Published in final edited form as:
Synlett. 2010 July 1; 2010(11): 1641–1646. doi:10.1055/s-0029-1220128.

Efficient Suzuki and Stille Reactions for Regioselective Strategies of Incorporation of the 1,3-Oxazole Heterocycle. Mild Desulfonylation for the Synthesis of C-4 and C-5 Monosubstituted Oxazoles

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Abstract

Suzuki and Stille cross-coupling reactions are surveyed for site-selective C-4 and C-5 elaboration of 2-(phenylsulfonyl)-1,3-oxazole derivatives. Conditions for mild reductive desulfonylations provide for direct incorporation of the intact oxazole heterocycle through bonding at C-4 and C-5.

Keywords

cross-coupling reactions; arylation; alkenylation; reductive desulfonylation

Oxazoles represent an important class of five-membered heterocycles.[1] In recent years, this heterocyclic system has frequently been identified as a significant structural feature, embedded within the architecture of complex natural products.[2] Several interesting antibiotics prominently display 1,3-oxazoles as a result of cyclodehydration of serine or threonine residues in the course of biosynthesis.[3] Not surprisingly, a number of cyclodehydration strategies, beginning with acyclic amides, have been developed to provide for the *de novo* preparation of substituted 1,3-oxazoles.[4] These pathways for oxazole synthesis have limitations, which are often based on the reactivity and the availability of the starting amide precursors. As a result, there is a need for generally applicable techniques, which permit regioselective incorporation of the intact oxazole heterocycle. Our studies have documented a synthetic design utilizing 2-(phenylsulfonyl)-1,3-oxazole (**1**) for site specific arylations, alkenylations, and alkylations of the heterocyclic ring leading to the production of 2,4- and 2,5-disubstituted oxazoles **2** as well as 4- and 5-monosubstituted-1,3-oxazoles **3** (Scheme 1).

Several laboratories have described examples of cross-coupling processes of arylation and alkenylation at C-2 of the oxazole nucleus,[5] and Stille reactions of 2-phenyl-1,3-oxazole have led to C-4 and C-5 arylation reactions.[6] Recently, Stambuli and coworkers have described the selective C-5 deprotonation of 2-methylthio-1,3-oxazole with *tert*-butyllithium affording access to 2,5-disubstituted oxazoles.[7] These efforts have advanced the previous studies of Shafer and Molinski,[8] as well as a previous report by Marino and Nguyen disclosing the regioselective allylation of 2-(*n*-butylthio)-1,3-oxazole.[9]

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In 1997, we reported the site-selective (C-4) deprotonation of 1-[2′-(trimethylsilyl) ethoxymethyl]-2-(phenylsulfonyl)-imidazole (**4**), and subsequent reactions with a variety of electrophiles (Scheme 2).[10] As illustrated with the formation of **6**, mild removal of SEM protection and reductive desulfonation with 2% Na(Hg) provided a scheme for imidazole incorporation.

Our studies also examined the analogous (C-5) ring metalation of 2-(phenylsulfonyl)-1,3-oxazole and alkylations of this reactive carbanion. Subsequent reactions for displacement of the 2-(phenylsulfonyl) group have established a general route to 2,5-disubstituted-1,3-oxazoles.[11] Prior literature reveals relatively little information regarding useful methods for C-4 and C-5 halogenation of oxazoles.12 However, the well-behaved carbanion from **7** (Scheme 3, R = SO_2Ph, X = Li) facilitates convenient halogenation and stannylation reactions yielding **9** and **10**, respectively.[11] Furthermore, we have shown that 5-bromo-2-(phenylthio)-1,3-oxazole (**8**) undergoes a facile base-induced isomerization, characterized as a halogen dance rearrangement to provide access to the 4-bromo-1,3-oxazole **11** (85%).[13] In this letter, we have described a survey of Suzuki and Stille cross-coupling reactions, which demonstrate the utility of these derivatives for a convenient general preparation of 2,5- and 2,4-disubstituted oxazoles. In addition, we have documented the use of sodium hydrosulfite for reductive desulfonylations to yield C-4 and C-5 monosubstituted-1,3-oxazoles.

A compilation of our results for Suzuki cross-coupling arylation reactions is summarized in Table 1. These reactions have evaluated the effective use of the C-5 iodide **9** and C-4 bromide **11** with a series of commercially available arylboronic acids. High yields of the expected products are uniformly obtained using 10 mol% $Pd(PPh_3)_4$ at 70 °C to 80 °C in a mixture of THF and toluene containing aqueous Na_2CO_3 or K_2CO_3 (2:2:1 by volume).

The effective coupling of iodide **9** or bromide **11** with boronic acids suggested its use as a cross-coupling partner in Stille reactions. Indeed, this expection is confirmed by the Stille reactions of **9** and **11** with tri-*n*-butylvinylstannane (1.2 equiv) under standard conditions to afford oxazoles **20** and **21** in 85% and 74% yields, respectively (Table 2). Likewise, Stille coupling also proceeded uneventfully to afford the trisubstituted alkene **22**.

To survey the utility of Stille cross-coupling reactions of the readily available 5-(tri-*n*-butylstannyl)oxazole **10** (from Scheme 3), we employed a variety of aryl, alkenyl and allyl halides. The results of this study are summarized in Table 3. In this regard, the Stille reaction leading to the C-5 linked bisoxazole **24** (entry 3) is particularly noteworthy, and entry 4 documents the facile formation of the conjugated trisubstituted alkene **25** in excellent yield. Entry 6 indicates that π-allyl Stille reactions of stannane **10** will produce regioisomeric products. However, prenylation predominantly leads to bond formation at the less hindered allylic position giving **27** as the major isomer (ratio 7:1).

Finally, our studies have found conditions for the mild reductive desulfonylation of 2-(phenylsulfonyl)-1,3-oxazoles using aqueous sodium hydrosulfite. A survey of reactions in Table 4 demonstrates the effective replacement of the C-2 sulfonyl substituent with hydrogen. Reactions are conducted with excess sodium hydrosulfite (5 equiv) in aqueous *N*-methylpyrrolidone (1:1 by volume) in the presence of sodium bicarbonate at 80 °C. These reductions were complete within three hours and have consistently provided good yields of the desired 4- and 5-monosubstituted-1,3-oxazoles. Common *O*-protecting ethers (PMB and THP) are stable under the reaction conditions, whereas the labile *N*-Boc protection of the indoles **31** and **34** is cleaved via hydrolysis.

In summary, our studies of ring metalation of the oxazole nucleus have provided convenient access to C-4 and C-5 halogenation and C-5 stannylation for use in cross-coupling reactions. A survey of Suzuki and Stille processes for arylation and alkenylation demonstrates broad

versatility of these oxazole derivatives as coupling partners, and illustrates a general strategy for the regioselective preparation of 2,4- and 2,5-disubstituted-1,3-oxazoles. These findings provide for the incorporation of the intact oxazole heterocycle through bonding at C-4 or C-5 by using the phenylsulfonyl moiety as a blocking unit of the reactive C-2 position. Mild conditions for reductive desulfonylation have been described. Applications for natural product synthesis will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge the support of Indiana University and partial support of the National Institute of Health (GM 042897). We acknowledge the assistance of Fese Mokube (Indiana University) for the preparation of vinyl stannane in Entry 3, Table 2.

References and Notes

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2. For examples, see: (a) Ichiba T, Yoshida WY, Scheuer PJ, Higa T, Gravalos DG. J Am Chem Soc 1991;113:3173. (b) Shin-ya K, Wierzba K, Matsuo K, Ohtani T, Yamada Y, Furihata K, Hayakawa Y, Seto H. J Am Chem Soc 2001;123:1262. [PubMed: 11456694] (c) Searle PA, Molinski TF. J Am Chem Soc 1995;117:8126. (d) Rosener JA, Scheuer PJ. J Am Chem Soc 1986;108:846. (e) Dalisay DS, Rogers EW, Edison AS, Molinski TF. J Nat Prod 2009;72:732. [PubMed: 19254038] (f) Li J, Burgett AWG, Esser L, Amezcua C, Harran PG. Angew Chem Int Ed 2001;40:4770. (g) Irschik H, Jansen R, Gerth K. J Antibiot 1995;48:31. [PubMed: 7868386]
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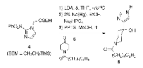
13. Williams DR, Fu L. Synlett 2010:591.

Scheme 1.

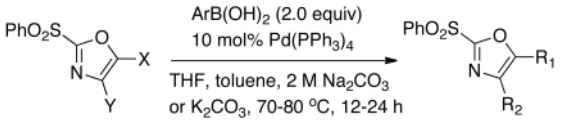


Scheme 2.

Scheme 3.

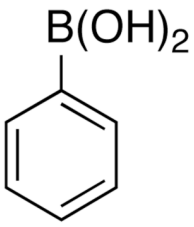
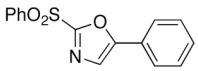
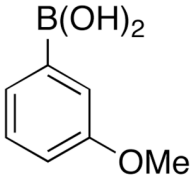
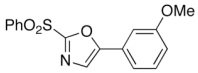
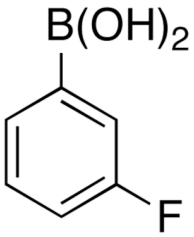
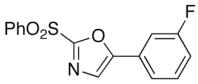
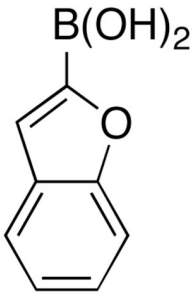
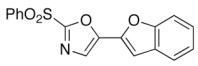
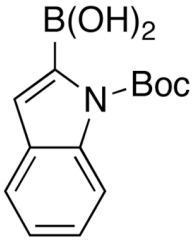
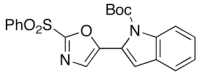
Table 1

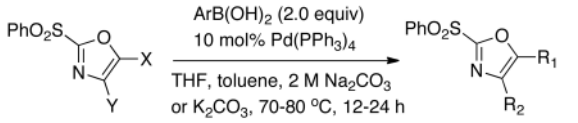
Suzuki arylations of 5-iodo (**9**) or 4-bromo-2-(phenylsulfonyl)-1,3-oxazole (**11**)



9 X = I, Y = H
11 X = H, Y = Br

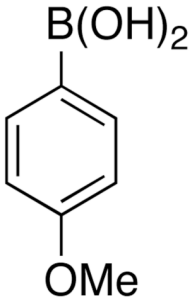
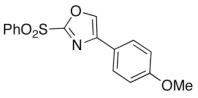
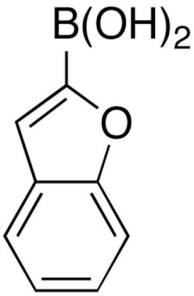
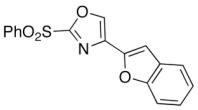
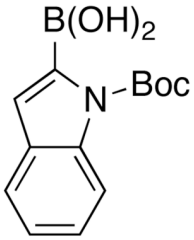
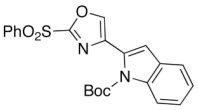
12-16 R_1 = Ar, R_2 = H
17-19 R_1 = H, R_2 = Ar

Entry	Boronic acid	Product[a]		Yield (%)[b]
1			**12**	91
2			**13**	96
3			**14**	92
4			**15**	94
5			**16**	96



9 X = I, Y = H
11 X = H, Y = Br

12-16 R_1 = Ar, R_2 = H
17-19 R_1 = H, R_2 = Ar

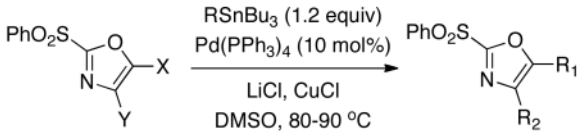
Entry	Boronic acid	Product[a]		Yield (%)[b]
6			**17**	96
7			**18**	89
8			**19**	87

[a] Reaction conditions: Under N_2 atmosphere, $Pd(PPh_3)_4$ (10 mol%) was added into a degassed mixture of sulfone **9** (1.0 equiv) and aryl boronic acid (2.0 equiv) in THF, toluene and 2M aqueous Na_2CO_3/K_2CO_3 (2:2:1 by volume) (0.04 M concentration), and the reaction was heated to 70-80 °C;

[b] Yields are provided for purified products following flash silica gel chromatography.

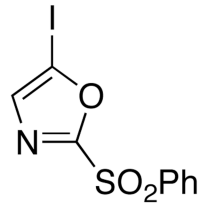
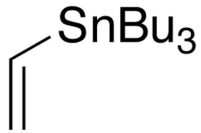
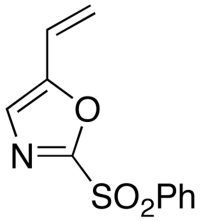
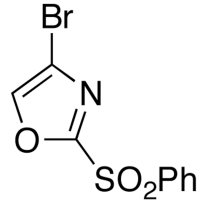
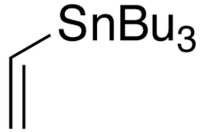
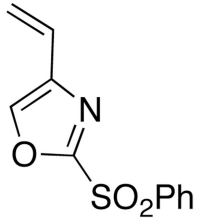
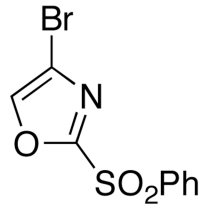
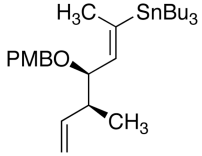
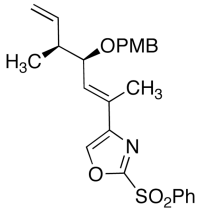
Table 2

Stille reaction of oxazoles **9** and **11**



9 X = I, Y = H
11 X = H, Y = Br

20-22

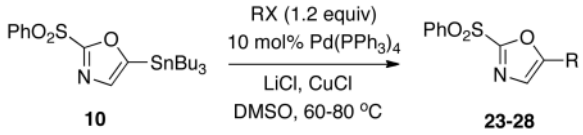
Entry	Oxazole	Stannane	Product[a]		Yield (%)[b]
1				**20**	85
2				**21**	74
3				**22**	70

[a] Reaction conditions: Under N_2 atmosphere, $Pd(PPh_3)_4$ (10 mol%) was added into a degassed mixture containing sulfone **10** (1.0 equiv) and organic halide (1.2 equiv) in the presence of CuCl (5 equiv) and LiCl (6 equiv) in DMSO (0.05 M concentration), and reactions were heated to 80-90 °C;

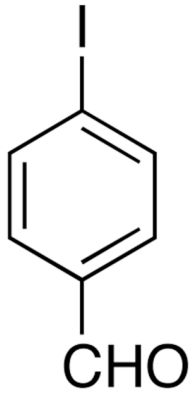
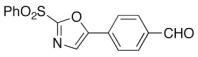
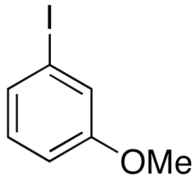
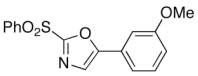
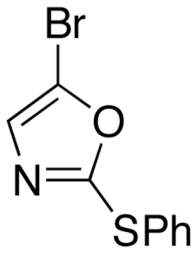
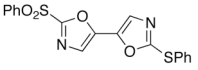
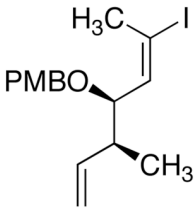
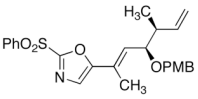
[b] Yields are provided for purified products following flash silica gel chromatography.

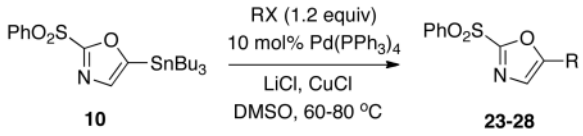
Table 3

Stille cross-coupling reactions of oxazole **10**

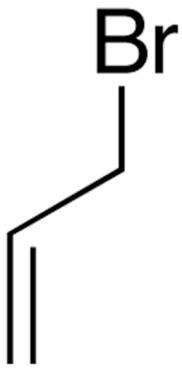
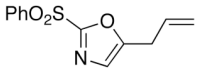
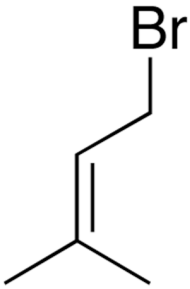
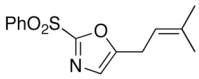
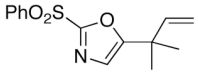


10 **23-28**

Entry	Halide	Product[a]		Yield (%)[b]
1			**23**	96
2			**13**	98
3			**24**	71
4			**25**	92



10 **23-28**

Entry	Halide	Product[a]		Yield (%)[b]
5			**26**	94
6		 	**27** **28**	86[c]

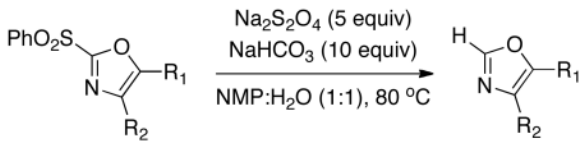
[a] Reaction conditions: Under N_2 atmosphere, $Pd(PPh_3)_4$ (10 mol%) was added into a degassed mixture containing sulfone **10** and organic halide (1.2 equiv) in the presence of CuCl (5 equiv) and LiCl (6 equiv) in DMSO (0.05 M concentration), and reactions were heated to 60-80 °C;

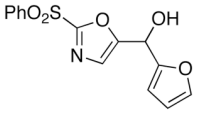
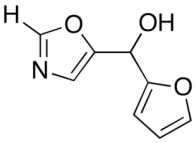
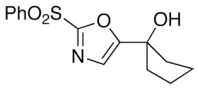
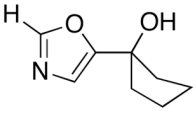
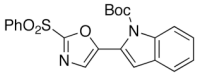
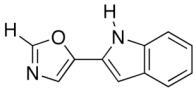
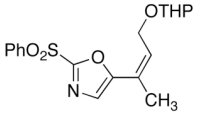
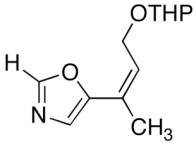
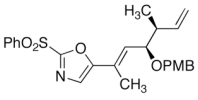
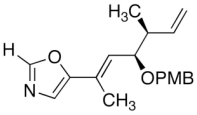
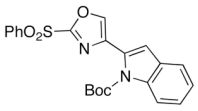
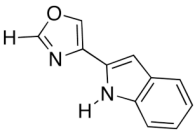
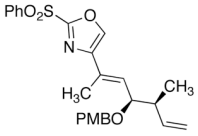
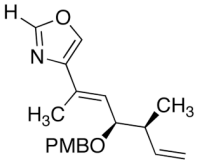
[b] Yields are provided for purified products following flash silica gel chromatography;

[c] Ratio for **27** and **28** is 7:1.

Table 4

Reductive desulfonylation with sodium hydrosulfite



Entry	Sulfone	Product[a]		Yield (%)[b]
1			**29**	89
2			**30**	92
3			**31**	89
4			**32**	93
5			**33**	97
6			**34**	91
7			**35**	94

[a] Reaction conditions: Sulfone (1.0 equiv) was added into a mixture of *N*-methylpyrrolidone and water (1:1 by volume) (0.05 M concentration) containing sodium bicarbonate (10 equiv) and sodium hydrosulfite (5 equiv) at room temperature;

[b] Yields are provided for purified products following flash silica gel chromatography.