q, *J* = 7.2 Hz), 1.39 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 156.4, 148.4, 136.0, 105.8, 61.7, 14.2. 2,4-Diiodo-5-carbethoxyoxazole **(10c)**: TLC on silica gel, 2.1:1 hexane/EtOAc, R_f = 0.50. Pure material was obtained by crystallization from ethyl acetate: mp 178.5−179 °C, white needles; molecular ion calcd for $C_6H_5I_2NO_3$ 392.83630, found *m/e* = 392.8352, error = 3 ppm; IR (KBr, cm^{-1}) 1705, C=O; 300 MHz NMR ($CDCl_3$, ppm) 4.42 (2H, q, *J* = 7.2 Hz), 1.42 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 156.1, 149.4, 106.7, 92.3, 62.2, 14.2.

General Procedure for the Synthesis of 4-Iodo-5-alkyloxazoles 8d and 8e. Method B. Lithium hexamethyldisilazide (0.75 mmol) was prepared as described for method A. In a separate flask, the oxazole substrate **5d** or **5e** (0.627 mmol) was dissolved in a mixture of 1.6 mL of THF/1.25 mL of DMPU and cooled to −40 °C, and the LiHMDS solution was added via cannula. The resulting solution was stirred at −40 °C. After 1 h, a solution of I_2 (237 mg, 0.933 mmol, Mallinckrodt) in 2.1 mL of THF was added dropwise by syringe over a period of 15 min, and the solution was cooled to −78 °C. After 1 h at −78 °C, 1,10-phenanthroline (5 mg, 0.025 mmol, Aldrich) in 0.5 mL of THF was added via cannula and *n*-BuLi (2.0−2.3 equiv, 1.60 M in hexane, Aldrich) was added dropwise until a rust color persisted. The solution was immediately quenched with 400 μL of H_2O and then poured onto a mixture of ether (50 mL), H_2O (15 mL), and 10% $Na_2S_2O_3$ (10 mL). The organic layer was washed with H_2O (2 × 20 mL) and dried ($MgSO_4$).

4-Iodo-5-(2-phenylethyl)oxazole (8d). Reactants (method B): 5-(2-phenylethyl)oxazole (**5d**) (109 mg, 0.627 mmol), I_2 (237 mg, 0.933 mmol, Mallinckrodt), LiHMDS (0.75 mmol), and *n*-BuLi (0.9 mL, 1.60 M, Aldrich). After removal of solvent (aspirator), the residue was purified by flash chromatography on EM silica gel 60 (20 × 2 cm), 5.7:1 hexane/ether eluent; fraction volumes of 15 mL with an initial volume of 40 mL. Fractions 5−6 contained 2 mg of impure material assumed to be 2,4-diiodooxazole **10d** by analogy; fractions 9−14 contained 104 mg (64%) of **8d**, >98:2 **8d:9d** ratio by ^1H NMR analysis; fractions 26−45 contained 16 mg of recovered oxazole **5d**. **8d**: TLC on silica gel, 2.1:1 hexane/EtOAc, R_f = 0.59; molecular ion calcd for $C_{11}H_{10}INO$ 298.9810, found *m/e* = 298.9819, error = 3 ppm; IR (neat, cm^{-1}) 3128, =C−H; 3026, =C−H; 1497, C=C; 300 MHz NMR ($CDCl_3$, ppm) 7.67 (1H, s), 7.32−7.14 (5H, m), 3.03−2.91 (4H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 153.6, 151.2, 139.9, 128.6, 128.3, 126.5, 79.9, 33.8, 27.2.

4-Iodo-5-(*tert*-butyldimethylsilyloxypropyl)oxazole (8e). Reactants (method B): 5-(*tert*-butyldimethylsilyloxypropyl)-oxazole (**5e**) (119 mg, 0.495 mmol), I_2 (189 mg, 0.743 mmol, Mallinckrodt), LiHMDS (0.6 mmol), and *n*-BuLi (0.615 mL, 1.60 M, Aldrich). After removal of solvent (aspirator), the residue was purified by flash chromatography on EM silica gel 60 (20 × 2 cm), 9:1 hexane/ether eluent; fraction volumes of 15 mL with an initial fraction of 40 mL. Fractions 2−4 contained 2 mg of impure material assumed to be 2,4-diiodooxazole **10e** by analogy; fractions 6−11 contained 114 mg (63%) of **8e**, >98:2 **8e:9e** ratio by ^1H NMR analysis; fractions 26−31 contained 17 mg of recovered oxazole **5e**. **8e**: TLC on silica gel, 3:2 hexane/EtOAc, R_f = 0.50; HRMS calcd for $C_{11}H_{19}INO_2Si$ (M - 15) 352.0232, found *m/e* = 352.0211, error = 6 ppm; IR (neat, cm^{-1}) 3118, =C−H; 1105, C−O; 300 MHz NMR ($CDCl_3$, ppm) 7.77 (1H, s), 3.64 (2H, t, *J* = 6.1 Hz), 2.78 (2H, t, *J* = 7.5 Hz), 1.87−1.82 (2H, m), 0.91 (9H, s), 0.60 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 154.4, 151.1, 79.3, 61.7, 30.7, 25.9, 21.76, 18.3, −5.3.

2-Iodo-(*p*-tolyl)oxazole (9a) Using Diiodoethane as the Electrophile. To a solution of hexamethyldisilazane was added HMDS (0.16 mL, 0.758 mmol, Aldrich, distilled from CaH_2) in 0.50 mL of THF cooled to 0 °C dropwise *n*-BuLi (0.50 mL, 1.49 M in hexane, Aldrich). The solution was stirred for 10 min at 0 °C and then warmed to room temperature for an additional 20 min. In a separate flask, 5-(*p*-tolyl)oxazole (**5a**) (100 mg, 0.627 mmol) was dissolved in 2.85 mL of THF and cooled to −78 °C, and the LiHMDS solution was added via cannula. The resulting solution was stirred at −78 °C. After 1 h, a solution of 1,2-diiodoethane (202 mg, 0.717 mmol, Aldrich) in 1.7 mL of THF was added dropwise by syringe. The resulting mixture was allowed to warm to room temperature for 1 h and then poured into a mixture of ether (50 mL) and 10% $Na_2S_2O_3$ (10 mL). The organic layer was washed with H_2O (20 mL) and dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on EM silica gel 60 (17 × 2 cm), 4:1 hexane/ether eluent, fraction volumes of 15 mL after an initial fraction of 30 mL. Fractions 2−3 contained 3 mg (1%) of 2,4-diiodooxazole **10a**; fractions 4−9 contained 166 mg (93%) of 2-iodooxazole **9a** as a white solid.

5-(*p*Tolyl)-5′-(2-phenylethyl)- 2,4′-bisoxazole (15). To a solution of 5-(*p*-tolyl)oxazole (**5a**) (54 mg, 0.336 mmol) in 1.4 mL of THF cooled to −78 °C was added *n*-BuLi (0.23 mL, 1.6 M in hexane, Aldrich). After 0.5 h, a solution of $ZnCl_2$ (0.34 mL, 1.0 M in ether, Aldrich) was added. The resulting mixture was allowed to warm to room temperature. In a separate flask a solution of $Pd_2(dba)_3$ (16 mg, 0.017 mmol, Aldrich) and (*o*-furyl)$_3$P (15 mg, 0.066 mmol, Aldrich) in 0.3 mL THF was stirred until the red wine color disappeared. To the catalyst solution was added a solution of 4-iodo-(5-phenylethyl)oxazole (**8d**) (50 mg, 0.168 mmol) in 0.4 mL of THF, followed by the 2-chlorozincoxazole solution. The resulting mixture was stirred at room temperature for 22 h, and then saturated NH_4Cl (3 mL) was added. The layers were separated, the aqueous layer was then extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by preparative layer silica gel (20 × 20 × 0.2 cm), 1.5:1 hexane/ether eluent to give 28 mg (50%) of 2,4′-bisoxazole **15**, 25 mg of recovered 5-(*p*-tolyl)oxazole (**5a**), and 19 mg of recovered 4-iodooxazole **8d**. **15**: TLC on silica gel, 3:2 hexane/ether, R_f = 0.19. Pure material was obtained by crystallization from ethyl acetate: mp 107.5−108.0 °C, white needles; molecular ion calcd for $C_{21}H_{18}N_2O_2$ 330.13680, found *m/e* = 330.1371, error = 0 ppm; base peak = 239 amu; IR (KBr, cm^{-1}) 3115, =C−H; 1502, C=C; 300 MHz NMR ($CDCl_3$, ppm) 7.85 (1H, s), 7.60 (2H, d, *J* = 8.1 Hz), 7.39 (1H, s), 7.30−7.17 (7H, m), 3.48 (2H, t, *J* = 7.9 Hz), 3.07 (2H, t, *J* = 7.9 Hz), 2.39 (3H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) 154.7, 152.8, 151.2, 149.7, 140.1, 138.5, 129.5, 128.5, 128.3, 126.4, 125.2, 125.0, 124.3, 122.5, 33.8, 27.6, 21.4.

Acknowledgment. This work was supported by NIH Grant CA17918.

Supporting Information Available: ^1H NMR spectra for **5c**−**e**, **8a**−**e**, **9a**, **10a**−**c**, **9c**, and **15**. See any current masthead page for ordering and Internet access information.

JO981367D