Nickel-Catalyzed Synthesis of Oxazoles via C–S Activation
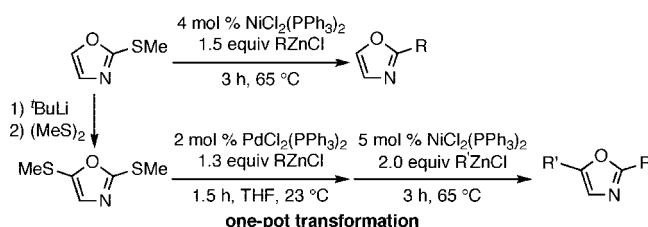
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ABSTRACT

The synthesis of 2-substituted oxazoles is achieved via nickel-catalyzed cross-coupling reaction of 2-methylthio-oxazole and various organozinc reagents. An extension of this method is demonstrated with a chemoselective, one-pot synthesis of unsymmetrical 2,5-disubstituted oxazoles. This synthesis of 2- and 2,5-substituted oxazoles using this method provides great advantages over previous methods for these compounds and is highly complementary to current cyclodehydration strategies.

Oxazoles are an important class of heterocycle that exhibit diverse biological activities.[1] Natural products containing the oxazole substructure have been shown to exhibit potent anticancer, -fungal, and -bacterial properties.[2] Oxazoles that are monosubstituted at *C*-2 have been used as synthetic intermediates in the synthesis of natural products[3] and pharmaceuticals.[4] However, a potential limitation to a greater use of 2-substituted oxazoles in synthetic chemistry may be caused by the lack of practical methods to produce 2-substituted oxazoles.

Current methods for the synthesis of oxazoles include cyclodehydration reactions,[5] oxidations of oxazolines,[6] direct metalations of the parent oxazole,[7] and metal-catalyzed cross-coupling reactions.[8] The most common method to prepare oxazoles involves cyclodehydrations, but this method provides low yields of 2-substituted oxazoles.[9] A general synthesis of 2-substituted oxazoles was reported via palladium-catalyzed Negishi cross-coupling using 2-oxazolylzinc chloride with aryl bromides.[10] The reaction works well for some aryl substrates but requires the use of 1.4 equiv of

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the parent oxazole, which is costly and reportedly prepared in low yields in the laboratory.[3a]

One of the reasons successful cross-coupling chemistry has not transformed routes to functionalized oxazoles is the instability of the electrophilic oxazole partners. For instance, monosubstituted boron and stannyl oxazoles have been reported to be unstable[4] or difficult to prepare.[10] However, thioalkyloxazoles have been synthesized and shown to be stable under harsh reaction conditions described in previous work reported by the groups of Molinski[11] and Marino,[12] who utilized thioalkyl groups to block the reactive *C*-2 position on oxazole. Furthermore, the synthesis of **1** occurs in high yield and avoids the parent oxazole. We hypothesized that 2-methylthio-oxazole (**1**) should be stable enough to undergo metal-catalyzed cross-coupling reactions via routes that are similar to the established Fukuyama coupling reactions of thioesters.[13] Moreover, a number of studies concerning oxidative addition reactions of aryl and vinyl sulfides have been reported in the literature.[14]

We decided to investigate the nickel-catalyzed coupling reaction of oxazoles and organozinc reagents. Several representative results for initial conditions that were screened are shown in Table 1. Triphenylphosphine (PPh$_3$) was

Table 1. Initial Conditions Screened to Produce 2-Substituted Oxazoles
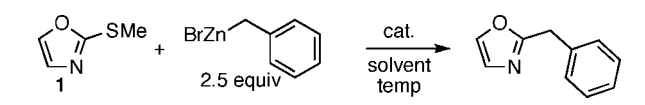
entry	catalyst	solvent	T (°C)	time (h)	yield (%)^a
1	2 mol % Pd(PPh$_3$)$_4$	toluene	80	2	83
2	2 mol % Pd(PPh$_3$)$_4$	THF	60	2	82
3	2 mol % PdCl$_2$(PPh$_3$)$_2$	DMF	80	19	0
4	2 mol % PdCl$_2$(PPh$_3$)$_2$	toluene	80	2	75
5	no catalyst	THF	60	6	0
6	1 mol % Pd$_2$dba$_3$ 4 mol % P^{t}Bu$_3$	THF	60	24	29
7	2 mol % Pd(PPh$_3$)$_4$ 1.5 equiv CuTC	THF	60	12	0
8	2 mol % PdCl$_2$(PPh$_3$)$_2$ 1.5 equiv CuTC	THF	60	12	0
9	2 mol % Ni(acac)$_2$	THF	60	12	35
10	5 mol % Ni(PPh$_3$)$_4$	THF	60	12	84
11	2 mol % Ni(PPh$_3$)$_4$	toluene	80	19	48
12	2 mol % Ni(PPh$_3$)$_4$	THF	60	12	54
13	5 mol % NiCl$_2$(PPh$_3$)$_2$	THF	60	12	86
14	5 mol % NiCl$_2$(PPh$_3$)$_2$	toluene	80	12	50

^{a} Isolated yields.

identified as the most promising ligand regardless of metal; therefore, we focused our screening on PPh$_3$-ligated catalysts. The two highest product yields occur with 2 mol % of

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Pd(PPh$_3$)$_4$ in toluene, which gives 83% yield of isolated 2-benzyl-oxazole (entry 1), while 5 mol % NiCl$_2$(PPh$_3$)$_2$ in THF at 60 °C gives 86% of the corresponding product (entry 13). A coordinating solvent, such as DMF, failed to give good yields of product (entry 3), while the presence of copper thiophene-2-carboxylate (CuTC) completely shut down catalyst activity (entries 7 and 8). The reaction does not proceed in the absence of catalyst (entry 5). Inspection of the literature related to this type of oxazole coupling revealed the work of Pridgen, who reported five examples of a nickel-catalyzed cross-coupling of 2-methylthio-4,5-diphenyloxazole with Grignard reagents.[15] These reaction conditions only work with fully substituted oxazoles.

From our initial investigations in this reaction and the relative cost of nickel versus palladium, we decided to employ reactions of NiCl$_2$(PPh$_3$)$_2$ as the optimal catalyst system. Compound **1** was reacted with 1.5 equiv of a variety of zinc reagents in THF at 60 °C (Table 2). The test reactant,

Table 2. Metal-Catalyzed Synthesis of 2-Substituted Oxazoles

entry	zinc reagent	catalyst	time	product	yield(%)^a
1	BrZn–CH$_2$Ph	NiCl$_2$(PPh$_3$)$_2$	6 h		85
2	ClZn–CH$_2$CH$_2$Ph	Pd(PPh$_3$)$_4$	6 h		58^b
3	ClZn–Ph	NiCl$_2$(PPh$_3$)$_2$	6 h		82
4	ClZn–C$_6$H$_4$CH$_3$	NiCl$_2$(PPh$_3$)$_2$	6 h		82
5	BrZn–(dimethoxyphenyl)	NiCl$_2$(PPh$_3$)$_2$	2 h		81
6	BrZn–(methylenedioxyphenyl)	NiCl$_2$(PPh$_3$)$_2$	2 h		84
7	ClZn–C$_6$H$_4$CF$_3$	NiCl$_2$(PPh$_3$)$_2$	6 h		88
8	ClZn–C$_6$H$_4$F	NiCl$_2$(PPh$_3$)$_2$	6 h		86
9	ClZn–(pyridyl)	NiCl$_2$(PPh$_3$)$_2$	18 h		52
10	ClZn–(thienyl)	NiCl$_2$(PPh$_3$)$_2$	6 h		83^c
11	ClZn–(furyl)	NiCl$_2$(PPh$_3$)$_2$	6 h		80
12	ClZn–C≡C–Ph	Pd(PPh$_3$)$_4$	6 h		56

^{a} Yields are an average of two isolated reactions. ^{b} 2.5 equiv of zinc reagent was employed. ^{c} 1.8 equiv of zinc reagent was employed.

benzylzinc bromide, gave the corresponding 2-benzyl-oxazole in 86% yield. The lone report of the synthesis of 2-benzyl-oxazole in the literature required six total steps (five linear steps) in less than 30% overall yield. Our method

involves three total steps in a 61% overall yield. Alkylzinc halides gave lower yields of product and required the use of Pd(PPh$_3$)$_4$ as catalyst (entry 2). Arylzinc halides provided the corresponding 2-aryl-oxazoles in very good yields regardless of electron-donating (entries 4–6) or electron-withdrawing character (entries 7 and 8). 3-Pyridylzinc halides gave the corresponding 3-pyridyl-oxazole product in lower yield likely due to usual complications seen with metal-catalyzed reactions. Other heteroarylzinc reagents gave oxazole products in good yields (entries 10 and 11), while zinc acetylides required conditions similar to alkylzinc reagents (entry 12).

To examine the versatility of this process, we investigated a regioselective synthesis of 2,5-disubstituted oxazoles. There are several pharmaceuticals that contain the 2,5-disubstituted oxazole core. 2,5-Disubstituted oxazoles have also been employed as synthetic intermediates in the synthesis of diazonamide A.[2b] A one-pot regioselective synthesis of 2,5-disubstituted oxazoles would be a major improvement over previous methods and showcases the selectivity and power of this method. Initially, we sought to employ a single catalyst for the two reactions that would react with the first addition of zinc reagent selectively at the more reactive C-2 position. At the end of this time, the second zinc reagent would be added to react at the C-5 position. Using the method reported by Molinski,[11] we prepared 2,5-bis(methylthio)-oxazole (2) and ran some initial experiments to test the feasibility of this transformation. Employing a nickel catalyst unselectively functionalized both the C-2 and C-5 position. Switching the catalyst to the less reactive palladium complex provided selective substitution at C-2; however, the addition of the second zinc reagent failed to produce appreciable amounts of product, as this catalyst was not reactive enough to substitute at the C-5 position. However, the addition of 2 mol % of PdCl$_2$(PPh$_3$)$_2$ and 1.3 equiv of the corresponding zinc reagent at ambient temperature for less than 2 h gave a high yield of the 2-aryl-5-methylthio oxazole (eq 1).
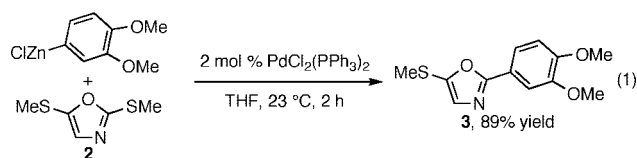
Taking direction from the above results, we decided to employ the less reactive palladium catalyst to activate the methylthio group at the C-2 position. After complete conversion of 2 was detected by GC, the more reactive nickel catalyst was added with the second organozinc reagent. The two catalytic reactions combine in one-pot to give 74–82% overall yield for both steps (Table 3). The methylthio group

Table 3. One-Pot Synthesis of Unsymmetrical 2,5-Disubstituted Oxazoles

entry	ArZnCl	Ar'ZnCl	product[a]	yield(%)
1	ClZn–C$_6$H$_5$	(MeO)$_2$C$_6$H$_3$–ZnCl		74
2	ClZn–C$_6$H$_5$	methylenedioxyphenyl–ZnCl		82
3	ClZn–C$_6$H$_4$–OCF$_3$	methylenedioxyphenyl–ZnCl		77

[a] Yields are an average of two isolated reactions.

at the C-5 position drastically improves the reactivity of the methylthio group at C-2, as the first reaction employing a palladium catalyst is typically complete within 2 h at ambient temperature, whereas monosubstituted methylthio oxazole 1 required heating at 60 °C, with the same catalyst and organozinc reagent. Currently, the optimum conditions for these reactions require the addition of 2 mol % of PdCl$_2$-(PPh$_3$)$_2$ and 1.3 equiv of organozinc to 2 for less than 2 h, followed by the addition of 5 mol % of NiCl$_2$(PPh$_3$)$_2$ and the second zinc reagent, to provide the unsymmetrical 2,5-disubstituted oxazoles in good yields (Table 3).

In summary, we have demonstrated a direct approach for the synthesis of 2-substituted oxazoles, which provides a powerful complement to current popular methods to construct oxazoles. A one-pot regioselective synthesis of 2,5-disubstituted oxazoles was also presented. Future work for this method includes the preparation of other mono- and disubstituted oxazoles, as well as investigating the mechanism of this reaction to increase the scope and yields of this transformation.

Supporting Information Available: Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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