Palladium Cross-Couplings of Oxazoles

By Emmanuel Ferrer Flegeau

A thesis presented for the degree of

DOCTOR OF PHILOSOPHY IN

ORGANIC CHEMISTRY

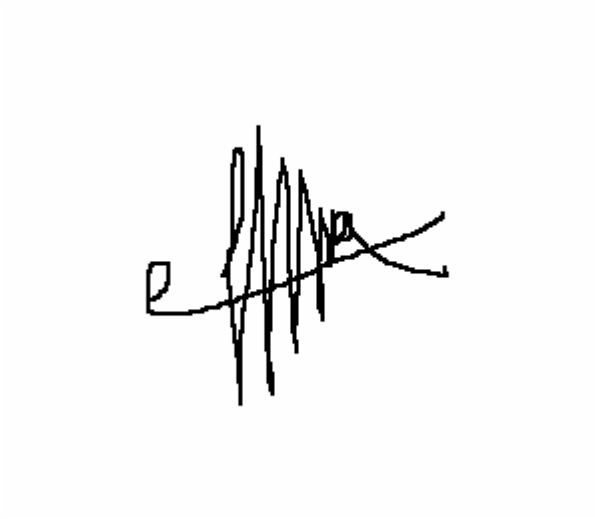
Edinburgh University

April 2008

a Gabi y Lola

Declaration

I declare that this thesis is my own composition and that the work of which it is a record was carried out by myself unless otherwise acknowledged. No part of this thesis has been submitted in any other application for a higher degree.



Emmanuel Ferrer Flegeau 2008

Courses and Lectures Attended

1. Organic Research Seminars, various speakers, Department of Chemistry, Edinburgh University (3 years attendance).

2. EastChem Symposium, various speakers, 2004, St Andrews.

3. Organon Symposium, various speakers, Glasgow, attended both 2005 and 2006.

4. Process Chemistry Workshop, Sandwich UK organised by GSK, AZ and Pfizer, attended November 2006.

5. Firbush Meeting, Edinburgh University, Firbush Sport Centre, Scotland. 1st price poster competition of organic division in 2006, oral presentation 2007.

6. GlazoSmithKline CASE students Symposium, various speakers, oral presentation, Tonbridge, UK, September 2007.

7. 8th Tetrahedron Symposium, various speakers, Berlin, June 2007. Poster presentation

Acknowledgements

The first person I would like to thank is my supervisor Dr Michael. F. Greaney for trusting me from the very beginning of my PhD. Mike is the kind of supervisor that I think everyone should deserve to have. He gives you freedom and at the same time supervision if required. Throughout all my PhD he has pushed me to follow my own path suggesting options all the way long, but never interfering with the direction I wanted, which I think this how a PhD should be about, finding your own research space. I am also very grateful for the passion he shows in science and with organic chemistry, which he is perfectly able to communicate to his students. This has greatly contributed to direct me career wise. At the beginning of my PhD I had no idea what to do with my scientific skills and now I am preparing myself to go to a super group in Tokyo University. More importantly, he has shown me how to be successful in science without forgetting the most important part, which is how to have fun with science. Thanks very much Mike.

I would also like to thank Edinburgh University and the School of Chemistry for the great University that it is. Facilities, people and a general good vibe definitely contribute to have great science and at the same time to fully enjoy your PhD every day. In particular, I would like to thank the NMR service, John Millar and Juraj both have been of great help and I doubt very much I would have never got some of the results without their help with the NMR machines. I also would like to thank Alan Taylor from the Mass Spectrometry Service at Edinburgh University and the EPSRC National Spectrometry Service Centre at University of Wales, Swansea for all the mass spectrometry analysis carried out for my PhD. I also would like to thank stores at the School of Chemistry for their help and great day-to-day humour, especially Raymond. I would like to thank Helen Lamb for proof reading this thesis entirely

before submission. She has helped me in such a way that I can now write English alot better; thanks for taking the time to do it properly.

There are a few people from the Greaney group I am very grateful too. Dr Jone Iriondo for her help and also her friendship; Dr Frederic Douelle for just being the coolest dude on this planet; Gemma Turner for having such great ideas and helping me everyday with my work; Dr Craig Mcgowan for a really good bench mate and letting me listen to all the jazz I wanted; Dr Baolu Shi for the same; Aileen, Karsten, Stephan, for being really nice to me and to the group; and everyone else in the group past and present.

I spent three months as a CASE student in the GSK research and development site of Tonbridge in Kent, UK. I would like to thank my industrial Supervisor Dr Matt Popkin for making my time over there smooth and easy going, for helping with the chemistry and overall for just being nice to me. I also would like to thank his team who helped me every time I asked them, Hannah and Dr Laura Mace.

As part of my PhD training I got to know this incredible city of Edinburgh and its citizens. I have made a lot of good friends that have of course contributed in making my life here very enjoyable. I would like to thank the surfing team Gorka, Fred, Ed and Diego. Many excellent weekends on the north and west coast of Scotland have just been amasing. Many people to thank so I am going to concentrate with the band I had here for some time. I would like to thank Ben Slade for being such a good guitar player and musician and also for being such a good friend. Arnaud Fourmon for drumming services, friendship, providing a place to play and being there when required. Thanks to our first bass player Michele who gave a good vibe to the band and had a very good taste in music. Thanks to the second bass player, Bob Slade for a superb style and great personality. Then we also had contributions, Ralph on Keyboards, the two fantastic French Juliens on tenor and alto saxophone, Guilleme on percussion and more people… I would like to give a special thanks to the neighbours of 10 East Norton Place for not phoning the police every Thursday night while the rehearsals. I also would like to thank other friends… Martina, Joa, Ed Ridgeway, mad Dave, space Dave, Martita, Claire, Louisa, Carmen, Laia, Thais, Tony and Maite.

The next person I would like to thank is Valentina. I met Valentina in the beginning of my PhD after a hard days work and since that day my life has never been the same. She has giving me love, passion and most important for this project, strength when I needed it and courage when I did not have it. She has helped me in finding that personal path in life, making me believe that I was possible all the way through. No one has been so close to me in all my life. Especially when results are not great and mood is all down you need someone special to make you believe that it is all fine, that it is just part of the process. I think we should all deserve someone like her at some point in our life. Thank you so much Vale. Thanks to her parents Gianni and Tere who have been so supportive in all aspects.

I would like to finish with my family, Dad, Lola, Gabi and Mum wherever you are. Thanks for letting me do I wanted without criticisms or restrictions. I would like to thank my grandmother and "auntie" Maminette and Paulette who have undoubtedly contributed to make me become a scientist.

Emmanuel Ferrer Flegeau, April 2008

Abstract

A review covering the literature until April 2008 concerning organometallic reactions to funcionalise oxazoles is described. A protocol for the functionalisation of the oxazole 2- and 4-positions using the Suzuki coupling reaction is described. 2-Aryl-4-trifloyloxazoles undergo rapid, microwave-assisted coupling with a range of aryl and heteroaryl boronic acids in good to excellent yields. The methodology is similarly effective using 4-aryl-2-chlorooxazoles as the coupling partner and has been extended to the synthesis of a novel class of homo- and heterodimeric 4,4-linked dioxazoles. In addition, 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. Furthermore, C-2 direct arylation of oxazoles is discussed. This methodology is extended to the synthesis of C2-C4' linked bis and tris oxazoles of the type found in the Ulapualide A family of natural products.

PREFACE

Parts of this thesis have been adapted from the following articles co-written by the author:

"Suzuki Couplings of Oxazoles." Emmanuel Ferrer Flegeau, Mathew E. Popkin, Michael F. Greaney; *Org. Lett.* **2006**, *8*, 2495 -2498.

"Regioselective Palladium Cross-Couplings of 2,4-Dihalooxazoles: Convergent Synthesis of Trisoxazoles." Emmanuel Ferrer Flegeau, Mathew E. Popkin, Michael F. Greaney; *J. Org. Chem.* **2008**, *73*, 3303-3306.

"Direct Arylation of Oxazoles at C_2. A concise approach to consecutively linked oxazoles." Emmanuel Ferrer Flegeau, Mathew E. Popkin, Michael F. Greaney; *Org. Lett.* **2008**, ASAP.

Table of Contents

Abbreviations

Cy	cyclohexyl
CuTc	copper (I) thiophene-2-carboxylate
DAST	diethylaminosulphur trifluoride
dba	dibenzylidenacetone
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
dppf	1,1'-bis(diphenylphosphino)ferrocene
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethyl propylene urea
DMSO	dimethylsulfoxide
Eq	equation
equiv	equivalent(s)
GC	gas chromatography
h	hour
HBP	Hermann-Beller palladacycle
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Im	imidazole
IMes	1,3-bis(mesityl)imidazol-2-ylidene
LC-MS	liquid chromatography-mass spectrometry
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidione
PEPPSI-iPr	[1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Py	pyridine

Ra-Ni	Raney-Nickel
RT	room temperature
TBAF	tetrabutylammonium fluoride
TFP	trifuran-2-yl-phosphine
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TFAA	trifluoroacetic anhydride
TMEDA	*N*,*N*,*N'*,*N''*-tetramethylethylene-1,2-diamine
TBDPS	*t*-butyldiphenylsilyl
X-PHOS	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Chapter 1

Organometallic Reactions to Functionalise Oxazoles

1.1 Introduction[1,2]

Hantzsch first discovered oxazoles in 1887.[3] Since then, this particular heterocyclic family has hugely expanded and oxazoles are found today in a myriad of applications. They play an important role in areas such as natural products, medicinal chemistry and material sciences. Oxazoles are numbered around the ring starting at the oxygen atom and they are named 1,3-oxazoles designating the position of the heteroatoms in the ring (Figure 1).

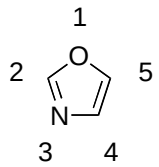


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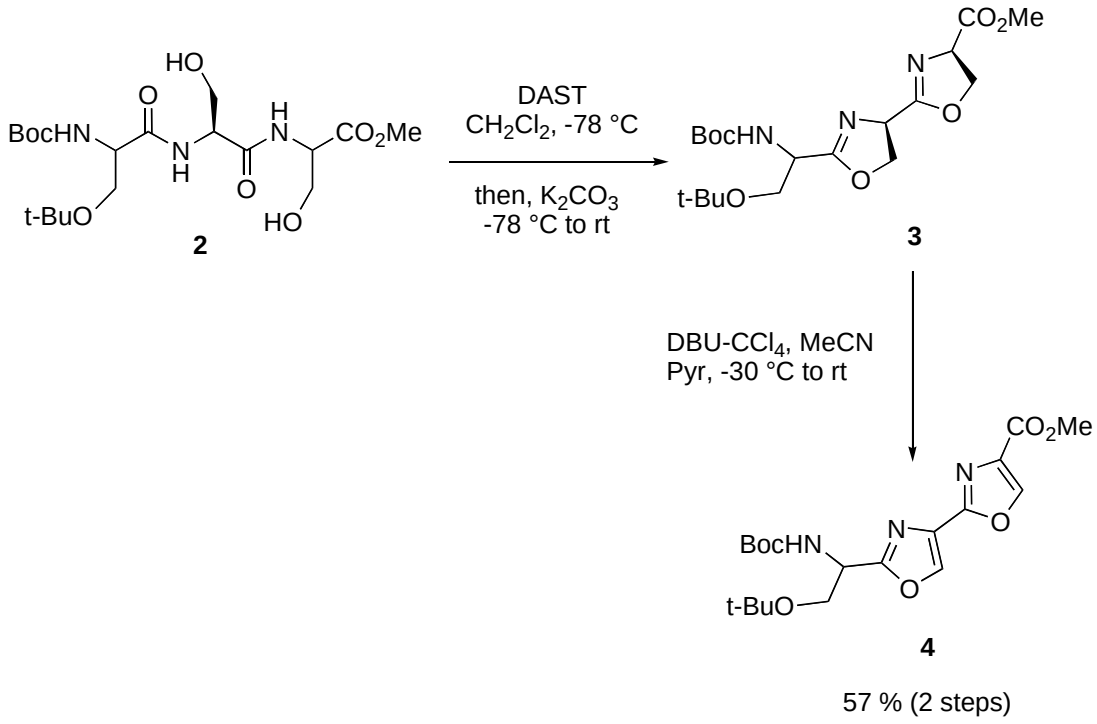
Figure 1. 1,3-oxazole.

The acidities for each C-H bond of the ring have been measured experimentally and also calculated theoretically.[1] Due to the combined inductive effect of both oxygen and nitrogen atoms of the ring, the acidity of each proton decreases in the order $C_2 > C_5 > C_4$. However, some exceptions are known depending on the substitution of the ring. The acidity of C_2-H is estimated to be $pK_a \sim 20$ and the basicity for oxazole itself is estimated at $pK_b \sim 1$ making it a weakly basic heterocycle.[1]

Oxazoles show particular resonances in both ^{1}H and ^{13}C NMR spectra. Typical values for ^{1}H-NMR will range between 7.00 and 8.00 ppm depending on the

substituents. The ^{13}C-NMR will display resonances usually between 120 and 140 ppm.

Although oxazoles possess a sextet of π-electrons, most of its reactivity indicates that the delocalisation is quite incomplete, having but little aromatic character. A clear indication of this is that they are known to be suitable dienes or dienophiles in the Diels-Alder reaction, evidencing the natural reactivity of the double bonds rather than the delocalised electrons of the ring. Electrophilic aromatic substitution of the ring is known but the chemistry of oxazoles found in the literature is dominated by their tendency to undergo ring opening rather than preserve its cyclic aromatic form.[2] Despite its tendency to give open ring products, most oxazole synthesis involves the cyclisation of acyclic precursors and subsequent oxidation to obtain oxazoles. By far the most common approach is the dehydration of β-hydroxyamides affording oxazolines, which can be oxidised to give the corresponding oxazoles.

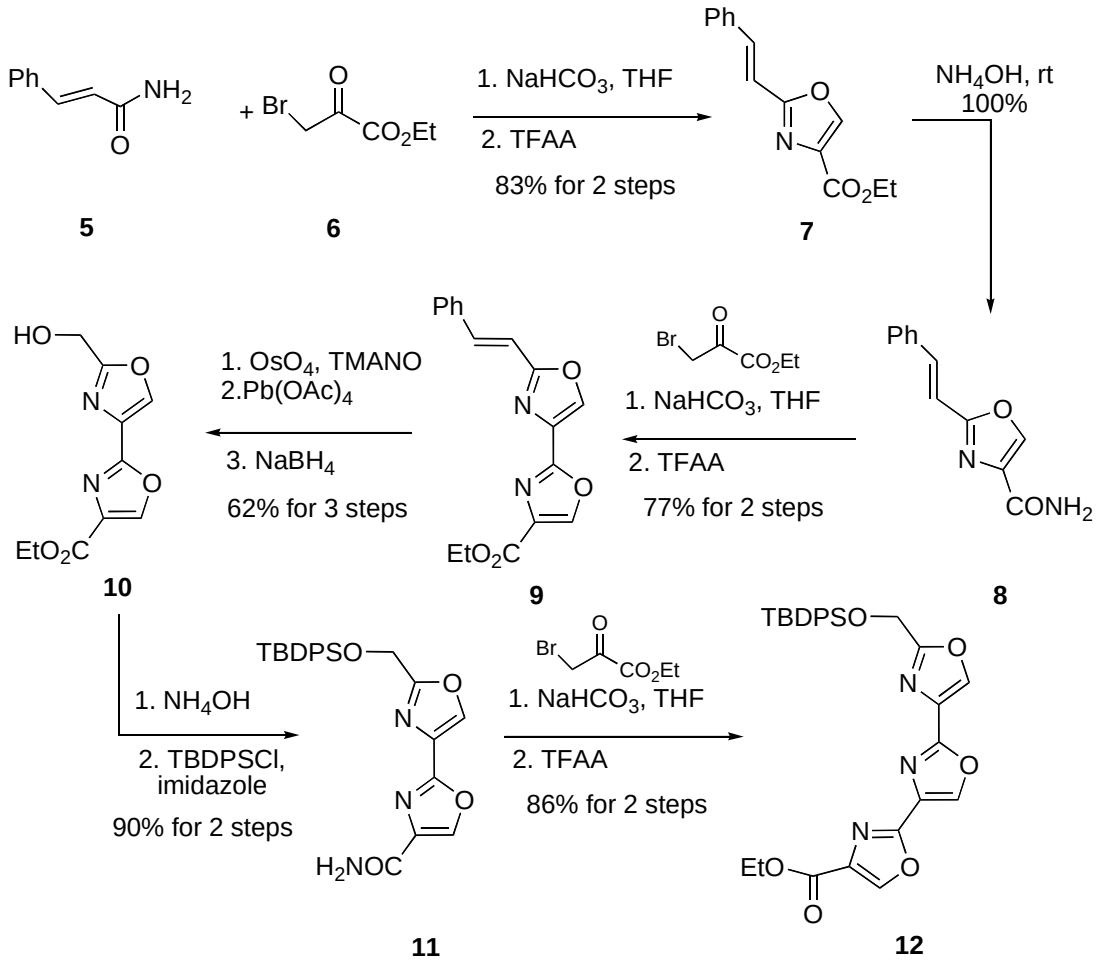


Scheme 1. Alvarez's synthesis of bis-oxazole **4** via cyclisation/oxidation sequence.

This approach is usually referred to as synthesis of oxazoles from peptide precursors, but many more methods based on similar principles are known.[4] A recent example of this strategy is Alvarez's total synthesis of the IB-01211 natural product.[5] Peptide **2** was used early in the synthesis as a precursor of bis-oxazole **4** using a cyclisation-oxidation sequence (Scheme 1).

The synthesis of cyclic compounds from acyclic precursors has several disadvantages. The most obvious drawback is that the synthesis of these acyclic intermediates can be highly complicated, depending on the desired final substitution of the target oxazole. In certain cases, it may not be successful due to the difficulties encountered in the elaboration of too complex precursors. On the other hand, even if the synthesis of the required linear precursors has been successful, the usually harsh conditions employed in the dehydration/oxidation sequence may render it incompatible with such rich functionalised starting materials. Furthermore, the application of selective protecting groups is necessary, sometimes several times, resulting in lengthy synthetic sequences.

An illustration of this particular drawback is the efficient but lengthy preparation of tris-oxazole by Panek and co-workers en route to the total synthesis of the natural product Mycalolide A (Scheme 2).[6] Condensation between cinnanamide **5** and ethyl bromopyruvate **6** using Hantzsch-type conditions gave the corresponding hydroxyl oxazoline. This condensation was immediately followed by dehydration with TFAA affording the functionalised oxazole **7** in 83 % yield. Then, conversion of the ethyl ester to the corresponding amide followed by a second Hantzsch reaction gave bis-oxazole **9**. The upper end of **9** was elaborated in a 3 step oxidative sequence to give the corresponding aldehyde, which by reduction gave the primary alcohol **10** in an overall yield of 62 %. Amidation of the ester followed by protection of the alcohol provided bis-oxazole **11** in 90 % yield. Finally, **11** was subjected to a third Hantzsch reaction (2 steps) to give the advanced intermediate tris-oxazole **12** in 86% yield (Scheme 2, 12 steps in total).



Scheme 2. Panek's synthesis of tris-oxazole **12**.

From a lead discovery perspective in medicinal chemistry, the synthesis of acyclic precursors for later cyclisation can also be a drawback. Prior to cyclisation, the making of a diversified set of acyclic starting materials is required, early stage rather than the late stage diversification (Figure 2). In the optimisation process of a drug candidate, changes to the basic structure of the drug are usually required. Due to the presence of multiple functional groups, which are often incompatible with the existing synthetic methods, this necessarily implies early modifications in the synthesis. In many cases, the modifications need to be performed on very basic

building blocks, which, in turn, may alter or even completely modify the already planned/optimised medicinal synthetic route. This is economically unfavourable and also time consuming for the industry.

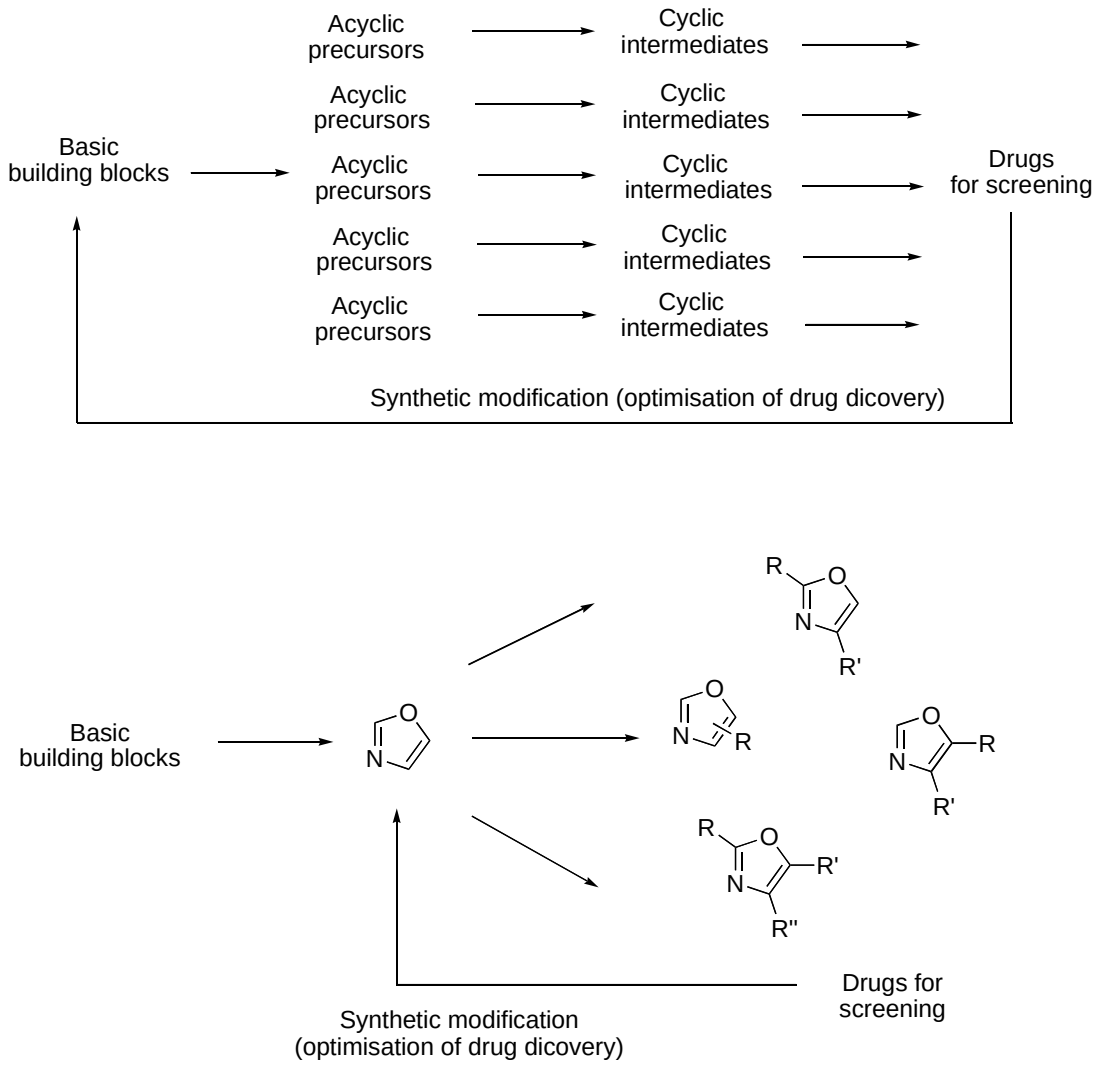


Figure 2. Early stage vs late stage diversification.

An alternative is to prepare the oxazole heterocycle at an early stage in the synthesis and to carry out subsequent functionalisations on each position of the ring. Oxazoles themselves exhibit rich and varied reactivity, which allows for

functionalisations at each ring atom. Because of their low aromatic character, they display reactions of both aromatic substitution and reactions of double bonds. Electrophilic aromatic substitutions, including bromination, nitration and Friedel-Crafts reaction, are known and they preserve the aromaticity of the ring. Additions across the C_4-C_5 double bond that disrupt aromaticity are also common.[2]

Although the oxazole ring is considered electron-rich when compared to benzene (6 π electrons for 5 atoms in the ring), the 1,3-disposition of the heteroatoms makes the C_2 position electrophilic. This gives oxazoles the unique ability to react with electrophiles and also with nucleophiles. Indeed, nucleophilic additions at C_2 and subsequent transformations into other heterocycles are well established.[1,2] Formal [3 + 2] cycloadditions of oxazoles with dipolarophiles are also related to this electrophilic behaviour.[2] As mentioned earlier, the 1,3 disposition of heteroatoms is also responsible for the observed differential proton acidities around the ring. This rich acid-base chemistry allows for selective deprotonation reactions and subsequent functionalisations at each of the carbon atoms. Nucleophilic aromatic substitution reactions on halooxazoles, alkoxyoxazoles and also oxazole sulfones give substituted oxazoles as well as ring-opening adducts, depending on the nucleophiles used.

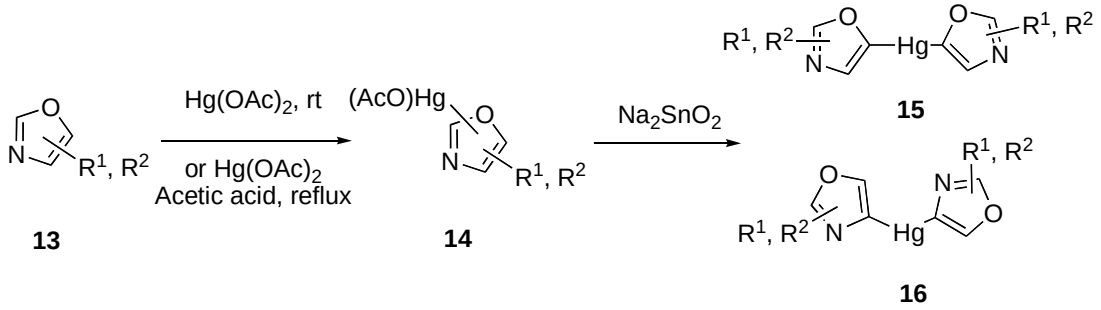
This reactivity provides the means to obtain a countless number of acyclic products, partially oxidised oxazoles such as oxazolines and oxazolones and even other classes of heterocycles. However, although this vast field related to oxazoles is of interest, this chapter will cover exclusively organometallic reactions to functionalise oxazoles giving products with the aromatic ring remaining fully intact.

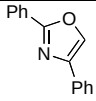
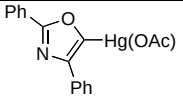
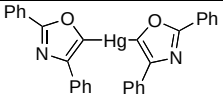
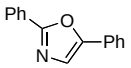
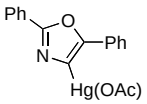
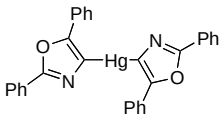
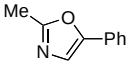
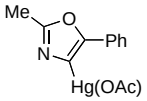
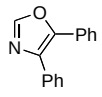
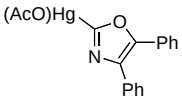
1.2 Stochiometric organometallic reactions of oxazoles

The first metallo-oxazoles synthesised were mercury derivatives and they are attributed to Shvaika and Klimisha, who studied these compounds in 1966.[7,8] Mercuration of oxazoles was achieved through an electrophilic reaction using $Hg(OAc)_2$. The authors found that room temperature conditions were enough to mercurate the C_5-H of oxazoles, whereas more drastic conditions were needed to

mercurate C_2-H and C_4-H. In a first step, mercury (II) aceto oxazole species **14** were obtained from substituted oxazoles **13**, and in a second step, using sodium stannite the oxazol-yl substituted mercury derivatives **15** and **16** were synthesised. The synthesis of these compounds is shown in Table 1.[7]

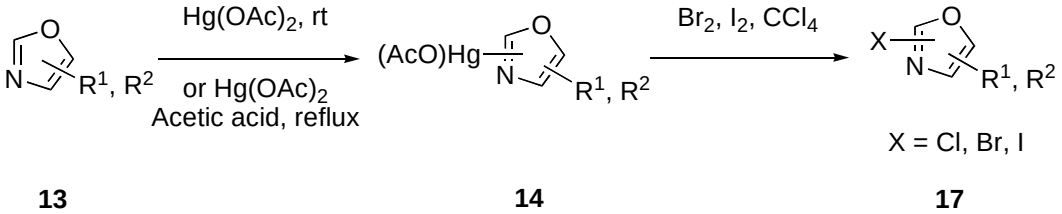
Table 1. Synthesis of mercurioxazole derivatives.



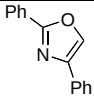
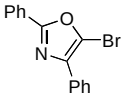
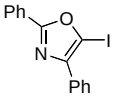
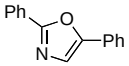
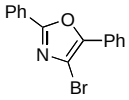
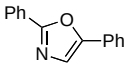
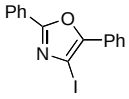
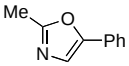
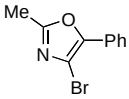
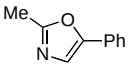
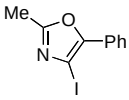
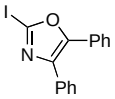
Entry	oxazole **13**	product **14**	Yield of **14** (%)	Product **15** or **16**	Yield (%) of **15** or **16**
1			92		60
2			92		68
3			22	-	-
4			80	-	-

In the same year, in a subsequent communication, the same authors described the preparation of halogenoxazoles **17** from *in situ* preparation of mercuriooxazole derivatives **14** previously described (Table 2).[8]

Table 2. Synthesis of halogenooxazoles from mercurial derivatives.

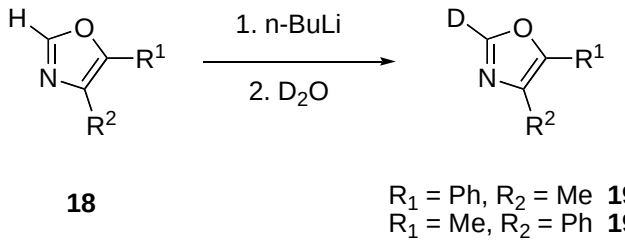


13 **14** **17**

Entry	Oxazole **13**	Halogen	Product **17**	Yield of **17**(%)
1		Br_2		72
2		I_2		64
3		Br_2		80
4		I_2		85
5		Br_2		65
6		I_2		55
7		I_2		60

Lithiation of oxazoles

Lithiation of oxazoles is the most studied metallation reaction of oxazoles and has been extensively used to functionalise positions 2, 4 and 5 of the ring.[9,2] In 1968, Bowie and co-workers first demonstrated that 2-unsubstituted oxazoles **18** could be metallated by butyllithium in C_2-H. The resulting lithiated species were trapped with deuterium oxide (Scheme 3).[10]

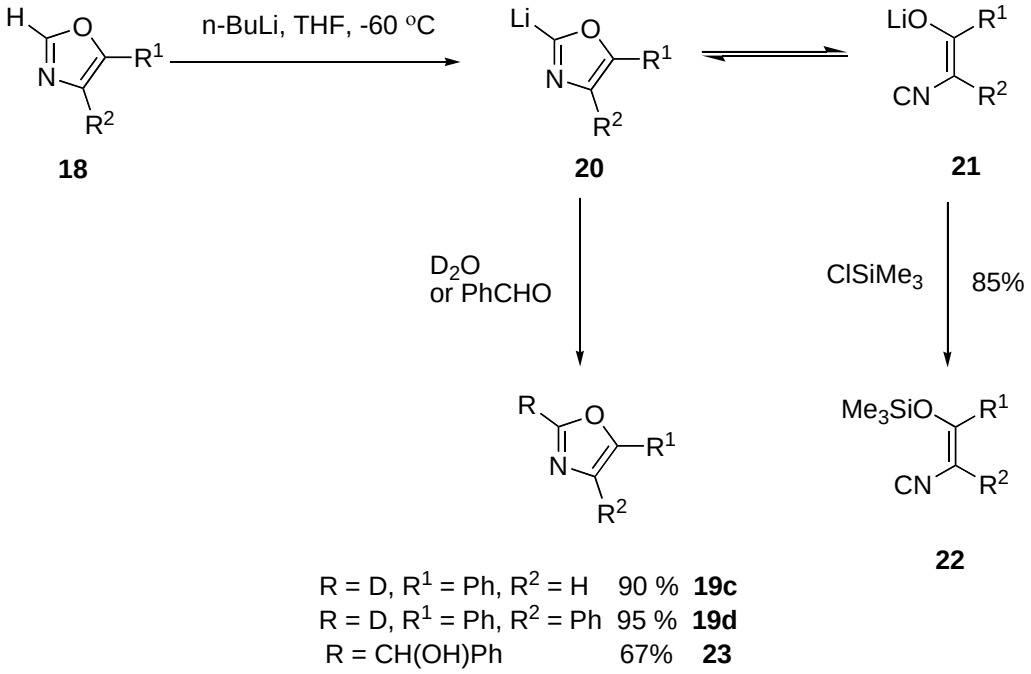


18

R_1 = Ph, R_2 = Me **19a**
R_1 = Me, R_2 = Ph **19b**

Scheme 3. Lithiation of 2-unsubstituted oxazoles **18** followed by deuteration quenching.

In 1975, Schröder and co-workers showed evidence for an equilibrium between the C_2-lithiated oxazole **20** and its ring-opened lithium enolate **21**. The choice of the trapping agent determined the product obtained; deuterium oxide and benzaldehyde gave the C_2 products **19c-d** and **23** in good to excellent yields, whereas TMSCl only gave the acyclic form in very good yield (Scheme 4).



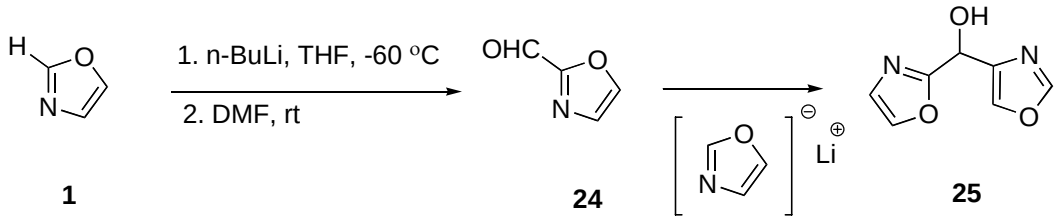
18 **20** **21**

22

R = D, R^1 = Ph, R^2 = H 90 % **19c**
R = D, R^1 = Ph, R^2 = Ph 95 % **19d**
R = CH(OH)Ph 67% **23**

Scheme 4. Equilibrium between ring-opening and oxazole forms for C_2-lithiated oxazoles.

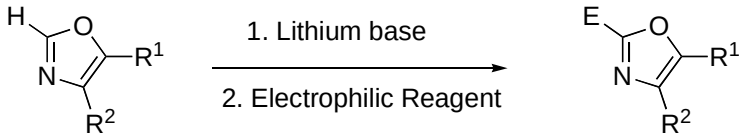
The equilibrium disclosed by Schröder illustrated that the use of 2-lithiooxazoles would be quite problematic in synthesis. When 2-lithiooxazole was combined with DMF at -75 °C and the mixture was allowed to rise to room temperature, the expected aldehyde on C_2 was obtained quantitatively. However, reaction of this product with a second equivalent of lithiooxazole did not provide the C_2 product this time, instead, reaction on C_4 giving the unsymmetrical bis(oxazolyl)methanol **25** was observed (Scheme 5).[11]



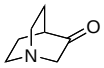
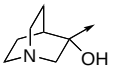
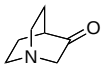
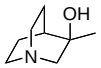
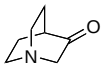
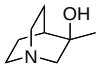
Scheme 5. Difference in reactivity of lithiated oxazoles.

In the early days,[9] reactivity at the 4-position of lithioxazoles had been generally found to occur with reactive electrophiles such as aldehydes. Less reactive electrophiles such as DMF, benzophenone and ethyl formate gave 2-substituted products **19**. In contrast, electrophiles such as iodobutane, benzyl bromide or ethyl carbonate did not react at all even after prolonged time reactions at room temperature. Butyllithium, lithium diisopropylamide (LDA), LHMDS and other bases have been successfully used to lithiate C_2-H of oxazoles, and, despite the difficulties many 2-substituted products **19** and also 4-substituted oxazoles **27** have been prepared accordingly. These earlier results are summarised in Tables 3 and 4.[9]

Table 3. Synthesis of 2-substituted oxazoles from oxazol-2-yllithium derivatives.

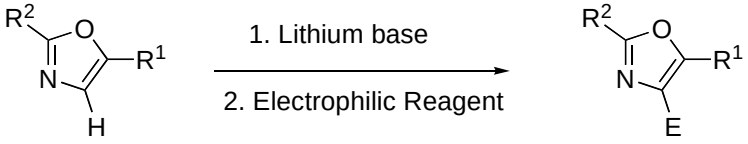


18 **19**

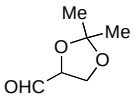
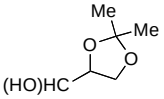
Entry	R^1	R^2	E. Reagent	E	Yield of **19** (%)	Ref.
1	H	H	D_2O	D	90	11
2	H	H	DMF	CHO	50[a]	11
3	H	H			19	12
4	Ph	H	D_2O	D	90	13
5	Ph	H	HCONMe(pyrid-2-yl)	CHO	61	14
6	Ph	H	PhCONMe(pyrid-2-yl)	PhCO	18	14
7	Ph	H	Me_3SiCl	Me_3Si	50[c]	15
8	C_6H_4OMe	H	Me_3SiCl	Me_3Si	35[c]	15
9	H	Me	PhCHO	Ph CH(OH)	30	15, 16
10	H	Me	Me_3SiCl	Me_3Si	60[c]	16
11	H	Me	Me_3SiCl	Me_3Si	60	15, 17
14	Me	Me	D_2O	D	100	18
15	CO_2Et	Me	CCl_4	Cl	29	19
16	CO_2Et	Me	Br_2	Br	21	19
17	CO_2Et	Me	I_2	I	42	19
18	Ph	Me	D_2O	D	-	10a
19	Me	Ph	D_2O	D	-	10a
20	Ph	Ph	PhCHO	PhCH(OH)	67	13
22	H	Me			36	20
23	H	H			19	20

[a]Variable yields after work-up due to volatility of product. [b]Minor product, isolated only at ambient temperature or above; the major product is the 4-substituted isomer (Table 4). [c]After distillation of a mixture of acyclic and cyclic compounds.

Table 4. Synthesis of 4-substituted oxazoles from oxazol-4-yllithium derivatives.



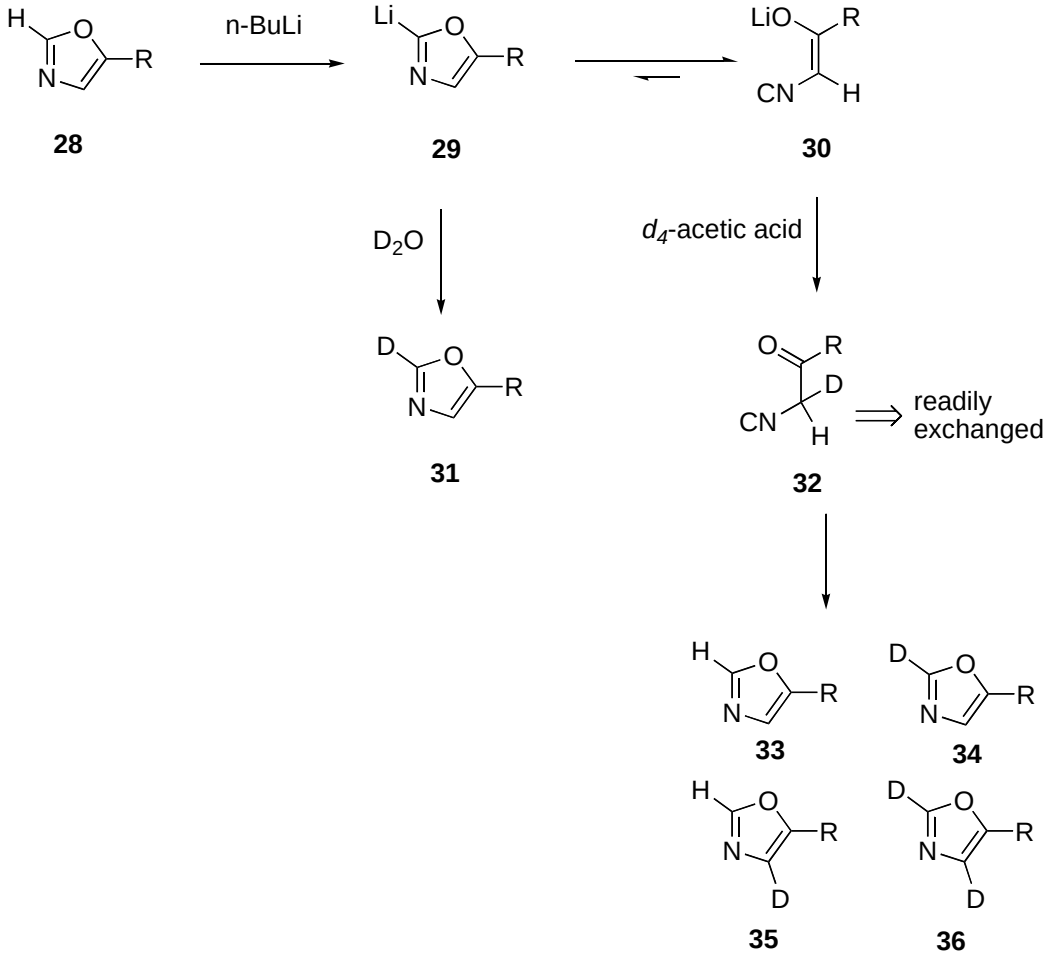
26 **27**

Entry	R^1	R^2	E. Reagent	E	Yield (%)	Ref.
1	H	H	$CHOC_4H_9$	$CH(OH)C_4H_9$	28[a]	11
2	H	H			65[a]	11
3	H	H	PhCHO	PhCH(OH)	20[a,b]	11
4	H	H	Thiazol-2-ylCHO	thiazol-2-yl CH(OH)	65[a]	11
5	H	H	Thiazol-4-ylCHO	thiazol-4-yl CH(OH)	62[a]	11
7	Ph	Ph	$TMSO(CH_2)_6I$	$TMSO(CH_2)_6$	45	21
8	Ph	Ph	$TBDMSO(CH_2)_8Br$	$TBDMSO(CH_2)_8$	60	21
9	Ph	Ph	DMF	CHO	50	20
10	Ph	Ph	PhCOCl	PhCO	73	20
11	Ph	Ph	$C_5H_{11}CHO$	$C_5H_{11}CH(OH)$	82	20
12	Ph	Ph	$TBDMSO(CH_2)_3CHO$	$TBDMSO(CH_2)_3CH(OH)$[d]	47	21
13	Ph	Ph	PhCHO	Ph CH(OH)	94, 70	21
14	Ph	Ph	Me_2CO	$Me_2C(OH)$	80	21
15	Ph	Ph	Me_3SiCl	Me_3Si	83, 92	23,24
16	Ph	Ph	Et_3SiCl	Et_3Si	71	20**Error! Bookmark not defined.**
17	C_6H_4OMe-4	C_6H_4OMe-4	D_2O	D	50	21

[a]These aldehydes react via generation of the oxazol-2-yllithium. [b]At room temperature $PhCH_2OH$ is formed in 34% yield along with a trace amount (2%) of the corresponding 2-isomer (amount depends on the temperature).

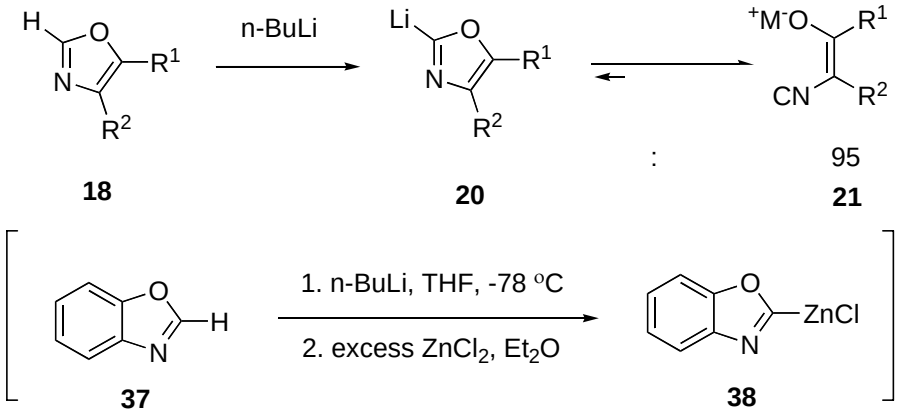
Hughes and co-workers carried out a study of the equilibrium of the 2-lithioxazole species **29** and the acyclic isocyanoenolate species **30** using ^{1}H-NMR and ^{13}C-NMR spectroscopy. The authors stated that the predominant form under the reaction

conditions was the acyclic form **30**, as found by NMR comparison and also deuterium quenches type of experiments. Interestingly, it was observed that different deuterated products **33-36**, including C_2, C_4, C_2/C_4 products, were obtained depending on the acidity of the deuterating agent, the substitution of the oxazole at C_5 and also the reaction times, suggesting that a fast equilibrium was operating on the quenches (Scheme 6). Furthermore, if the mixture was transmetallated at -78 °C with $ZnCl_2$ and the resulting organozinc species quenched with D_4-acetic acid, then, 85% of deuterium incorporation was found to occur at C_2, therefore, suggesting that transmetallation to zinc shifted the equilibrium to the cyclic 2-zincated oxazole species (Scheme 6).[22]



Scheme 6. Hugues' study of the formic equilibrium of 2-lithiooxazoles species.

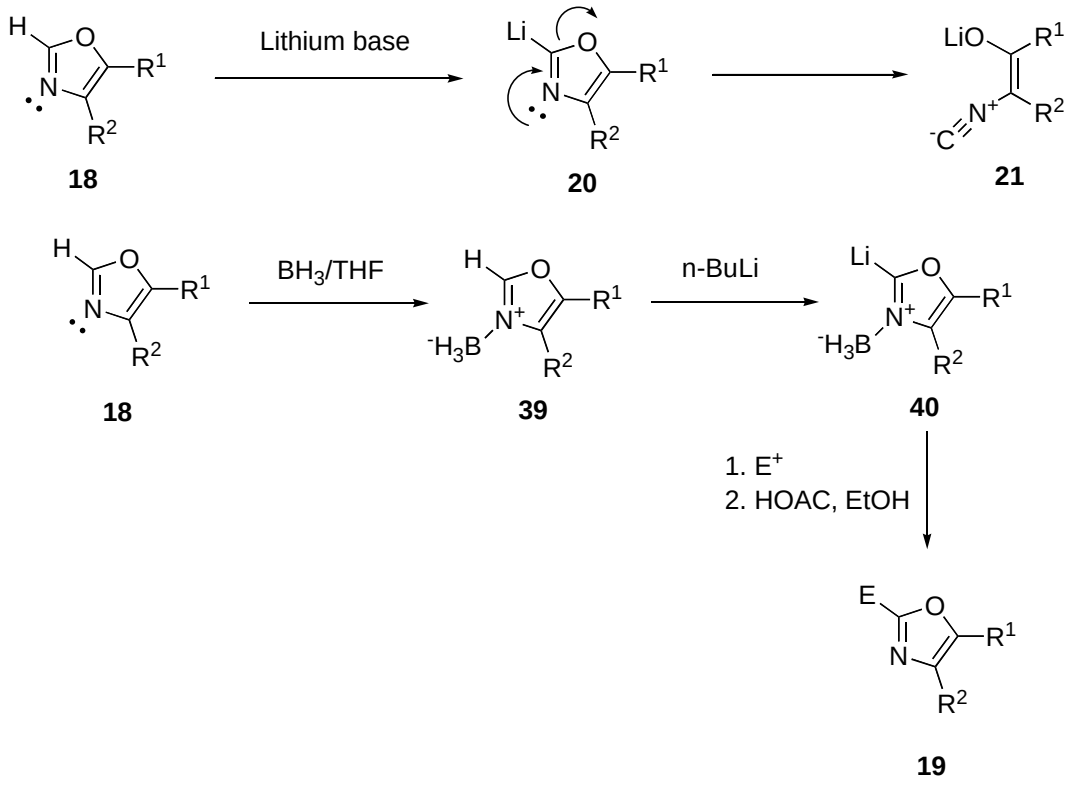
A few years later, the Boche group extensively investigated the equilibrium dilemma using ^{13}C-NMR, IR, single-crystal X-ray and molecular orbital calculations. They soon confirmed the results previously reported by Hugues. These authors concluded that the acyclic species of the lithiation of 1,3-oxazole and other derivates were predominant in solution up to 95 ± 5%. In addition, on the related benzoxazole system **37**, which had been treated with n-BuLi at -78 °C followed by addition of $ZnCl_2$, the authors also found the cyclic 2-zincated benzoxazole **38** present in the ^{13}C-NMR spectrum. This group succeeded in crystallising a dimer of **38** from THF and reported the results of their solid-state structure elucidation. In a second related study, using molecular orbital calculations, the authors studied oxazole structures and found complete concordance with the previously reported experimental results. The cyclic species **20** were considerably less stable than **21**, owing to the oxophilic nature of Li^+, whereas the more covalent C-Zn contributed to the enhanced stability of **38** versus **37** (Scheme 7).[23]



Scheme 7. Studies on lithioxazoles and benzoxazole by the Boche group.

In 1996, Vedejs and co-workers reported a practical solution to the electrocyclic ring-opening problem of 2-lithiooxazoles. Suppression of the electrocyclic pathway could be achieved via Lewis acid complexation. Accordingly, the electron pair of the

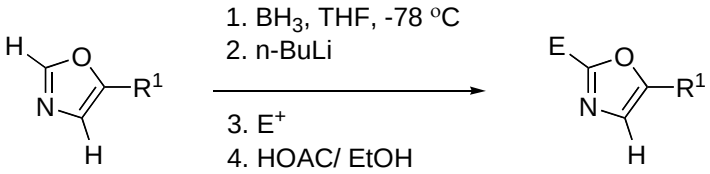
nitrogen atom of the ring of **20** was prevented from developing into the isonitrile species **21**, therefore, ensuring that only C_2 products **19** would be obtained. In addition, the authors anticipated that complexation of **18** should enhance the acidity of C_2-H (Scheme 8).[24]



Scheme 8. Suppression of the electrophilic ring-opening pathway by Lewis acid complexation.

This methodology resulted in a practical method for the funcionalisation of oxazoles at C_2, including electrophiles that would normally couple to C_4 (such as aldehydes), and also alkyl electrophilic reagents that gave substantially lower yields if no complexation was used (Table 4).

Table 4. Functionalisation of oxazoles at C_2 using borane pre-complexation.



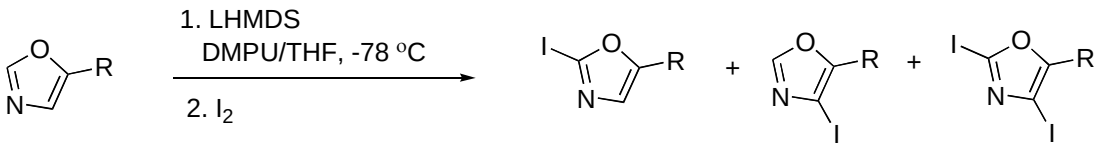
28 **41**

Entry	R^1	E	Electrophile	Yield of **41** (%)
1	Ph	PhCH(OH)	PhCHO	94[a]
2	Ph	PhCH(OH)	PhCHO	88, 81
3	Ph	PhCH(OH)	PhCHO	90[b]
4	Ph	$PhCH_2CH_2(OH)$	$PhCH_2CH_2CHO$	84
5	H	PhCH(OH)	PhCHO	70[b]
6	$CH_2CH_2CH(CH_3)OTBS$	PhCH(OH)	PhCHO	84
7	Ph	Me_3Si	Me_3SiCl	78[c]
8	Ph	Cl	C_2Cl_6[d]	86
9	Ph	5-phenyloxazol-2-yl	C_2Cl_6[e]	79
10	Ph	CH_3	CH_3I	74
11	Ph	$PhCH_2CH_2Otf$	$PhCH_2CH_2OTf$	65

[a]Reaction using LiTMP as the base. [b]Reaction using *s*-BuLi as the base. [c]Yield of the borane complex prior to decomplexation. [d]2 equivalents were used. [e]0.5 equivalents were used.

Using the ambivalent reactivity of oxazoles, Vedejs and Luchetta developed a very useful methodology to regioselectively iodinate oxazoles at C_4 (Table 5).

Table 5. Synthesis of 4-iodooxazoles.



28 **42** **43** **44**

Entry	R	Yield of **42** + **43** (%)	[**43**:**42**]	[(**42** + **43**):**44**]
1	*p*-tolyl	73	32:1	15:1
2	Ph	67	32:1	52:1

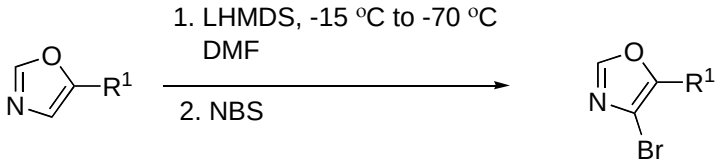
3	CO_2Et	44	5.3:1	6.3:1
4	$(CH_2)_2Ph$	43	> 49:1	4:1
5	$(CH_2)_2Ph$	64[a]	> 49:1	99:1
6	$(CH_2)_3OTBS$	34	> 49:1	1:1
7	$(CH_2)_3OTBS$	63[a]	> 49:1	99:1

[a]After iodine addition, the crude mixture was treated with n-BuLi at -78 °C until a phenantroline endpoint was detected.

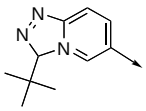
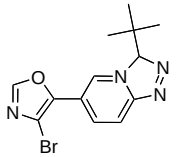
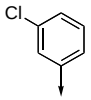
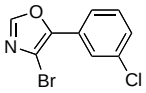
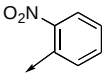
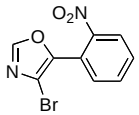
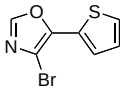
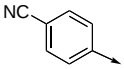
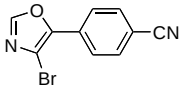
When lithiating 5-phenyloxazole and quenching the reaction mixture with I_2 a complex mixture of C_2, C_4, C_2-C_4 products **42-44** was initially obtained with LHMDS being selective towards the C_4-I product **43** compared to C_2-I product **42** in a [3:1] ratio. Switching to n-Buli inverted this ratio in favour of the C_2-I product **42**, and adding some acetonitrile as a co-solvent increased in 40% the amount of 2,4-diiodooxazole **44**. It was found that addition of DMPU prior adding the base to the reaction gave consistently C_4-I/C_2-I species in a [97:3] along with 5% of 2,4-diiodooxazole **44**. This methodology was extended to prepare a series of 4-iodo-5-substituted oxazoles (Table 5). Furthermore, it was also discovered that the use of 1,2-diiodoethane (without DMPU) gave exclusively C_2-I products.[25]

Vedejs' method has been recently extended to the synthesis of 4-bromooxazoles **45**. As part of a medicinal chemistry program, Li and co-workers needed specifically a 4-iodo-5-substituted type of oxazoles. However, Vedej's method did not provide good yields or good selectivity on their substrate. As a result, the authors investigated selective C_4 brominations under similar conditions. In their studies, they found that DMPU could be replaced by the cheaper DMF and using NBS as the brominating agent, after optimisation, an excellent 87 % yield of 4-bromo derivative with less than 0.2 % of the 2-bromo species could be isolated. The method was extended to synthesis of a series of 4-bromo-5-substituted oxazoles in high yields (Table 6).[26]

Table 6. Selective 4-bromination of 5-substituted oxazoles.



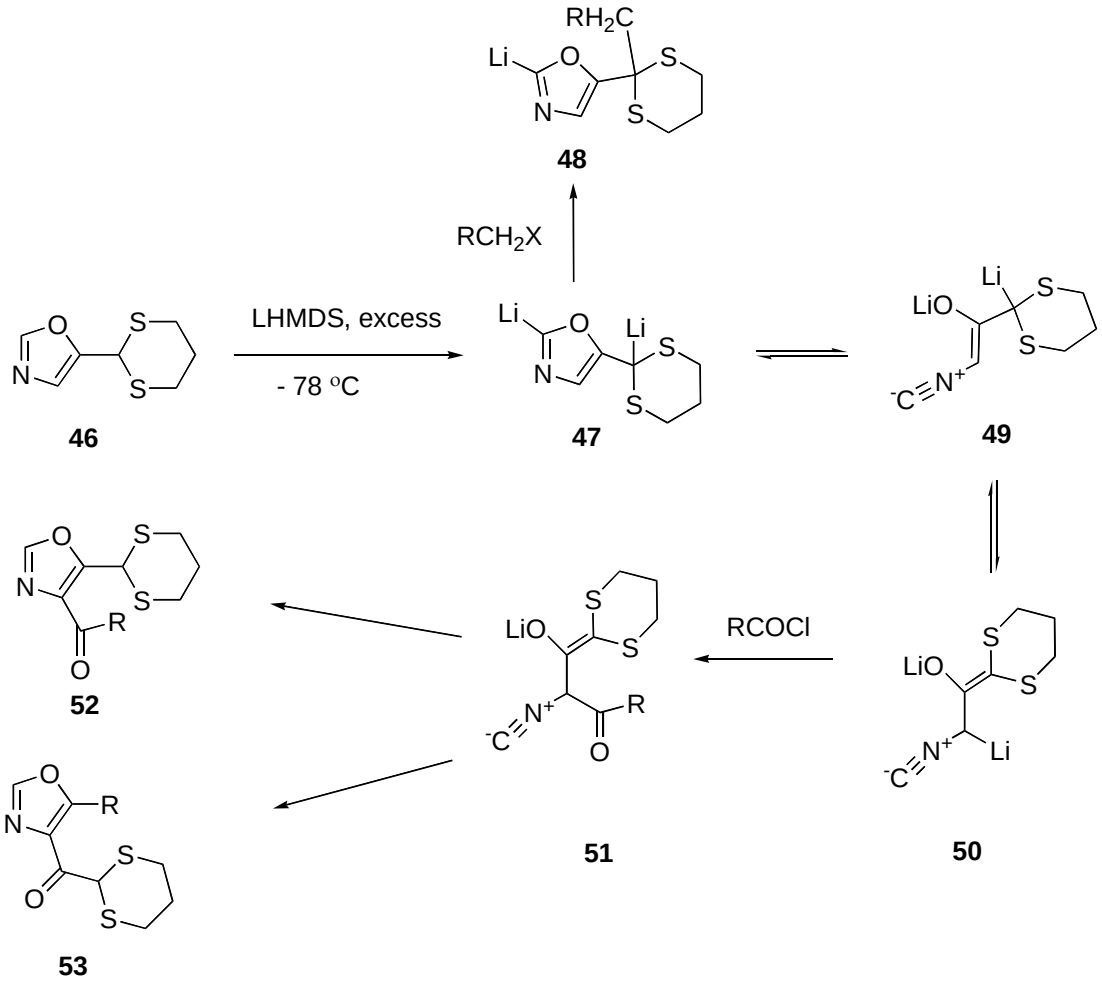
28 **45**

Entry	R^1	Product **45**	Yield of **45** (%)
1			87
2			82
3			78
4			87
5			78

Williams and McClymont published interesting work based on the varied reactivity of lithiooxazoles. These authors investigated the alkylation and acylation of 5-(1,3-dithian-2-yl)oxazole **47** generated from the lithiation of 5-(1,3-dithian) oxazole **46**. Initially, it was shown through deuterium incorporation studies that deprotonation using excess LHMDS occurred firstly at C_2-H and secondly at the dithiane carbon atom. Thus, they found that alkylating agents usually afforded exclusively the side chain analogues **48**; however, reactive electrophiles such as CH_3I and TMSCl afforded complex mixtures of C- and O-alkylated products with secondary halides being unreactive. On the other hand, acylation did not produce the expected products. Instead, rearrangement products corresponding to 4,5-disubstituted oxazoles **52** and **53** were isolated. These results were mechanistically

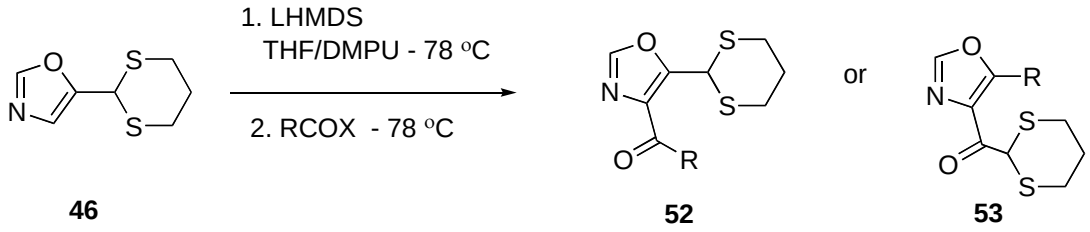
explained via deprotonation and formation of the dianion species, which through equilibrium with the isocyanovinyllithium alkoxides could give C_4 acylation. Cyclisation through both carbonyl groups would give the observed products (Scheme 9).

This reaction represents the first example of a base-induced at low temperature Cornforth rearrangement. A selection of examples with different acylating reagents used in this reaction is shown in Table 7.

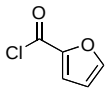
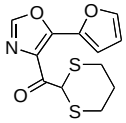
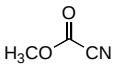
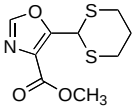
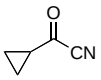
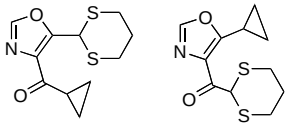


Scheme 9. Lithiation of 5-(1,3-dithian)oxazole.

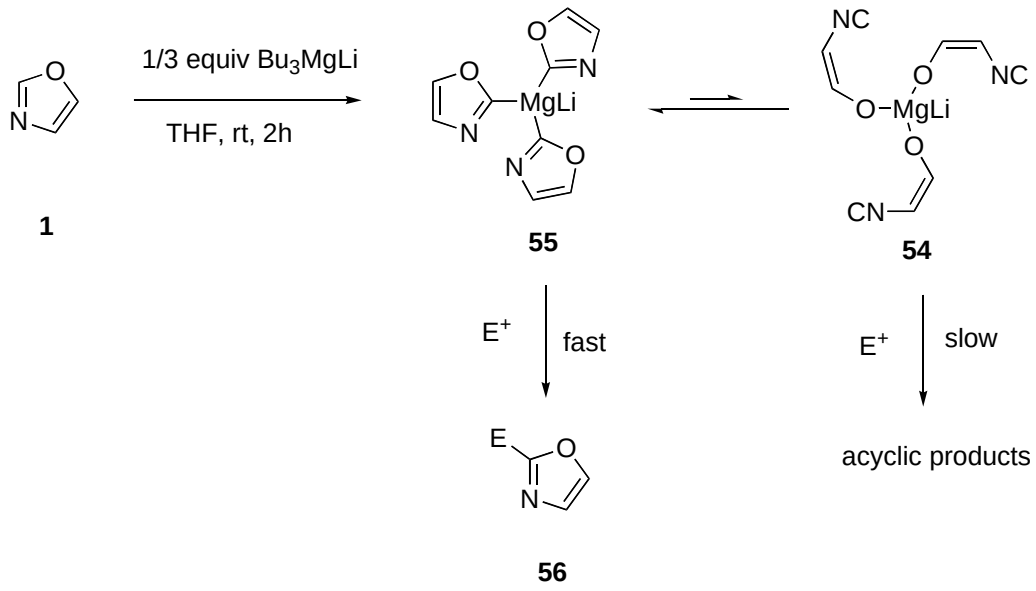
Table 7. Acylation of 5-(1,3-dithian-2-yl)oxazole.



46 **52** **53**

Entry	Electrophile	Product **52** or **53**	Yield (%)
1			55
2			84
3		 1.8 : 1	98

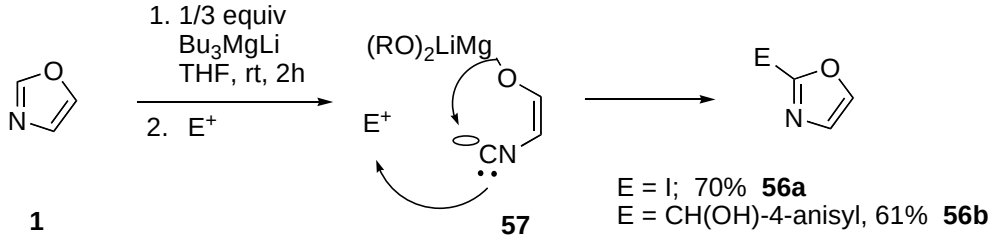
More recently, Mongin and co-workers have reported the deprotonation of the parent 1,3-oxazole and the related benzoxazole using lithium magnesates (Scheme 10).



1 **55** **54** **56**

Scheme 10. Deprotonation of 1,3-oxazole and reaction with electrophiles.

These organometallics are more attractive than the lithium species because they can be generated at room temperature and react with electrophiles giving C_2 products exclusively, without the assistance of Vedejs' borane pre-complexation. Furthermore, they can also be used in cross coupling reactions (see next section). The authors conducted NMR studies on the lithium magnesates species of benzooxazole and the parent oxazole observing rapid conversion to the more stable acyclic isocyano enolate. However, the isolation of 2-subsituted benzoxazoles and oxazoles prompted them to interpret these results with two possible explanations. Either the equilibration between the open and closed structures was faster than the trapping of the acyclic form with the closed isomer being more reactive (Scheme 10), or the open isomer could react with the electrophile via an intramolecular type reaction (Scheme 11).[27]



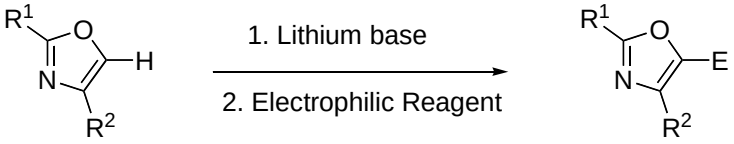
Scheme 11. Intramolecular type of mechanism to obtain 2-substituted oxazoles **56**.

Although lithiation at the C_5-H position of the ring is easier because no ring-opening complications are present, comparatively few reports based on the metalation of oxazoles at this position have emerged in the literature. These results are summarised in Table 8.

Metalation at C_5-H is generally not possible on unsubstituted C_2-H oxazoles unless special activation, such as by an ester functionality, is present at C_4 position rendering C_5-H more acidic than C_2-H (for example entry 1, Table 8).[28,29] To assist this problem, Shafter and Molinski have recently described a general method for the preparation of 5-substituted oxazoles without substitution on the 2-position.[30] The

authors blocked C_2 of the ring with a methylthio group, which was stable under n-BuLi in THF/TMEDA at -78 ºC. The obtained oxazole-5-yllithium derivatives were reacted with a variety of electrophiles and, following reductive desulfurisation gave 5-substituted oxazoles in 59-68% yield (Table 9).

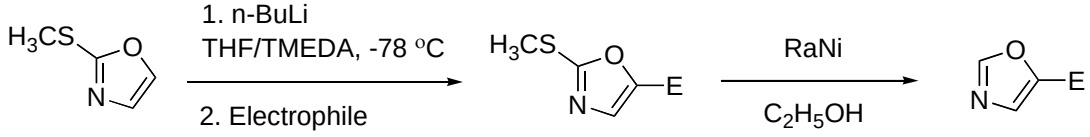
Table 8. Synthesis of substituted oxazoles from oxazol-5-yllithium derivatives.



58 **59**

Entry	R^1	R^2	Reagent	E	Yield (%)	Ref.
1	Me	CO_2H	D_2O	D	92, 77	[28, 29]
2	Me	CO_2H	MeI	Me	~ 10	[28, 29]
3	Me	CO_2H	Me_3SiCl	$SiMe_3$	86	[31]
4	Me	CO_2Me	D_2O	D	99, 92	[28, 29]
5	Me	CO_2Bu-*t*	Me_3SiCl	$SiMe_3$	62	[32]
6	Ph	Ph	MeI	Me	85	[33]
7	Ph	Ph	Me_3SiCl	$SiMe_3$	88	[33]

Table 9. Synthesis of 5-substituted oxazoles.



60 **61** **62**

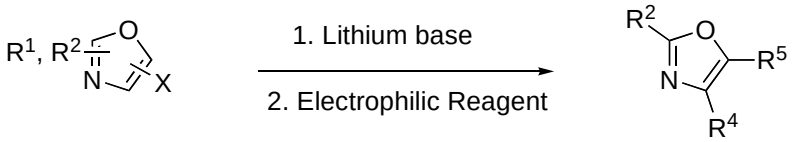
Entry	Electrophile	Yield of **61** (%)	Yield of **62** (%)
1	benzaldehyde	84	68
2	p-anisaldehyde	85	-[a]
3	*p*-bromobenzaldehyde	84	-[a]
4	2-naphptaldehyde	77	60
5	2-furaldehyde	72	-[a]
6	citral	83	-[a]

7	decylaldehyde	73	60
8	pivaldehyde	69	59
9	2,3-*o*-isopropylidene-*D*-glyceraldehyde	60	-[a]
10	3-methyl-2-butanone	39	-[a]
11	cyclohexanone	53	60
12	benzoyl chloride	38	-[a]
13	pivaloyl chloride	71	-[a]

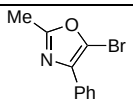
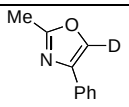
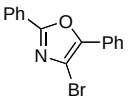
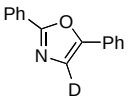
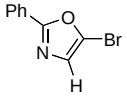
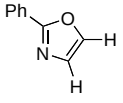
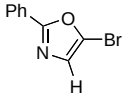
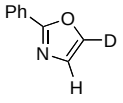
[a] Experiment not carried out.

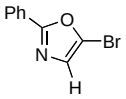
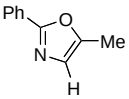
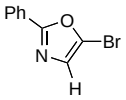
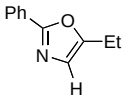
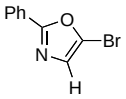
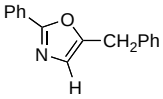
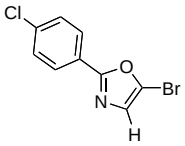
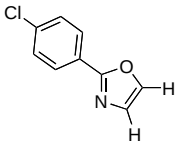
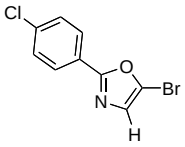
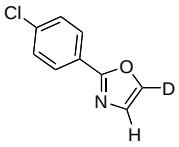
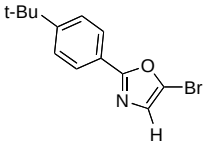
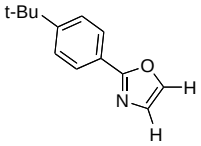
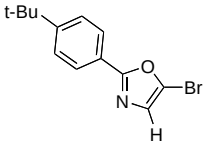
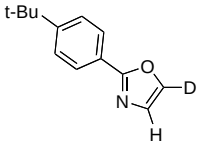
Halogen/lithium exchange reactions are rare due to the general scarcity of halogenated oxazoles. Bowie and co-workers were probably the first group to report lithium/halogen exchange reactions for oxazoles. They first reported the lithiation of a 5-bromooxazole derivative and its subsequent quenching with D_2O (Entry 1, Table 10).[10a] In a later publication, a 4-bromooxazole was deuterated in similar conditions (Entry 2, Table 10).[10b] Arao and co-workers chose 5-bromooxazoles to conveniently functionalise the 5-position of 2-substituted oxazoles in generally high yields (Entries 3-11, Table 10).[34,39]

Table 10. Synthesis of substituted oxazoles from lithium/halogen exchange reactions.



63 **64**

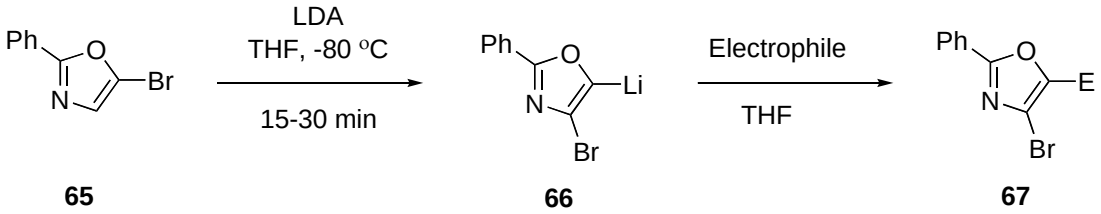
Entry	Halogenated oxazole **63**	Electrophile	Product **64**	Yield (%)	Ref.
1		D_2O		-	10a
2		D_2O		-	10b
3		H_2O		88	34
4		D_2O		84	34

5		MeI		73	[34]
6		EtI		70	[34]
7		$PhCH_2Br$		72	[34]
8		H_2O		84	[34]
9		D_2O		80	[34]
10		H_2O		85	[34]
11		D_2O		86	[34]

Very recently, Stanetty and co-workers have published the first halogen dance reaction of oxazoles, resulting in a general methodology for the synthesis of 2-phenyl-4-bromo-5-substituted oxazoles (Table 11).[35]

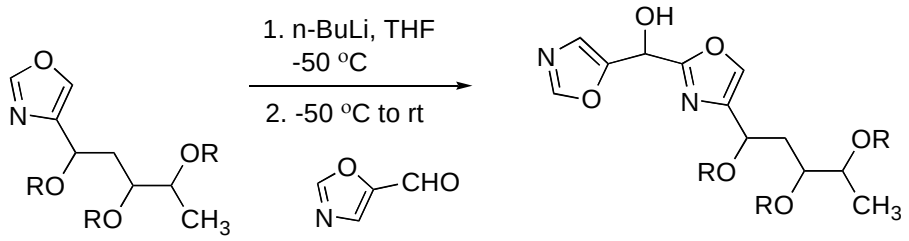
Lithiation of oxazoles has even been applied to natural products synthesis. Crews and co-workers, in their preparation of bengazole A, an antihelminthic agent isolated from marine sponges, employed a lithiooxazole and an oxazole substituted at C_5 with the aldehyde functionality. In this way, the required C_2 and C'_5 substitution of the natural product was obtained; however, the synthesis was racemic, nonstereospecific and no yield was provided for this transformation (Scheme 12).[36]

Table 11. Halogen dance reaction on 2-phenyl-5-bromooxazole.



65 **66** **67**

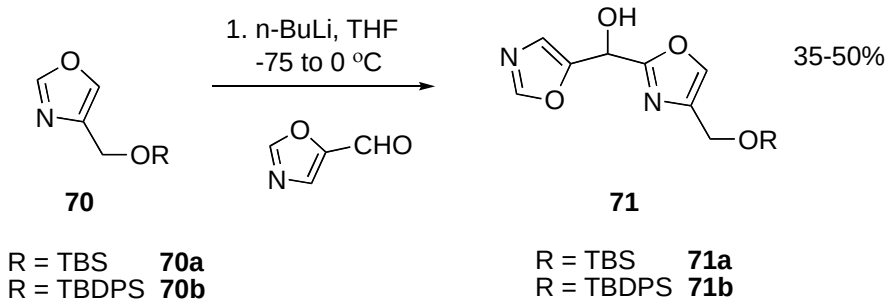
Entry	Electrophile	E	Yield of **67** (%)
1	H_2O	H	60
2	Benzaldehyde	PhCH(OH)	78
3	TMSCl	TMS	68
4	$Cl_3CH_2CH_2Cl_3$	Cl	68
5	Br_2	Br	30
6	1,2-dibromoethane	Br	11
7	1,2-dibromo-1,1,2,2-tetrachloroethane	Br	76
8	I_2	I	66
9	DMF	CHO	58
10	CO_2	COOH	63
11	Cyclohexanone	$C_6H_{10}OH$	69



68 R = TBDMS **69**

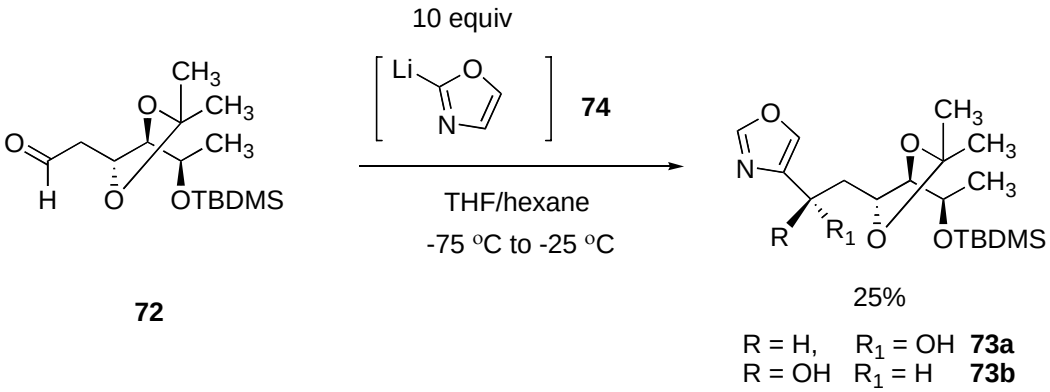
Scheme 12. Key step in Crews' synthesis of bengazole A.

Shioiri and co-workers have also contributed to the synthesis of bengazole A. In a similar approach, they lithiated 4-substituted oxazoles followed by condensation with 5-oxazol-ylaldehyde in modest to medium yields. Attempts to improve the yield of this transformation either using Lewis acid complexation, alternate bases, or through the use of co-solvents for the reaction were unsuccessful (Scheme 13).[37]



Scheme 13. Synthesis of the bengazole's A core.

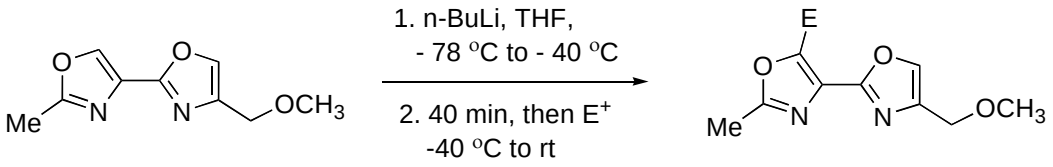
Molinski and co-workers made use of the ambivalent reactivity of oxazole with the first report of a C_4 direct condensation with aldehydes in natural products synthesis. They synthesised the core of bengazole A using a large excess of 2-lithiooxazole **74** and aldehyde **72**, producing the desired target in low yield and as a [1:1] mixture of epimers (**73a** and **73b**). The low yield observed was attributed to the low reactivity of **74** and the formation of side products such as competing β-elimination and products from the enolisation of **72** (Scheme 14).[38]



Scheme 14. Molinski's synthesis of advanced intermediate **73**.

Also in the context of natural product synthesis, the group of Williams described a regioselective metalation on 2,4'-bis-oxazole **75**. As reported, lithiation was accomplished regioselectively on C_5-H due to heteroatom complexation and an internally directed deprotonation. This hypothesis was supported by semi-empirical calculations using AM1 and PM3 Hamiltonians, which confirmed the proposed pathway to have the lowest energy. The obtained lithiated bis-oxazole was reacted with several electrophiles, some of these results are shown in Table 11.[39]

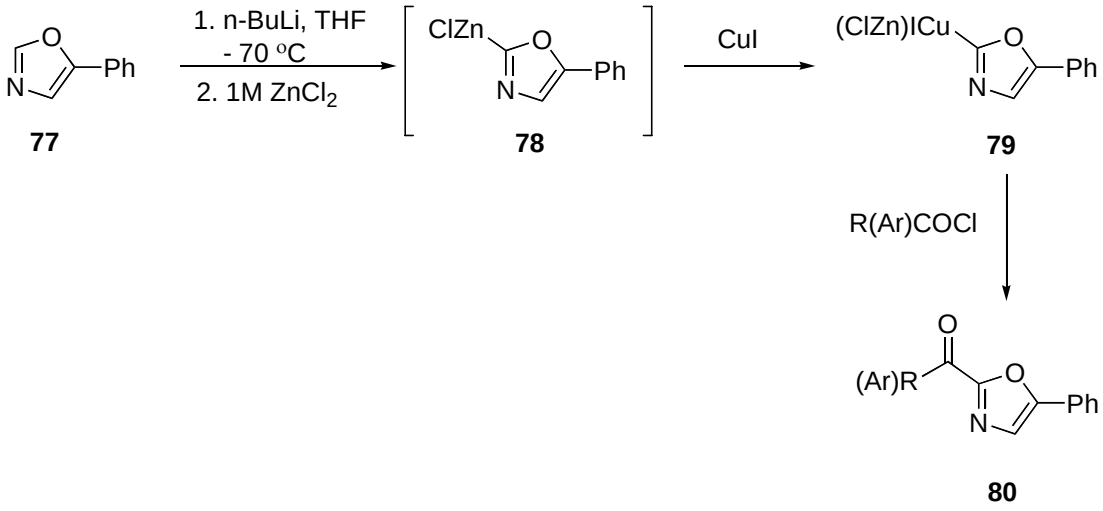
Table 11. Regioselective lithiation studies on 2,4'-bis-oxazole followed by electrophilic quenching.



75 **76**

Entry	Electrophile	E	Yield of **76** (%)
1	CH_3I	CH_3	63
2	$(CH_3)_3SiCl$	$(CH_3)_3Si$	83
3	NCS	Cl	50
4	C_6H_5CHO	C_6H_5CHOH	85
5	$(CH_3)_2CHCHO$	$(CH_3)_2CHCHOH$	84

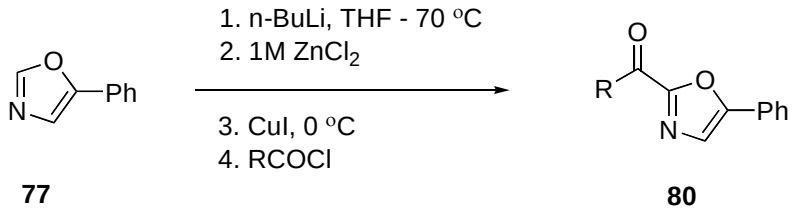
Other metallooxazoles have been prepared from lithiated oxazoles by transmetalation reactions. For example, Anderson and co-workers reported a general methodology to synthesise 2-acyl-5-phenyloxazoles **80** inaccessible by other protocols. Transmetallation from Li to Zn using $ZnCl_2$ and then to copper using CuI was necessary because the organozinc species were unreactive towards the acid chlorides employed (Scheme 15).[40]



Scheme 15. Synthesis of bimetallic species **79** to generate 2-acyl-5-phenyloxazoles **80**.

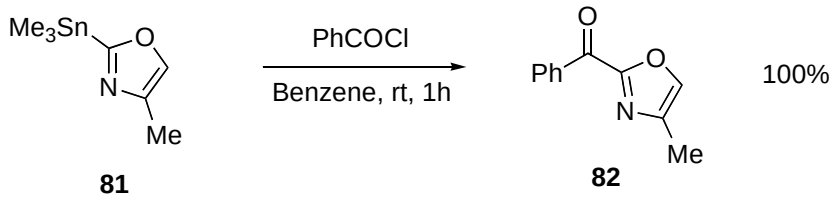
This methodology was applied to the synthesis of 2-acyl-5-phenyloxazoles in generally good yield. Table 16 summarises these results.

Table 16. Synthesis of 2-acyl-5-phenyloxazoles.



Entry	RCOCl	Yield of **80** (%)
1	C_6H_5COCl	70
2	4-CH_3O-C_6H_4COCl	65
3	4-NO_2-C_6H_4COCl	80
4	C_6H_5CH=$CHCOCl$	58
5	$CH_3(CH_2)_2COCl$	67
6	$CH_3CHCOCl$	67
7	$(CH_3)_3CCOCl$	64

Dondoni and co-workers have prepared 2-stannyloxazoles from the corresponding lithio derivates and have used them as precursors to 2-acyl and 2-aryl oxazoles. Most examples cover palladium catalysed Stille reactions; however, coupling with conventional acylating agents has also been disclosed (Scheme 16).[41]



81 **82**

Scheme 16. Acylation of 2-trimethyltin-4-methyloxazole **81**.

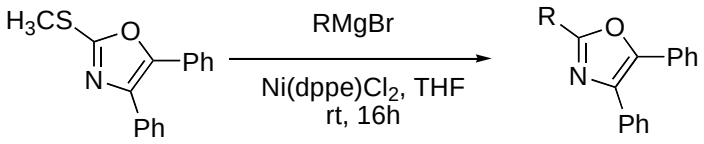
1.3 Transition metal-catalysed cross-coupling reactions of Oxazoles.

Transition metal-mediated carbon-carbon bond formation is arguably the single biggest advance to have taken place in organic synthesis over the past thirty years. Coupling two sp^2 carbons together was almost an impossible transformation, and now it is carried out routinely in both academic laboratories and industrial processes.[42] Heterocyclic cross-coupling reactions, however, remain considerably more under-developed. Primary classes of heterocycles containing one heteroatom have been extensively studied compared to heterocycles with more than one heteroatom.[43] This is especially true for oxazoles since the number of cross-couplings reported is very low. The last few years have produced, however, a significant increase in the number of cross-coupling reactions involving the oxazole heterocyclic system. Although other metals have also been used, cross-coupling reactions catalysed by palladium complexes have dominated the field. Construction of substituted oxazoles as well as poly-oxazoles has been achieved through the use of

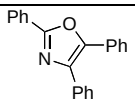
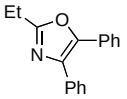
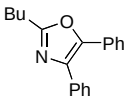
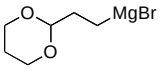
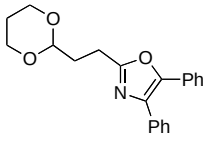
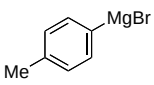
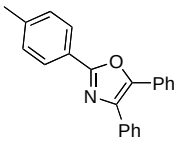
palladium catalysed cross-coupling reactions. Appropriately functionalised oxazoles can participate in transition metal catalysed cross-coupling reactions, being either the organometallic reagent or the coupling partner. Halo-, OTf-, or SCH_3-substitued type of oxazoles have been used as the coupling partners.

In 1984, Pridgen, using a nickel catalysed cross-coupling methodology of Grignard reagents with 2-(methylthio)-4,5-diphenyloxazole, reported the first transition metal catalysed cross-coupling reactions involving oxazoles. This pioneering methodology was quite effective and is particularly useful to prepare 2-alkyl-4,5-diphenyloxazoles in good yields, usually difficult to obtain by other methods. This methodology is shown in Table 17.[44]

Table 17. Nickel catalysed cross-coupling reactions of Grignard reagents with 2-methylthio-4,5-diphenyloxazole **83**.



83 **84**

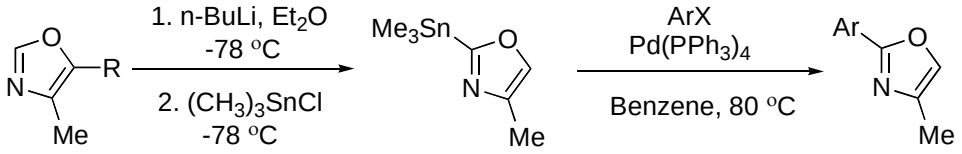
Entry	RMgBr	Product **84**	Yield of **84** (%)
1	PhMgBr		90
2	EtMgBr		95
3	BuMgCl		96
3			76
4			82

Since then, the field has been expanding rapidly and now several protocols have been developed for the Stille, Sonogashira, Heck, Suzuki, Negishi as well as direct arylation methods.

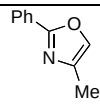
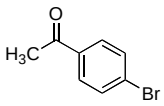
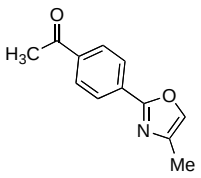
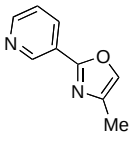
1.3.1 Stille couplings

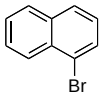
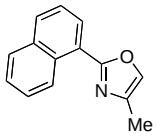
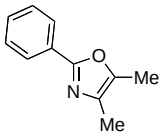
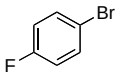
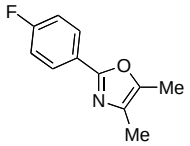
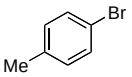
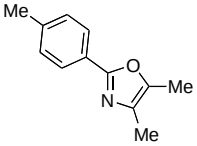
In 1987, the first Stille coupling of oxazoles was reported by the Dondoni group. They carried out an exhaustive study on several variously substituted 2-trimethylstannyl oxazoles. Lithiation of 4-methyloxazoles followed by quenching with trimethyltin chloride or tributyltin chloride provided the required 2-stannyloxazoles, which were coupled under standard Stille conditions with a variety of aryl halides and also heteroaryl halides. A selection of examples is shown in Table 18.[17]

Table 18. Synthesis of 2-aryl-4-methyloxazoles using the Stille coupling.

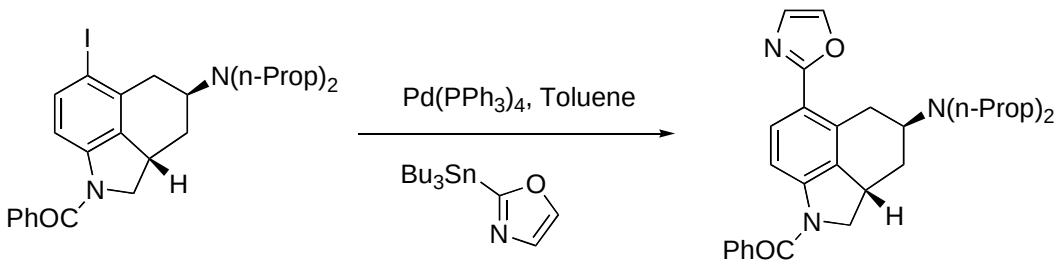


85 **81** **86**

Entry	R	Ar-X	Product **86**	Yield of **86** (%)
1	H	PhI		80
2	H			100
3	H			100

4	H			92
5	Me	PhI		100
6	Me			100
7	Me			70

In 1994, as part of a program to evaluate indole derivatives as anti-emetic agents, chemists from the Lilly Company reported the Stille coupling between oxazole stannane **89** and the complex heterocycle **87** (Scheme 17).[45]

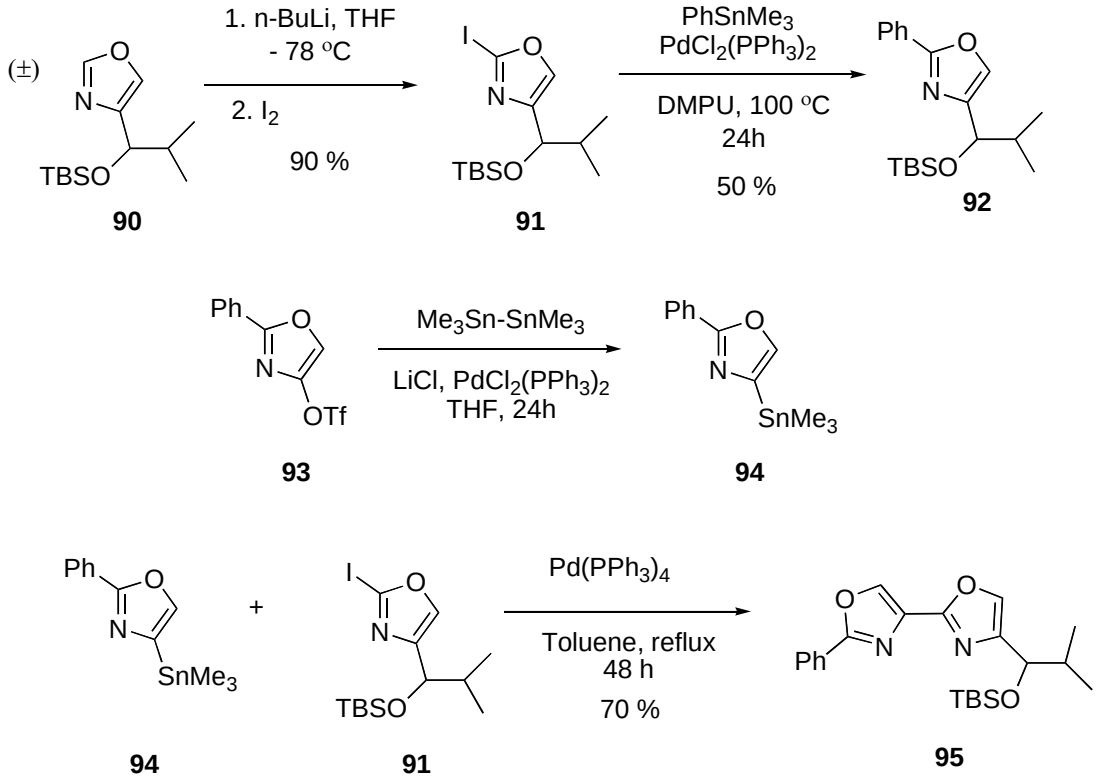


87 **89** **88**

Scheme 17. Stille coupling between indole **87** and 2-stannyl-oxazole **89**.

In 1995, in model studies towards the synthesis of the natural product hennoxazole A, Barrett and Kohrt considered the Stille coupling to connect the 2,4'-linked bis-oxazole entity contained in the natural product. The authors prepared 2-iodooxazole **91** in 90% yield from lithiation of oxazole **90** and subsequent quenching with I_2. Under standard Stille conditions, **91** was coupled to phenyltrimethyltin and gave the coupling product **92** in 50% yield. Attempts to convert iodooxazole **91** to

the organostannane coupling partner failed. Alternatively, triflate **93** was coupled with hexamethyldistannane in the presence of $PdCl_2(PPh_3)_2$ and gave the stannyloxazole **94**, which underwent palladium catalysed coupling with the corresponding 2-iodooxazole **91** in 70 % yield (Scheme 18). This report represents the first synthesis of a bis-oxazole moiety using a transition metal catalysed cross-coupling methodology.[46]

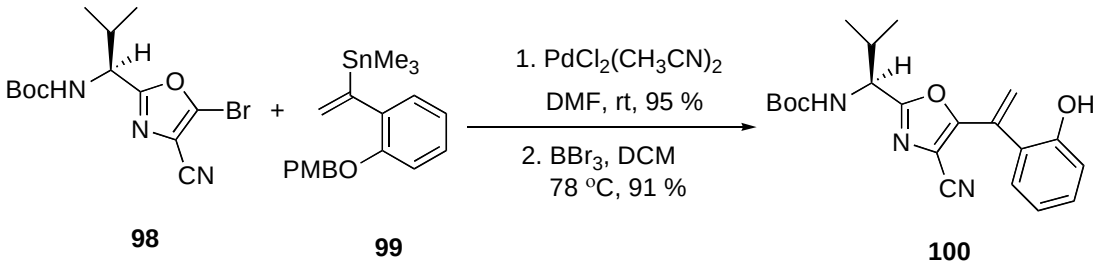


Scheme 18. Model studies towards the synthesis of hennoxazole A.

A year later, this time in model studies towards the total synthesis of dimethyl sulfomycinamate, Kelly and co-workers also reported the use of oxazoles triflates as coupling partners in Stille couplings. Palladium catalysed coupling between triflate **96** with a variety of organostannes gave the coupling products **97** in excellent yields (Table 19).[47]

The macrocylclic core of the impressive natural product diazonamide A has also served as an application of the Stille coupling. In 1998, Harran and co-workers

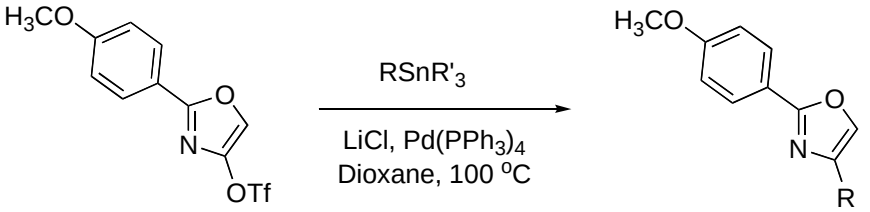
investigated the palladium catalysed Stille reaction of stannyl styrene **99** with 5-bromooxazole **98** obtaining excellent results (Scheme 20).[48]



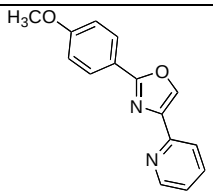
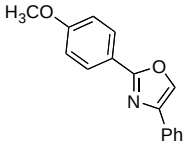
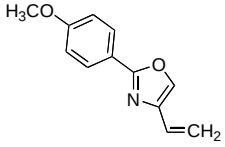
98 **99** **100**

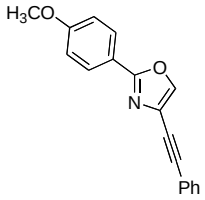
Scheme 20. Model studies towards the synthesis of Diazonamide A.

Table 19. Synthesis of 2,4-disubstituted oxazoles using the Stille reaction on oxazole triflate **96**.



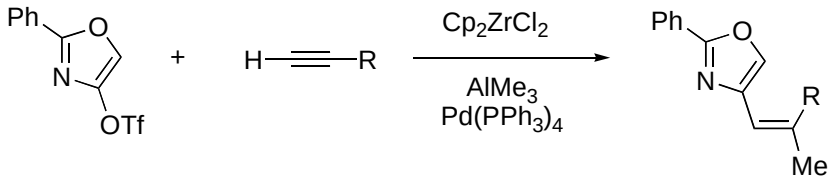
96 **97**

Entry	R	Product **97**	Yield of **97** (%)
1	2-Pyridyl		85
2	Ph		91
3	$CH{=}CH_2$		99

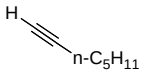
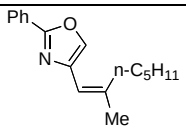
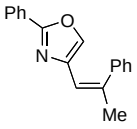
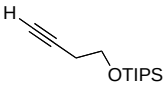
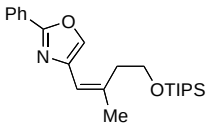
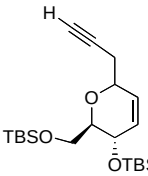
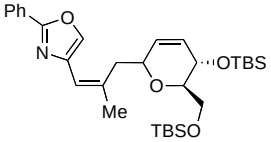
4	—C≡CPh		92

Towards the synthesis of the complex macrocyclic natural product phorboxazole A, Panek and Schaus also employed oxazole triflates as coupling partners in their synthetic methodology to produce 4-vinyloxazoles. They carried out, in a one pot transformation, a series of carboalumination reactions catalysed by Cp_2ZrCl_2 of terminal alkynes, followed by $Pd(PPh_3)_4$ catalysed coupling reaction with triflate **93** with good overall results in the coupling yields (Table 20).

Table 20. Carboalumination reactions on terminal alkynes followed by palladium catalysed coupling of oxazole triflate **93**.

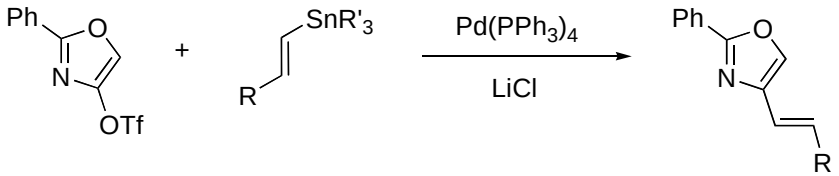


93 **94** **95**

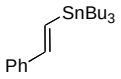
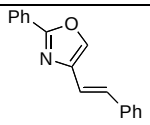
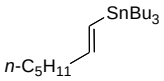
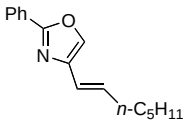
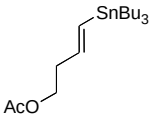
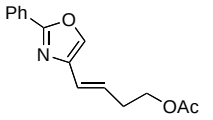
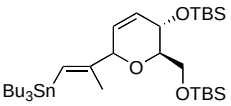
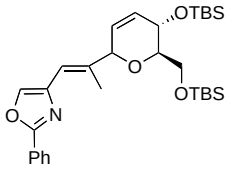
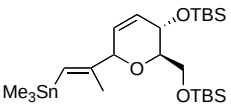
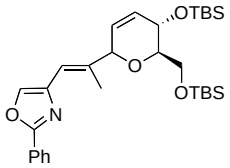
Entry	Alkyne	Product **95**	Yield of **95** (%)
1			75
2			70
3			72
4			68

Sadly, this strategy failed when applied to the actual natural product. The authors decided to reconsider their approach by carrying out standard Stille couplings on *E*-alkenes instead. This new methodology gave excellent results for the model substrates and 60 % yield when applied to the phorboxazole A fragment. However, in order to achieve good rates of reaction, a modification of the stannane substitution was necessary (Table 21).[49]

Table 21. Stille coupling of *E*-alkenes with triflate **93**.

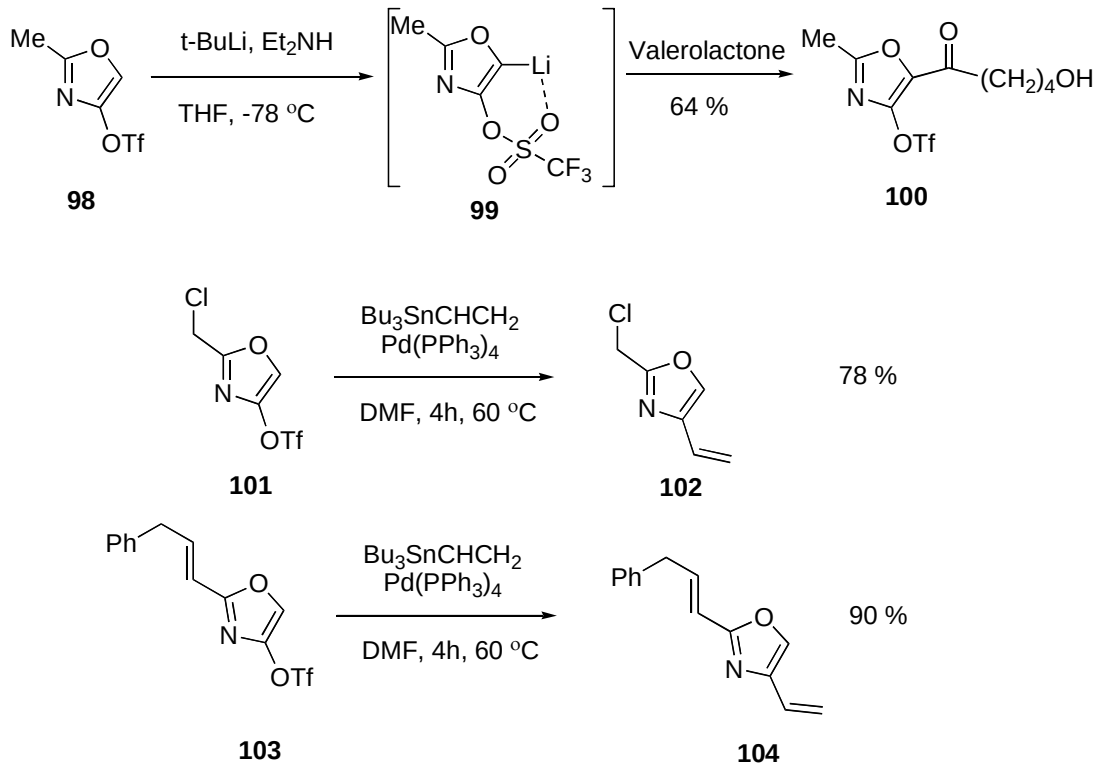


93 **96** **97**

Entry	Stannane	Product **97**	Yield of **97** (%)
1			75
2			80
3			84
4			20[a]
5			60[a]

[a] $Pd_2(dba)_3 \cdot CHCl_3$ (6 mol %), P(*t*-Bu)$_3$ (12 mol %), LiCl, NMP, 60 °C were used instead.

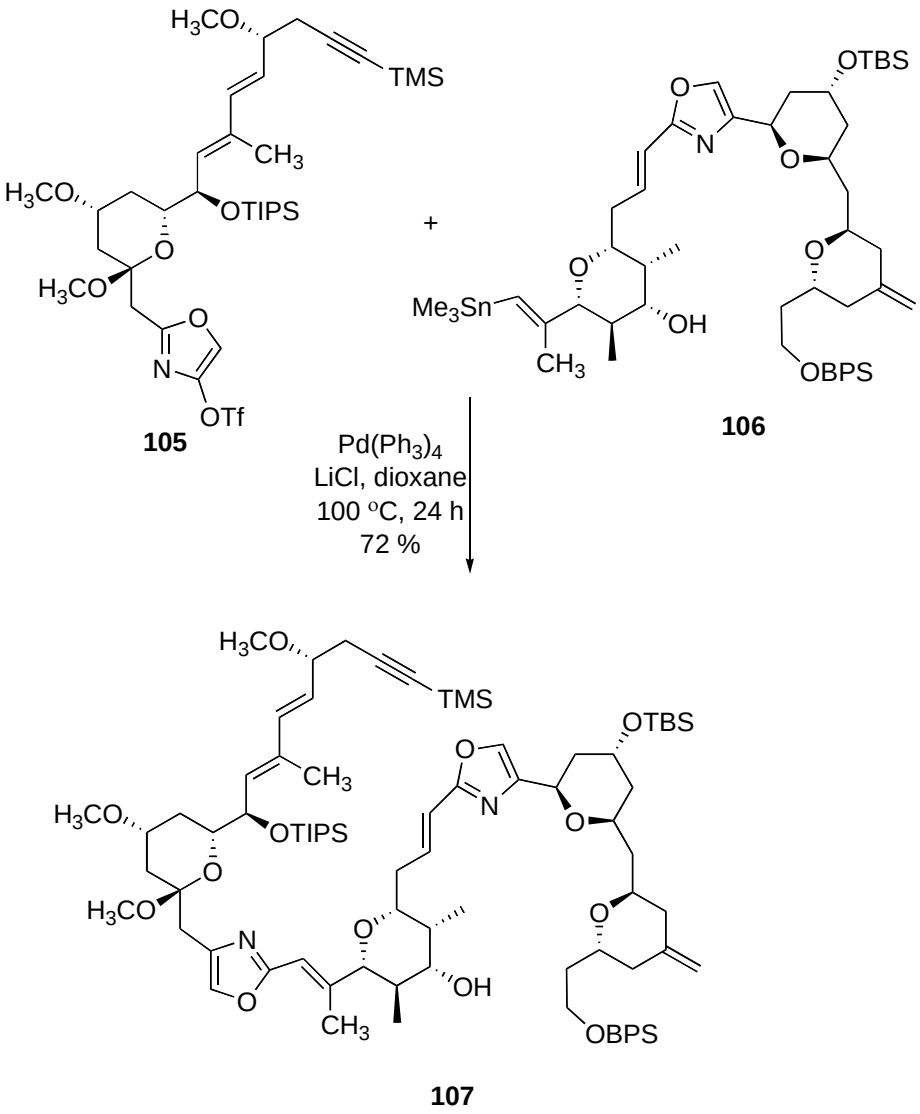
Smith and co-workers reported a novel methodology to synthesise 2-substituted-4-trifloyloxazoles, including 2-alkyl type of substituents, inaccessible by the existing methods in the literature. The chemistry of these novel oxazoles triflates was initially explored through metalation reactions and also lateral reactions (Scheme 21). Surprisingly, these authors observed that lithiation of triflate **98** with t-BuLi and quenching with valerolactone afforded alcohol **100** as the exclusive product in 64 % yield. Lithiation on the C_2 methyl group was not observed, the lithiation on C_5 was assumed to be both the thermodynamic and kinetic product of lithiation, presumably due to the directing effect of the C_4-OTf group. In addition, in order to demonstrate further utility of the triflate group, they carried out Stille couplings using vinyl tributyltin under standard Stille conditions that gave the coupling products in 78 % and 90 % yield respectively (Scheme 21).[50]



Scheme 21. Synthetic studies on 2-substituted-4-trifloy-oxazoles.

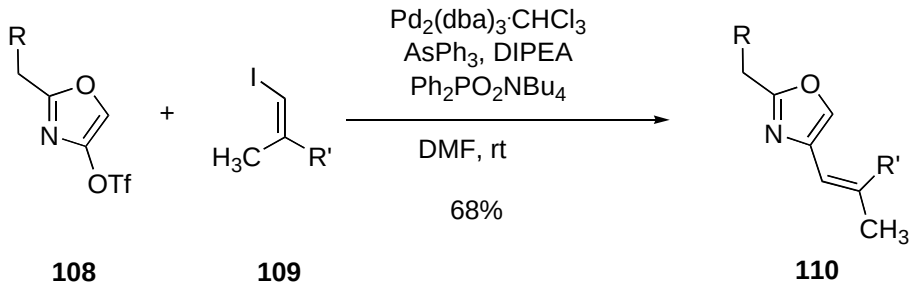
This methodology has been applied to the key step of the total synthesis of phorboxazole A as reported by the same authors. In order to connect the two main

fragments of the macrolide precursor, the Stille coupling was efficiently applied. Impressively, this is probably the most challenging palladium-catalysed coupling involving an oxazole heterocycle to be found in the literature. It was carried out under standard Stille conditions and yielded the desired adduct in 72 % yield (Scheme 22).[51]



Scheme 22. Key step in Smith's total synthesis of phorboxazole A.

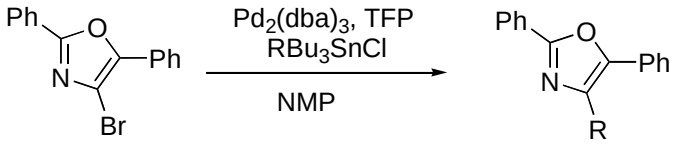
In order to make the total synthesis more scalable and also more convergent, the same group has recently proposed a second-generation total synthesis, which also includes a Stille reaction to couple the main fragments together. However, this time the roles in the reaction were inverted turning the oxazole into the nucleophile and the alkene into the electrophilic partner. Under the milder Liebeskind conditions, the fragments were coupled in 68 % yield at room temperature (Scheme 23).[52]



108 **109** **110**

Scheme 23. Stille coupling on Smith's second generation total synthesis of phorboxazole A.

Clapham and Sutherland have been interested in synthesising a variety of 4-functionalised-2,5-diphenyloxazoles to evaluate their scintillation efficiencies for use as reporter tags in molecular recognition systems. The mild conditions usually employed in the Stille reaction made it their ideal choice for constructing these structures. They could efficiently introduce vinyl, allyl or aryl substituents using 4-bromo-2,5-diphenyl as the electrophilic partner; however, it failed to produce the styrene-containing 2,5-diphenyloxazoles (Scheme 24).

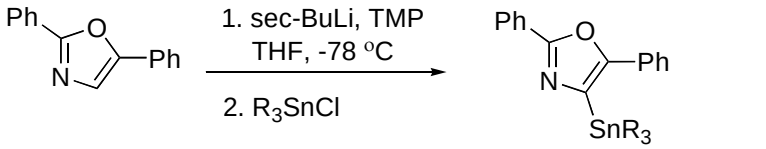


111

R = allyl, 98% **112a**
R = vinyl, 49% **112b**
R = Phenyl 85 % **112c**

Scheme 24. Stille couplings on 4-bromo-4,5-diphenyloxazole **111**.

As an alternative, the authors sought to swap the roles in the reaction by synthesising 2,5-diphenyl-4-trialkylstannanyloxazole **114**, and use them as the nucelophilic partners in the Stille coupling. In contrast with Barrett's difficulties in preparing 2-oxazolylstannane via direct lithium halogen exchange and transmetalation to tin, good yields were found on the lithiation and subsequent quenching of the reaction mixtures with trialkylstannyl chlorides of **113** (Scheme 25).



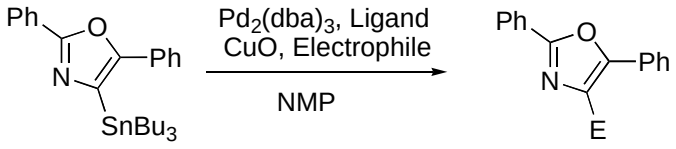
113

R = Me 67% **114a**
R = Bu 75% **114b**

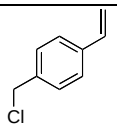
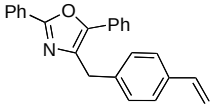
Scheme 25. Lithiation of 2,5-diphenyloxazole **113** and transmetalation to trialkyltin derivatives **114**.

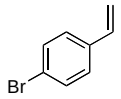
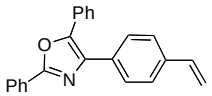
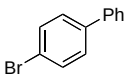
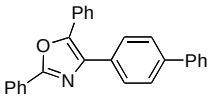
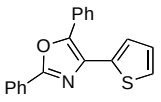
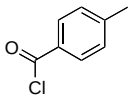
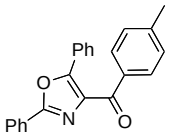
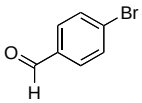
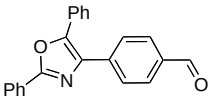
The authors examined the coupling of 4-stannyloxazole **115a** with a range of electrophiles and observed a dramatic effect when using stochiometric CuO in the rates of the reactions and also in the yield of the products obtained. Table 22 summarises these results.[53]

Table 22. CuO-enhanced Stille couplings of 2,5-diphenyl-4-tributylstannanyloxazole **115a** with various electrophiles.

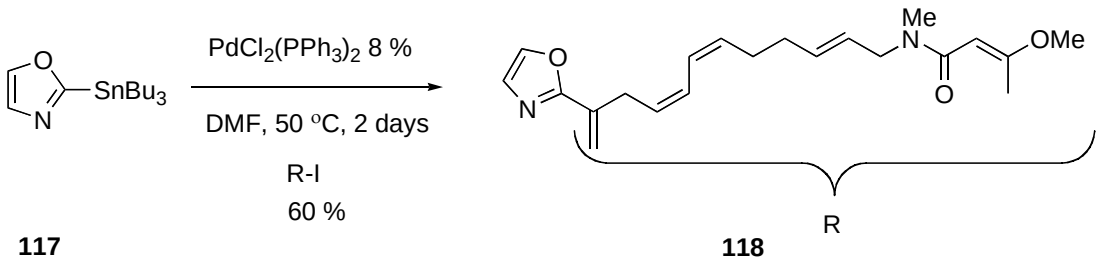


115a **116**

Entry	Electrophile	Conditions	Product **116**	Yield of **116**(%)
1		$AsPh_3$, 65 °C, 4h		95

2		TFP, 65 °C, 16h		58
3		TFP, 65 °C, 24h		51
4		TFP, 80 °C, 24h		42
5		$AsPh_3$, 65 °C, 4h		69
6		TFP, 65 °C, 16h		82

Very recently, towards the total synthesis of the oxazole-containing natural product Ajudazol A, Taylor and co-workers have described an impressive Stille coupling as the key step to connect the diene-rich side chain with the C_2 carbon of the oxazole unit. After the synthesis of the side chain, the Stille coupling with 2-(tributylstannyl)oxazole was investigated and, due to thermal stability issues with the long side chain, milder conditions were required. A range of palladium catalysts was examined, and the best combination proved to be $PdCl_2(PPh_3)_2$ in DMF at 50 °C, which gave the required adduct in a 60 % yield (Scheme 26).[54]



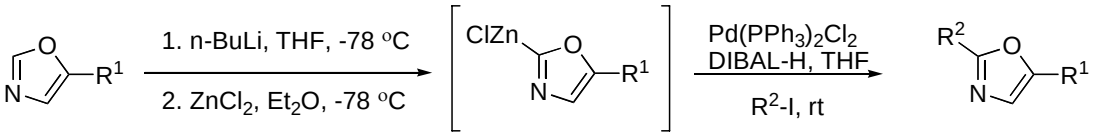
117 **118**

Scheme 26. Stille coupling as the key step in Taylor's synthesis of a fragment of Ajudazol A.

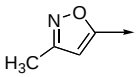
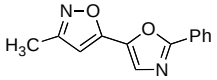
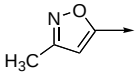
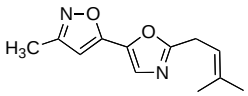
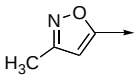
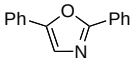
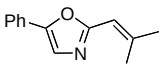
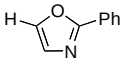
1.3.2 Negishi couplings

As described earlier, Hughes and co-workers transmetallated lithiooxazole **29** with $ZnCl_2$ and, subsequently, they described the first Negishi couplings on the oxazole heterocyclic system. They performed their couplings at room temperature using pre-reduced $Pd_2(PPh_3)_2Cl_2$ with DIBAL-H and found good reactivity for most aryl iodides. Due to a competitive decomposition side reaction of the intermediate organozinc complex, aryl bromides were not effective substrates.[22]

Table 23. Negishi coupling on C_2 of oxazoles.



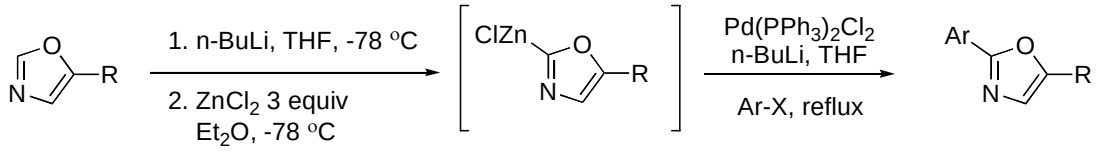
28 **119** **120**

Entry	R^1	R^2-I	Product **119**	Yield of **120** (%)
1		Ph-I		68
2				78
3			No reaction	0
4	Ph	Ph-I		69
5	Ph			78
6	H	Ph-I		53

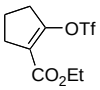
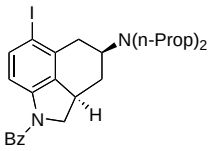
Following Hughes pioneering report, Anderson and co-workers enlarged the field describing a general synthesis of 2-substituted- and 2,5-disubstituted-oxazoles also using oxazol-2-ylzinc chlorides in the context of the Negishi reaction. The scope of the reaction was expanded to aryl iodides and aryl triflates, the latter being the most

reactive, aryl bromides proved to be less reactive. The best conditions found included 5 mol % of $PdCl_2(PPh_3)_2$ pre-reduced with 10 mol % of n-BuLi in refluxing THF. Representative examples are shown in Table 24.[55]

Table 24. Negishi couplings on C_2 of oxazoles.



28 **119** **120**

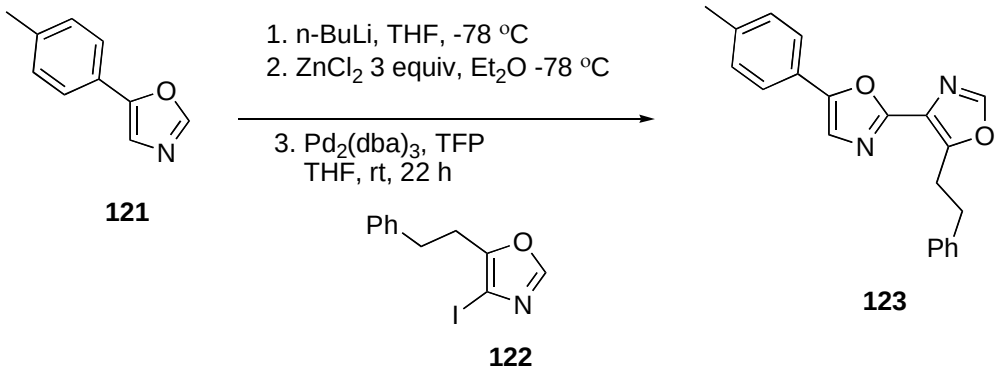
Entry	R	Ar-X	X	Yield of **120** (%)
1	H	1-napthyl	OTf	83
2	H	4-CH_3CO-C_6H_4	OTf	67
3	Ph	1- napthyl	Br	38
4	H	1- napthyl	I	65
5	Ph	1- napthyl	OTf	67
6	Ph	2-CH_3-C_6H_4	I	68
7	Ph	4-CH_3O-C_6H_4	I	64
8	Ph	4-NO_2-C_6H_4	I	56
9	H		OTf	84
10	H		I	52

Very similarly, in order to evaluate 2-(4-methoxyphenyl)oxazole as a nonlinear optical chromophore, Miller and co-workers prepared this compound from 2-bromooxazole and (4-methoxyphenyl)zinc chloride in the presence of $Pd(PPh_3)_4$ and isolated the desired coupling product in 75 % yield.[56]

In a different context, Vedejs and Luchetta prepared a bis-oxazole structure by coupling 2-oxazolzinc species, generated from lithiation of **121** followed by transmetallation to zinc, to 4-iodo-5-substituted oxazole **122** using $Pd_2(dba)_3$ as the

palladium source and trifuranylphosphine (TFP) as the ligand. The desired product **123** was obtained in a 50 % yield (Scheme 27).[25]

More recently, Reeder and co-workers have reported an improved methodology based on Anderson's work. Interestingly, better yields and faster reaction rates were obtained when changing to solid $ZnCl_2$ instead of the ether solutions usually employed for the transmetallation step from lithium to zinc species. Furthermore, the same authors described a scalable procedure allowing for the preparation of larger amounts of products (over 1 Kg).[57]



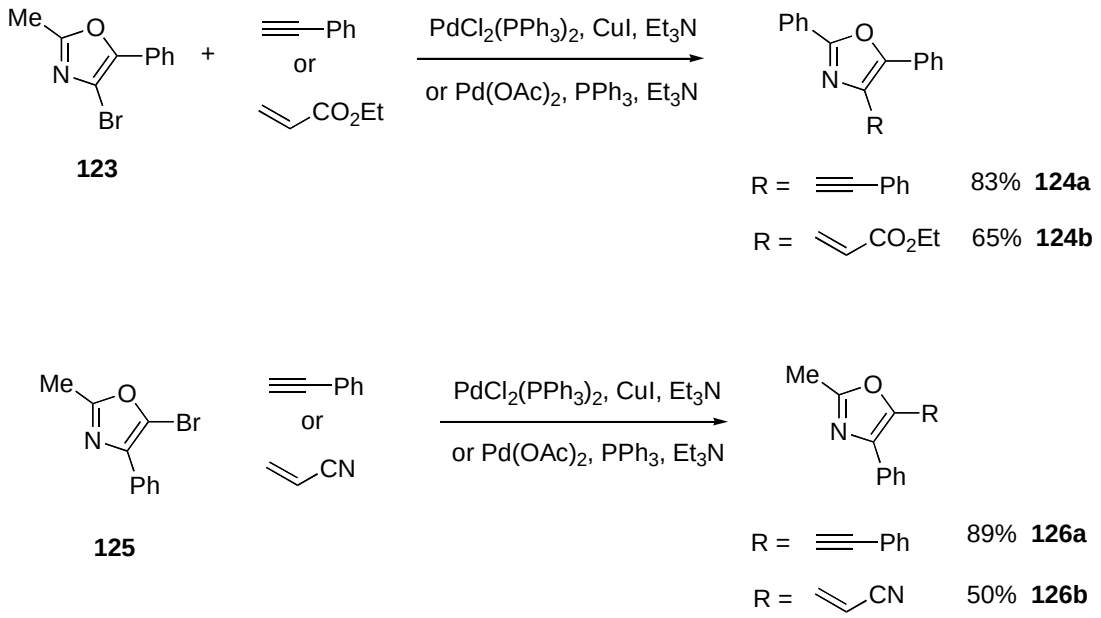
Scheme 27. Negishi coupling between 4-iodooxazole **122** and **121**.

1.3.3 Sonogashira couplings and Heck reactions

The Yamanaka group reported the first Sonogashira along with the first Heck couplings of oxazoles in 1987. They described the palladium catalysed reactions of bromooxazoles **123** and **125** with terminal alkynes and also alkenes in medium to excellent yields (Scheme 28).[58]

As part of their program of introducing heterocycles into complex molecules, Panek and co-workers, carried out extensive Sonogashira cross-coupling reactions on both oxazole and thiazole triflates. Due to the advantage of generating the requisite copper

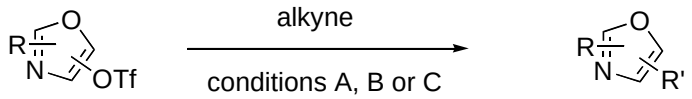
acetylide in situ, this protocol avoids the need for a stochiometric amount of metal, making the Sonogashira reaction an ideal choice to functionalise heterocyclic systems.



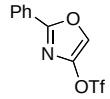
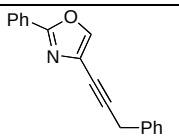
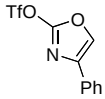
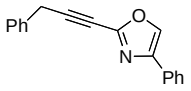
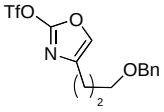
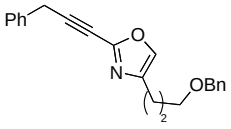
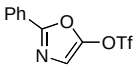
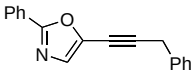
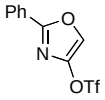
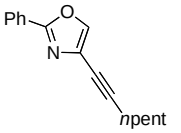
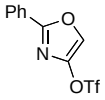
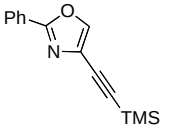
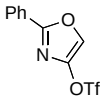
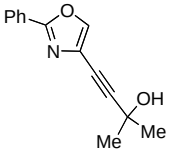
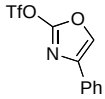
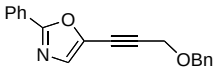
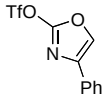
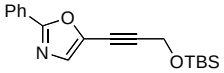
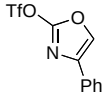
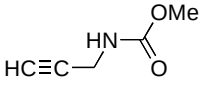
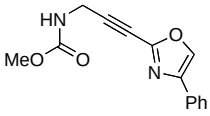
Scheme 28. Sonogashira and Heck couplings on bromooxazoles.

The authors reported the synthesis of several oxazole triflates to effect functionalisations on C_2 and also on C_4 of the ring. Due to stability issues of 2-trifloyl oxazoles, as well as competitive homo-coupling of alkynes, the authors investigated and developed three different sets of conditions in order to comply with the most sensitive substrates. Furthermore, the compatibility of the alkyne functionality was also investigated and good reactivity was observed with a wide variety of functional groups. A selection of examples is shown in Table 25.[59]

Table 25. Sonogashira couplings of funcionalised trifloyl oxazoles **127** with terminal alkynes.

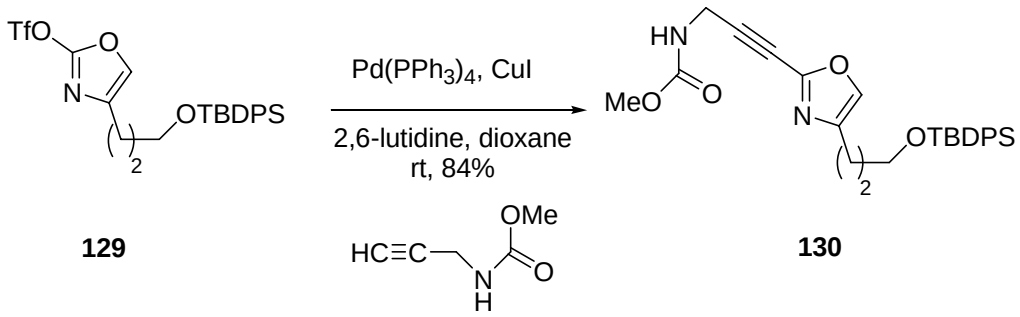


127 **128**

Entry	Oxazole triflate	Alkyne	Method[a]	Product **128**	Yield of **128** (%)
1		$HC{\equiv}C(CH_2)_2Ph$	A		86
2		$HC{\equiv}C(CH_2)_2Ph$	C		76
3		$HC{\equiv}C(CH_2)_2Ph$	C		83
4		$HC{\equiv}C(CH_2)_2Ph$	A		89
5		HC≡C-*n*Pent	A		71
6		HC≡C-TMS	A		69
7		$HC{\equiv}C(OH)Me_2$	A		42
8		$HC{\equiv}CCH_2OBn$	B		54
9		$HC{\equiv}CCH_2OTBS$	B		75
10			C		71

[a]Method A: 5 % $Pd(PPh_3)_4$, 10 % CuI, 1.1 equiv. of alkyne, 5 equiv. of Et_3N, 0.1 M DMF, 65 °C. Method B: 5 % $Pd(PPh_3)_4$, 10 % CuI, 1.1 equiv. of alkyne, 5 equiv. of 2,6-Lutidine, 0.1 M DMF, rt. Method C: 5 % $Pd(PPh_3)_4$, 10 % CuI, 1.1 equiv. of alkyne, 5 equiv. of 2,6-Lutidine, 0.1 M 1,4-dioxane, rt.

The same authors applied this methodology to the synthesis of the C_1'-C_{11}' oxazole-containing side chain of Leucascandrolide A in 84% yield (Scheme 29).[60]



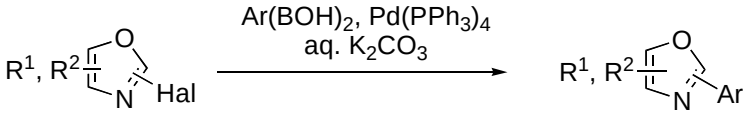
Scheme 29. Synthesis of the C_1'-C_{11}' oxazole-containing side chain of Leucascandrolide A

1.3.4 Suzuki couplings

As part of a medicinal chemistry program, chemists at Neurogen required a flexible and high yielding route to access variously substituted oxazoles. They reported the Stille, Suzuki, Negishi and Sonogashira couplings of different organometallic species to 2-, 4- and 5-halo-oxazoles. The couplings were carried out under standard conditions and yielded the corresponding substituted oxazoles in generally high yields. A selection of examples in the context of the Suzuki reaction is shown in Table 26.[61,62]

Taylor and co-workers have carried out extensive regioselective Stille and Suzuki couplings on 4-bromomethyl-2-chlorooxazole **133**. Good selectivity was found to occur at the 4-bromomethyl position, and subsequent coupling of the isolated product **134** at the 2-chloro-position gave a medium yield of the desired 2,4-disubstituted oxazole **135**. Optimisation studies led to the development of a general methodology to synthesise 2,4-disubstituted oxazoles in generally good yields. The Suzuki couplings employed in this strategy are shown in Table 27.[63]

Table 26. Suzuki coupling of halooxazoles.



131 **132**

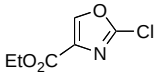
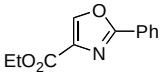
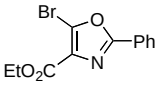
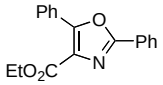
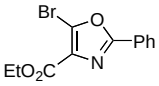
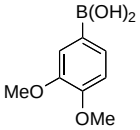
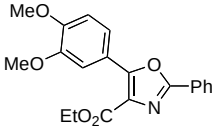
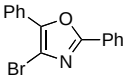
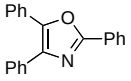
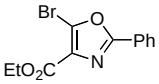
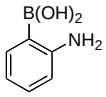
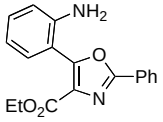
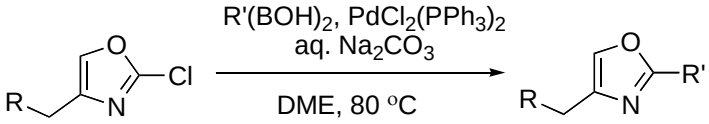
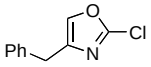
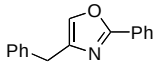
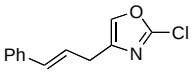
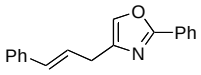
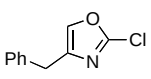
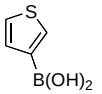
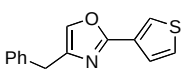
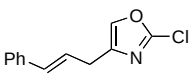
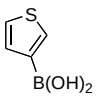
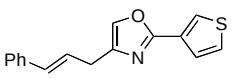
Entry	halooxazole	$ArB(OH)_2$	Product **132**	Yield of **132**(%)
1		$PhB(OH)_2$		87
2		$PhB(OH)_2$		93
3				91
4		$PhB(OH)_2$		89
5				78

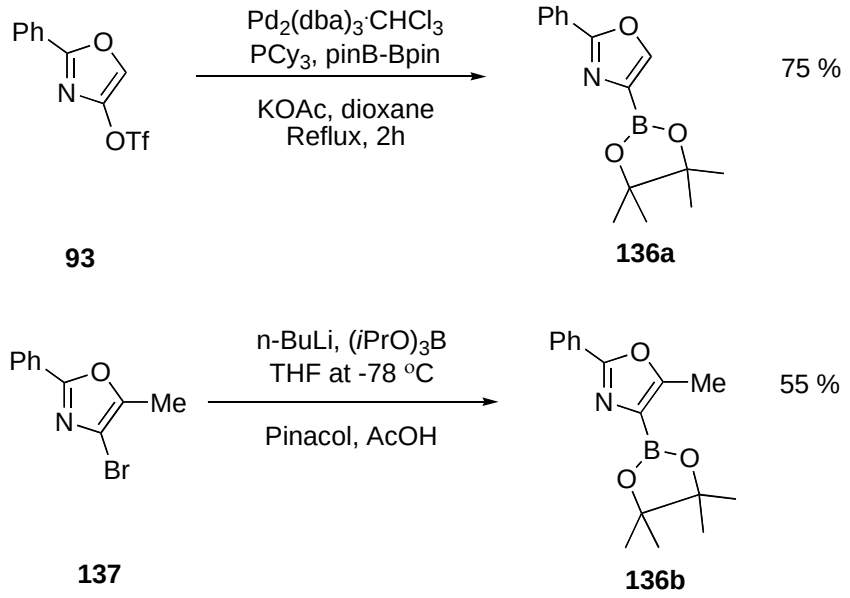
Table 27. Suzuki couplings on 2-chlorooxazoles **134**.



134 **135**

Entry	2-chlorooxazole **134**	$R'B(OH)_2$	Product **135**	Yield of **135** (%)
1		$PhB(OH)_2$		97
2		$PhB(OH)_2$		81
3				60
4				67

Very recently, Inoue and co-workers have reported the synthesis of the first oxazol-4-ylboronates from triflate oxazoles using Miyaura's borylation conditions and also from 5-methyl-4-bromo-2-phenyloxazole using conventional borylation conditions (Scheme 30).

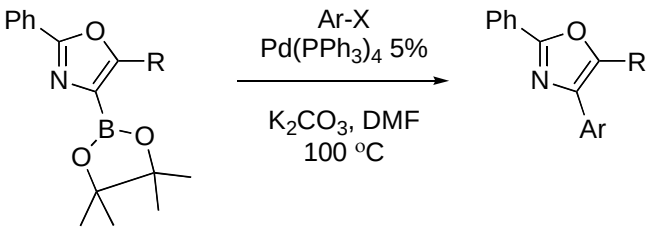


Scheme 30. Synthesis of the first oxazole-4-ylboronates.

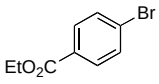
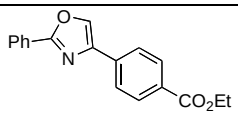
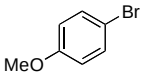
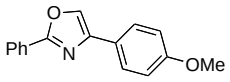
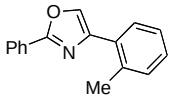
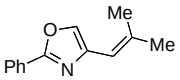
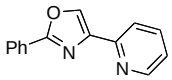
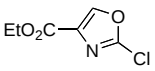
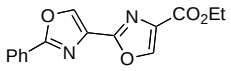
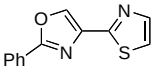
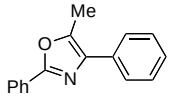
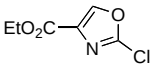
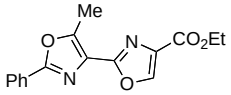
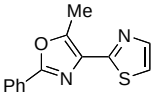
These reagents in combination with various aryl halides were used in standard Suzuki reactions, giving medium to excellent yields of the desired coupling products (Table 28).[64]

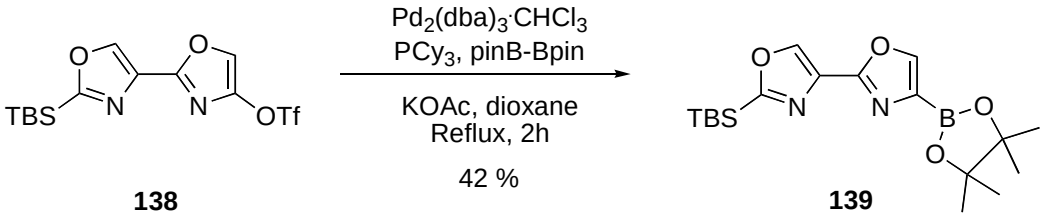
Shortly afterwards, the same authors disclosed a two-step strategy for the synthesis of C_2-C_4 linked poly-oxazole using the Suzuki-Miyaura reaction. Their tactic was based on a repetitive procedure involving bis-oxazole **139** containing the appropriate pinacol boronic ester functionality on C_4 and also a silyl group on C_2 susceptible to electrophilic displacement by a halide source. Boronic ester **139** was synthesised from the corresponding triflate **138** using Miyaura's conditions in 42 % yield (Scheme 31).

Table 28. Suzuki couplings of oxazol-4-ylboronates **136**.



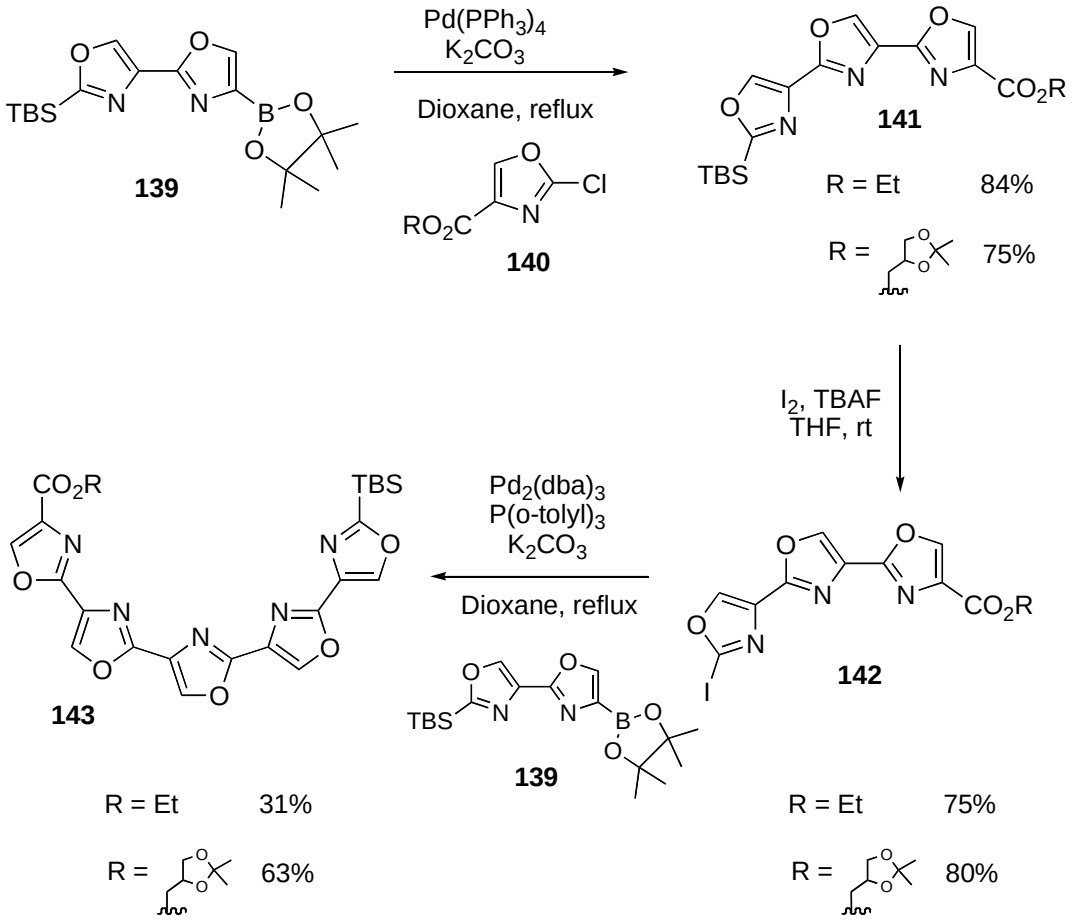
136 **137**

Entry	R	Halide	Product **137**	Yield of **137**(%)
1	H			83
2	H			56
3	H			54
4	H			65
5	H			73
6	H			71
7	H			80
8	Me			98
9	Me			84
10	Me			88



Scheme 31. Synthesis of oxazol-4-ylboronate **139**.

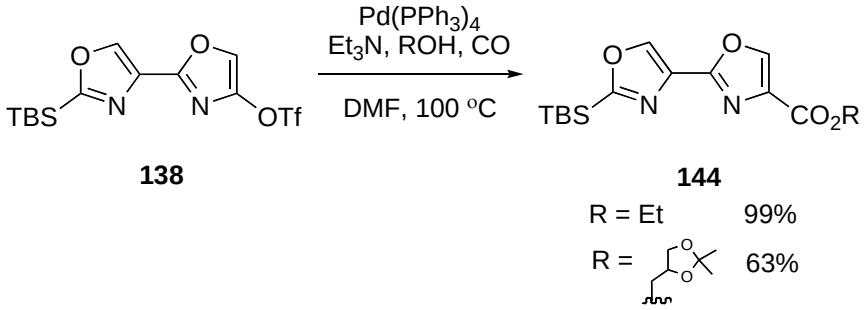
Accordingly, oxazole-4-ylboronate **139** was coupled with 2-chlorooxazole **140** under standard Suzuki conditions and gave tris-oxazole **141**. Nucleophilic displacement of the TBS group by TBAF/I_2 gave **142** with the required functionalisation on C_2 essential to carry out the next iterative Suzuki coupling. As before, palladium catalysed cross-coupling of iodide **142** with **139** provided the pentakis-oxazole structure **143** in 31% yield (Scheme 32).



Scheme 32. Synthesis of pentakis-oxazoles **143** using the Suzuki-Miyaura reaction.

The authors remarked that as the number of oxazoles increased per iteration, the yields also decreased for each coupling. This problem was attributed to the low solubility of the longer poly-oxazoles in organic solvents. As a result, in order to improve their solubility, it was decided to modify the ester part of the poly-oxazoles using solketal esters rendering it more soluble in organic media. Switching to a different ester proved successful and tris-oxazole and penta-oxazole structures could be obtained this time in 75 % and 63 % yield respectively (Scheme 32).[65]

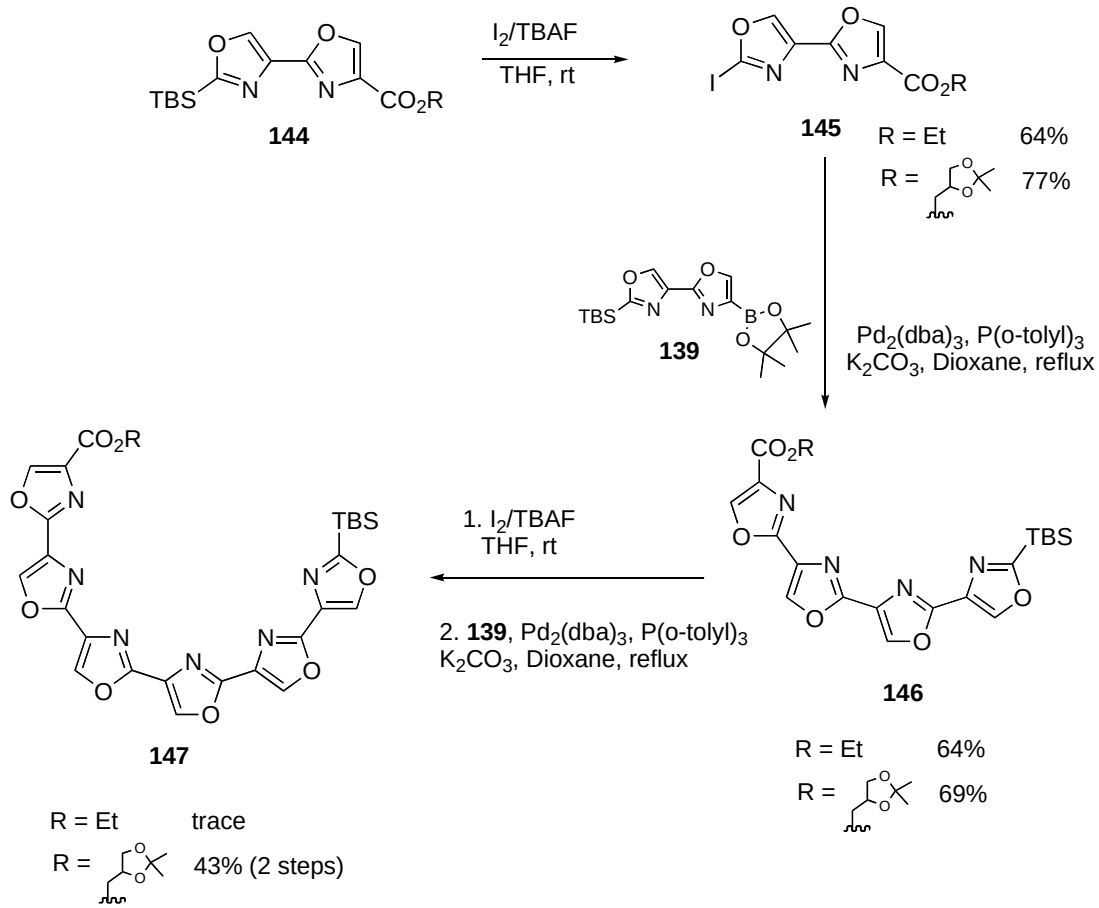
Alternatively, even numbered poly-oxazoles could also be carried out with the existing method. Thus, carboalkylation of triflate **138** was carried out by treatment with $Pd(PPh_3)_4$ in the presence of a large excess of ethanol or solketal, 2 equivalents of triethylamine and carbon monoxide in DMF at 100 °C, providing the desired esters **144** in 99 % and 63 % yield respectively (Scheme 33).



Scheme 33. Carboethoxylation of triflate **138.**

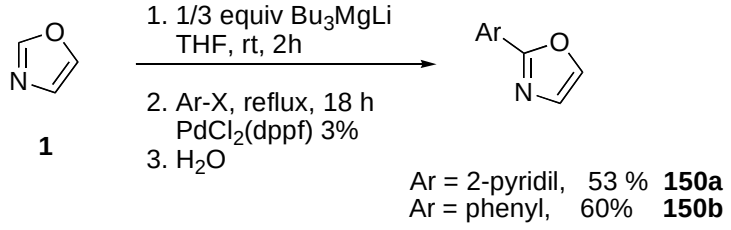
Immediately after deprotection of the silyl group, and using the same sequence as before, tetra-oxazole and also hexa-oxazole structures were obtained in medium to good yields (Scheme 34).

As an extension of their C_4 selective bromination, Li and co-workers carried out some Suzuki couplings on 4-bromo-5-substituted oxazoles in generally medium to excellent yields (Table 29).



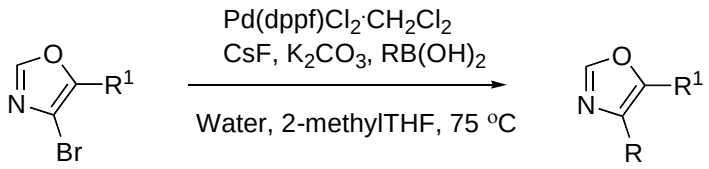
Scheme 34. Synthesis of tetra- and hexa-oxazoles using the Suzuki-Miyaura reaction.

As demonstrated by Mongin and co-workers, other metals than tin, zinc or boron can undergo palladium catalysed cross-coupling reactions of oxazoles. As shown earlier, lithium magnesates are suitable for hydrogen magnesium exchange reactions on oxazole and benzoxazole at room temperature, and can also be coupled to aromatic halides in the presence of $PdCl_2$(dppf) as shown in Scheme 35.[27]

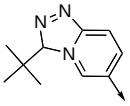
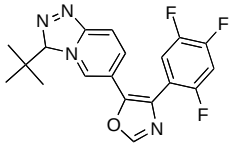
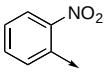
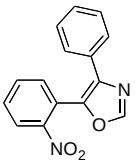
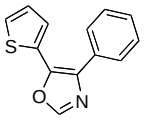


Scheme 35. Palladium catalysed cross-coupling reactions of in situ generated lithiummagnesates oxazoles with aryl halides.

Table 29. Suzuki couplings on 4-bromooxazoles derivatives.



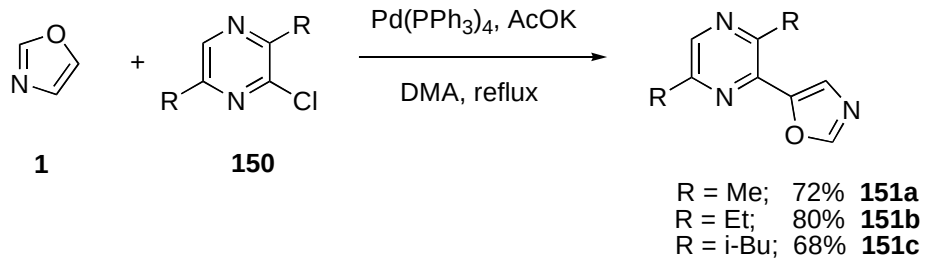
148 **149**

Entry	R^1	Product **149**	Yield of **149** (%)
1			92
2			61
3			54

1.3.5 Direct arylations

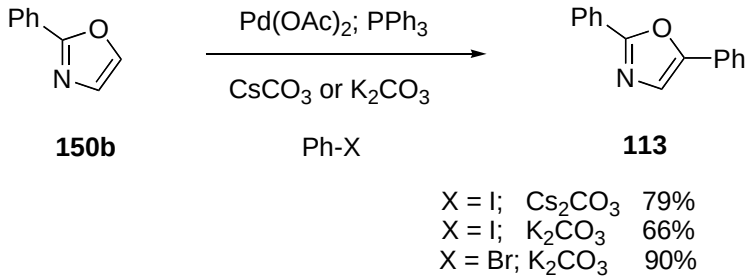
Direct arylations are scarcer compared to other cross-coupling such as the Sonogashira or the Stille reactions, and comparatively many more direct arylations on the related benzoxazole have been reported. However, some examples in the recent literature have been disclosed.

As part of a program to extensively investigate the direct arylation of heterocyclic halides and aromatic heterocycles, the Ohta group, in 1992, became the first to report the direct coupling of aromatic halides with oxazoles on C_5-H. They reported the coupling reactions between chloropyrazines **150** and 1,3-oxazole **1** in the presence of $Pd(PPh_3)_4$ and AcOK, which gave the coupling products **151a-c** in good yields (Scheme 36).[66]



Scheme 36. Direct arylation of chloropyrazines **150** and 1,3-oxazole **1**.

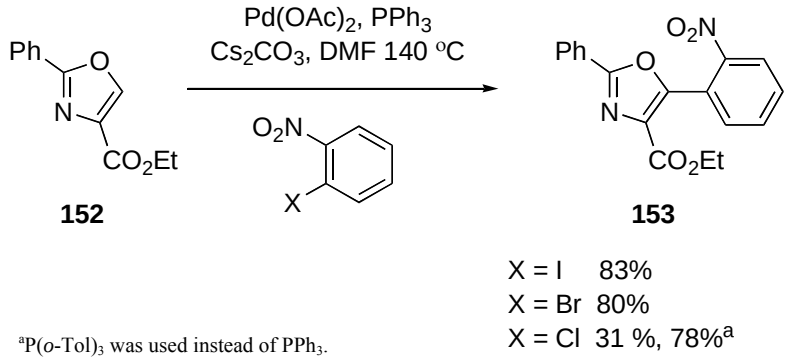
In 1998, Miura and co-workers disclosed a study to investigate the effects of base and additives on the palladium-catalysed direct arylation of azoles, including imidazoles, thiazoles and oxazoles with aryl iodides and bromides. In particular, the authors studied the C_5-H phenylation of 2-phenyloxazole, 1-benzyl-2-methyl-1H-imidazole and 2-methylthiazole under various conditions and concluded that the reactions using phenyl iodide in combination with K_2CO_3 were less efficient than those using phenyl bromide. Additionally, CuI promoted the reaction in the case of thiazoles; however, no benefit was observed for oxazoles or imidazoles (Scheme 37).



Scheme 37. Phenylation studies on C_5 of 2-phenyloxazole.

In 2003, as an alternative to the Suzuki coupling, Hodgetts and Kershaw investigated the inter- and intramolecular direct coupling of a small number of oxazoles. Under $Pd(OAc)_2$ and PPh_3 with Cs_2CO_3 in DMF at 140 °C, aryl iodides and bromides gave very good yields of the coupling products, whereas aryl chlorides could not be coupled efficiently. The authors realised that in order to increase the yield of the reaction for aryl chlorides longer reactions were needed; however,

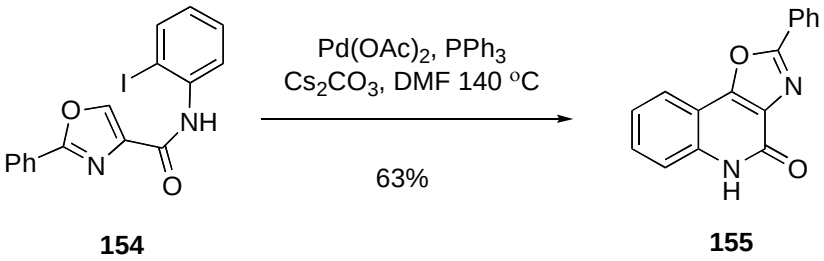
decomposition of the palladium complexes was also observed for prolonged reaction times. To circumvent this problem, PPh_3 was replaced with the bulkier ligand P(*o*-tol)$_3$ based on the assumption that sterically demanding ligands form more stable PdL_2 complexes and that quaternization of the phosphorous by the aryl halide is minimized. This initiative proved very successful and gave the desired coupling product in 78 % yield (Scheme 38).[62]



152 **153**

Scheme 38. Direct arylation of oxazole **152** with aryl halides.

Under the same conditions, intramolecular direct arylation of **154** was also successful and provided the desired adduct in a good 63 % (Scheme 39).

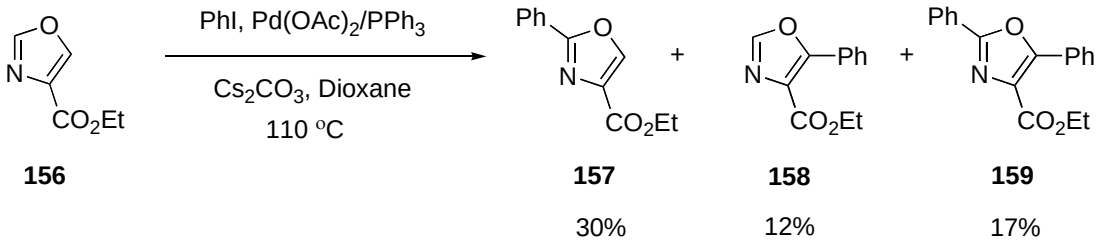


154 **155**

Scheme 39. Intramolecular direct arylation of oxazole **154**.

More recently, Hoarau and co-workers have reported a rigorous study of the regioselective palladium catalysed phenylation of ethyl 4-oxazolecarboxylate **156**, which was chosen as a substrate for the model system due to its ready accessibility and the existence of two reactive sites at C_2 and C_5 permitting selective phenylation

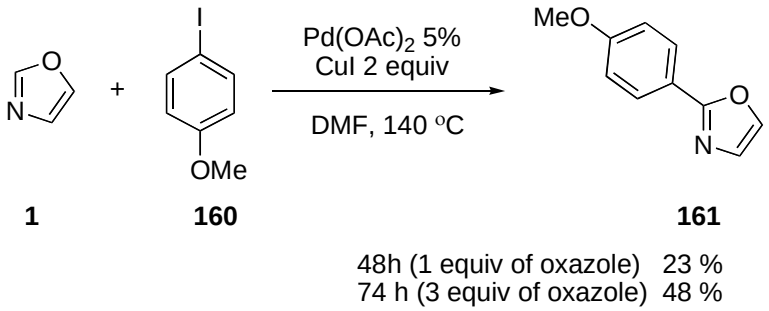
under proper choice of experimental conditions. In a typical experiment, ethyl ester **156** was combined with phenyliodide, $Pd(OAc)_2$, PPh_3 and Cs_2CO_3 in refluxing dioxane for 18h, producing a mixture of C_2, C_5, C_2/C_5 phenylation products **157-159** (Scheme 40).[67]



Scheme 40. Phenylation of ethyl-4-oxazolecarboxylate.

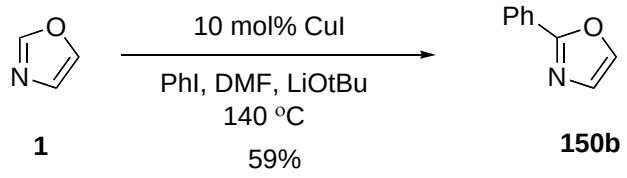
Interestingly, under these conditions a switch to DMF as the solvent provided C_2 product **157** exclusively in a moderate 40 % yield. After this, the authors decided to keep the original conditions while screening different bulky electron-rich ligands. They obtained high yields of C_2 phenlylated product **157** using Buchwald's 2-(dicyclohexylphosphino)-biphenyl ligand and also with the carbene 1,3-bis-(mesitylimidazol)carbene (IMes). After some studies on the influence of catalyst/ligand ratio and the effect of the solvent, it was concluded that the C_2 phenyl derivative **157** was always obtained as the major product. In particular, **157** could be obtained in an excellent 86 % yield for the arylation carried out in toluene as the reaction solvent and using P(*o*-Tol) as the palladium ligand. The authors attributed this selectivity to steric hindrance being the most significant factor operating in the regiocontrol process.[67]

Bellina and co-workers have studied the direct arylations of imidazoles, thiazoles and also oxazoles using a palladium catalysed with copper-mediated procedure. They obtained the C_2 arylation product of **1** in 23 % yield after 48h reaction at 140 °C in DMF and in 74 % yield after 74h using excess of **1** (Scheme 41).[68]



Scheme 41. Palladium catalysed copper-mediated direct arylation of 1,3-oxazole **1**.

Based on the observation that copper salts can affect regioselectivity the palladium catalysed electron-rich heterocycle arylation, Daugulis and Do have recently reported an interesting copper catalysed direct arylation of heterocycle C-H bonds.[69] The authors stated that most efforts in cross-coupling methodologies are directed towards the replacement of aryl iodides with cheaper aryl chlorides but, in fact, it is more cost efficient to replace the expensive palladium complexes with copper-based catalysts. It was presumed that using a stronger base instead of the commonly employed cesium or potassium carbonates should generate the organocopper species and the best results were obtained by using aryl iodides in combination with Li*t*BuO in DMF or other polar solvents at high temperatures. Several heterocycles were efficiently arylated using this methodology, including 1,3-oxazole **1** in 59 % yield (Scheme 42). In addition, the authors carried out some mechanistic investigations and concluded that the reaction could proceed, either via a copper-assisted benzyne type of mechanism, or by heterocycle deprotonation followed by lithum/copper transmetallation and reaction with the aryl iodide species giving the observed products.[69]

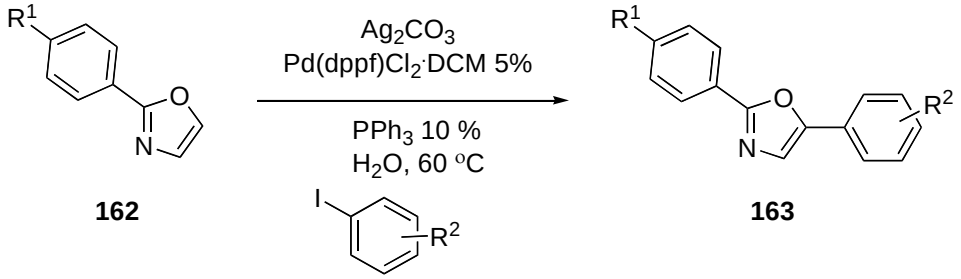


Scheme 42. Copper-catalysed direct phenylation of 1,3-oxazole on C_2.

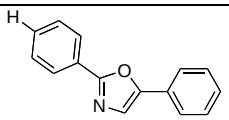
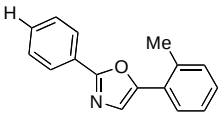
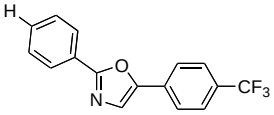
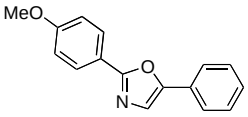
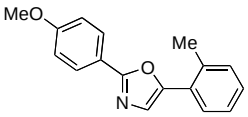
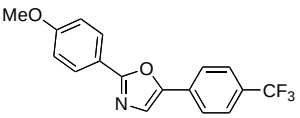
Very recently, Greaney and co-workers have reported a silver-mediated mild direct arylation method to arylate thiazoles and also oxazoles. The authors found that, when using water as the reaction solvent, excellent conversion and a notable increase in the rates of the reaction was observed.[70]

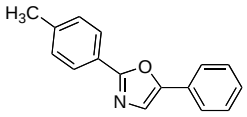
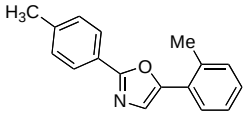
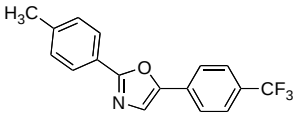
This method was applied to the development of a general methodology to couple oxazoles at C_5 including the synthesis of natural products, a selection of examples is shown in Table 30.[71]

Table 30. C_5 Ag-mediated, on water direct arylation of 2-substituted oxazoles.



162 **163**

Entry	R^1	Product **163**	Yield of **163** (%)
1	H		92
2	H		83
3	H		80
4	OMe		83
5	OMe		98
6	OMe		98

7	CH_3		92
8	CH_3		90
9	CH_3		90

Chapter 1 references

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Chapter 2

Suzuki Couplings of Oxazoles

2.1 Introduction

The 2,4-substitution pattern found in naturally occurring oxazoles has resulted in the development of great variety of condensation methods often involving the preparation of appropriately substituted acyclic amides and their subsequent dehydrative cyclisation.[1] An alternative strategy is to prepare the oxazole heterocycle at an early stage and, using palladium chemistry, carry out subsequent functionalisations at each position. In recent years, this idea has been exemplified in the development of Stille,[2] Sonogashira,[3] Negishi,[4] and direct arylation methods[5] for the functionalisations of oxazoles. By contrast, at the start of this work, the Suzuki-Miyaura coupling had seen relatively little application.[6] The limited availability of known halogenated oxazoles and the scarcity of oxazole boronic acids or esters in the literature before 2006 has certainly influenced the number of Suzuki couplings of oxazoles reported.

Among metal-mediated cross-coupling reactions, the palladium-catalysed cross-coupling reaction between different types of organoboron compounds and various organic electrophiles, such as halides and triflates, in the presence of a base provides a powerful and general methodology for the formation of carbon-carbon bonds. The coupling reaction offers several advantages: ready and wide availability of commercially available organoboron compounds; mild reaction conditions; water stability; toleration of a broad range of functional groups; good regio- and stereoselectivity; small quantities of catalysts; application to one-pot synthesis; non toxic reaction boron sub-products; and easy separation of inorganic boron compounds.[7]

As a popular choice, the Suzuki reaction has been used extensively to functionalise many heterocyclic systems. The heteroatoms commonly associated with heterocycles are known to exert an influence in the coordination sites of the metal catalysts, very often inhibiting them and affecting dramatically the outcome of reactions.[8]

2.2 Catalytic cycle[7,9]

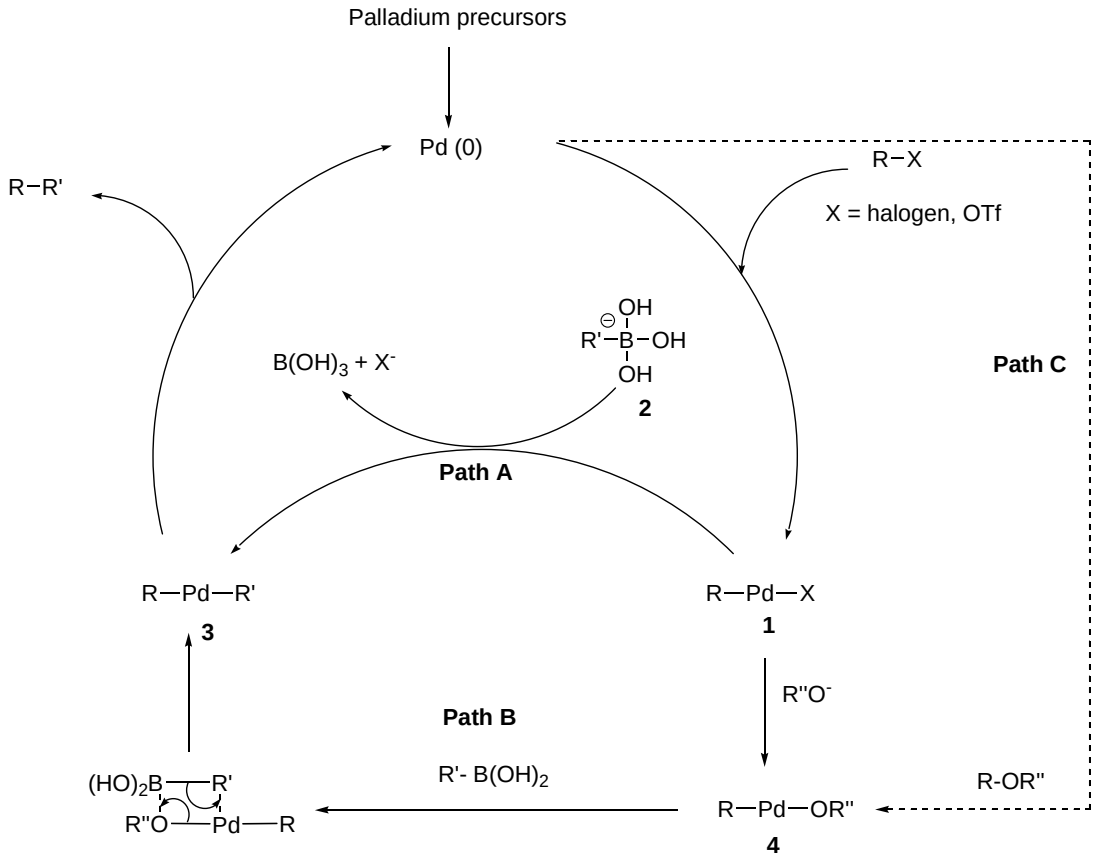
The cross-coupling reaction of organoboron compounds follows an analogous catalytic cycle to main palladium cross-coupling reactions (Stille, Negishi and Sonogashira) (Scheme 1).

(a) Formation of the active species from palladium precursors.
(b) Oxidative addition of organic halides or other electrophiles to a Palladium (0) complex yielding R-Pd-X species **1**.
(c) Transfer of the organic group between R-Pd-X **1** and $R'B(OH)_3^-$ **2** species to generate Pd complex **3**.
(d) Reductive elimination of **3** to give the product R-R' and to regenerate the Pd (0) complex.

(a) The generation of catalytically active species Pd(0) from the corresponding palladium precursors has been rate-limiting in several cases. Several authors have shown that, even when the same phosphine or carbene ligand is used in a particular reaction, the source of palladium has an important influence on the catalytic rates.[9]

(b) The insertion of palladium (0) species into an aryl halide or triflate bond is called oxidative addition. Several studies have been carried out to establish the effect of different ligands on the oxidative addition step of the catalytic cycle. Sterically demanding ligands have the ability to stabilise low-coordination palladium complexes, which because of their low electron count are more reactive. In addition,

electron-donating ligands generate an electron-rich metallic complex, which undergoes faster oxidative addition reactions. The different rates observed for aryl halides and triflates are I > Br > OTf > Cl.[7]



Scheme 1. Catalytic cycle for the cross-coupling of organoboron compounds catalysed by Pd.

(c) The transmetalation step is the less well-understood phase in the catalytic cycle. Current studies indicate that there are three possible processes, paths A-C (Scheme 1) for transferring the organic group on the boron species to the oxidative addition product **1**. The addition of inorganic bases has been shown to accelerate dramatically this transfer. It has been observed that boronic acids do not react with R-Pd-X species, but in control experiments it has been shown that ate complexes such as Bu_4BLi or Ph_4BNa readily undergo the palladium catalysed coupling reaction in the absence of a base. This suggests that quaternary boron anions enhance the nucleophilicity of the organic group; hence the transfer to the electrophilic R-Pd-X

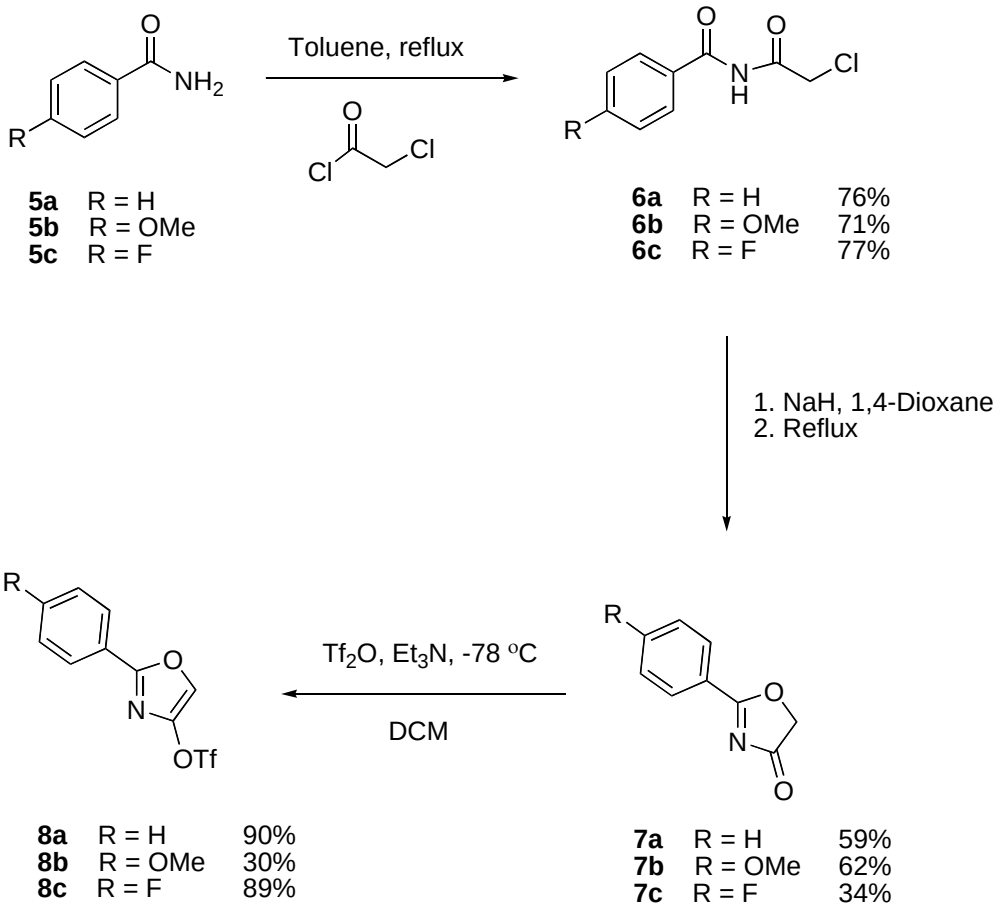
species is faster. The transmetalation rates for **1** are I < Br < Cl, in reverse order to the oxidative addition step (path A). Another possibility is the ligand exchange between R-Pd-X and a base R"O^- to form oxo-palladium (II) species **4**, which undergoes rapid transmetalation with boronic acids without the aid of a base (path B). It is known that the halogen or triflate group on R-Pd-X **1** is readily displaced by an alkoxy, hydroxy, or acetoxy anion to provide a basic R-Pd-OR" complex, but other routes to these species are also feasible (path C). As they are highly dependent on the organoboron reagents and the reaction conditions used, it is not obvious in most reactions which transmetalation process is predominant.[7d]

(d) The final step in the catalytic cycle is called reductive elimination. It is generally accepted that this step is faster when palladium is coordinated to electron withdrawing and sterically demanding ligands. It has been shown that, for very bulky ligands, sterics are the main factor dominating over electronic effects. Thus, even very electron rich bulky ligands will facilitate the reductive elimination step.[7,9]

2.3 Suzuki coupling of oxazoles.

The C_2 and C_4 positions on the oxazole ring were chosen with a view of developing a versatile Suzuki methodology for the generation of a range of 2,4-arylated and heteroarylated oxazoles. The C_4 position was first attempted and known oxazole triflates were chosen as suitable electrophiles. The synthesis of oxazoles triflates from oxazolones, first introduced by Barrett[10] and Kelly[11] in the context of the Stille reaction, enables the regiocontrolled installation of an electrophile functional group for subsequent palladium cross coupling. This strategy avoids potential regioselectivity problems inherent to direct halogenation at the oxazole 4-position and has been employed successfully in several Stille and Sonogashira oxazole cross-coupling reactions.[12] Consequently, in order to diversify the method, three electronically different 2-aryl-4-trifloyl oxazoles **8a-c** were chosen and prepared (Scheme 2).

Accordingly, amides **5a-c** were condensated with chloroacetyl chloride giving the corresponding chloroimides in good yields (71 to 76 %) after re-crystallisation from toluene.

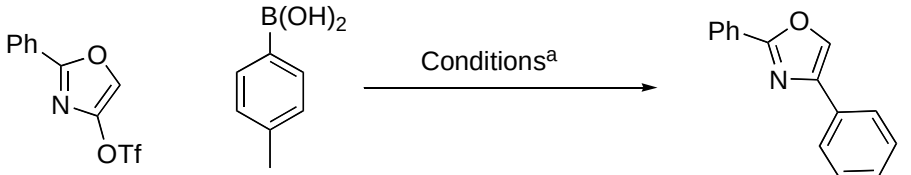


Scheme 2. Synthesis of 2-aryl-4-trifloyloxazoles **8a-c**.

Deprotonation with NaH followed by thermal cyclisation provided oxazolones **7a-c** in 34% to 59% yield after column chromatography. Finally, standard triflation using triflic anhydride and triethylamine gave triflates **8a-c** in medium to excellent yields. Triflates **8a-c** are stable and crystalline solids that can be stored for several months at -20 °C.

In order to set the reaction parameters, a model system and a range of conditions were first explored for the optimisation of the Suzuki coupling of triflate **8a** and tolylboronic acid **9a** (Table 1).

Table 1. Optimisation of Suzuki coupling of triflate **8a** with tolylboronic acid.[a]



8a **9a** **10a**

Entry	Catalyst	Base	Time	Solvent	Yield of **10a**(%)[g]
1	$PdCl_2(dppf)$	K_3PO_4	48 h	1,4 dioxane	Traces
2	$PdCl_2(dppf)$	NaOH	20 h	1,4 dioxane	0
3	$PdCl_2(dppf)$	KO^tBu	20 h	1,4 dioxane	0
4	$Pd(PPh_3)_4$	NaOH	16 h	aq dioxane	Traces
5	$Pd(PPh_3)_4$	NaOH	16 h	CH_3CN	Traces
6	$PdCl_2(PPh_3)_2$	Na_2CO_3 2M	48 h	THF[d]	16
7	$PdCl_2(PPh_3)_2$	Na_2CO_3 2M	16 h	1,4 dioxane	48
8	$Pd(OAc)_2$, PCy_3[b]	KF	72 h	THF	Traces
9	$Pd(OAc)_2$, PCy_3[c]	KF	72 h	THF	36
10	$PdCl_2(PPh_3)_2$	Na_2CO_3 2M	20 min	1,4 dioxane[e]	94
11	$PdCl_2(PPh_3)_2$[f]	Na_2CO_3 2M	40 min	1,4 dioxane[e]	67

[a]Conditions: 5mol% catalyst loading, 3 equiv of base, reflux. [b]1 mol % of $Pd(OAc)_2$ and 1.2 mol % of PCy_3. [c]5 mol % of $Pd(OAc)_2$ and 6 mol % of PCy_3. [d]Reaction was carried out at 60 °C. [e]Microwave irradiation at 150 °C for 20 min. [f]1 mol % catalyst loading. [g]Isolated yield after SiO_2 chromatography.

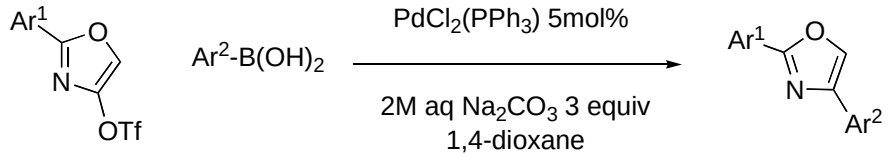
It was immediately clear that the substrate **8a** could not tolerate bases such as KO^tBu or NaOH often employed in the reaction (Table 1, entries 1-5), as extensive degradation of the triflate was observed with very little coupled product **10a** being observed. Use of a Na_2CO_3 (aqueous, 2M) with $PdCl_2(PPh_3)_4$ as catalyst provided the first signs of a successful reaction. Refluxing in THF for 2 days, using aqueous

Na_2CO_3 as a base, produced **10a** in 16% yield (entry 6), which could be improved to 48% by switching to the higher-boiling point solvent 1,4-dioxane (Table 1, entry 7).

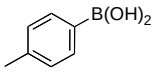
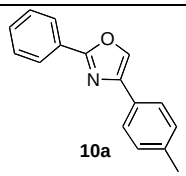
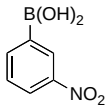
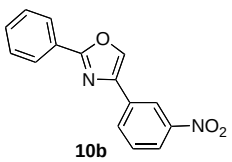
The combination of a $Pd(OAc)_2/PCy_3$ catalyst system with potassium fluoride as a base, reported to be effective for the Suzuki coupling of aryl triflates under mild conditions,[13] proved ineffective with the oxazole substrate producing a low yield of coupled product after prolonged reflux with a slow rate reaction observed (Table 1, entries 8 and 9). In order to achieve higher temperatures than the solvents boiling point, microwave heating was then considered. It was observed that 20 min irradiation at 150 °C in 1,4-dioxane (Table 1, entry 10) produced the desired 4-tolyl oxazole **10a** in an excellent 94% yield. The catalyst loading could be reduced to 1% but at the expense of a longer reaction time and a decrease in yield (Table 1, entry 11).

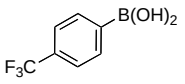
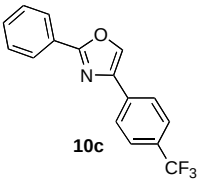
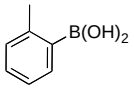
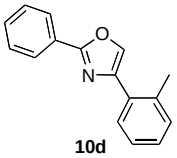
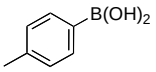
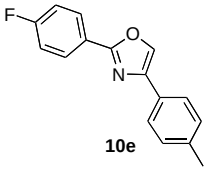
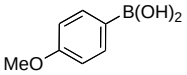
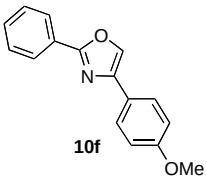
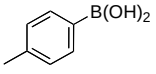
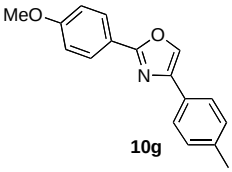
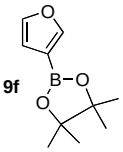
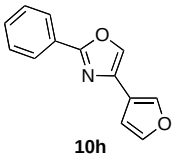
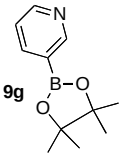
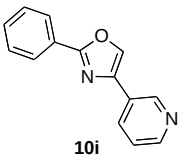
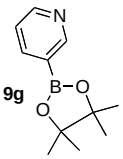
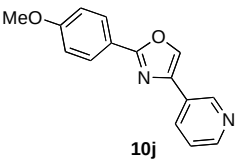
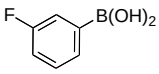
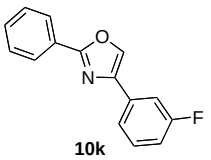
The methodology was extended to the synthesis of a range of 2,4-disubstituted oxazoles (Table 2).

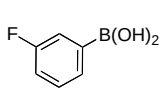
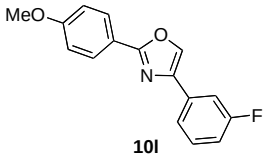
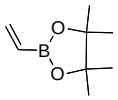
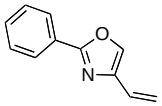
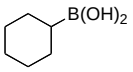
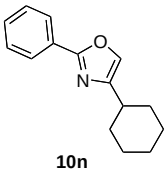
Table 2. Suzuki coupling of oxazolyl 4-triflates.



8 **9** **10**

Entry	Boronic acid/ester	Product	Yield (%)[a]
1	 **9a**	 **10a**	94
2	 **9b**	 **10b**	92

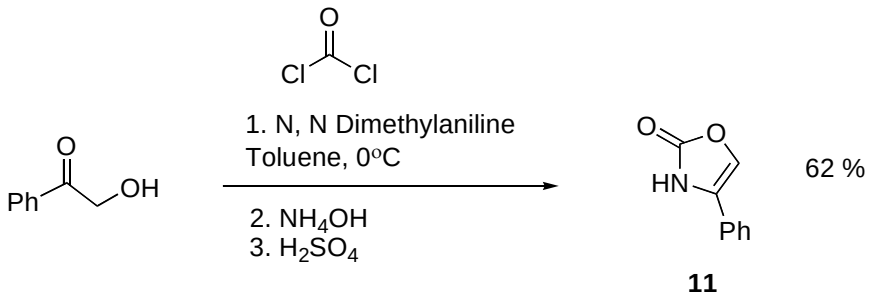
3	 **9c**	 **10c**	87
4	 **9d**	 **10d**	91
5	 **9a**	 **10e**	75
6	 **9e**	 **10f**	89
7	 **9a**	 **10g**	82
8	 **9f**	 **10h**	79
9	 **9g**	 **10i**	73
10	 **9g**	 **10j**	89
11	 **9h**	 **10k**	91

12	 **9h**	 **10l**	85
13	 **9i**	 **10m**	0
14	 **9j**	 **10n**	0

[a]Isolated yield after SiO_2 chromatography.

Excellent reactivity was observed for a variety of electron-deficient and electron-rich aryl boronic acids (Table 2, entries 1-12), ortho-substituted aryl boronic acids (entry 4), as well as heteroaromatic picacol boronic esters (entries 8-10), with yields being uniformly good to excellent. The reaction was tolerant of alternative aryl groups in the 2-position, with electron-donating (Table 2, entries 7, 10 and 12) and electron-withdrawing groups (Table 2, entry 5) producing high yields of 4-substituted oxazoles. The scope of the reaction was limited to aryl and heteroaryl substituents with no products were formed for the couplings between vinyl pinacol boronic ester **9i** or cyclohexyl boronic acid **9j** with triflate **8a** (entries 13 and 14).

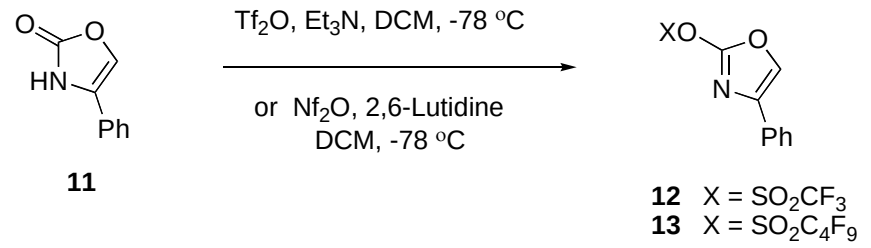
Having established a robust protocol for Suzuki coupling at the 4-position, arylation at the 2-position was next investigated. A similar strategy was first adopted for the preparation of the Suzuki electrophile by synthesising the known 4-phenyl-4-oxazalin-2-one **11** (Scheme 3).[3c]



Scheme 3. Synthesis of 4-phenyl-4-oxazalin-2-one **11.**

Accordingly, nucleophilic attack of 2-hydroxyacetophenone in basic media to phosgene gave the corresponding chloroformate, which *in situ* was converted to carbamate using aqueous ammonia. In situ cyclisation followed by dehydration provided the oxazolone **11** in 62% after column chromatography.

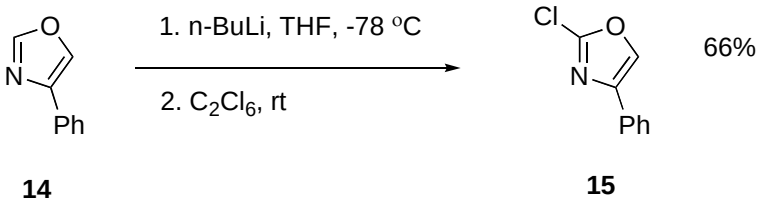
Attempts to convert **11** to the known 2-trifloyl oxazole **12** were successful; however, it was quite thermally unstable and decomposed immediately when exposed to high temperatures. The synthetically equivalent nonaflate **13** proved slightly more robust and could be isolated and purified by column chromatography. However, when subjected to the reaction conditions for Suzuki coupling, it likewise rapidly decomposed (Scheme 4).



Scheme 4. Synthesis of triflate **12** and nonaflate **13**.

Efforts to transform **11** into alternative Suzuki electrophiles using $POBr_3$, $(Ph)_3PBr_2$, or $(Ph)_2POCl$ were unsuccessful. As an alternative to the triflate group at

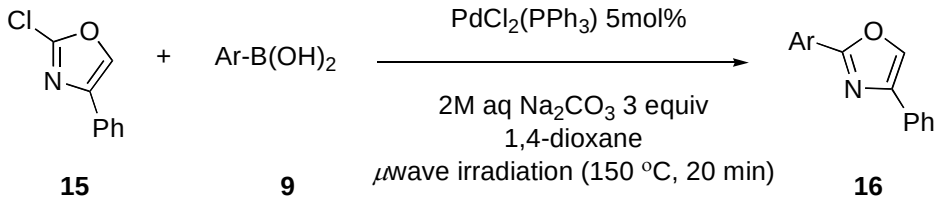
the 2-position, it was decided to prepare 2-chlorooxazoles, readily synthesised by Vedejs' protocol of oxazole lithiation and subsequent trapping with hexachloroethane, a method that avoids ring-opening complications of the lithiooxazole. As a result, chlorooxazole **15** was prepared from the known 4-phenyloxazole in 66% yield after column chromatography (Scheme 5).[14]

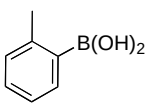
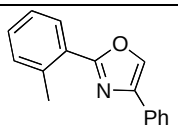


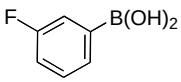
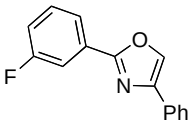
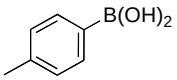
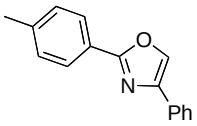
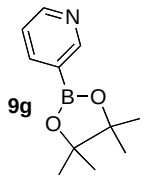
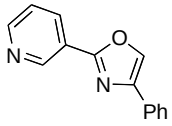
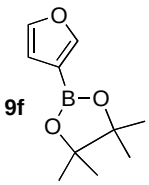
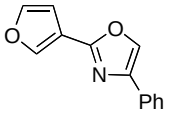
Scheme 5. Synthesis of chlorooxazole **15**.

The 2-chloro-4-phenyloxazole **15** proved to be an excellent substrate for Suzuki coupling under the optimised conditions. A range of boronic acids could be coupled to the chloride in generally excellent yields (Table 3, entries 1-5).

Table 3. Synthesis of 2,4-disubstituted oxazoles from **15**.



Entry	Boronic acid/ester **9**	Product **16**	Yield of **16** (%)[a]
1	 **9d**	 **16a**	80

2	 **9h**	 **16b**	80
3	 **9a**	 **16c**	88
4	 **9g**	 **16d**	91
5	 **9f**	 **16e**	82

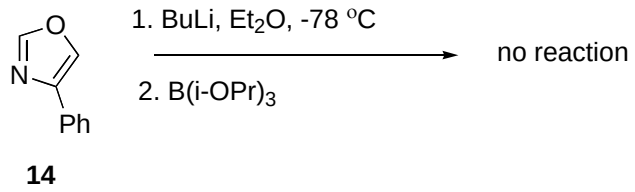
[a]Isolated yields after SiO_2 column chromatography.

2.4 Synthesis of bis-oxazoles using the Suzuki-Miyaura reaction.

With an arylation methodology in place for the oxazole 2- and 4- positions, the coupling of two oxazole units to make a bis-oxazole was envisaged. Since no examples of this type of strategy had been reported before the start of this work, this reaction would represent the first steps in the development of a general Suzuki coupling methodology. The challenge was to successfully synthesise an oxazole boronic acid, a class of compound rarely described in the literature before 2006.[6c,g,h,i]

A first preparation of an oxazole boronic ester was attempted on oxazole **14**. Following the conditions described by Brown and co-workers, 4-phenyloxazole **14** was selectively lithiated on C_2 and the resulting anion was quenched with B(i-OPr)$_3$

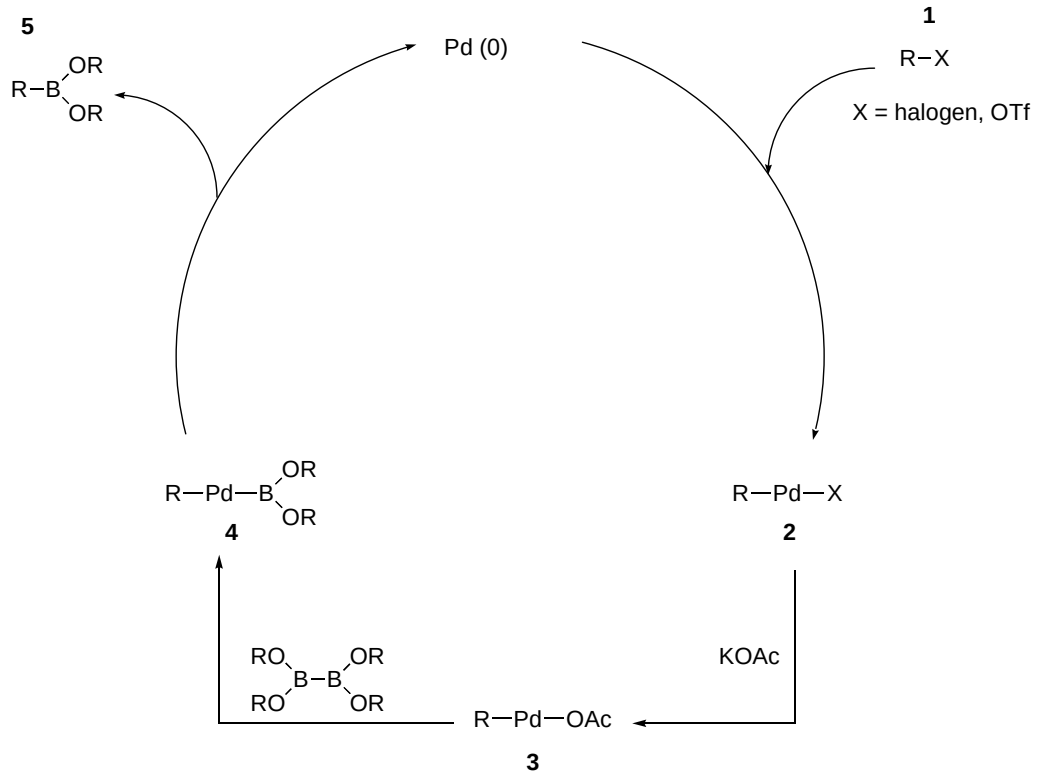
Unfortunately, only starting material could be recovered from the reaction mixture (Scheme 6).[15]



14

Scheme 6. Attempts to borate **14** on C_2.

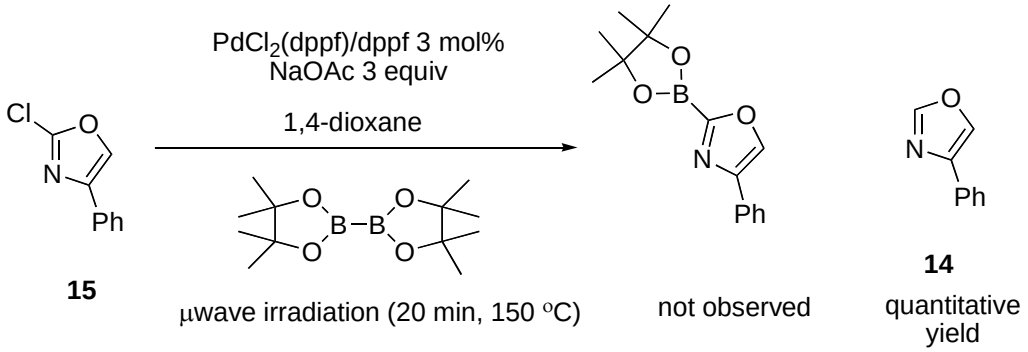
In order to obtain the desired oxazole boronic ester, the Miyaura reaction was next considered. This reaction, developed by Miyaura and co-workers, describes the palladium catalysed cross-coupling reaction of alkoxydiboron reagents with haloarenes and aryl triflates giving aryl boronic esters. The catalytic cycle for this reaction is presented in Scheme 7.[16]



Scheme 7. Catalytic cycle for the Miyaura reaction.

The catalytic cycle for the Miyaura reaction is related to path B of the Suzuki reaction. Oxidative addition of Pd (0) on **1** followed by displacement of X (halogen or triflate group) by OAc^- gives the reactive intermediate R-Pd-OAc **3**. Transmetalation of **3** occurs readily with diboron species and, following reductive elimination, the product **5** is formed along with Pd (0) that completes the cycle. The high reactivity of the (acetoxo)palladium (II) species **3** is attributed to the high reactivity of the Pd-O bond and the high oxophilicity of the boron center.[16d]

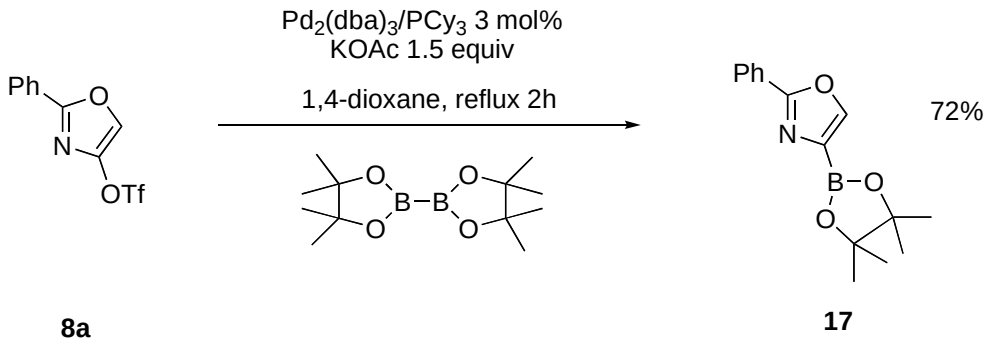
Following the original conditions, chlorooxazole **15** was treated with Bis-pinacolato diboron, $PdCl_2$(dppf)/dppf and NaOAc in 1,4-dioxane (Scheme 8).



Scheme 8. Attempt to borylate on C_2 using the Miyaura reaction.

Unfortunately, none of the desired oxazole boronic ester was formed. Instead, a quantitative yield of oxazole **14** could be isolated from the reaction mixture. The carbon-boron bond can be susceptible to protonolysis when adjacent to a heteroatom, leading to stability problems and handling difficulties. When subjected to similar conditions, this protodeboronation effect has also been observed in the borylation of 2-chloropyridine.[16c]

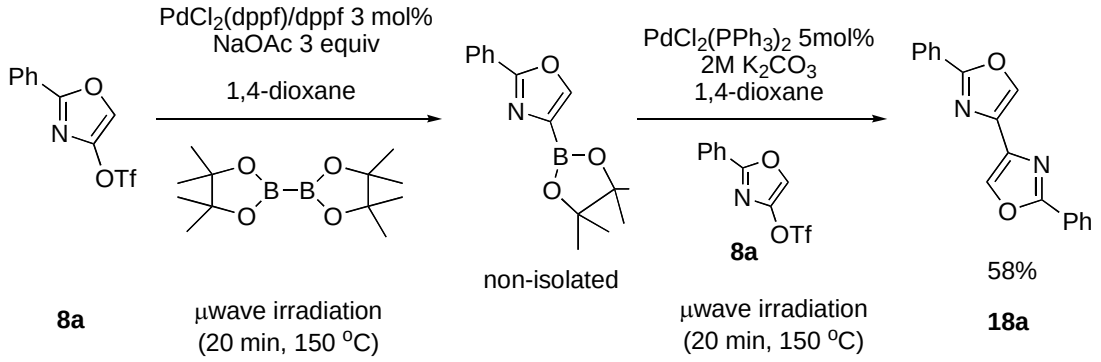
The C_4 position of the oxazole was next addressed. Miyaura's original conditions were applied to triflate **8a** (Scheme 9).



Scheme 9. Synthesis of oxazole boronic ester **17**.

This time, the desired boronic ester **17** was obtained in 72% yield after re-crystallisation.

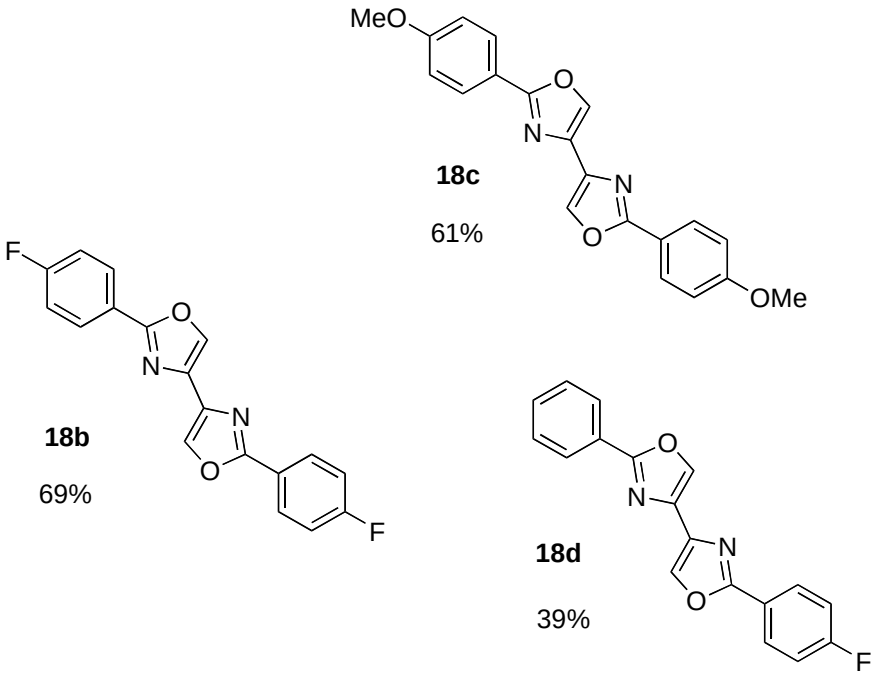
It was later realised that bis-oxazoles could be generated by *in situ* formation of boronic ester followed by one-pot Suzuki coupling. Accordingly, triflate **8a** was treated with bis-pinacolatodiboron under microwave-accelerated Miyaura conditions until the starting material had disappeared by TLC. The same reaction vessel was then re-charged with 5 mol% of $PdCl_2(PPh_3)_2$, aqueous sodium carbonate, and an additional equivalent of the triflate **8a** (Scheme 10).



Scheme 10. Synthesis of 4,4-bis-oxazole **18a**.

As a result, 4,4-bis-oxazole **18a** could be isolated in a 58% yield after column chromatography.

The same one-pot procedure could be applied to triflates **8b** and **8c** producing the homodimers **18b** and **18c** in good yield, as well as the cross-coupling of triflates **8a** and **8b** to give the heterodimer **18d** in 39% yield (Scheme 11).



Scheme 11. 4,4-bis-oxazoles **18b-d**.

2.5 Conclusions

A protocol for the arylation of the oxazole 2- and 4-positions using the Suzuki reaction was successfully developed. Firstly, the 4-position of the oxazole was investigated. A set of three electronically different oxazolyl 4-triflates was synthesised and a range of conditions was investigated for the construction of the model system. The best conditions involved $PdCl_2(PPh_3)_4$ and aqueous Na_2CO_3 in 1,4-dioxane combined with the use of microwave irradiation which resulted in the

formation of the coupling product in excellent yield. Accordingly, a range of 2,4-diarylated oxazoles could be synthesised efficiently. Secondly, the 2-position of the oxazole was explored. A versatile 2-chlorooxazole was chosen as a suitable electrophile coupling succesfully to boronic acids and esters under the discovered Suzuki conditions. This methodology was further extended to the synthesis of a range of 2,4-disubstituted oxazoles in high yields.

The use of microwave heating was clearly influential in the success of the reaction. Not only was it beneficial in terms of yield of products obtained but also in the reactions time. In order to obtain synthetically useful yields, most palladium cross-coupling reactions on heterocyclic systems found in the literature necessarily require 24 hours or more of reaction times.[8] On the other hand, in order to achieve faster reaction rates, microwave irradiation heats the reaction vessels well above the solvent boiling point. In the presented study, each reaction was heated 150 °C for 20 minutes reaction. This is clearly a limitation because thermally sensitive electrophiles will decompose before any product is formed. This exact scenario happened when applying oxazoyl-2-triflates and its synthetically equivalent nonaflate, which completely decomposed before producing any coupled products. Fortunately, another more thermally robust chlorooxazole was found as an alternative.

The method presented has been able to couple a good range of aryl and heteroaryl boronic acids or ester. However, despite the clear success, the scope of the method is limited to these type of examples. In order to expand the methodology, cyclohexyl boronic acid and triflate **8a** were combined and subjected to the above conditions without any product being formed. Equally, vinyl pinacol boronic ester did not couple efficiently with **8a** under these conditions. These later results necessarily restrict the method to only aryl and heteroaryl substituents.

The methodology was extended to the synthesis of bis-oxazoles. At the start of this work, no examples had been published regarding the synthesis of oxazole boronic acids or esters. Two borylation methods were explored, first on 2-position

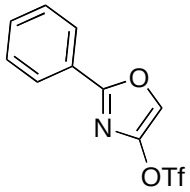
and then on 4-position of the oxazole. Borylation on C_2 repeatedly failed with the two methods explored. The first method involved classic selective lithiation of the oxazole on C_2-H, followed by quenching the reaction mixture with tri-*iso*propyl borate. No products were formed and no information could be extracted from the experiment. However, using the second method, the Miyaura reaction, a very fast protodeboronation was observed restricting, under these conditions, the use of C_2 oxazole boron species as nucleophiles in the Suzuki reaction. Later, in a related study, Inoue and co-workers also pointed out this lack of success in the borylation on 2-position of oxazoles.[6a] Fortunately, borylation on C_4 was successful using the Miyaura reaction on triflate **8a**. Although the boronic ester obtained could be isolated and purified in good yield, one pot procedure was considered more attractive. As a result, four novel 4,4'-dioxazoles structures could be synthesised for the first time. These represent the first steps in the development of a general Suzuki coupling strategy for the synthesis of poly-oxazoles (see Chapter 3).

Experimental Procedures Chapter 2

General

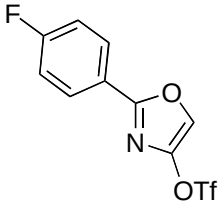
^{1}H-NMR and ^{13}C NMR spectra were recorded on Brüker dpx360 (360 MHz) and dpx250 (250 MHZ) instruments. Microwave reactions were carried out in a Smith Synthesizer Microwave (300 W). Melting point measurements were obtained from a Gallenkamp melting point apparatus and are uncorrected. Electrospray high-resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using a Finnigan MAT 900 XLT double focusing mass spectrometer. FAB HRMS was carried out by the University of Edinburgh School of Chemistry mass spectrometry service using a Kratos MS50 instrument. The data is recorded as the ionisation method followed by the calculated and measured masses. TLC was performed on Merck $60F_{254}$ silica plates and visualised by UV light. The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. 1,4 Dioxane was distilled over sodium and benzophenone prior use. Triethylamine and 2,6 lutidine were distilled over CaH_2 prior to use. All other chemicals were purchased from a chemical supplier and used as received. Et_2O and THF were dried by passage through activated alumina columns using a solvent purification system from www.glasscontour.com. Anhydrous DMF was purchased from Aldrich. DMPU was distilled over CaH_2 under high vacuum. Cs_2CO_3 was bought anhydrous from Aldrich and used without special precautions. All other reagents were purchased from a chemical supplier and used as received.

2-Phenyloxazol-4-yl trifluoromethanesulfonate **8a**



2-Phenyloxazol-4-yl trifluoromethanesulfonate **8a** was synthesised according to an established procedure:[12d] 2-Phenyl-4-oxazolone **7a** (3.00 g, 18.62 mmol, 1 equiv) was dissolved in DCM (75 mL, 0.25 M) and cooled to -78 ºC. To the solution was added Et_3N (5.3 mL, 37.24 mmol, 2 equiv), then slowly Tf_2O (4.8 mL, 27.93 mmol, 1.5 equiv). After warming to rt over 20 min, the reaction was quenched with H_2O (100 mL), extracted 3× (150 mL) into DCM. The organic layers were combined, washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, hexanes/ethyl acetate 1%) gave the desired trifloyloxazole (4.90 g, 90% yield) as a white solid (mp < 25 °C). This compound gave spectral data in good agreement to that previously reported.[12d] **^{1}H-NMR** ($CDCl_3$, 250 MHz) δ 7.39-7.42 (3H, m), 7.65 (1H, s), 7.91-8.01 (2H, m).

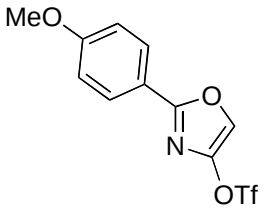
2-(4-Fluorophenyl)oxazol-4-yl trifluoromethanesulfonate **8c**



2-(4-Fluorophenyl)oxazol-4-yl trifluoromethanesulfonate **8c** was synthesised using Panek's method with minor modifications:[12d] In a dry round bottom flask equipped with a reflux condenser were combined 4-flurobenzamide (10 g, 70.4 mmol, 1 equiv) and chloroacetyl chloride (8.5 mL, 105.6 mmol, 1.5 equiv) and toluene (100 mL). The mixture was heated to 110 °C for 2 h until disappearance of the starting material by thin layer chromatography. Then, the mixture was allowed to cool down slowly and the chloroimide crystallised in the flask. Filtration, washing with hexane and drying in air yielded the chloroimide **6c** (11.708 g, 77% yield) as white needles; The chloroimide product **6c** was then added to a mixture of sodium hydride (2.370 g, 59.24 mmol, 1.1 equiv, 60% suspension in oil) and 1,4 dioxane

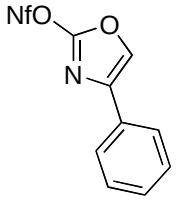
(0.06 M) at 0 °C. After stirring for 30 min, the mixture was warmed to rt and refluxed for 12 h. The mixture was filtered through celite and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane/ethyl acetate 4:6) gave the desired oxazolone **7c** (3.310 g, 34% yield) as a white solid; The pure oxazolone **7c** (3.240 g, 18.13 mmol, 1 equiv) was then dissolved in 50 mL of dry DCM and the solution cooled to -78 °C. To the solution was added Et_3N (5.1 mL, 36.26 mmol, 2equiv) and Tf_2O (4.7 mL, 27.19 mmol, 1.5 equiv). After warming to rt over 1 h, the reaction was quenched with H_2O (50 mL) then extracted 3 × (150 mL) into DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, hexanes/ethyl acetate 9:1) gave the desired trifloyloxazole **8c** (5.027 g, 89% yield) as a yellow solid (mp < 21 °C); **^{1}H-NMR** ($CDCl_3$, 360 MHz) δ 7.13-7.18 (2H, m), 7.72 (1H, s), 7.98-8.03 (2H, m); **^{13}C-NMR** ($CDCl_3$, 90 MHz) δ 116.58 (CH, d, *J*= 16.3 Hz), 118.97 (quat, d, *J*= 319.3 Hz), 122.82 (quat, d, *J*= 3.2 Hz), 126.71 (CH), 129.17 (CH, d, *J*= 11.9 Hz), 146.32 (quat), 159.21 (quat), 165.04 (quat, d, *J*= 253.2 Hz); **HRMS** (ES) calculated for $C_{10}H_5F_4NO_4S$; 311.9948, found 311.9946.

2-(4-Methoxyphenyl)oxazol-4-yl trifluoromethanesulfonate **8b**



2-(4-methoxyphenyl)oxazol-4-yl trifluoromethanesulfonate **8b** was synthesised according to the established procedure and gave spectral data in good agreement to that previously reported.[11] **^{1}H-NMR** ($CDCl_3$, 250 MHz) δ 3.81 (3H, s), 6.95 (2H, d, *J* = 9Hz), 7.61 (1H, s), 7.95 (2H, d, *J* = 9 Hz).

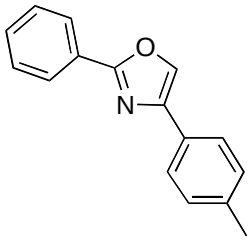
4-Phenyloxazol-2-yl nonafluorobutanesulfonate **6**



4-Phenyl-2-oxazolone[12d] **7a** (100 mg, 0.62 mmol, 1 equiv) was dissolved in DCM (8 mL, 0.25M) and cooled to -78 °C. To the solution was added 2,6-lutidine (0.14 mL, 1.24 mmol, 2 equiv) followed by dropwise addition of Nf_2O (0.29 mL, 0.93 mmol, 1.5 equiv). After warming to rt over 20 min, the reaction was quenched with H_2O, extracted 3 × (50 mL) into DCM. The organic layers were combined, washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, hexanes/DCM 7:3) gave the desired nonaflate **13** (230 mg, 84% yield) as a pale yellow oil; **^{1}H-NMR** ($CDCl_3$, 360 MHz) δ 7.37-7.45 (3H, m), 7.68-7.71 (2H, m), 7.79 (1H, s); **^{13}C-NMR** ($CDCl_3$, 90 MHz) δ 125.44 (CH), 128.87 CH), 129.09 (CH), 129.26 (quat), 132.70 (CH), 141.68 (quat), 150.11 (quat); **^{19}F-NMR** ($CDCl_3$, 250 MHz): -127.0 (2F, m), -121.9 (2F, m), -108.0 (2F, t, *J*= 13.4 Hz), -81.8 (3F, t, *J*= 9.6 Hz).

General procedure for the synthesis of 2,4 diaryl-oxazoles through Suzuki coupling of 2-aryl-oxazol-4-yl trifluoromethanesulfonates with aryl boronic acids: The following procedure for the preparation of **10a** is representative.

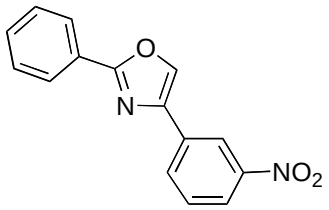
2-Phenyl-4-p-tolyloxazole **10a**



A microwave vial was charged with 2-phenyloxazol-4-yl trifluoromethanesulfonate **8a** (100 mg, 0.34 mmol, 1 equiv), 4-tolylboronic acid **9a** (52 mg, 0.37 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), sodium carbonate (0.53 mL 2M, 1.06 mmol, 3 equiv) and 1,4 dioxane (5 mL). The vial was sealed and stirred until complete dissolution of the boronic acid occurred. The mixture was then irradiated for 20 minutes at a pre-selected temperature of 150 °C in a Smith synthesiser. The vial was then automatically cooled with air jet cooling and the crude reaction mixture filtered through a pad of celite® and washed thoroughly with acetone. The organic layers were concentrated *in vacuo* and the residue was purified by flash chromatography (silica, hexanes/DCM 6:4) to give the coupled product **10a** (75 mg, 94% yield) as a white solid; mp = 110-111 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz): δ 2.44 (3H, s), 7.31-7.35 (2H, m), 7.46-7.49 (3H, m), 7.75-7.77 (2H, m), 7.98 (1H, s), 8.18-8.16 (2H, m); **^{13}C-**

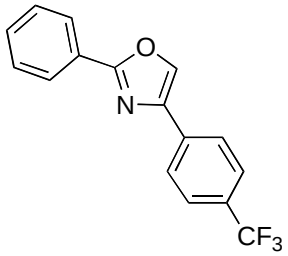
NMR ($CDCl_3$, 63 MHz) δ 21.31 (CH_3), 125.50 (CH), 126.46 (CH), 127.54 (quat), 128.26 (quat), 128.71 (CH), 129.40 (CH), 130.29 (CH), 132.98 (CH), 137.91 (quat), 142.00 (quat), 161.78 (quat); **HRMS** (ES) calculated for $C_{16}H_{13}NO$ 236.1070; found 236.1069.

4-(3-Nitrophenyl)-2-phenyloxazole **10b**



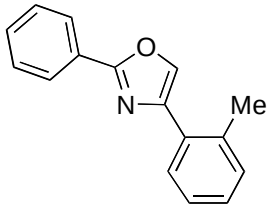
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 5:5) gave the coupled product **10b** (83 mg, 92% yield) as a white solid; mp = 161-163 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz): δ 7.57-7.60 (3H, m), 7.69 (1H, dd, *J*= 8.0 Hz, *J*= 8.0 Hz), 8.21-8.25 (5H, m), 8.75 (1H, s); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 120.32 (CH), 122.54 (CH), 126.47 (CH), 126.84 (quat), 128.74 (CH), 129.60 (CH), 130.69 (CH), 131.20 (CH), 132.83 (quat), 134.43 (CH), 139.91 (quat), 148.53 (quat), 162.29 (quat); **HRMS** (ES) calculated for $C_{15}H_{10}N_2O_2$ 267.0764; found 267.0761.

2-Phenyl-4-(4-(trifluoromethyl)phenyl)oxazole **10c**



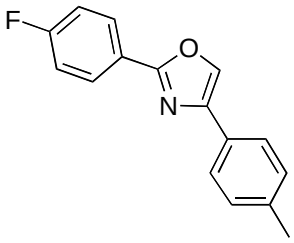
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 6:4) gave the coupled product **10c** (86 mg, 87% yield) as a white solid; mp = 144-145 °C;. **^{1}H-NMR** ($CDCl_3$, 250 MHz): δ 7.39-7.42 (3H, m), 7.59 (2H, d, *J*= 8.5 Hz), 7.82 (2H, d, *J*= 8.5 Hz), 7.94 (1H, s), 8.01-8.05 (2H, m); **^{13}C-NMR** ($CDCl_3$, 90 MHz) δ 125.47 (quat), 125.66 (CH), 125.73 (CH), 126.28 (quat), 127.14 (CH), 128.3 (quat, q, J= 277.4 Hz), 128.69 (CH), 128.80 (quat), 130.66 (CH), 134.42 (CH), 140.77 (quat), 162.26 (quat); **HRMS** (ES) calculated for $C_{16}H_{10}NOF_3$ 290.0787; found 290.0788.

2-Phenyl-4-o-tolyloxazole **10d**



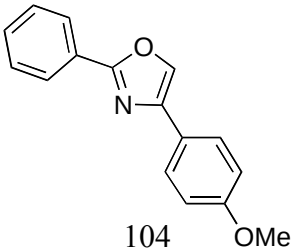
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 5:5) gave the coupled product **10d** (73 mg, 91% yield) as a white solid; mp = 67-68 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz): δ 2.50 (3H, s), 7.22-7.30 (3H, m), 7.46-7.49 (3H, m), 7.81 (1H, s), 7.93 (1H, d, *J*= 6.5 Hz), 8.11-8.15 (2H, m); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 22.72 (CH_3), 126.05 (CH), 126.47 (CH), 127.47 (quat), 127.93 (CH), 128.66 (CH), 128.71 (CH), 130.31 (quat), 130.38 (CH), 131.76 (CH), 135.20 (CH), 135.54 (quat), 140.97 (quat), 160.88 (quat); **HRMS** (ES) calculated for $C_{16}H_{13}NO$ 236.1070; found 236.1071.

2-(4-Fluorophenyl)-4-p-tolyloxazole **10e**



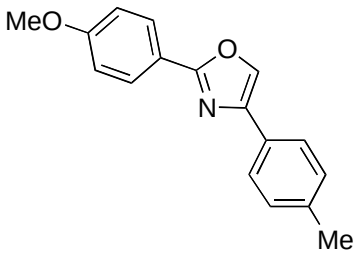
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 5:5) gave the coupled product **10e** (61 mg, 75% yield) as a white solid; mp = 140-141 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz): δ. 2.45 (3H, s), 7.18-7.31 (4H, m), 7.76 (2H, d, *J* = 1.6 Hz), 7.96 (1H, s), 8.13-8.19 (2H, m); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ.21.29 (CH_3), 115.87 (CH, d, *J*= 22 Hz), 123.89 (quat), 125.48 (CH), 128.15 (quat), 128.57 (CH, d, *J*= 8.6 Hz, 129.41 (CH), 132.97 (CH), 137.98 (quat), 142.03 (quat), 160.95 (quat), 164.02 (quat, d, *J*= 249.3 Hz); **HRMS** (FAB) calculated for $C_{16}H_{12}ONF$ 254.09812; found 254.09861.

4-(4-Methoxyphenyl)-2-phenyloxazole **10f** [17]



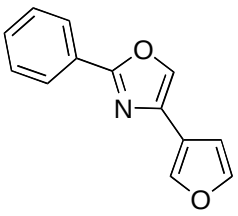
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 6:4) gave the coupled product **10f** (76 mg, 89% yield) as a white solid. This compound showed identical spectral data to that previously reported; mp = 105-106 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz): δ 4.04 (3H, s), 7.16 (2H, d, *J* = 8.9 Hz), 7.65-7.67 (3H, m), 7.94 (2H, d, *J* = 8.9 Hz), 8.06 (1H, s), 8.10-8.14 (2H, m); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 55.28 (CH_3), 114.12 (CH), 123.80 (quat), 126.43 (CH), 126.90 (CH), 127.54 (quat), 128.70 (CH), 130.26 (CH), 132.37 (CH), 141.74 (quat), 159.51 (quat), 161.73 (quat).

2-(4-Methoxyphenyl)-4-p-tolyloxazole **10g**



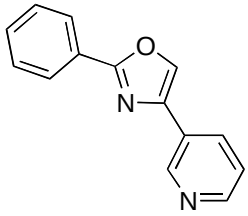
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 2:8) gave the coupled product **10g** (68 mg, 82% yield) as a white solid; mp = 130-131 °C; **^{1}H-NMR** ($CDCl_3$, 360 MHz): δ 2.44 (3H, s), 3.90 (3H, s), 7.03 (2H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.5 Hz), 7.76 (2H, d, *J* = 8.1 Hz), 7.92 (1H, s), 8.11 (2H, d, *J* = 11.8 Hz); **^{13}C-NMR** ($CDCl_3$, 90 MHz) δ 21.27 (CH_3), 55.31 (CH_3), 114.08 (CH), 120.38 (quat), 125.45 (CH), 128.10 CH), 128.41 (quat), 129.34 (CH), 132.44 (CH), 137.74 (quat), 141.76 (quat), 161.27 (quat), 161.83 (quat); **HRMS** (ES) calculated for $C_{17}H_{15}NO_2$ 266.1176; found 266.1176.

4-(Furan-3-yl)-2-phenyloxazole **10h**



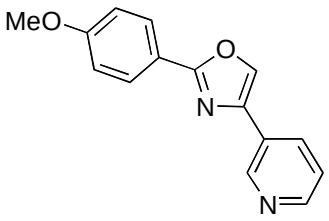
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 5:5) gave the coupled product **10h** (57 mg, 79% yield) as a yellow solid; mp = 81-82 °C; **^{1}H-NMR** ($CDCl_3$, 360 MHz): δ 6.65 (1H, s), 7.45-7.48 (4H, m), 7.76 (1H, s), 7.90 (1H, s), 8.06-8.09 (2H, m); **^{13}C-NMR** ($CDCl_3$, 90 MHz) δ 108.37 (CH), 117.20 (quat), 126.47 (CH), 127.27 (quat), 128.73 (CH), 130.44 (CH), 133.08 (CH), 134.98 (quat), 139.92 (CH), 143.60 (CH), 161.90 (quat); **HRMS** (ES) calculated for $C_{13}H_9NO_2$ 212.0706; found 212.0706.

3-(2-Phenyloxazol-4-yl)pyridine **10i**



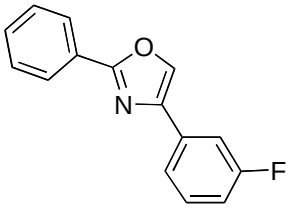
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 5:5) gave the coupled product (55 mg, 73% yield) as a yellow solid; mp = 92-93 °C; **^{1}H-NMR** ($CDCl_3$, 360 MHz): δ 7.38(1H, m), 7.36-7.39 (3H, m), 8.04 (1H, s), 8.10-8.16 (3H, m), 8.57 (1H, m), 9.05 (1H, m); **^{13}C-NMR** ($CDCl_3$, 90 MHz) δ 124.80 (CH), 127.61 (CH), 128.13 (quat), 128.44 (quat), 129.88 (CH), 131.76 (CH), 134.25 (CH), 135.11 (CH), 140.10 (quat), 147.80 (CH), 149.83 (CH), 163.47 (quat); **HRMS** (ES) calculated for $C_{14}H_{10}N_2O$ 223.0866; found 223.0867.

3-(2-(4-Methoxyphenyl)oxazol-4-yl)pyridine **10j**



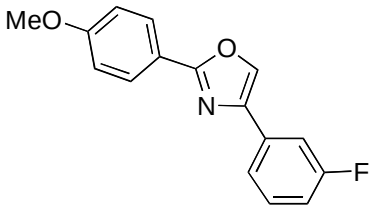
Prepared according to the general procedure. Purification by flash chromatography (silica, EtOAc) gave the coupled product **10j** (70 mg, 89% yield) as a white solid; mp = 120-122 °C; **^{1}H-NMR** (DMSO, 250 MHz): δ 3.79 (3H, CH_3), 7.06 (2H, d, *J* = 8.8 Hz), 7.46 (1H, m), 7.58 (2H, d, *J* = 4.1 Hz), 7.95 (1H, d, *J* = 8.8 Hz) 8.17 (1H, m), 8.73 (1H, s), 9.03 (1H, bs); **^{13}C-NMR** (DMSO, 63 MHz) δ 55.35 (CH_3), 114.55 (CH), 119.07 (quat), 12.88 (CH), 126.82 (quat), 127.90 (CH), 132.51 (CH), 135.74 (CH), 138.05 (quat), 146.32 (CH), 148.78 (CH), 161.27 (quat), 161.44 (quat); **HRMS** (ES) calculated for $C_{15}H_{12}N_2O_2$ 253.0972; found 253.0972.

4-(3-Fluorophenyl)-2-phenyloxazole **10k**



Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 6:4) gave the coupled product **10k** (74 mg, 91% yield) as a white solid; mp= 71-72 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz): δ 6.92 (1H, m), 7.28-7.40 (6H, m), 7.87 (1H, s), 8.00-8.04 (2H, m); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 112.60 (CH, d, *J* = 23 Hz), 114.87 (CH, d, *J* = 21 Hz), 121.16 (CH), 126.51 (CH), 127.24 (quat), 128.76 (CH), 130.19 (CH), 130.53 (CH), 133.90 (quat), 141.02 (quat), 163.35 (quat, d, *J* = 245 Hz), 162.03 (quat); **HRMS** (ES) calculated for $C_{15}H_{10}NOF$ 240.0819; found 240.0818.

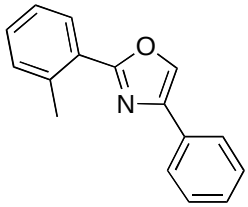
- 4-(3-Fluorophenyl)-2-(4-methoxyphenyl)oxazole **10l**



Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 2:8) gave the coupled product **10l** (71 mg, 85% yield) as a white solid; mp = 87-88 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz): δ 3.77 (3H, s), 6.89 (3H, m), 7.28 (1H, m), 7.46-7.49 (2H, m), 7.82 (1H, s), 7.95 (2H, d, *J* = 7.4 Hz); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 55.35 (CH_3), 112.54 (CH, d, *J* = 22.9 Hz), 114.16 (CH), 114.75 (CH, d, *J* = 21.1 Hz), 121.10 (quat), 121.14 (CH), 128.20 (CH), 130.21 (CH, d, *J* = 0.2 Hz), 133.37 (CH), 133.48 (quat), 140.70 (quat), 161.49 (quat), 162.11 (quat), 163.13 (quat, d, *J* = 245.3 Hz); **HRMS** (ES) calculated for $C_{16}H_{12}FNO_2$ 270.0925; found 270.0928.

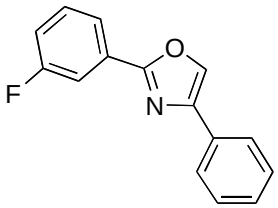
General procedure for the synthesis of 2,4 diaryl-oxazoles through Suzuki coupling of 2-chloro-4-phenyl-oxazole with aryl boronic acids. The procedure for compound **16a** is representative:

4-Phenyl-2-o-tolyloxazole **16a**



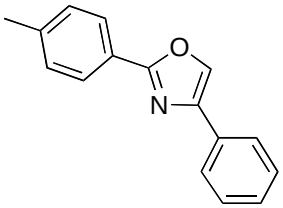
A microwave vial was charged with 2-chloro-4-phenyl oxazole (100 mg, 0.55 mmol, 1 equiv), o-tolylboronic acid (83 mg, 0.61 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), sodium carbonate (0.82 mL 2 M, 1.65 mmol, 3 equiv) and 1,4 dioxane (5 mL). The vial was sealed and stirred until complete dissolution of the boronic acid occurred. The mixture was then irradiated for 20 minutes at a pre-selected temperature of 150 °C in a Smith synthesiser. The vial was then cooled with air jet cooling and the crude reaction mixture filtered through a pad of celite® and washed thoroughly with acetone. The organic layers were concentrated *in vacuo* and the residue was purified by flash chromatography (silica, hexanes/DCM 7:3) to give the coupling product as a yellow oil **16a** (104 mg, 80% yield); **^{1}H-NMR** ($CDCl_3$, 250 MHz) δ 2.54 (3H, s), 7.07-7.13 (3H, m), 7.17-7.23 (3H, m), 7.59-7.63 (2H, m), 7.75 (1H, s), 7.83 (1H, m); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 21.99 (CH_3), 125.57 (CH), 125.89 (CH), 126.42 (quat), 127.99 (CH), 128.69 (CH), 128.84 (CH), 129.97 (CH), 131.22 (quat), 131.56 (CH), 132.95 (CH), 137.64 (quat), 141.55 (quat), 162.24 (quat); **HRMS** (ES) calculated for $C_{16}H_{13}NO$ 236.1070; found 236.1070.

2-(3-Fluorophenyl)-4-phenyloxazole **16b**



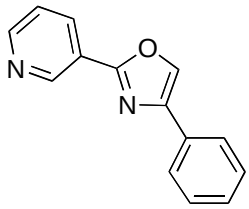
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 6:4) gave the coupled product **16b** (106 mg, 80% yield) as a white solid; mp = 70-72 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz) δ 7.41 (1H, m), 7.63-7.70 (4H, m), 8.06-8.20 (5H, m); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 113.42 (CH, d, *J* = 23.8 Hz), 117.28 (CH, d, *J* = 21.2 Hz), 122.13 (CH, d, *J* = 3.0 Hz), 125.31 (quat), 125.57 (CH), 128.19 (CH), 128.76 (CH), 130.47 (CH, d, *J* = 8.1 Hz), 130.80 (quat), 133.69 (CH), 135.35 (quat), 142.14 (quat), 163.83 (quat, d, *J* = 244.7 Hz); **HRMS** (ES) calculated for $C_{15}H_{10}NOF$ 240.0819; found 240.0819.

4-Phenyl-2-p-tolyloxazole **16c**



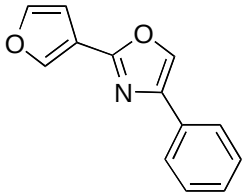
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 6:4) gave the coupled product **16c** (113 mg, 88% yield) as a white solid with identical spectral data to that previously published;[18] **^{1}H-NMR** ($CDCl_3$, 250 MHz) δ 2.41 (3H, s), 7.25-7.44 (5H, m), 7.82-8.02 (4H, m), 7.94 (1H, s).

3-(4-Phenyloxazol-2-yl)pyridine **16d**



Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/Et_2O 4:6) gave the coupled product **16d** (111 mg, 91% yield) as a white solid with identical spectral data to that previously published;[19] **^{1}H-NMR** ($CDCl_3$, 250 MHz) δ 7.27-7.46 (4H, m), 7.79-7.82 (2H, m), 7.99 (1H, s), 8.34-8.37 (1H, m), 8.67 (1H, d, *J* = 4 Hz), 9.33 (1H, bs).

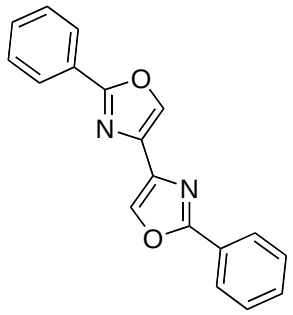
2-(Furan-3-yl)-4-phenyloxazole **16e**



Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/DCM 5:5) gave the coupled product **16e** (95 mg, 82%) as a white solid; mp = 78-79 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz) δ 6.49-6.85(1H, m), 7.25-7.29 (3H, m), 7.39 (1H, m), 7.68 (2H, d, *J* = 5.0 Hz), 7.77 (1H, s), 8.18 (1H, s); **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 108.62 (CH), 115.46 (quat), 125.55 (CH), 128.06 (CH), 128.68 (CH), 130.89 (quat), 132.58 (CH), 141.54 (quat), 142.64 (CH), 143.85 (CH), 157.09 (quat); **HRMS** (ES) calculated for $C_{13}H_9NO_2$ 212.0706; found 212.0704.

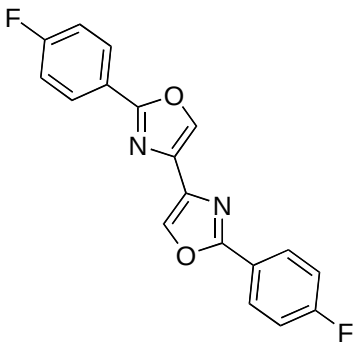
General procedure for the synthesis of 4,4-dioxazoles: The following procedure for the preparation of compound **18a** is representative.

2-Phenyl-4-(2-phenyloxazol-4-yl)oxazole **18a**



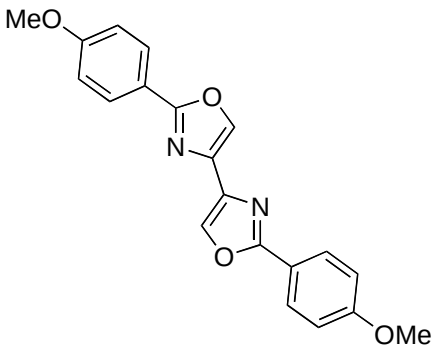
2-Phenyl-4-(2-phenyloxazol-4-yl)oxazole was prepared in a 2 step one pot procedure: A microwave vial was charged with 2-phenyloxazol-4-yl trifluoromethanesulfonate **8a** (119 mg, 0.41 mmol, 1.2 equiv), bis(pinacolato)diboron (116 mg, 0.45 mmol, 1.3 equiv), $PdCl_2$(dppf) (3 mol%), dppf (3 mol%), sodium acetate (102 mg, 1.22 mmol, 3 equiv) and 1,4 dioxane (5 mL). The mixture was then irradiated in a Smith synthesiser for 20 minutes at a pre-selected temperature of 150 °C. After the reaction the vial was cooled with air jet cooling to room temperature. The vial was opened and 2-phenyloxazol-4-yl trifluoromethanesulfonate **8a** (100 mg, 0.34 mmol, 1 equiv), $PdCl_2(PPh_3)_4$ (5 mol%) and sodium carbonate 2M (0.53 mL, 1.06 mmol, 3 equiv) were added to the reaction mixture. The vial was resealed and the mixture was again irradiated for 20 minutes at a pre-selected temperature of 150 °C. The vial was cooled with air jet cooling and the crude mixture was filtered through a pad of celite® with thorough acetone washing. The organic layers were concentrated *in vacuo* and the residue was purified by flash chromatography (silica, hexanes/DCM 5:5) to give the bis-oxazole product **18a** (57 mg, 58% yield) as a white solid; mp = 110-111 °C; **^{1}H-NMR** ($CDCl_3$, 360 MHz): δ 7.46-7.50 (6H, m), 8.08-8.13 (6H, m); **^{13}C-NMR** ($CDCl_3$, 90 MHz) δ 126.58 (CH), 127.19 (quat), 128.78 (CH), 130.60 (CH), 134.75 (quat), 134.99 (CH), 162.16 (quat). **HRMS** (ES) calculated for $C_{18}H_{12}N_2O_2$ 289.0972; found 289.0971.

2-(4-Fluorophenyl)-4-(2-(4-fluorophenyl)oxazol-4-yl)oxazole **18b**



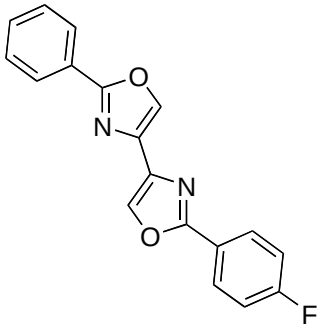
Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/EtOAc 8:2) gave a white solid which was further purified by trituration from hexane to afford the dioxazole product **18b** (72 mg, 69% yield) as a white solid; mp = 258-259 °C; **^{1}H-NMR** (DMSO, 360 MHz): 7.40-7.45 (4H, m), 8.07-8.11 (4H, m), 8.59 (2H, s); **^{13}C-NMR** (DMSO, 90 MHz) δ 115.55 (CH, d, *J* = 22.0 Hz), 122.82 (q, d, *J* = 2.7 Hz), 128.18 (CH, d, *J* = 9.0 Hz), 133.60 (quat), 135.59 (CH), 160.12 (quat), 163.15 (quat, d, *J* = 247.0 Hz); **HRMS** (ES) calculated for $C_{18}H_{10}N_2O_2F_2$ 325.0783; found 325.0783.

- 2-(4-Methoxyphenyl)-4-(2-(4-methoxyphenyl)oxazol-4-yl)oxazole **18c**



Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/EtOAc 7:3) gave the dioxazole product **18c** (78 mg, 61% yield) as a white solid; mp=180 °C (decomp.); **^{1}H-NMR** ($CDCl_3$, 250 MHz): 3.88 (CH_3, s), 6.99 (4H, d, *J* = 10.0 Hz), 8.04 (4H, d, *J* = 10.0 Hz), 8.07 (2H, s). **^{13}C-NMR** ($CDCl_3$, 63 MHz) δ 55.39 (CH_3), 114.17 (CH), 120.01 (quat), 128.26 (CH), 134.37 (CH), 134.57 (quat), 161.51 (quat), 162.20 (quat). **HRMS** (ES) calculated for $C_{20}H_{16}N_2O_4$ 349.1183; found 349.1187.

2-(4-Fluorophenyl)-4-(2-phenyloxazol-4-yl)oxazole **18d**



Prepared according to the general procedure. Purification by flash chromatography (silica, hexanes/EtOAc 9:1) gave the dioxazole product **18d** (44 mg, 38% yield) as a white solid; mp = 184-186 °C; **^{1}H-NMR** ($CDCl_3$, 250 MHz): 7.13-7.20 (2H, m), 7.46-7.49 (3H, m), 8.06-8.13 (6H, m); **^{13}C-NMR** ($CDCl_3$, 90 MHz) δ 115.92 (CH, d, *J* = 22 Hz), 123.48 (quat), 126.54 (CH), 127.09 (quat), 128.66 (CH), 128.72 (CH), 128.75 (CH), 128.94 (quat), 130.57 (CH, d, *J* = 2.7 Hz), 134.60 (q, d, *J* = 10.0 Hz), 135.04 (CH), 161.35 (quat), 162.24 (quat), 164.2 (quat, d, *J* = 250 Hz); **HRMS** (FAB) calculated for $C_{18}H_{11}N_2O_2F$ 307.08828; found 307.08821.

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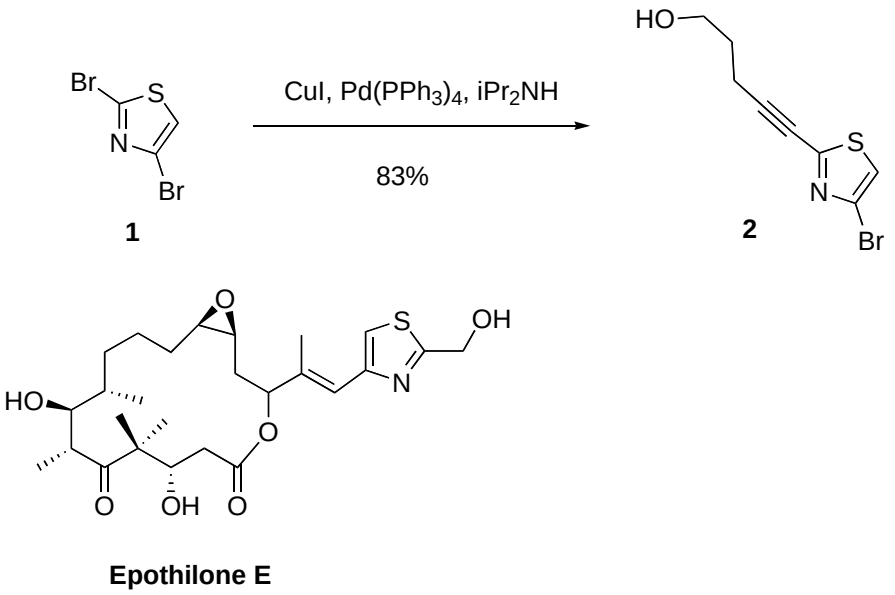
Chapter 3

Regioselective palladium catalysed cross-couplings of oxazoles. Synthesis of Tris-oxazoles.

3.1 Introduction

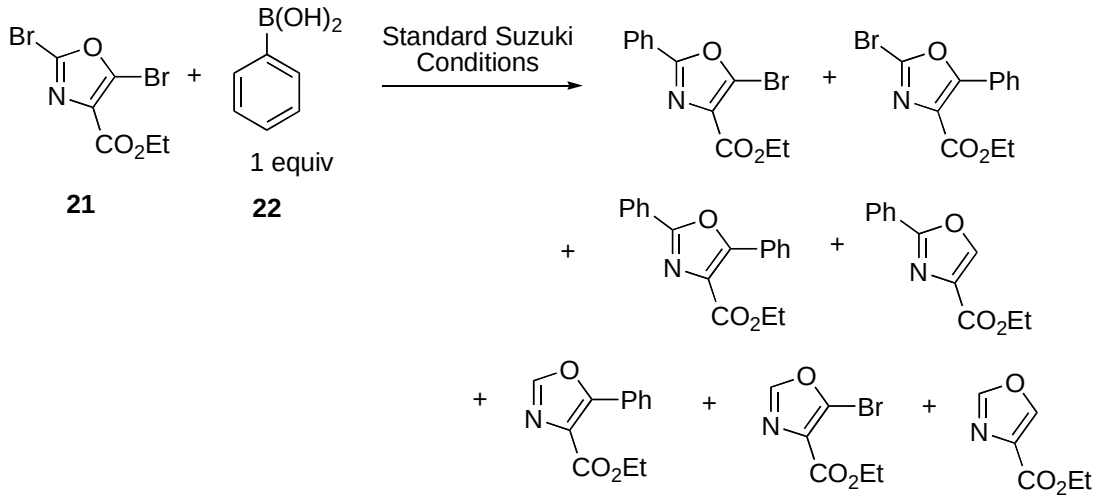
Directed insertion on multiply halogenated heterocycles to perform cross-coupling reactions at specific carbons of the ring is commonly referred to as regioselective cross-coupling.[1] In heterocyclic chemistry, the same principle has been applied not only in the context of cross-coupling reactions, but also for example, in directed metallation methods and also in halogen/metal exchange reactions. Catalytic cross-coupling reactions are synthetically more attractive because they only require sub-stochiometric amounts of catalysts whereas equimolar amounts of reductive metal complexes are needed if directed metalation or halogen/metal exchange reactions want to be employed. As an illustration of this approach, a Sonogashira regioselective cross-coupling in Nicolaou's approach to epothilone E and analogues, is shown in Scheme 1.[2]

The difference of electrophilicity of the carbon atoms in 2,4-dibromothiazole **1** makes C-2 more electrophilic due to the proximity of the oxygen and nitrogen atoms. The reason for this effect is because it is the only position that gives a low energy anion. In the oxidative addition step Pd^0 acts as a nucleophile and will preferentially attack the most electron-deficient position of the ring. This is of course, for cross-coupling reactions where the oxidative addition is the rate-determining step, showing a high preference in favour of the most electrophilic position. Moreover, the oxidative addition step may be influenced by coordination of the metal to a heteroatom of the heterocycle. This is especially true for N-containing heterocycles where the basic nitrogen atom may direct the coupling to the ortho position of the ring.



Scheme 1. Regioselective Sonogashira cross-coupling on 2,4-dibromothiazole **1**.

Many examples of regioselective cross-coupling reactions have been reported for the majority of the heterocyclic systems, however this particular strategy on oxazoles is extremely rare.[1] Hodgetts and Kershaw have reported the Suzuki reaction of 2,5-dibromooxazole **21** with 1 equivalent of phenylboronic acid **22** to give a complex mixture products (Scheme 2).



Scheme 2. Suzuki reaction on 2,5-dibromooxazole **21** with phenyl boronic acid **22**.

Analysis of the crude reaction mixture by ^{1}H-NMR and LC-MS indicated the presence of mono- and disubstituted coupled products as well as products arising from the debromination of the coupled species and of the starting material (Scheme 2).[3] The most likely reason for the lack of examples in oxazoles is the extraordinary low availability of poly-halogenated oxazoles. In fact, only the already mentioned 2,5-dibromooxazole and 2,4-diiodo-5-substituted oxazoles have been reported so far, the former being described as unwanted reaction sub-products with no synthetic application.[4]

Adding selectively one substituent in the presence of several halogens in the heterocycle has the great advantage of avoiding the subsequent necessary step to re-halogenate the molecule after the substituent has been introduced. Particularly in natural product synthesis this synthetic step may be difficult or even impossible to perform in the presence of other functional groups, making the regioselective approach an attractive alternative. On the other hand, poly-halogenations of heterocycles are sometimes more easily controlled than mono-halogenations rendering this technique even more convenient in synthesis.

3.2 Aims

Several natural products, such as Telomestatin[5] or Ulapualide A,[6] contain three or more successive C_2-C_4' linked poly-oxazole units instead of a single oxazole (Figure 1). This particular archetype is a consequence of their biosynthetic assembly from serine or threonine residues.[7] These compounds have fascinating structures, show a wide range of biological properties, and therefore make ideal targets for the synthetic chemist.[8]

In oxazoles, position C_4 is specifically difficult to halogenate, due to C-2 and C-5 being more conveniently accessed due to their nucleophilicity and their natural reactivity towards electrophilic halogenating agents. In 1999 Vedej's and co-workers described a method to selectively iodinate C_4 of 5-substituted oxazoles.

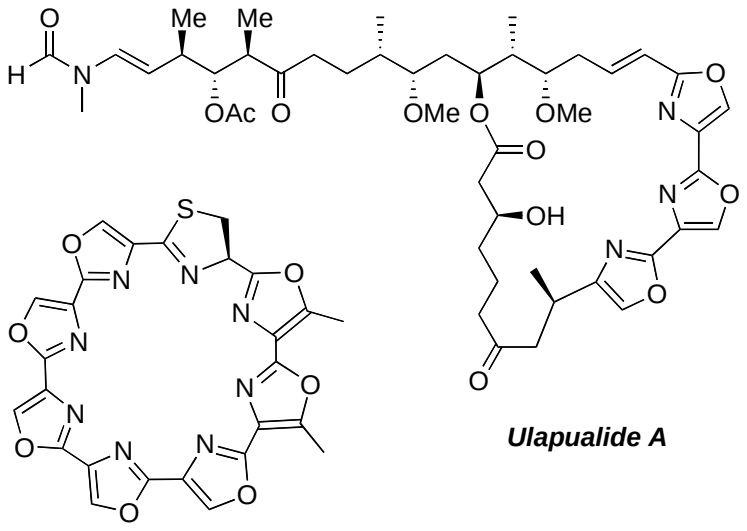
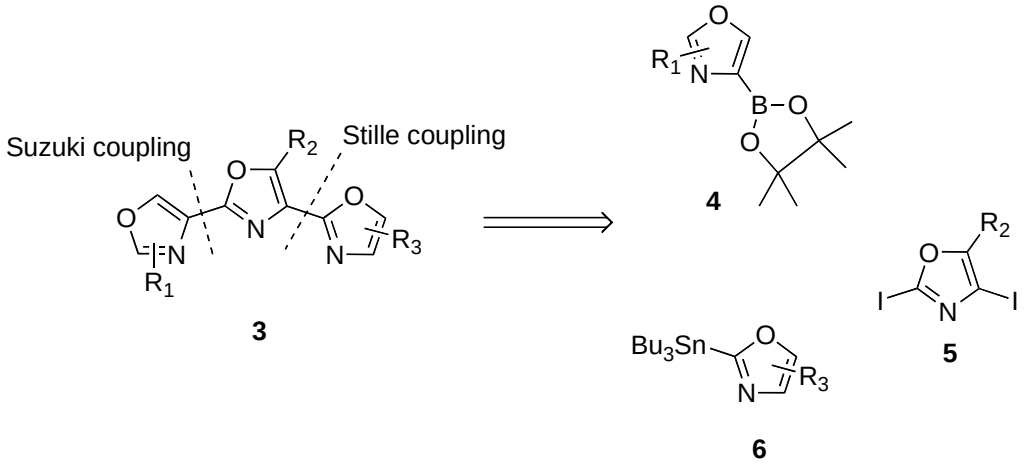


Figure 1. Poly-oxazole-containing natural products.

As covered in Chapter 1, 2,4-diiodooxazoles had been described in that work as unwanted reaction products.[4] In this context, it was envisaged they could be precursors of tris-oxazoles. Due to their unique 2,4-di-functionalisation, it was expected they would undergo preferential oxidative addition of Pd^0 at the more reactive C_2 position, followed by Suzuki-Miyaura cross-coupling with an oxazol-4-ylboronate **4**. The C_4-I bond would be left intact for a second cross-coupling with a 2-metallo-oxazole **6** (Scheme 3).



Scheme 3. Regioselective palladium catalysed strategy for the synthesis of tris-oxazoles.

The regioselective palladium catalysed cross-coupling chosen was the Suzuki-Miyaura reaction for two reasons; previous results had been successful in the synthesis of 4,4-dioxazoles (Chapter 2).[9] Also because of the relatively facile accessibility and excellent stability of the known oxazol-4-ylboronates **4**, which are synthesised in four steps from available starting materials and were amenable to multi-gram scale necessary to perform optimisation studies.

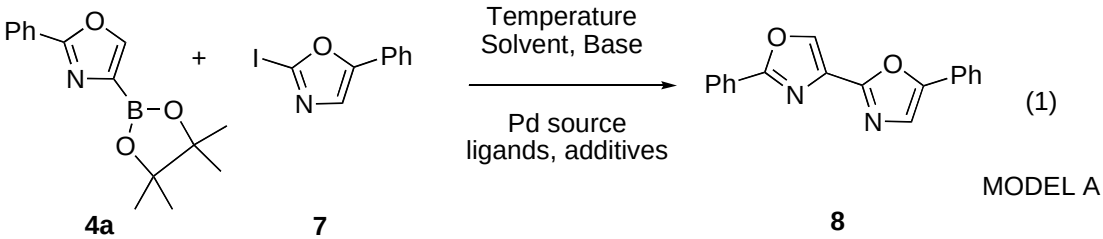
Borylation on C_2 was required in order to use the Suzuki-Miyaura reaction in the second coupling. However, all attempts to borylate on C_2 have failed (see Chapter 2).[10]

As a result, the Stille reaction was considered a good alternative since oxazol-2-ylstannanes are known nucleophile partners in palladium catalysed oxazole cross-coupling reactions. They are easily accessed via selective C-2 metalation with strong lithium bases, and subsequent quenching of the acyclic isocyano enolate lithium salt with Bu_3SnCl or Me_3SnCl to give the ring closed form.[11]

3.3 Models A and B

In order to simplify the approach and to define the reaction parameters, it was elected to break down the proposed regioselective tri-oxazole synthesis into two parts, examining each C-C bond formation separately on mono-iodooxazoles prior to using the bis-iodooxazoles **5** (models A and B).

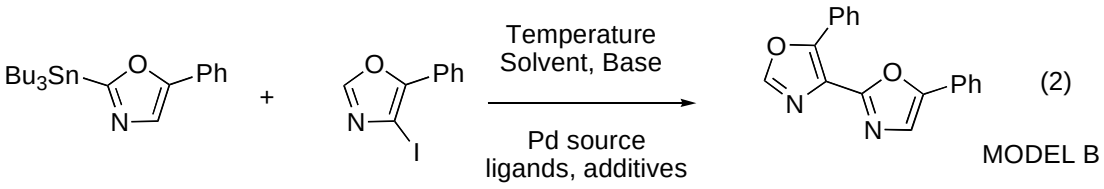
Model A was chosen as a simplified version of the Suzuki reaction. Iodooxazole **7** was chosen as the electrophile having only one reactive site on C-2, therefore regioselective issues should be avoided (Equation 1).



4a **7** **8** (1)

MODEL A

Model B was chosen for the Stille reaction, using a simpler electrophile such as 4-iodo-5-phenyloxazole **9** (Equation 2).



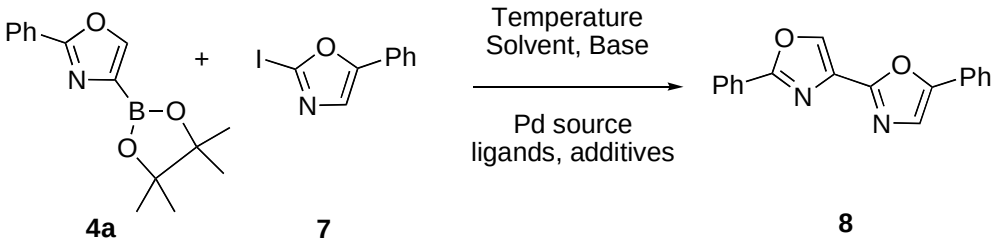
6a **9** **10**

Both iodooxazoles **7** and **9** can be prepared in multigram quantities, enabling comfortable optimisation of the reactions.

3.3.1 Model A: Suzuki-Miyaura reaction

A range of conditions for Suzuki coupling of oxazol-4-ylboronate **4a** and iodooxazole **7** were explored, the results are shown in Table 1.

Table 1. Model A. Suzuki Reaction between oxazol-4-ylboronate **4a** and 2-iodo-5-phenyloxazole **7**.[a]



4a **7** **8**

Entry	Time	Solvent	Pd source	Base	Temp	Additives	Yield of **8** (%)
1	2h	DMF	$Pd(PPh_3)_4$	K_2CO_3	100 ºC	none	49
2	4 d	THF	$Pd(PPh_3)_4$	No base	rt	1,1 eq of CuTc	complex mixture
3	4 d	THF	$Pd_2(dba)_3$	KF	rt	10% $[(tBu)_3PH]BF_4$	complex mixture
4	20 min	Dioxane	$PdCl_2(PPh_3)_2$	aq Na_2CO_3 2M	150 ºC μwaves	none	34
5	20	DMF	$Pd(PPh_3)_4$	K_2CO_3	150 ºC	none	79

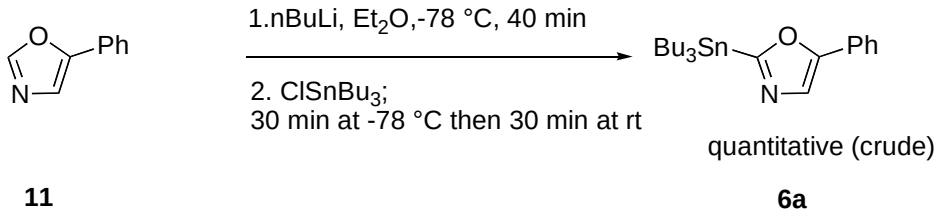
	min				μwaves		
6	20 min	DMF	$Pd_2(dba)_3$	K_2CO_3	150 ºC μwaves	PCy_3	87

Conditions: 1.1 equiv of **3**, 1 equiv of **6**, 3 equiv of base, 3mL of solvent.

Standard Suzuki-Miyaura conditions at 100 °C in DMF gave bis-oxazole **8** in 49% yield (entry 1). Milder conditions such as the ones developed by Liebeskind,[12] and also Fu,[13] gave a complex mixture of products that could not be separated (entries 2 and 3 respectively). It was quickly found that the use of microwave irradiation not only shortened reaction times but also increased the yields dramatically; the best of all was a combination of $Pd_2(dba)_3$ 5% with PCy_3 10% in DMF giving the desired product **8** in an excellent 87% of isolated material (entries 4, 5 and 6).

3.3.2 Model B: Stille reaction

According to a known procedure oxazol-2-ylstannane **6a** was then synthesised by treating 5-phenyloxazole **11** with nBuLi at -78 °C, and quenching the reaction mixture with Bu_3SnCl which gave **6a** in quantitative crude yield (Scheme 4).[14]



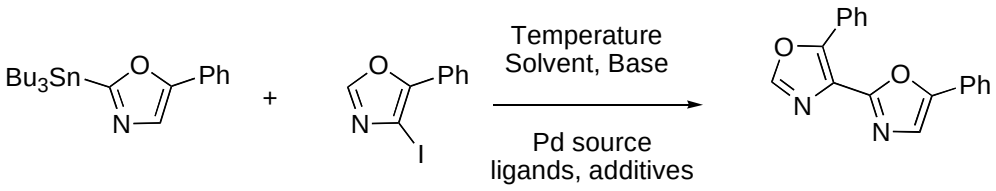
11 **6a**

Scheme 4. Synthesis of stannane **6a**

Stannane **6a** had stability limitations, being very sensitive to hydrolysis and although it could to be stored at -10 °C for short periods of time, it was best to use freshly prepared.[15] A range of conditions was examined for the Stille coupling between 2-oxazoyl stannane **6a** and iodooxazole. The optimisation results for model B are shown in Table 2.

Standard conditions proved to be successful, but only a moderate yield of **10** was obtained even after two days under reflux conditions (entry 1). Fu's trialkylphosphonium salt[13] at room temperature, under microwaves irradiation or in combination with Cu_2O only led to complex mixtures or slow reaction rates (entries 2, 3, 5 and 8). The ligand tri-furylphosphine (TFP) in conjunction with $Pd_2(dba)_3$ and Cu_2O gave a modest 35% of isolated **10,** but a slow reaction rate was obtained if combined with $Cu(OAc)_2$ (entries 4 and 6 respectively). Liebskind's copper-mediated Stille coupling under mild conditions[16] gave a slow reaction rate in our system (entry 7). After considerable optimisation search, it was finally realised that higher yields could be achieved if higher loadings (3 equivalents) of stannane **6a** where used in the reaction. Hence, the best of all combinations appeared to be same catalyst system used for model A. Finally, $Pd_2(dba)_3$ 5% and PCy_3 10% in DMF and under microwave irradiation gave an excellent 87% yield of bis-oxazole **10** after column chromatography (entry 10).

Table 2. Model B. Optimisation of Stille coupling between 2-oxazoyl stannane **6a** and 4-iodo-5-phenyloxazole **9**.



6a **9** **10**

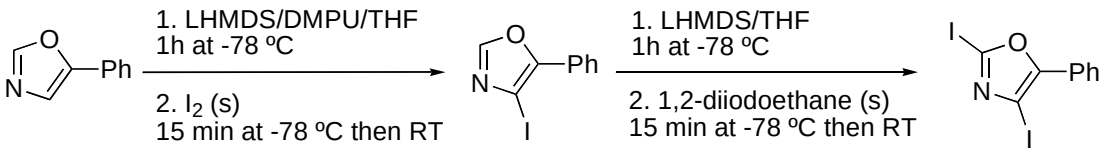
Entry	Time	Solvent	Palladium source	Base	Temp.	Additives	Yield of **10**[a] (%)
1	2 days	DME	$PdCl_2(PPh_3)_2$	none	Reflux	none	42
2	3h	NMP	$Pd_2(dba)_3$	CsF	RT	12% $[(tBu)_3PH]BF_4$	slow
3	5'	NMP	$Pd_2(dba)_3$	CsF	150 ºC, μwaves	12% $[(tBu)_3PH]BF_4$	Complex mixture
4	2h	NMP	$Pd_2(dba)_3$	No base	100 ºC	10% TFP and 1eq Cu_2O	35

5	4 days	NMP	$Pd_2(dba)_3$	KF	rt	20% $[(tBu)_3PH]BF_4$ and 1eq Cu_2O	slow
6	2 days	NMP	$Pd_2(dba)_3$	none	rt	20% TPF and 1eq $CuAc_2$	26
7	4 days	NMP	none	none	none	1.5 eq CuTC	slow
8	10 min	DMF	$Pd_2(dba)_3$	CsF	150 ºC, μwaves	10% $[(tBu)_3PH]BF_4$	Complex mixture
9[b]	20 min	DMF	$Pd_2(dba)_3$	none	150 ºC, μwaves	10% PCy_3	54
10[c]	5 min	DMF	$Pd_2(dba)_3$	none	150 ºC, μwaves	10% PCy_3	87

[a] Isolated yields. [b] 1.5 equiv. of stannane **3** were used.[c] 3 equiv. of stannane **3** were used.

3.4 Regioselective Suzuki coupling. Preliminary results.

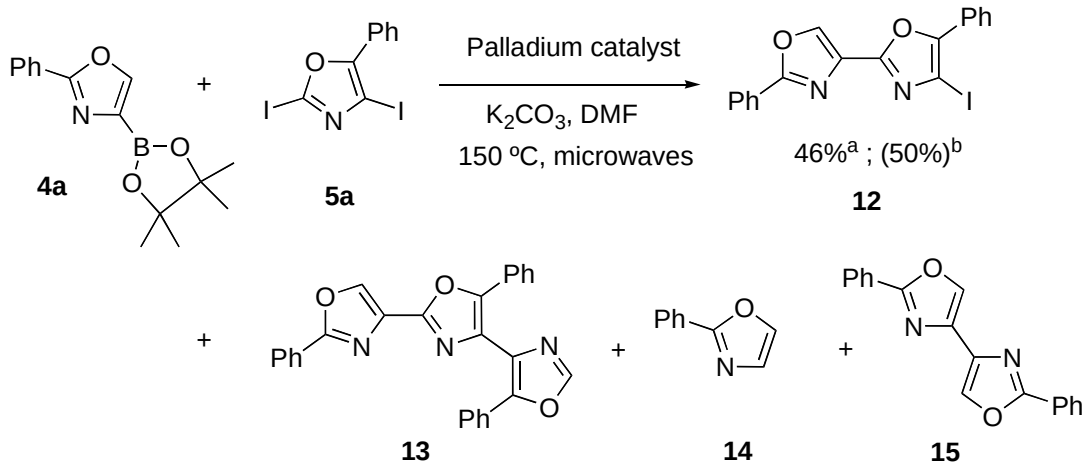
With the idea of merging both models A and B into the synthesis of tris-oxazoles, 2,4-diiiodo-5-phenyloxazole **5a** was synthesised in 2 steps from the known 5-phenyloxazole[17] **11** by Vedejs' selective 4-iodination in 65% yield followed by C-2 iodination using 1,2-diiodoethane to give diiodooxazole **5a** in quantitative yield (Scheme 5).[4]



11 **9** **5a**

Scheme 5. Synthesis of 2,4 diiodo-5-phenyloxazole **5a**

In a preliminary experiment, Suzuki coupling between oxazol-4-ylboronate **4a** and diiodooxazole **5a** was regioselective on C-2 giving the desired dioxazole **12** in 46% yield using $Pd_2(dba)_3/PCy_3$ and 50% yield if $Pd(PPh_3)_4$ was used (Scheme 6).

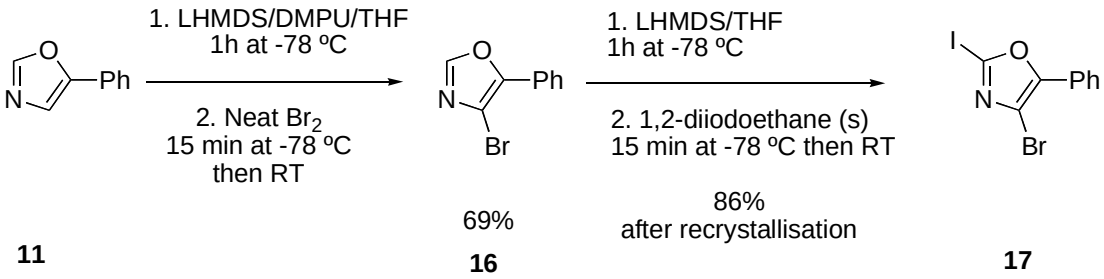


Conditions: 1equiv. of **3** and **11,** 2 equiv. of K_2CO_3, 5 min at 150 ºC (microwave irradiation). [a]$Pd_2(dba)_3$ 5%, PCy_3 10%, [b]$Pd(PPh_3)_4$ 5%.

Scheme 6. Regioselective coupling between oxazol-4-ylboronate **4a** and 2,4-diiodooxazole **5a**.[a]

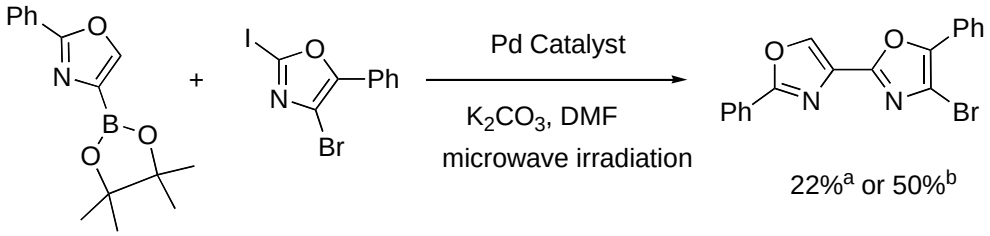
Careful analysis of the reaction mixture by HPLC and LC-MS revealed the formation of trimer **13** (presumably the palladium catalysed product of the reaction between **12** and boronic ester **4a**), **14** (protodeboronation of **4a**) and homo-coupled **15** probably dimerised from boronic ester **4a**. The main concern was that under the reaction conditions the desired **12** was also reacting with the boronic ester **4a** and consequently decreasing the yield of **12**. It was sought to decrease reactivity of **12** by modifying its precursor **5a**. Thus, if a Br atom would be selectively placed in C-4 instead of I, then oxidative addition on newly formed **12** would be diminished and therefore the yield should be improved. It was necessary to develop the synthesis of such a compound because there are no examples in the literature of hybrid bis-halooxazoles. Selective C-4 bromination on 5-phenyloxazole **11** was carried out using a modification of Vedejs' procedure and 4-bromo-5-phenyloxazole **16** was obtained in a good 69% yield after column chromatography. Then, iodination on C-2

using LHMDS and 1,2-diiodoethane gave the desired bis-halooxazole **17** in an excellent 86% after re-crystallisation (Scheme 7).



Scheme 7. Synthesis of 2-iodo-4-bromo-5-phenyloxazole

Initial attempts at regioselective Suzuki-Miyaura coupling of **17** with boronic ester **4a** using $Pd_2(dba)_3/PCy_3$ produced the bis-oxazole in a disappointing 22% yield. However, 50% yield was obtained when $Pd(PPh_3)_4$ was used instead (Scheme 8).



[a]$Pd_2(dba)_3$ 5% and PCy_3 10%, 150 °C µwaves. [b]$Pd(PPh_3)_4$ 5%, 150 °C µwaves.

Scheme 8. Regioselective Suzuki coupling between oxazol-4-ylboronate **4a** and 2,4-dihalooxazole **17**.

This result points to the ability of the bulkier and electron-rich PCy_3 ligand to facilitate oxidative addition, eroding the selectivity in this system.

Further optimisation of this reaction was carried out using statistical experimental design (see below).

3.5 Statistical Experimental Design of Experiment

3.5.1 Introduction

Experiments in general, whatever the discipline or methodology, involve changing controlled parameters or input factors and recording the output responses or dependant variables. In the case of a chemical transformation input factors may be temperature, concentration or reagent equivalents. Typical output responses are those thought to be a meaningful reflection of the progress of the process such as the yield of product.

The established methodology for performing optimisation of experiments is to vary one single factor while keeping all other factors as fixed and under control as is experimentally possible. Response is then measured as a function of the variable to generate a simple mathematical model from which predictions may be made. The method assumes each factor acts *independently* on the response and ignores the effect of any interactions between two or more factors. By varying only one factor at a time the effect of a factor is estimated at set conditions so no information on possible interactions is available.

There is an alternative methodology to performing experiments, which can generate data more rich in information because experiments are planned using a more mathematical approach, which appears to contradict the traditionally accepted ideas. Using statistics and structured Design of Experiment (DoE), multiple variables are changed simultaneously in a structured, predetermined way and the response recorded. By analysing the data not only can the effect of single factors on the response be estimated but information on interactions, curvature and uncertainty can all be quantified. Definite decisions can be made based on conclusions general to the process rather than specific conditions. Designs of Experiment are often used for screening studies to investigate a large number of factors thought to influence the response. In addition to main effects, the factorial design gives information on

interactions of factors. By changing multiple factors at the same time it is possible to determine how the effects on response of varying one factor change at different levels of another factor.

Each factor investigated in DoE is evaluated at two levels; high and low. Reaction space is the imaginary area bound by the extremes (high and low) of the factors of interest. When three factors for example are arbitrarily chosen, a cube represents the reaction space. The *xyz* axes correspond to different levels of the continuous factors and so the corners of the cube represent different combinations of high and low factor levels. Eight experiments from the reaction space give rise to eight possible terms: x_0 -intercept term, x_1, x_2, x_3 are the main effects, x_1x_2, x_1x_3, x_2x_3 are the 2 factor interaction terms and $x_1x_2x_3$ the 3 factor interaction. The model thus generated is of the form:

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + b_{123}x_1x_2x_3$$

Where *y* is the response and *b* represent the coefficients. In coded form these coefficients generated are directly related to the significance of each factor. Having run the experiments and recorded the responses a design matrix is set up which in coded form merely assigns a sign (+ or -) to each coefficient in the model. The interaction of temp and time for example (x_1x_2) is given sign (-*- = +). Using a software package such as DX6 the coded coefficients are calculated using matrix algebra almost instantaneously. [18]

3.5.2 Fractional factorial designs

One of the drawbacks of a full-factorial design is the large number of experimental runs required as the number of factors is increased. When investigating factors at two levels the number of experiments for a full factorial design is 2^n where *n* is the number of factors in the design. In the case of an 8 factor design there will be 256 factorial points and an additional factor gives 512. Clearly, it soon becomes implausible to run full factorial experiments, especially when efficiency is one of the main premises for carrying out an experimental design in the first place. Very often

all these extra experiments give no additional useful information on main effects or possible interactions. Most of this additional resource is wasted in estimating extremely unlikely higher order interactions. Two factor interactions are common and quite conceivable. Three factor interactions are unlikely to have any real significance but four factor and higher interactions are barely worth a second thought. Very often in screening designs a large number of factors are investigated with the aim of identifying the significant few for further more detailed studies. All that is required is an estimate of the main effects and possible two factor interactions. The solution to this problem is fractionation of the design. The number of experiments may be reduced by ½, 1/8, 1/16, etc… in a systematic way so there is sufficient information in the design matrix to provide estimates of the main effects.

The DX-6 software automatically fractionates designs and uses a clear graphical diagram to assist in the selection of such designs. Figure 1 shows a screen shot of the software with the available design options. Full factorial designs are shown as white designs – all model terms calculated independently yet a great deal of useless information is gathered. Green designs provide estimates for all main effects and two factor interactions independently – very safe designs. Yellow and red designs be performed but with a higher risk of missing important information of the system (Figure 1).

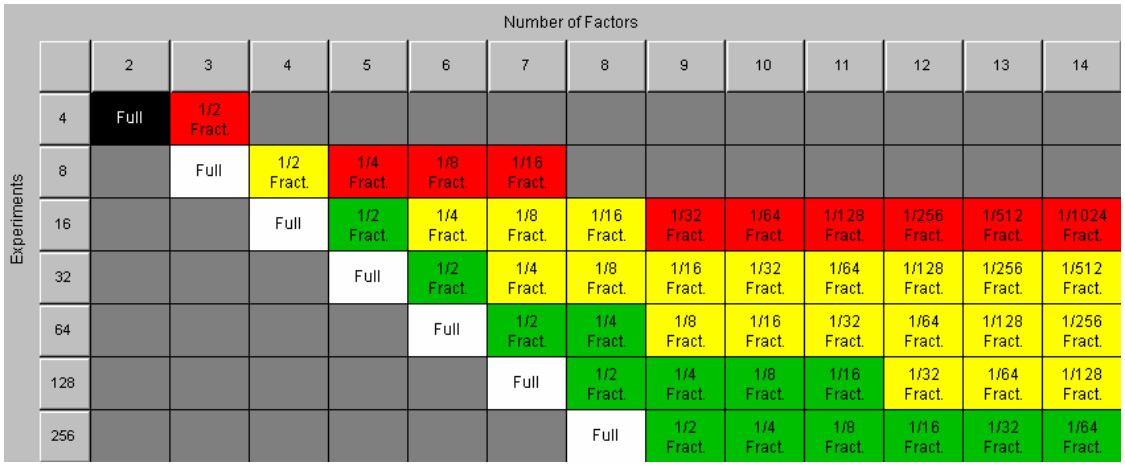
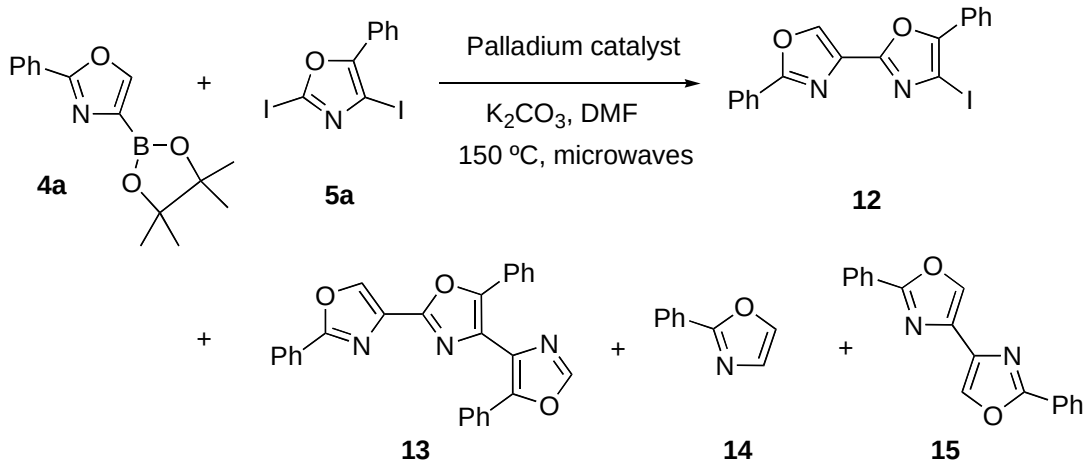


Figure 1. Screen shot from DX-6 software

3.6 Case Study: Regioselective Suzuki-Miyaura coupling

In order to further optimise and also to acquire a deeper understanding of the reaction parameters the regioselective Suzuki-Miyaura coupling was subjected to a statistical design of experiment.[19] The aim of the study was to investigate the main factors that would cause variations in the formation of bis-oxazole **18**, and also to understand the main factors related with the formation of trimer **13**, protodeboronated **14**, and homocoupled **15** (Scheme 9).

With this information it would be possible to increase the yield effectively and also to have a better understanding of the robustness of this process.



Scheme 9. Case study: regioselective Suzuki-Miyaura cross-coupling.

3.6.1 Choice of independent factors

Five factors were considered as part of the factorial design and they were chosen according to the current reaction conditions and varied correspondingly as high and low factor levels.

- Factor A: Boronic ester stochiometry: it was understood from the preliminary results that the stochiometry of boronic ester **4a** was key in the reaction conditions because it was involved in the formation of all the unwanted side products. A factor range between 1 equivalent (the minimum) to 1.9 equivalents as a synthetically acceptable maximum was considered.

- Factor B: Catalyst loading: In cross-coupling reactions, catalyst loading is of major importance affecting the yield of products dramatically. As a general guideline, loadings of catalyst of 5 mol% are considered to be average in catalyst turn over, 10 mol% or more being poor, and 1% or less excellent.

- Factor C: Equivalents of base: The base in the Suzuki-Miyaura reaction is known to activate the boron species and is of vital importance, its stochiometry is usually between 2 to 5 equivalents. No base in the reaction conditions usually leads to very slow reaction rates. On the other hand, base sensitive substrates may suffer from it specially if it is in large excess. Therefore information regarding the effect of the base in the formation of products in the reaction would be of great value. The range factor for the base was chosen to be from 1 to 5 equivalents.

- Factor D: Concentration/Dilution: Concentration is also an important parameter in chemistry in general. The range factor for the concentration was taken from 40 volumes (low factor, highly diluted) to 10 volumes (high factor, concentrated).

- Factor E: Temperature: Microwave irradiation was used to heat the reaction vessels and from the preliminary results we observed good conversion at 150 °C at short reaction times (between 1 to 5 min), so the range factor was chosen from 130 °C to 150 °C and the time the vessel was irradiated was fixed to one minute.

Table 3. Choice of independent factors

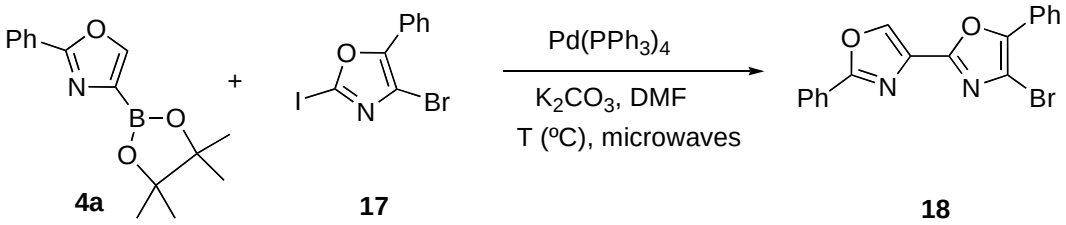
Factor	Units	Low	Mid	High
Boronate stochiometry (A)	equivalents	1.1	1.5	1.9
Catalyst Loading (B)	mol%	1.0%	5.0%	9.0%
Equivalents of base (C)	equivalents	1	3	5
Concentration/Dilution (D)	volumes	40	25	10
Temperature (E)	° C	130	140	150

3.6.2 Analysis and preliminary results for 1st fractional experiment.

If every combination of the high and low factor levels were investigated (full factorial design) there would be $2^5 = 32$ experiments. Performing a full factorial design would need a large amount of boronic ester **4a,** which is synthesised in 4 steps from available starting materials. Synthesis of **4a** in large scale was difficult to pursue and in consequence an approach where a lower amounts of **4a** were needed was considered more attractive. It was decided that ¼ fractional (red design) would be sufficient to provide estimates of the main effects and the two factor interactions. The fractionated design was planned as a single block of 8 factorial points with the inclusion of 2 centre points to estimate curvature and pure error.

The experiments were carried out in an automated microwave reactor were the temperature and time reaction were pre-programmed. The yield response for product **18** was determined by HPLC areas comparison using an authentic sample of **18**. The results for the ¼ fractional factorial design are depicted in Table 4.

Table 4. ¼ Fractional Factorial Design for the regioselective Suzuki reaction



Entry	**4a**	$Pd(PPh_3)_4$	K_2CO_3	Concentration	Temperature[a]	Yield of **18**[b]
1	1.10 equiv	1 mol%	1 equiv	40 Volumes	150 °C	31%
2	1.90 equiv	1 mol%	1 equiv	10 Volumes	130 °C	67%
3	1.10 equiv	9 mol%	1 equiv	10 Volumes	150 °C	73%
4	1.90 equiv	9 mol%	1 equiv	40 Volumes	130 °C	69%
5	1.10 equiv	1 mol%	5 equiv	40 Volumes	130 °C	57%
6	1.90 equiv	1 mol%	5 equiv	10 Volumes	150 °C	45%
7	1.10 equiv	9 mol%	5 equiv	10 Volumes	130 °C	74%
8	1.90 equiv	9 mol%	5 equiv	40 Volumes	150 °C	40%
9	1.50 equiv	5 mol%	3 equiv	25 Volumes	140 °C	69%
10	1.50 equiv	5 mol%	3 equiv	25 Volumes	140 °C	68%

[a]The sample was irradiated on a microwave reactor for 1 min at the indicated temperature [b]Obtained by comparison of HPLC areas with an authentic sample of **18**.

Analysis for the formation of **18**

Half Normal plots are commonly used to graphically present correctly coded coefficients for easy assessment of significance.

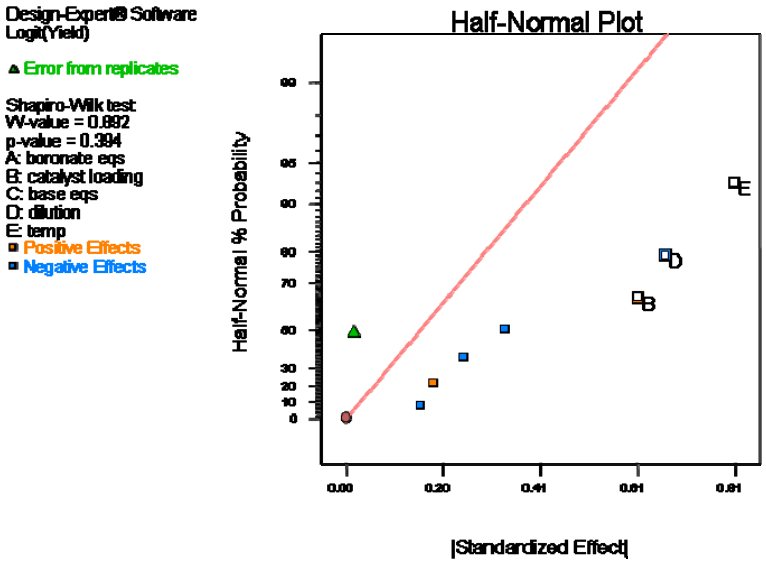


Figure 2. Half –Normal plot for the analysis of yield of **18**

They are based on the assumption that randomly chosen numbers should form a normal distribution. Insignificant effects whose variation is due to random causes alone should fall in an approximate straight line at the centre of the graph. Large effects, which are unlikely to be due to random variation should fall further to the right away from the straight line. In this case factor E (temperature) is the most significant factor (Figure 2).

These significant factors can be studied individually using one factor plots that give a reasonable idea of the effect of a factor versus the response

- Temperature: From the one factor plot it was deduced that the optimal yields should be obtained at temperatures around 130 °C (Figure 3).

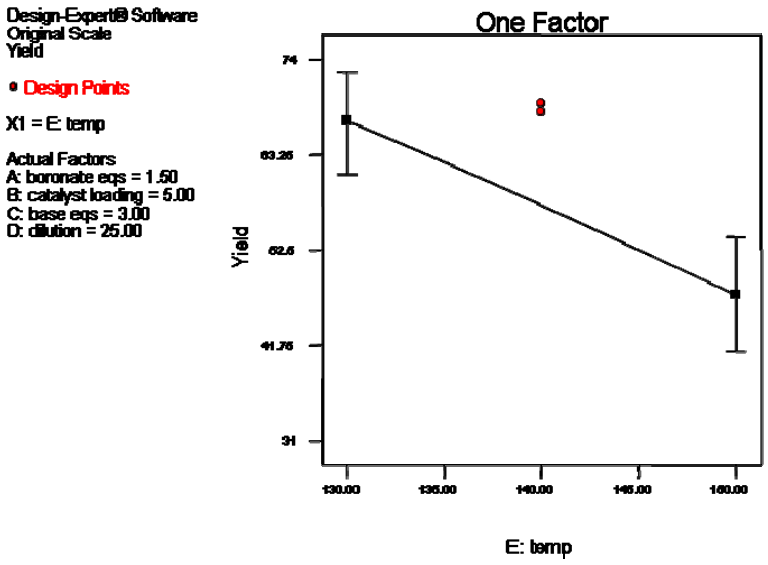


Figure 3. One factor plot for yield of **18** Vs temperature.

Following the temperature the most significant factors affecting the formation of **18** were catalyst loading and the concentration.

Concentration: From the one factor plot it was deduced that concentration decreases the yield of desired **18** (Figure 4).

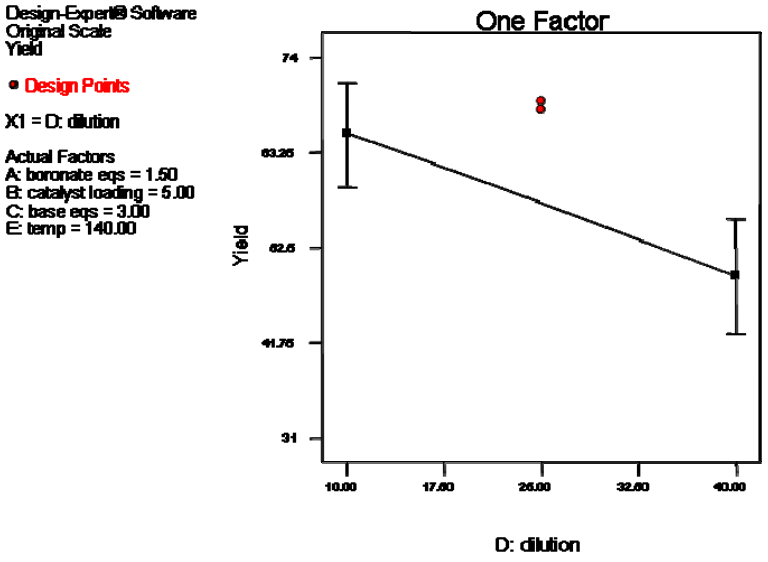


Figure 4. One factor plot for yield of **18** Vs concentration.

- Catalyst loading: It was deduced that high catalyst loading would increase the formation of **18** (one factor plot not shown).

Analysis of homocoupled **15**

Analysis of the half-normal plot shown that it was clear that the most important factor for the formation of homocoupled **15** is the equivalents of boronic ester **3** used in the reaction (Figure 5).

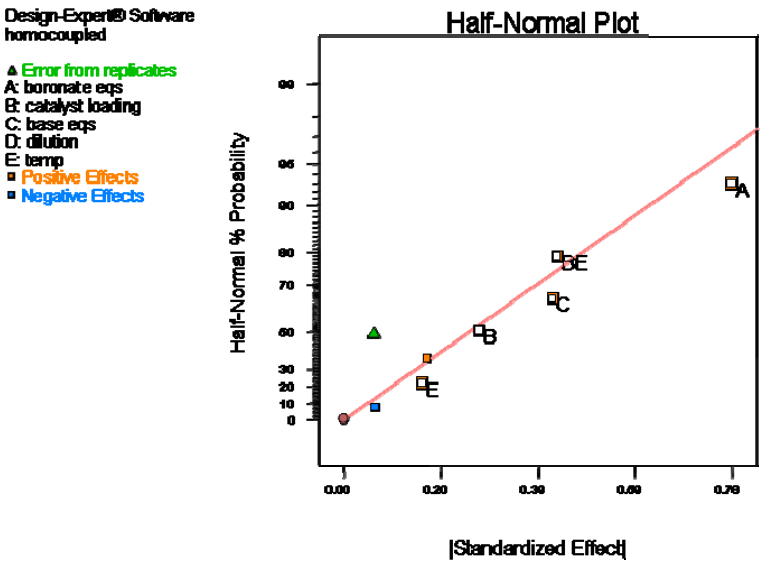


Figure 5. Half –Normal plot for the analysis of formation of **15**

Other parameters are also having an effect on the formation of this sideproduct however in a lot less importance.

- Formation of homocoupled **15** increases with the number of equivalents of boronic acid added in the reaction.

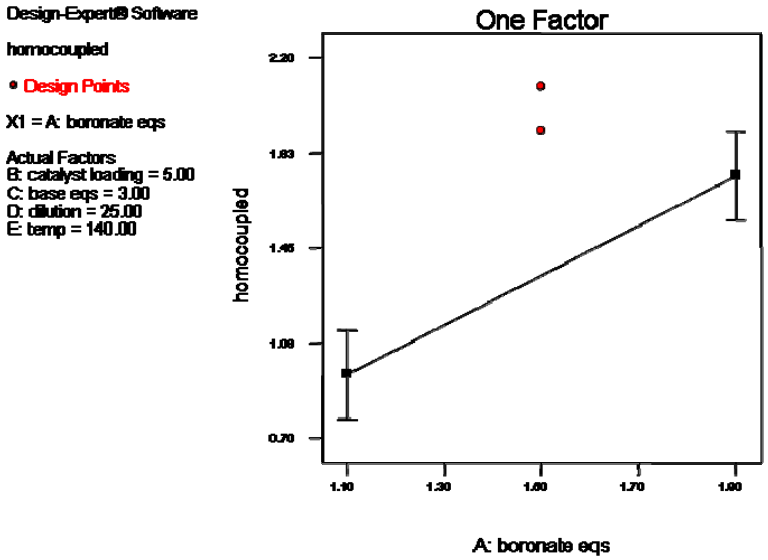


Figure 6. One factor plot for formation of **15** Vs boronic ester stochiometry

Analysis for protodeboronated **14**

The half-normal plot shows clearly that the only important parameter affecting the formation of **14** is the boronic ester **4a** stochiometry (Figure **7**).

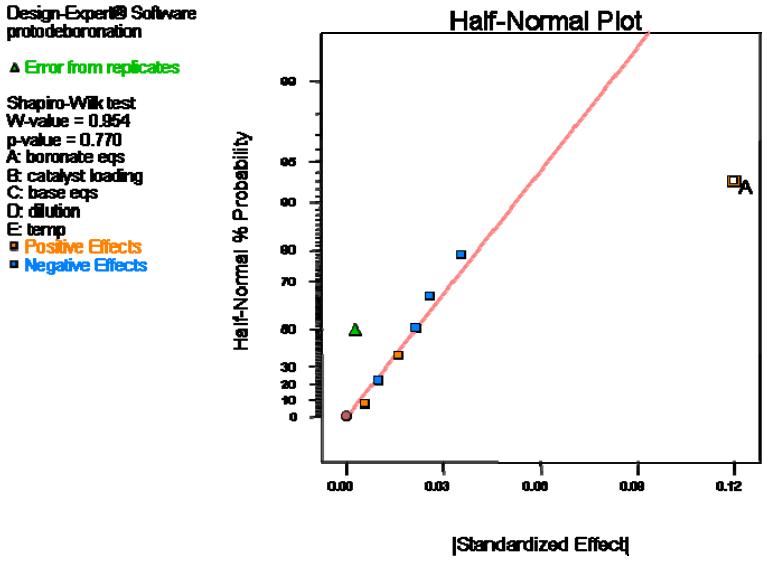


Figure 7. Half-Normal plot for the formation of protodeboronated **14**

- The one plot factor for this parameter shows formation of **14** is related to high amounts of boronic ester used in the reaction.

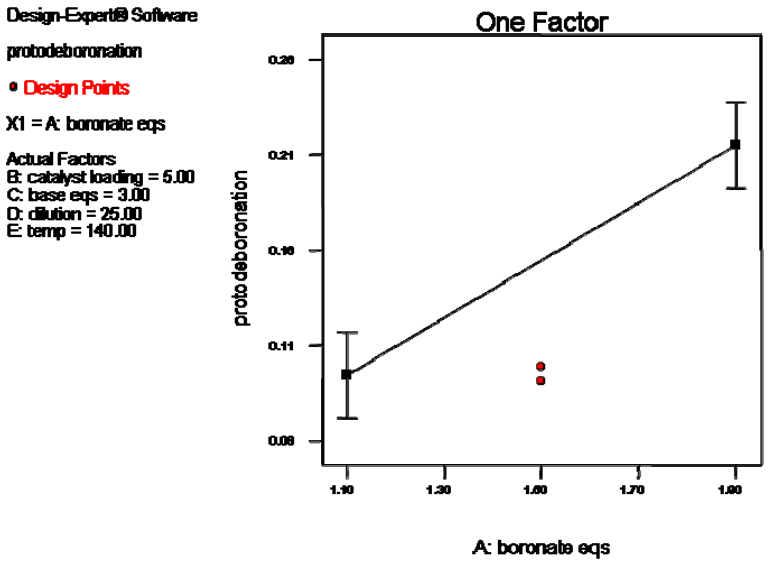


Figure 8. One factor plot for formation of **14** Vs boronic ester **4a** stochiometry.

Analysis of trimer **13**

The half-normal plot shows that the main parameters affecting the formation of unwanted **13** are the boronate stochiometry followed by the equivalents of base and the temperature of the reaction.

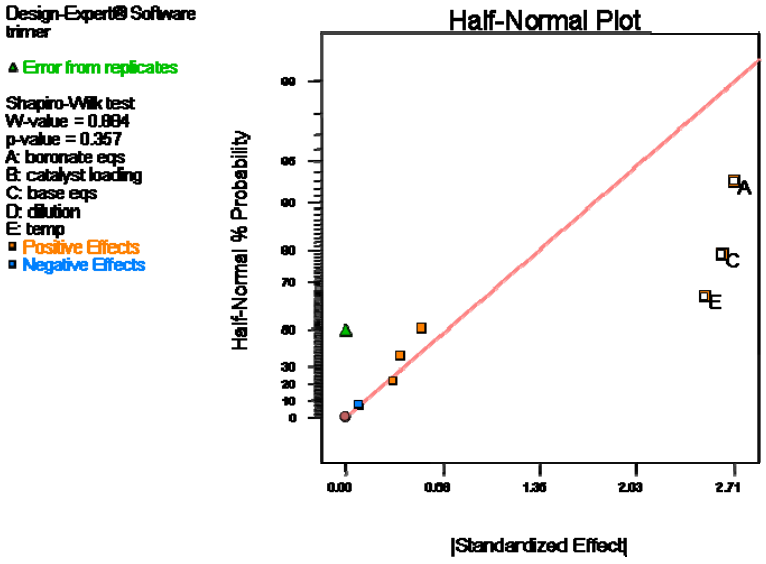


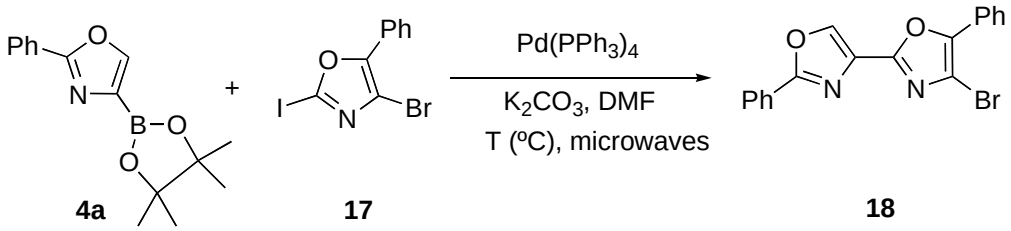
Figure 9. Half-Normal plot for the formation of trimer **13**.

3.6.3 2nd Fractional Design of experiment.

With all the information gathered from the first design it was possible to concentrate on the factors that predominantly affected the yield of desired **18** while keeping the non important ones at a constant. It was understood that the boronic ester **4a** stochiometry and the equivalents of base were not affecting the yield formation of **18** and therefore low levels of these should be used in the reaction conditions. Although being an important factor in the formation of **18**, the catalyst stochiometry was maintained constant at a general 5 mol% making the process synthetically more attractive.

In order to increase the yield of **18** a second fractional design of experiments was carried out. The second set of experiments was performed with only concentration and temperature as the variables of the system. The results are shown in Table 5.

Table 5. Results for the 2nd Design of Experiment



4a **17** **18**

Entry	Concentration (Volumes)	Temperature (°C)[a]	HPLC Yield (%)[b]	Isolated Yield of **18**[c]
1	20	120	69%	
2	15	130	78%	
3	10	120	66%	
4	15	130	73%	
5	10	140	77%	81%
6	20	140	76%	65%

Conditions: 1.2 equiv. of **4a**, 1. equiv of **17**, 5 mol% of $Pd(Ph_3)_4$, 2 equiv. of K_2CO_3 were used. [a]The sample was irradiated on a microwave reactor for 1 min at the indicated temperature [b]Obtained by comparison of HPLC areas with an authentic sample of **18**. [c]Yield after purification by column chromatography.

Under these conditions, 6 additional experiments were carried out. Compared to the first design the concentration range and also the temperature range were narrowed. The HPLC yields obtained for **18** were uniformly good under this set of conditions (entries 1-6). To compare the theoretical values obtained by HPLC, two of the reactions mixture were purified and bis-oxazole **18** was isolated in a very good 81% yield at a reaction temperature of 140 °C and a concentration of 10 volumes (entry 5).

The half-normal plot shown below points out clearly that the main effect under the new set of conditions is the temperature of the reaction being the concentration factor not important (Figure 10).

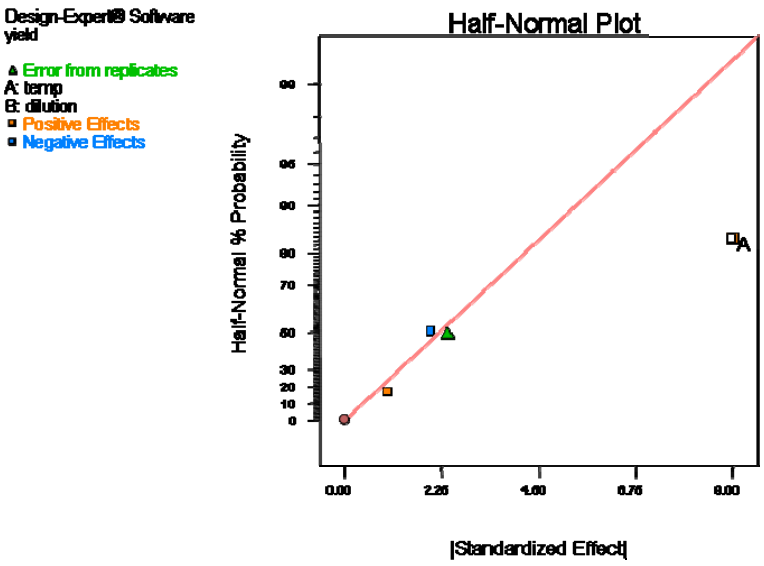


Figure 10. Half-Normal plot for the formation of product **18**

On the other hand the one factor plot shows the optimum temperature for the formation of **18** is 140 °C (Figure 11).

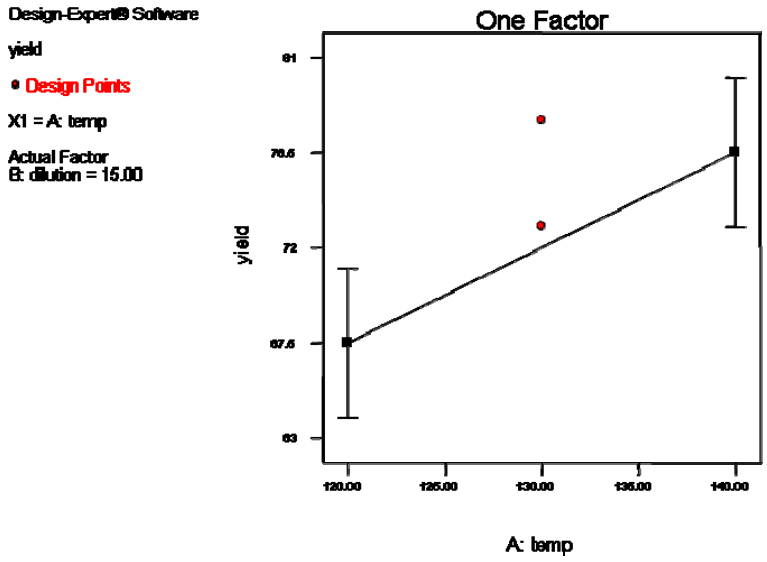


Figure 11. One factor plot for the yield of **18** Vs the temperature.

3.6.4 Conclusions

The Suzuki-Miyaura regioselective coupling on 2-iodo-4-bromo-5-phenyloxazole **17** has been studied with two fractional designs of experiments. In the first design 10 selected experiments were carried out and important information regarding the influence of each parameter in the process was acquired. The main effects are temperature, catalyst loading and concentration, directly affecting the formation **18**. As a preliminary result it was found that better yields of **18** should be obtained within the following range:

- Temperature should be kept at around 130 °C.
- The reaction should be as concentrated as possible (ca 10 volumes).
- Stochiometry of boronic ester **4a** or the base are not important in the formation of **18**.

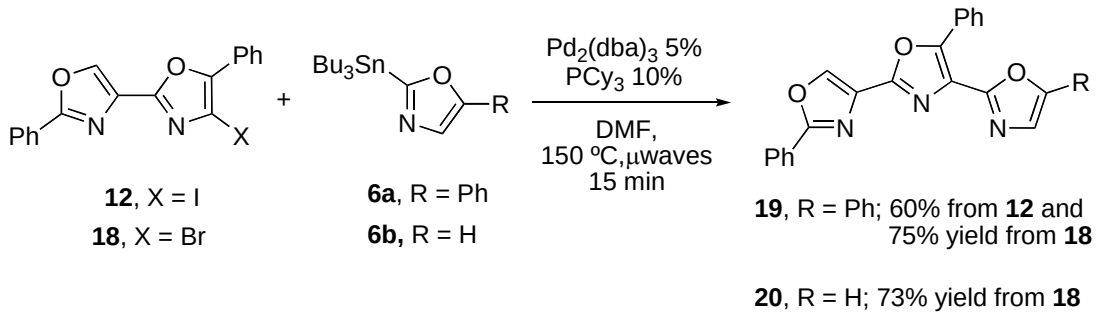
In the second design 6 additional experiments were carried out. Insignificant parameters were kept constant and at low values. Temperature and concentration ranges were narrowed therefore more accurate information could be extracted from the experiments. The results show a good distribution of yields of **18** for all the experiments conducted. The ideal range of conditions found for this reaction is the following:

- Concentration: Should be kept between 10 and 20 volumes.
- Temperature: under these conditions the optimal temperature found was 140 °C for 1 min using microwave irradiation.
- Boronic ester **4a**: 1.2 equivalents.
- 2-iodo-4-bromo-5-phenyloxazole **17**: 1 equivalent.
- Catalyst loading ($Pd(PPh_3)_4$): 5 mol% (or more).
- Equivalents of base (K_2CO_3): 2 equivalents.

This non-conventional optimisation has not only increased the yields of the desired product, but also it has given an idea of the robustness of the process. Very specific ranges of temperature and concentration need to be taken in order to achieve higher yields. Also a minimum of 5 % mol catalyst has to be used in order to attain a good yield of **18**. Outside these limits consistency cannot be obtained therefore under these parameters the process is not very robust. On the other hand small variations of boronic ester stochiometry **4a** or the equivalents of base will not affect the yield of **18** making the process more robust under these parameters.

3.7 Synthesis of Tris-Oxazoles

With both models A and B optimised the synthesis of tris-oxazoles was attempted. Either **12** and **18** were used as electrophiles under the model B conditions. The results are outlined in Scheme 10.



12, X = I
18, X = Br

6a, R = Ph
6b, R = H

19, R = Ph; 60% from **12** and 75% yield from **18**

20, R = H; 73% yield from **18**

Scheme 10. Stille couplings for the formation of tris-oxazoles.

Clean formation of the desired tris-oxazoles using the optimised Stille coupling conditions developed previously. Tris-oxazole **19** was obtained in good 60% yield from substrate **12** and 75% yield from substrate **18** after column chromatography. Coupling was also successful for the simple stannane **6b**, producing tris-oxazole **20** in 73% yield using the same procedure (Scheme 10).

3.8 Scope and Final Conclusions

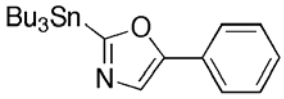
It has been proved for the first time that regioselective Suzuki-Miyaura cross-coupling reactions can be conducted on 2,4-dihalooxazoles species. Furthermore, the halogen left intact on position C-4 can be used in an immediate second Stille coupling to allow the formation of tris-oxazoles. In order to optimise both the Suzuki coupling and the Stille reaction, each C-C bond formation was examined separately

on mono-iodooxazoles to define the reaction parameters prior to using the bis-halooxazoles. Screening studies were carried out with the finding of high yielding conditions for both reactions. After this, preliminary results were obtained for the regioselective Suzuki reaction and a statistical design of experiment was carried out to get an understanding of important reaction parameters affecting the yield of the coupling product. This methodology has allowed the finding of a range of conditions where good yields of coupled product could be obtained along with information of the process robustness. Finally, application of the Stille conditions developed before provided the desired tris-oxazoles in good yields. The method clearly benefits from convergence allowing variations on the oxazole substituent at an early stage of the synthesis. In addition, the proposed synthesis provides high level of complexity in a minimum number of steps avoiding the preparation of complicated precursors.

The main drawbacks are probably related to the first palladium insertion where oxazole boronic esters were needed. The scarce availability of these in the literature compared to other heterocycles certainly restricts its application into other systems or natural product synthesis. Moreover, many oxazole-containing natural products have unsubstituted C-5 patterns.[8] The presented method uses 5-phenyloxazole **11** which can be iodinated selectively on C-4 using Vedejs' methodology.[4] This is clearly a limitation because C-5 substitution on the oxazole is needed prior the halogenating step and therefore full control over the C-5 position would be necessary in order to apply the method into more complex systems. Finally, the Stille coupling required three equivalents of stannane in order to achieve high yields in the coupling product. This is economically and also in terms of waste disposal very undesirable.

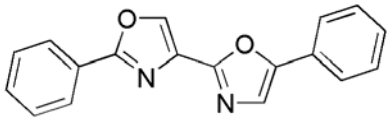
3.9 Experimental procedures Chapter 3

5-Phenyl-2-tributylstannanyl-oxazole **6a**



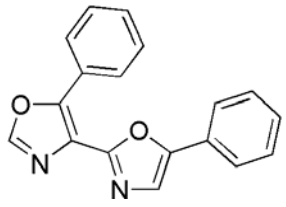
This compound was synthesised according to Dondoni's procedure.[11] 5-Phenyloxazole[17] **11** (500 mg, 3.447 mmol, 1equiv) was dissolved in dry diethyl ether (30 mL) and cooled to -78 °C. *n*BuLi [1,6 M in hexanes] (2.58 mL, 4.136 mmol, 1.2 equiv) was added dropwise under nitrogen to the resulting solution and stirred for 40 min at -78 °C. Then, $ClSnBu_3$ (0.93 mL, 3.447 mmol, 1 equiv) was added slowly to the reaction mixture and stirred additionally for 30 min at -78 °C. After this time, the cool bath was removed and the reaction mixture was allowed to warm to rt for about 30 min. The Et_2O was then removed by rotary evaporation and the obtained crude was re-dissolved in hexane (50 mL), filtered through basic celite and the solvent removed under *vacuo* to yield 1.508 g of crude 5-Phenyl-2-tributylstannanyl-oxazole **6a** as a red oil. Further purification, and complete characterisation were not successful. This compound was used without further purification in the next step. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 0.91 (9H, t, *J* = 7.33 Hz), 1.22-1.27 (6H, m), 1.31-1.42 (6H, m), 1.59-1.68 (6H, m), 7.27-7.28 (1H, m), 7.39-7.41 (3H, m), 7.65-7.67 (2H, m). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 10.73 (CH_3), 13.63 (CH_2), 27.10 (CH_2), 28.80 (CH_2), 122.05 (CH), 124.35 (CH), 127.95 (CH), 128.76 (quat), 128.78 (CH), 153.66 (quat), 172.48 (quat).

5,2'-Diphenyl-[2,4']bioxazolyl **8**



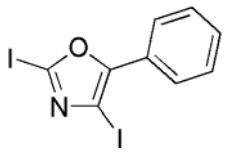
A 5 mL microwave vial was charged with oxazol-4-ylboronate **4a** (66 mg, 0.242 mmol, 1.1 equiv), 2-iodo-5-phenyloxazole[4] (60 mg, 0.220 mmol, 1 equiv), $Pd_2(dba)_3$ (10 mg, 5 mol%), PCy_3 (5 mg, 10 mol%), K_2CO_3 (92 mg, 0.660 mmol, 3 equiv) and 3 mL of anhydrous DMF. The microwave vial was then sealed, and the resulting mixture was stirred at rt aproximately 5 min before it was irradiated for 5 min at a pre-selected temperature of 150 °C in a Smith Synthesiser. The vial was then cooled with air jet cooling, it was 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 with Et_2O (2x). 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 8:2) to give the coupled product **8** (55 mg, 87% yield) as a light yellow solid. Mp = 162-164 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 7.34-7.49 (7H, m), 7.73 (2H, dd, J_1 = 8.4 Hz, J_2 = 1.1 Hz), 8.15-8.18 (2H, m), 8.31 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 123.10 (CH) 124.30 (CH), 126.46 (quat), 126.78 (CH), 127.46 (quat), 128.60 (CH), 128.76 (CH), 128.83 (CH), 130.98 (CH), 131.67 (quat), 138.00 (CH), 151.36 (quat), 154.62 (quat), 162.64 (quat). **HRMS** (ESI) calculated for $C_{21}H_{13}N_3O_3$ 355.0951 found 355.0949.

5,5'-Diphenyl-[2,4']bioxazolyl **10**



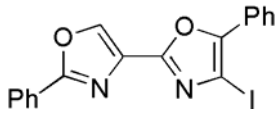
A 5 mL microwave vial was charged with 4-iodo-5-phenyloxazole[4] (100 mg, 0.369 mmol, 1 equiv), oxazol-4-ylstannane **6a** (481 mg, 1.107 mmol, 3 equiv), $Pd_2(dba)_3$ (17 mg, 5 mol%), PCy_3 (10 mg, 10 mol%), and 5 mL of anhydrous DMF. The microwave vial was then sealed, and the resulting mixture was stirred at rt for about 5 min before it was irradiated 5 min at a pre-selected temperature of 150 °C in a Smith Synthesiser. The vial was then cooled with air jet cooling and was opened and poured into a mixture of 10 mL of saturated KF_{aq} and 20 mL of EtOAc and stirred for 30 min. After this time the organic layer was separated and the aqueous layer was extracted with EtOAc (2x). The organic layers were combined, dried under 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 **10** (56 mg, 87% yield) as a white solid. Mp = 102-104 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 7.42-7.54 (7H, m), 7.74-7.76 (m, 2H), 8.04 (1H, s), 8.29-8.31 (2H, m). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 123.08 (CH), 124.20 (CH), 126.93 (quat), 127.29 (CH), 127.39 (quat), 128.40 (CH), 128.48 (CH), 128.73 (CH), 128.84 (quat), 129.77 (CH), 149.74 (CH), 150.03 (quat), 151.29 (quat), 154.91 (quat). **HRMS** (ESI) calculated for $C_{18}H_{12}N_2O_2$ 289.0972 found 289.0974.

2,4-Diiodo-5-phenyl-oxazole **5a**



2,4-Diiodo-5-phenyl-oxazole **5a** was synthesised according to Vedej's protocol with minor modifications.[4] 4-Iodo-5-phenyloxazole (100 mg, 0.369 mmol, 1 equiv) was dissolved in 10 mL of dry THF and cooled to -78 ºC. LHMDS (1M in THF, 0.41 mL, 0.41 mmol, 1.11 equiv) was added slowly and the reaction mixture was stirred one hour at -78 ºC. Then, solid 1,2-diiodoethane (121 mg, 0.420 mmol, 1.15 equiv) was added and the reaction mixture temperature was raised to rt. After 1h at rt, the reaction was quenched with a mixture of 50 mL of Et_2O + 10 mL of aqueous $Na_2S_2O_3$ (10%). The organic layer was washed with water (2x) and dried over $MgSO_4$, which, after removal of the solvent yielded 148 mg (quantitative yield) of the desired **5a** as a light yellow solid. This compound has been previously described.[4] **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 7.43-7.47 (3H, m), 7.91 (2H, d, *J* = 7.42 Hz).

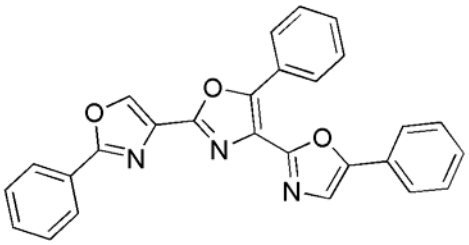
4-Iodo-5,2'-diphenyl-[2,4']bioxazolyl **12**.



A 5 mL microwave vial was charged with oxazol-4-ylboronate **4a** (60 mg, 0.220 mmol, 1 equiv), 2,4-diiodo-5-phenyloxazole **5a** (87 mg, 0.220 mmol, 1 equiv),

$Pd_2(dba)_3$ (10 mg, 5 mol%), PCy_3 (6 mg, 10 mol%), K_2CO_3 (92 mg, 0.660 mmol, 3 equiv) and 4 mL of anhydrous DMF. The microwave vial was then sealed, and the resulting mixture was stirred at rt for about 5 min before it was irradiated 10 min at a pre-selected temperature of 150 °C in a Smith Synthesiser. The vial was then cooled with air jet cooling, it was 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 with Et_2O (2x). 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 **12** (42 mg, 46% yield) as a yellow solid. Mp = 157-159 °C. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.40-7.51 (6H, m), 8.06 (2H, d, J = 7.2 Hz), 8.16 (2H, dd, J_1 = 7.2 Hz, J_2 = 1.1 Hz), 8.34 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 79.34 (quat), 126.22 (CH), 126.40 (quat), 126.89 (CH), 128.64 (CH), 128.83 (CH), 129.23 (CH), 130.94 (quat), 131.15 (CH), 138.67 (CH), 150.20 (quat), 155.64 (quat), 162.87 (quat), (one quaternary centre not found). **HRMS** (ESI) calculated for $C_{18}H_{11}N_2O_2I$ 413.9860 found 413.9859.

5, 5', 2''-Triphenyl-[2, 4', 2', 4''] teroxazole **19**

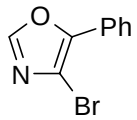


This compound can be synthesised from **12** or from **18**.

A 5 mL microwave vial was charged with bis-oxazole **18** (100 mg, 0.272 mmol, 1 equiv), oxazol-4-ylstannane **4a** (354 mg, 0.816 mmol, 3 equiv), $Pd_2(dba)_3$ (12 mg, 5 mol%), PCy_3 (8 mg, 10 mol%), and 1 mL of anhydrous DMF. The microwave vial was then sealed, and the resulting mixture was stirred at rt for about 5 min before it was irradiated 15 min at a pre-selected temperature of 150 °C in a Smith Synthesiser. The vial was then cooled with air jet cooling, it was opened and poured into a mixture of 30 mL of saturated KF_{aq} and 30 mL of EtOAc and stirred for 30 min.

After this time the organic layer was separated and the aqueous layer was extracted with EtOAc (2x). The organic layers were combined, dried under 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 yellow oil. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.42-7.54 (10H, m), 7.74 (2H, dd, J_1 = 8.4 Hz, J_2 = 1.3 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 123.25 (CH), 124.43 (CH), 125.53 (quat), 126.45 (quat), 126.89 (CH), 127.05 (quat), 127.60 (quat), 127.68 (CH), 128.50 (CH), 128.63 (CH), 128.85 (CH), 128.87 (CH), 129.93 (CH), 131.13 (CH), 138.01 (quat), 139.23 (CH), 150.07 (quat), 151.59 (quat), 154.15 (quat), 155.04 (quat), 162.82 (quat). **HRMS** (ESI) calculated for $C_{27}H_{17}N_3O_3$ 431.1264; found 431.1266.

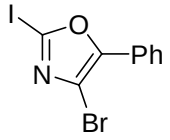
4-Bromo-5-phenyloxazole **16**



4-Bromo-5-phenyloxazole **16** was synthesised using Vedej's protocol[4] with modifications. 5-Phenyloxazole[17] (5,000 g, 34.471 mmol, 1 equiv) was dissolved in 50 mL of dry THF and 40 mL of DMPU (non anhydrous) and cooled to -78 ºC. LHMDS (1M in THF, 55mL, 55 mmol, 1.6 equiv) was added slowly with a syringe. The reaction mixture was stirred 1h at -78 ºC and then neat bromine (2.1 mL, 41.365 mmol, 1.2 equiv) was added drop wise to the reaction mixture, which was stirred for an additional 30 min at -78 ºC. The reaction mixture was then poured into a mixture of 200 mL of TBME + 200 mL of aqueous $Na_2S_2O_3$ (10%) at rt. The two layers were separated and the organic phase was washed 3 times with distilled water, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/TBME 10:0.5 to 10:1) and gave the desired bromooxazole **16** (5.318 g, 69% yield) as a white solid. Mp 60-61 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$)

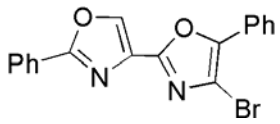
δ 7.37-7.86 (3H, m), 7.86 (1H, s), 7.92-7.95 (2H, m). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 110.90 (quat), 125.51 (CH), 126.69 (quat), 128.75 (CH), 129.06 (CH), 146.66 (quat), 149.58 (CH). **HRMS** (ESI) calculated for $C_9H_6{}^{79}BrNO$ 223.9705 found 223.9709.

2-Iodo-4-Bromo-5-phenyloxazole **17**



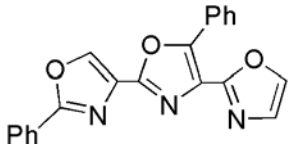
2-Iodo-4-Bromo-5-phenyloxazole **17** was synthesised using Vedej's protocol[4] with minor modifications. 4-Bromo-5-phenyloxazole **16** (5,000 g, 22.315 mmol, 1 equiv) was dissolved in 70 mL of dry THF and cooled to -78 ºC. LHMDS (1M in THF, 27 mL, 27 mmol, 1.21 equiv) was added slowly and the reaction mixture stirred one hour at -78 ºC. Then, solid 1,2-diiodoethane (7.624 g, 26.778 mmol, 1.2 equiv) was added and the reaction mixture and the temperature raised to rt. After 10 min complete consumption of the starting material was observed by HPLC and the reaction was quenched with a mixture of 200 mL of TBME + 200 mL of aqueous $Na_2S_2O_3$ (10%). The two layers were separated and the organic phase was washed 3 times with distilled water (100 mL), dried over magnesium sulphate and concentrated *in vacuo* to give an orange solid which was re-crystallised from toluene to afford 6.698g (86% yield) of pure bis-halooxazole **17** as a white solid. Mp = 104-106 ºC.**^{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 99.31 (quat), 112.48 (quat), 125.31 (CH), 125.92 (quat), 128.73 (CH), 129.39 (CH), 153.06 (quat). **HRMS** (ESI) calculated for C9H5NO ^{79}BrI 365.8594; found 348.8597.

4-Bromo-5,2'-diphenyl-[2,4']bioxazolyl **18**



A 5 mL microwave vial was charged with oxazol-4-ylboronate **4a** (72 mg, 0.265 mmol, 1.2 equiv), 2-iodo-4-bromo-5-phenyloxazole **17** (77 mg, 0.221 mmol, 1 equiv), $Pd(PPh_3)_4$ (13 mg, 5 mol %), K_2CO_3 (92 mg, 0.660 mmol, 3 equiv) and 1 mL of anhydrous DMF. The microwave vial was then sealed, and the resulting mixture was stirred at rt for about 5 min before it was irradiated 10 min at a pre-selected temperature of 150 °C in a Smith Synthesiser. The vial was then cooled with air jet cooling, it was 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 with Et_2O (2x). 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 **18** (65 mg, 81% yield) as a white solid Mp = 139-152 ºC. **^{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 112.30 (q), 125.47 (CH), 126.25 (q), 126.50 (q) 126.79 (CH), 128.64 (CH), 128.76 (CH), 128.94 (CH), 130.87 (q), 131.09 (CH), 138.67 (CH), 146.24 (q), 153.70 (q), 162.77 (q). **HRMS** (ESI) calculated for $C_{18}H_{11}N_2O_2{}^{79}Br$ 365.9998; found 366.0001.

5', 2'',-Diphenyl-[2,4';2',4''] teroxazole **20**



Prepared as compound **19**. A 5 mL microwave vial was charged with bis-oxazole **18** (100 mg, 0.272 mmol, 1 equiv), 2-(Tributylstannyl)oxazole[14] **17** (314 mg, 0.816 mmol, 3 equiv), $Pd_2(dba)_3$ (12 mg, 5 mol%), PCy_3 (8 mg, 10 mol%), and 1 mL of anhydrous DMF. Work up as **19**. The crude obtained was purified by flash chromatography (Silica, hexane/EtOAc 8:2) to give the couple product **20** (63 mg, 60% yield) as white solid. Mp = 179-182 ºC. **^{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 (2H, m), 8.35-8.37 (2H, m), 8.44 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 125.37 (quat), 126.42 (quat), 126.81 (CH), 126.86 (quat), 127.51 (CH), 128.28 (CH), 128.47 (CH), 128.79 (CH), 129.84 (CH), 131.05 (CH), 131.06 (quat), 138.82 (CH), 139.10 (CH), 149.91 (quat), 153.98 (quat), 155.78 (quat), 162.73 (quat). **HRMS** (ESI) calculated for $C_{21}H_{13}N_3O_3$ 355.0951 found 355.0949.

Design of experiments experimental data

The following procedure is identical for each reaction vessel. Reaction 1 (1st fractional design of experiment) is representative: A 5 mL microwave vial was charged with oxazol-4-ylboronate **4a** (66 mg, 0.243 mmol, 1.1 equiv), 2-iodo-4-bromo-5-phenyloxazole **17** (77 mg, 0.221 mmol, 1 equiv), $Pd(PPh_3)_4$ (3 mg, 1 mol %), K_2CO_3 (31 mg, 0.221 mmol, 3 equiv) and 2.6 mL of anhydrous DMF (40 vol).

Once each vessel had been charged with the reactants, they were sealed and irradiated for 1 min at the indicated temperature (150 °C for Reaction 1) in a Smith Synthesiser (Biotage). After this time, each vessel was opened and its contents diluted to 250 mL with distilled water. HPLC samples of each reaction were accordingly prepared. The HPLC yield was obtained by comparing the HPLC areas with an authentic sample of **18** of known concentration:

HPLC yield for reaction 1 is representative:
HPLC area of **18**: 265
HPLC area standard 1 (**18**): 1341 (Conc Std1 0.505 mg/mL)
Molecular weight product: 367.2 g/mol
Number of moles starting material: 0.221 mmol
HPLC yield reaction 1: 31% yield

1st fractional design of experiment data:

	Boronic ester			Catalyst loading		Base equivalents		
Reaction	Mass (mg)	mmol	equiv	Mass (mg)	mol%	mass	mmol	equiv
1	66	0.243	1.10	3	1%	31	0.221	1
2	114	0.420	1.90	3	1%	31	0.221	1
3	66	0.243	1.10	23	9%	31	0.221	1
4	114	0.420	1.90	23	9%	31	0.221	1
5	66	0.243	1.10	3	1%	153	1.105	5
6	114	0.420	1.90	3	1%	153	1.105	5
7	66	0.243	1.10	23	9%	153	1.105	5
8	114	0.420	1.90	23	9%	153	1.105	5
9	90	0.332	1.50	13	5%	92	0.663	3
10	90	0.332	1.50	13	5%	92	0.663	3

	Concentration	Temp	Response		DMF
Reaction	Volumes	° C	Yield %	Area of P (HPLC)	Volume (ml)
1	40	150	31%	265	2.6
2	10	130	67%	577	1.1
3	10	150	73%	632	0.7
4	40	130	69%	591	4.6
5	40	130	57%	492	2.6
6	10	150	45%	389	1.1
7	10	130	74%	636	0.7
8	40	150	40%	342	4.6
9	25	140	69%	595	2.2
10	25	140	68%	590	2.2

2nd Fractional design of experiment

		Boronic ester			Catalyst loading		Base equivalents		
Std	Run	Mass (mg)	mmol	equiv	Mass (mg)	Mol %	Mass (mg)	mmol	equiv
3	1	72	0.265	1.20	13	5%	62	0.442	2
5	2	72	0.265	1.20	13	5%	62	0.442	2
1	3	72	0.265	1.20	13	5%	62	0.442	2
6	4	72	0.265	1.20	13	5%	62	0.442	2
2	5	72	0.265	1.20	13	5%	62	0.442	2
4	6	72	0.265	1.20	13	5%	62	0.442	2

		Concentration	Temp	Response			DMF
Std	Run	Volumes	ºC	Yield %	Area of P (HPLC)	Isolated Yield	Volume (mL)
3	1	20	120	69%	597		1.4
5	2	15	130	78%	674		1.1
1	3	10	120	66%	571		0.7
6	4	15	130	73%	630		1.1
2	5	10	140	77%	668	81%	0.7
4	6	20	140	76%	659	65%	1.4

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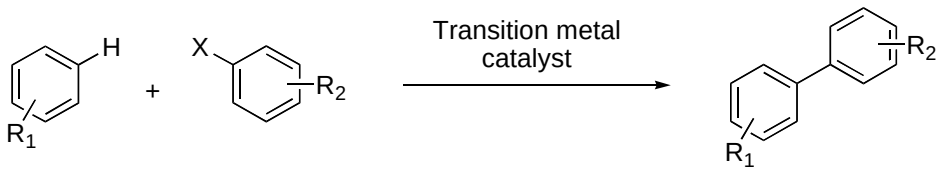
Chapter 4

Direct Arylation of oxazoles at C-2. Synthesis of tris-oxazole fragment of Ulapualide A

4.1 Introduction

Aromatic and heteroaromatic compounds are often found in pharmaceuticals and important biologically active compounds. For a long time, synthetic organic chemists have focused on the development of a variety of methods for the construction of such motifs. Many methods have been developed, however a rapidly expanding one is through the use of transition metal mediated reactions.[1] Typically, these transformations have been carried out with stochiometric quantities of a transition metal that have allowed high yielding transformations under excellent selectivity and high functional group tolerance. Although outstanding improvements have incorporated these processes into industrial applications, disposal of stochiometric activating agents is still a major concern for industry. In addition, preparation of pre-activated aryl substrates is time-consuming and an economically inefficient process. Apart from the difficulty associated with the preparation, the instability of organometallics is also of particular concern for heteroaromatics.[2]

A more advanced variant is the direct coupling of non-activated aryl C-H bonds with activated arene (usually an aryl halide) in the presence of catalysts; typically palladium, rhodium or ruthenium have been used (Scheme 1).[3]



Scheme 1. Direct coupling of nonactivated aryl C-H bond with aryl halides.

The ligands used with the transition metal catalyst are usually phosphines, and they vary depending on the aryl halide. More reactive aryl iodides are commonly associated with electron-rich monodentate phosphines such as PPh_3. However, in order to obtain useful synthetic yields, aryl bromides and chlorides necessarily need more sterically bulky and more electron rich ligands such as trialkyl phosphines, Buchwald's biphenyl phosphines or the popular *N*-heterocyclic carbenes.[4]

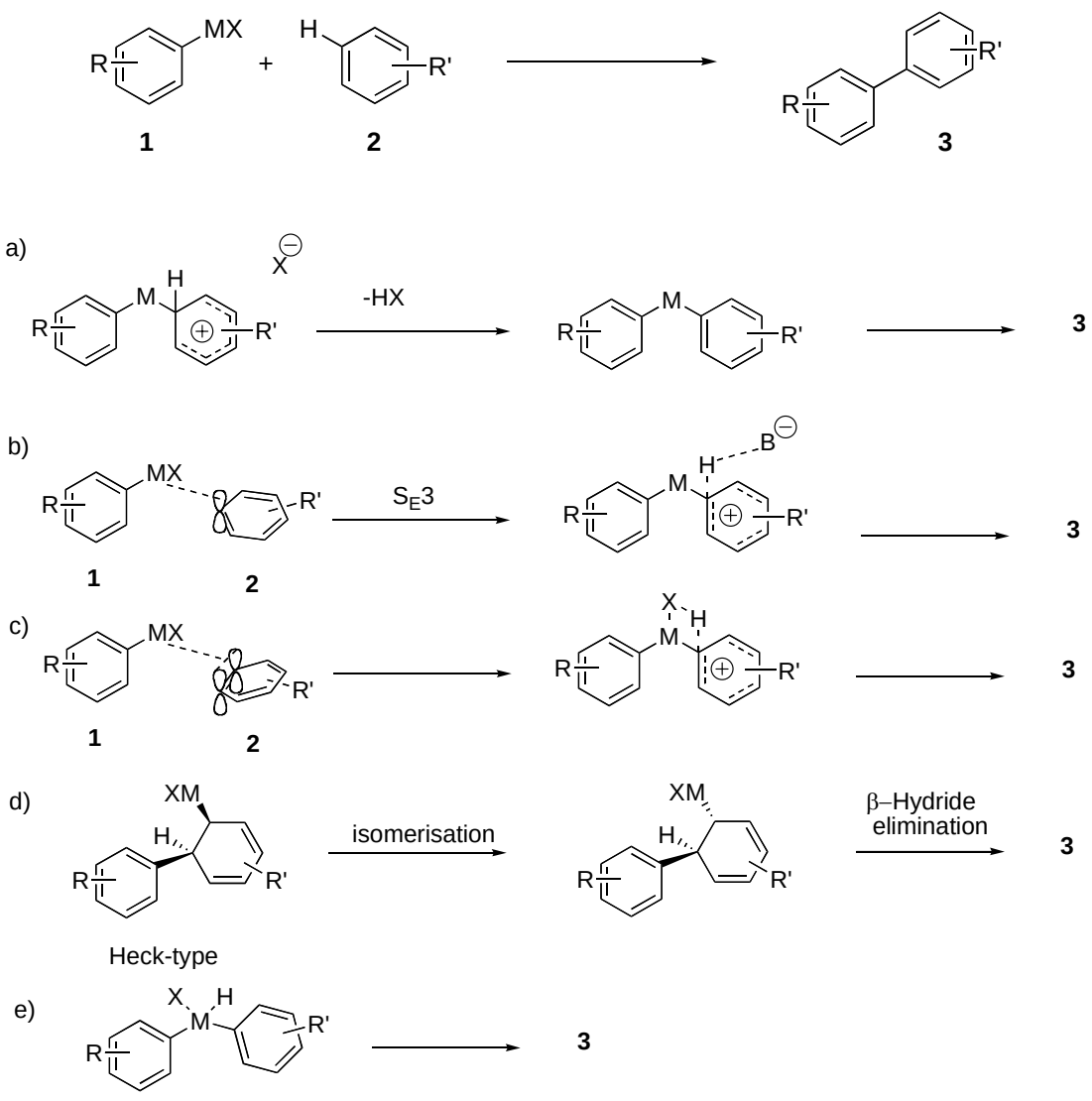
A base is usually required in direct arylation reactions. The exact role of the base still remains a mystery for most systems. Inorganic bases such as K_2CO_3, Cs_2CO_3, KOAc, *t*-BuOK and CsOPiv are usually employed. A solvent is also commonly used in direct arylations, being polar/aprotic the most common ones; although non-polar solvents such as toluene and xylene have successfully been used.

4.2 Mechanism of C-H insertion

Conventionally, direct arylation of arenes is proposed to occur via oxidative addition of the transition metal into the aryl halide followed by one of the carbon-carbon bond forming steps (Scheme 2):[3]

(a) Electrophilic aromatic substitution at the metal (S_EAr).
(b) Concerted S_E3 process.
(c) σ-Bond metathesis.
(d) Heck-type process through a formal β-hydride elimination.
(e) C-H bond oxidative addition

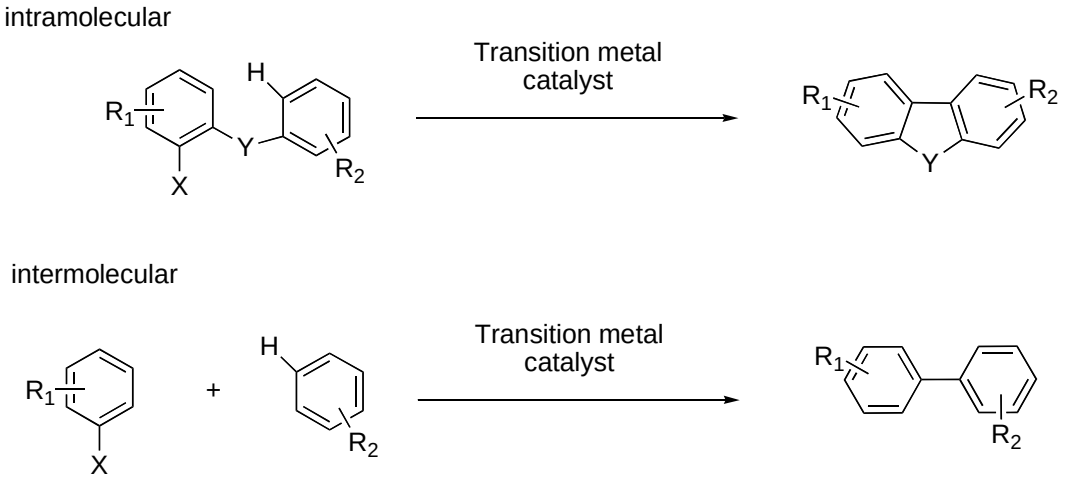
Although these processes have been observed in different systems, the exact mechanism is deeply dependent on the substrate, transition metal, solvent, base and ligand used.[3]



Scheme 2. Mechanisms of C-H insertion.

Regioselectivity

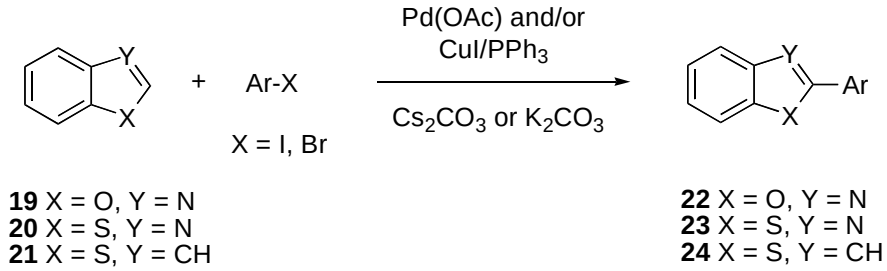
Direct arylation reactions can be performed in either an intramolecular or an intermolecular fashion (Scheme 3).



Scheme 3. Intramolecular Vs intermolecular direct arylation.

Intermolecular reactions are a greater challenge than intramolecular transformations because the catalyst has a higher degree of freedom when reacting with the C-H bond. Factors that influence the regioselectivity of the intermolecular direct arylation are related to the electronics of the arene and also through the use of a directing group.

In the case of azoles, and more particularly oxazoles, Ab initio calculations have revealed that the HOMO, indicating the most electron rich site, resides on C_2 and C_5 carbons of the oxazole ring. Arylation should then occur at these two positions.[5] It is currently believed that the direct arylation at C_5 involves an electrophilic palladation of the azole ring (Scheme 5, equation 1). However, it is the arylation at the C_2 carbon that has generated more controversy in the assignment of a mechanism. Miura and co-workers demonstrated the effect of copper in the arylation on C_2 of various azoles, with the finding that arylation on C_2 could be promoted with the use of CuI. The control experiments indicated that the arylation required both the palladium and copper species to obtain reasonable yields of C_2 arylated products. Given that the hydrogen attached on C_2 is more acidic, the authors hypothesised that the deprotonated form seemed to enable arylation (Scheme 4).[6]

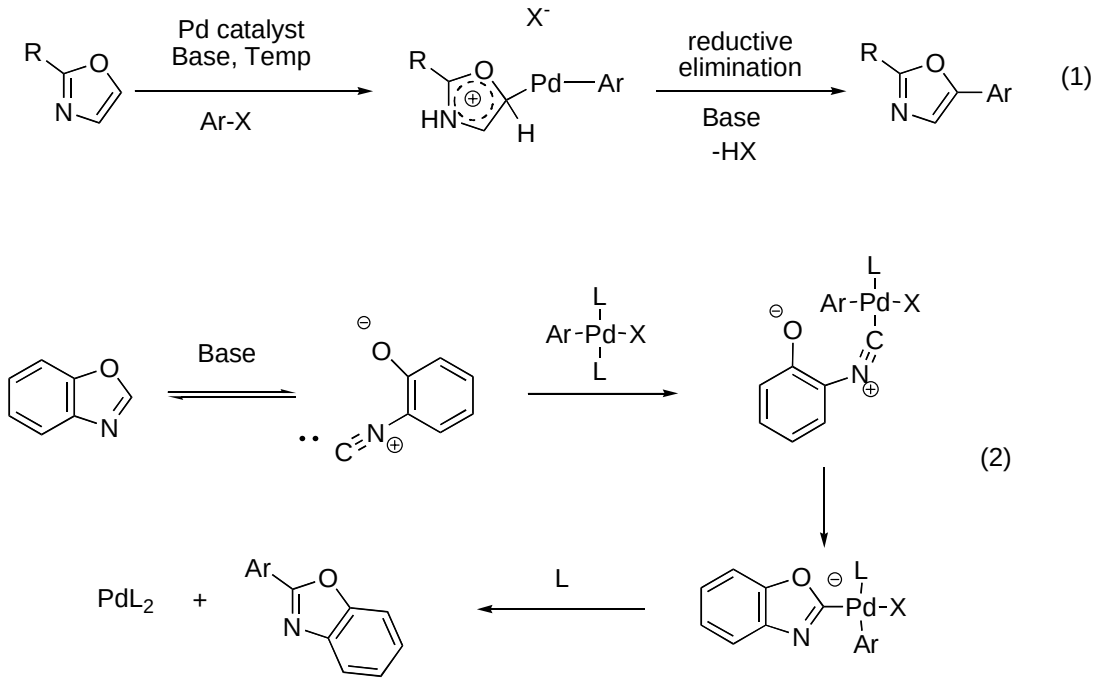


19 X = O, Y = N
20 X = S, Y = N
21 X = S, Y = CH

22 X = O, Y = N
23 X = S, Y = N
24 X = S, Y = CH

Scheme 4. Direct arylation of various azole promoted by CuI.

On the other hand, Hoarau and co-workers found that phenylation on C_2 of 4-oxazole carboxylate with palladium and CuI as a co-catalyst made the reaction fail, whereas the use exclusively of palladium catalysts in conjunction with sterically bulky ligands gave excellent C_2 arylation products. Rather than electronic or directing group factors, regioselectivity was assigned to a less hindered position of the oxazole ring (see Chapter 1).[5]



Scheme 5. Mechanistic pathways for the direct arylation of oxazole in C-5 and benzoxazole in C-2.

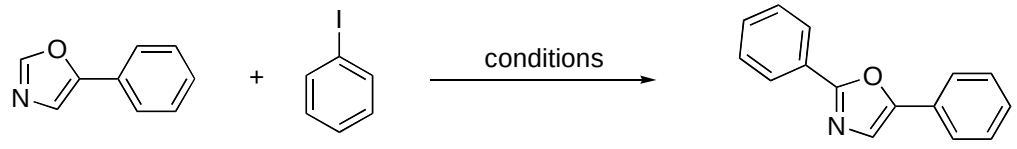
More recently, Zhuravlev and co-workers have disclosed mechanistic studies on the C_2 phenylation of the related benzoxazole system. An anionic mechanism involving deprotonation at C_2 was shown to be operative in contrast to the S_EAr mechanism usually invoked for direct arylation of π-excessive heterocycles (Scheme 5, equation 2).[7] These results have been exemplified by Daugulis who has recently reported a general copper-catalysed method for the C_2 phenylation of a variety of heterocycles including 1,3 oxazole in 59% yield (see Chapter 1).[8] The authors proposed that using copper salts and stronger bases than those usually employed in direct arylations could efficiently promote C_2 reactions. Preliminary mechanistic studies suggested that the reaction proceeded either via a copper-assisted benzyne type mechanism, or by the anionic/deprotonation mechanism previously introduced by Zhuravlev.

4.3 C_2-Direct arylation of oxazoles

In Chapter 3, tris-oxazole structures were achieved using a regioselective Suzuki-Miyaura reaction followed by a Stille coupling. This idea was conceived because of the existence of consecutive C_2-C_4 linked oxazole sequences, which are found in a variety of structurally complex, biologically active natural products. Therefore, control over the synthesis of the C_2-C_4 linkage would potentially lead towards the synthesis of poly-oxazoles as found in natural products. Although noumerous methods exist in the literature for the synthesis of poly-oxazoles, no reports have yet been disclosed using a direct arylation methodology.[9,10] It was envisaged that direct arylation on C_2 of oxazoles could be the beginning of a robust methodology to control the C_2-C_4 bond of poly-oxazoles.

The direct arylation of oxazoles at C_2-H is a relatively unexplored area in the literature with only a handful of examples to be found (see Chapter 1). At the start, preliminary studies were conducted in a series of simple systems. Literature reaction conditions were first explored on the direct phenylation of 5-phenyloxazole (Table 1).

Table 1. Preliminary studies on the C_2 phenylation of 5-phenyloxazole.



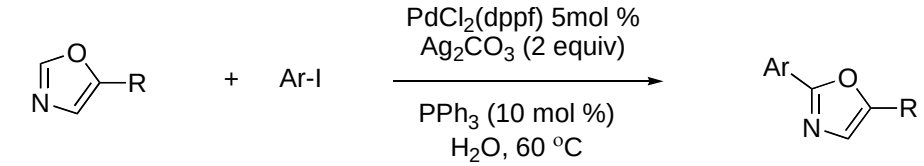
4a **5a** **6a**

Entry	Catalyst	Temp (°C)	Solvent	Base	Reaction time	Yield of **6a**[a]
1	$PdCl_2(dppf)/PPh_3$	60 °C	Water	Ag_2CO_3	17h	77%
2	HBP[b]	110 °C	Toluene	Cs_2CO_3	20h	traces
3	CuI	140 °C	DMF	LiOtBu	30 min	92%

[a] Isolated yield after column chromatography. [b] HBP = Hermann-Beller palladacycle.[12]

The mild conditions developed by Greaney and co-workers for the direct arylation of C_2 substitued azoles at the electron rich C_5 position[11] proved to be successful in this reaction and gave 77% yield of bis-arylated product **6a** as isolated material (entry 1). Surprisingly, the Hermann-Beller palladacycle[12] in toluene only gave traces of **6a** after extensive heating (entry 2). Daugulis' conditions[8] proved to be extremely efficient and gave and excellent 92% of **6** after 30 minutes at 140 °C. The scope of this arylation reaction was next investigated. A range of 2,5-disubstituted oxazoles was synthesised according to C_2 direct arylation of 5-substituted oxazoles **4** with a variety of aryl iodides **5**. Greaney's conditions were chosen due to their mildness and more likely application in natural systems (Table 2, entries 1-14).

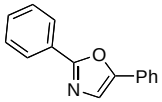
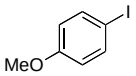
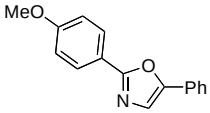
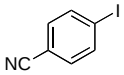
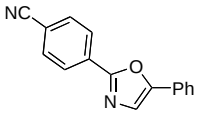
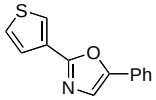
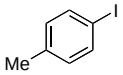
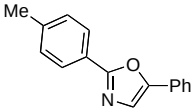
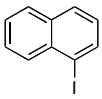
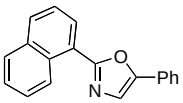
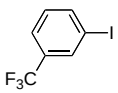
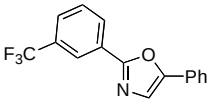
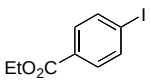
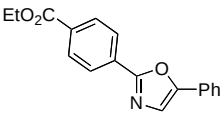
Table 2. C_2 Direct arylation of 5-substituted oxazoles with aryliodides.

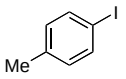
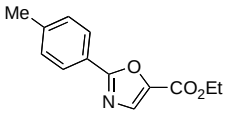
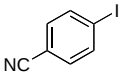
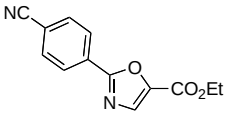
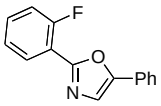
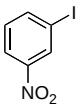
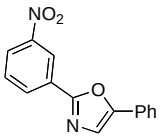
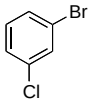
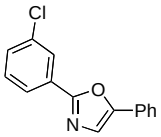
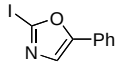
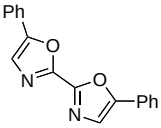


4a R = Ph
4b R = CO_2Et

5

6

Entry	Ar-X	Product	Yield of **6** (%)[a]
1		 **6a**	77
2		 **6b**	89
3		 **6c**	82
4		 **6d**	66
5		 **6e**	87
6		 **6f**	73
7		 **6g**	62
8		 **6h**	80

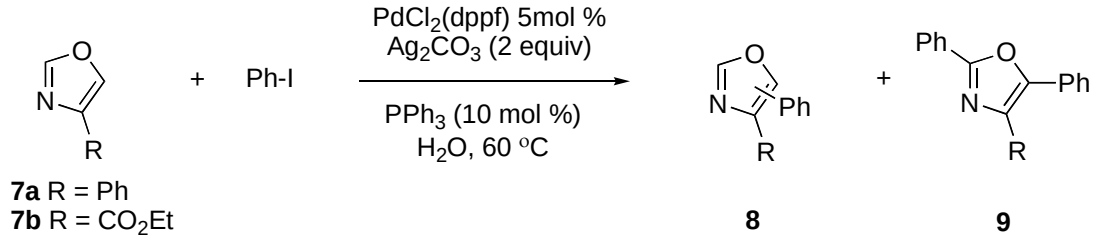
9		 **6i**	67
10		 **6j**	48
11		 **6k**	29
12		 **6l**	0
13		 **6m**	0
14		 **6n**	0

[a]Isolated yield after column chromatography.

Good general reactivity was observed for a range of aryl iodides, affording good to excellent yields of the 2,5-diarylated products (Table 2, entries 1-10). Electron-rich (entries 2, 5 and 9) aryl iodides reacted smoothly in clean transformations. Most electron-poor aryl iodides reacted well (entries 3, 7, 8 and 10), surprisingly though, some of them did not meet the same expectations (entries 11 and 12). It was observed that 3-iodothiophene was a productive coupling partner, producing arylated oxazole **6d** in 66% yield despite the presence of several reactive C-H bonds in its structure (entry 4). On the other hand, 2-iodo-5-phenyl oxazole was inert under the reaction conditions (entry 14). The electron poor oxazole **4b** was effective in the reaction, giving a good 67% yield of product **6i** when combined with 4-iodotoluene and an acceptable 48% yield of product **6j** if coupled with 4-iodobenzonitrile (entries

9 and 10). Direct arylation was attempted on an aryl bromide; however no product could be formed under these conditions (Table 2, entry 13).

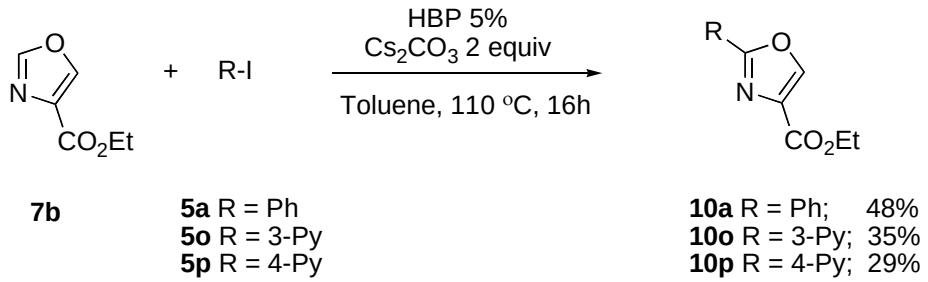
It was then decided to perform some reactions on unsubstituted C_5 oxazoles to observe any regioselective difficulties. The following experiments were carried out: 4-substituted oxazoles **7a-b** were phenylated under Greaney conditions (Scheme 4).



Scheme 4. Direct phenylation of 4-substituted oxazoles.

In both experiments, a mixture of mono- and bis-arylated products **8** and **9** was observed. These results show the conditions to be highly reactive because of their propensity to over-arylate all the compounds present in the reaction mixture.

By analogy to Hoarau's results,[5] oxazole **7b** was submitted to direct arylation conditions using the Hermann-Beller palladacycle (HBP) in toluene with cesium carbonate as a base which resulted in the formation of the C_2 coupling product **10a** exclusively in a moderate 48% yield as isolated material. The same conditions proved successful with 3- and 4-iodopyridine, which also resulted in the formation of the C_2 products **10o** and **10p** in 35% and 29% yield respectively (Scheme 5).

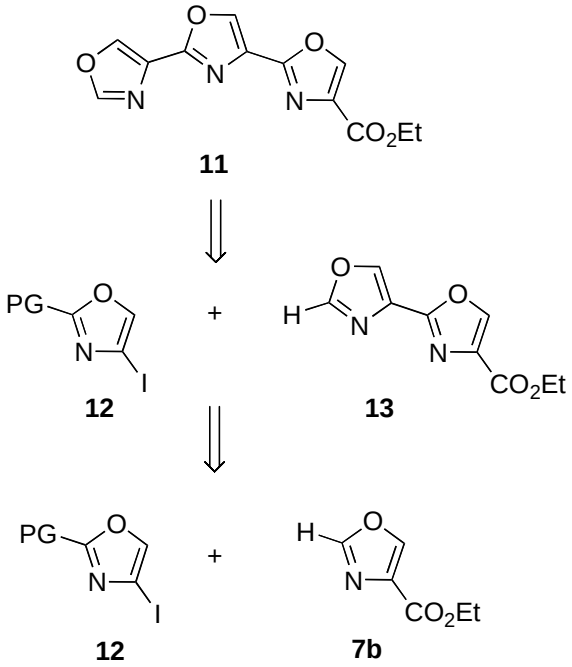


Scheme 5. Direct arylation of 4-oxazolecarboxylate **7b**.

4.4 Synthesis of poly-oxazoles. Synthesis of the tris-oxazole fragment of Ulapualide A.

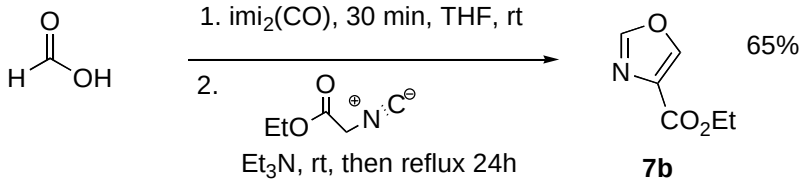
Coupling of two electron-rich heteroaromatics via direct arylation poses a greater synthetic challenge because the products formed usually contain *reactive* C-H bonds that may compete with the starting material to undergo further arylation, producing mixtures of products. The electron-rich oxazole C_5 position is of particular concern, as it is frequently found unsubstituted in natural products and is thus liable to compete with C_2 for arylation. The proposed strategy for tris-oxazole synthesis is shown in Scheme 6.

The direct arylation approach in principle enables a highly efficient route. Starting from the known 4-oxazole carboxylate **7b** and the protected 4-iodooxazole **12**, the target heterocycle **11** could be assembled using just two reactions, direct arylation and deprotection, each repeated once. As demonstrated by Hoarau the C_4 carboxylic ester on **7b** should retard any S_EAr arylation at C_5, whilst promoting coupling at C_2.



Scheme 6. Proposed strategy for the synthesis of tris-oxazoles via direct arylation (PG = Protecting group).

Oxazole **7b** was conveniently synthesised using the method of Schöllkopf and co-workers (Scheme 7).[13]

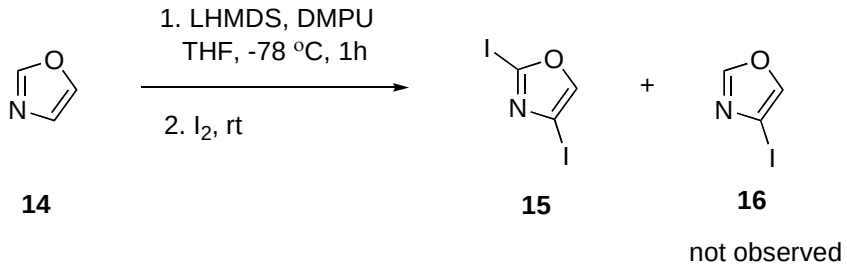


Scheme 7. Synthesis of ethyl 4-oxazolecarboxylate **7b**.

In this reaction, formic acid can be activated using the coupling agent carbonyl diimidazole. Once activated, nucleophilic attack of ethyl isocyanoacetate followed by thermal cyclisation provided oxazole **7b** in a good 65% yield of isolated material.

Following the proposed strategy in Scheme 6, oxazoles corresponding to **12** have not been reported in the literature. Iodination at the oxazole 4-position has been reported by Vedejs, who demonstrated that 5-substituted oxazoles undergo selective 4-iodination when lithiated in the presence of DMPU and iodine.[14] It was intriguing to see if 4-iodooxazole **16** could be accessed directly from the parent 1,3 oxazole **14** using the same reaction conditions. The resulting 4-iodooxazole could then be further functionalised at the C_2 position (Table 3).

Table 3. 2,4 diiodination of 1,3 oxazole



14 **15** **16**

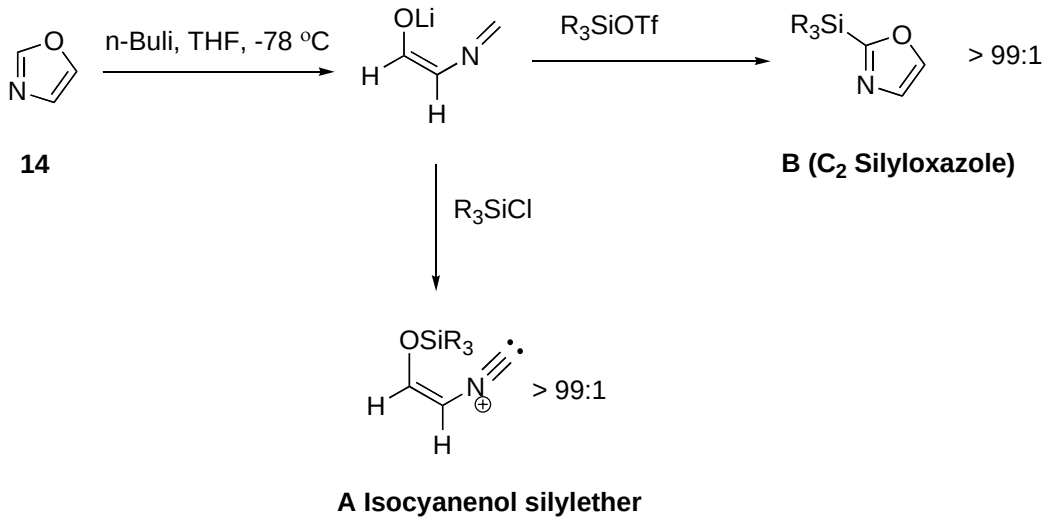
not observed

Entry	Reaction time[a]	Yield of **15** (%)[b]
1	5 minutes	Traces[c]
2	30 minutes	24
3	24 hours	38
4	7 days	64
5	14 days	77

Conditions: 2 equiv of LHMDS and 2 equiv of I_2 were used. [a]Reaction time after addition of I_2. [b]Isolated yields after column chromatography. [c]1 equiv of LHMDS and 1 equiv of I_2 were used.

A first experiment was carried out following the original conditions and, surprisingly, none of the expected 4-iodooxazole **16** was observed. Instead, small amounts of 2,4-diiodooxazole **15** could be isolated as the only product along with unreacted **14** (Table 3, entry 1). We realised that diiodo compound **15** would be useful if the more reactive C_2 iodide could be manipulated regioselectively. The yield of **9** could be improved to 77% using prolonged reaction times and 2 equivalents of both LHMDS and I_2 (Table 2, entries 2-5). Vedejs and co-workers

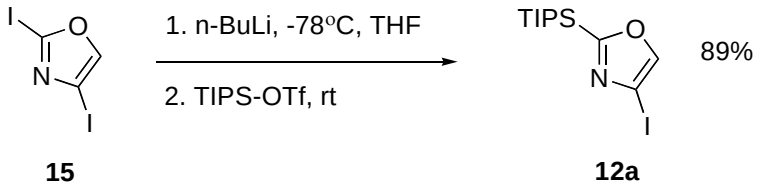
have also observed this increase in yields after a prolonged reaction time in the C_2 chlorination of oxazoles using hexachloroethane as the chlorinating agent.[14] The election of the protecting group was based on the precedents developed by Miller and co-workers. This group had found a dramatic difference in the reactivity of C_2 metalated oxazoles between silyl triflates and silyl chlorides. It had been reported that C_2 silylation of 1,3-oxazole **14** was accomplished by treatment with n-BuLi followed by quenching with silyltriflates yielding >99:1 C-silylated oxazole **B** versus isocyanenol silylether **A** (Scheme 8).[15]



Scheme 8. Silylation of 1,3-oxazole with silyl triflates and silyl chlorides.

Additionally, it had been noted that the TIPS (triisopropyl) derivative was a stable and practical protecting group throughout aqueous workups (non acidic) and column chromatography.

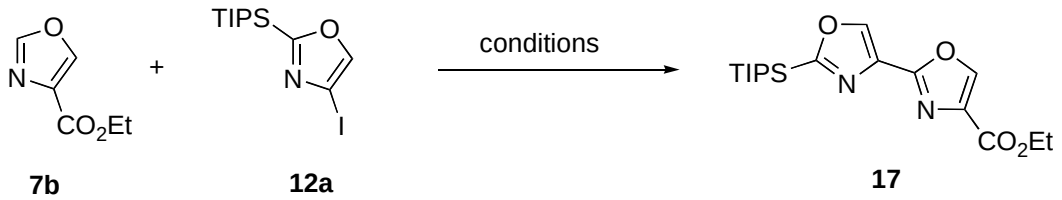
The requisite protecting group was successfully installed at C_2 of **15** via selective lithiation and quenching with TIPS-OTf producing the 2-silyl-4-iodooxazole **12a** in an excellent 89% yield. (Scheme 9).



Scheme 9. Selective TIPS-silylation of diiodooxazole **15**.

With ester **7b** and iodide **12a** in hand, the first direct arylation was attempted. A wide range of conditions was examined for this reaction (Table 4).

Table 4. Optimisation of conditions for the direct coupling of **7b** with **12a**.



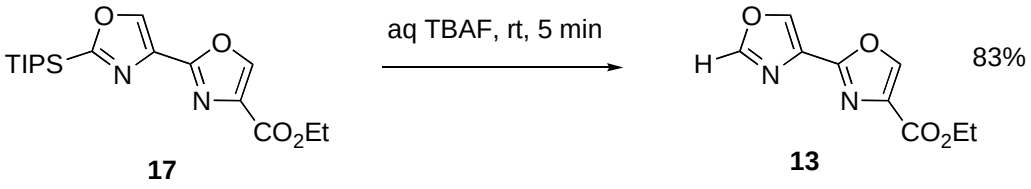
Entry	Catalyst	Ligand	Solvent	Yield of **17** (%)[c]
1[a]	$PdCl_2$(dppf)	PPh_3	Water	traces
2[b]	CuI	none	DMF	0
3	$Pd(OAc)_2$	P(o-Tol)$_3$	Toluene	38
4	$Pd(OAc)_2$	P(o-Tol)$_3$	DMF	0
5	$Pd(OAc)_2$	IMes	Toluene	Complex mixture
6	$Pd(OAc)_2$	X-PHOS	Toluene	Complex mixture
7	PEPPSI-IPr	none	Toluene	51
8	PEPPSI-IPr	none	1,4-dioxane	60
9	PEPPSI-IPr	none	DMF	40
10	HBP	none	Toluene	81
11	HBP	none	1.4-dioxane	46
12	HBP	none	DMF	14

HBP = Herman-Beller palladacycle. Conditions: 1 equiv of **12a** and 1.2 equiv of **7b**, 5 mol % of catalyst and 10 % mol of ligand, 1 mL of solvent, 2 equiv of Cs_2CO_3 and 110 °C in a sealed tube were used. [a]2 equiv of Ag_2CO_3 and 60 °C were used. [b]10 mol % of CuI.

Disappointingly, previously successful C_2 direct arylation conditions on water proved to be ineffective for iodide **12a**, giving only traces of the desired bis-oxazole **17** with a slow reaction rate being observed (entry 1). The copper-catalyzed arylation conditions recently described by Daugulis[8] were likewise unsuccessful with complete degradation of **12a** being observed after 30 min at 140 °C (entry 2). The first successful coupling was observed using Pd(OAc)/P(o-Tol)$_3$ in toluene, which gave bis-oxazole **17** in a modest 38% yield (entry 3). Switching to the more polar DMF, a common direct arylation solvent, under the same system completely degraded **12a** after 30 min at 110 °C (entry 4). The use of very bulky/electron rich Imes or XPHOS ligands only led to inseparable complex mixtures (entries 5 and 6).

A substantially better catalyst for this reaction proved to be the N-heterocyclic carbene based palladium complex PEPPSI-IPr,[16] which gave modest to good yields in DMF, toluene and 1,4-dioxane (entries 9, 7 and 8 respectively). Finally, it was found that the Herman-Beller palladacycle[12] in toluene gave a very good 81% yield of the bis-oxazole (entry 10). Lower yields were obtained if 1,4-dioxane or DMF were used as solvents in the reaction (entries 11 and 12).

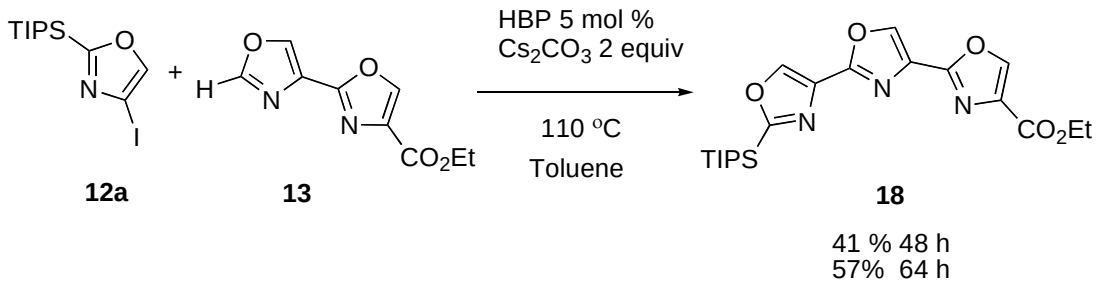
Deprotection of **17** was slow and low yielding under the reported acid conditions,[17] but successful using aqueous TBAF solution giving bis-oxazole **13** in 83% yield after 5 min at rt (Scheme 10).



Scheme 10. Deprotection of silylated **17** using aqueous TBAF.

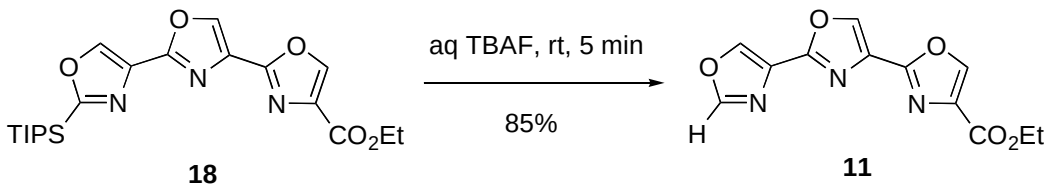
With an efficient route to bis-oxazole **13** established, synthesis of tris-oxazole **11** was first attempted. The second arylation was also performed using the Hermann-

Beller catalyst and, successfully, afforded tris-oxazole **18** in a 41% yield. Concentration of the reaction mixture and longer reaction times proved benefitial and tris-oxazole **18** could be isolated in 57 % of isolated product (Scheme 11).



Scheme 11. Synthesis of tris-oxazole **18** via direct arylation.

Facile deprotection with aqueous TBAF gave the tris-oxazole fragment found in Ulapualide A in 85% yield (Scheme 12).



Scheme 12. Synthesis of tris-oxazole fragment of Ulapualide A.

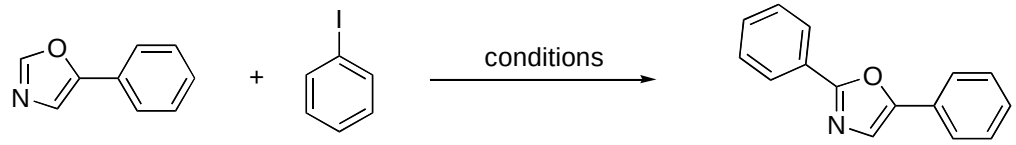
Removal of the TIPS protecting group was carried out as a second step; however, as an alternative, after the arylation reaction the reaction mixture could be quenched with aqueous TBAF (1M) to obtain deprotected **13** or **11** in a one pot procedure (see Conclusions, Scheme **13**).

4.5 Conclusions

The tris-oxazole fragment found in the Ulapualide A family of natural products was synthesised in four steps using a C_2 direct arylation method.

At the start, literature conditions were explored and a general C_2 direct arylation was successfully applied to the synthesis of 2,5-diarylated oxazoles. It is interesting to analyse some of the preliminary results. As shown in the introduction, in oxazoles, direct arylation should occur at the C_2 and C_5 carbons of the oxazole ring. Many more conditions have proved successful for the direct arylation of oxazoles on C_5 compared to C_2.[3c] In fact, before this work only three reports on C_2 direct arylation had been disclosed. The first report by Hoarau using ethyl 4-oxazolecarboxylate, followed by Belina's using the unsubstitued 1,3 oxazole[18] and then Daugulis also with the parent 1,3 oxazole. No reports have shown successful C_2 direct arylation on 5-phenyloxazole for example. A priori, this should be an easy transformation because C_5 is blocked and since C_4 is not nucleophilic enough only C_2 may be arylated. In fact, this arylation is not as straightforward as it may seem. In Table 1, three different reaction conditions were applied to the phenylation of 5-phenyl oxazole.

Table 1. Preliminary studies on the C_2 phenylation of 5-phenyloxazole.

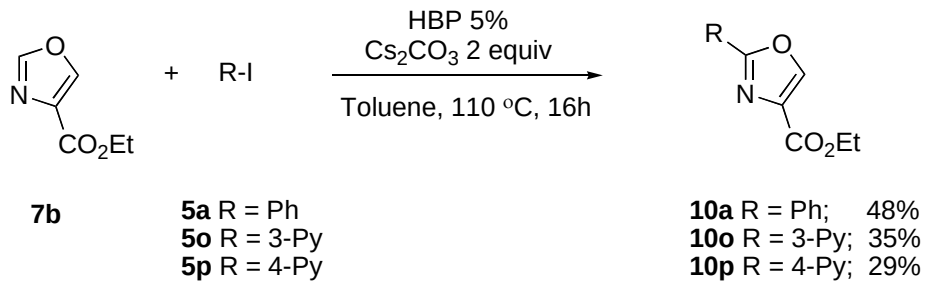


4a **5a** **6a**

Entry	Catalyst	Temp (°C)	Solvent	Base	Reaction time	Yield of **6a**[a]
1	$PdCl_2(dppf)/PPh_3$	60 °C	Water	Ag_2CO_3	17h	77%
2	HBP[b]	110 °C	Toluene	Cs_2CO_3	20h	traces
3	CuI	140 °C	DMF	LiOtBu	30 min	92%

[a] Isolated yield after column chromatography. [b] HBP = Hermann-Beller palladacycle.[12]

Surprisingly, the Herman-Beller palladacycle did not catalyse the reaction at all. The reason behind this behaviour is due to electronics of the ring since steric hindrance is unlikely in this case. If the oxazole ring is C_4 substituted with a carboxylic ester then C_2 phenylation occurs in a decent 48% yield (Scheme 4).



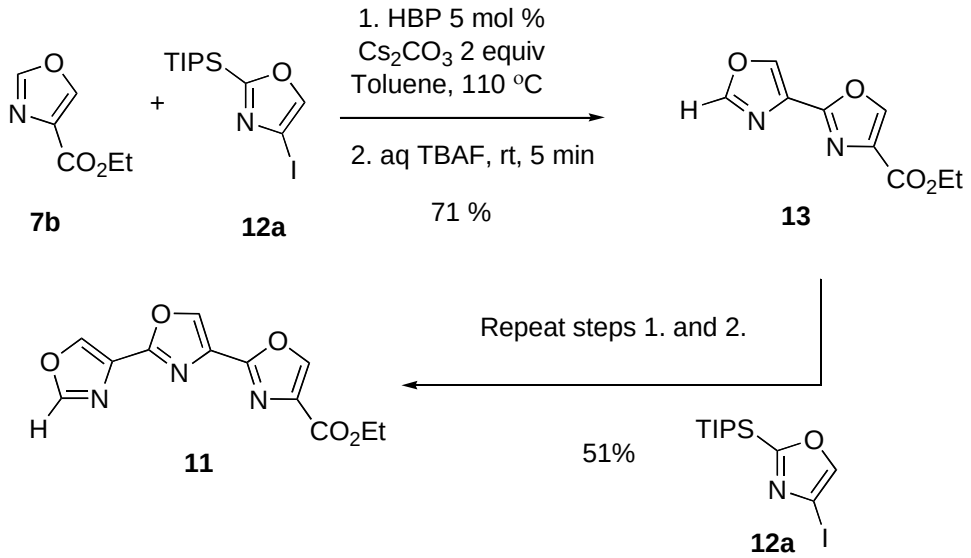
Scheme 4. Direct arylation of 4-oxazolecarboxylate **7b**.

This suggests that some *activation* of the ring in **7b** might be operating in favour of the anionic mechanism shown by Zhuralev.[7] On the other hand, Daugulis' conditions did work very well, the use of a strong base deprotonates C_2-H facilitating the ring opening of the oxazole to give to coupling product in high yield (Table 1, entry 3). These results confirm the anionic mechanism to be operative and more favourable than the electrophilic aromatic substitution in the C_2 direct arylation of oxazoles.

Tris-oxazole construction began with the synthesis of a key intermediate 4-iodooxazole **12a** equipped with a silyl protecting group in C_2. This compound was obtained from 2,4-diiodooxazole. This later compound is a remarkably useful building block in oxazole synthesis because it combines the 2,4-disubstitution pattern and also an unsubstituted C_5 carbon. Those features are commonly found in oxazole-containing natural products.[19] Despite the obvious qualities of such intermediate, no synthetic equivalents have been yet released to the scientific community. This is hardly surprising because several synthetic equivalents are well known in the related

1,3-thiazole system, illustrating the disparity in reactivity between oxazoles and thiazoles.[20]

The first coupling was carried out through the examination of a range of different conditions and, as a result, bis-oxazole intermediate **13** could be synthesised efficiently. Finally, after a facile deprotection reaction, the same sequence was applied to **13** which, after the same deprotection conditions, gave the desired fragment of the natural product Ulapualide A. It has been noted that removal of the protecting group could be carried out as an extension of the work up, after the arylation reactions rendering the overall synthesis to just two steps (Scheme 13).



Scheme 13. Overall synthesis of the tris-oxazole fragment contained in Ulapualide A.

Given that bis-oxazole **13** has 3 potentially reactive C-H bonds, in addition to the 3 reactive C-H bonds of the product **18**, all potentially competing in the reaction mixture, the medium yield obtained for the second arylation was accepted as a reasonable result. The fact that it is possible to obtain high levels of complexity such as tris-oxazoles structures in a minimum number of synthetic steps makes this method highly desirable. On the other hand, only catalytic amounts of metallic complexes are needed to carry out the transformations avoiding the activation of coupling partners with stochiometric amounts of metals.

4.6 Future work

Many recently discovered natural products contain the oxazole heterocycle ring system. Appart from other applications, these natural compounds are potentially pharmacological interesting substances, therefore, technological developments to synthesise them will possibly benefit the society in a long-term basis.

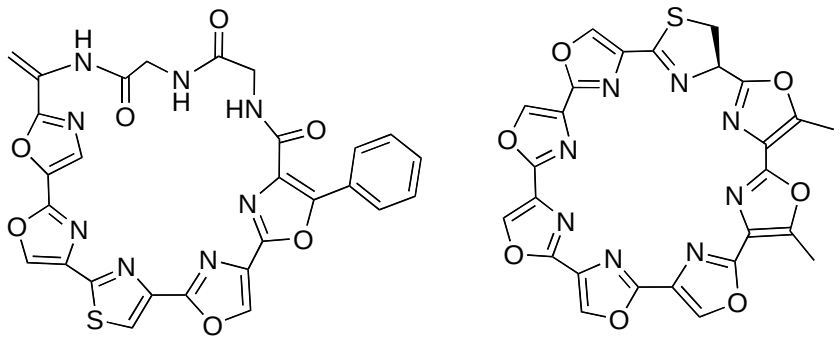
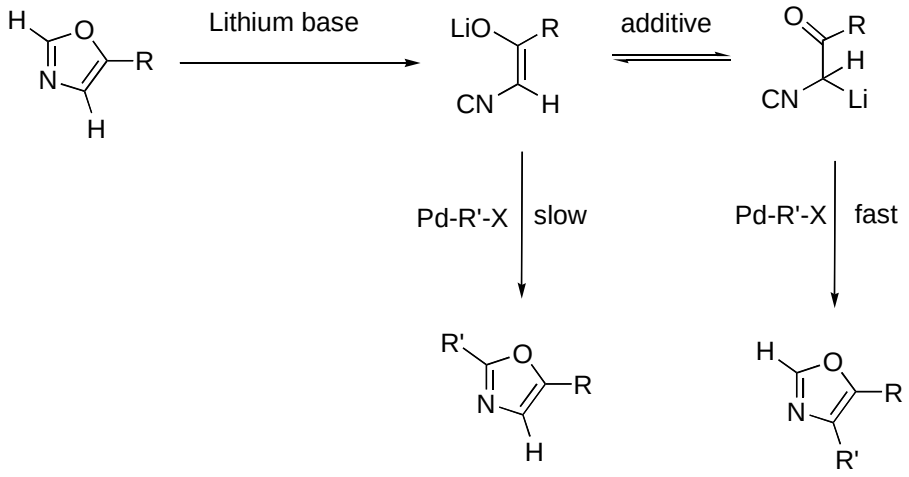


Figure 1. Oxazole-contaning natural products.

From the very beginning, this work has focused on the intention of developing an understanding on how to funcionalise oxazoles via palladium cross-couplings reactions, always having in mind the goal of applying these results into natural substances. Because most of these fascinating natural substances are found in a poly-oxazole form, the project has concentrated on the creation of oxazole-oxazole bonds in various positions of its ring for the synthesis of bis- or tris-oxazoles as contained in several natural products. In this context, the best results have been obtained with direct arylations, and this is where future work should focus in.

Positions C_2-H and C_5-H have been successfully arylated, however without activation or forcing conditions the more electron-deficient C_4-H still remains a challenge. On Chapter 1 interesting chemistry regarding the ring-opening of oxazoles when treated with lithium bases was disclosed. Early results pointed that electrophiles react either on positions 2 or 4 depending on the conditions used. On

the other hand, Daugulis[8] and Zhuralev[7] have recently shown a ring-opening pathway for the arylation on C_2 of azoles. Under the right conditions it is very likely that direct arylation could be directed to position 4 of the ring (Scheme 14).



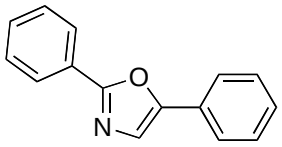
Scheme 14. Direct arylation of oxazoles on C_4-H

The use of a lithium strong base would induce the ring-opening of the oxazole, the electrophile would consist on the oxidative addition product of an aryl halide with a palladium catalyst and additives like DMPU, DMF should provide means to arylate the 4 position.

After controlling the 4-position the synthetic chemist will have two different tools based on direct arylation to assemble poly-oxazoles and, in this way, challenging molecules such as Telomestain or IB-01211 could be efficiently synthesised (Figure 1).

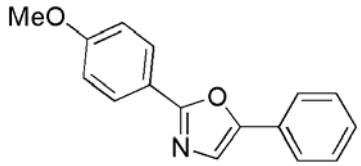
4.7 Experimental procedures Chapter 4

Representative procedure for the direct arylation of 5-substituted oxazoles with aryl iodides on water: 2,5-Diphenyloxazole 6a



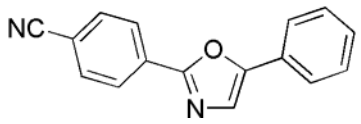
A 5 mL microwave vial was charged with 5-phenyloxazole[21] (50 mg, 0.345 mmol, 1 equiv), phenyliodide (86 mg, 0.414 mmol, 1.2 equiv), $PdCl_2$(dppf)·DCM (14 mg, 5 mol %), Ag_2CO_3 (190 mg, 0.690 mmol, 2 equiv) and PPh_3 (9 mg, 10 mol %). A magnetic stirrer bar was added and the mixture of solids was gently stirred for a few seconds to ensure all solids were well mixed. Distilled water (2 mL) was added and the vial was covered with a serum cap. The vial and its contents were then heated and stirred in a pre-heated oil bath at 70 °C for 16 h. After this time the reaction mixture was cooled down to rt and poured into a mixture of brine (20 mL) and DCM (10 mL). The vial was thoroughly rinsed with an additional 20 mL of DCM. The organic layer was separated, and the aqueous phase extracted twice with DCM. The organic layers were combined, dried over magnesium sulphate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexane/EtOAc 9:1) to afford the coupled product **6a** as a white solid (56 mg, 77 % yield). This compound is known.[22] **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 7.35 (1H, m), 7.52-7.43 (6H, m), 7.74-7.72 (2H, m), 8.13-8.11 (2H, m). **^{13}C-NMR** (90 MHz, $CDCl_3$), δ 161.13 (quat), 151.24 (quat), 130.31 (CH), 128.92 (CH), 128.80 (CH), 128.42 (CH), 128.00 (quat), 127.43 (quat), 126.26 (CH), 124.18 (CH), 123.43 (CH).

5-Phenyl-2-(4-methoxyphenyl)oxazole **6b**



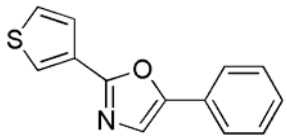
Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 9:1) to afford the coupled product **6b** as a white solid (77 mg, 89 % yield). This compound is known.[22] **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 3.88 (3H, s), 7.00 (1H, dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz), 7.33-7.45 (6H, m), 7.63 (1H, m), 7.70 (2H, d, J = 7.63). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 55.32 (CH_3), 110.85 (CH), 116.68 (CH), 118.65 (CH), 123.31 (CH), 124.09 (CH), 127.85 (quat), 128.35 (CH), 128.50 (quat), 128.81 (CH), 129.81 (CH), 151.19 (quat), 159.78 (quat), 160.91 (quat).

5-Phenyl-2-(4-cyanophenyl)oxazole **6c**



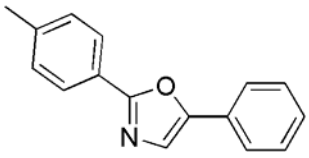
Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 8.5:1.5) to afford the coupled product **6c** as a white solid (70 mg, 82 % yield). **Mp** = 174-175 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 7.38 (1H, d, J = 6.4 Hz), 7.49-7.44 (3H, m), 7.76-7.70 (4H, m), 8.18 (2H, d, J = 7.3 Hz). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 113.37 (quat), 118.31 (quat), 124.00 (CH), 124.35 (CH), 126.47 (CH), 127.31 (quat), 128.99 (CH), 128.99 (CH), 131.04 (quat), 132.57 (CH), 152.39 (quat), 159.06 (quat). **HRMS** (ESI) calculated for $C_{13}H_{10}N_2O_3$ 242.06859; found 242.06849.

5-Phenyl-2-thiophene-3-yl-oxazole **6d**



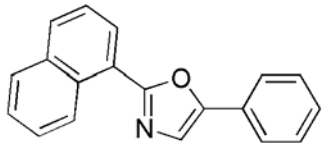
Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 9:1) to afford the coupled product **6d** as a white solid (52 mg, 66 % yield). **Mp** = 38-41 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) 7.33-7.45 (5H, m), 7.67-7.71 (3H, m), 7.99 (1H, dd, J_1 = 3.0 Hz, J_2 = 1.2 Hz). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 122.97 (CH), 124.04 (CH), 125.21 (CH), 125.88 (CH), 126.67 (CH), 127.84 (quat), 128.30 (CH), 128.84 (CH), 129.36 (quat), 150.49 (quat), 158.11 (quat). **HRMS** (ESI) calculated for $C_{13}H_9NOS$ 227.0399; found 227.0402.

5-Phenyl-2-*p*-tolyl-oxazole **6e**



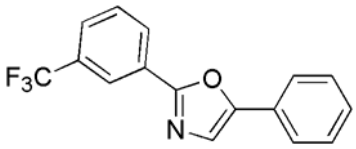
Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 9:1) to afford the coupled product **6e** as a white solid (71 mg, 87 % yield). This compound is known.[22] **^{1}H-NMR** (360 MHz, $CDCl_3$) 2.51 (3H, s), 7.45-7.37 (3H, m), 7.56-7.51 (3H, m), 7.81 (2H, 7.81, dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 8.10 (2H, d, J = 8.2 Hz).**^{13}C-NMR** (90 MHz, $CDCl_3$) δ 21.47 (CH_3), 123.23 (CH), 124.00 (CH), 124.63 (quat), 126.13 (CH), 127.98 (quat), 128.20 CH), 128.80 (CH), 129.43 (CH), 140.52 (quat), 150.80 (quat), 161.26 (quat).

5-Phenyl-2-naphtalen-1-yl-oxazole **6f**



Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 9.8:0.2) to afford the coupled product **6f** as a white solid (68 mg, 73 % yield). This compound is known.[22] **^{1}H-NMR** (360 MHz, $CDCl_3$) 7.37 (1H, t, *J* = 7.4 Hz), 7.48 (2H, t, *J* = 7.6 Hz), 7.56-7.60 (3H, m), 7.69 (1H, ddd, J_1 = 8.5 Hz, J_2 = 6.8 Hz, J_3 = 1.4 Hz), 7.79 (2H, dd, J_1 = 8.3 Hz, J_2 = 1.1 Hz), 7.92 (1H, *J* = 8.2 Hz), 7.97 (1H, d, *J* = 8.2 Hz), 8.31 (1H, dd, J_1 = 7.3 Hz, J_2 = 1.2 Hz), 9.37 (1H, d, *J* = 8.6 Hz). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 123.99 (CH), 123.86 (quat), 124.26 (CH), 124.91(CH), 126.13 (CH), 126.23 (CH), 127.52 (CH), 127.69 (CH), 127.95 (quat), 128.43 (CH), 128.52 (CH), 128.91 (CH), 130.12 (quat), 131.11 (CH), 133.92 (quat), 150.90 (quat), 160.98 (quat).

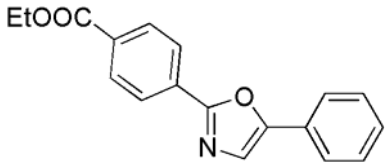
5-Phenyl-2-(3-trifluoromethyl-phenyl)-oxazole **6g**



Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 9.2:0.8) to afford the coupled product **6g** as a white solid (62 mg, 62 % yield). **Mp**= 125-128 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$)

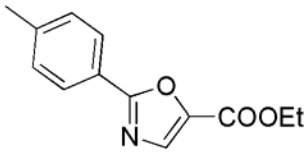
7.36 (1H, *J* = 7.4 Hz), 7.46-7.48 (3H, m), 7.60 (1H, t, *J* = 7.8 Hz), 7.71 (3H, t, *J* = 8.0 Hz), 8.27 (1H, d, *J* = 7.8 Hz), 8.36 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 123.04 (CH, d, *J* = 3.67 Hz), 123.59 (CH), 123.76 (CF_3, *J* = 272.45 Hz), 124.30 (CH), 126.66 (CH, d, *J* = 3.49 Hz), 127.58 (quat), 128.17 (quat), 128.76 (CH), 128.97 (CH), 129.24 (CH), 129.38 (CH), 131.42 (quat, q, *J* = 65.63 Hz), 151.91 (quat), 159.63 (quat). **HRMS** (ESI) calculated for $C_{16}H_{10}F_3NO$ 289.07090; found 289.07082.

4-(-5-Phenyl-oxazol-2-yl)-benzoic acid ethyl ester **6h**



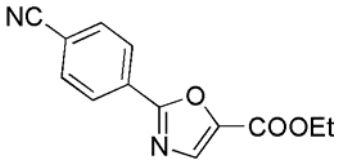
Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 9:1) to afford the coupled product **6h** as a white solid (81 mg, 80 % yield). **Mp** = 116-117 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) 1.41 (3H, t, *J* = 7.1 Hz), 4.40 (2H, q, *J* = 7.1 Hz), 7.34 (1H, t, *J* = 7.3 Hz), 7.41-7.46 (3H, m), 7.70 (2H, d, *J* = 7.1 Hz), 8.13 (4H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.25 (CH_3), 61.16 (CH_2), 123.77 (CH), 124.24 (CH), 125.92 (CH), 127.59 (quat), 128.66 (CH), 128.88 (CH), 129.94 (CH), 130.96 (quat), 131.62 (quat). **HRMS** (ESI) calculated for $C_{18}H_{15}N_1O_3$ 293.10464; found 293.10434.

2-*p*-Tolyl-oxazole-5-carboxylic acid ethyl ester **6i**



Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 9:1) to afford the coupled product **6i** as an oil (55 mg, 67 % yield). **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.40 (3H, t, *J* = 7.1 Hz), 2.40 (3H, s), 4.40 (2H, q, *J* = 7.1 Hz), 7.28 (2H, dd, J_1 = 8.6 Hz, J_2 = 0.6 Hz), 7.81 (1H, s), 8.02 (2H, d, *J* = 8.2 Hz). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.27 (CH_3), 21.58 (CH_3), 61.36 (CH_2), 123.66 (quat), 127.16 (CH), 129.59 (CH), 135.30 (CH), 141.98 (quat), 142.14 (quat), 157.91 (quat), 164.44 (quat). **HRMS** (ESI) calculated for $C_{13}H_{13}NO_3$ 231.08899; found 231.08898.

2-(4-Cyano-phenyl)-oxazole-5-carboxylic acid ethyl ester **6j**

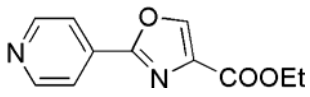


Synthesized according to the general procedure. The residue was purified by flash chromatography (silica, hexane/EtOAc 9:1) to afford the coupled product **6j** as a white solid (41 mg, 48% yield). **Mp** = 115-116 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.41 (3H, t, *J* = 7.1 Hz), 4.42 (2H, q, *J* = 7.1 Hz), 7.78 (2H, d, *J* = 8.7 Hz), 7.86 (1H, s), 8.24 (2H, d, *J* = 8.7 Hz). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.23 (CH_3), 61.76

(CH_2), 114.86 (quat), 117.95 (quat), 127.55 (CH), 130.06 (quat), 132.67 (CH), 135.33 (CH), 143.17 (quat), 157.44 (quat), 161.96 (q). **HRMS** (ESI) calculated for $C_{13}H_{10}N_2O_3$ 242.0686; found 242.0687.

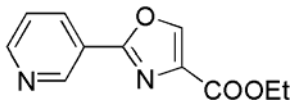
Synthesis of 2,4-diarylated products 10a, 10o and 10p. The synthesis of 10p is representative.

2-Pyridin-4-yl-oxazole-4-carboxylic acid ethyl ester **10p**.



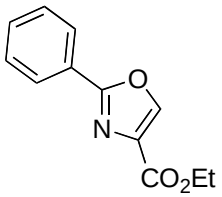
A 5 mL microwave type vial was charged with 50 mg of 4-iodopyridine (50 mg, 0.236 mmol, 1 equiv), 4-oxazolecarboxylate[13] **7b** (40 mg, 0.283 mmol, 1.2 equiv), Hermann's palladacycle (11 mg, 5 mol %), Cs_2CO_3 (155 mg, 0.472 mmol, 2 equiv) and anhydrous toluene (2 mL). The vial was equipped with a magnetic stirrer bar, sealed and flushed with N_2. The vial and its contents were heated and stirred in a preheated oil bath at 110 °C for 16 h. After this time the vial was cooled to rt and the reaction mixture was filtered through CELITE®. After filtration, the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica, EtOAc) to give the coupled product **10p** as a yellow solid (15 mg, 29% yield). Mp = 109-110 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 7.13 Hz), 4.43 (2H, q, J = 7.13 Hz), 7.95 (2H, dd, J_1 = 4.50 Hz, J_2 = 1.65 Hz), 8.34 (1H, s), 8.77 (2H, dd, J_1 = 4.50 Hz, J_2 = 1.55 Hz). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.28 (CH_3), 61.57 (CH_2), 120.31 (CH), 133.29 (q), 135.24 (q), 144.54 (CH), 150.66 (CH), 160.13 (q), 160.81 (q). **HRMS** (ESI) calculated for $C_{11}H_{10}N_2O_3$ 218.0686; found 218.0683.

2-Pyridin-3-yl-oxazole-4-carboxylic acid ethyl ester **10o**.



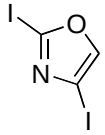
Synthesised as **10o**. Starting from 3-iodopyridine. The residue was purified by flash column chromatography (silica, Hexanes/EtOAc 8:2) to give the coupled product **10o** as a yellow solid (15 mg, 29% yield). Mp = 97-98 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.405 (3H, t, J = 7.14 Hz), 4.43 (2H, q, J = 7.14 Hz), 7.42 (1H, ddd, J_1 = 8.04 Hz, J_2 = 4.86 Hz, J_3 = 0.82 Hz), 8.32 (1H, s), 8.37-8.41 (1H, m), 8.72 (1H, dd, J_1 = 4.86 Hz, J_2 = 1.66 Hz), 9.32 (1H, dd, J_1 = 2.15, J_2 = 0.70 Hz). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.29 (CH_3), 61.48 (CH_2), 122.74 (q), 123.59 (CH), 134.10 (CH), 134.93 (q), 144.11 (CH), 147.95 (CH), 151.79 (CH), 160.14 (q), 160.99 (q). **HRMS** (ESI) calculated for $C_{11}H_{10}N_2O_3$ 218.0686; found 218.0682.

2-Phenyl-oxazole-4-carboxylic acid ethyl ester **10a**.



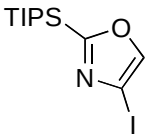
Synthesised as **10o**. Starting from phenyliodide. The residue was purified by flash column chromatography (silica, Hexanes/EtOAc 9:1) to give the coupled product **10a** as a yellow solid (25 mg, 48% yield). This coumpound is known.[23] **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.32 (3H, t, J = 7.13 Hz), 4.40 (2H, q, J = 7.13 Hz), 7.43-7.45 (3H, m), 8.08 (2H, dd, J_1 = 7.51 Hz, J_2 = 2.10 Hz), 8.25 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.21, 61.22, 126.32, 126.74, 128.75, 131.00, 134.61, 143.62, 161.30, 162.30.

2,4-Diiodooxazole **15**



The compound was synthesised according to Vedejs' procedure with modifications.[14] 1,3-Oxazole (1.00 mL, 14.900 mmol, 1 equiv) was dissolved into a mixture of anhydrous THF (6.4 mL), anhydrous DMPU (5.2 mL), and cooled to -78 ºC. LHMDS (32.80 mL, 1M in THF, 2.2 equiv) was then added dropwise and stirred for 1 h. After this time, solid iodine (7.600 g, 29.800 mmol, 2 equiv) was added to the reaction mixture and stirred for an additional 30 min at -78 ºC. The cooling bath was then removed and the reaction mixture was left to warm to rt and stirred for 14 days under a low positive pressure of N_2. The reaction mixture was then poured into a mixture of aqueous $Na_2S_2O_3$ (10%, 100 mL) and diethyl ether (100 mL). The organic layer was washed with brine (100 mL) and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 9:1) to give the title compound **15** (3.701 g, 77 % yield) as a white solid. **Mp** = 98-100 ºC. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 7.76 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 83.12 (quat), 101.56 (quat), 148.93 (CH). **HRMS** (ESI) calculated for $C_3H_1NOI_2$ 320.8142; found 320.8145.

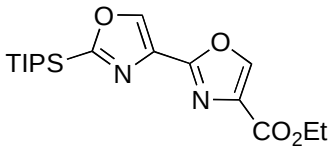
4-Iodo-2-triisopropylsilanyl-oxazole **12a**



2,4-Diiodooxazole **15** (500 mg, 1.558 mmol, 1 equiv) was dissolved in dry THF (15 mL) and cooled to -78 ºC. *n*-BuLi (1.17 mL, 1.870 mmol, 1.2 equiv) was added dropwise to the cooled solution and the mixture was stirred for 20 min.

Triisopropylsilyl trifluoromethanesulfonate (0.44 mL, 1.636 mmol, 1.05 equiv) was then added slowly and the reaction mixture was stirred an additional 10 min at -78 ºC. At this point the cooling bath was removed and the reaction mixture was stirred for an additional 30 min at room temperature. The reaction mixture was quenched with water (50 mL) and diluted with diethyl ether (50 mL), the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexanes/DCM, 8:2) yielded 487 mg (yield 89%) of the desired product **15** as a light yellow oil. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.11 (18H, d, *J* = 7.2 Hz), 1.34-1.46 (3H, m), 7.79 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 10.90 (CH), 18.28 (CH_3), 81.83 (quat), 144.47 (CH), 171.00 (quat). **HRMS** (ESI) calculated for $C_9H_8N_2O_4$ 351.0510; found 351.0500. Further purification can be obtained by Kügelrohr distillation (recommended for the direct couplings).

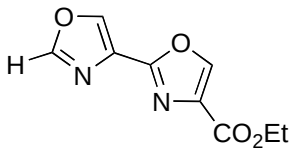
2'-Isopropylsilanyl-[2,4']-bioxazolyl-4-carboxylic acid ethyl ester **12**



A 5 mL microwave type vial was charged with 50 mg of **12a** (50 mg, 0.142 mmol, 1 equiv), 4-oxazolecarboxylate[13] **7b** (25 mg, 0.177 mmol, 1.2 equiv), Hermann's palladacycle (7 mg, 5 mol %), Cs_2CO_3 (93 mg, 0.284 mmol, 2 equiv) and anhydrous toluene (1 mL). The vial was equipped with a magnetic stirrer bar, sealed and flushed with N_2. The vial and its contents were heated and stirred in a preheated oil bath at 110 °C for 16 h. After this time the vial was cooled to rt and the reaction mixture poured into a mixture of water (20 mL) and Et_2O (30 mL). The organic phase was separated and the aqueous layer was re-extracted twice with Et_2O. The organic layers were combined, dried over magnesium sulphate and after filtration the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica, hexane/EtOAc 9:1) to give the coupled product **17** as a yellow oil (42 mg, 81%

yield). **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.18 (18H, d, *J* = 7.50 Hz), 1.38 (3H, t, *J* = 7.14 Hz), 1.40-1.49 (3H, m), 4.45 (2H, q, *J* = 7.14 Hz), 8.27 (1H, s), 8.52 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 10.91 (CH), 14.27 (CH_3), 18.28 (CH_3), 61.33 (CH_2), 129.63 (quat), 134.41 (quat), 141.98 (CH), 143.44 (CH), 156.42 (quat), 161.08 (quat), 170.52 (quat). **HRMS** (ESI) calculated for $C_{18}H_{28}N_2O_4Si$ 364.1813; found 364.1809.

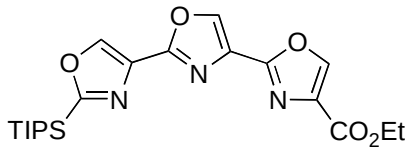
[2,4']Bioxazolyl-4-carboxylic acid ethyl ester **13**



A 10 mL round bottom flask was charged with **17** (97 mg, 0.266 mmol, 1 equiv), THF (5 mL) and aqueous TBAF (1 M, 0.41 mL, 0.410 mmol, 1.5 equiv). The reaction mixture was stirred for 5 min at rt, then diluted with water and extracted thrice with DCM. The organic phase was washed with saturated aqueous NH_4Cl, brine (2 ×) and dried over magnesium sulphate, which after filtration and concentration *in vacuo* gave bis-oxazole **13** as a white solid (88 mg, 83% yield). **Mp** = 117-119 ºC. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.34 (3H, t, *J* = 7.1 Hz), 4.36 (2H, q, *J* = 7.1 Hz), 7.98 (1H, s), 8.26 (1H, s), 8.37 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.17 (CH_3), 61.33 (CH_2), 129.48 (quat), 134.48 (quat), 139.65 (CH), 143.62 (CH), 151.78 (CH), 151.78 (CH), 155.33 (quat), 160.79 (quat). **HRMS** (ESI) calculated for $C_9H_8N_2O_4$ 208.0479; found 208.0480.

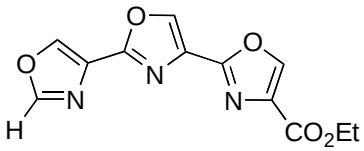
Alternatively, compound **13** can be prepared by re-diluting the dry crude from the previous step with 5 mL of THF, adding TBAF (0.14 mL, 1M in THF, 1.0 equiv) and stirring 5 min at rt. The mixture was then diluted with DCM and washed with NH_4Cl and brine (2 ×), dried over magnesium sulphate and after filtration the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica, hexane/EtOAc 1:1) to give the coupled product **13** as a white solid (21 mg, 71% yield, 2 steps).

2''-Triisopropylsilanyl-[2,4';2',4''] teroxazole-4-carboxylic acid ethyl ester **18**



A 5 mL microwave type vial was charged with 50 mg of **12a** (50 mg, 0.142 mmol, 1 equiv), **13** (35 mg, 0.170 mmol, 1.2 equiv), Herman's palladacycle (7 mg, 5 mol%), Cs_2CO_3 (93 mg, 0.284 mmol, 2 equiv) and anhydrous toluene (2 mL). The vial was equipped with a magnetic stirrer bar, sealed and flushed with N_2. The vial and its contents were then heated and stirred in a preheated oil bath at 110 °C for 48 h. After this time the vial was cooled to rt and the reaction mixture was poured into a mixture of water (20 mL) and Et_2O (30 mL). The organic phase was separated and the aqueous layer was re-extracted twice with Et_2O. The organic layers were combined, dried over magnesium sulfate and after filtration the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica, hexane/EtOAc 8:2) to give the title compound **18** (25 mg, 41% yield) as a yellow oil. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.14 (18H, d, *J* = 7.48 Hz), 1.38 (3H, t, *J* = 7.13 Hz), 1.46-1.55 (3H, m), 4.41 (2H, q, *J* = 7.13 Hz), 8.30 (1H, s), 8.42 (1H, s), 8.53 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 10.91 (CH_3), 14.29 (CH), 18.28 (CH_3), 61.40 (CH_2), 129.57 (quat), 130.64 (quat), 134.61 (quat), 139.19 (CH), 141.94 (CH), 143.65 (CH), 155.52 (quat), 156.87 (quat), 160.88 (quat), 170.68 (quat). **HRMS** calculated for $C_{21}H_{29}N_3O_5Si$ 432.1949; found 432.1945.

[2, 4';2'; 4''] Teroxazole-4-carboxylic acid ethyl ester **11**



A 10 mL round bottom flask was charged with **18** (50 mg, 0.116 mmol, 1 equiv), THF (4 mL) and aqueous TBAF (1 M, 0.17 mL, 0.170 mmol, 1.5 equiv). The reaction mixture was stirred for 5 min at rt, diluted with water and extracted thrice with DCM. The organic phase was washed with aqueous saturated NH_4Cl, brine (× 2) and dried over magnesium sulphate, which after filtration and concentration gave tris-oxazole **11** as a white solid (27 mg, 85% yield). **Mp** = 207-208 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.39 (3H, t, *J* = 7.1 Hz), 4.42 (2H, q, *J* = 7.1 Hz), 8.03 (1H, d, *J* = 0.9 Hz), 8.31 (1H, s), 8.41 (1H, d, *J* = 0.9 Hz), 8.43 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.28 (CH_3), 61.45 (CH_2), 129.58 (quat), 130.87 (quat), 134.69 (quat), 139.41 (CH), 139.69 (CH), 143.75 (CH), 151.93 (CH), 155.30 (quat), 155.89 (quat), 160.86 (quat). Mp = 209-211 °C. **HRMS** calculated for $C_{12}H_9N_3O_5$ 275.0537; found 275.0531.

Alternatively, compound **11** can be prepared by re-diluting the dry crude from the previous step with 5 mL of THF, adding TBAF (0.14 mL, 1M in THF 1.0 equiv) and stirring 5 min at rt. The mixture was then diluted with DCM and washed with NH_4Cl and brine (2 ×), dried over magnesium sulphate and after filtration the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica, hexane/EtOAc 3:7) to give the coupled product **11** as a white solid (20 mg, 51% yield, 2 steps).

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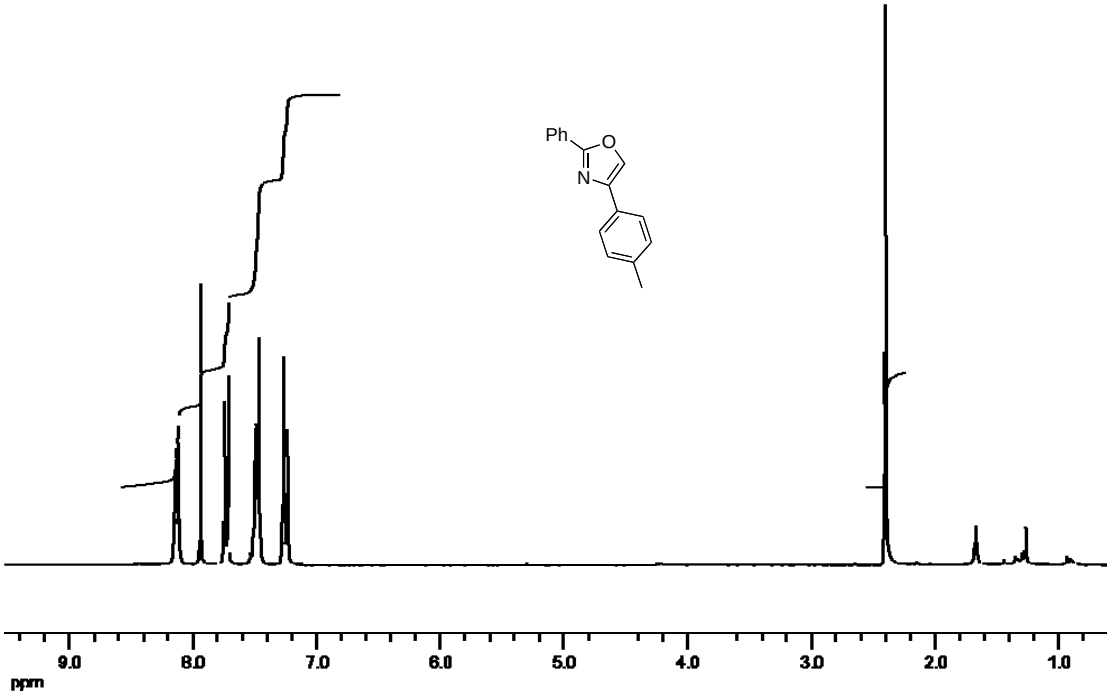
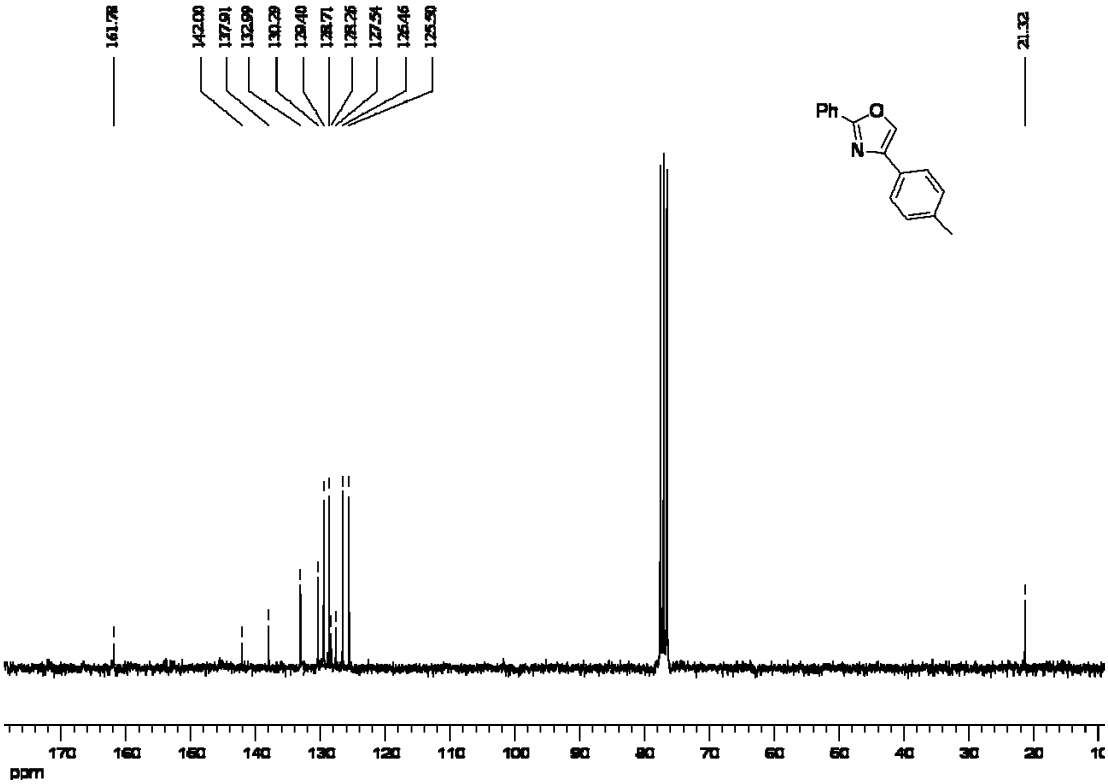
Appendix A

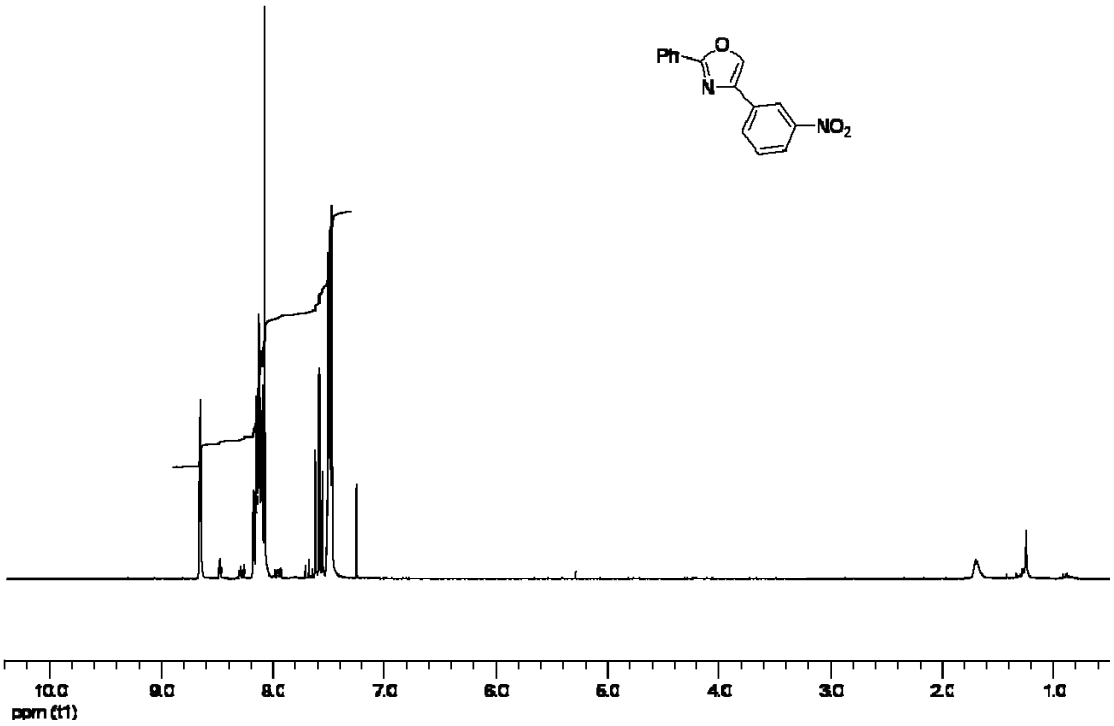
Spectroscopic Data for Chapter 2

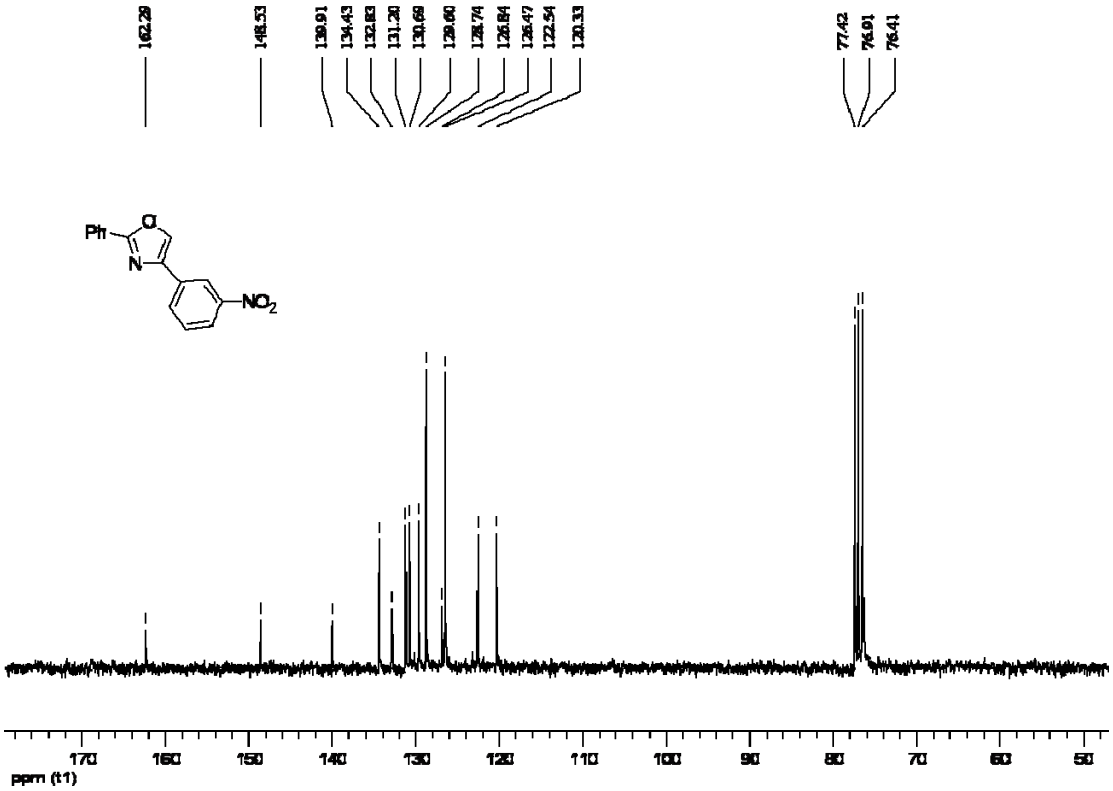
^{1}H NMR and ^{13}CNMR of 2-Phenyl-4-p-tolyloxazole **10a**



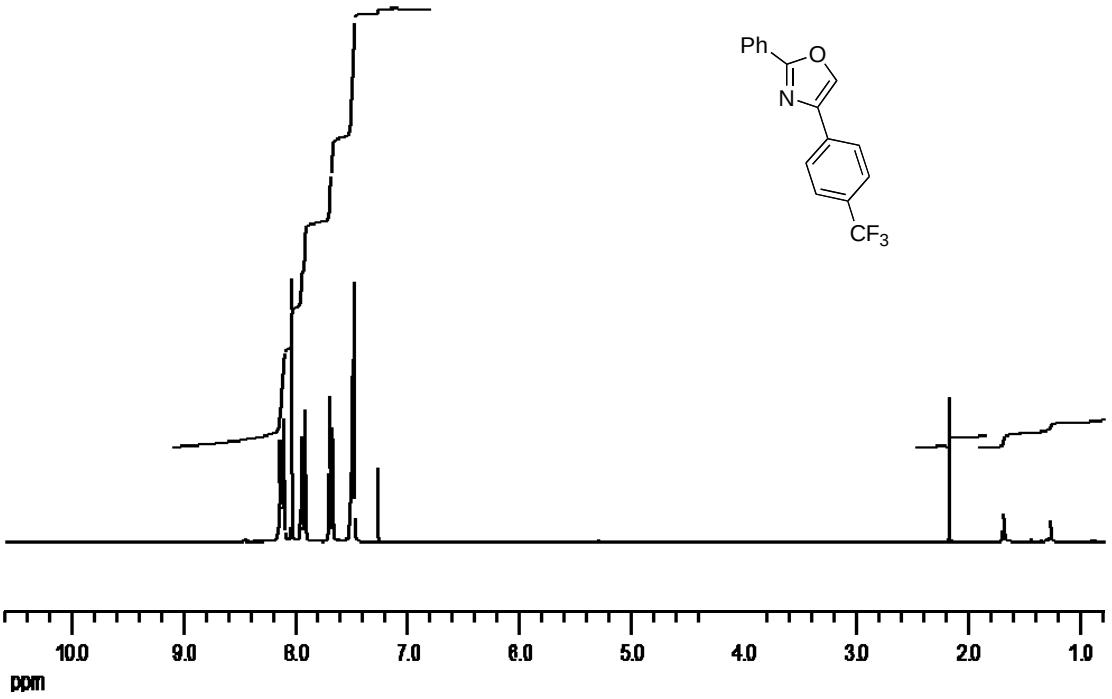


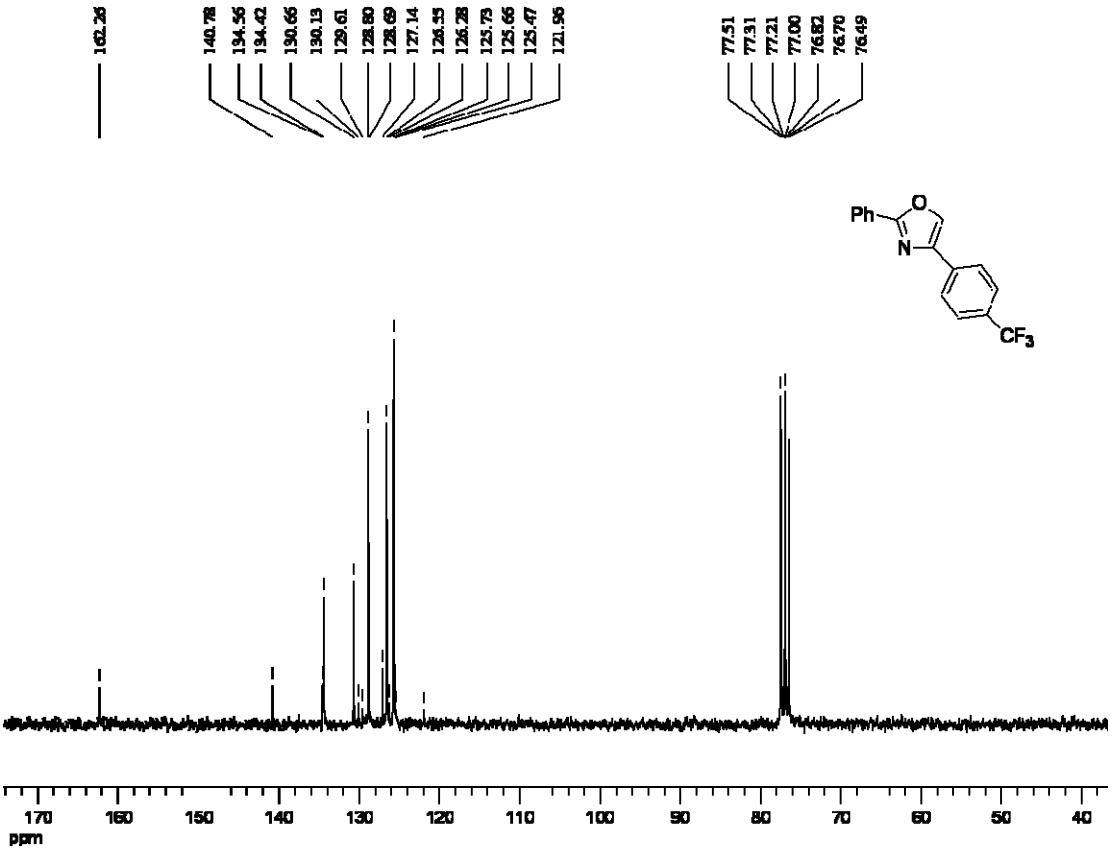
^{1}H and ^{13}C NMR of 4-(3-Nitrophenyl)-2-phenyloxazole **10b**



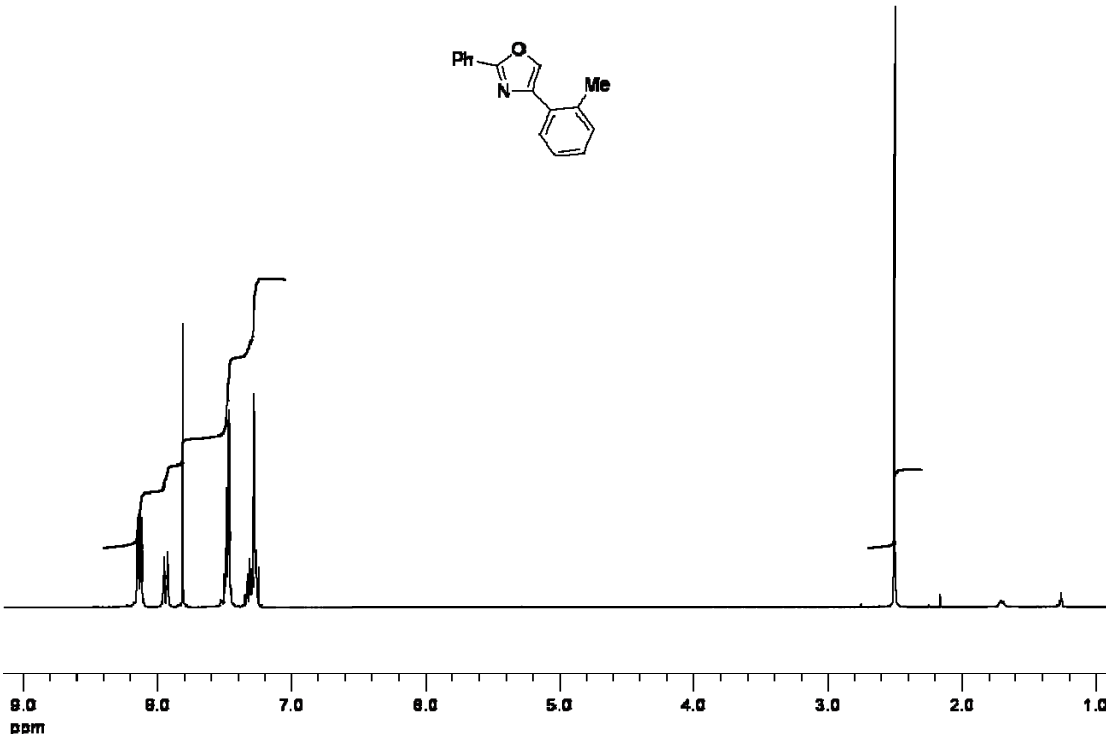


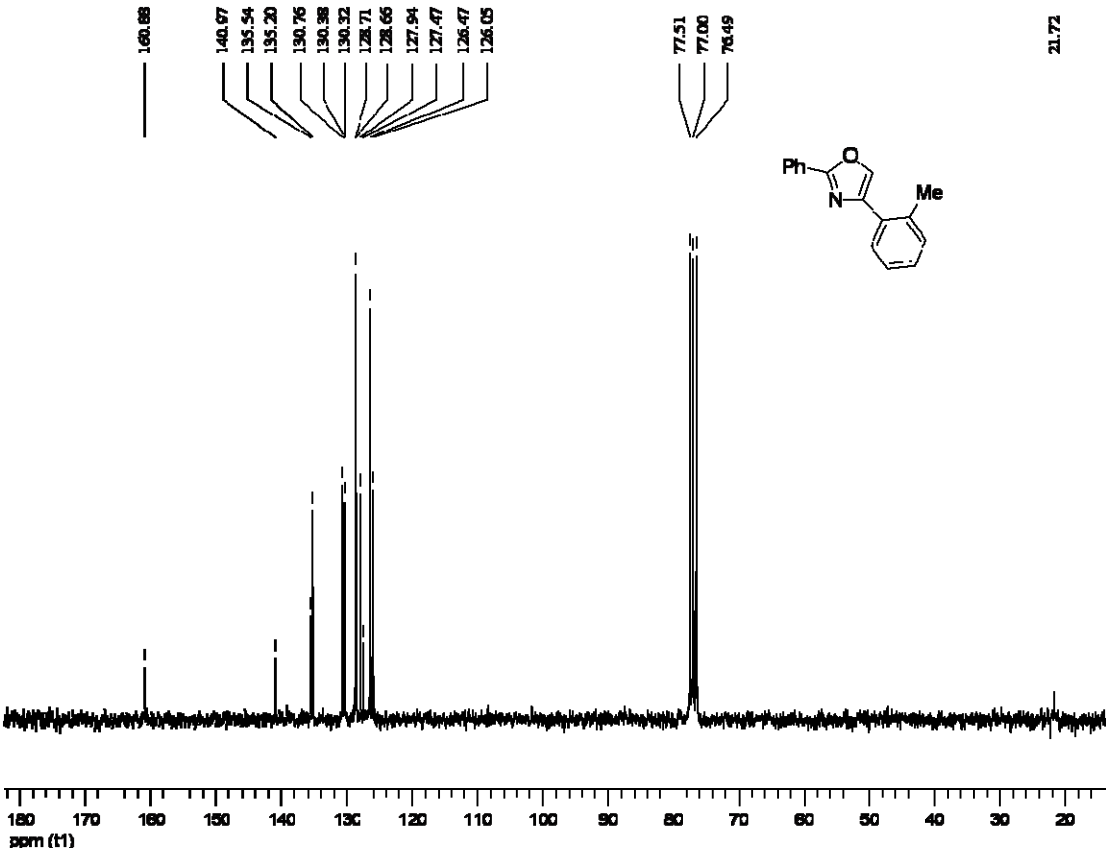
^{1}H and ^{13}C NMR of 2-Phenyl-4-(4-(trifluoromethyl)phenyl)oxazole **10c**



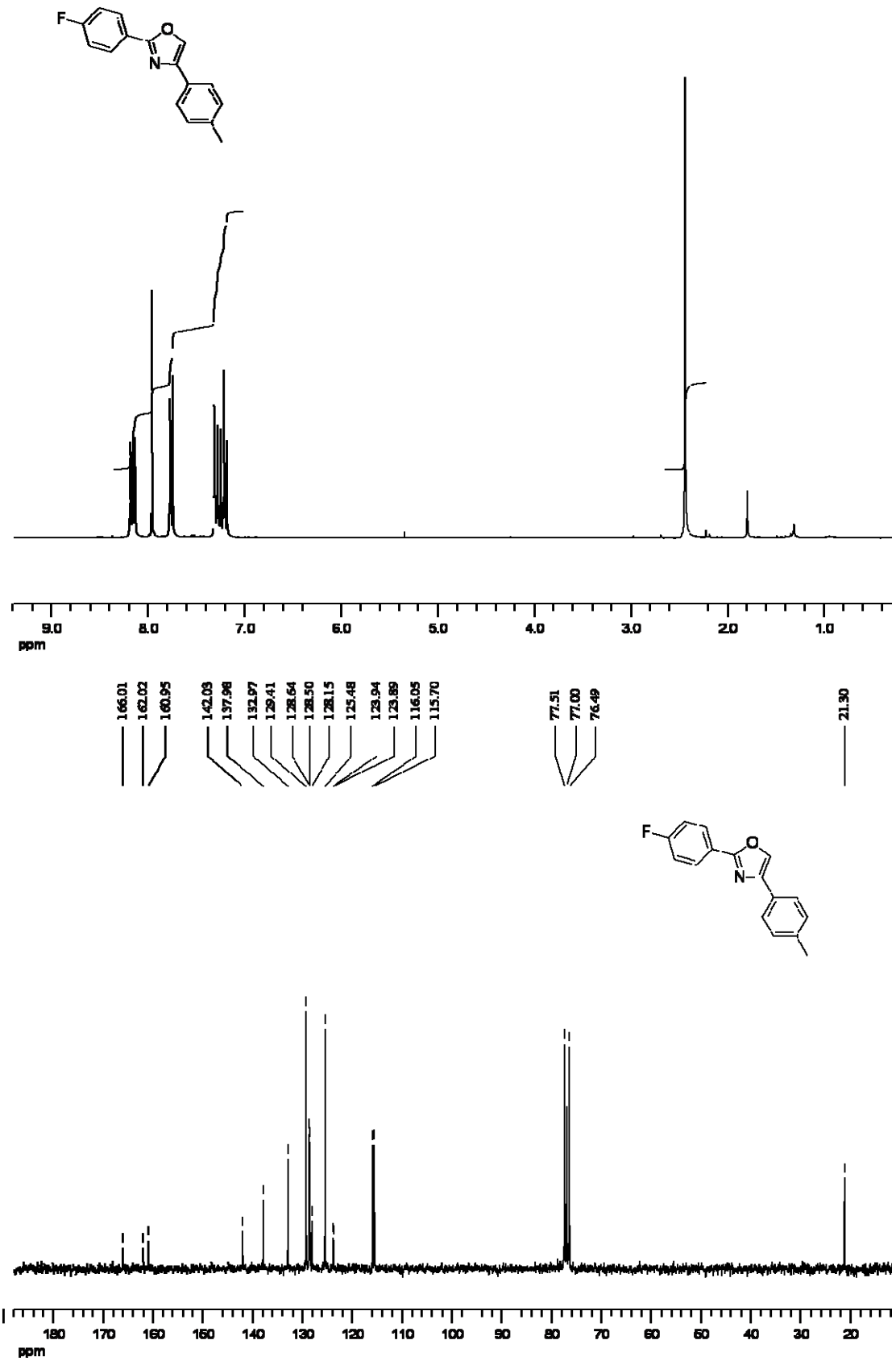


^{1}H and ^{13}C NMR of 2-Phenyl-4-o-tolyloxazole **10d**

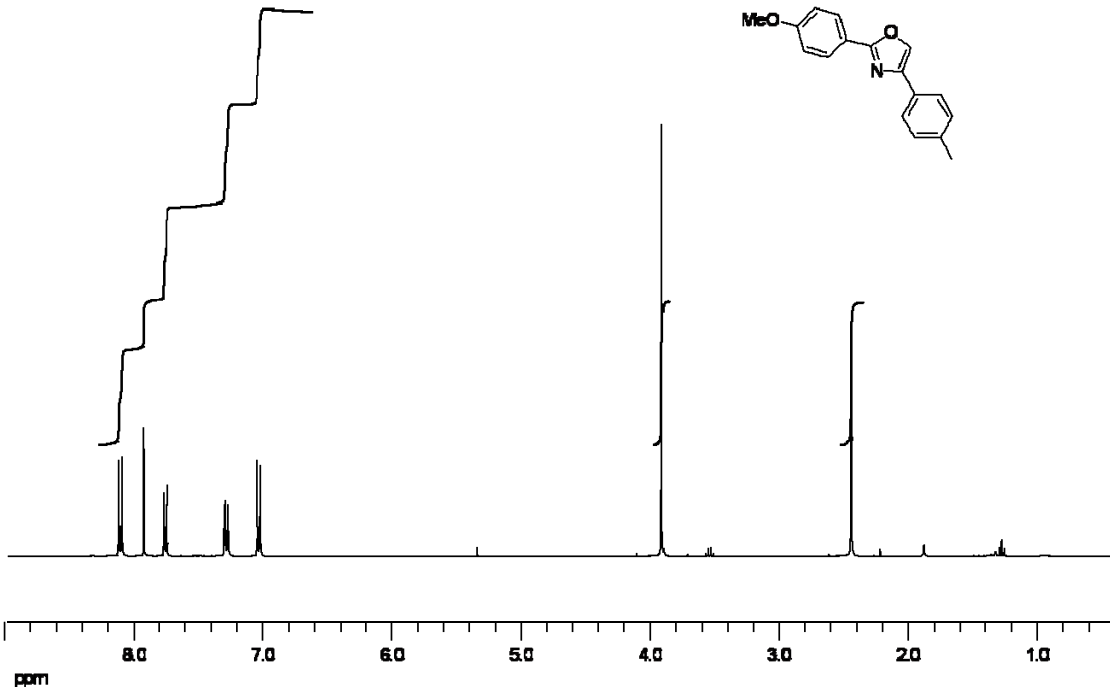


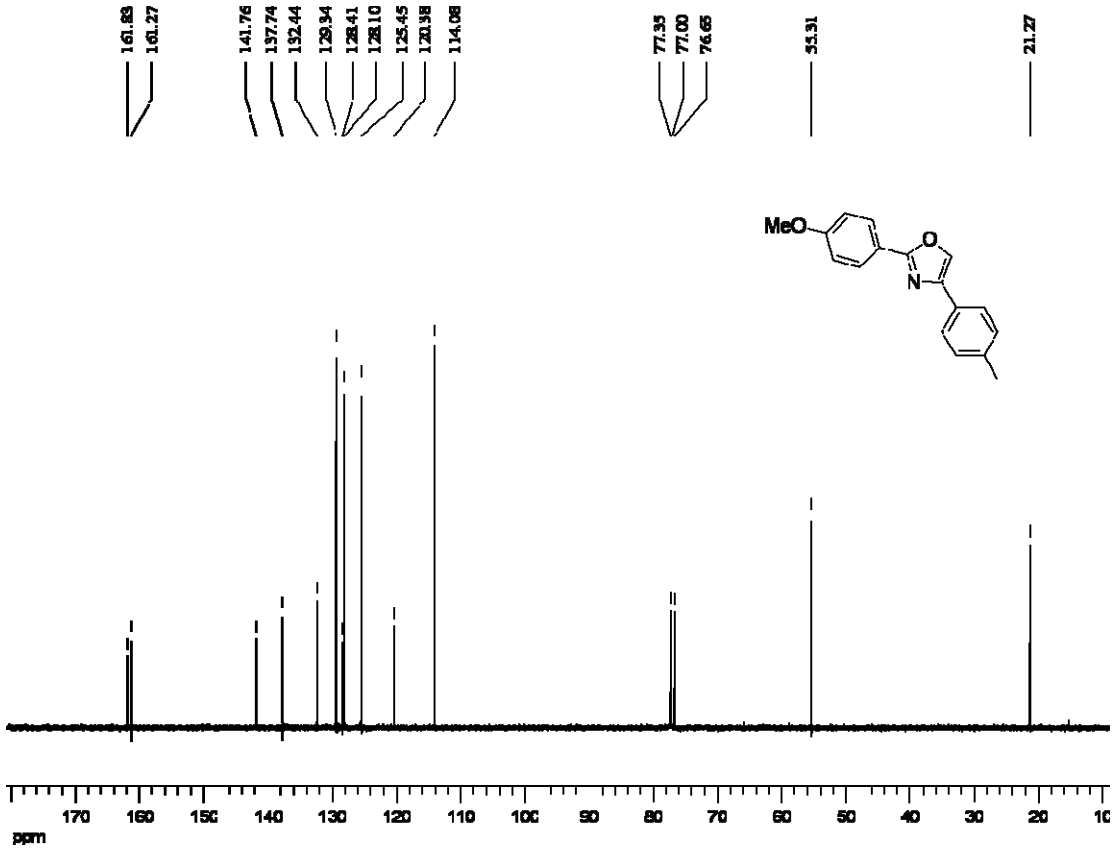


^{1}H and ^{13}C NMR of 2-(4-Fluorophenyl)-4-p-tolyloxazole **10e**

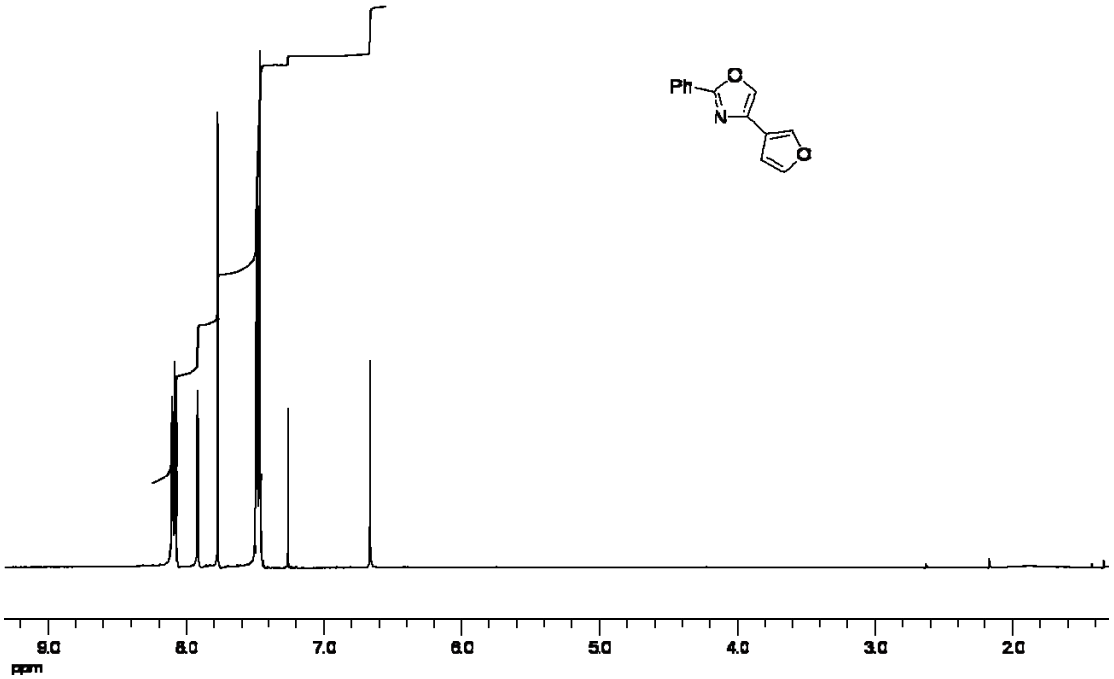


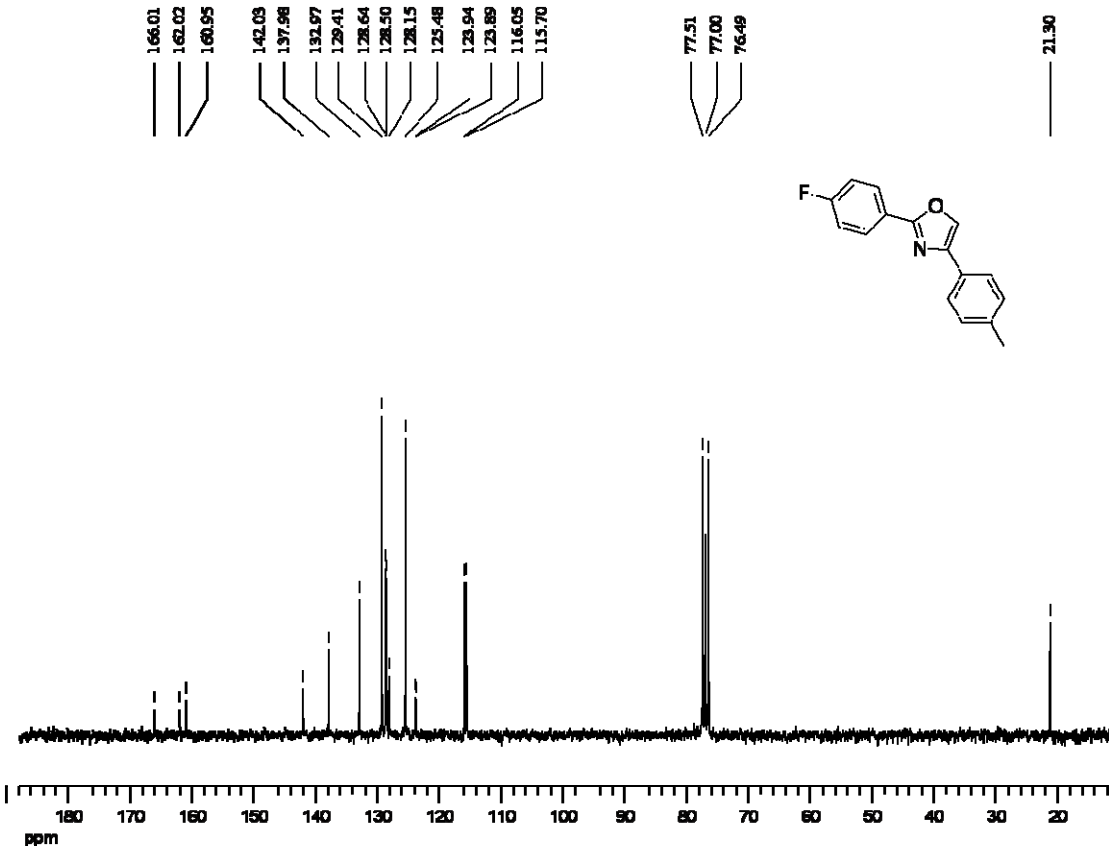
^{1}H and ^{13}C NMR of 2-(4-Methoxyphenyl)-4-p-tolyloxazole **10g**



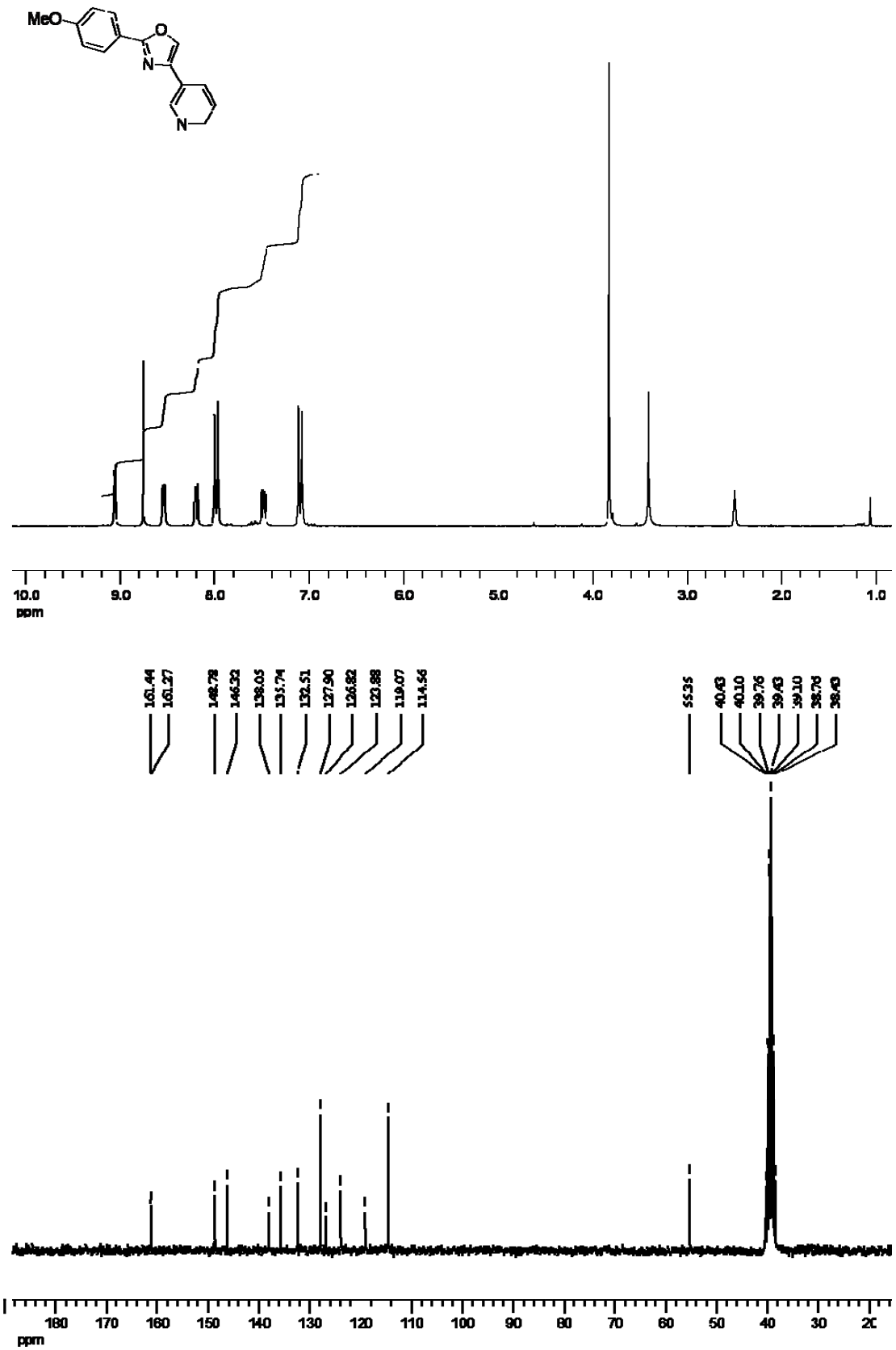


4-(Furan-3-yl)-2-phenyloxazole **10h**

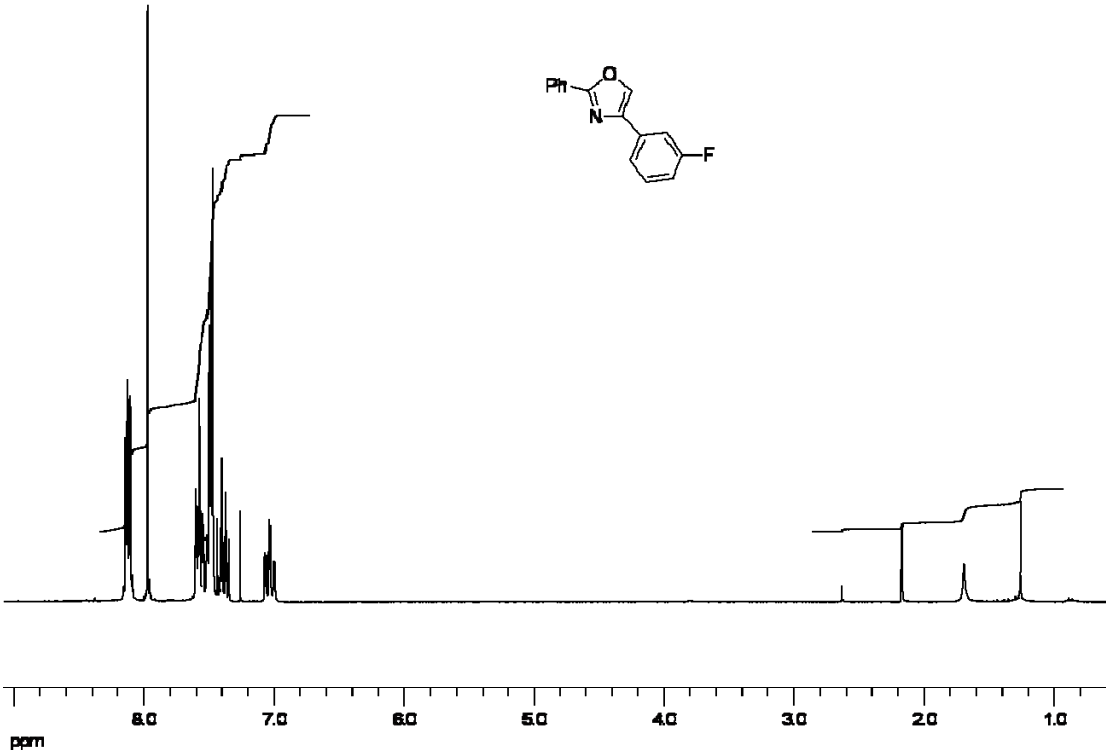


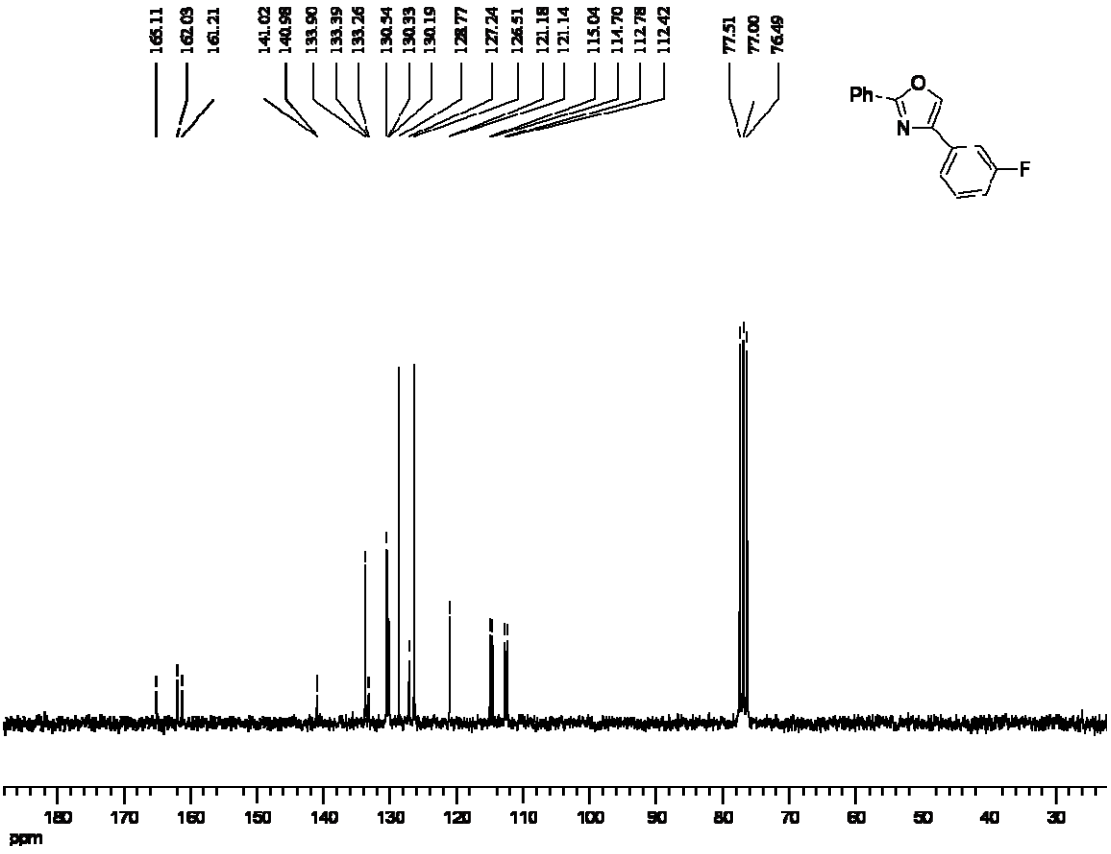


^{1}H and ^{13}C NMR of 3-(2-(4-Methoxyphenyl)oxazol-4-yl)pyridine **10j**

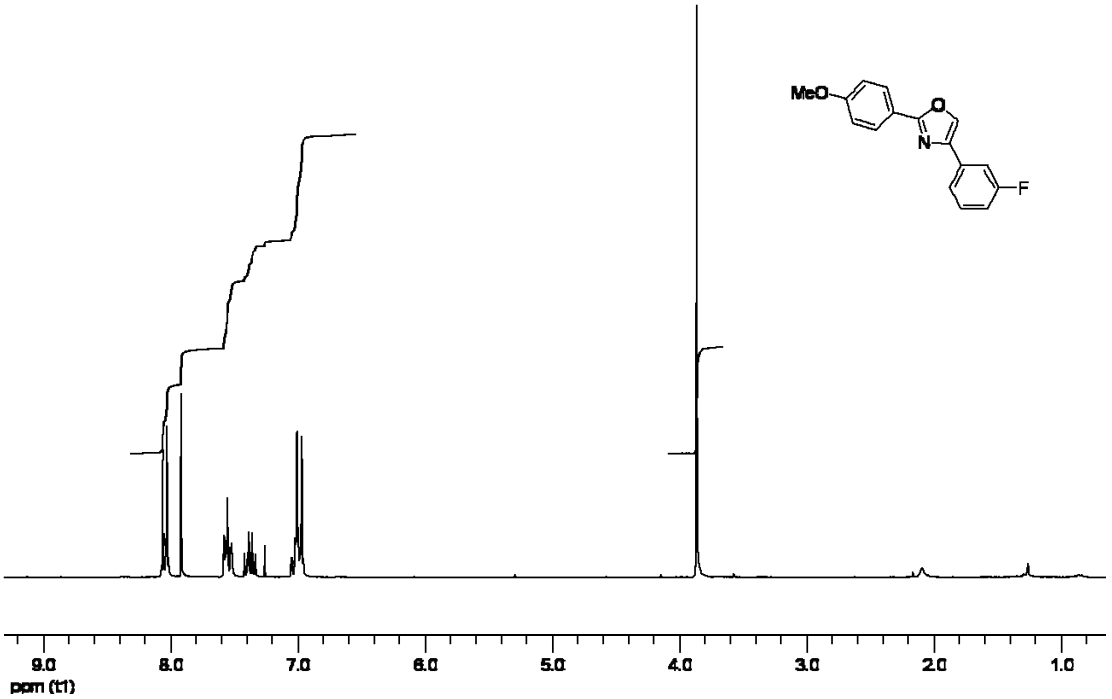


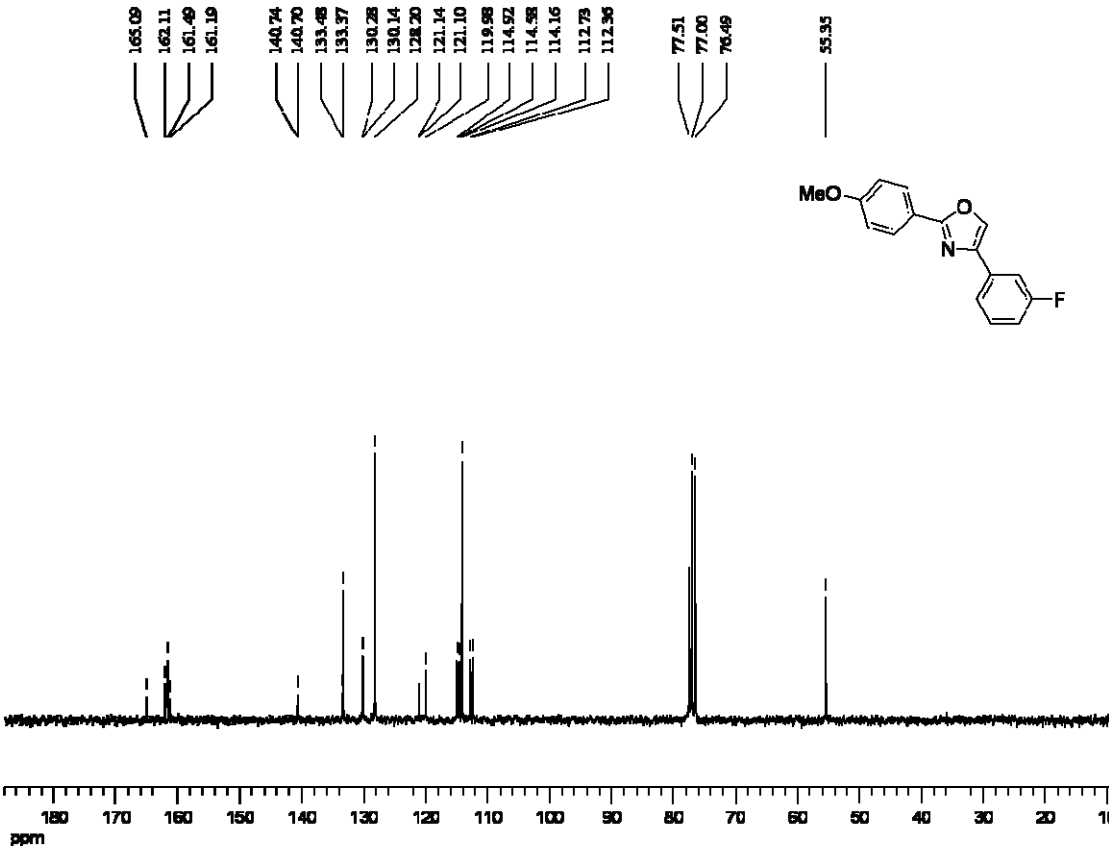
4-(3-Fluorophenyl)-2-phenyloxazole **10k**



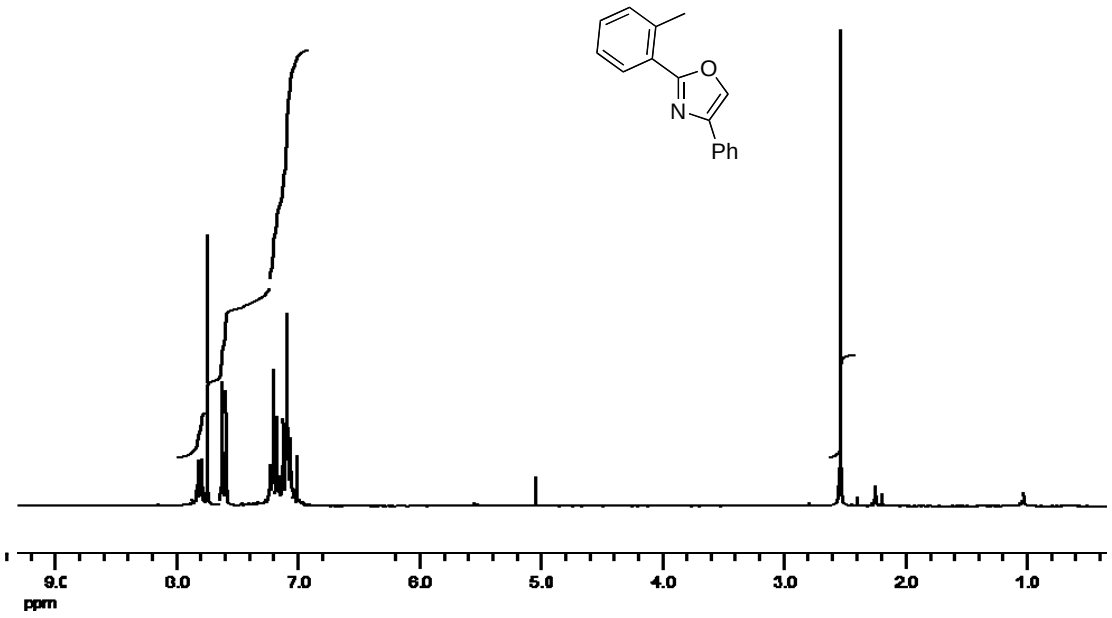


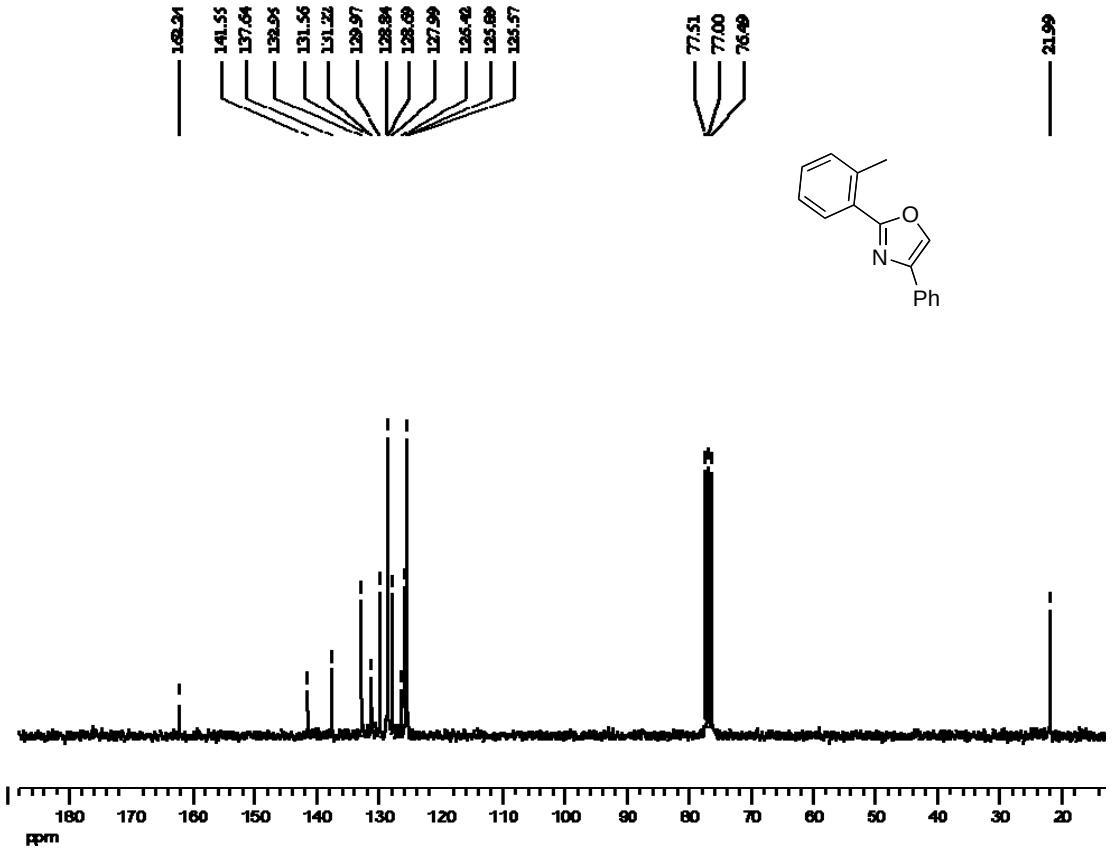
^{1}H and ^{13}C NMR of 4-(3-Fluorophenyl)-2-(4-methoxyphenyl)oxazole **10l**



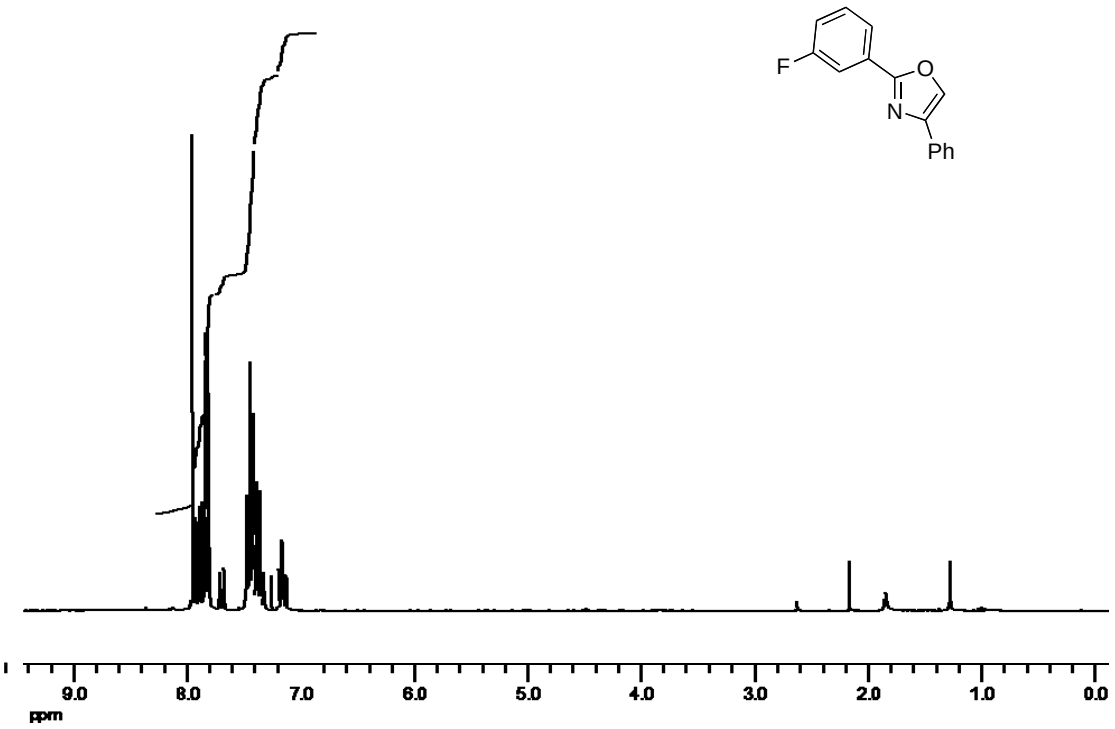


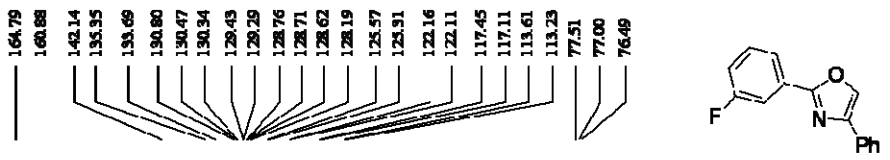
^{1}H and ^{13}C NMR of 4-Phenyl-2-o-tolyloxazole **16a**

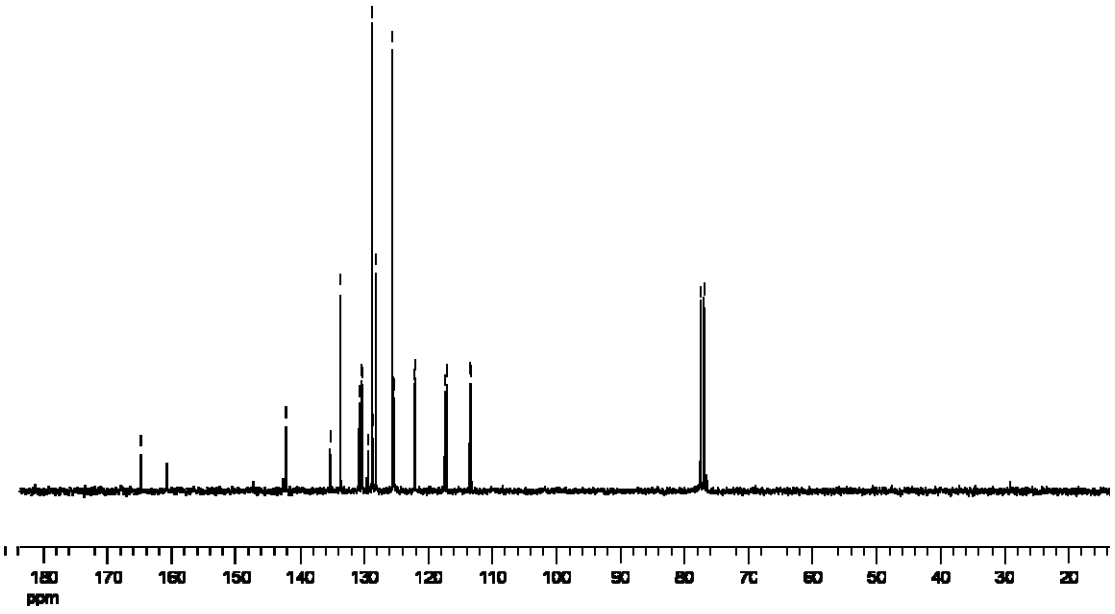




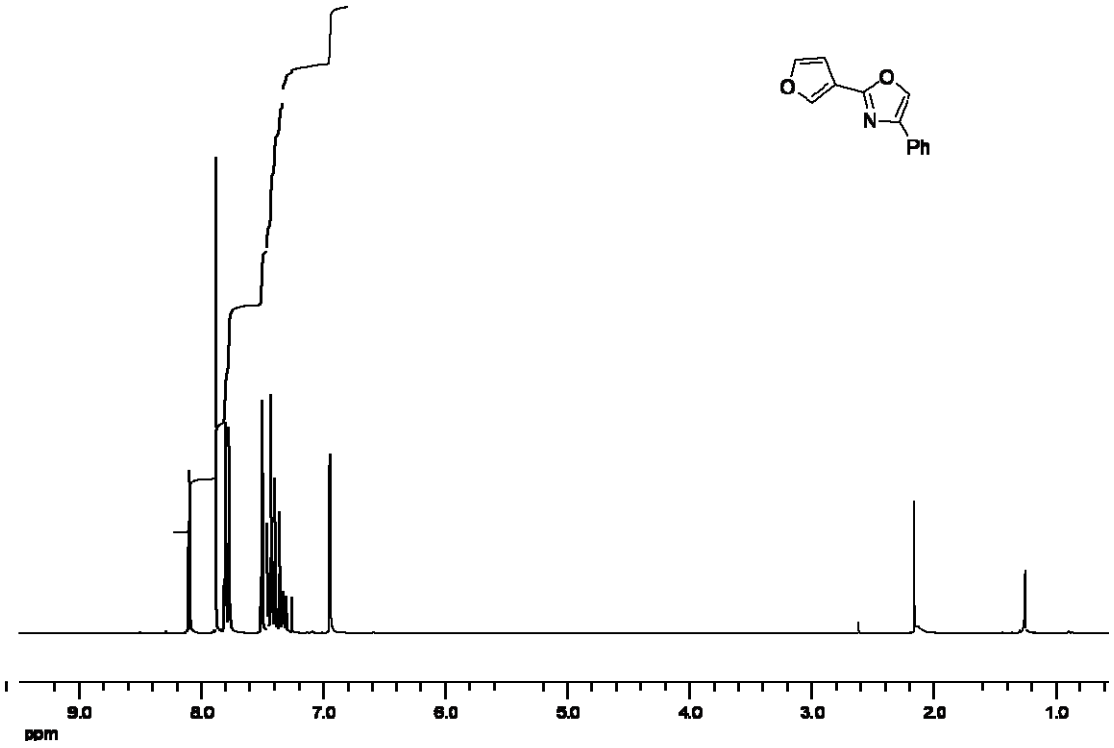
^{1}H and ^{13}C NMR of 2-(3-Fluorophenyl)-4-phenyloxazole **16b**

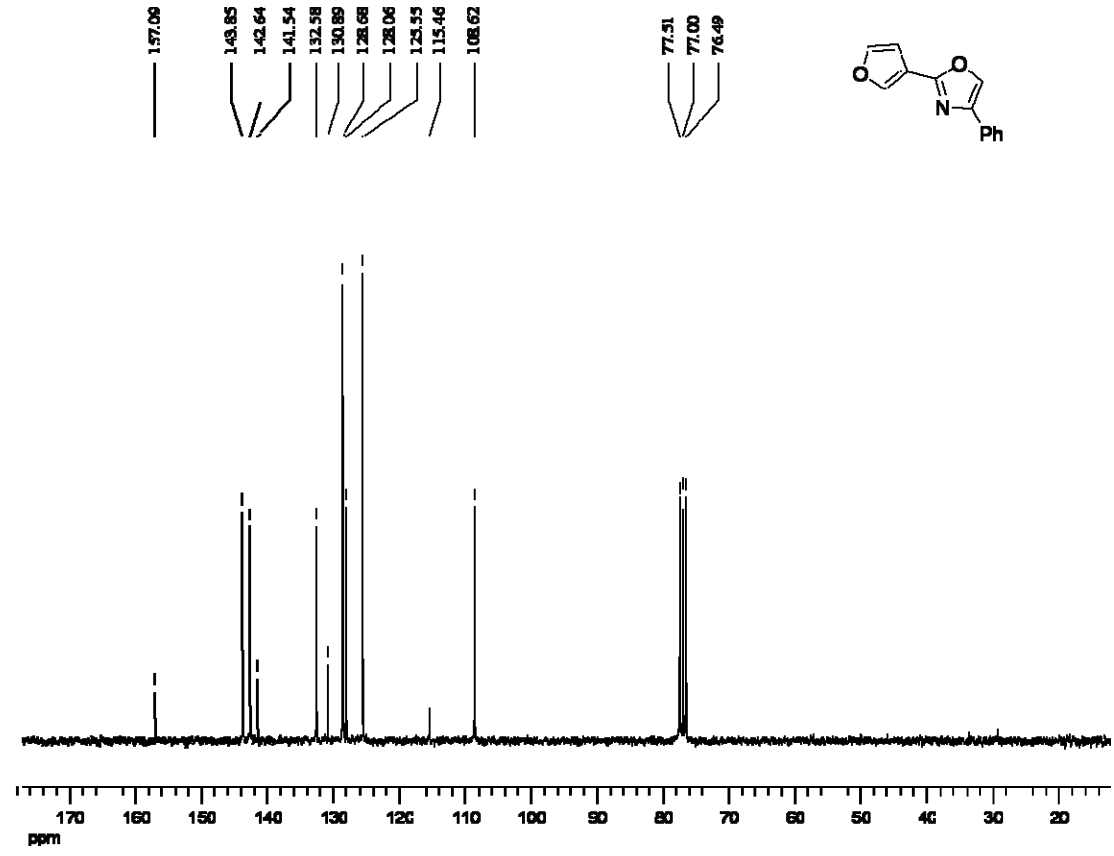




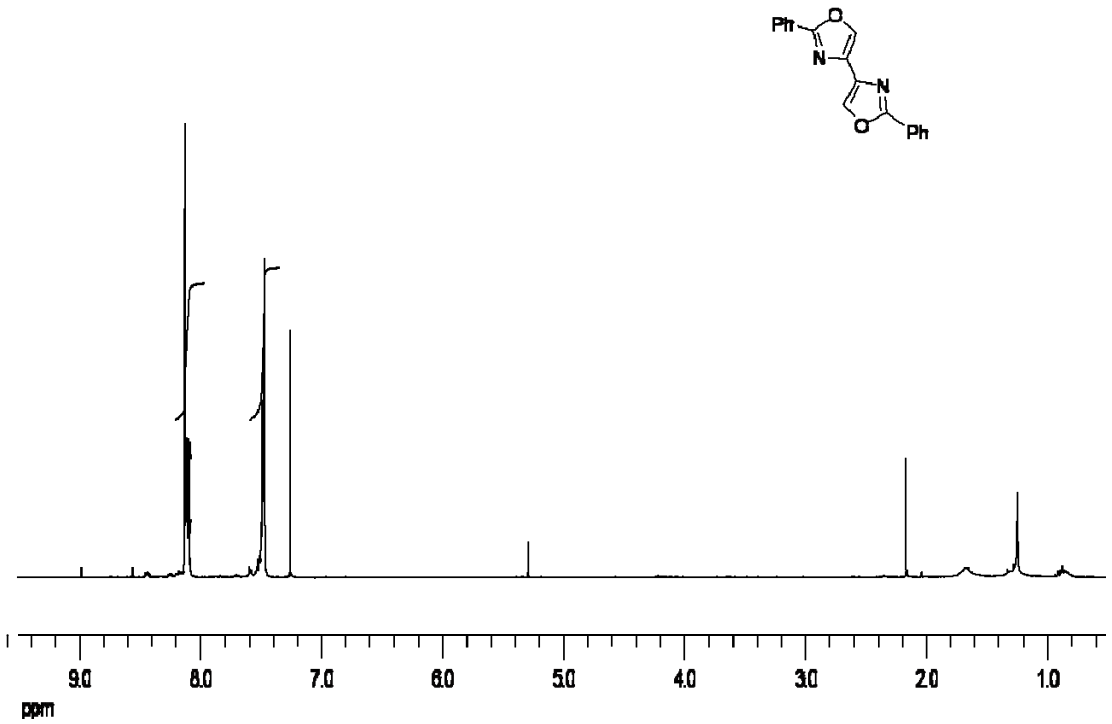


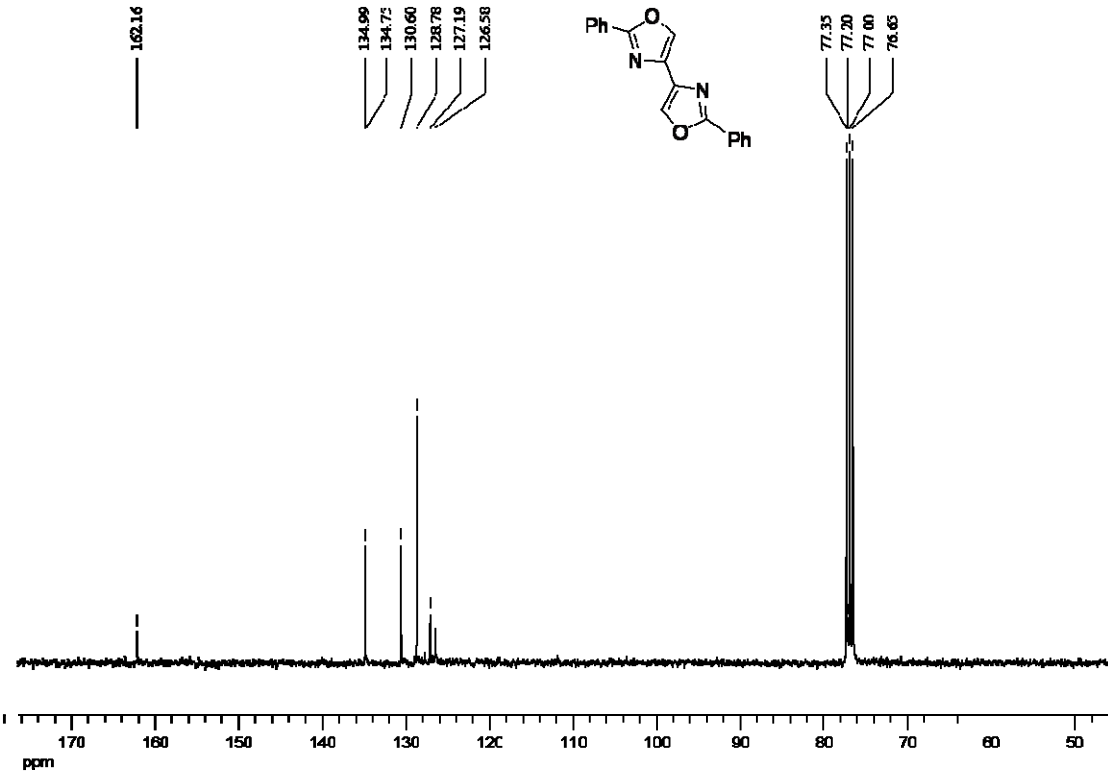
^{1}H and ^{13}C NMR of 2-(Furan-3-yl)-4-phenyloxazole **16e**



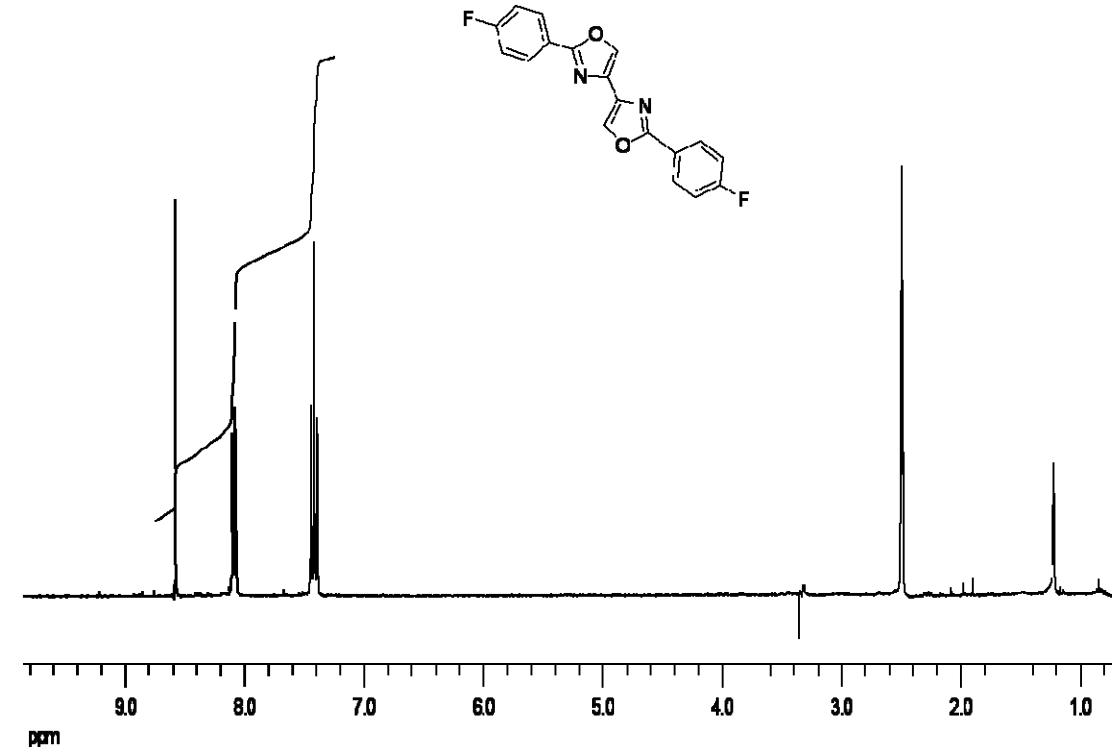


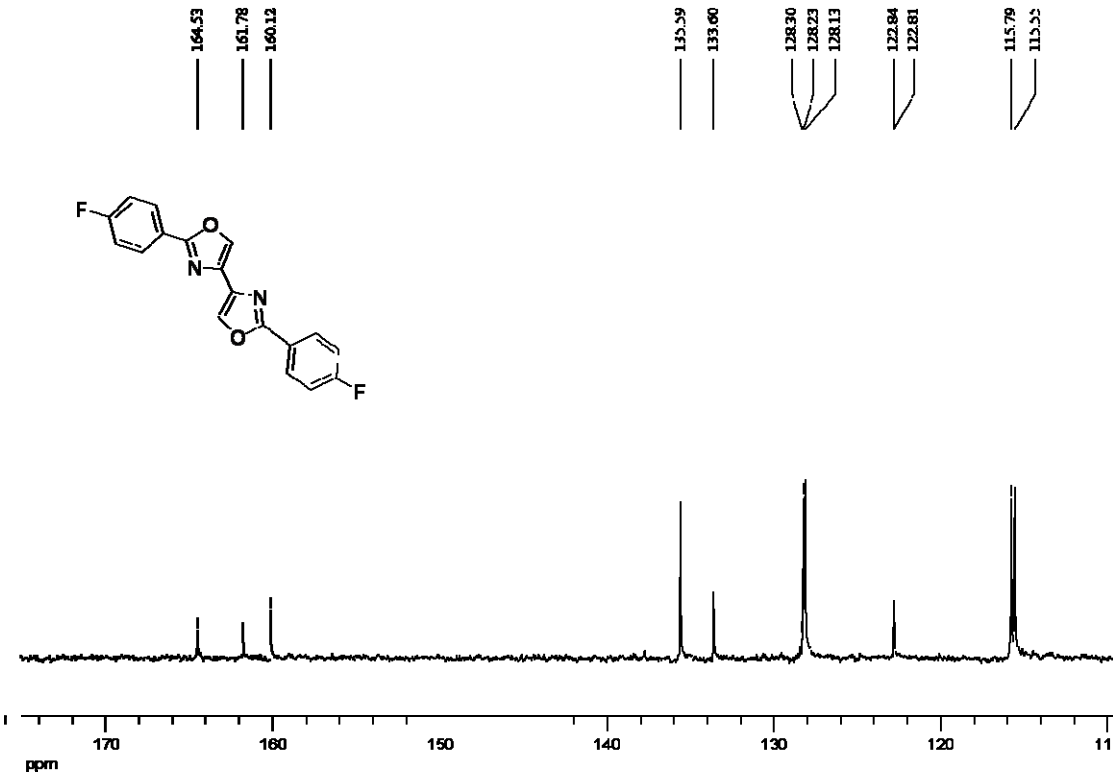
^{1}H and ^{13}C of 2-Phenyl-4-(2-phenyloxazol-4-yl)oxazole **18a**



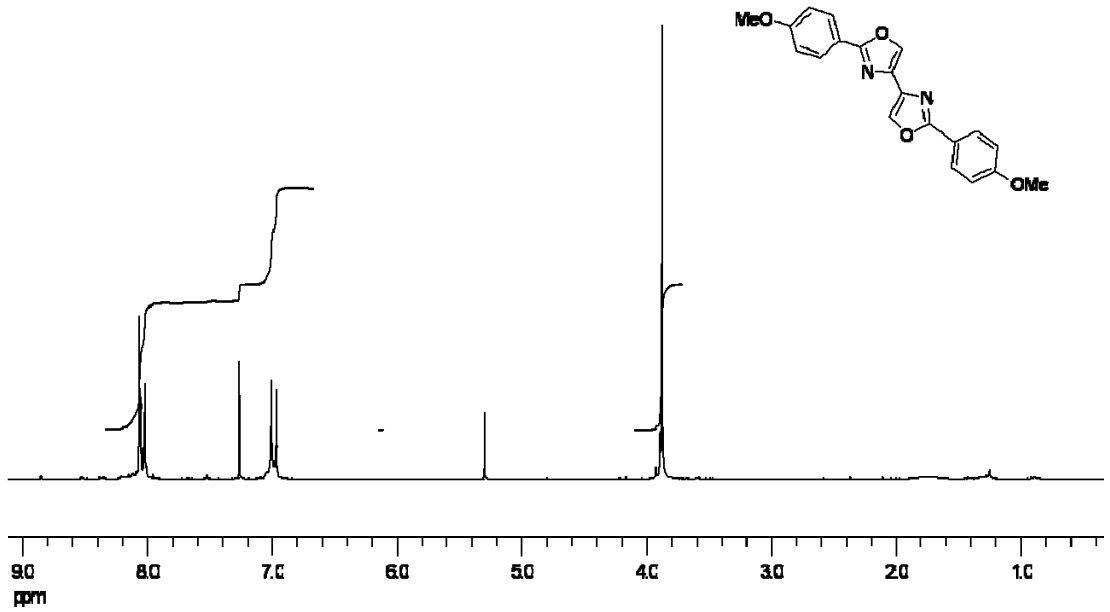


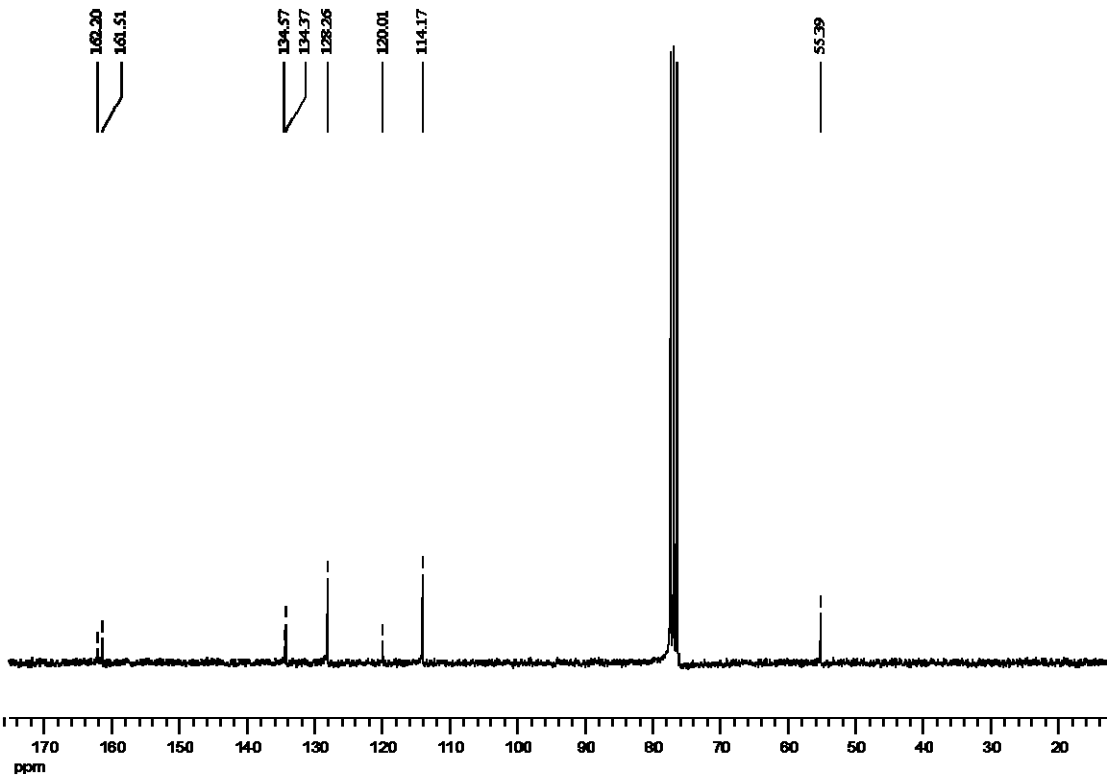
^{1}H and ^{13}C NMR of 2-(4-Fluorophenyl)-4-(2-(4-fluorophenyl)oxazol-4-yl)oxazole **18b**.



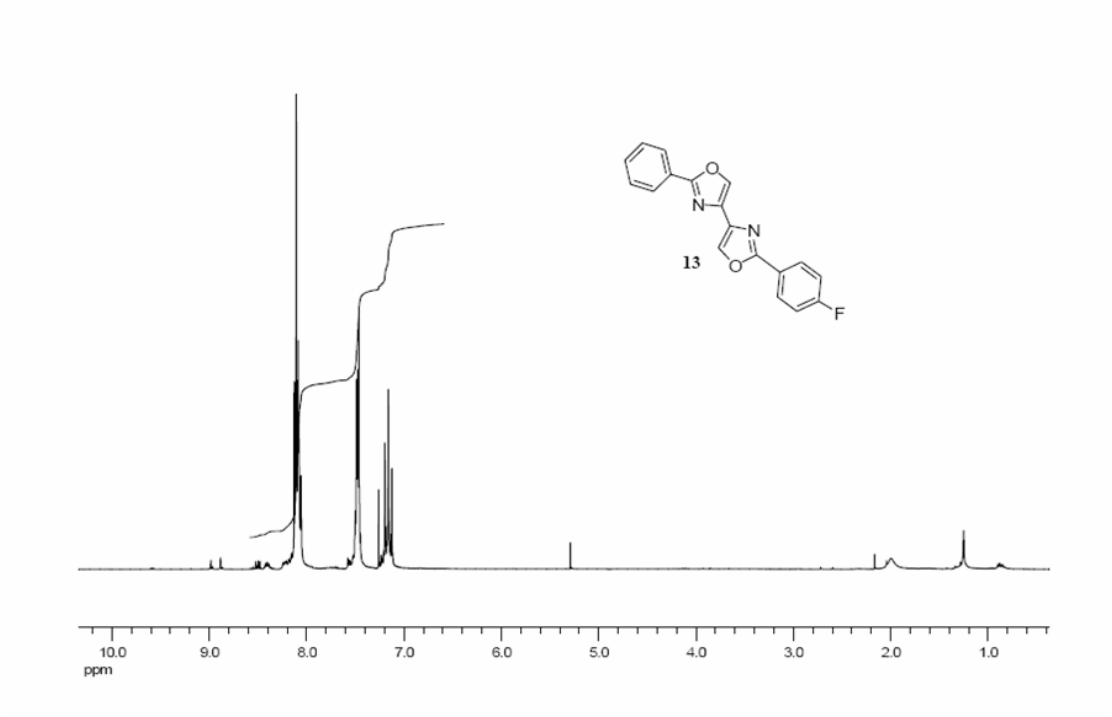


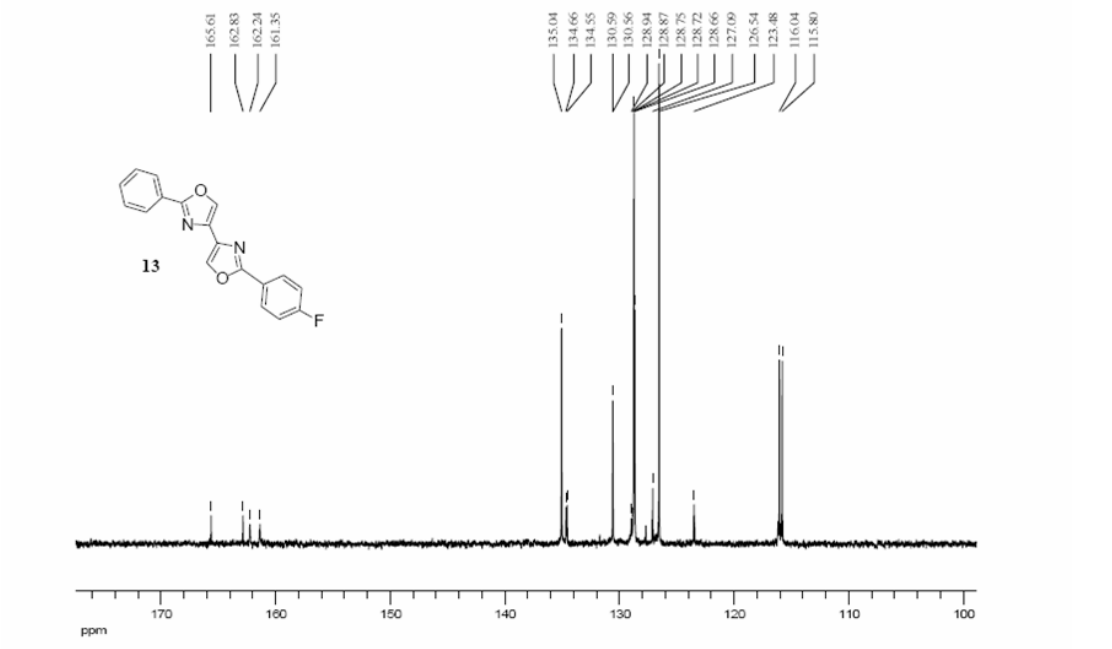
^{1}H and ^{13}C NMR of 2-(4-Methoxyphenyl)-4-(2-(4-methoxyphenyl)oxazol-4-yl)oxazole **18c**





^{1}H and ^{13}C NMR of 2-(4-Fluorophenyl)-4-(2-phenyloxazol-4-yl)oxazole **18d**

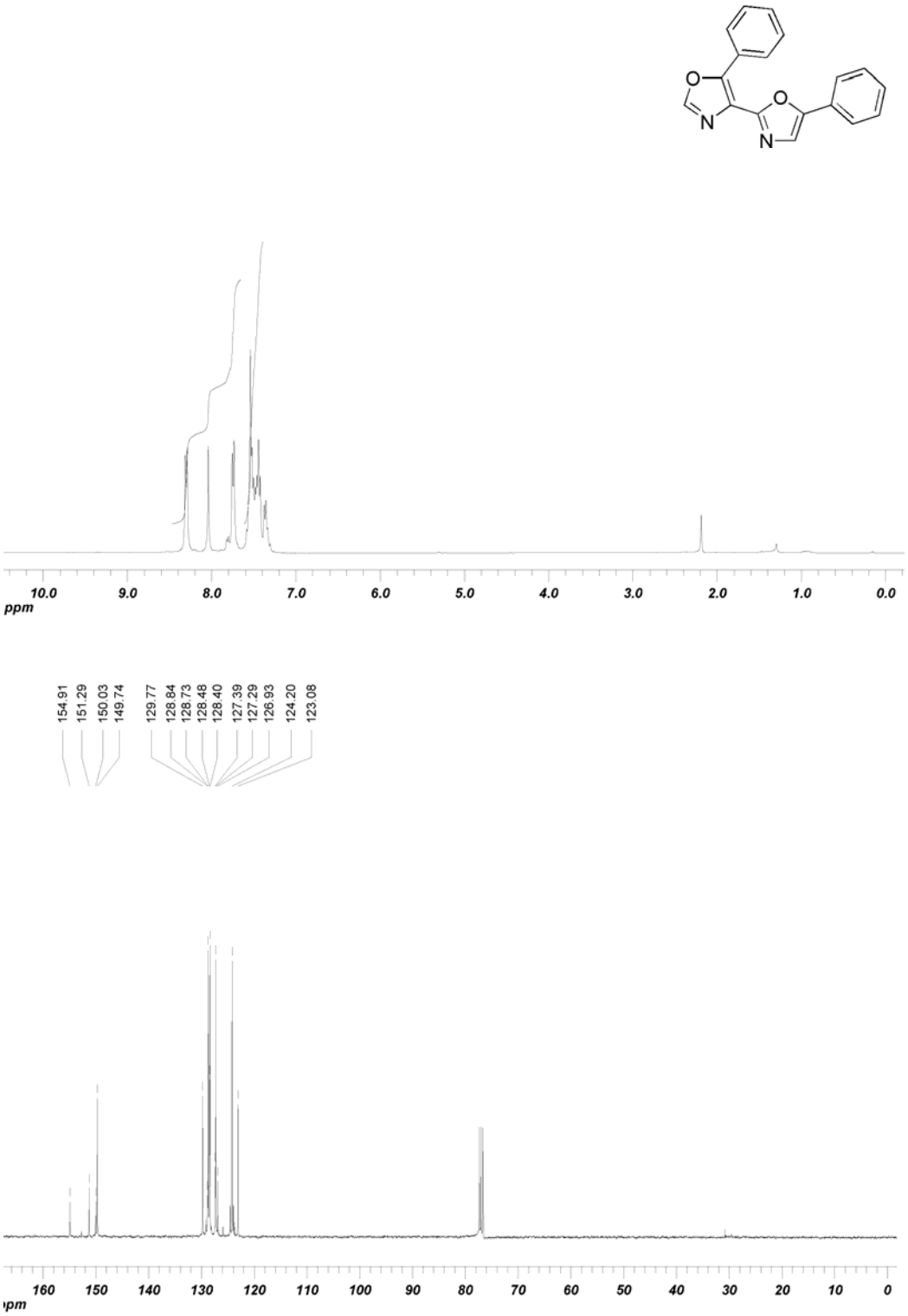




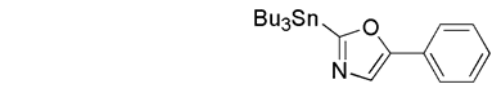
Appendix B

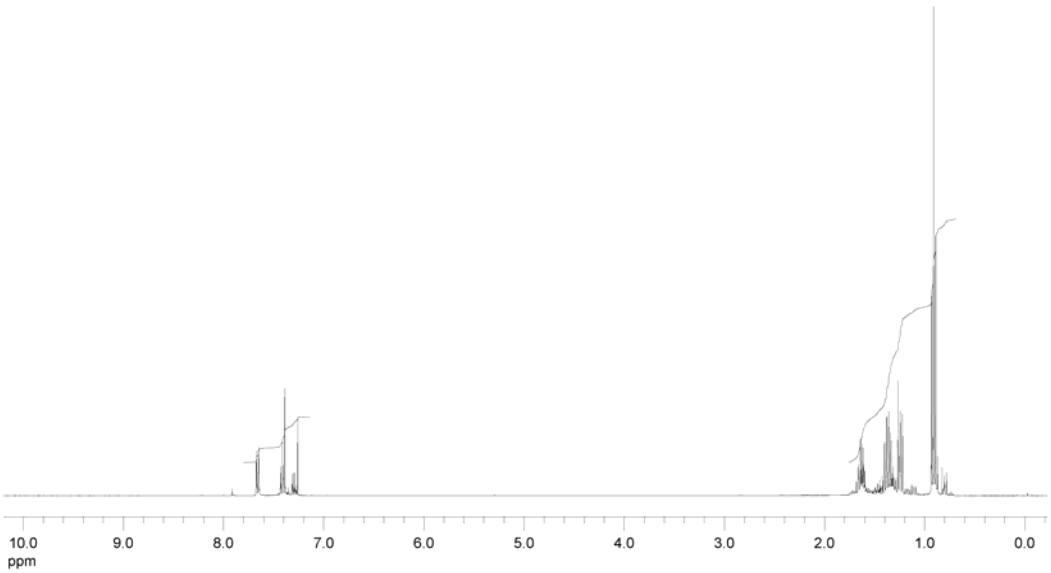
Spectroscopic Data for Chapter 3

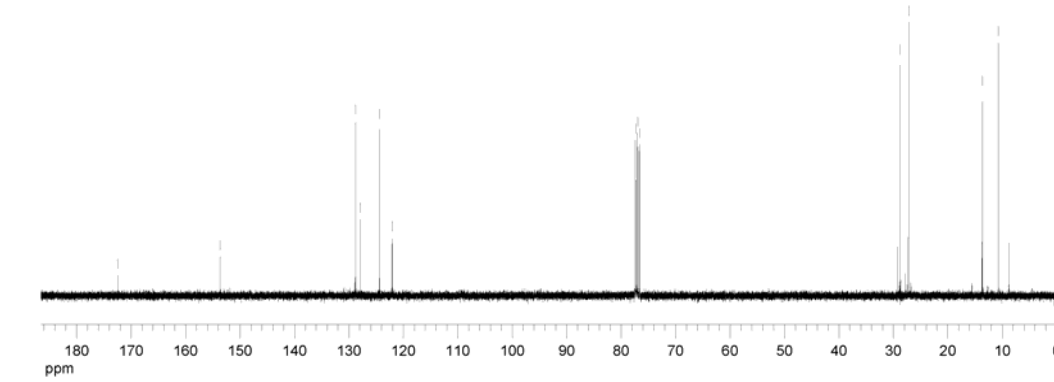
^{1}H and ^{13}C NMR for 5,2'-Diphenyl-[2,4']bioxazolyl **8**



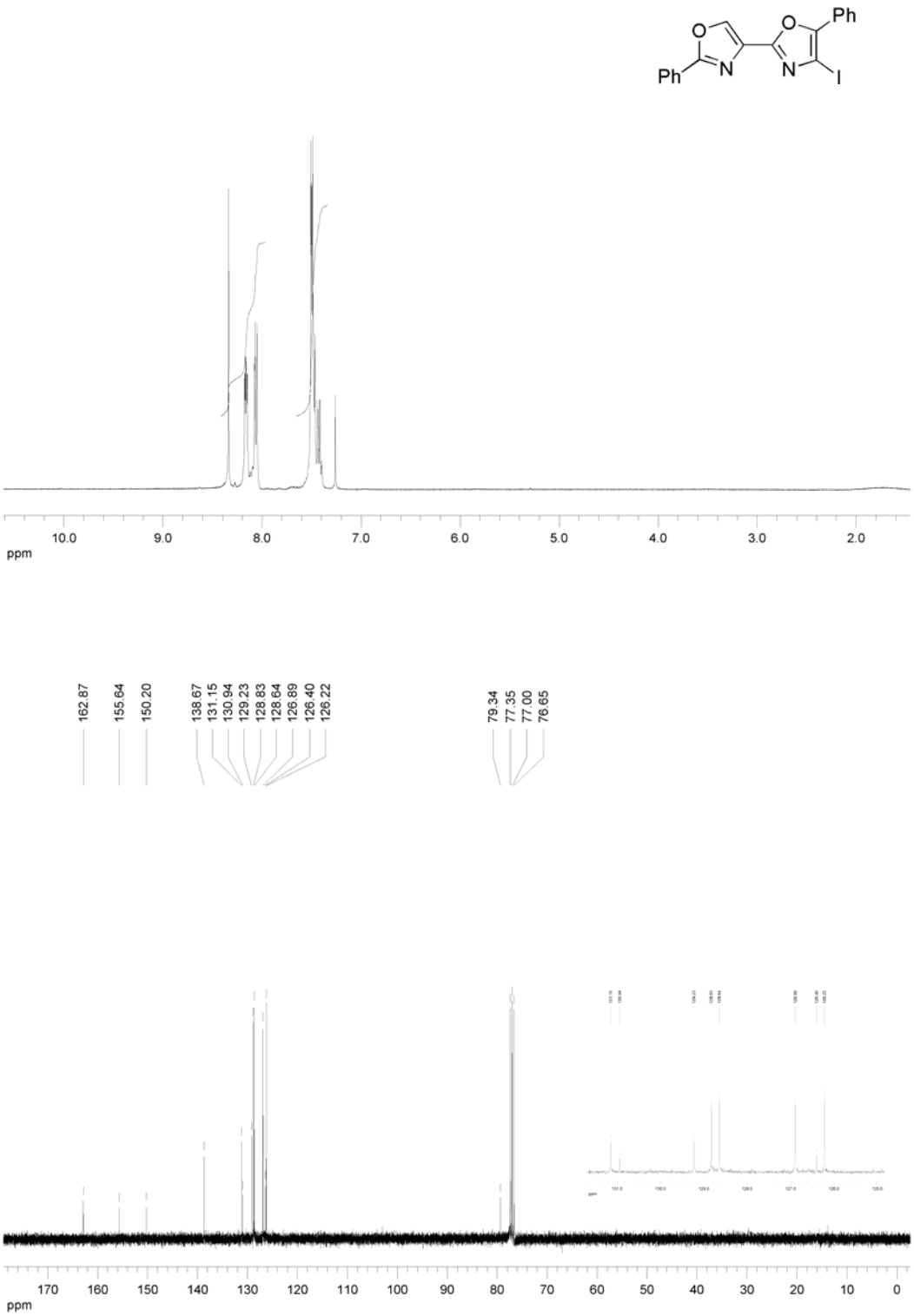
^{1}H and ^{13}C NMR for 5-Phenyl-2-tributylstannanyl-oxazole **6a**



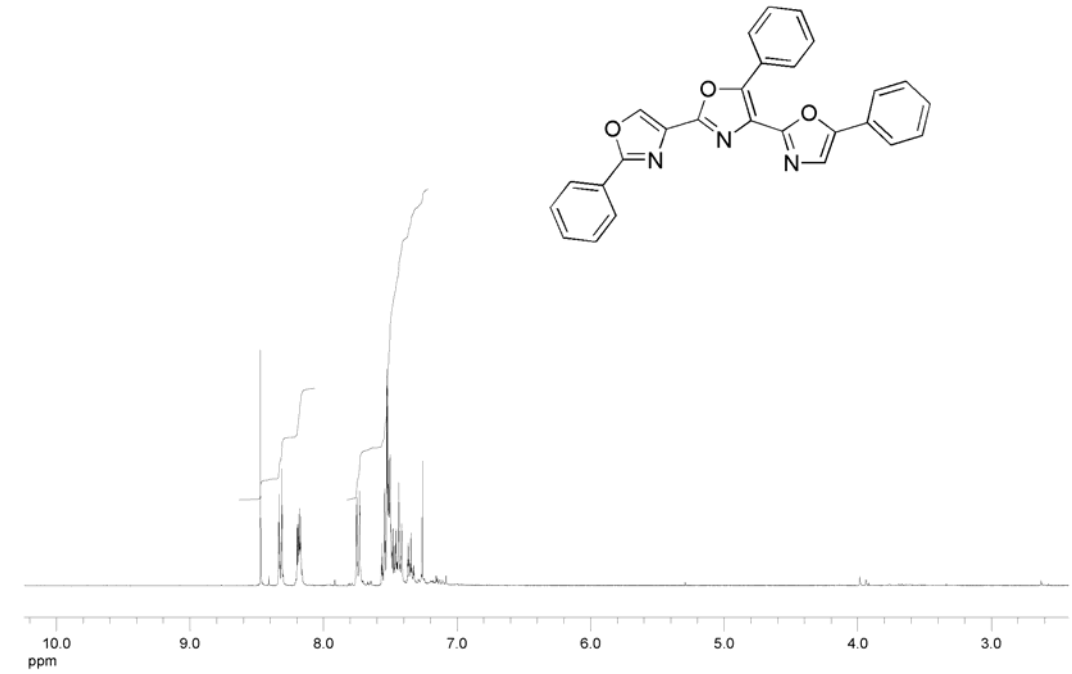


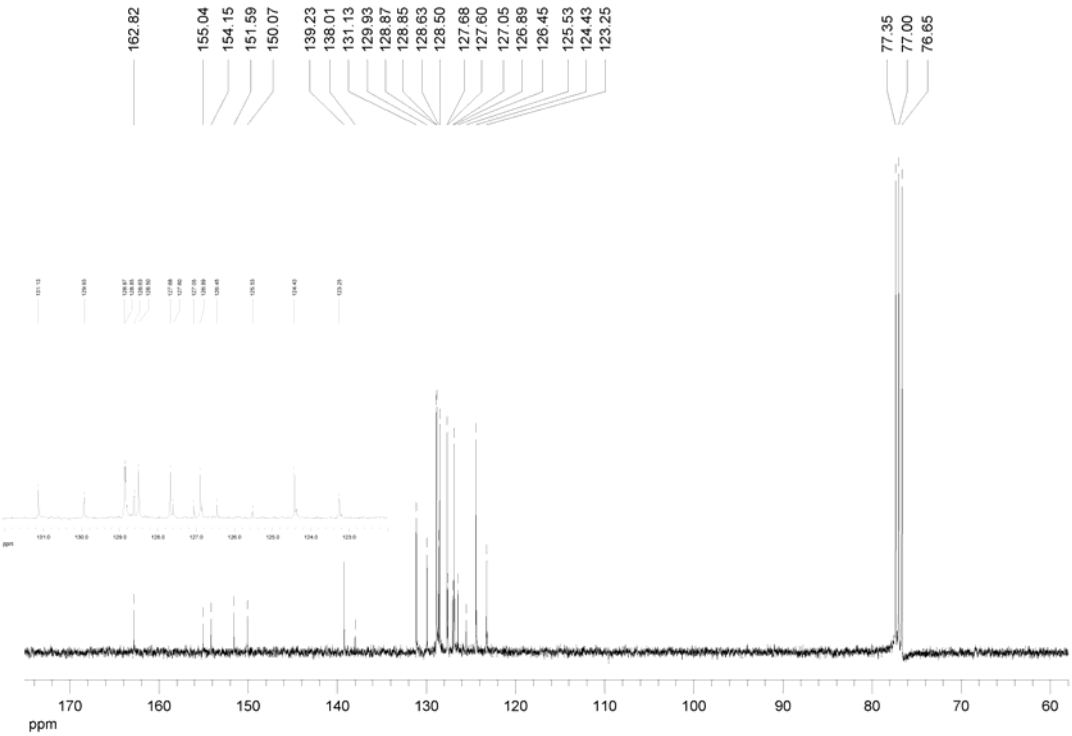


^{1}H and ^{13}C NMR for 4-Iodo-5,2'-diphenyl-[2,4']bioxazolyl **12**

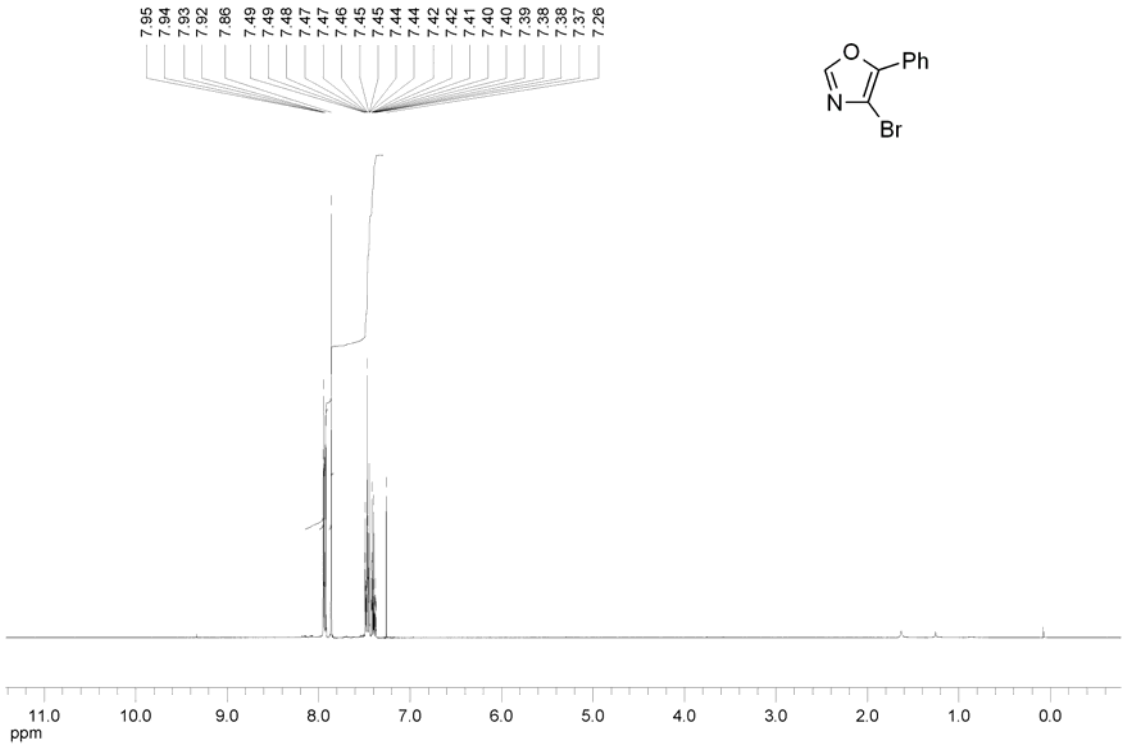


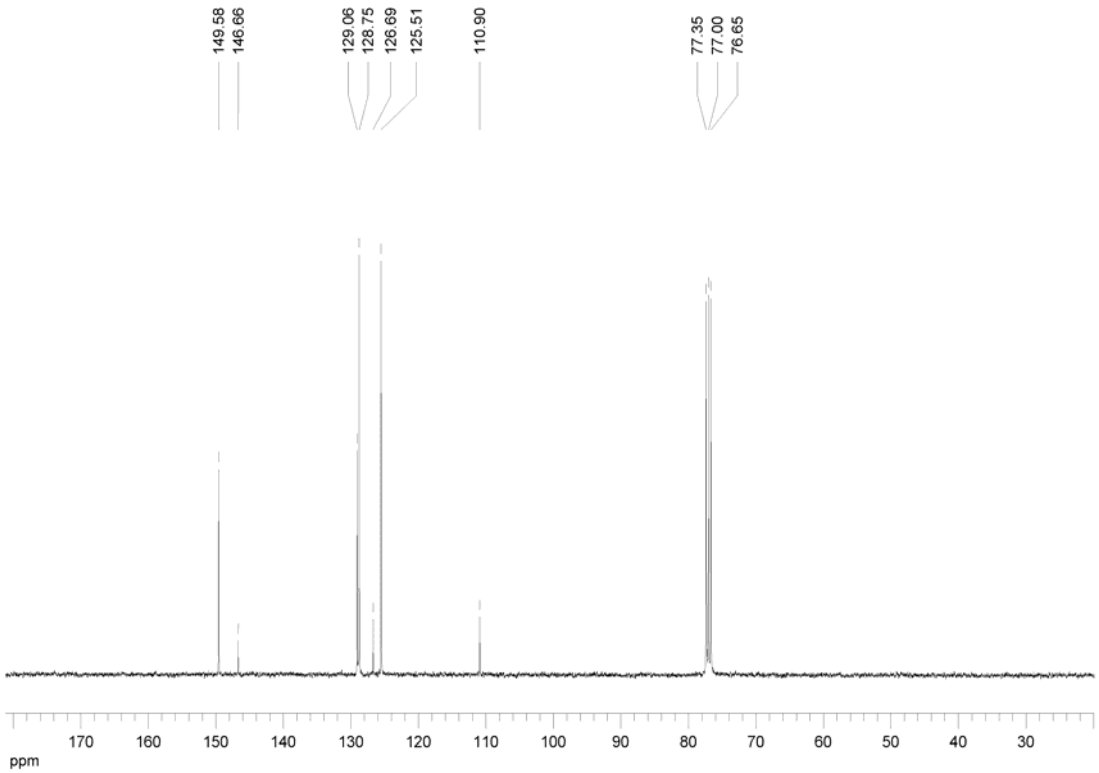
^{1}H and ^{13}C NMR for 5, 5', 2''-Triphenyl-[2, 4', 2', 4''] teroxazole **19**



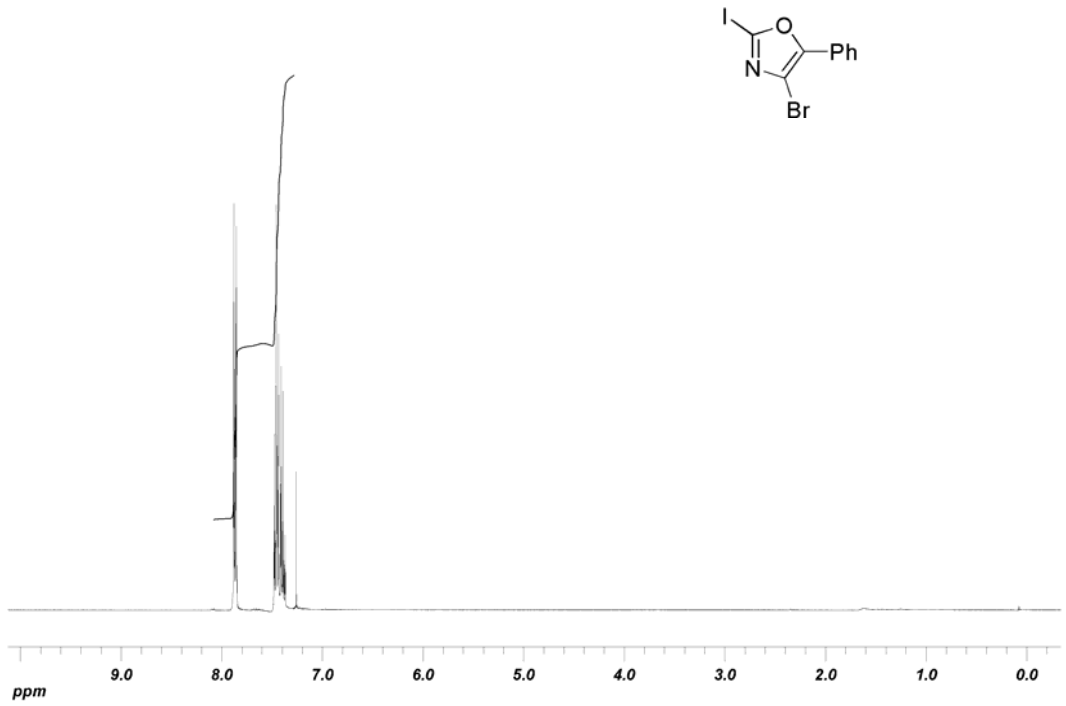


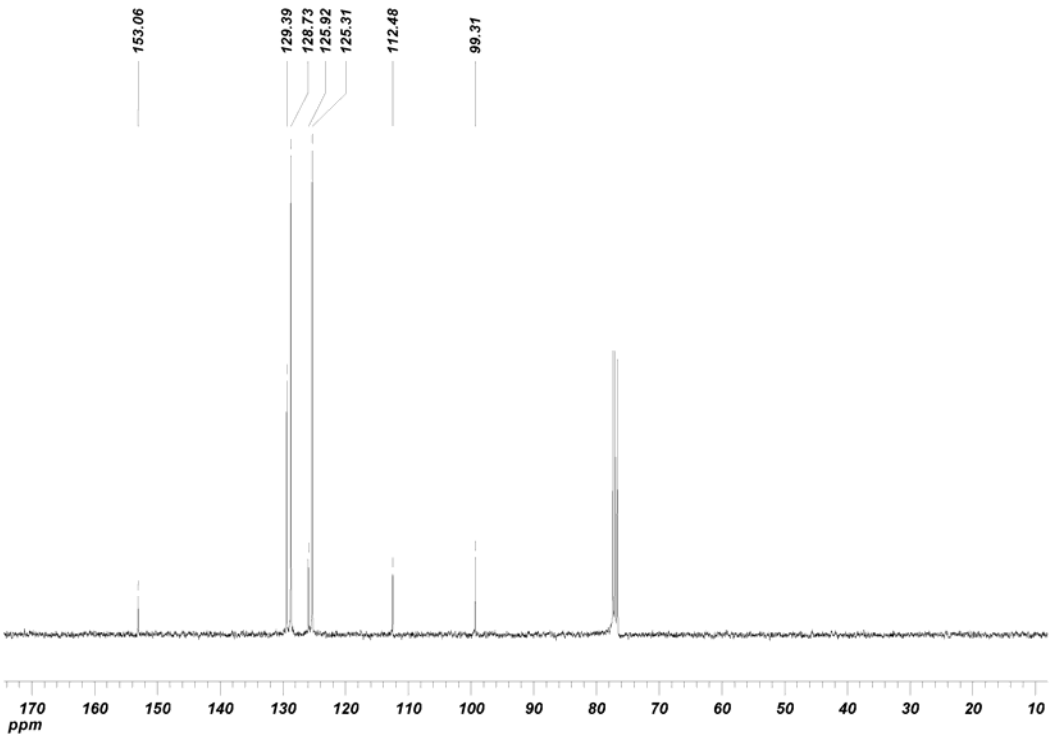
^{1}H and ^{13}C NMR for 4-bromo-5-phenyloxazole **16**



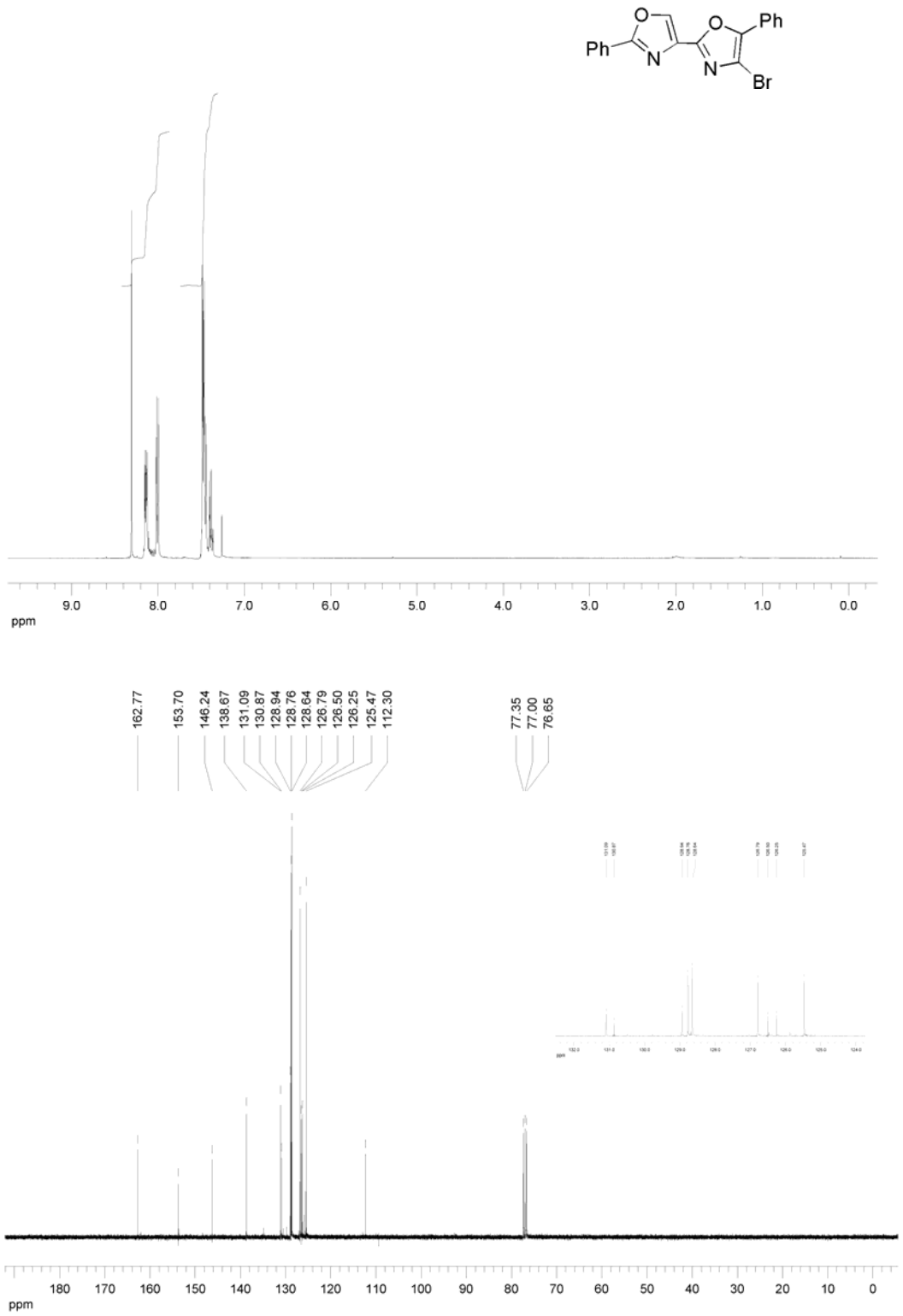


^{1}H and ^{13}C NMR for 2-iodo-4-bromo-5-phenyloxazole **17**

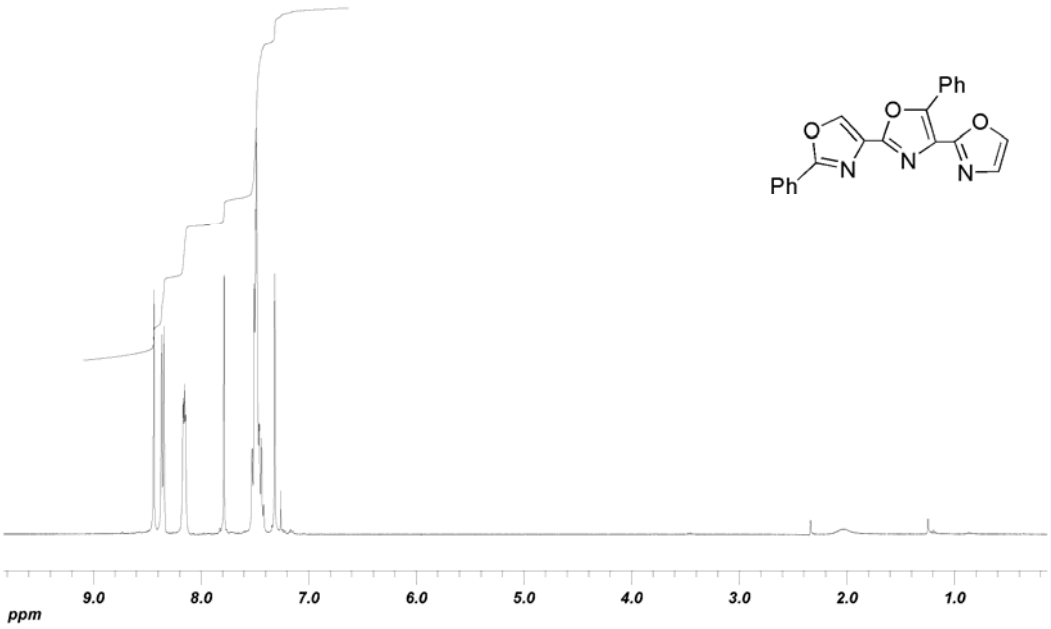


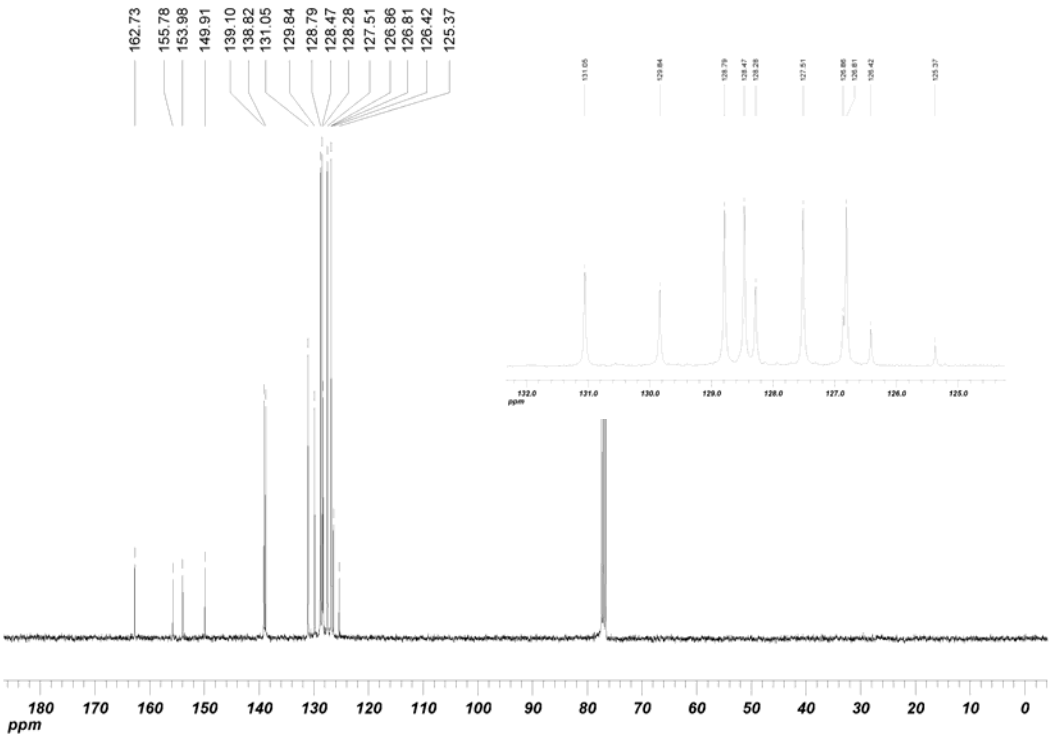


^{1}H and ^{13}C NMR for 4-Bromo-5,2'-diphenyl-[2,4']bioxazolyl **18**



^{1}H and ^{13}C NMR for 5', 2'',-Diphenyl-[2,4';2',4''] teroxazole **20**

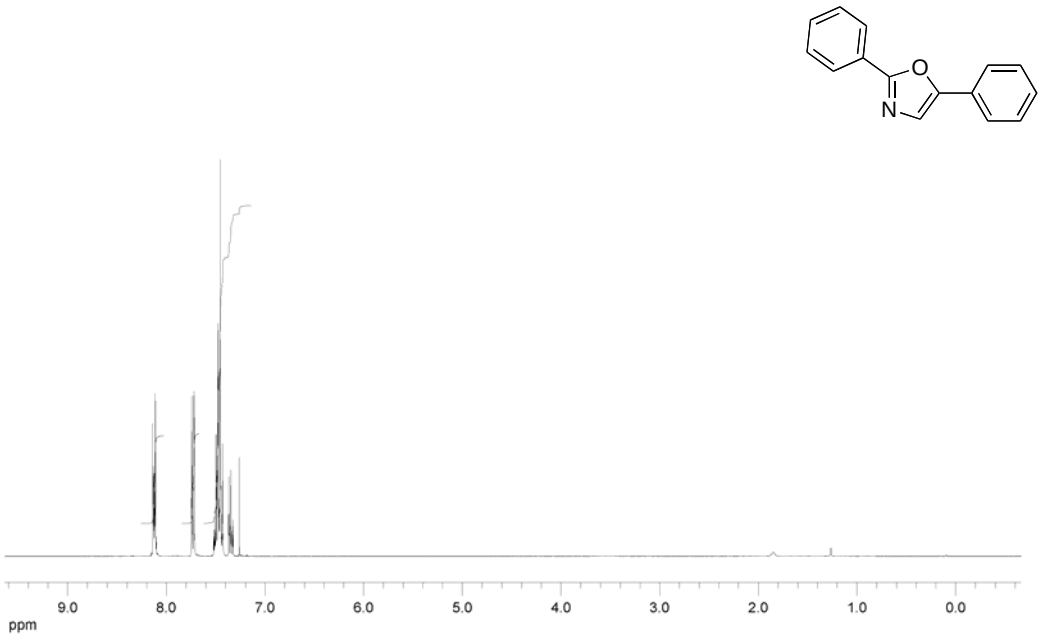


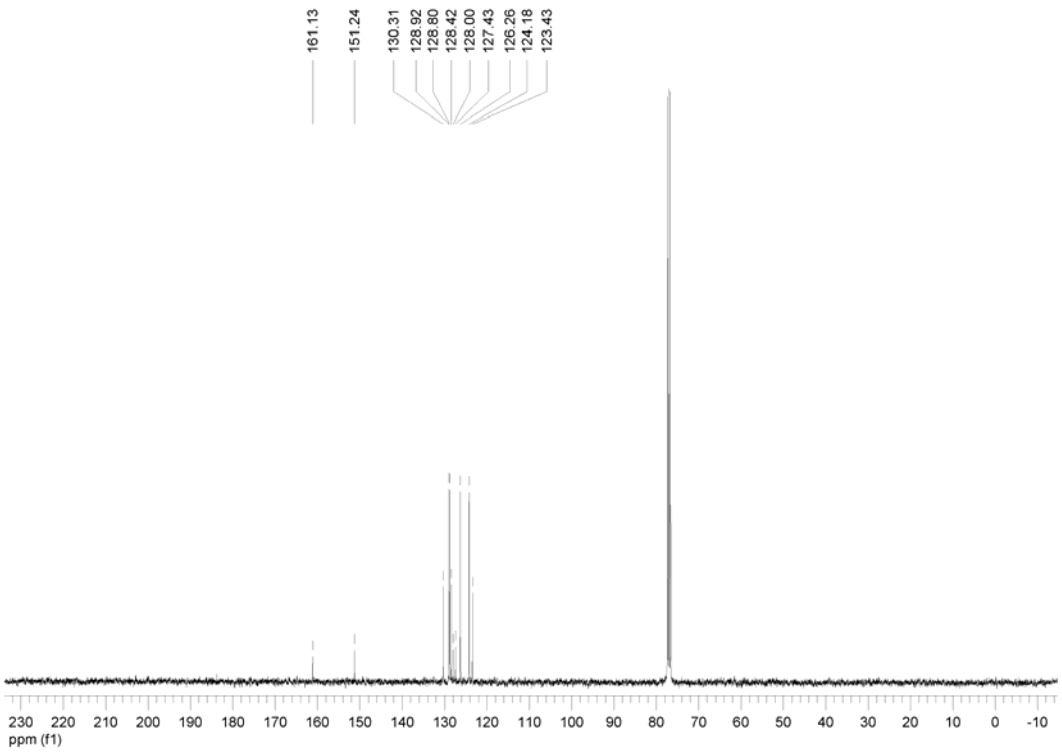


Appendix C

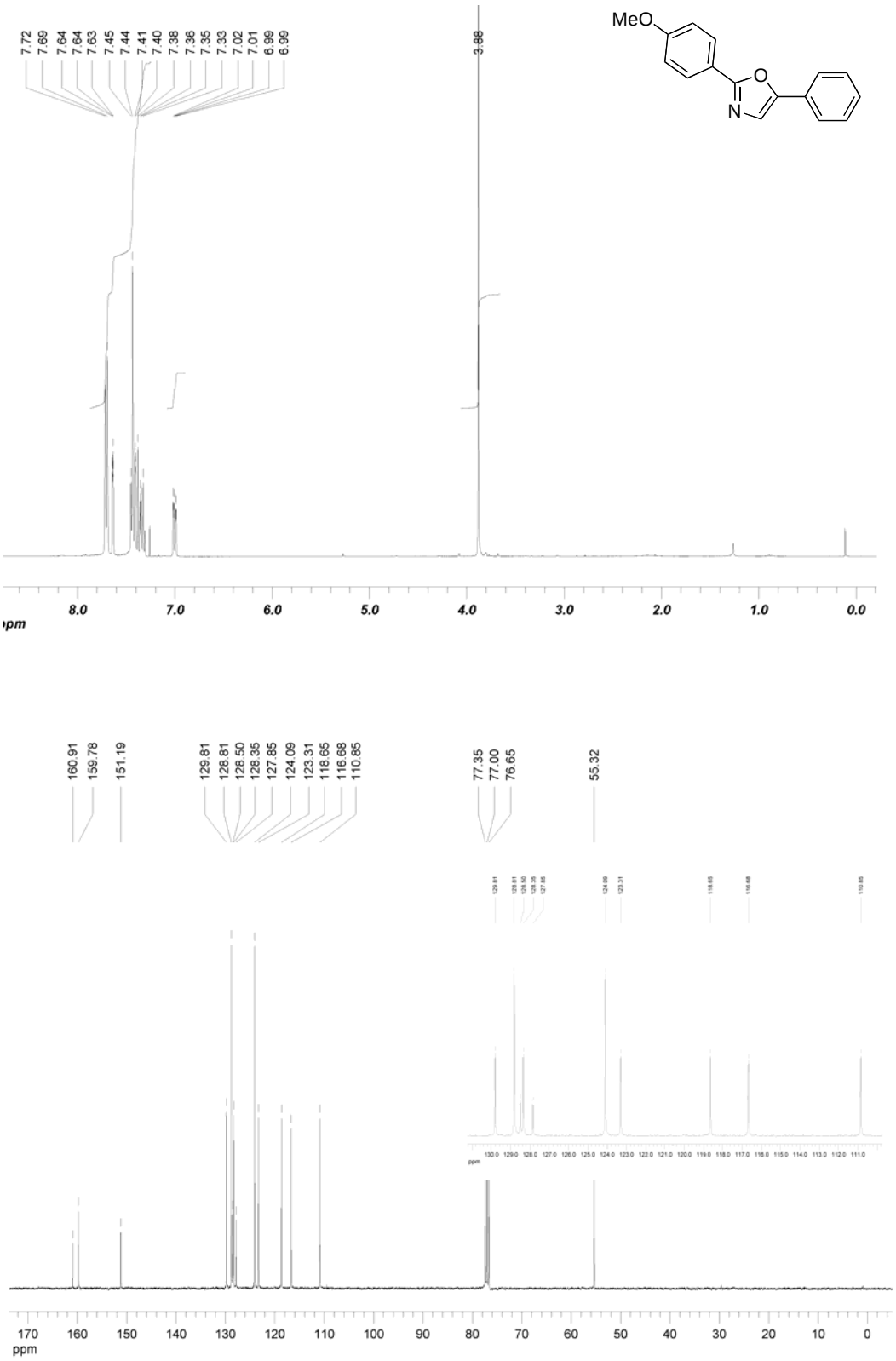
Spectroscopic Data for Chapter 4

^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 2,5-diphenyloxazole **6a**.

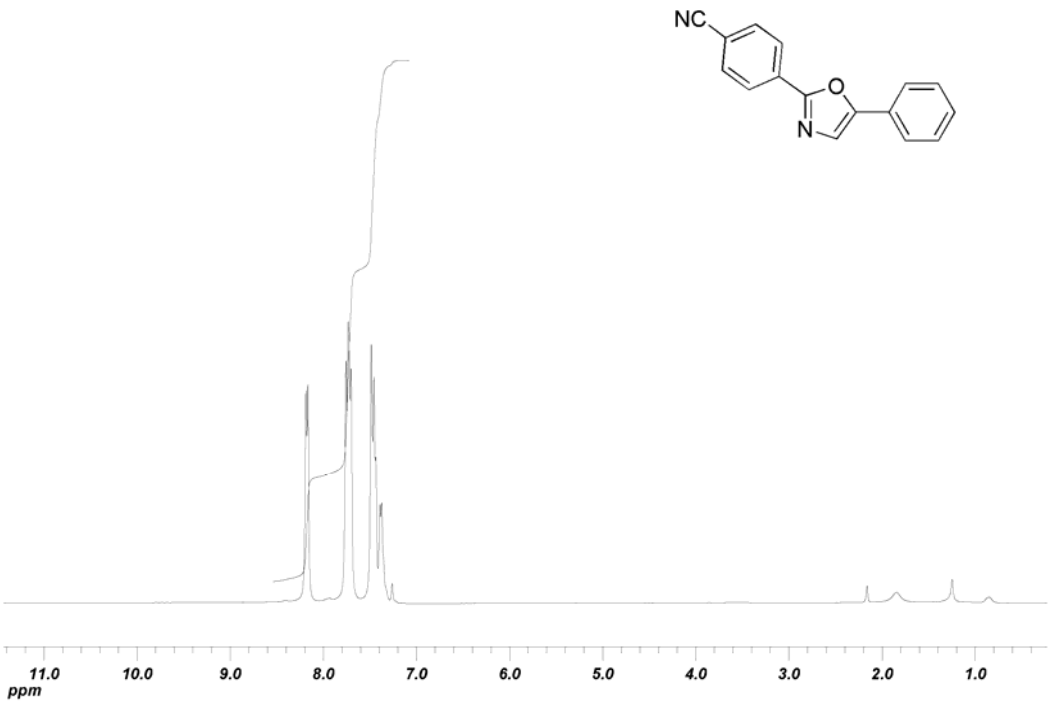


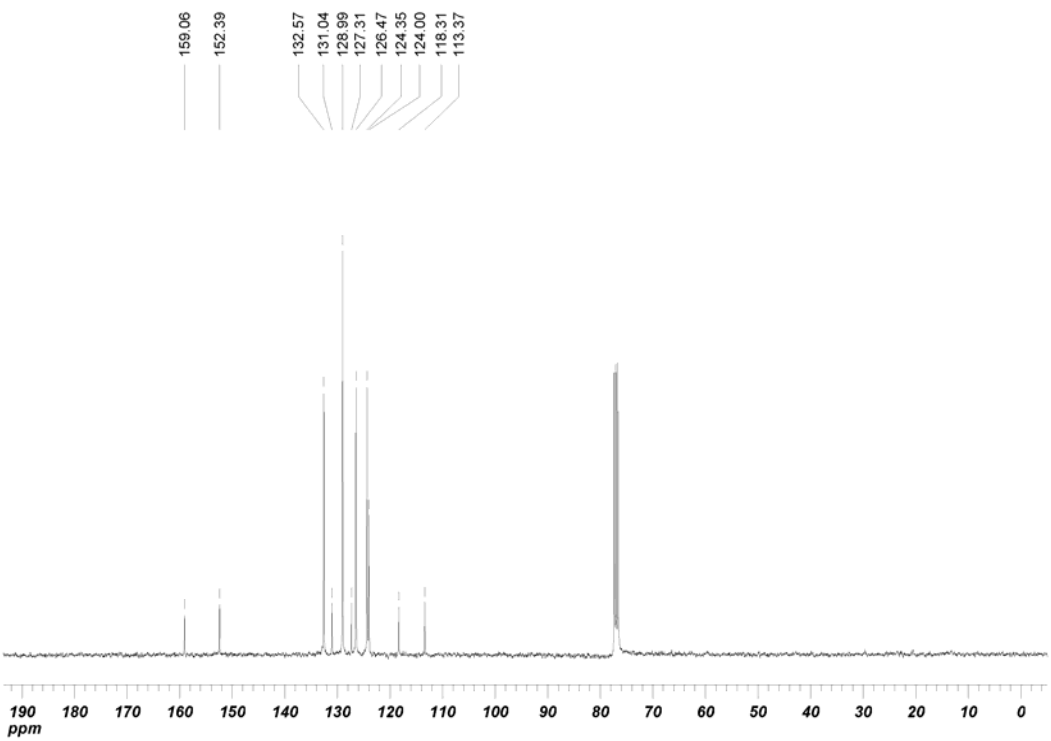


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 5-phenyl-2-(4-Methoxy-phenyl) oxazole) **6b**.

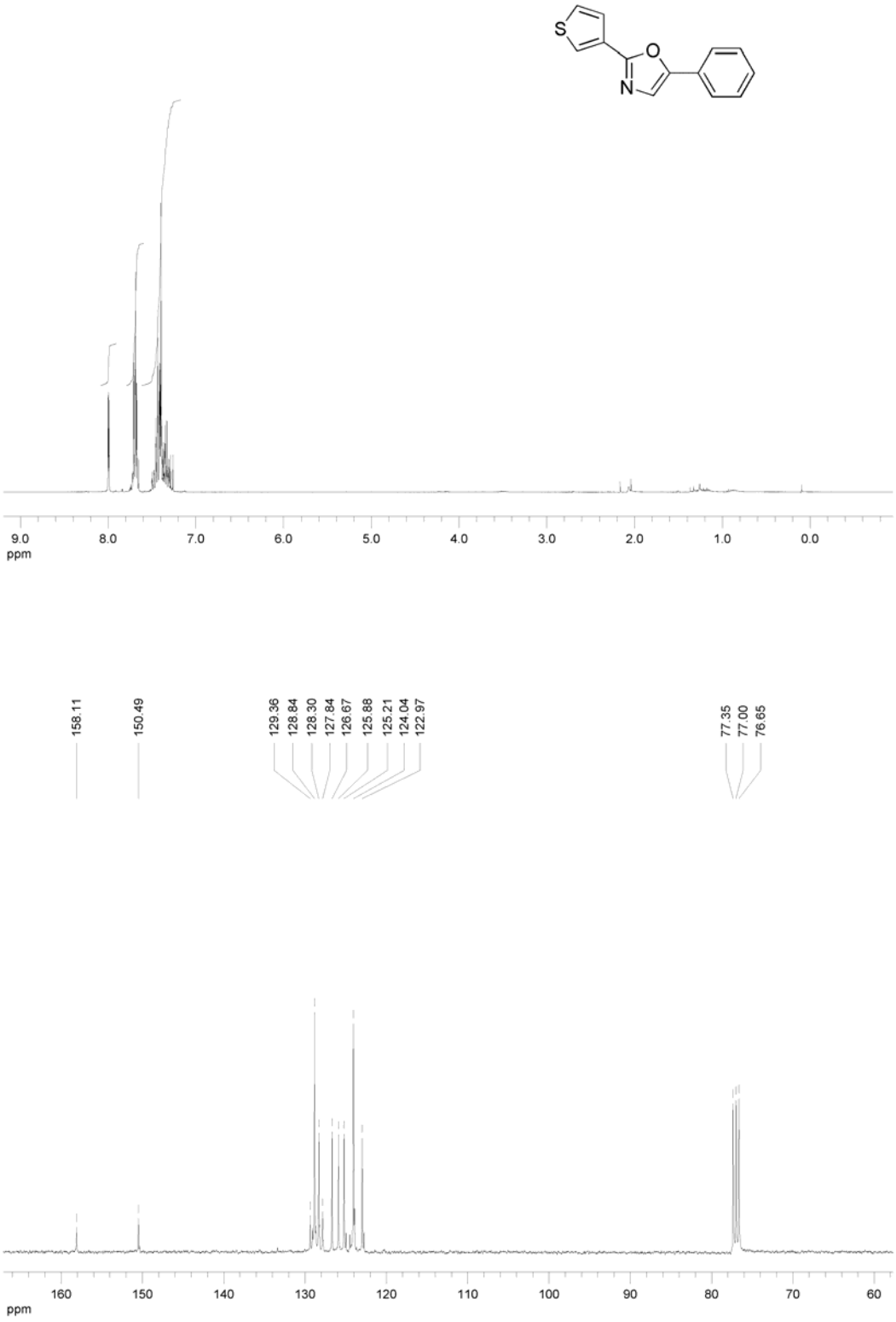


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 4-(5-Phenyl-oxazol-2-yl)-benzonitrile **6c**.

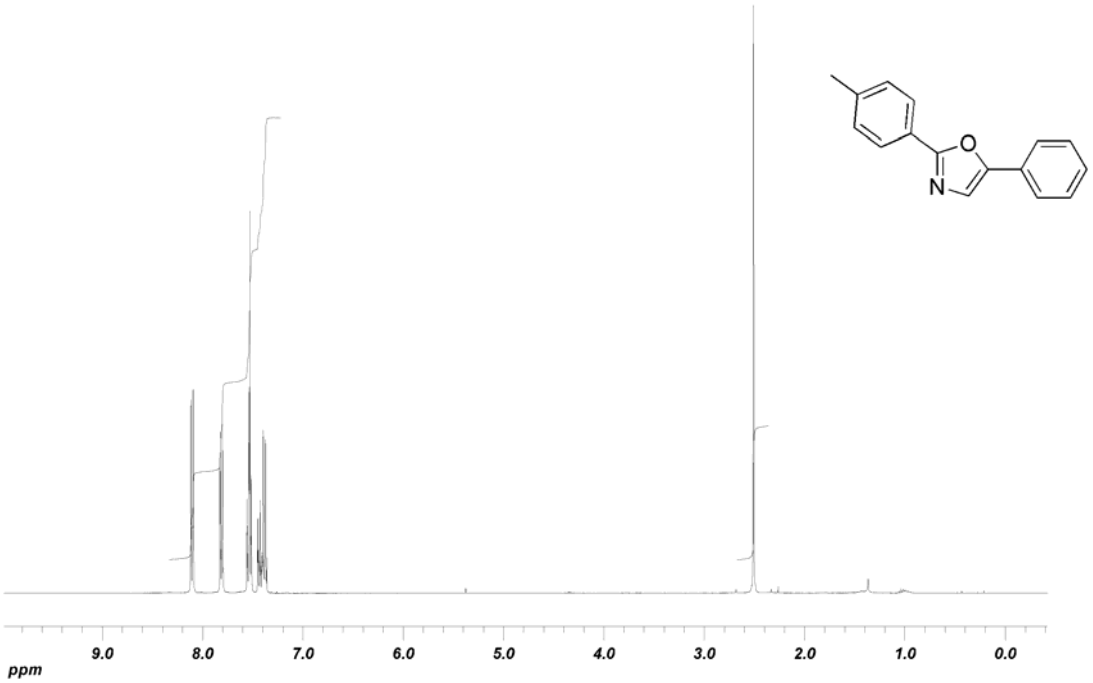


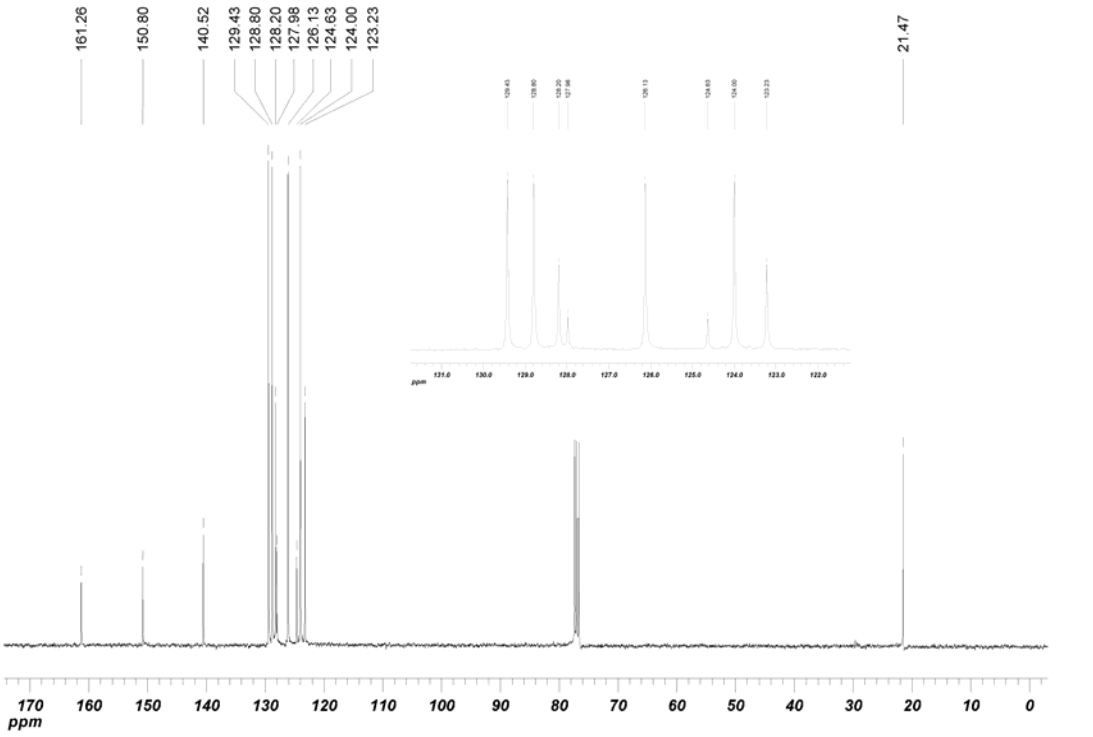


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 5-Phenyl-2-thiophene-3-yl-oxazole **6d**.

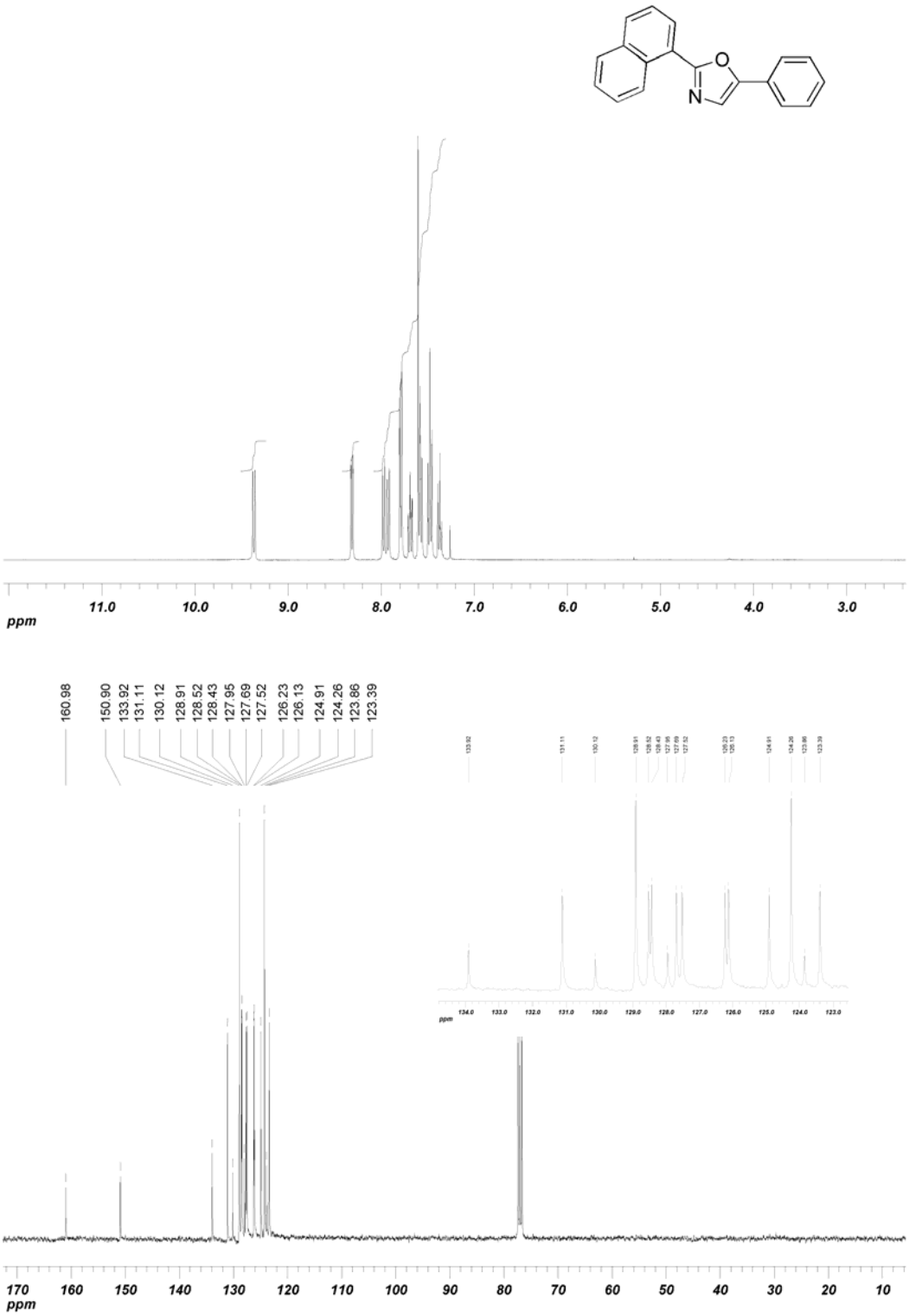


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 5-Phenyl-2-p-tolyl-oxazole **6e**.

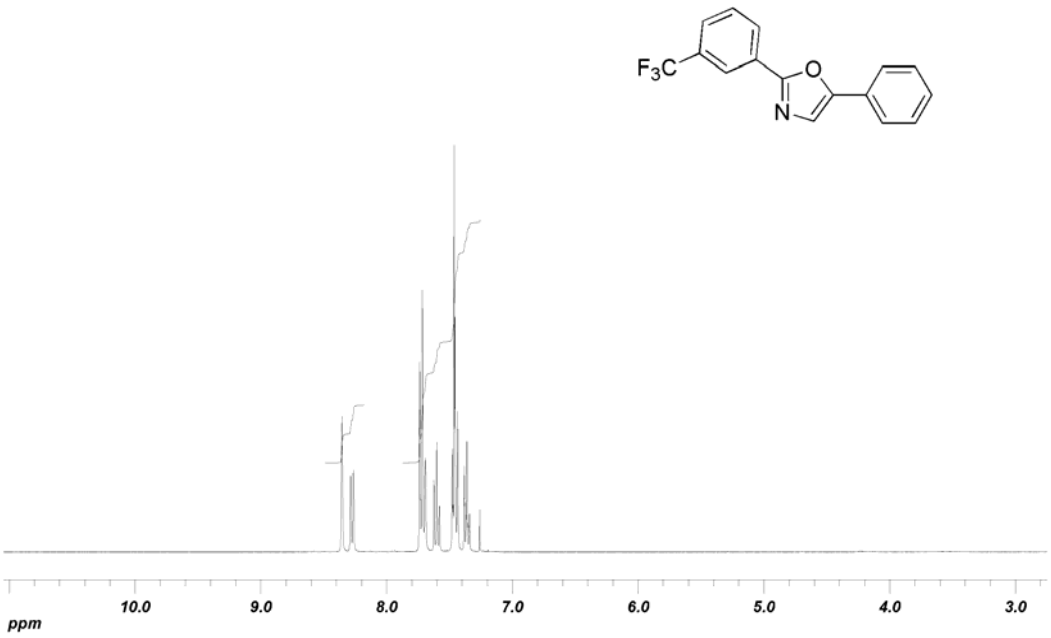


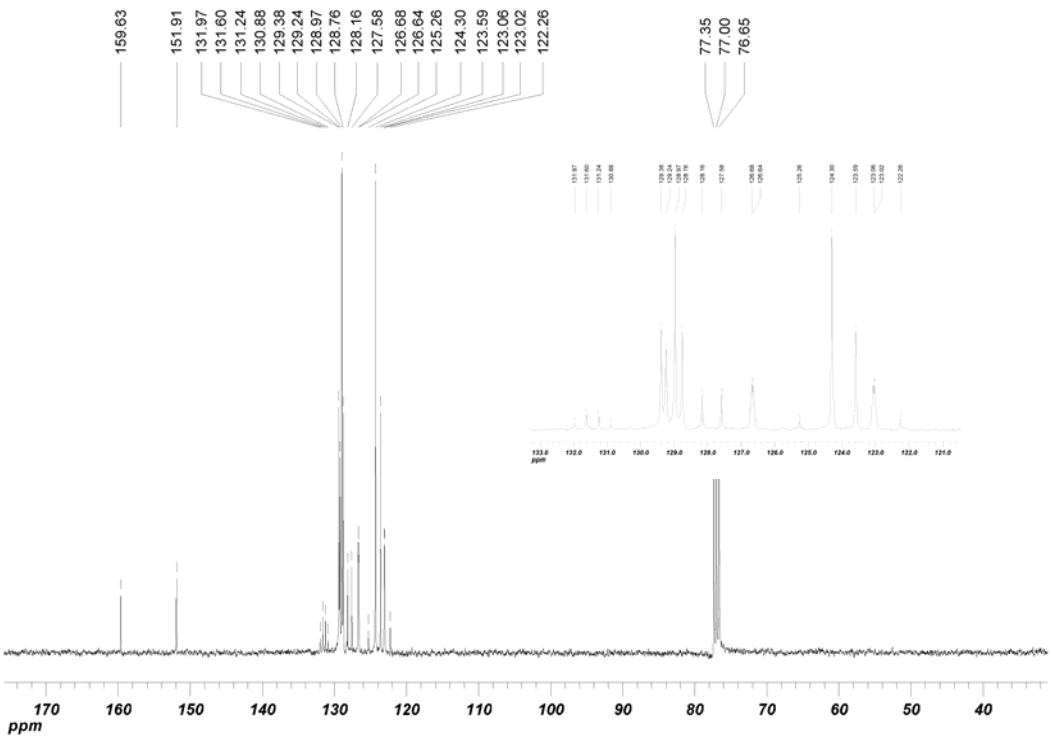


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 2-Naphtalen-1-yl-5-phenyl-oxazole **6f**.

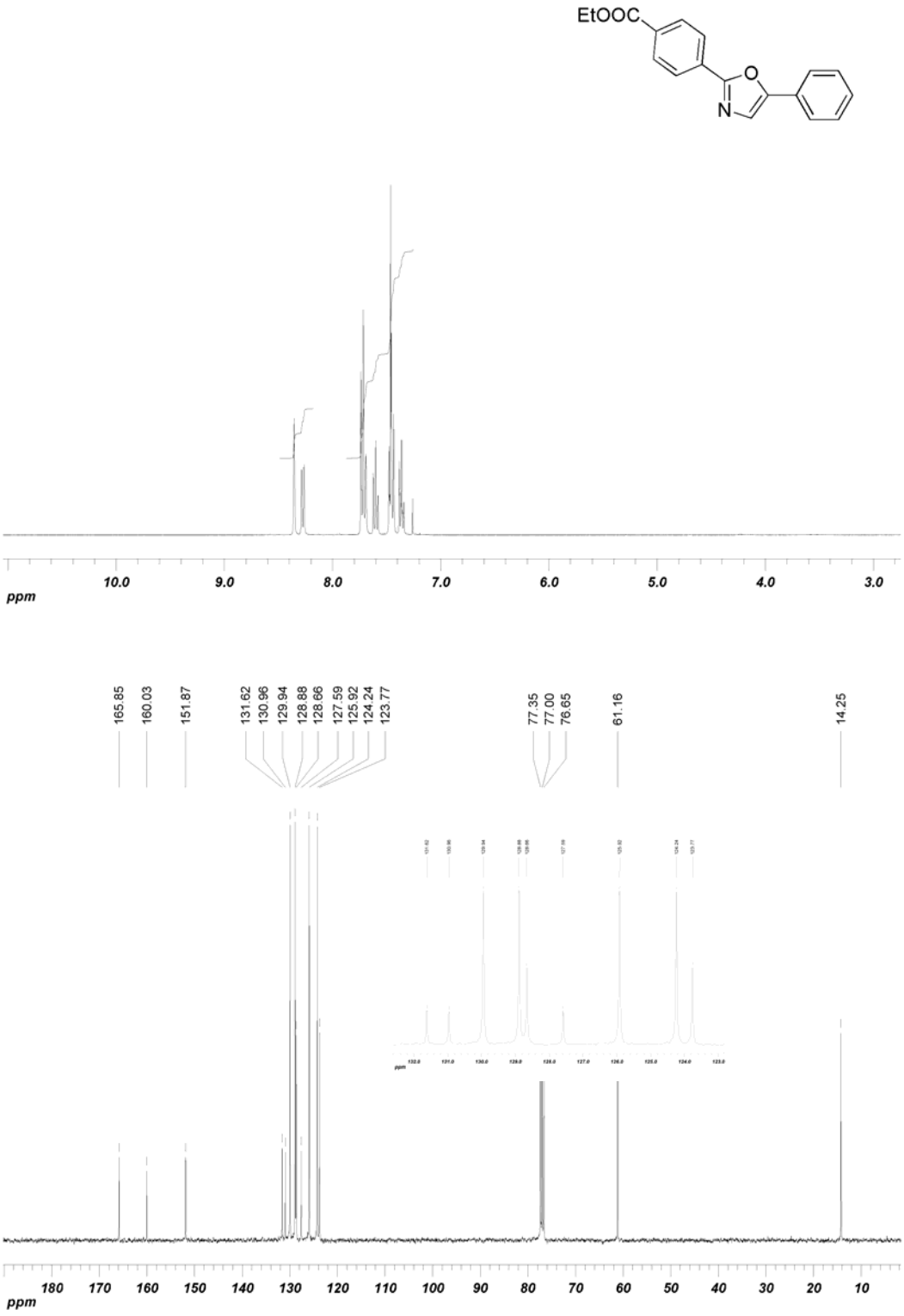


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 5-phenyl-2-(3-triofluoromethyl-phenyl)-oxazole **6g**.

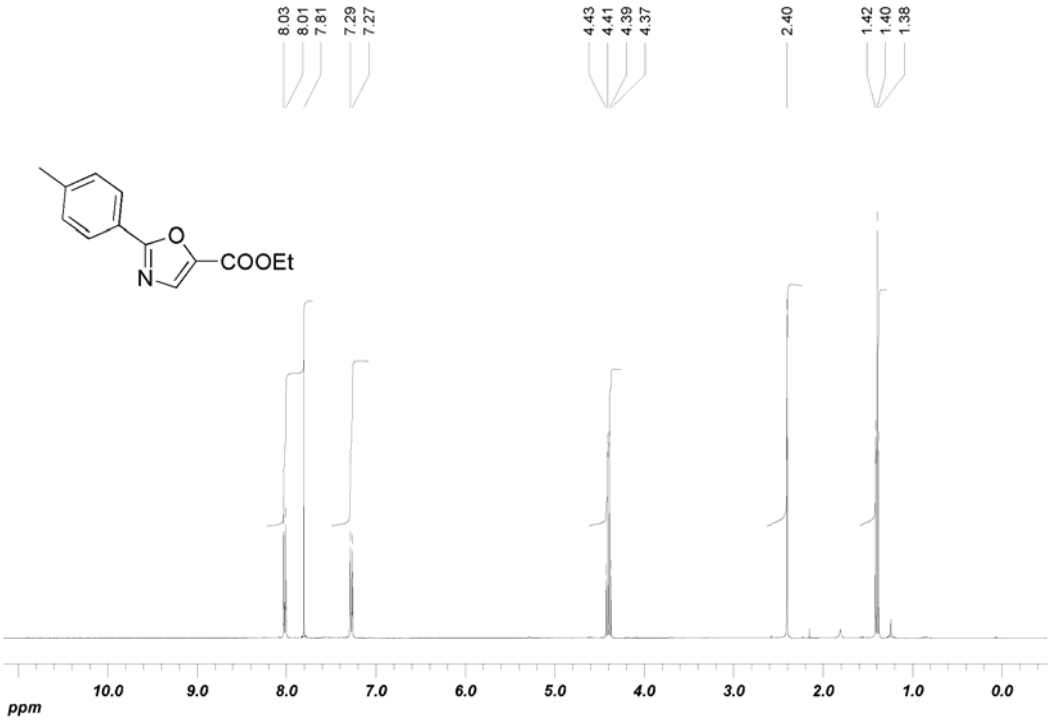


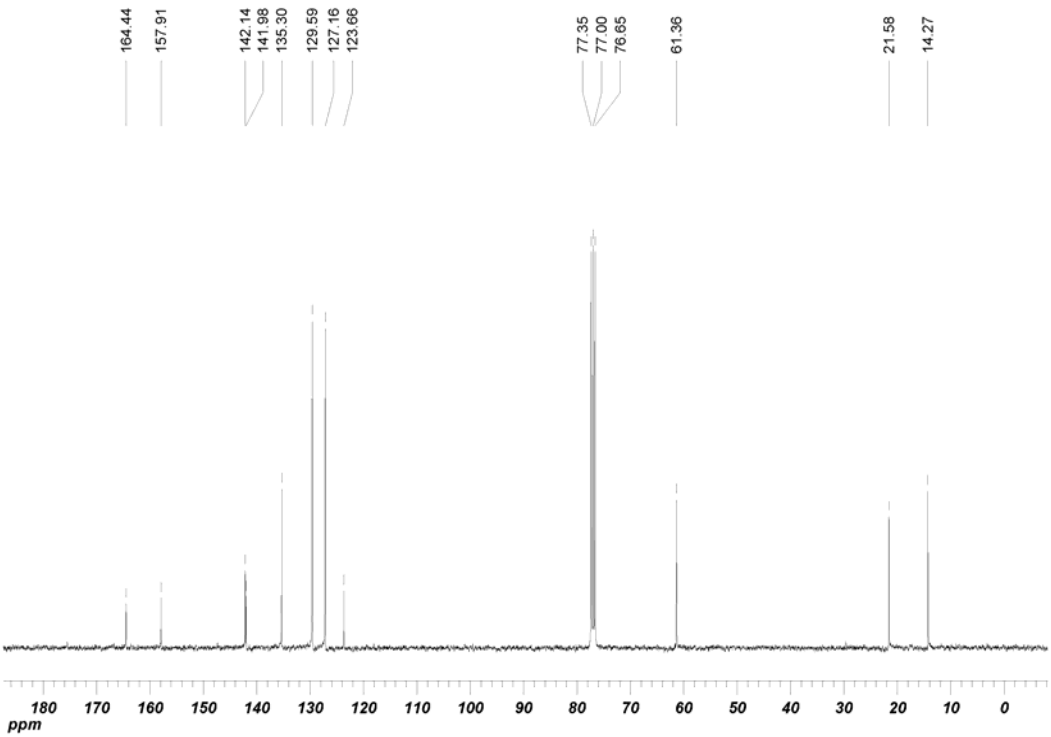


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 4-(-5-Phenyl-oxazol-2-yl)- benzoic acid ethyl ester **6h**.

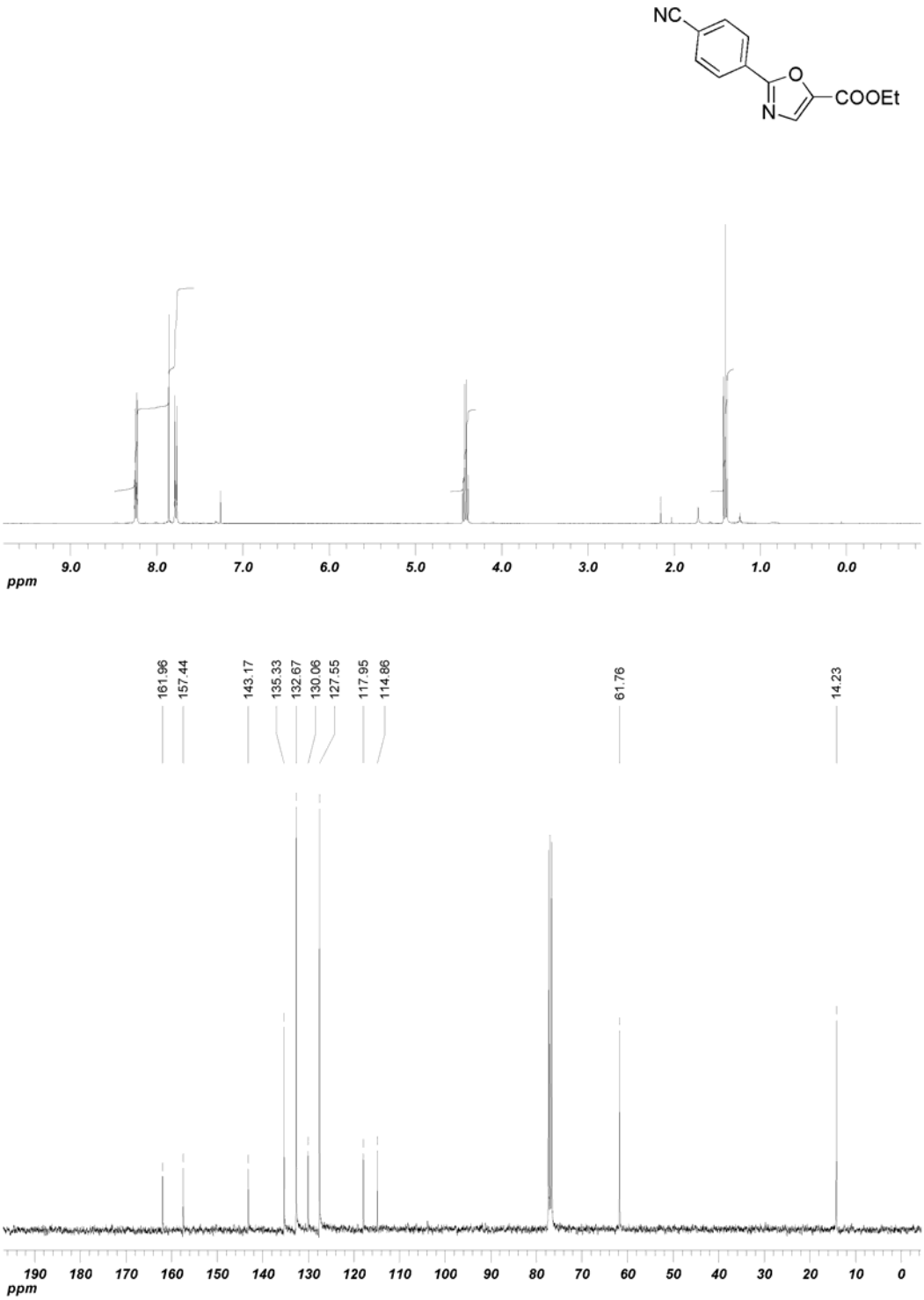


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 2-p-Tolyl-oxazole-5-carboxylic acid ethyl ester **6i**.

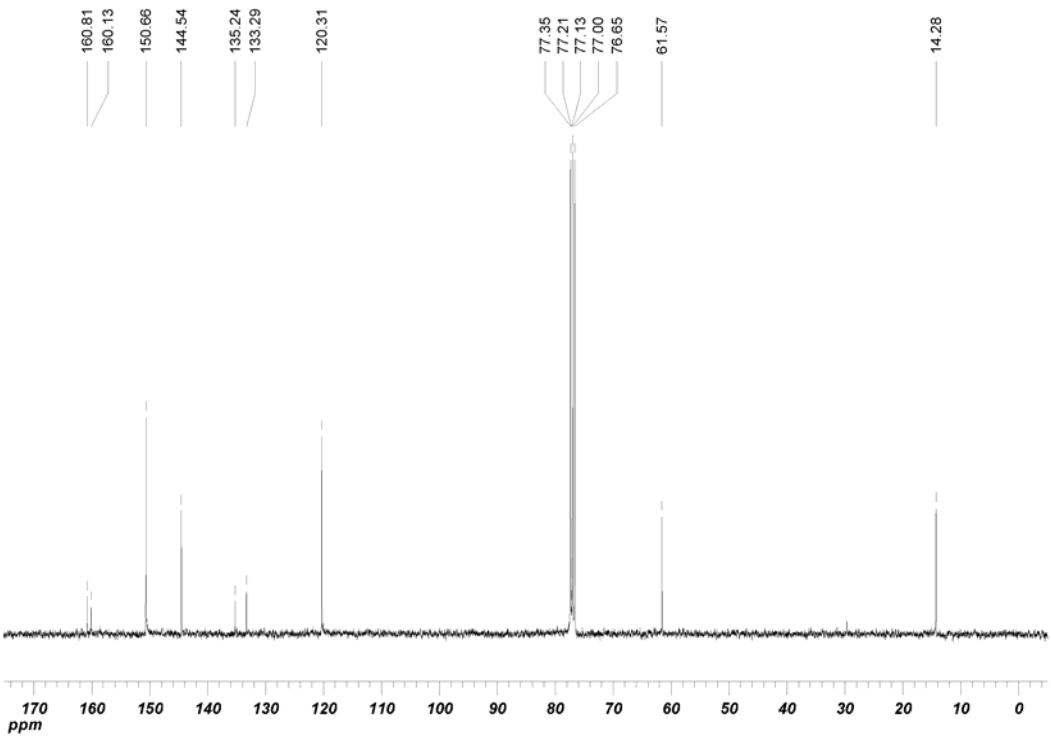




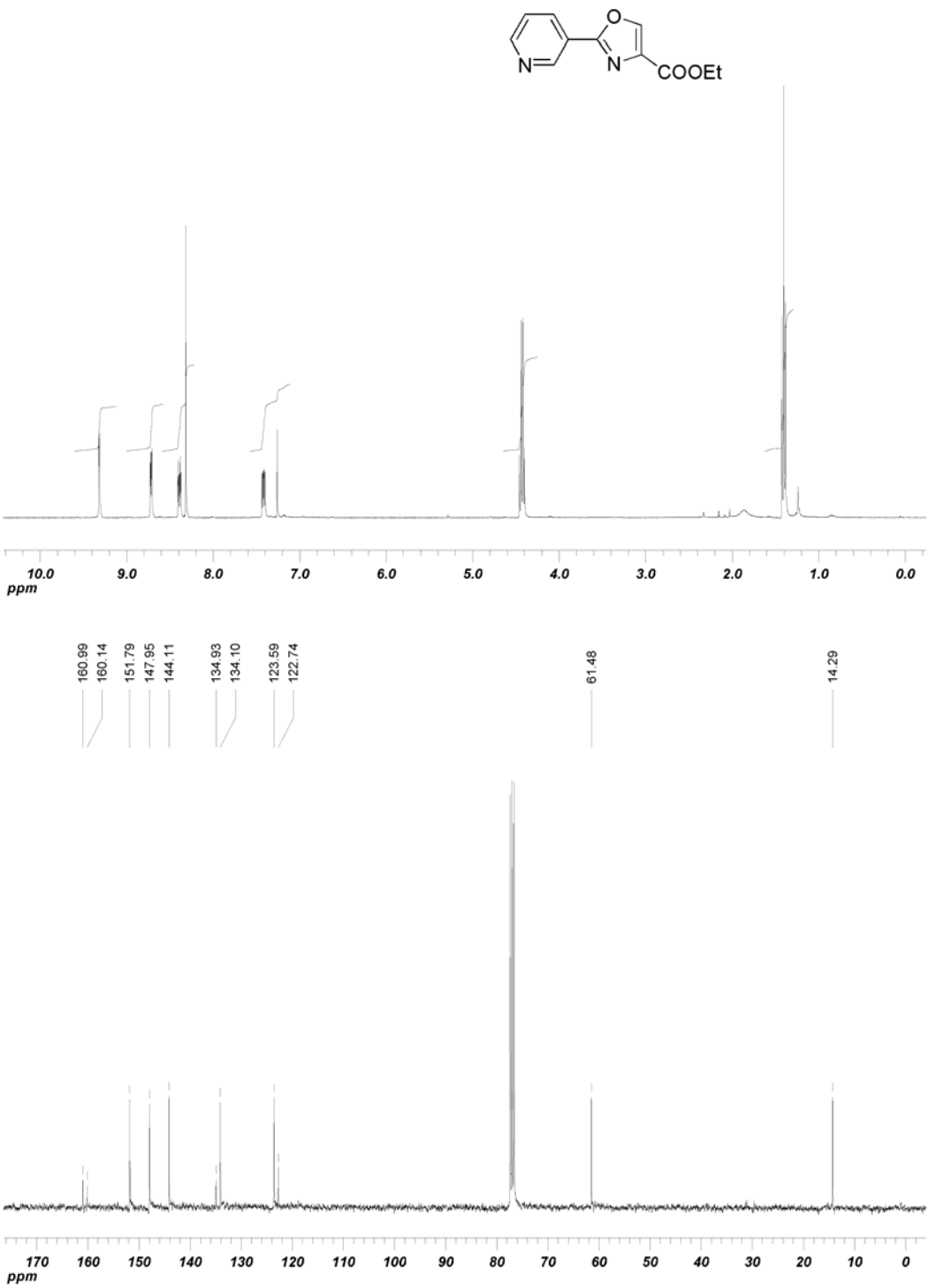
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 2-(4-Cyano-phenyl)-oxazole-5-carboxylic acid ethyl ester **6j**.



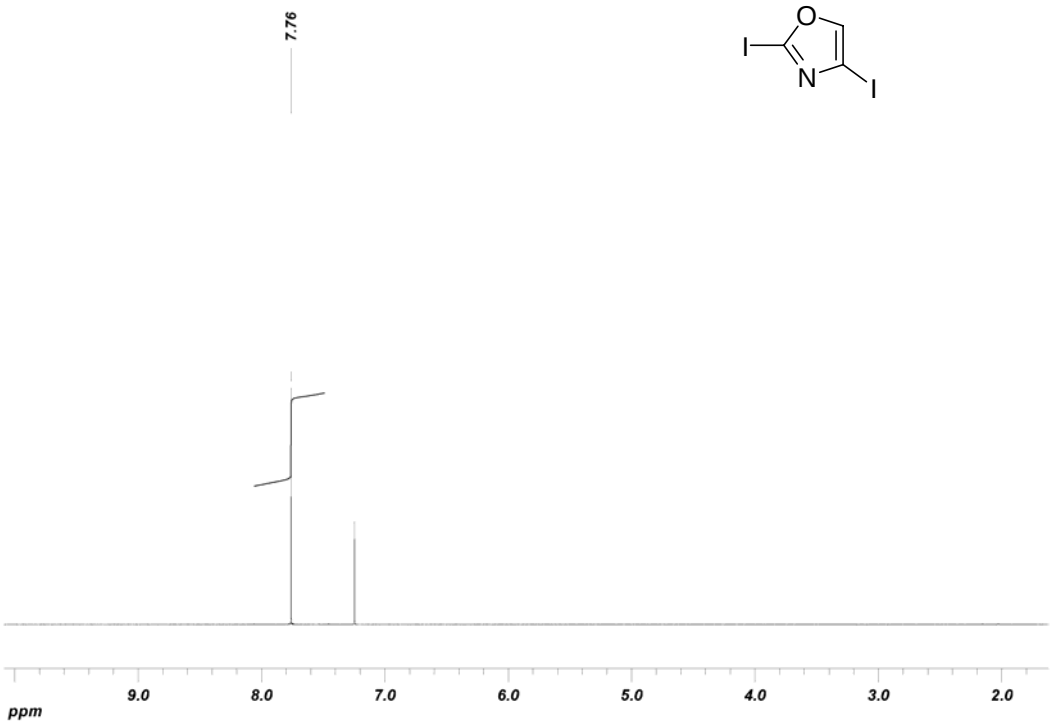
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for *2-Pyridin-4-yl-oxazole-4-carboxylic acid ethyl ester* **10p**.

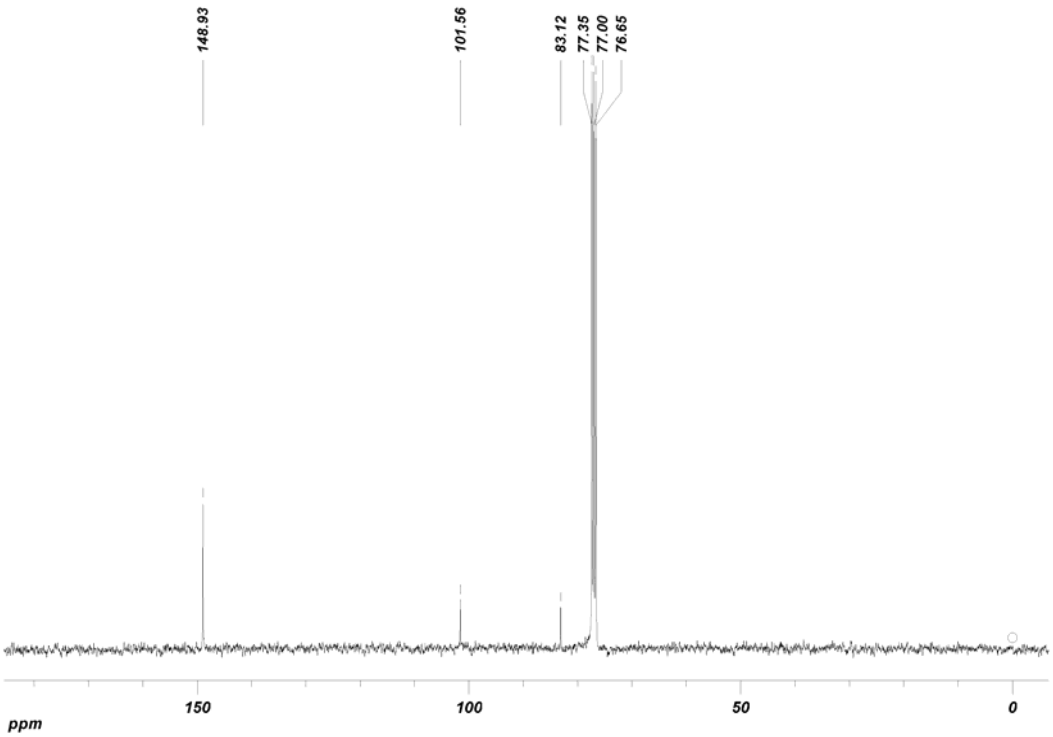


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for *2-Pyridin-3-yl-oxazole-4-carboxylic acid ethyl ester* **10o**.

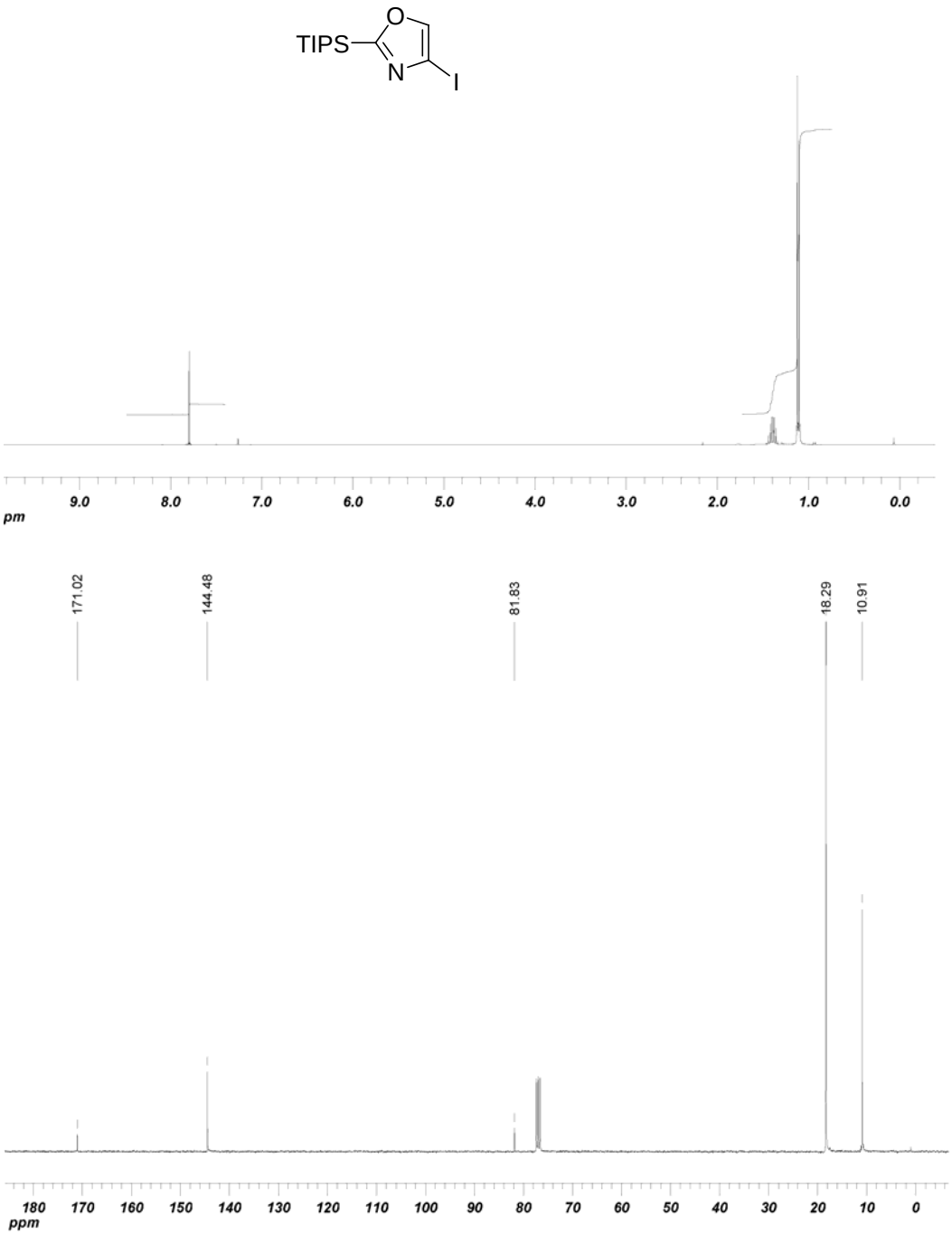


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 2,4-diiodooxazole **15**.

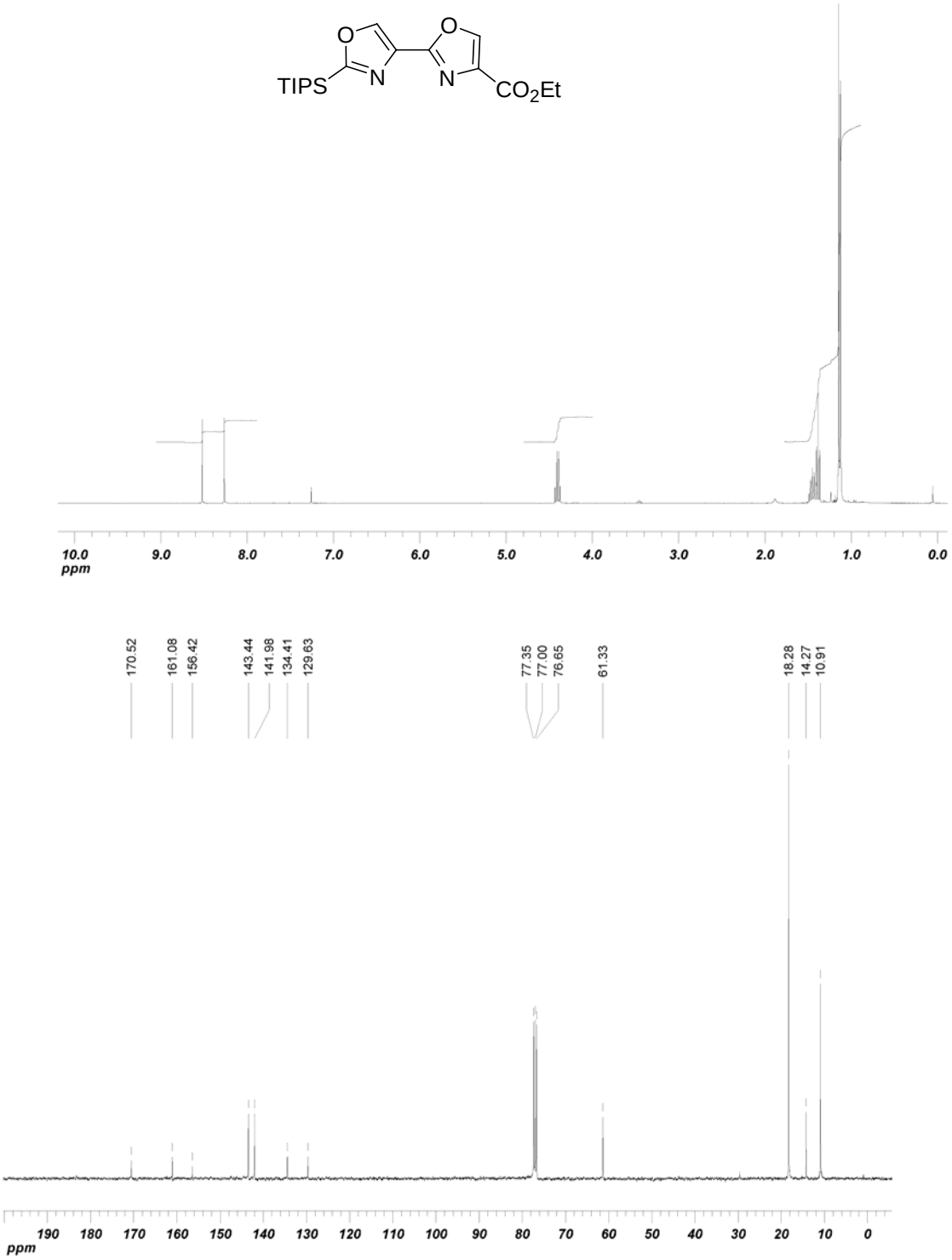




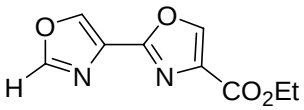
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 4-iodo-2-triisopropylsilanyl-oxazole **12a**.

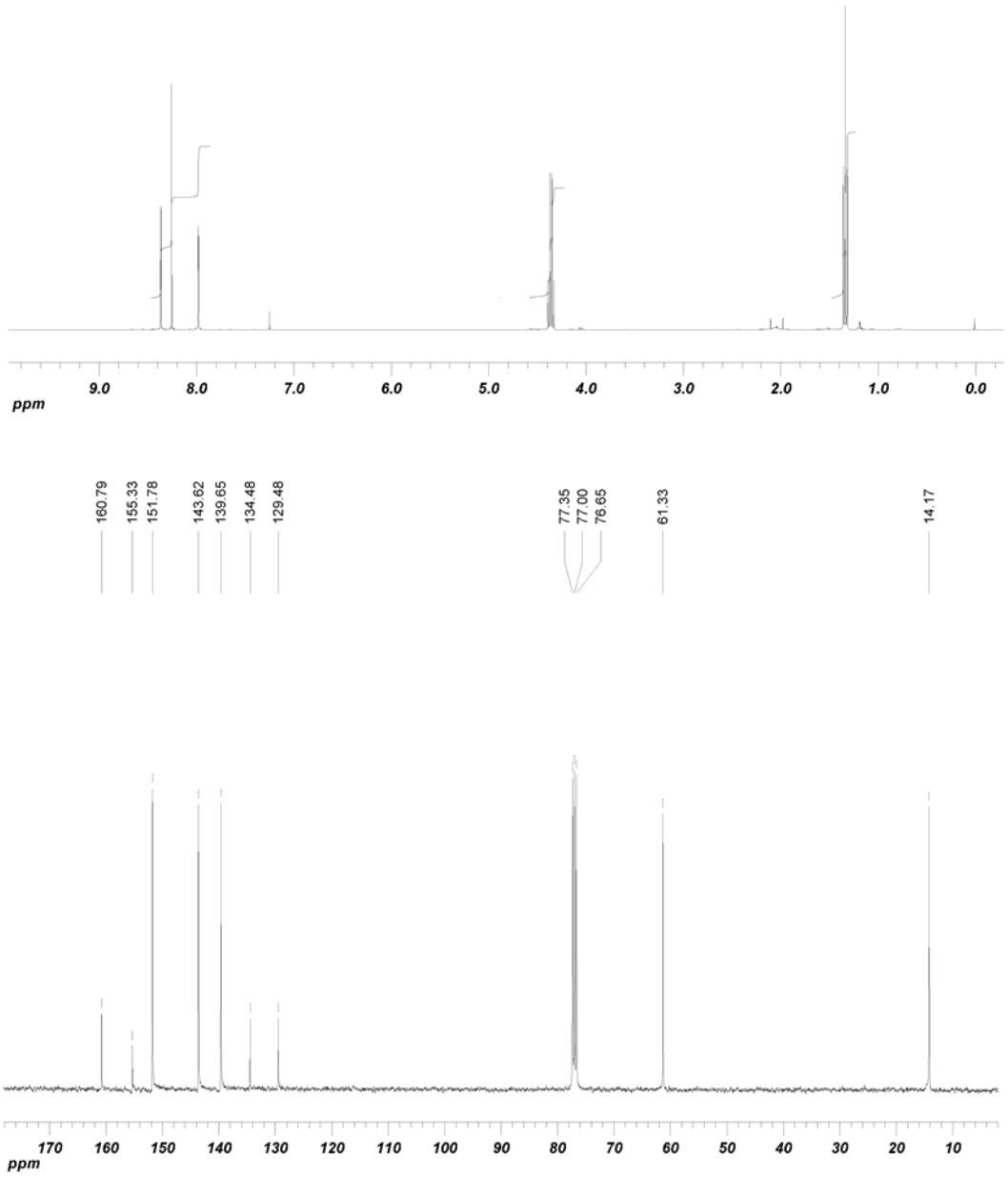


^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 2'-isopropylsilanyl-[2,4']-bioxazolyl-4-carboxylic acid ethyl ester **17**.

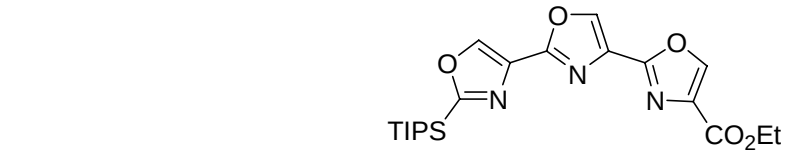


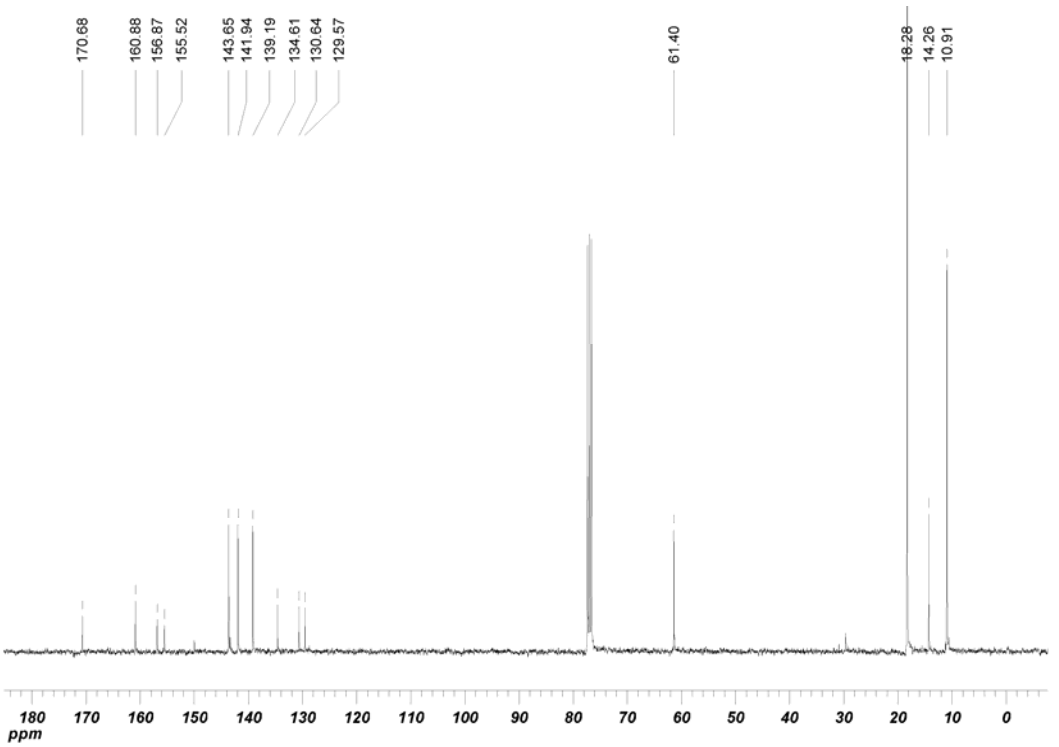
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for [2,4']Bioxazolyl-4-carboxylic acid ethyl ester **13**.



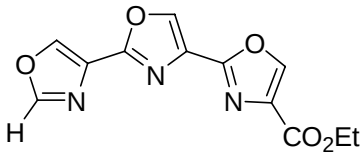


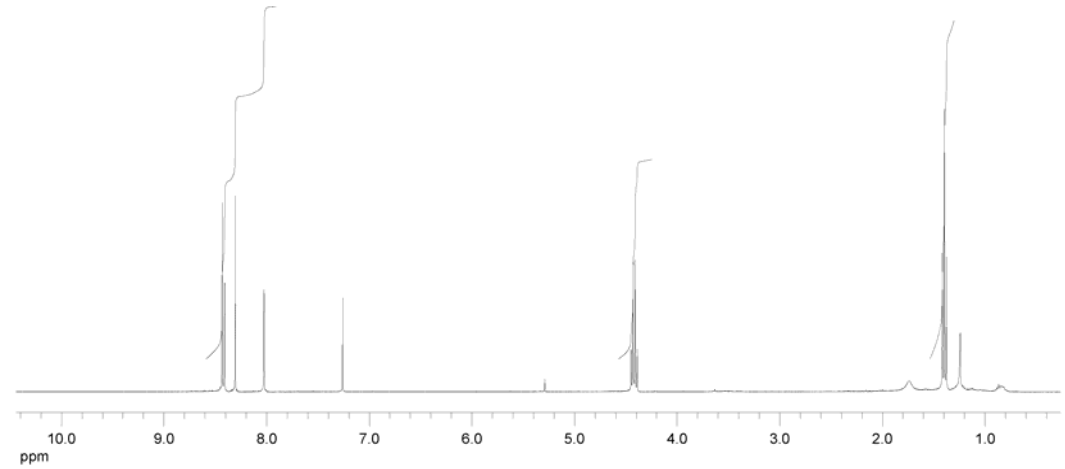
^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for 2''-Triisopropylsilanyl-[2,4';2',4''] teroxazole-4-carboxylic acid ethyl ester **18**.

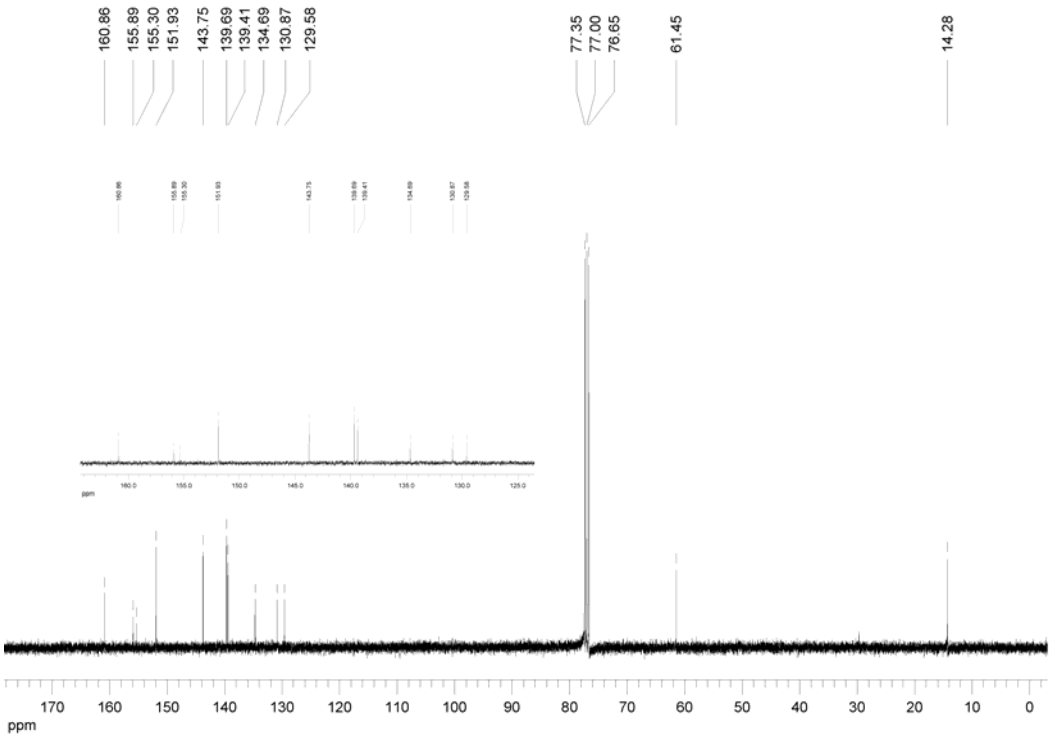




^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$) for [2, 4';2'; 4''] Teroxazole-4-carboxylic acid ethyl ester **11**.







Appendix D

Publications

ORGANIC LETTERS

2006
Vol. 8, No. 12
2495−2498

Suzuki Coupling of Oxazoles

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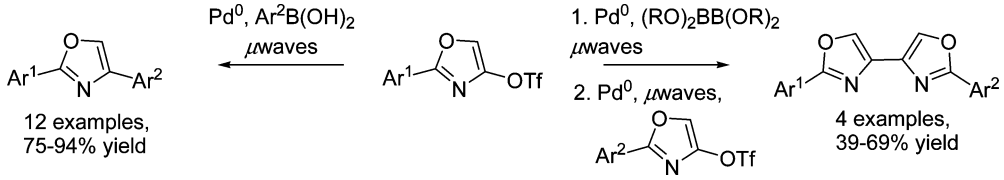
Received March 10, 2006

ABSTRACT



A protocol for the functionalization of the oxazole 2- and 4-positions using the Suzuki coupling reaction is described. 2-Aryl-4-trifloyloxazoles undergo rapid, microwave-assisted coupling with a range of aryl and heteroaryl boronic acids in good to excellent yields. The methodology is similarly effective using 4-aryl-2-chlorooxazoles as the coupling partner and has been extended to the synthesis of a novel class of homo- and heterodimeric 4,4-linked dioxazoles.

The oxazole heterocycle is a fundamental ring system found throughout chemistry in areas such as natural products, pharmaceuticals, agrochemicals, peptidomimetics, and polymers.[1] Naturally occurring oxazoles are usually found with a 2,4-substitution pattern,[2] a consequence of their biosynthetic assembly from serine residues, although 2,5-substituted oxazole natural products are known.[3]

A variety of venerable condensation methods are known for oxazole synthesis, often involving the preparation of appropriately substituted acyclic amides and their subsequent dehydrative cyclization.[4] Although tried and tested, the frequently harsh reaction conditions characteristic of the classical methods can make them unsuitable for the synthesis of multifunctional oxazoles of the type found in natural products. From a lead discovery perspective in medicinal chemistry, which frequently requires the rapid synthesis of diverse heterocycles, the preparation of oxazoles using condensation reactions can be a drawback, as it necessitates the synthesis of diversified acyclic precursors prior to cyclization, i.e., early stage rather than late stage diversification. An alternative strategy is to prepare the oxazole heterocycle at an early stage and carry out subsequent functionalizations at each position using palladium cross-coupling chemistry. This idea has been exemplified in the development of Stille,[5] Sonogashira,[6] Negishi,[7] and direct

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(2) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249−263.

(3) O'Donovan, D. G.; Horan, H. *J. Chem. Soc. C* **1971**, 331−334.

(4) For a recent review, see: Yeh, V. *Tetrahedron* **2004**, *60*, 11995−12042.

(5) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 693−696. (b) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415−416. (c) Kelly, T. R.; Lang, F. *Tetrahedron Lett.* **1995**, *36*, 5319−5322. (d) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623−4633. (e) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167−8170. (f) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640−8641. (g) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469−471. (h) Smith, A. B., III; Minbiole, K. P.; Freeze, S. *Synlett* **2001**, *11*, 1739−1742. (i) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942−10953.

(6) (a) Sakamoto, T.; Nagata, H.; Kondo, Y.; Shiraiwa, M.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 823−828. (b) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2485−2488. (c) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812−6815. (d) Su, Q.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *48*, 1223−1225.

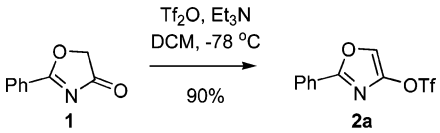
(7) (a) Harn, N. K.; Gramer, C. J.; Anderson, B. A. *Tetrahedron Lett.* **1995**, *36*, 9453−9456. (b) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583−585. (c) Anderson, B. A.; Becke, L. M.; Booher, R. N.; Flaugh, M. F.; Harn, N. K.; Kress, T. J.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem.* **1997**, *62*, 8634−8639. (d) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011−1014. (e) Reeder, M. R.; Gleaves, H. E.; Hoover, S. A.; Imbordino, H. R.; Pangborn, J. J. *Org. Process Res. Dev.* **2003**, *7*, 696−699.

10.1021/ol060591j CCC: $33.50
Published on Web 05/11/2006

arylation methods[8] for the functionalization of oxazoles in recent years. The Suzuki coupling, by contrast, has seen relatively little application:[9] Hodgetts described the coupling of phenyl boronic acid to 2-, 4-, and 5-halo-oxazoles,[10] of 2-aminophenyl boronic acid to 5-halo-oxazoles, and of 3,4-dimethoxyphenyl boronic acid to 2-bromooxazole; Taylor has examined the coupling of phenyl and 3-thiophene boronic acid to two 2-chloro oxazoles.[11] We chose to examine the functionalization of the oxazole 2- and 4-positions with a view of developing a versatile Suzuki methodology for the generation of a range of arylated and heteroarylated oxazoles.

We began by preparing 2-phenyl-4-trifloyloxazole, **2a**, from oxazolone **1** to study Suzuki coupling at the oxazole 4-position (Scheme 1). The synthesis of trifloyl oxazoles

Scheme 1. Synthesis of 2-Phenyl-4-trifloyloxazole

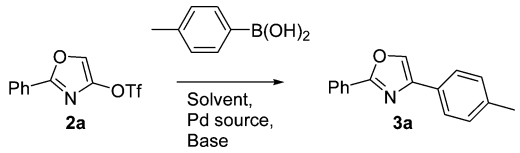


from oxazolones, first introduced by Barrett[5b] and Kelly[5c] in the context of the Stille reaction, enables the regiocontrolled installation of an electrophile functional group for subsequent palladium cross-coupling. This strategy avoids potential regioselectivity problems inherent to direct halogenation at the oxazole 4-position and has been employed successfully in several Stille and Sonagashira oxazole cross-coupling reactions.[5g−i,6b−d] Triflate **2** is a crystalline solid that can be stored for several months at −20 °C.

A range of conditions were examined for the Suzuki coupling of **2a** with tolylboronic acid (Table 1). It was immediately clear that the substrate could not tolerate strong bases such as KO^{t}Bu or NaOH often employed in the reaction (Table 1, entries 1−5), as they caused extensive degradation of the triflate with very little coupled product (**3a**) being observed. Use of a weaker base with $PdCl_2(PPh_3)_2$ as catalyst provided the first signs of a successful reaction; refluxing in THF for 2 days using aqueous Na_2CO_3 as base produced **3a** in 16% yield (Table 1, entry 6), which could be improved to 48% by switching to the higher-boiling solvent dioxane (Table 1, entry 7).

The combination of a PCy_3/$Pd(OAc)_2$ catalyst system with potassium fluoride as base, reported to be effective for the

Table 1. Optimization of Suzuki Coupling of Triflate **2a** with Tolylboronic Acid[a]



entry	catalyst	base	time	solvent	yield[g]
1	$PdCl_2(dppf)$	K_3PO_4	48 h	dioxane	traces
2	$PdCl_2(dppf)$	NaOH	20 h	dioxane	0%
3	$PdCl_2(dppf)$	KO^{t}Bu	20 h	dioxane	0%
4	$Pd(PPh_3)_4$	NaOH	16 h	aq dioxane	traces
5	$Pd(PPh_3)_4$	NaOH	16 h	CH_3CN	traces
6	$PdCl_2(PPh_3)_2$	Na_2CO_3, 2 M	48 h	THF[d]	16%
7	$PdCl_2(PPh_3)_2$	Na_2CO_3, 2 M	16 h	dioxane	48%
8	$Pd(OAc)_2$, PCy_3[b]	KF	72 h	THF	traces
9	$Pd(OAc)_2$, PCy_3[c]	KF	72 h	THF	36%
10	$PdCl_2(PPh_3)_2$	Na_2CO_3, 2 M	20 min	dioxane[e]	94%
11	$PdCl_2(PPh_3)_2$[f]	Na_2CO_3, 2 M	40 min	dioxane[e]	67%

[a] Conditions: 5 mol % catalyst loading, 3 equiv of base, reflux. [b] 1% of $Pd(OAc)_2$ and 1.2% of PCy_3. [c] 5% of $Pd(OAc)_2$ and 6% of PCy_3. [d] Reaction was carried out at 60 °C. [e] Microwave irradiation at 150 °C for 20 min. [f] 1 mol % catalyst loading. [g] Isolated yield after SiO_2 chromatography.

Suzuki coupling of aryl triflates under mild conditions,[12] proved ineffective with the oxazole substrate producing a low yield of coupled product after prolonged reflux (Table 1, entries 8 and 9). The beneficial effect of combining a weak base with higher reaction temperatures led us to examine the reaction under microwave heating. We were pleased to observe that irradiation in dioxane for 20 min at 150 °C (Table 1, entry 10) produced the desired 4-tolyl oxazole in an excellent 94% yield. The catalyst loading could be reduced to 1% but at the expense of a longer reaction time and a decrease in yield (Table 1, entry 11).

The methodology was extended to the synthesis of a range of 2,4-disubstituted oxazoles (Table 2). We were pleased to observe excellent reactivity for a variety of electron-deficient and electron-rich aryl boronic acids (Table 2, entries 1−12), ortho-substituted aryl boronic acids (Table 2, entry 4), as well as heteroaromatic pinacol boronic esters (Table 2, entries 8−10) with yields being uniformly good to excellent. The reaction was tolerant of alternative aryl groups in the 2-position, with electron-donating (Table 2, entries 7, 10, and 12) and electron-withdrawing groups (Table 2, entry 5) producing high yields of 4-substituted oxazoles.

Having established a robust protocol for Suzuki coupling at the 4-position, we then turned our attention to the 2-position. We initially investigated a similar strategy for the preparation of the Suzuki electrophile by synthesizing 4-phenyl-4-oxazalin-2-one **4**[6b] and attempting to convert it to the known 2-trifloyl oxazole **5** (Scheme 2). Although the triflate could be prepared and isolated as described by Panek,[6b] it was quite thermally unstable and decomposed

(8) (a) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257−272. (b) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467−473. (c) Hoarau, C.; Du Fou de Kerdaniel, A.; Bracq, N.; Grandclaudon, P.; Couture, A.; Marsais, F. *Tetrahedron Lett.* **2005**, *46*, 8573−8577.

(9) (a) Maekawa, T.; Sakai, N.; Tawada, H.; Murase, K.; Hazama, M.; Sugiyama, Y.; Momose, Y. *Chem. Pharm. Bull.* **2003**, *51*, 565−573. (b) Buzon, R. A., Sr.; Castaldi, M. J.; Li, Z. B.; Ripin, D. H. B.; Tao, Y. PCT Int. Appl. WO 2004020438 A2 20040311, 2004; *Chem. Abstr.* **2004**, *140*, 235721. (c) Tanaka, T.; Hirai, K.; Takemura, C.; Kita, H. Japanese Patent JP 2005223238 A2 20050818, 2005; *Chem. Abstr.* **2005**, *143*, 239833.

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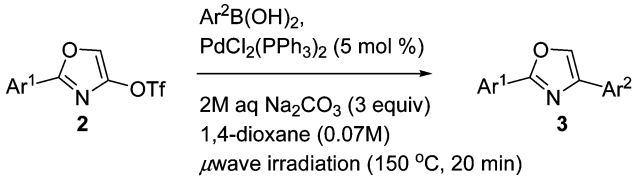
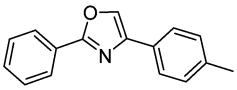
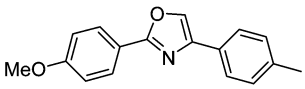
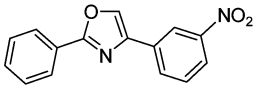
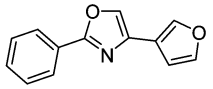
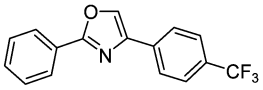
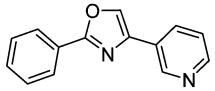
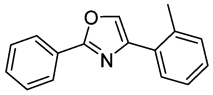
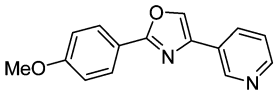
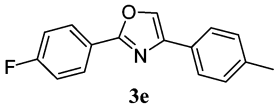
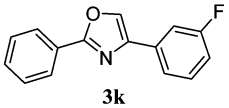
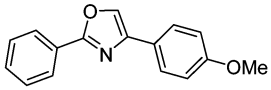
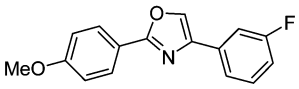
(11) Young, G. L.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 3797−3801.

(12) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

Table 2. Suzuki Coupling of Oxazolyl 4-Triflates



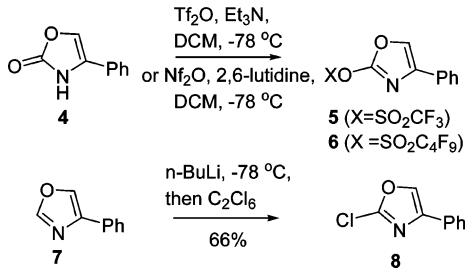
entry	product 2	yield (%)[a]	entry	product 2	yield (%)[a]
1	 **3a**	94	7	 **3g**	82
2	 **3b**	92	8[b]	 **3h**	79
3	 **3c**	87	9[b]	 **3i**	73
4	 **3d**	91	10[b]	 **3j**	89
5	 **3e**	75	11	 **3k**	91
6	 **3f**	89	12	 **3l**	85

[a] Isolated yield after SiO_2 chromatography. [b] Pinacolato boronic ester used in coupling.

immediately when exposed to the high temperatures of our Suzuki reactions.

The nonaflate **6** proved slightly more robust and could be isolated and purified by column chromatography. However, when subjected to the reaction conditions for Suzuki coupling, it likewise rapidly decomposed. Efforts to transform **4** into alternative Suzuki electrophiles using $POBr_3$, $(Ph)_3PBr_2$, or $(Ph)_2POCl$ were unsuccessful. As an alternative to the triflate group at the 2-position, we decided to prepare 2-chloro oxazoles, readily synthesized by Vedejs' protocol of oxazole lithiation and subsequent trapping with hexachloroethane, a method that avoids ring-opening complications of the lithiooxazole.[13] The 2-chloro-4-phenyloxazole **8** proved to be an excellent substrate for Suzuki coupling under our optimized conditions. A range of boronic acids could be coupled to the chloride in generally excellent yields (Table 3, entries 1−5).

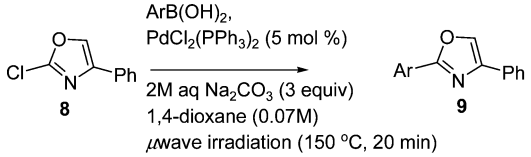
Scheme 2. Activation of the Oxazole 2-Position

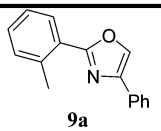
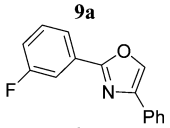
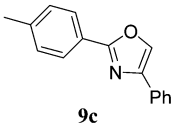
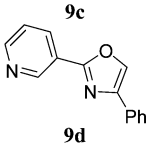
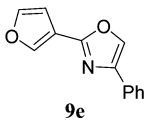


With an arylation methodology in place for the oxazole 2- and 4-positions, we were interested in extending the reaction to the coupling of two oxazole units to make a dioxazole. This reaction would represent the first steps in the development of a general Suzuki coupling strategy for the synthesis of polyoxazoles. The challenge here is to successfully synthesize an oxazole boronic acid, a class of compound rarely described in the literature.[9c,14] The carbon−boron bond can be susceptible to protonolysis when adjacent to a heteroatom, leading to stability problems and handling

(13) Atkins, J. M.; Vedejs, E. *Org. Lett.* **2005**, *7*, 3351−3354.

Table 3. Synthesis of 2,4-Disubstituted Oxazoles from **8**



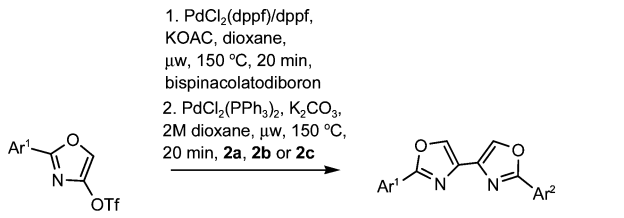
entry	product (5)	yield (%)[a]
1	 **9a**	80
2	 **9b**	80
3	 **9c**	88
4[b]	 **9d**	91
5[b]	 **9e**	82

[a] Isolated yield after SiO_2 chromatography. [b] Pinacolato boronic ester used in coupling.

difficulties.[15,16] As a result, we decided to examine the in situ generation of boronic esters and their subsequent one-pot Suzuki coupling. Accordingly, we treated triflate **2a** with bispinacolatodiboron under microwave-accelerated Miyaura conditions until the starting material had disappeared by TLC (Scheme 3). The same reaction vessel was then recharged with 5 mol % of $PdCl_2(PPh_3)_2$, aqueous sodium carbonate, and an additional equivalent of the triflate **2a**. We were

(14) During the preparation of this paper, a protocol for the synthesis and Suzuki coupling of oxazol-4-ylboronates was reported: Araki, H.; Katoh, T.; Inoue, M. *Synlett* **2006**, 555−558.

Scheme 3. Synthesis of 4,4-Dioxazoles Using the Suzuki−Miyaura Reaction



2a, Ar^1=Ph
2b, Ar^1=*p*-fluorophenyl
2c, Ar^1=*p*-methoxyphenyl

10, Ar^1=Ar^2=Ph (58%)
11, Ar^1=Ar^2=*p*-fluorophenyl (69%)
12, Ar^1=Ar^2=*p*-methoxyphenyl (61%)
13, Ar^1=Ph, Ar^2=*p*-fluorophenyl (39%)

pleased to observe that microwave heating to 150 °C for 20 min produced the novel homodimeric dioxazole **10** in 58% yield.

The Suzuki−Miyaura reaction could also be applied to the 2-(*p*-fluorophenyl)- and 2-(*p*-methoxyphenyl)-substituted oxazole triflates **2b** and **2c** producing the homodimers **11** and **12** in good yield, as well as the cross-coupling of triflates **2a** and **2b** to give the heterodimer **13** in 39% yield.

To conclude, we have developed a protocol for the arylation of the oxazole 2- and 4-positions using the Suzuki coupling. The method is quick, versatile, works in high yield, and has been applied to the preparation of a new class of dimeric 4,4-linked dioxazoles. Future work will develop Suzuki coupling strategies for polyoxazole synthesis.

Acknowledgment. We thank GSK and the University of Edinburgh for funding, Prof Mark Bradley and Biotage for the use of a Smith synthesizer, and the EPSRC mass spectrometry service at the University of Swansea.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060591J

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(16) Attempted Miyaura borylation of 4-phenyl-2-chlorooxazole, **8**, gave a quantitative yield of 4-phenyloxazole, indicating that rapid protodeboronation may restrict the use of 2-halo-oxazoles as nucleophiles in the Suzuki−Miyara reaction under these reaction conditions.

JOC*Note*

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

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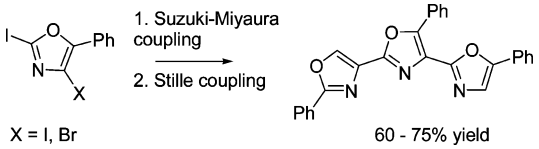
Received January 18, 2008



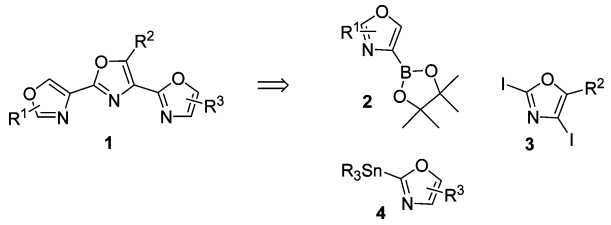
A regioselective Suzuki−Miyaura cross-coupling of 2,4-dihalooxazoles followed by a Stille coupling has been successfully developed. The procedure affords convergent syntheses of trisoxazoles in high yield and in a minimum number of steps.

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

[†] University of Edinburgh.
[‡] GlaxoSmithKline.

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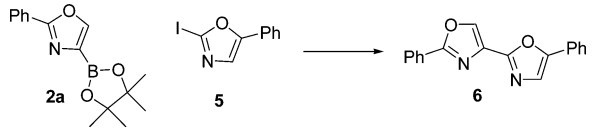
10.1021/jo800121y CCC: $40.75
Published on Web 03/12/2008

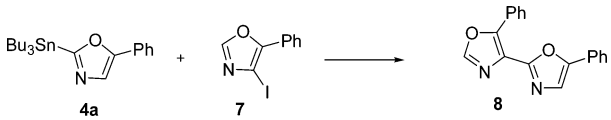
TABLE 1. Suzuki−Miyaura Coupling between Oxazol-4-ylboronate 2a and 2-Iodo-5-phenyloxazole 5[a]



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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(18) See Supporting Information for details.

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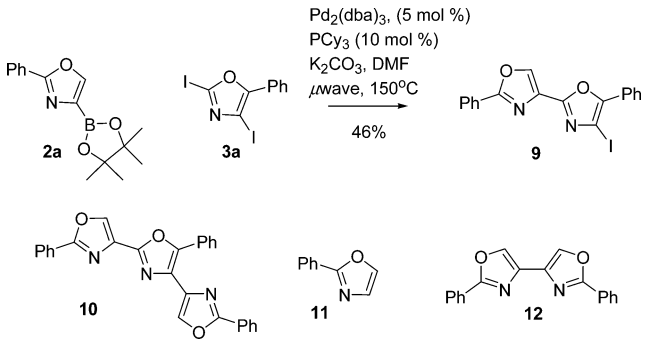
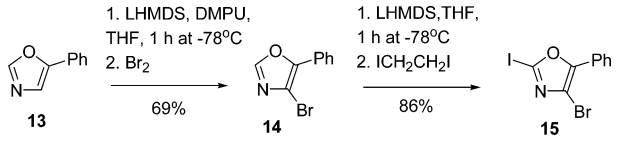
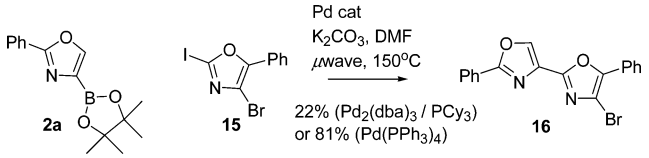
SCHEME 2. Regioselective Coupling between Oxazol-4-yl-boronate 1 and 2,4-Diiodooxazole 2



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.

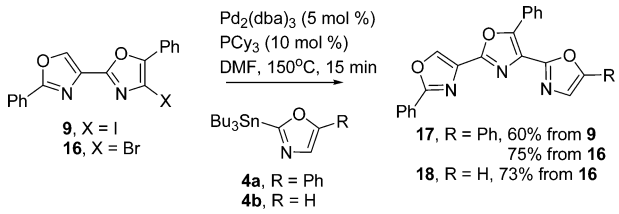
Finally, we were pleased to observe clean formation of the desired trisoxazoles using the optimized Stille coupling conditions developed previously. Trisoxazole **17** was obtained in 60% yield from iodide **9** and stannane **4a** and 75% yield using the bromide **16**. Coupling was also successful 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.

Acknowledgment. We thank the University of Edinburgh and GSK for funding, Professor Mark Bradley for the use of a Smith synthesizer, and EPSRC mass spectrometry center at the University of Swansea.

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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ORGANIC LETTERS

XXXX
Vol. xx, No. x

Direct Arylation of Oxazoles at C2. A Concise Approach to Consecutively Linked Oxazoles

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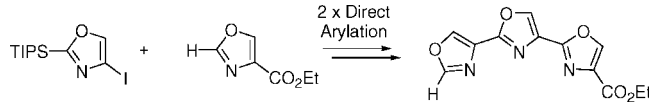
Received April 15, 2008

ABSTRACT



The synthesis of bis- and trisoxazoles via direct arylation is discussed. A variety of aryl groups can be installed at the 2-position of 5-aryl and 5-carboxy-substituted oxazoles under mild conditions using palladium catalysis on water. The direct arylation method can be extended to the synthesis of bis- and trisoxazoles if 2-triisopropylsilyl-4-iodooxazole is used as the electrophile in the arylation.

Consecutive C2−C4′ linked oxazole sequences are found in a variety of structurally complex, biologically active natural products.[1] Examples include the bisoxazole hennoxazole A[2] (antiherpes simplex virus activity), the antifungal trisoxazole ulapualide A,[3] and the potent telomerase inhibitor telomestatin, containing seven linked oxazoles and a thiazoline[4] (Figure 1). The C2−C4′ linkage pattern found in polyoxazole sequences is a result of their biosynthetic assembly from serine residues.[5] Consequently, the biomimetic cyclocondensation of peptide precursors is a popular approach to the polyoxazole motif in natural product synthesis, although numerous other methods exist.[6,7]

We have recently described a Suzuki−Miyaura cross-coupling route to the synthesis of bis- and trisoxazole structures.[8,9] While the approach was successful for several phenylated trisoxazoles, it was constrained in terms of substrate scope by the requirement for a stoichiometric organometallic as the nucleophilic coupling partner, a particularly problematic issue given the instability and preparation difficulties associated with certain azolyl organometallics (e.g., oxazoly-2-boronic acids).[10] A more advanced approach would be to employ transition-metal-

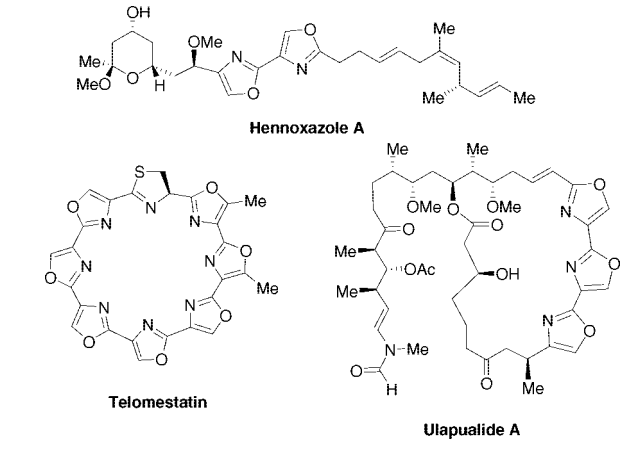


Figure 1. Oxazole containing natural products.

[†] University of Edinburgh.
[‡] GlaxoSmithKline.

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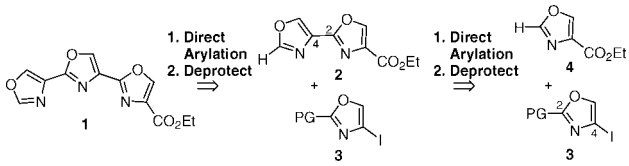
10.1021/ol800869g CCC: $40.75
Published on Web 06/10/2008

catalyzed direct arylation for oxazole−oxazole coupling, whereby the stoichiometric organometallic is dispensed with and the heteroaryl is arylated at the position of a C−H bond.[11]

The idea is shown in Scheme 1 for synthesis of the trisoxazole unit from ulapualide A: starting from the known[12] oxazole **4** containing an electron-withdrawing carboxylate at the 4-position and the protected 4-iodooxazole **3**, the target heterocycle **1** could be assembled using just two reactions, direct arylation, and deprotection, each repeated once. The route would thus be extremely quick, iterative, and offer the potential for convergency.

Scheme 1. Proposed Strategy for the Synthesis of Trisoxazoles via Direct Arylation (PG = Protecting Group)



The chemistry proposed in Scheme 1 presents a number of challenges to direct arylation chemistry. Oxazole−oxazole arylation has not been reported and will require the development of a C2 selective reaction using the novel bifunctionalized oxazole **3**. Compound **3** has C2 protected with a group that must be stable to the arylation conditions and can be easily cleaved to produce bisoxazole **2** for the second arylation. More importantly, the coupling of two electron-rich heteroaromatics via direct arylation poses a greater synthetic challenge than is usually encountered because the products formed contain *reactive* C−H bonds that may compete with the starting material to undergo further arylation, producing mixtures of products. For the system at hand, the electron-rich oxazole C5 position is of particular concern, as it may compete with C2 for arylation.

We began by examining the direct arylation of the oxazole 2-position using simple aryl iodides. We have recently developed a mild and general palladium-catalyzed method for the arylation of C2-substituted thiazoles at the electron-rich C5 position.[13] We were interested in being able to apply this method to the C2 position of oxazoles with the aim of building up more complexity toward the synthesis of C2−C4′ linked bis- and trisoxazoles of the type found in natural products. The arylation of oxazoles at C2 is a relatively unexplored area in the literature.[14] Recent work from Piguel describes microwave-accelerated arylation of the oxazole C2 position using palladium catalysis in the presence of a stoichiometric amount of copper.[15] Hoarau has reported a careful study on the regioselective C2 phenylation of ethyl 4-oxazolecarboxylate with iodobenzene.[16] Mechanistic studies from Zhuravlev on the C2 arylation of the related benzoxazole system have implicated an anionic cross-coupling mechanism involving deprotonation at C2 as being operative,[17] in contrast to the S_EAr mechanism usually invoked for direct arylation of π-excessive heterocycles.

We began by applying our on water arylation conditions to the synthesis of 2,5-disubstituted oxazoles via C2 direct arylation of 5-substituted oxazoles **5** with a range of aryl iodides **6** (Table 1, entries 1−12). Using a reaction system of $PdCl_2(dppf)/PPh_3$ and silver carbonate on water at 60 °C, we were pleased to observe good reactivity for a range of aryl iodides, affording good to excellent yields of the 2,5-diarylated products. The reaction was effective for both electron-rich (entries 2, 5, 9−11) and poor (entries 3, 7, 8, and 12) aryl iodides, producing clean transformations in each case. We were pleased to observe that 3-iodothiophene was a productive coupling partner, producing arylated oxazole **7d** in a good 66% yield despite the presence of several reactive C−H bonds in its structure. The electron-poor oxazole **5d** was effective in the reaction, giving a good 67% yield of product **7k** when combined with 4-iodotoluene and an acceptable 48% yield of product if coupled with 4-iodobenzonitrile (entries 11 and 12).

We then turned our attention to the synthesis of a protected oxazolyl-4-iodide (**3** in Scheme 1) that would function as an electrophile in our proposed polyoxazole direct arylation route. Oxazoles corresponding to **3** have not been previously described in the literature. Iodination at the oxazole 4-position has been reported by Vedejs, who demonstrated that 5-substituted oxazoles undergo selective 4-iodination when lithiated in the presence of DMPU and iodine.[9c] We were intrigued to see if we could access 4-iodooxazole **10** directly

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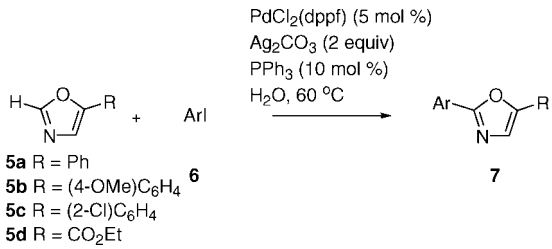
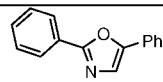
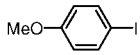
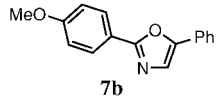
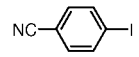
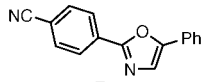
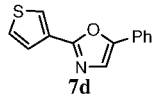
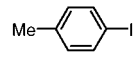
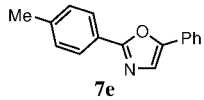
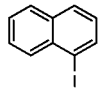
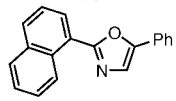
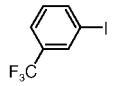
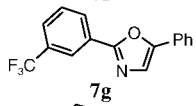
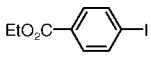
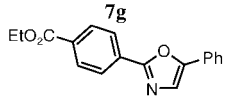
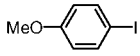
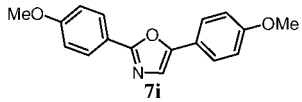
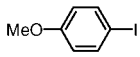
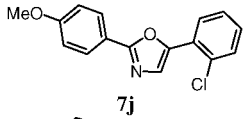
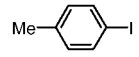
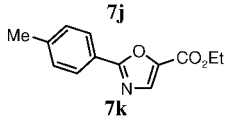
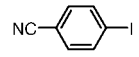
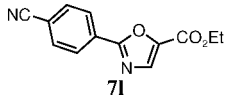
Table 1. C2 Direct Arylation of 5-Substituted Oxazoles with Aryliodides[a]

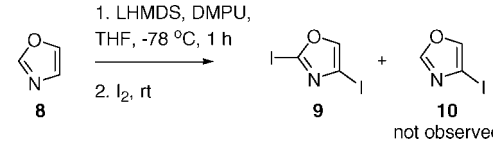


entry	Ar-X	product	yield (%)[a]
1		 **7a**	77
2		 **7b**	89
3		 **7c**	82
4		 **7d**	66
5		 **7e**	87
6		 **7f**	73
7		 **7g**	62
8		 **7h**	80
9		 **7i**	84
10		 **7j**	89
11		 **7k**	67
12		 **7l**	48

[a] Conditions: oxazole (1 equiv) and aryl iodide (1.2 equiv). [b] Isolated yield after SiO_2 column chromatography.

from the unsubstituted parent 1,3-oxazole **8** using the same reaction conditions. The resulting 4-iodooxazole could then be further functionalized at the C2 position (Table 2).

Table 2. 2,4-Diiodination of 1,3-Oxazole[a]

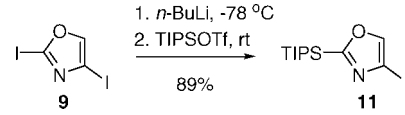


entry	reaction time[b]	yield of **9** (%)[c]
1	5 min	traces[d]
2	30 min	24
3	24 h	38
4	7 days	64
5	14 days	77

[a] Conditions: 2 equiv of LHMDS and 2 equiv of I_2. [b] Reaction time after addition of I_2. [c] Isolated yields after silica gel column chromatography. [d] 1 equiv of LHMDS and 1 equiv of I_2 were used.

A first experiment was carried out following the original conditions, and surprisingly, none of the expected 4-iodooxazole **10** was observed. Instead, small amounts of 2,4-diiodooxazole **9** could be isolated as the only product along with unreacted **8** (entry 1). The yield of **9** could be improved to 77% using prolonged reaction times and 2 equiv of both LHMDS and I_2 (Table 2, entries 2−5).[18] 2,4-Diiodooxazole **9** was isolated as a stable crystalline solid which could be stored at room temperature without noticeable decomposition for several weeks. The requisite protecting group was successfully installed at C2 via selective lithiation and quenching with TIPS-OTf,[19] producing the 2-triisopropylsilyl-4-iodooxazole **11** in an excellent 89% yield (Scheme 2).

Scheme 2. Synthesis of Key Building Block **11**

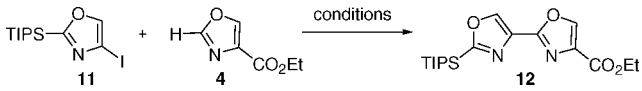


With iodide **11** in hand, we were ready to perform the first oxazole−oxazole arylation. Using 4-oxazolecarboxylate, **4**, as the coupling partner, we anticipated that the C4 electron-withdrawing group would retard any S_EAr arylation at C5, while promoting a deprotonation mechanism at C2. Hoarau and co-workers have demonstrated that C2 over C5 regioselectivity is possible in the phenylation of **4** using bulky ligands.[16] A wide range of conditions was examined for the direct arylation of **4** with iodide **11** (Table 3). Disappointingly, our previously successful C2 direct arylation conditions on water proved to be ineffective for iodide **11**, giving only traces of the desired bisoxazole with a slow reaction rate

(18) This increase in yields after a prolonged reaction time has been observed in a similar context. See ref 7f.

(19) Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A. *Tetrahedron Lett.* **2002**, 935–938.

Table 3. Direct Arylation of **4** with **11**: Optimization Data[a]



entry	catalyst	ligand	solvent	yield of **12** (%)[b]
1[c]	$PdCl_2$(dppf)	PPh_3	water	traces
2[d]	CuI	none	dmf	0
3	$Pd(OAc)_2$	P(*o*-Tol)$_3$	toluene	38
4	$Pd(OAc)_2$	P(*o*-Tol)$_3$	dmf	0
5	$Pd(OAc)_2$	IMes	toluene	complex mixture
6	$Pd(OAc)_2$	X-PHOS	toluene	complex mixture
7	PEPPSI-IPr	none	toluene	51
8	PEPPSI-IPr	none	1,4-dioxane	60
9	PEPPSI-IPr	none	DMF	40
10	HBP	none	toluene	81

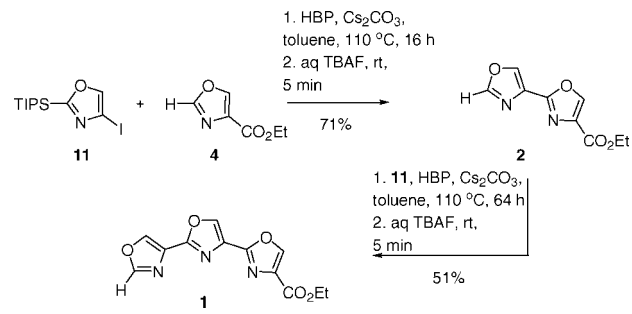
[a] HBP = Hermann−Beller palladacycle. Conditions: 1 equiv of **11** and 1.2 equiv of **4**, 5 mol % of catalyst and 10 mol % of ligand, 1 mL of solvent, 2 equiv of Cs_2CO_3, and 110 °C in a sealed tube. [b] Isolated yield after silica/gel column chromatography. [c] Ag_2CO_3 (2 equiv) at 60 °C. [d] CuI (10 mol %) at 140 °C.

being observed (entry 1). The copper-catalyzed arylation conditions recently described by Daugulis[14b] were likewise unsuccessful with complete degradation of **11** being observed after 30 min at 140 °C (entry 2). The first successful coupling was observed using Pd(OAc)/P(*o*-Tol)$_3$ in toluene, which gave bisoxazole **12** in a modest 38% yield (entry 3). Switching to the more polar DMF, a common direct arylation solvent, under the same system completely degraded **11** after 30 min at 110 °C (entry 4). The use of very bulky/electron-rich Imes or XPhos ligands only led to inseparable complex mixtures (entries 5 and 6).

A substantially better catalyst for the arylation proved to be the N-heterocyclic carbene-based palladium complex PEPPSI-IPr,[20] which gave moderate to good yields in toluene, 1,4-dioxane, and DMF (entries 7, 8, and 9). Finally, to our delight, we found that the Herrmann−Beller palladacycle[21] in toluene gave a very good 81% yield of the bisoxazole (entry 10).

Deprotection of **12** was slow and low yielding under acidic conditions[22] but successful upon brief exposure to aqueous TBAF solution at room temperature, giving the bisoxazole **2** in 71% yield over the two steps (Scheme 3). With an

Scheme 3. Synthesis of the Trisoxazole Moiety Found in Ulapualide A



efficient route to bisoxazole **2** established, synthesis of trisoxazole **1** was attempted. We were pleased to find that a second direct arylation using the same catalyst system was successful, affording the protected trisoxazole in 57% yield. Facile deprotection with aqueous TBAF gave trisoxazole **1** in 51% yield over the two steps, representing an overall six-step preparation from commercially available 1,3-oxazole in 25% overall yield.

This is the quickest synthesis of trisoxazoles reported to date,[6] although the research groups of Vedejs[7f] (eight steps, 39%) and Panek[23] (13 steps, 26%) have described higher yielding routes. The modularity and speed of the direct arylation approach offers significant benefits and should compliment existing methods for polyazole synthesis.

In conclusion, we have developed arylation methods for the C2 position of oxazoles and applied them to the synthesis of bis- and trisoxazoles. Using commercially available 1,3-oxazole as a starting point, the trisoxazole structure found in the ulapualide family of natural products has been prepared in six steps.

Acknowledgment. We thank the University of Edinburgh and GSK for funding and the EPSRC mass spectrometry centre at the University of Swansea.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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