

## 2-Metallated Oxazoles; pKa Dependent Deuterations, NMR Studies and Palladium Catalysed Couplings.

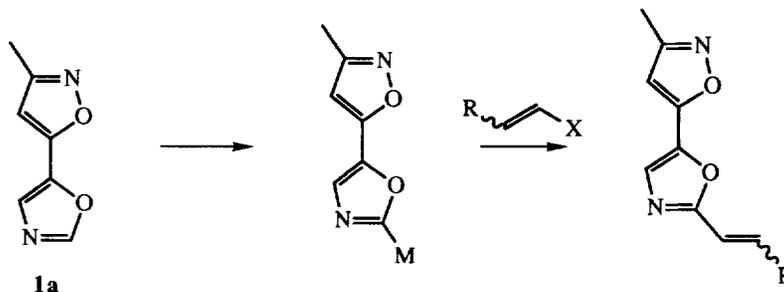
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**Abstract:** Deuteration experiments on 2-lithiated oxazoles show a pKa dependent regioselectivity suggesting that the ring cleaved tautomer dominates the equilibrium. Transmetalation to the zinc derivative gives a species which behaves as a C2 ring closed nucleophile as judged by deuteration and palladium catalysed coupling experiments. These conclusions are supported by nmr spectroscopy studies of the metallated species.

We recently had occasion to examine the 2-metallation and subsequent cross coupling of oxazole **1a** with vinyl halides (**Scheme 1**).



Scheme 1

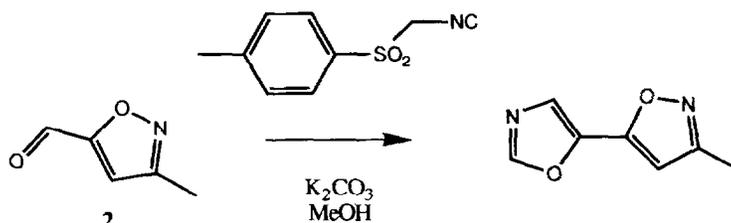
The cross coupling of 2-stannylated oxazoles has been reported<sup>1</sup>. Whilst this represents a valuable synthetic tool for research purposes toxicity and purification problems associated with organostannanes currently make their late inclusion in the large scale synthesis of drug substances undesirable. The zinc derivatives were of particular interest due to their anticipated compatibility with sensitive functionality and the proven utility of other hetero-aryl zincs in cross coupling reactions<sup>2</sup>.

To generate the metallated species it was intended to deprotonate with an alkyllithium at C2 followed by transmetalation. The 2-position of simple oxazoles is known to be the most acidic<sup>3</sup> but the derived 2-lithio oxazoles show ambident nucleophilicity attributed to a ring-chain equilibrium<sup>4-6</sup> (**Scheme 2**).



Scheme 2

The oxazole **1a** was prepared according to Scheme 3 from the isoxazolocarboxaldehyde<sup>7</sup> **2** by condensation with toluenesulfonylmethylisocyanide<sup>8</sup>.



Scheme 3

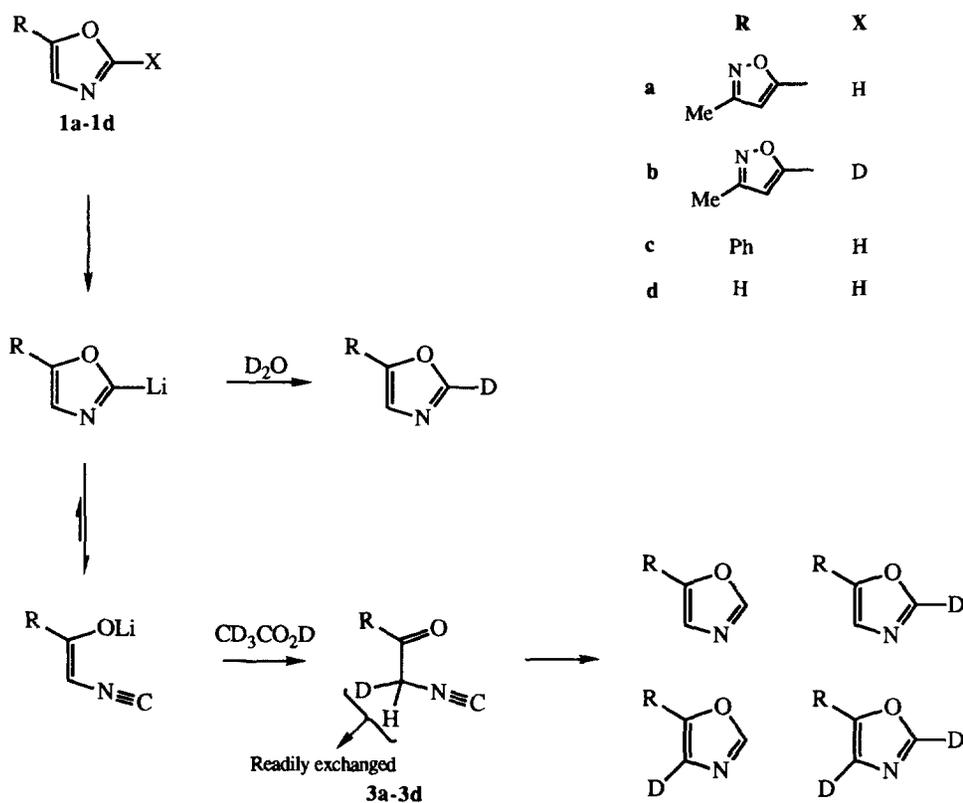
Treating oxazole **1a** at  $-78^\circ\text{C}$  in THF with *n*-BuLi generates an intense red species which is stable at room temperature over 24 hours. Quenching with  $\text{D}_4$ -acetic acid caused instant loss of colour. Isolation, using an aqueous ammonium chloride work-up, gave an essentially quantitative recovery with  $\sim 50\%$  deuterium incorporation at both C2 and C4 of the oxazole ring by  $^1\text{H}$  nmr.  $^2\text{H}$  nmr confirmed the absence of incorporation at other positions in particular no incorporation was observed in the methyl side chain. The kinetic acidity at C2 was demonstrated by treating the 2-deuterio analogue **1b** as before but with an acetic acid quench, which quantitatively removed all the deuterium. When the lithio species was inverse quenched into excess  $\text{D}_4$ -acetic acid the incorporation rose to  $\sim 80\%$  at both C2 and C4<sup>9</sup>. Partial quenching with  $\text{D}_4$ -acetic acid (0.5eq.) followed by water led to a reduced incorporation but similar distribution of deuterium (29% at C2, 31% at C4). These results contrast with literature precedent<sup>4,6</sup>, using  $\text{D}_2\text{O}$ , where only incorporation at C2 was reported.

The disparity between our results and previous literature prompted us to examine the quench with  $\text{D}_2\text{O}$ . The lithio species was prepared as before then quenched with a large excess of  $\text{D}_2\text{O}$ , the intense red colour partitioned into the aqueous phase where it slowly discharged over  $\sim 30$  minutes. The oxazole was isolated with high recovery and was completely deuterated at C2 with about 10% incorporation at C4. Clearly the acidity of the quenching agent is important.

These results would suggest that quenching with  $\text{D}_4$ -acetic acid occurs predominantly on the ring open isomer to give the isocyanoketone **3a** which undergoes rapid proton scrambling prior to ring closure. In addition the ring closure in this case is fast relative to the rate of addition to account for the difference in incorporation between normal and inverse quenching. In contrast it would appear that  $\text{D}_2\text{O}$  does not quench the ring open form significantly but reacts with the ring closed form to give primarily the 2-deuteriooxazole. The slowness of this reaction, as judged by the disappearance of colour, is more likely to be due to a very low equilibrium concentration of the ring closed anion rather than a slow quench (Scheme 4). These results would be entirely consistent with the anticipated difference in pKa for the isocyanoketone and the oxazole.

Further supporting evidence was obtained when 5-phenyloxazole **1c** was used in the deuteration reactions. Quenching with  $\text{D}_4$ -acetic acid caused immediate loss of colour but led to a very low deuterium incorporation at both C2 and C4 (15% equally at C2 and C4); however the  $^1\text{H}$  nmr spectrum of the crude product showed signals consistent with the presence of the isocyanoketone **3c** which converted to the oxazole

on attempted chromatography. Stirring the quenched reaction for 2 hours prior to aqueous work-up gave high (75%) incorporation at both C2 and C4. These results are consistent with **Scheme 4** with a slow ring closure and the deuterium being washed out of the isocyanoketone **3c** during the aqueous partition. Clearly the rate of ring closure is dependent on the 5 substituent.



**Scheme 4**

These results, summarised in **Table 1**, demonstrate that deuterium quenches of systems where dynamic equilibria are possible or expected must be interpreted very carefully.

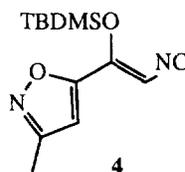
Oxazole	Reaction Conditions	Quench Method		% D at C2	% D at C4
		Reagent	Conditions		
<b>1a</b>	5 minutes at ambient	D <sub>4</sub> AcOH	Quench at -70°C	57	60
<b>1a</b>	18 hours at ambient	D <sub>4</sub> AcOH	Quench at -70°C	50	54
<b>1a</b>	5 minutes at ambient	D <sub>4</sub> AcOH	Inverse quench at ambient	75	75
<b>1a</b>	5 minutes at ambient	D <sub>4</sub> AcOH	0.5eq then H <sub>2</sub> O	15	25
<b>1c</b>	5 minutes at ambient	D <sub>4</sub> AcOH	Quench at -70°C, 5 mins at ambient then partition	15	15
<b>1c</b>	5 minutes at ambient	D <sub>4</sub> AcOH	Quench at -70°C 2hrs at ambient then partition	75	75
<b>1b</b>	5 minutes at ambient	AcOH	Quench at ambient	0	0
<b>1a</b>	5 minutes at ambient	D <sub>2</sub> O	Quench at -70°C 1 hour at ambient	100	10

**Table 1 Deuteration Experiments.**

The lithio derivatives were transmetalated to the corresponding zinc complexes by treating a THF solution at -78°C with 1.1 equivalents of ZnCl<sub>2</sub> in ether. For **1a** and **1c** this was accompanied by a colour change from red to purple (the parent lithio oxazole and its derived zinc complex are both colourless). Precipitation was observed at low temperatures but an homogeneous solution was obtained on warming to room temperature.

Quenching these solutions with D<sub>4</sub>-acetic acid gave near quantitative recoveries of the oxazoles with >85% D incorporation (<sup>1</sup>H nmr) exclusively at C2 (<sup>2</sup>H nmr). With respect to the reservations concerning deuteration mentioned earlier these results suggest exclusive nucleophilic behaviour through C2 and that the zinc complexes, without implication to the actual structures in solution, may be treated as the ring closed organometallics.

In order to gain greater understanding of the nature of the species in solution an nmr spectroscopy study was undertaken. As a model for the open chain structure the silyl ether **4** was prepared by treating the lithiated derivative of the oxazole **1a** with tert-butyldimethylsilylchloride, a reaction with good precedent in the literature<sup>5</sup>.



The lithio derivative was prepared as usual, allowed to attain ambient temperature and the solvents removed under reduced pressure. The residue was dissolved in THF containing 20% D<sub>8</sub> THF to provide a lock signal and the <sup>1</sup>H and <sup>13</sup>C nmr spectra recorded. The zinc derivative was prepared by adding a solution of anhydrous zinc chloride in THF to the solution generated above.

The <sup>1</sup>H nmr (Fig. 1) and <sup>13</sup>C nmr (fig. 2), in particular the very large up field shift (2.2ppm) in the proton spectrum for the residual CH (proton a) of the oxazole ring, clearly show that at ambient temperature in THF the lithiooxazole species bears a far greater relationship to the silyl ether than the oxazole **1a**. The quality of spectra obtained for the zinc derivative were poor but the grouping of signals around the original oxazole signals in both the <sup>1</sup>H and <sup>13</sup>C spectra tend to support assignment of a ring closed structure probably as a mixture of structures.

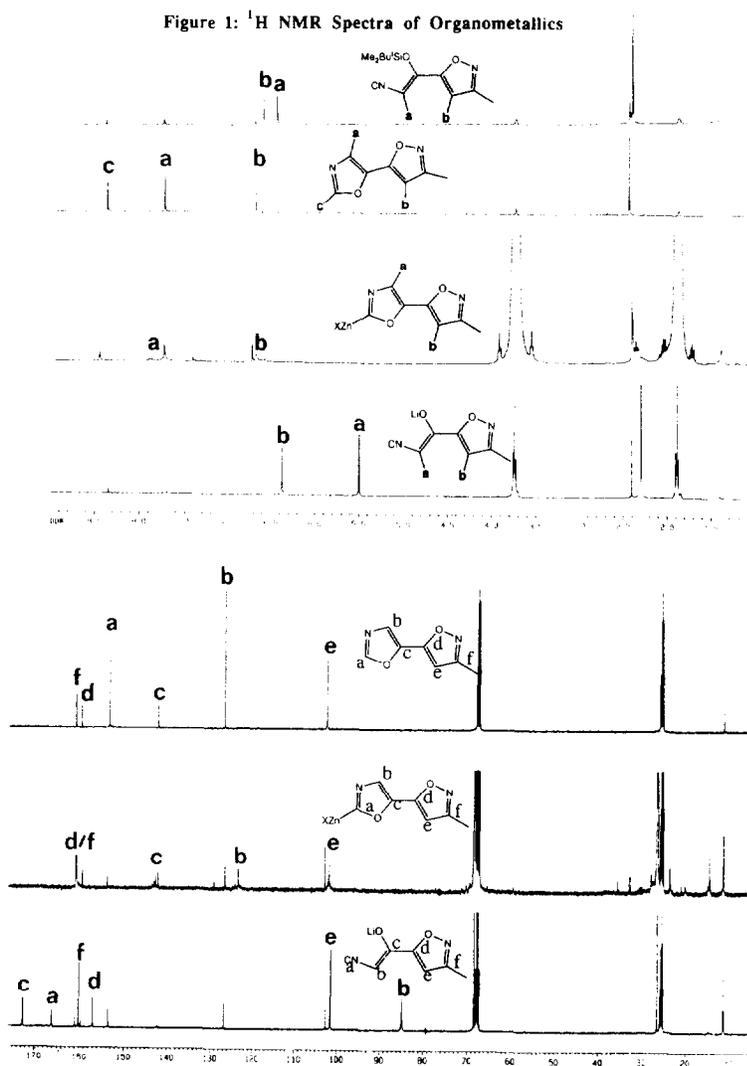


Figure 2: <sup>13</sup>C NMR Spectra of Organometallics

In order to eliminate effects due to the adjacent isoxazole ring the experiments were repeated using oxazole **1d** itself. In this case the  $^1\text{H}$  nmr (fig. 3) and  $^{13}\text{C}$  nmr (fig. 4) show very clearly the difference in structure between the lithio and zinc derivatives strongly supporting assigning an isocyanoenolate structure **5** to the former and an aryl-metal structure **6** to the latter.

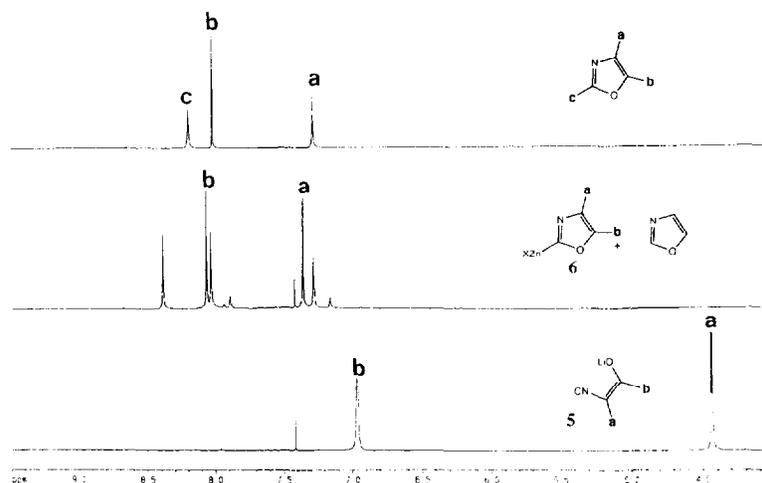


Figure 3:  $^1\text{H}$  NMR Spectra of Oxazole Organometallics

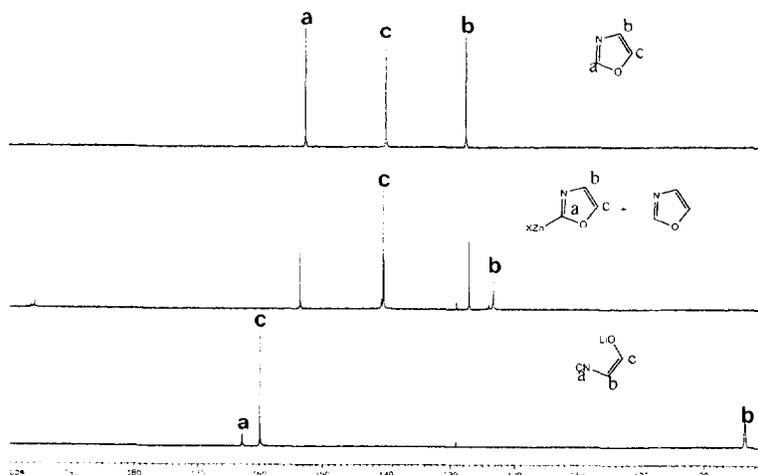


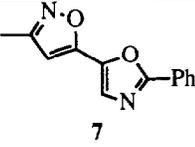
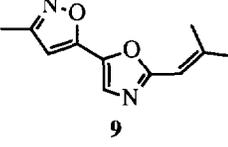
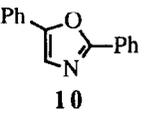
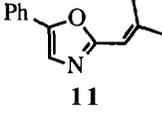
Figure 4:  $^{13}\text{C}$  NMR Spectra of Oxazole Organometallics

Palladium catalysed cross couplings of the zinc species were examined using 10mol%  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  pre-reduced with  $\text{DiBALiH}$ . The results are summarised in Table 2. Aromatic iodides appeared to be more reactive than the hindered vinyl iodide (as judged by tlc); the corresponding vinyl bromide is inert at  $20^\circ\text{C}$ .

Some cross coupling with the vinyl bromide was observed at higher temperatures but competing decomposition of the zinc complex was a problem. These results are entirely consistent with other reported palladium cross coupling reactions<sup>2</sup>.

It is clear from these results that the organo zinc complexes from lithiated oxazoles are potentially useful for the controlled C2 functionalisation of the ring.

**Table 2. Palladium Catalysed Couplings**

Oxazole	Electrophile	Product	Yield
<b>1a</b>	PhI/3hr	 <b>7</b>	68% (10% <b>1a</b> )
<b>1a</b>	 <b>8</b> 6Hrs	 <b>9</b>	78% (11% <b>1a</b> )
<b>1a</b>	 24hrs	No reaction	
<b>1c</b>	PhI/2hrs	 <b>10</b>	69% (8% <b>1c</b> )
<b>1c</b>	 <b>8</b> 24hrs	 <b>11</b>	78% (15% <b>1c</b> )
<b>1d</b>	PhI/3hr	 <b>12</b>	53%

### Experimental.

#### *5-(3-methyl-5-isoxazolyl)oxazole 1a.*

To a stirred suspension of potassium carbonate (13.8g, 0.1 mol) in methanol (1L) was added 4-toluenesulphonylmethylisocyanide (19.5g, 0.1 mol). The reaction was heated to 45°C and 3-methylisoxazole-5-carboxaldehyde<sup>7</sup> (2) was added and the reaction heated under reflux for 1 hour. The reaction was concentrated to dryness under reduced pressure and the residue partitioned between ethyl acetate (500ml) and water (100ml). The organic phase was washed with 5% aqueous potassium carbonate (2 x 100ml) then brine (2 x 25ml). The combined aqueous washings were extracted with ethyl acetate (300ml) which was washed as before. The combined ethyl acetate extracts were dried (K<sub>2</sub>CO<sub>3</sub>), concentrated under reduced pressure and the residue purified by flash-chromatography (eluent ethyl acetate/hexane, 40/60) followed by crystallisation from diisopropyl ether to give **1a** as colourless needles (9.75g, 65%). m.p. 87.5°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270MHz) 2.36 (3H, s), 6.4 (1H, s), 7.55 (1H, s), 7.98 (1H, s); <sup>13</sup>C NMR and DEPT 135 parity (CDCl<sub>3</sub>, 67.8MHz) 11.4,+, 102,+, 126,+, 141.1,0, 151.5,+, 158.6,0, 160.2,0; IR (CHCl<sub>3</sub> solution) 3140w, 3010m, 2395w (overtone), 1660w, 1500m, 1410m, 1205vs, 1110m, 1060w, 925m, 900m. m/z (EI+) 152 (21%), 151 (85), 150 (100), 122 (25), 96 (50), 82 (95), 68 (70), 54 (60), 40 (60). C<sub>7</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> requires C = 56%, H = 4.03, N = 18.66; found C = 56.27, H = 4.06, N = 18.78.

#### *Lithiations (General Procedure)*

To a stirred solution of oxazole (**1a-d**) (1mmol) in tetrahydrofuran (5ml) at -70°C was added n-butyl lithium (1mmol of a 1.6M solution in hexanes). The reaction was allowed to attain ambient temperature then used for the following studies.

#### **Deuterations:**

##### *D<sub>4</sub>-Acetic acid quench of lithiated 5-(3-methyl-5-isoxazolyl)oxazole (1a).*

A solution of lithiated oxazole (**1a**) (1mmol) was cooled to -70°C then a solution of D<sub>4</sub>-acetic acid (3mmol) in THF (2ml) was added, the reaction was allowed to attain ambient temperature then partitioned between diethyl ether and saturated aqueous ammonium chloride solution. The organic phase was dried over sodium sulphate, concentrated under reduced pressure and the <sup>1</sup>H and <sup>2</sup>H nmr spectra recorded. <sup>1</sup>H nmr (CDCl<sub>3</sub>, 250MHz) 2.36 (integral 1/H), 6.4 (0.91/H), 7.55 (0.4/H), 8.0 (0.43/H); <sup>2</sup>H nmr (CHCl<sub>3</sub>(10% D), 41.3MHz) 7.6 (1D, C4D), 8.0 (1D) no other signals.

This reaction was repeated but pre-ageing the lithiated oxazole (**1a**) for 18 hours at ambient temperature prior to quenching with D<sub>4</sub>-acetic acid. <sup>1</sup>H nmr (CDCl<sub>3</sub>, 250MHz), 2.36 (integral 1/H), 6.4 (0.98/H), 7.55 (0.46/H), 8.0 (0.5/H); <sup>2</sup>H nmr (CHCl<sub>3</sub>(10% D) 41.3MHz) 7.6 (1D), 8.0 (1D), no other signals.

The reaction was repeated quenching with a solution of D<sub>4</sub>-acetic acid in THF (250ml of a 10% solution 0.5mmol) after stirring for 30 minutes water (2ml) was added and the reaction stirred for 1 hour prior to working up as usual. <sup>1</sup>H nmr (CDCl<sub>3</sub> 270MHz) 2.36 (integral 1/H), 6.4 (1/H), 7.55 (0.69), 8.0 (0.81); <sup>2</sup>H nmr (CHCl<sub>3</sub> (10% D) 41.3MHz) 7.6, 8.0 no other signals detected.

*Inverse quench into D<sub>4</sub>-acetic acid of lithiated 5-(3-methyl-5-isoxazolyl)oxazole 1a.*

To a stirred solution of oxazole **1a** (1mmol) in tetrahydrofuran (5ml) at -70°C was added n-butyl lithium (1mmol of a 1.6M solution in hexanes). The reaction was allowed to attain ambient temperature then quenched into a solution of D<sub>4</sub>-acetic acid (3mmol) in tetrahydrofuran (5ml). The reaction was partitioned between diethyl ether (20ml) and sat. aq. potassium carbonate solution (5ml). The organic phase was dried over potassium carbonate and concentrated (~98% recovery). <sup>1</sup>H nmr (CDCl<sub>3</sub>, 270MHz) 2.36 (integral 1/H), 6.4 (0.9/H), 7.55 (0.2/H), 7.96 (0.2/H), <sup>2</sup>H nmr (CHCl<sub>3</sub>(10% D), 61.42MHz) 7.55 (1D), 8.0 (1D) no other signals. m/z (EI+) 154 (5%), 153 (14), 152 (83), 151 (47), 150 (12), 82 (100).

*D<sub>2</sub>O quench of lithiated 5-(3-methyl-5-isoxazolyl)oxazole 1a.*

A solution of lithiated oxazole **1a** (1mmol) was cooled to -70°C then D<sub>2</sub>O (2ml) was added, the reaction was allowed to attain ambient temperature, stirred for one hour then extracted with diethyl ether. The organic phase was dried over sodium sulphate, concentrated under reduced pressure (yield 92%) and the <sup>1</sup>H and <sup>2</sup>H nmr spectra recorded. <sup>1</sup>H nmr (CDCl<sub>3</sub>, 270MHz) 2.36 (Integral 1/H), 6.4 (0.87/H), 7.55 (0.96/H); <sup>2</sup>H nmr (CHCl<sub>3</sub> (10%D), 41.3MHz) 6.4 (0.1D), 8 (1D), no other signals observed.

*D<sub>4</sub>-acetic acid quenches of lithiated 5-phenyloxazole<sup>8</sup> 1c.*

To a solution of 5-phenyloxazole<sup>8</sup> (145mg, 1mmol) in tetrahydrofuran (5ml) at -70°C was added n-butyl lithium (700µl, 1.6M in hexanes, 1.1mmol). The reaction was allowed to attain ambient temperature then quenched with D<sub>4</sub>-acetic acid (250µl, ), partitioned between diethyl ether (20ml) and sat. aq. ammonium chloride solution (10ml), the organic phase was dried over potassium carbonate and concentrated under reduced pressure (yield 142mg). <sup>1</sup>H nmr (CDCl<sub>3</sub>, 200MHz) the spectrum was complicated due to the presence of two components one corresponding to 5-phenyloxazole in which the 2 proton signal at 7.9ppm and the 5 proton signal at 7.36 of the oxazole were both reduced in intensity by ~24% versus the ortho proton signals of the phenyl ring at 7.6-7.7ppm in addition a second set of ortho proton signals at 7.8-7.9ppm were observed together with a singlet at 4.9ppm. This material was purified by flash column chromatography to return 137mg of material which was clean 5-phenyloxazole by <sup>1</sup>H nmr (CDCl<sub>3</sub>, 200MHz) 7.28-7.43 (4H, m, 0.96, ar H), 7.6-7.7 (2H, m, 1/H, ar H), 7.9 (1H, s, relative integral 0.8/H, C2H), the peak height ratio of the oxazole signals at 7.9 and 7.36ppm remained the same as that in the undeuterated material but were reduced by about 8% relative to the ortho protons at 7.6-7.7.

To a solution of 5-phenyloxazole<sup>8</sup> (145mg, 1mmol) in tetrahydrofuran (5ml) at -70°C was added n-butyl lithium (700µl, 1.6M in hexanes, 1.1mmol). The reaction was allowed to attain ambient temperature then quenched with D<sub>4</sub>-acetic acid (250µl, ) and D<sub>2</sub>O (0.5ml) and stirred for 2 hours. The reaction was partitioned between diethyl ether (20ml) and saturated aqueous ammonium chloride solution (10ml), the organic phase was dried over sodium sulphate, concentrated under reduced pressure and the residue dissolved in toluene (5ml) and concentrated under reduced pressure (yield 141mg). <sup>1</sup>H nmr (CDCl<sub>3</sub>, 270MHz) 7.3-7.5 (m) 7.6-7.7 (2H, m), 7.9 (0.3H, s), <sup>2</sup>H nmr (CHCl<sub>3</sub> (10% D) 61.4MHz) 7.36 (0.86D), 7.9 (1D),. m/z (EI+) 148 (21%), 147 (100), 146 (62), 145 (82)

**Preparation of Zinc derivatives.**

To a solution of the lithiated oxazole cooled to  $-70^{\circ}\text{C}$  was added a solution of zinc chloride in ether (1 eq of a 1M solution), the reaction was allowed to attain ambient temperature and used as is.

**Deuterium quenches:***2-Deuterio-5-(3-methyl-5-isoxazolyl)oxazole 1b.*

A solution of the zinc derivative prepared from 5-(3-methyl-5-isoxazolyl)oxazole **1a** (1.6g, 10.7mmol) was quenched with D<sub>4</sub>-acetic acid (3ml) and D<sub>2</sub>O (10ml). The reaction was stirred for 16 hours then partitioned between diethyl ether (200ml) and aqueous potassium carbonate (20ml 10% solution), the organic phase was washed with saturated aqueous ammonium chloride solution (50ml) then saturated brine (50ml), dried over sodium sulphate then concentrated under reduced pressure (crude yield 1.63 g, 85% D incorporation at C2). The residue was recrystallised from diisopropyl ether (yield 0.64g 39%). mp  $87.9^{\circ}\text{C}$ : <sup>1</sup>H nmr (CDCl<sub>3</sub>, 270MHz) 2.36 (3H, s), 6.4 (1H, s), 7.55 (1H, s), 8.0 (0.15H, s); <sup>2</sup>H nmr (CHCl<sub>3</sub> (10% D) 61.4MHz) 8.0 (1D) no other signals detected: <sup>13</sup>C nmr and DEPT 135 parity (CDCl<sub>3</sub> 67.8MHz) 11.3,+ , 102,+ , 126,+ , 141.1,0, 151.3 (D coupled), 158.6,0, 160.1,0: m/z (EI+) 154 (3%), 153 (35), 152 (64), 151 (100), 150 (29), 123 (10), 82 (73), 69 (20), 54 (20), 41 (20).

*2-Deuterio-5-phenyloxazole.*

A solution of the zinc derivative prepared from 5-phenyloxazole<sup>8</sup> **1c** (145mg, 1mmol) was quenched with D<sub>4</sub>-acetic acid (250μl). The reaction was stirred for 4 hours then partitioned between diethyl ether (20ml) and saturated aqueous ammonium chloride solution (10ml). The organic phase was dried over sodium sulphate then concentrated under reduced pressure. The residue was dissolved in toluene (5ml) and concentrated under reduced pressure (yield 153mg >100%) <sup>1</sup>H nmr (CDCl<sub>3</sub> 270MHz) 7.2-7.5 (4H, m), 7.5-7.7 (2H, m), 7.9 (0.05H, s); <sup>2</sup>H nmr (CHCl<sub>3</sub> (10% D) 61.4MHz) 8.0 (1D s) no other signals: <sup>13</sup>C nmr and DEPT 135 parity (CDCl<sub>3</sub>, 67.8MHz) 151.7,0, 150 (D coupled), 121.2,+ , 127.6,+ , 128.4,0, 128.8,+ , 129,+ : m/z (EI+) 148 (8%), 147 (53), 146 (95), 118 (100), 91 (78), 77 (45), 63 (30), 51 (30).

*5-(Z-2-isocyano-1-(tert-butyldimethylsilyloxy)ethenyl)-3-methylisoxazole 4*

To a stirred solution of 5-(3-methyl-5-isoxazolyl)oxazole **1a** (300mg 2mmol) in THF (2ml) at  $-70^{\circ}\text{C}$  was added n-butyl lithium (1.4ml of a 1.6M solution in hexanes 2.24mmol), the reaction was allowed to attain ambient temperature then cooled to  $-70^{\circ}\text{C}$ . A solution of tert-butyldimethylsilyl chloride (350mg 2.3mmol) in THF (2ml) was added and the reaction allowed to attain ambient temperature. After 2 hours at ambient the reaction was concentrated under reduced pressure, the residue suspended in hexane and filtered through celite to remove lithium chloride. The filtrate was concentrated under reduced pressure to give an oil containing **4**, **1a** and excess silylating agent in the ratio of 1:0.2:0.1. <sup>1</sup>H nmr (D<sub>8</sub>-THF, 200MHz) 0.22 (6H, s), 1.03 (9H, s), 2.25 (3H, s), 6.28 (1H, s), 6.45 (1H, s); <sup>13</sup>C nmr and DEPT 135 parity (D<sub>8</sub>-THF 67.8MHz) 12.6 (CH<sub>3</sub>), 20.5 , 27.5 (CH<sub>3</sub>), 106.5 (CH<sub>3</sub>), 109.5, 146.7, 162.4, 166.8, 175.3 (C); IR (liquid film) 2060, 2080, 2130: m/z (CI+) 282 (36% m+NH<sub>4</sub><sup>+</sup>), 265 (100 m+H), hi-res C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>Si requires 264.1297 found 264.1296.

**NMR Studies on metallated oxazoles.**

The lithiated oxazoles were prepared on a 1 mmol scale according to the general procedure. The solutions were concentrated under reduced pressure to dryness and the residues dissolved in tetrahydrofuran (1ml) containing 20% D<sub>8</sub>-tetrahydrofuran which had been distilled from potassium/benzophenone. Half the sample was transferred to an nmr tube under argon and the <sup>1</sup>H and <sup>13</sup>C nmr spectra recorded. The remaining sample was cooled to -70°C and a solution of zinc chloride (1ml of an 0.5M solution in THF containing 20% D<sub>8</sub>-THF) was added. The reaction was allowed to attain ambient temperature and transferred to an nmr tube under argon and the <sup>1</sup>H and <sup>13</sup>C nmr spectra recorded. The spectra thus obtained are reproduced in the text.

**Palladium catalysed cross couplings.****General Procedure.**

To a stirred suspension of bis-(triphenylphosphine)palladium dichloride (140mg 0.2mmol) in THF (10ml) at 0°C was added a solution of di-isobutylaluminium hydride (400μl of a 1M solution in toluene, 0.4mmol). The vinyl or aryl halide (2.2mmol) was added and the solution thus generated added to a solution of the zinc oxazole derived from 2mmol of the relevant oxazole. The reaction was stirred at ambient temperature until no further reaction was observable by tlc (times shown in text). The reaction was partitioned between ether (50ml) and saturated aqueous ammonium chloride solution (20ml), the organic phase dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by chromatography with samples for analysis being further purified by either recrystallisation or sublimation.

*2-Phenyl-5-(3-methyl-5-isoxazolyl)oxazole 7* (from 5-(3-methyl-5-isoxazolyl)oxazole **1a** and iodobenzene):

Recrystallised from diethyl ether at -20°C mp 98-98°C: <sup>1</sup>H nmr (CDCl<sub>3</sub> 270MHz) 2.38 (3H, s), 6.43 (1H, s), 7.45-7.55 (3H, m), 7.63 (1H, s), 8.05-8.2 (2H, m); <sup>13</sup>C nmr and DEPT 135 parity (CDCl<sub>3</sub> 67.8MHz) 11.4,+, 101.5,+, 126.6,0, 126.8,+, 128,+, 129,+, 131.2,+, 140.7,0, 159.8,0, 160.1,0, 162.6,0: m/z (EI+) 227 (37%), 226 (100), 144 (30), 116 (77), 105 (42); C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> requires C=69.02, H=4.46, N=12.38 found C=68.69, H=4.68, N=12.36.

*2-(2,2-Dimethylethenyl)-5-(3-methyl-5-isoxazolyl)oxazole 9* (from 5-(3-methyl-5-isoxazolyl)oxazole **1a** and 1-iodo-2-methylpropene<sup>10</sup> **8**):

Recrystallised from diisopropyl ether/hexane mp 93.2°C: <sup>1</sup>H nmr (CDCl<sub>3</sub> 270MHz) 2.01 (3H, d ~1Hz), 2.27 (3H, d ~1Hz), 2.35 (3H, s), 6.17 (1H, m), 6.3 (1H, s), 7.52 (1H, s); <sup>13</sup>C nmr and DEPT 135 parity (CDCl<sub>3</sub> 67.8MHz) 11.4,+, 20.7,+, 27.5,+, 111.1,+, 127.4,+, 138.9,0, 148.9,0, 159.1,0, 160.1,0, 162.4,0: m/z (EI+) 205 (75%), 204 (100), 189 (23), 164 (20), 122 (70), 94 (83), 82 (95); C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> requires C=64.69, H=5.92, N=13.72, found C = 64.81, H = 5.8, N = 13.83.

*2,5-Diphenyloxazole<sup>11</sup> 10* (from 5-phenyloxazole **1c** and iodobenzene):

Sublimed mp 71°C (lit 72-74°C<sup>12</sup>): <sup>1</sup>H nmr (CDCl<sub>3</sub>, 270MHz) 7.3-7.6 (7H, m), 7.7-7.8 (2H, m), 8-8.2 (2H, m); <sup>13</sup>C nmr and DEPT 135 parity (CDCl<sub>3</sub> 67.8MHz) 123.5,+, 124.2,+, 126.3,+, 127.5,0, 128.1,0,

128.5,+, 128.8,+, 129,+, 130.3,+, 151.3,0, 161.2,0: m/z (EI+) 222 (85%), 221 (100) 193 (36), 166 (58), 165 (83), 85 (80), 83 (87).

2-(2,2-Dimethylethenyl)-5-phenyloxazole **11** (from 5-phenyloxazole **1c** and 1-iodo-2-methylpropene<sup>10</sup> **8**):

<sup>1</sup>H nmr (CDCl<sub>3</sub> 270MHz) 2.0 (3H, s), 2.28 (3H, s), 6.18 (1H, br s), 7.2-7.5 (4H, m), 7.6-7.8 (2H, m): <sup>13</sup>C nmr and DEPT 135 parity (CDCl<sub>3</sub> 67.8MHz) 20.6,+, 27.3,+, 122.8,+, 124,+, 128.1,+, 128.3,0, 128.9,+, 145.9,0, 149.6,0, 161.3,0: IR (liquid film) 3120, 3060, 2820, 1660, 1610, 1595, 1530, 1510, 1490, 1445, 1380, 1270, 1190, 1115, 1060, 1025, 970, 945, 910, 830: m/z 199 (100%) C<sub>13</sub>H<sub>13</sub>NO requires 199.0999 found 199.0998.

2-Phenyloxazole<sup>12</sup> **12** (from oxazole **1d** and iodobenzene):

<sup>1</sup>H nmr (CDCl<sub>3</sub> 270MHz) 7.24 (1H, s), 7.3-7.4 (3H, m), 7.7 (1H, s), 8-8.1 (2H, m): <sup>13</sup>C nmr and DEPT 135 parity (CDCl<sub>3</sub> 67.8MHz) 126.4,+, 127.5,0, 128.4,+, 128.8,+, 130.3,+, 138.6,+, 162,0 (C2): m/z (CI+) 146 (100 m+H)

#### References and Notes.

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