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**REGIOSELECTIVE PALLADIUM
CATALYSED CROSS-COUPLING OF
OXAZOLES**

Regioselective Palladium Catalyzed Cross-Coupling of Oxazoles

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Abstract – A survey blanket the writing until April 2008 concerning organometallic reactions to functionalise oxazoles is portrayed. An order for the functionalisation of the oxazole 2-and 4-positions utilizing the Suzuki coupling response is portrayed. 2-Aryl-4-triflyloxazoles experience quick, microwave-aided coupling with an extent of aryl and heteroaryl boronic acids in great to fantastic yields. The technique is so also viable utilizing 4-aryl-2-chlorooxazoles as the coupling mate and has been augmented to the union of a novel class of homo-and heterodimeric 4,4'- interfaced dioxazoles. Moreover, a regioselective Suzuki-Miyaura cross-coupling of 2,4-dihalooxazoles emulated by a Stille coupling has been effectually improved.

The strategy bears focalized blends of trisoxazoles in towering yield and in a least number of steps. Besides, C-2 coordinate arylation of oxazoles is examined. This procedure is developed to the blend of C2-C4' interfaced bis and tris oxazoles of the sort discovered in the Ulapualide A group of common items.

INTRODUCTION

Directed insertion on multiply halogenated heterocycles to perform crosscoupling reactions at specific carbons of the ring is commonly referred to as regioselective cross-coupling. 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-stoichiometric amounts of catalysts whereas equimolar amounts of reductive metal complexes are needed if directed metalation or halogen/metal exchange reactions want to be employed.

The difference of electrophilicity of the carbon atoms in 2,4-dibromothiazole 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 crosscoupling 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.

Characteristically happening polyoxazoles usually show a 2-4 substitution plan, a result of their biosynthetic gathering from serine deposits. In certain characteristic features, such as telomestatin or ulapualide A, three or increasingly successive C2-C4'linked polyoxazoles are available as opposed to single oxazole units. The aforementioned fuses have intriguing structures, indicate a wide extend of living lands, and in this manner make perfect targets for the manufactured scientist.

A plenty of techniques have been created for the development of C2-C4'linked polyoxazoles. Even though the aforementioned strategies contrast significantly in their engineered methodology, they offer a normal direct approach, including an elevated number of continuous steps every time an oxazole ring ought to be presented. An elective approach is to utilize the palladium-catalyzed crosscoupling of properly functionalized oxazole units, a difficult response that has showed up just once in a while in the written works.

The main case was reported in 1995 by Barrett, utilizing a Stille coupling to plan a bisoxazole in a methodology to the characteristic item Hennoxazole A. Since that time, bisoxazole blend has been reported by Vedejs utilizing a Negishi coupling and by our particular assembly and that of Inoue utilizing the Suzuki-Miyaura response of oxazolyl boronate esters. Inoue has not long ago augmented this work to the preparation of some challenging pentakis and hexakis polyoxazole structures. Nonetheless, the linearity of this approach joined together with an

extensive arrangement of a regular boronic ester middle of the road vitally limits its degree. Given later infrastructures in azole cross-coupling reactions, we were fascinated by improving our particular strategy dependent upon a focalized approach to the blend of trisoxazoles.

2,4-Diiodooxazoles 3, known in the literary works from work of Vedejs, might be wanted to experience special oxidative expansion of Pd0 at the increasingly reactive C2 position, emulated by Suzuki-Miyaura cross-coupling with an oxazol-4-ylboronate 2. The C4-I bond might be abandoned whole for a brief moment cross-coupling with a 2-metallo-oxazole 4, structuring the trisoxazole 1. Particular cross-coupling on dihalooxazoles is a well preceded system yet has yet to be had an association with polyoxazole blend.

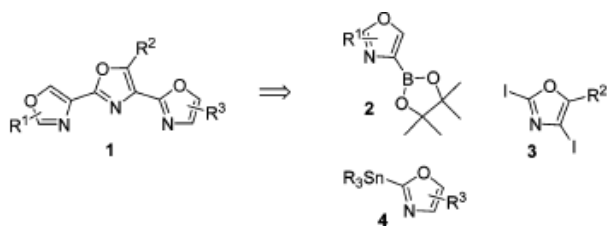


Figure. Cross-Coupling Strategy for the Synthesis of Trisoxazoles

We chose to break down the suggested regioselective trisoxazole combination into two parts, inspecting every C-C bond framing in parts on monoiodooxazoles to describe the response parameters, before utilizing the diiodooxazoles. Likewise, we started by looking at a disentangled form of the recommended Suzuki-Miyaura response, utilizing 2-phenyl-oxazol-4-yl boronate ester 2a and 2-iodo-5-phenyloxazole, both of which might be ready in multigram amounts. Standard Suzuki-Miyaura conditions at 100 °C in DMF processed dioxazole in 49% yield. Milder conditions for example those improved by Liebeskind and Fu gave a perplexing mixture of items that n'tn't be split. It was swiftly discovered that the utilization of microwave light not just abbreviated response times and yet expanded the yields breathtakingly, a fusion of Pd₂(dba)₃ (5 mol %) with PCy₃ (10 mol %) in DMF giving the fancied item in an incredible 87% segregated yield. With an exceptional yield of the Suzuki-Miyaura coupling under control, we created to the second cross-coupling. We settled on a Stille coupling as the system of decision, given that oxazol-2-ylstannanes are known nucleophiles in Pd-catalyzed oxazole cross-coupling REACTIONS.

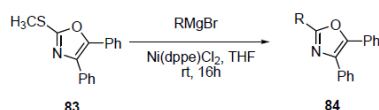
We orchestrated oxazol-2-ylstannane 4a by trapping 5-phenyloxazole with n-BuLi at -78 °C and extinguishing the response mixture with Bu₃SnCl. The coming about stannane did not store well what's more was best utilized newly ready. Standard conditions gave a moderate yield of 8 after 2 days reflux in DME (entrance 1). Milder Stille reactant frameworks were not adequate for this substrate: Fu's (tBu)₃PHBF₄ salt₁₅ utilized at room temperature, under microwave light or

in combo with Cu₂O, just expedited complex mixtures or moderate response rates. The ligand trifurylphosphine (TFP) in combo with Pd₂(dba)₃ and Cu₂O gave an unobtrusive 35% of separated, yet a moderate response rate if joined together with Cu(OAc)₂. Liebeskind's copper-interceded Stille coupling gave a moderate response rate in our framework. After extensive enhancement, we acknowledged that higher yields could be accomplished if higher loadings of stannane 4a were utilized within the response. Subsequently, the best of all consolidations gave off an impression of being same impetus framework utilized for the Suzuki-Miyaura coupling: Pd₂(dba)₃ (5 mol %) and PCy₃ (10 mol %) in DMF and under microwave illumination gave an amazing 87% yield of disconnected.

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 carbons together was almost an impossible transformation, and now it is carried out routinely in both academic laboratories and industrial processes. 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. This is especially true for oxazoles since the number of crosscouplings 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 SCH₃-substituted 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.



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

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

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.

AIMS

Numerous common items, for example Telomestatin or Ulapualide A, hold three or progressively successive C₂-C₄' interfaced poly-oxazole units as a substitute for a specific oxazole. This specific prime example is a result of their biosynthetic get together from serine or threonine buildups. The aforementioned fuses have captivating structures, demonstrate a extensive variety of biotic lands, and subsequently make perfect focuses for the manufactured scientific expert.

In oxazoles, position C₄ is particularly troublesome to halogenate, because of C-2 and C-5 being all the more helpfully entered because of their nucleophilicity and their regular reactivity towards electrophilic halogenating operators. In 1999 Vedej's and colleagues portrayed a system to specifically iodinate C₄ of 5-substituted oxazoles.

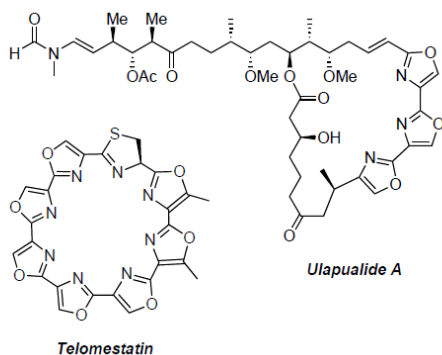


Figure : Poly-oxazole-containing natural products.

The regioselective palladium catalysed cross-coupling picked was the Suzuki- Miyaura response for two explanations; past outcomes had been efficacious in the combination of 4,4-dioxazoles. Additionally as a result of the moderately effortless receptiveness and superb soundness of the known oxazol-4-ylboronates, which are synthesised in four steps from ready beginning materials and were agreeable to multi-gram scale fundamental to perform optimisation studies.

Borylation on C₂ was needed so as to utilize the Suzuki-Miyaura response in the second coupling. Nonetheless, all endeavors to borylate on C₂ have slipped up. Thus, the Stille response was thought about an exceptional elective since oxazol-2-ylstannanes are known nucleophile associates in palladium catalysed oxazole crosscoupling responses. They are effectively gained entrance to through particular C-2 metalation with solid lithium bases, and resulting extinguishing of the non-cyclic isocyano enolate lithium salt with Bu₃SnCl or Me₃SnCl to give the ring shut structure.

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 figure.

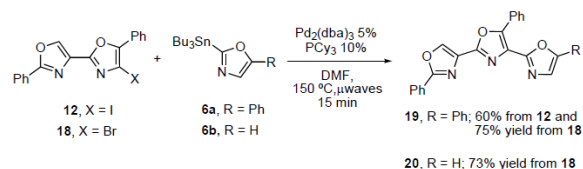


Figure. Stille couplings for the formation of tris-oxazoles.

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.

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).
- Stoichiometry 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.

It has been proved for the first time that regioselective Suzuki-Miyaura crosscoupling 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 bishalooxazoles.

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.

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