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$Pd(OAc)_2$/2-aryl-2-oxazolines catalyzed Suzuki coupling reactions of aryl bromides and arylboronic acids

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Abstract—A series of 2-aryl-2-oxazolines were prepared and examined as ligands for the Suzuki coupling reaction of aryl bromides and arylboronic acids. 2,2′-(1,3-Phenylene)bisoxazoline/$Pd(OAc)_2$ was found to be an efficient catalyst for a variety of substrates to afford the coupling products in good to excellent yields.

The palladium-catalyzed Suzuki coupling reaction of aryl halides with arylboronic acids (or esters) has become a general and convenient synthetic method in organic chemistry for biaryl compounds,[1] which has been applied to many areas,[2] including natural product syntheses.[3] Triarylphosphine/Pd complexes are commonly used as catalysts for the reaction.[1a] In the past few years, great advances have been made in developing active and efficient catalysts by modifying traditional ligands and discovering new ones. Sterically demanding, electron-rich phosphines, such as tri-*t*-butylphosphine and its analogs,[4] di(*t*-butyl)aryl and dicyclohexylaryl phosphines[5] have shown high coupling activities for a variety of substrates. Trialkylphosphonium hydroboronofluorides have recently been reported as replacements for trialkylphosphines while retaining their high coupling activities and overcoming the air-sensitive problem of phosphine-based catalysts.[6] Other phosphine ligands/complexes, such as phosphine oxides,[7] phospha-palladacycles,[8,9] water-soluble phosphines[10] and chelating phosphine compounds[11] have also been developed. In the meantime, new types of non-phosphine ligands/complexes, such as heterocyclic carbenes,[12] imine and amine palladacycles,[13] oxime palladacycles[14] and diazabutadienes,[15] have also emerged for use in the Suzuki reaction.

2-Aryl-2-oxazoline palladacycles can be prepared from $Pd(OAc)_2$ and oxazolines either in acetic acid at reflux[16] or *ortho*-lithiation of the oxazolines, followed by quenching with a palladium salt.[17] They have been reported as catalysts for the Michael addition[17,18] and the Heck reaction.[19] Oxazoline ligands are expected to have advantages over phosphine ligands due to their ease of synthesis and air stability. We report here our initial results for 2-aryl-2-oxazolines as ligands for the Suzuki coupling reaction and the influence on the coupling reaction of electronic properties of substituents on the phenyl ring of the 2-aryl-2-oxazolines. The oxazolines in Table 1 (except for 4,4-dimethyl-2-phenyl-2-oxazoline, which is commercially available) were prepared from the corresponding aryl nitriles and 2-amino-2-methylpropanol or aminoethanol at 120°C in ethylene glycol in the presence of catalytic amounts of K_2CO_3,[20] and characterized by ^1H, ^{13}C NMR spectra and elemental analysis.

With these oxazolines in hand, they were examined as ligands in the coupling reaction of 4-bromoanisole and phenylboronic acid (1.5 equiv.) in the presence of 2 mol% of $Pd(OAc)_2$, 2 mol% of oxazoline, and 2 equiv. of Cs_2CO_3 in dioxane at 80°C. We thought that oxazoline palladacycles might be generated in situ from $Pd(OAc)_2$ and oxazolines under reaction conditions which would simplify the reaction operations. Towards this end, two different procedures of in situ generation of the oxazoline palladacycles were examined. In the first one, $Pd(OAc)_2$ and 4,4-dimethyl-2-phenyl-2-oxazoline were heated in dioxane at 80°C for 30 min, followed by the addition of the substrates to the yellow cooled solution at room temperature, and the mixture was then heated to 80°C. In the second one, all the reaction reagents were added together at room temperature and the mixture was heated. To our delight, the two different procedures afforded the coupling product in good and comparable yields. Subsequently, the second procedure was adopted for the other coupling

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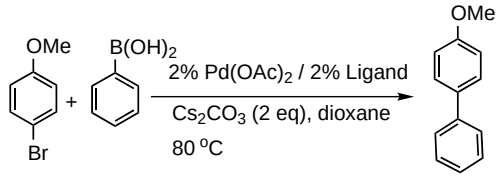
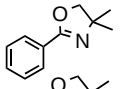
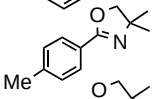
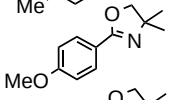
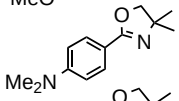
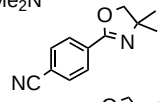
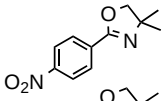
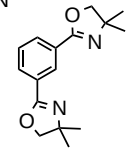
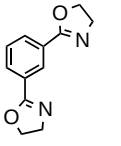
reactions. Using this procedure, all the reactions proceeded to completion in 4 h as monitored by TLC.

Electronic effects of the substituents on the phenyl ring of the oxazolines play a significant role on the coupling reaction as indicated in Table 1. Compared to 4,4-dimethyl-2-phenyl-2-oxazoline (entry 1), the oxazolines with electron-donating groups on the phenyl ring gave the product in low yields, while those with electron-withdrawing groups afforded 4-methoxybiphenyl in slightly higher yields. For instance, 2-aryl-2-oxazolines with methyl and *N*,*N*-dimethylamino groups diminished the yield to 56 and 61% from 80%, respectively (entries 2 and 4); oxazolines with a cyano or nitro group afforded the product in 83 and 88% (entries 5 and 6). These observations, at first glance, seem to be in contrast to those for other systems.[15] Actually, we observed that the reactions with the oxazolines bearing the electron-donating groups gave rise to more debromination by-product as indicated by TLC. The low yield of these coupling reactions is a result of the diminished aryl bromides due to the competitive debromination reaction of the aryl bromide enhanced by the electron-rich nature on the palladium center, which resulted from the electron-donating groups on the phenyl ring of the oxazolines. It is also worth noting that these results are likely a reflection of electronic effects of the different substituents, without steric contributions. Such effect could be very useful in investigations of the mechanisms of the coupling reactions.

Table 1. Effect of different ligands/$Pd(OAc)_2$ on the Suzuki coupling reaction of 4-bromoanisole with phenylboronic acid



Entry	Ligand		Yield (%)[a,b]
1			80
2		**(1)**	56
3		**(2)**	66
4		**(3)**	61
5		**(4)**	83
6		**(5)**	88
7		**(6)**	82
8		**(7)**	96

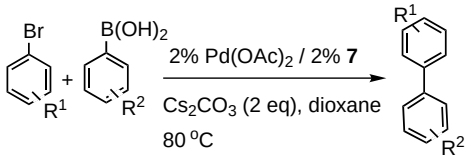
[a] *Reaction conditions*: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), $Pd(OAc)_2$ (2.0 mol%), ligand (2.0 mol%), Cs_2CO_3 (2.0 mmol), dioxane (4 mL), 80°C, 4 h.
[b] Isolated yield of average of two runs.

Among the 2-aryl-2-oxazolines examined, bisoxazoline **7** was found to be the best ligand, giving the desired product in almost quantitative yield. This great improvement in the reaction yield is likely a result of chelating effects as observed for other ligands.[11,15] However, its 4,4-dimethyl counterpart **6** gave lower yields. This result is probably due to the steric effects of the four methyl groups present which hinder the two nitrogen atoms of the two oxazoline rings from effectively binding to the palladium atom.

The scope of the Suzuki coupling reactions using bisoxazoline **7** as the ligand was investigated. The reaction is general for a variety of substrates as illustrated in Table 2. The coupling reaction is very tolerant of functional groups for both aryl bromides and arylboronic acids, and the reactions with both electron-withdrawing and electron-donating substituents gave the desired biaryl products in good to excellent yields.

In summary, we have demonstrated a general and efficient catalytic system based on $Pd(OAc)_2$/bisoxazoline **7** for the Suzuki coupling reaction of aryl bromides

Table 2. Suzuki coupling reaction of aryl bromides and arylboronic acids catalyzed by **7**/$Pd(OAc)_2$



Entry	R^1	R^2	Yield (%)[a,b]
1	4-Cl	H	81
2	3-NO_2	H	76
3	4-NO_2	H	96
4	4-Me	H	77
5	3-Me	H	89
6	[c]	H	75
7	3-NO_2	4-NO_2	93
8	4-Me	4-OMe	82
9	4-Me	2-Me	77
10	2-CN	3,4-Methylenedioxo	95

[a] *Reaction conditions*: aryl bromide (1.0 mmol), boronic acid (1.5 mmol), $Pd(OAc)_2$ (2.0 mol%), ligand **7** (2.0 mol%), Cs_2CO_3 (2.0 mmol), dioxane (4 mL), 80°C, 4 h.
[b] Isolated yield of average of two runs.
[c] The substrate is 6-bromo-2-naphthol.

and arylboronic acids. Different substituents on the phenyl ring of 2-aryl-2-oxazoline have a dramatic influence on the coupling reaction. Investigations are underway to determine the influence of electronic effects and chelating effects on the reaction.

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