

Palladium-catalyzed coupling reactions for the preparation of concatenated azoles

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Abstract

The coupling reactions mediated by sp^2 - sp^2 transition metals, mostly Pd, allowed the chemoselective preparation of some synthetic compounds and intermediate structures of great complexity. This work describes the methodology used to obtain several derivatives with bisoxazole and thiazole-oxazole units. The required organozinc reagents were prepared from *n*-BuLi and ZnCl₂, and the bimetallic derivative of ethyl oxazole-4-carboxylate was obtained by a second transmetalation with CuI.

Keywords: Organometallic, oxazole, thiazole, transmetalation, coupling reactions

Introduction

In recent decades, some marine natural products have been found to be an important source of new bioactive compounds and drug leads. The chemical structures of marine products with heterocycles, such as 2,4'-bisoxazole, trisoxazole and 2,4'-thiazole-oxazole, substituted in different positions of the ring are common in different families of natural products (Figure 1).

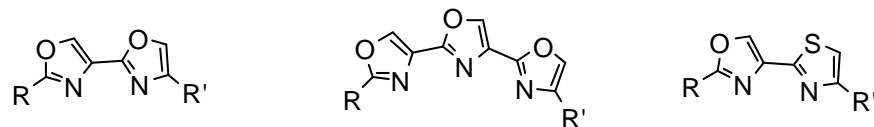


Figure 1. Concatenated 2,4'-bioxazole, trisoxazole and 2,4'-thiazole-oxazole presents in natural products.

These heterocyclic fragments are abundant in many secondary metabolites isolated from marine organisms and, in many cases, they exhibit unusual and unexpected biological activities. However, at the same time these compounds possess complex structure, which makes their synthesis rather difficult.

Many examples of these compounds are characterized by a bisoxazole motive in their structure.¹ Some of these include: hennoxazole A (antiherpes), isolated from the sponge *polyfibrospongia*; telomestatine, a chemotherapeutic agent that inhibits telomerase and shows a correlation between its activity and tumor growth; leucamide A, isolated from the Australian sponge *Leucetta microraphis* with cytotoxic activity; ulupualide A, which has an unusual range of biological activities, such as cytotoxic and antifungal properties, and participates in cell proliferation in leukemia; and finally, merchercharmycin and some of its reported analogs, which have shown cytotoxic activity against cancer cells.²

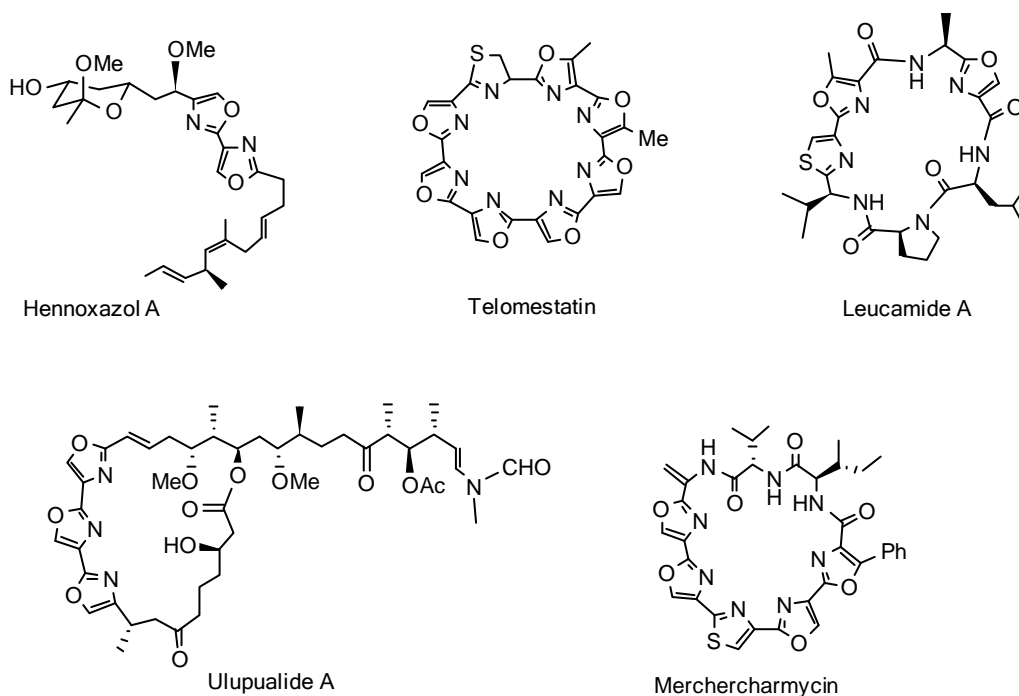


Figure 2. Compounds with oxazole and thiazole rings in their structure.

A great effort has been put into the synthesis of oxazole-containing compounds, because of the broad spectrum of biological activity.¹⁻⁴ Transition metal-catalyzed cross-coupling reactions have emerged as a powerful synthetic tool that allows a wide range of cross-coupling partners to be combined efficiently.⁵ This method has been used for C-C bond formation in many synthetic procedures. Negishi⁶ reactions allowed a vast number of cross-couplings, as highlighted by the Pd-catalyzed cross-coupling reactions.

The formation of the C-C bond with oxazole has not been used much due the instability that the oxazole exhibits when it is metalated by alkyllithiums.⁷⁻⁸ But if zinc chloride (ZnCl₂) is added to the Li compound, an immediate ring closure leads to the formation of a ClZn substituted oxazole. The intermediate ClZn-oxazole has been used for Pd catalyzed cross-coupling reactions with aryl and vinyl halides to yield substituted oxazoles.⁹ However, few examples have been described in which Pd catalyzed cross-coupling reactions are used in the preparation of dimers and trimers of thiazoles¹⁰⁻¹³ and oxazoles.¹⁴⁻²⁰

Results and Discussion

This work reports the use of ZnCl₂ for the formation of derivatives containing bisoxazole and oxazole-thiazole. The initial studies performed were based on the methodology reported by Hodges *et al.*⁷ These authors described that metalation of the oxazole with *n*-butyllithium leading to the formation of 2% of oxazole substituted at the 2 position and 20% of the product at the 4 position of the ring. Based on this study, different tests were carried out to obtain the activated oxazole at the 4 position. The preparation of 4-(tributylstannyl)oxazole, 4-bromooxazole and oxazole-4-boronic acid were unsuccessful.²¹

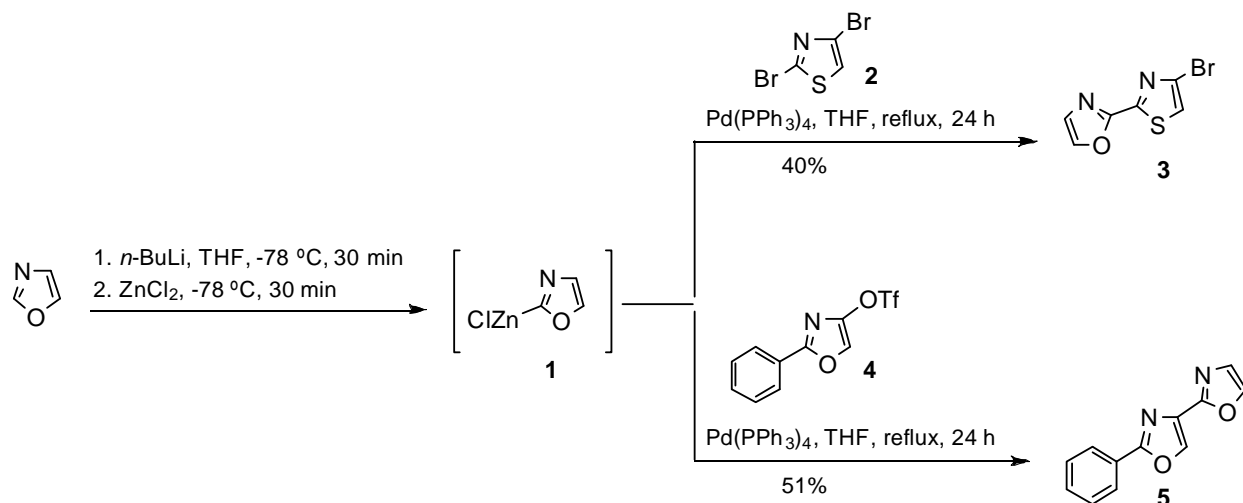
On the other hand, it was tested a direct oxidative cross-coupling reaction catalized by Pd(0) between 2,4-dibromothiazole and oxazole. Several coupling reactions were tried without detection of 2-(4-bromothiazol-2-yl)oxazole. The formation of small amounts of the 2,2'-bisoxazole was detected using Pd(OAc)₂ and PPh₃ but we did not have any signs of achieving a coupling reaction with 2,4-dibromothiazole (see experimental procedure).

Negishi cross-couplings

Although the oxazole can be metalated in the 2 position with alkyl lithium giving the corresponding 2-lithium oxazole as Hodges described⁷, the balance with the intermediate reaction causes instability in the ring. A work published by Reeder *et al.*⁹ explains that the balance may promote ring closure by the addition of an excess of zinc chloride obtaining a covalent character of the carbonzinc bond.

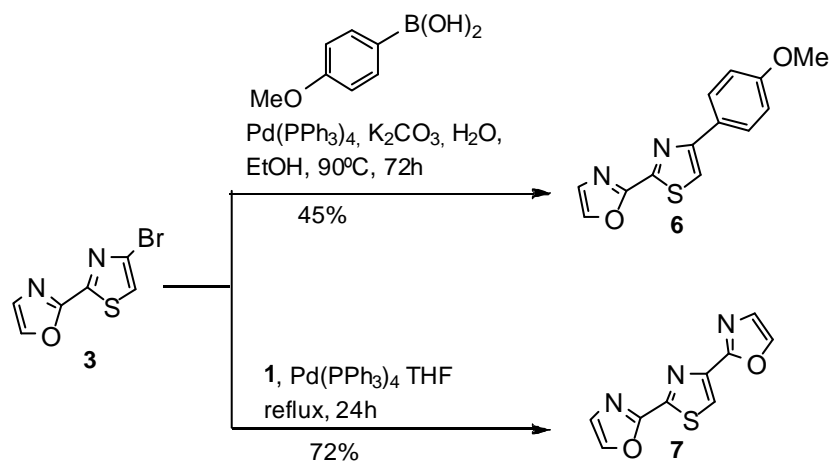
Zinc-derivative **1** was obtained by reaction of oxazole with *n*-BuLi, followed by *in situ* addition of solid ZnCl₂ in anhydrous THF at -78 °C for 30 min. The cross-coupling reaction between **1** and 2,4-dibromothiazole in the presence of Pd (0) under reflux gave chemoselectively **3** in 40 % yield. The reactivity of oxazole derivative **1** was also tested for cross-coupling with

triflate **4**.²² The reaction using Pd (0) as catalyst in THF at reflux temperature afforded **5** in a 51% yield (Scheme 1).



Scheme 1. Cross-coupling reaction between 2,4-dibromothiazole and triflate **4** with zinc derivative **1**, respectively.

The bromothiazole **3** was used for new coupling reactions with arylboronic acid or with zinc derivative **1**. Cross-coupling between **3** and 4-methoxyphenylboronic acid using K₂CO₃ and Pd (0) gave **6** in 45% yield. The same reaction conditions were used for the reaction coupling between **3** and **1**, obtaining **7** in a 72 % yield (Scheme 2).



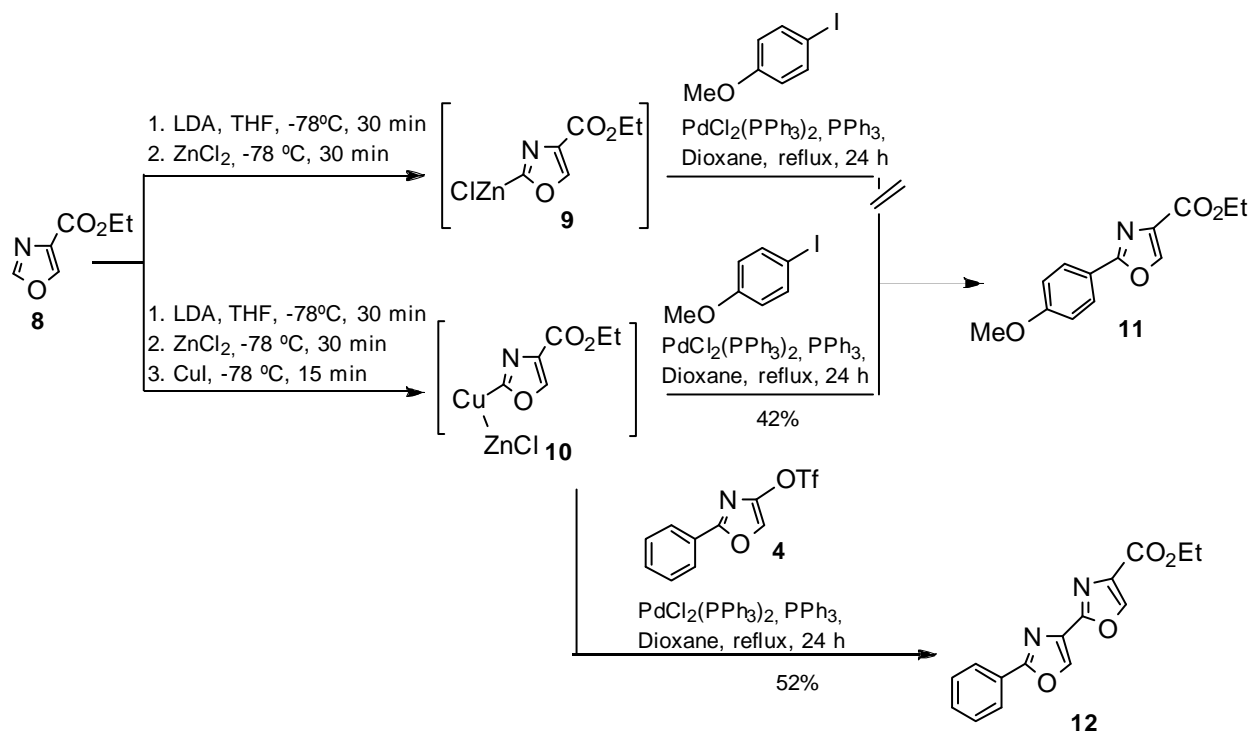
Scheme 2. Cross-coupling Pd (0) catalyzed reaction using 4-bromo-2-(2-oxazolyl)thiazole.

The metalation of ethyl oxazole-4-carboxylate **8** was also tested for cross-coupling reactions because the possibility of the posterior transformation of the ester into a new azole ring is well

known.¹ The metalation of **8** was performed with LDA instead of *n*-BuLi to avoid side reactions with the ester group. However, the same reaction conditions with ZnCl₂ to afford **9** and posterior addition of 4-iodoanisole gave only starting material (Scheme 3).

Harn *et al.*²³ described the acylation of oxazole with acid chlorides using a metaloxazole. A double transmetalation of 2-lithiooxazole was produced by treatment first with ZnCl₂ and finally with CuI. These reaction conditions were used to prepare the organometallic **10** by double transmetalation and the cross-coupling reaction was assayed with 4-iodoanisole catalyzed by Pd (0). Compound **11** substituted at the 2 position of the oxazole ring was obtained. The cross-coupling of the organometallic **10** and triflate **4** under the same conditions as before provided **12** in 52% yield (Scheme 3).

The stabilization of the oxazole ring with ZnCl₂ and CuI allowed the coupling with 4-iodoanisole and with oxazole triflate obtaining the bisoxazole having a 2-4 link between the two heterocycles as it is present in several natural compounds.



Scheme 3. Cross-coupling Pd (0) catalyzed reaction using the bimetallic derivative ethyl oxazole-4-carboxylate **10**.

Conclusions

The organometallic derivatives of B, Zn, Sn of the oxazole are difficult to obtain due to the great instability of the ring. In this work, it has been demonstrated that soft organometallic reagents

obtained by metalation with *n*-BuLi and transmetalation with solid ZnCl₂ allow cross-coupling with halogen derivatives such as 2,4-dibromothiazole and triflate derivatives. The ethyl oxazole-4-carboxylate requires an *in situ* double transmetalation with ZnCl₂ and CuI of lithiooxazole to obtain a bimetallic species with copper and zinc sufficiently stable to carry out coupling reactions catalyzed by palladium.

Experimental Section

General. Melting points (mp) were determined in a Buchi Melting Point B540 in open capillaries and are uncorrected. IR spectra were recorded on a NICOLET 6700 FT-IR spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer. Multiplicity of the carbons was assigned with DEPT and gHSQC experiments. Usual abbreviations for off-resonance decoupling used in this word include: (s) singlet, (d) doublet, (t) triplet, and (q) quartet. The same abbreviations have also been used for the multiplicity of signals in ¹H NMR, plus: (m) multiplet, (dd) double doublet, (br s) broad singlet, and (br d) broad doublet. Spectra were referenced to appropriate residual solvent peaks (CDCl₃ and MeOD). Masses were obtained in a Waters alliance 2795 HPLC system equipped with a 2487 UV-vis detector coupled to a ZQ electrospray mass detector. The samples were run with MeCN (0.07% HCO₂H) and H₂O (0.1% HCO₂H). HRMS were performed on a Bruker Autoflex high-resolution mass spectrometer by the Mass Spectrometry Service of the University of Santiago de Compostela.

2,2'-Bisoxazole. To a solution of oxazole (75 μL, 1.14 mmol) in dry THF (5 mL) **2** (415 mg, 1.71 mmol), Pd(OAc)₂ (19 mg, 0.085 mmol), PPh₃ (44 mg, 0.17 mmol,) and CsCO₃ (742 mg, 2.28 mmol) were added and the reaction mixture was then stirred at reflux for 48 h. The organic solution was poured into saturated aqueous NH₄Cl and extracted with ethyl acetate, dried over MgSO₄ and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (elution with hexane/EtOAc, 95:5-70:30) to give 2,2'-bisoxazole. White solid, yield 20%, 31mg. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (sa, 2H), 8.01 (sa, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 139.8 (2d), 140.1 (2d), 140.2 (s), 152.0 (s). MS (ES): *m/z* 137 (C₆H₄N₂O₂ + H, 100).

4-Bromo-2-(2-oxazolyl)thiazole (3). A solution of oxazole (0.162 mL, 2.46 mmol) in dry THF (5 mL) was cooled at -78 °C and *n*-BuLi 1.6 M in hexane (1.18 mL, 2.96 mmol) was added slowly. The reaction mixture was stirred by 30 min at -78 °C and solid ZnCl₂ (1 g, 7.41 mmol) was added and the mixture stirred by an additional 30 min. After this time, **2** (300 mg, 1.23 mmol), Pd(PPh₃)₄ (142 mg, 0.123 mmol) were added and the reaction mixture stirred at reflux for 24 h. The organic solution was poured into saturated aqueous NH₄Cl and extracted with ethyl acetate, dried over MgSO₄ and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (elution with hexane/ EtOAc, 95:5-70:30) to give **3**. Yellow solid,

yield 40%, 114 mg, mp 150-152 °C. IR (ν_{\max} cm^{-1}): 3119, 3138, 3066, 1503, 1448, 1114, 1030, 954, 796, 780 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.31 (d, J 0.4 Hz, 1H), 7.38 (s, 1H), 7.80 (d, J 0.4 Hz, 1H). ^{13}C NMR (400 MHz, CDCl_3): δ 120.1 (d), 127.2 (d), 129.6 (d), 141.2 (s), 155.5 (s), 156.2 (s). MS (ES): m/z 231 ($\text{C}_6\text{H}_3\text{N}_2\text{OSBr}^{79} + \text{H}$, 98), 233 ($\text{C}_6\text{H}_3\text{N}_2\text{OSBr}^{81} + \text{H}$, 100). HRMS: m/z calcd. for $\text{C}_6\text{H}_3\text{N}_2\text{OS}^{79}\text{Br}$: 229.9149; and for $\text{C}_6\text{H}_3\text{N}_2\text{OS}^{81}\text{Br}$: 231.9129; found: 229.9149 and 231.9135 respectively.

2-Phenyl-4-(2-oxazolyl)oxazole (5). *n*-BuLi 1.6 M in hexane (1.39 mL, 2.23 mmol) was added slowly over a solution of oxazole (120 μL , 1.81 mmol) in dry THF (6 mL) and cooled at -78 °C. The mixture of reaction was stirred for 30 min at -78 °C and then solid ZnCl_2 (760 mg, 5.43 mmol) was added and the stirring continued for an additional 30 min. After this time, **4** (177 mg, 0.604 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (71 mg, 0.060 mmol) were added and the reaction mixture was stirred at reflux for 24 h. The organic solution was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate, dried over MgSO_4 and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (elution with hexane/ EtOAc, 95:5-70:30) to give **5**. Yellow solid, yield 51%, 65 mg, mp 103-105 °C. IR (ν_{\max} cm^{-1}): 3142, 3119, 3089, 1557, 1450, 1114, 1100, 708, 684 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.24 (sa, 1H), 7.7-7.49 (m, 3H), 7.73 (sa, 1H), 8.13-8.15 (m, 2H), 8.26 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3): δ 128.4 (s), 128.8 (2d), 129.4 (d), 129.7 (2d), 131.3 (d), 131.9 (s), 138.2 (d), 139.3 (d), 155.8 (s), 163.2 (s). HRMS: m/z calcd. for $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_2$: (M + Na) 235.0478; found 235.0468.

4-(4-Methoxyphenyl)-2-(2-oxazolyl)thiazole (6). A solution of K_2CO_3 (180 mg, 1.3 mmol) in water (3 mL) was added over a solution of 4-methoxyphenylboronic acid (99 mg, 0.65 mmol) in EtOH (3 mL). **3** (100 mg, 0.43 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (25 mg, 0.021 mmol) were added over the stirring mixture and the stirring continued at 90°C for 72 h. The organic solution was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate, dried over MgSO_4 and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (elution with hexane/ EtOAc, 95:5-70:30) to give **6**. Yellow solid, yield 45%, 49 mg, mp 124-126 °C. IR (ν_{\max} cm^{-1}): 3112, 2920, 1610, 14577, 1252, 1016, 868, 751 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 3.85 (s, 3H), 6.97 (d, J 8.8 Hz, 2H), 7.32 (sa, 1H), 7.49 (s, 1H), 7.81 (sa, 1H), 7.91 (d, J 8.8 Hz, 2H). ^{13}C NMR (400 MHz, CDCl_3): δ 55.3 (q), 113.5 (d), 114.1 (d), 126.5 (s), 127.9 (2d), 128.9 (2d), 139.7 (d), 154.1 (s), 156.6 (s), 157.2 (s), 160.0 (s). MS (ES): m/z 259 ($\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2\text{S} + \text{H}$, 100). HRMS: m/z calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: (M + Na) 281.0355; found 281.0352.

2,4-Bis(2-oxazolyl)thiazole (7). *n*-BuLi 1.6 M in hexane (97 μL , 150 μmol) was added slowly over a solution of oxazole (8.5 μL , 130 μmol) in dry THF (5 mL). The reaction was stirred at -78 °C for 30 min and then solid ZnCl_2 (53 mg, 390 μmol) was added and the stirring continued for an additional 30 min. After this time, **3** (20 mg, 87 μmol), $\text{Pd}(\text{PPh}_3)_4$ (10 mg, 8.7 μmol) were added and the reaction mixture stirred at reflux for 24 h. The organic solution was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate, dried over MgSO_4 and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (elution with hexane/ EtOAc, 95:5-70:30) to give **7**. Yellow solid, yield 72%, 13.8 mg, mp 133-135 °C. IR (ν_{\max} cm^{-1}): 3174, 3088, 1112, 1026, 770 cm^{-1} . ^1H NMR (400 MHz, MeOD): δ 7.38 (sa, 1H), 7.43

(sa, 1H), 8.06 (sa, 1H), 8.15 (sa, 1H), 8.42 (s, 1H). ^{13}C NMR (400 MHz, MeOD): δ 124.5 (d), 129.0 (d), 130.0 (d), 141.3 (d), 142.6 (d), 145.5 (s), 156.9 (s), 157.1 (s), 158.5 (s). MS (ES): m/z 219 ($\text{C}_9\text{H}_5\text{N}_3\text{O}_2\text{S}$, 100). HRMS: m/z calcd. for $\text{C}_9\text{H}_5\text{N}_3\text{O}_2\text{S}$: (M + H) 220.0180; found 220.0183.

Ethyl 2-(4-methoxyphenyl)oxazole-4-carboxylate (11) 2 M LDA (0.42 mL, 0.85 mmol) was added slowly over a solution of ethyl oxazole-4-carboxylate (100 mg, 0.71 mmol) in dry THF (5 mL). The reaction was stirred at $-78\text{ }^\circ\text{C}$ for 30 min. Then, solid ZnCl_2 (283 mg, 2.12 mmol) was added and the mixture stirred for an additional 30 min. Finally, CuI (135 mg, 0.71 mmol) was added and the reaction mixture stirred for 15 min at $-78\text{ }^\circ\text{C}$. 4-Iodoanisole (81 mg, 0.35 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (49 mg, 0.070 mmol) and PPh_3 (37 mg, 0.141 mmol) were added in dry dioxane (3 mL) and the reaction mixture was stirred at reflux for 24 h. The organic solution was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate, dried over MgSO_4 and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (elution with hexane/AcOEt, 8:2) to give **11**. White solid, yield 42%, 37 mg, mp $105\text{-}107\text{ }^\circ\text{C}$. IR ($\nu_{\text{max}}\text{ cm}^{-1}$): 3145, 2915, 2848, 1727, 1613, 1500, 1262, 1107, 843, 734 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.38-1.42 (t, 3H), 3.86 (s, 3H), 4.39-4.45 (q, 2H), 6.96 (d, J 8.8 Hz, 2H), 8.05 (d, J 8.8 Hz, 2H), 8.22 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3): δ 14.7 (q), 55.8 (q), 61.8 (t), 114.8 (2d), 119.8 (s), 129.2 (2d), 134.6 (s), 143.5 (d), 159.8 (s), 161.2 (s), 161.5 (s). MS (ES): m/z 248 ($\text{C}_{13}\text{H}_{13}\text{NO}_4 + \text{H}$, 100). HRMS: m/z calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}_4$: (M + Na) 270.0736; found 270.0737.

Ethyl 2-(2'-phenyloxazole-4'-yl)oxazole-4-carboxylate (12). 2 M LDA (0.32 mL, 0.65 mmol) was added slowly over a solution of ethyl oxazole-4-carboxylate (76 mg, 0.65 mmol) in dry THF (5 mL). The reaction was stirred at $-78\text{ }^\circ\text{C}$ for 30 min. Solid ZnCl_2 (223 mg, 1.63 mmol) was then added and the mixture stirred by additional 30 min. Finally, CuI was added (103 mg, 0.546 mmol) and the reaction mixture stirred for 15 min at $-78\text{ }^\circ\text{C}$. **4** (80 mg, 0.273 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (38 mg, 0.054 mmol) and PPh_3 (28 mg, 0.109 mmol) were added in dry dioxane (3 mL) and the reaction mixture was stirred at $100\text{ }^\circ\text{C}$ for 24 h. The organic solution was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate, dried over MgSO_4 and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (elution with hexane/ EtOAc, 8:2) to give **12**. White solid, yield 52%, 40 mg, mp $189\text{-}191\text{ }^\circ\text{C}$. IR ($\nu_{\text{max}}\text{ cm}^{-1}$): 3127, 2914, 2849, 1720, 1487, 1329, 1271, 1115, 1027, 829, 780 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.41 (t, 3H), 4.43 (q, 2H), 7.48-7.52 (m, 3H), 8.12-8.15 (m, 2H), 8.32 (s, 1H), 8.42 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3): δ 14.2 (q), 61.9 (t), 126.2 (s), 127.5 (2d), 128.9 (2d), 131.8 (d), 135.5 (s), 135.7 (s), 139.2 (d), 143.8 (d), 159.9 (s), 161.5 (s), 162.9 (s). HRMS: m/z calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_4$: (M + Na) 307.0689; found 307.0695.

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21. *n*-BuLi in THF was added to oxazole at -78 °C after stirring at that temperature for 1h the electrophile (ClSnBu₃ or Br(CH₂)₂Br or B(OMe)₃ was added. After the workup a complex mixture of products were obtained.
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