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Suzuki Coupling of Oxazoles

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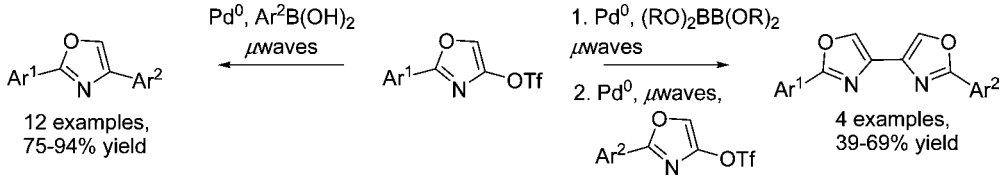
ABSTRACT



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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(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.

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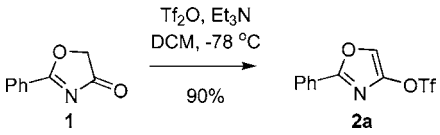
arylation methods[8] for the functionalization of oxazoles in recent years. The Suzuki coupling, by contrast, has seen relatively little application:[9] Hodgetts described the coupling of phenyl boronic acid to 2-, 4-, and 5-halo-oxazoles,[10] of 2-aminophenyl boronic acid to 5-halo-oxazoles, and of 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

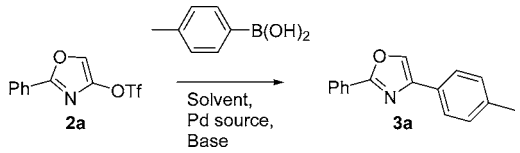


from oxazolones, first introduced by Barrett[5b] and Kelly[5c] in the context of the Stille reaction, enables the regiocontrolled installation of an electrophile functional group for subsequent palladium cross-coupling. This strategy avoids potential regioselectivity problems inherent to direct halogenation 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.

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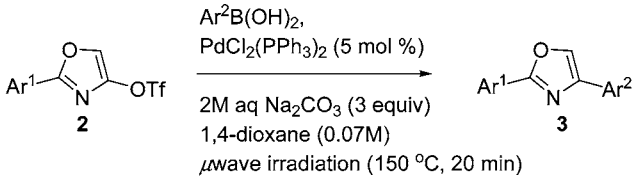
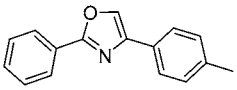
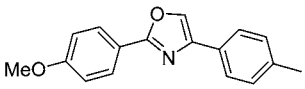
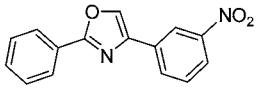
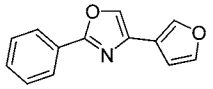
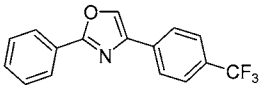
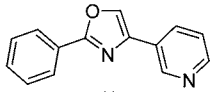
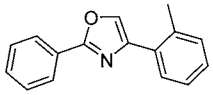
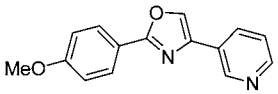
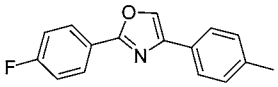
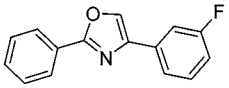
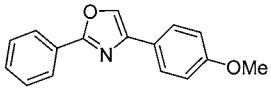
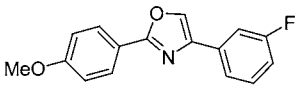
(12) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

Table 2. Suzuki Coupling of Oxazolyl 4-Triflates



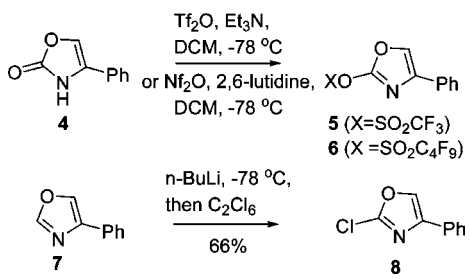
entry	product 2	yield (%)[a]	entry	product 2	yield (%)[a]
1	 **3a**	94	7	 **3g**	82
2	 **3b**	92	8[b]	 **3h**	79
3	 **3c**	87	9[b]	 **3i**	73
4	 **3d**	91	10[b]	 **3j**	89
5	 **3e**	75	11	 **3k**	91
6	 **3f**	89	12	 **3l**	85

[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).

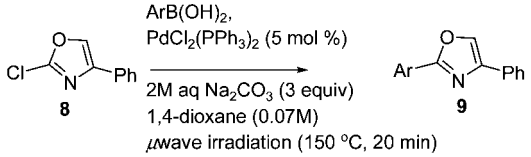
Scheme 2. Activation of the Oxazole 2-Position

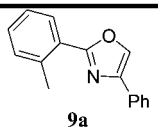
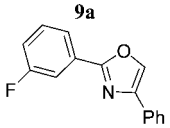
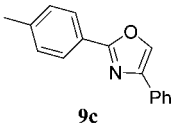
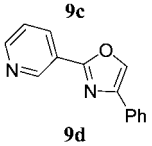
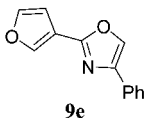


With an arylation methodology in place for the oxazole 2- and 4-positions, we were interested in extending the reaction to the coupling of two oxazole units to make a dioxazole. This reaction would represent the first steps in the development of a general Suzuki coupling strategy for the synthesis of 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**



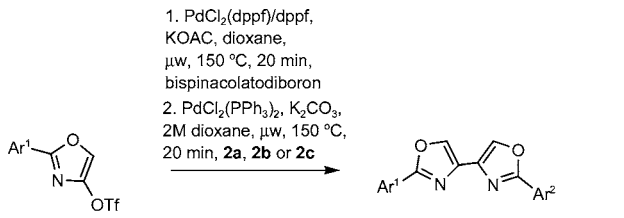
entry	product (5)	yield (%)[a]
1	 **9a**	80
2	 **9b**	80
3	 **9c**	88
4[b]	 **9d**	91
5[b]	 **9e**	82

[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.

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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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(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.