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Effective C5-Arylation of Peptide-Integrated Oxazoles: Almazole D

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Abstract. An efficient functionalization approach of oxazoles by using Pd-catalyzed cross-coupling reactions is reported. Oxazolone formation and subsequent sulfamoylation *in situ* are facilitated by employing *N*,*N*-diethylsulfamoyl imidazolium triflate. Cross-couplings provide both oxazole-arenes and oxazole-heteroarenes and were compatible with sensitive and epimerization-prone substrates, as exemplified by the total synthesis of the natural product almazole D.

Keywords: Cross-coupling; peptides; natural products; total synthesis; heterocycles.

Oxazoles are a prominent scaffold in both, natural products[1] and drug discovery.[2] In natural products, oxazoles are typically derived from serine or threonine by cyclodehydration and oxidation,[3] resulting in C5-H or C5-Me substitution. Oxazoles with C5-aryl substituents may be produced by *β*-oxidation and cyclization of phenylalanine, tyrosine, histidine, or tryptophan residues.[4] Examples are breitfussin A (**1**, **Figure 1**) and B (**2**),[5] almazole D (**3**),[6] martefragin A (**4**),[7] and diazonamide (**5**),[8] all featuring indoles, or the phenyl-oxazole urukthapelstatin A (**6**).[9] In medicinal chemistry, oxazoles have been found to show antibiotic,[10] antitubercular,[11] cytotoxic,[12] neuroprotective,[13] anti-inflammatory,[14] and fungicidal[15] activity. Also, arylated oxazoles feature interesting fluorescence properties and have hence been used as probes.[16]

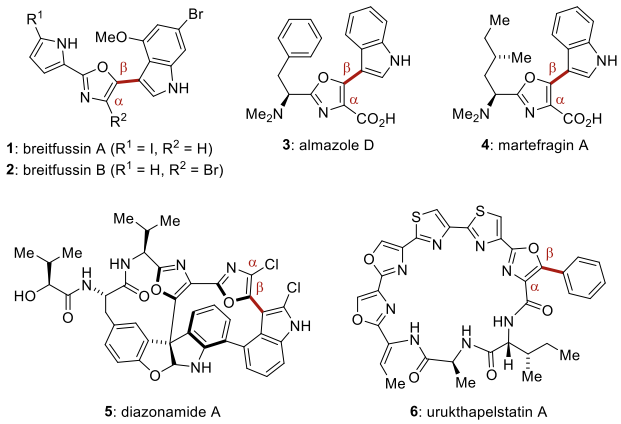

Figure 1. Naturally occuring C5-arylated oxazoles.

For highly substituted oxazoles some *de novo* syntheses have been described that allow for their assembly,[17] but are difficult to apply for late-stage diversification. Moreover, (catalytic) C–H activation of the oxazole ring has been reported,[18–20] such as C5-functionalization by imidation,[21] alkylation,[22] acylation,[23] alkenylation,[24] or arylation.[25] Several protocols for regioselective C–H activation have been developed,[19,20,26,27] but typically were applied to structurally simple oxazoles stabilized by a C2-(hetero)aryl group. Alternatively, transition metal-mediated cross-couplings of 5-bromooxazoles[27–29] and oxazolyl-5-ethers[30] have been realized, but often suffer from limited substrate scope as well as modest stability of the oxazole ring such activated (Hetero)aryl esters,[31] carbonates,[32] carbamates,[32,33] sulfonates,[34] and sulfamates[32,33,35] have been explored as C–O electrophiles in selected cross-couplings. Applications of these transformations to complex substrates remain rare and are likely to be highly substrate dependent.

To facilitate accessing highly functionalized oxazoles more generally, we envisioned to swiftly generate suitable oxazole electrophiles from open chain precursors (**Scheme 1**, top), as substrates for cross-couplings. Oxazolyl-triflates[36,37] have been applied for C2- and C4-functionalization of oxazoles, but 5-triflyloxy-oxazoles have been reported to be unstable.[36,37] Only a single case of a Sonogashira coupling is reported.[37]

Toward identifying more broadly useful 5-oxazolyl electrophiles, both an efficient access to 5-(*4H*)-oxazolones and their functionalization was required, in order to allow their reliable cross-coupling. For identifying a combination of matching reagents and derivatization, various functionalized oxazoles **9a–g** were scouted by using modified Erlenmeyer azlactone synthesis conditions (**Scheme 1**), starting from carboxylic acid **7** (15-87% yield). Additionally, oxazolyl ether **9h** was prepared by dehydration of diethylamido malonate **10** (66% yield). The library of functionalized oxazoles such obtained (**9a–h**) was then subjected to cross-coupling studies with $PhB(OH)_2$, by varying the catalyst, ligand, solvent, and reaction temperature for the different substrates.

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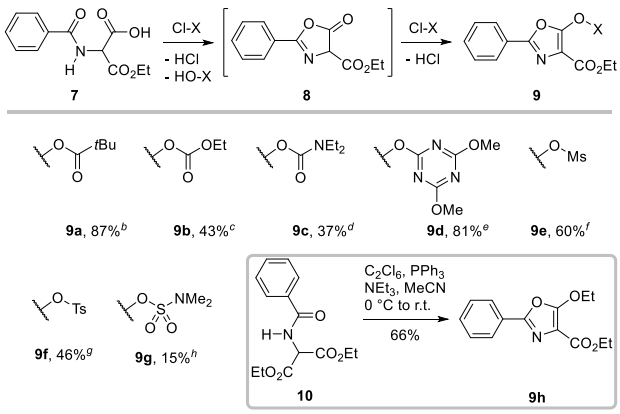
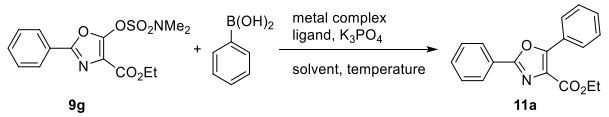


Scheme 1. Synthesis of different oxazole C–O electrophiles. [a]Reagents and conditions: RCOCl (4 equiv.), NMM (5 equiv.), THF, or RSO_2Cl (3-5 equiv.), NMI (4-5 equiv.), THF. [b]PivCl; [c]EtOCOCl; [d]Et_2NCOCl; [e]$C_5H_6ClN_3O_2$; [f]MsCl; [g]TsCl; [h]Me_2NSO_2Cl.

While a spectrum of Ni- and Pd-based catalysts were studied, the delicate character of this transformation became readily apparent (**Table 1** and S.I.). To our delight, sulfamate **9g** emerged from this screening effort as a promising electrophile when submitted to $Pd(OAc)_2$/XPhos in *t*BuOH and K_3PO_4 (**Table 1** and S.I.).

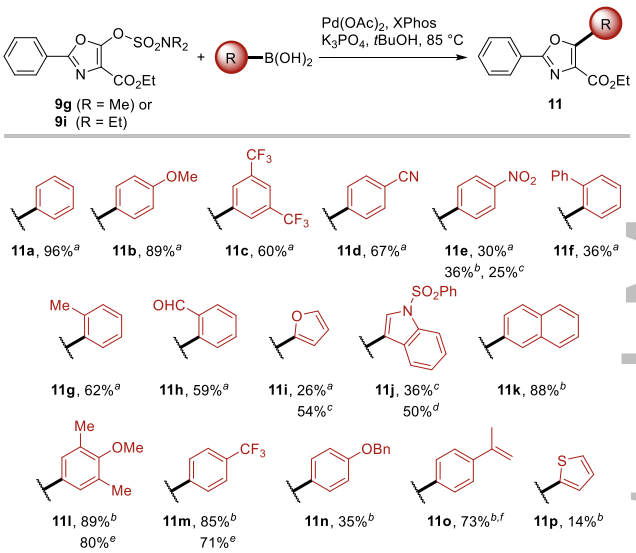
Table 1. Selected cross-coupling conditions for oxazolyl-sulfamates.



	complex[a]	ligand	solvent	yield[b] (%)
1	$NiCl_2(PCy_3)_2$	-	toluene[d]	0
2	$NiCl_2$(dppe)	-	toluene[d]	0
3	$Pd(OAc)_2$	Mo-Phos[c]	*t*BuOH[e]	<5
4	$Pd(OAc)_2$	BrettPhos[c]	*t*BuOH[e]	54 (51)[g]
5	$Pd(OAc)_2$	XPhos[c]	*t*BuOH[e]	98 (96)[g]
6	$Pd(OAc)_2$	XPhos[c]	dioxane[f]	62 (59)[g]
7	$Pd(OAc)_2$	XPhos[c]	DMF[f]	<5
8	$Pd(OAc)_2$	XPhos[c]	DME[e]	48

[a][Ni]: 10 mol %; [Pd]: 2 mol % $Pd(OAc)_2$ and 4 mol % ligand; [b]by HPLC; [c]see S.I.; [d]110 °C; [e]85 °C; [f]100 °C; [g]isolated yield in brackets.

We then explored the scope of this cross-coupling reaction by studying 2-phenyloxazolyl-sulfamates **9g** and **9i** and different boronic acids (**Scheme 2**). The coupling of regular and electron rich aryl boronic acids performed smoothly (80-96%, **11a**, **b**, **k**, **l**). Electron-poor substrates with CF_3 and CN substituents were tolerated, too (60-67%, **11c**, **d**). A nitro group in the *para*-position was less productive (30% yield) but the *N*,*N*-diethylsulfamate substrate **9i** provided a slightly better yield (**11e**). Coupling efficiency for hindered, *ortho*-substituted boronic acids was apparently depending on sterics (30–62%, **11f**–**h**). Electron-rich, heteroaromatic 2-furanylboronic acid and protected 3-indolylboronic acid could be employed as well (**11i**, **j**). By using KF instead of K_3PO_4 in higher boiling *i*AmOH, yields for the heteroaromatic boronic acids were improved (**11i**, **j**), but not for 4-nitrophenylboronic acid (**11e**). Since *N*,*N*-diethylsulfamate **9i** proved to be a more productive electrophile, its coupling efficiency was further evaluated (**11k**–**p**). Electron-rich substrates readily underwent the cross-coupling giving yields up to 89% (**11k**, **l**, 80% on 1 mmol scale). A trifluoromethylated substrate was coupled in 85% yield (71% on 1 mmol scale, **11m**). A benzyl ether was found labile, resulting in a diminished yield of 35% (**11n**), whereas alkenylation proceeded smoothly (**11o**, 73% yield). Coupling of a thiophene proved to be surprisingly difficult, giving a poor yield when using either K_3PO_4 or KF in *t*BuOH (14%, **11p**). Taken together, these data indicated that K_3PO_4 as base was superior for cross-couplings to aryl boronic acids, whereas KF was more suitable for heteroaryl boronic acids.

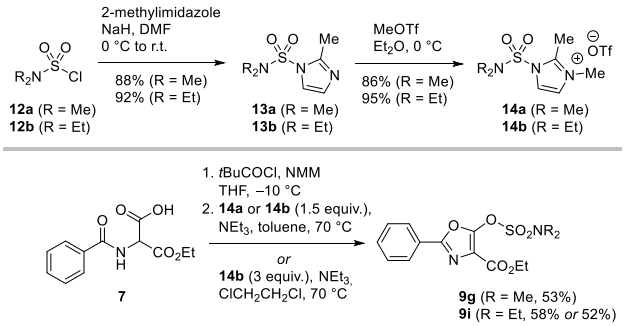


Scheme 2. Scope of the Suzuki–Miyaura-type cross-couplings. [a]**9g** was used; [b]**9i** was used; [c]KF and *i*AmOH at 110 °C were used to couple sulfamate **9g**; [d]KF and *i*AmOH at 110 °C were used to couple sulfamate **9i**; [e]reaction was performed on 1 mmol scale; [f]isopropenylboronic acid pinacol ester was used.

This profiling of a test substrate set the stage to implement the sulfamate cross-coupling chemistry to structurally more sophisticated peptidic substrates. Now effective access to oxazolyl sulfamates became important. Unfortunately, *O*-sulfamoylation of oxazolones by using commonly available sulfamoyl chloride reagents remained sluggish. We therefore employed the more electrophilic *N*,*N*-dialkylsulfamoyl imidazolium triflates **14a** and **14b** (**Scheme 3**), which were easily synthesized in high yield and on multi-gram scale from sulfamoyl

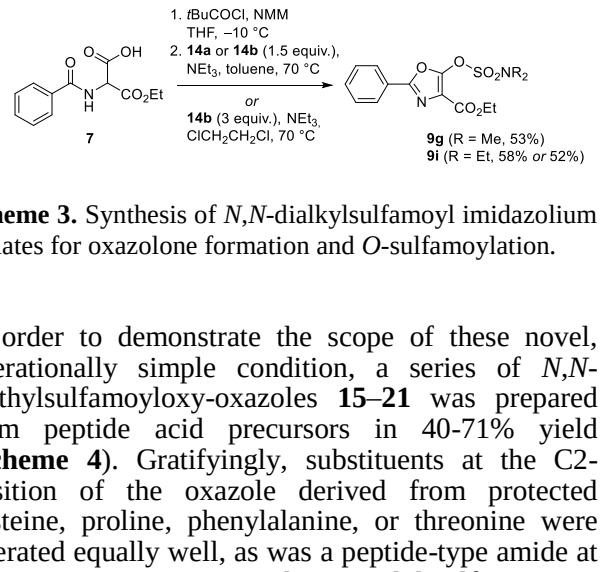
10.1002/adsc.202001262

chlorides **12a** and **12b** by substitution with 2-methylimidazole und quaternization.[38] The reagents **14a** and **14b** provided sulfamates **9g** and **9i** in good yields of 53% and 58%, respectively, starting from carboxylic acid **7** (**Scheme 3** and S.I.). Moreover, the target oxazolyl-sulfamates could be either formed by sequentially using pivaloyl chloride and the sulfamoyl imidazolium triflate, or *β*-carboxy amides – i.e. peptide acids – could be directly transformed to *C*-terminal oxazolones in one step by exposing them to an excess of reagents **14a** or **14b**.

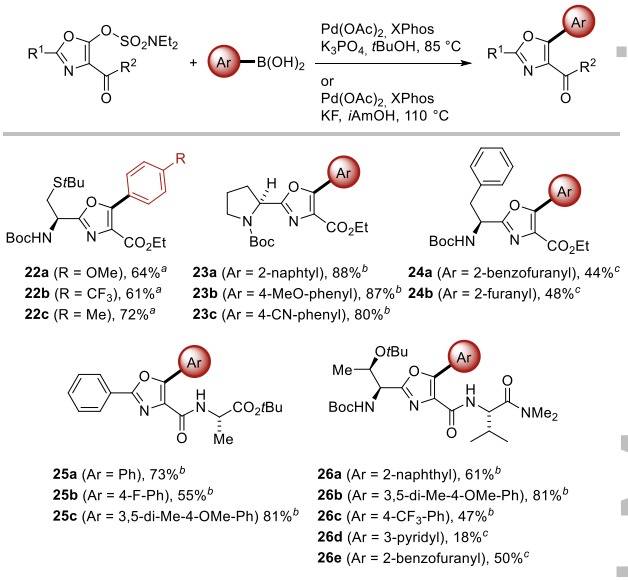


Scheme 3. Synthesis of *N*,*N*-dialkylsulfamoyl imidazolium triflates for oxazolone formation and *O*-sulfamoylation.

In order to demonstrate the scope of these novel, operationally simple condition, a series of *N*,*N*-diethylsulfamoyloxy-oxazoles **15**–**21** was prepared from peptide acid precursors in 40-71% yield (**Scheme 4**). Gratifyingly, substituents at the C2-position of the oxazole derived from protected cysteine, proline, phenylalanine, or threonine were tolerated equally well, as was a peptide-type amide at the C4-position. Surprisingly, oxazolyl-sulfamates **15** and **17** remained unproductive in cross-couplings (**Scheme 5**), indicating the *S*Tr group to be incompatible with this chemistry. The more stable *tert*-butyl thioether **16** proceeded well,[29] but some *β*-elimination of the thioether was observed. Using KF as base suppressed this side reaction, to provide the coupling products **22a**–**c** (61-72%). Excellent yields were obtained for the coupling of proline-derived sulfamate **18** with various aromatic boronic acids (**23a**–**c,** 80-88%). Heteroaryl couplings were then investigated for sulfamate **19**. Both 2-benzofuranyl- and 2-furanyl-boronic acid could be coupled, to give the bi-heteroarenes **24a** and **24b** (44% and 48%). To test whether amide groups at the C4-position were tolerated, the oxazolyl-sulfamates **20** and **21** were studied. They gave successful cross-couplings with yields up to 81% (**25a-c**, **26a-e**), again with more variable efficiency for heterocyclic boronic acids (**26d, e**). Importantly, C_α-epimerization was not observed in any of the cases studied (^{1}H-NMR).



Scheme 4. Facile one-pot synthesis of oxazolyl-*N*,*N*-diethylsulfamates **15**–**21**.

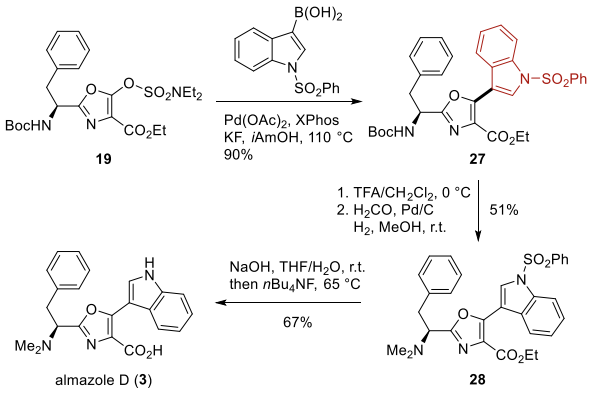


Scheme 5. Substrate scope and functional group tolerance of sulfamate couplings. [a]Pd(OAc)$_2$, XPhos, KF, *t*BuOH, 85 °C; [b]Pd(OAc)$_2$, XPhos, K$_3$PO$_4$, *t*BuOH, 85 °C; [c]Pd(OAc)$_2$, XPhos, KF, *i*AmOH, 110 °C.

To further prove the utility of the oxazolyl sulfamate cross-coupling, we applied this method to a synthesis of the natural product almazole D (**3**, **Scheme 6**).[6] Oxazolyl-sulfamate **19** was easily obtained from an open-chain precursor peptide in 55% yield (see S.I.). Subsequent cross-coupling of sulfamate **19** with protected 3-indolylboronic acid performed excellently and gave oxazolyl-indole **27** in 90% yield. Boc group cleavage and dimethylation provided dimethylamine **28** in 51% yield. Finally, alkaline ester hydrolysis and *N*-desulfonylation with *n*Bu$_4$NF completed a facile total synthesis of almazole D (**3**, 67% yield),[39] with perfectly matching analytical data, by employing the newly developed method as a key step.

In conclusion, we have shown that 5-oxazolyl-sulfamates are privileged electrophiles for Pd-catalyzed late-stage C5-arylations of oxazoles, which may even be peptide-embedded. Competent 5-oxazolyl-sulfamates can be directly accessed from

peptides by using *N*,*N*-dialkylsulfamoyl imidazolium triflates. The developed couplings were shown to be racemization-free and applicable to a broad range of functionalized substrates, as exemplified by the total synthesis of the antibacterial natural product almazole D (**3**). This methodology is hence expected to considerably facilitate natural product synthesis, medicinal chemistry, and materials chemistry research.



Scheme 6. Streamlined total synthesis of almazole D.

Experimental Section

General Procedure: *i*AmOH (0.05 mol/L) was added to the corresponding oxazolyl-sulfamate (1 equiv.), boronic acid (2 equiv.), $Pd(OAc)_2$ (0.1 equiv.), Xphos (0.2 equiv.), and KF (4 equiv.) and the mixture was stirred at 110 °C for the given time. Water or aqueous $KHSO_4$ (5%) was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were treated with Na_2SO_4, filtered, and evaporated under reduced pressure. The obtained residue was purified by flash chromatography to afford the desired product.

Acknowledgements

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Ansgar Oberheide, Hans-Dieter Arndt*