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Palladium-Catalyzed C-2 C−H Heteroarylation of Chiral Oxazolines: Diverse Synthesis of Chiral Oxazoline Ligands

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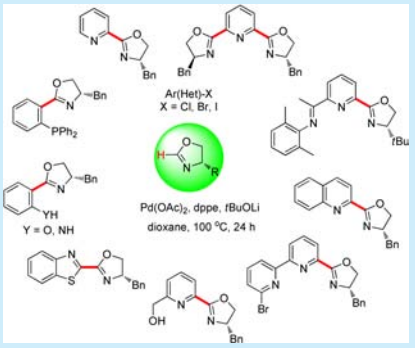
Supporting Information

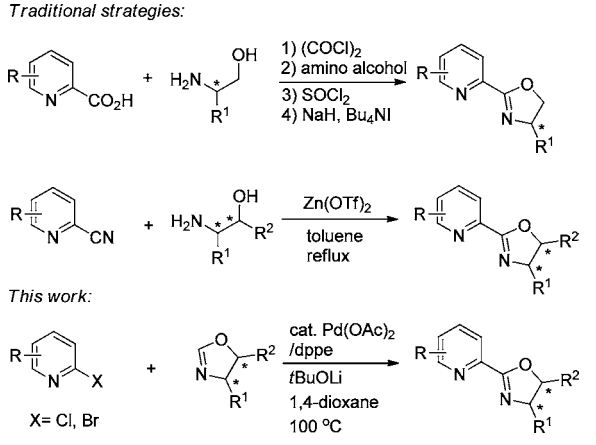
ABSTRACT: A direct, efficient, and practical protocol to install a chiral oxazoline unit onto aryl/heteroaryl rings via palladium-catalyzed C−H functionalization of 2-positions of oxazolines with a variety of halides using dppe as the ligand has been developed. Various chiral oxazoline ligands could be synthesized, even in a 10-g scale process. This protocol is a good supplement to traditional methods and for diverse synthesis of chiral oxazoline ligands.



Facile design and efficient synthesis of chiral ligands are of great importance in synthetic chemistry. Because of their easy accessibility and wide applicability in transition-metal-catalyzed asymmetric transformations, chiral oxazoline units that are known to coordinate a metal center readily have become one of the most successful and versatile ligands for asymmetric catalysis.[1] Chiral oxazoline pyridines, one of the most often used chiral ligands, could be obtained by two common synthetic strategies (Scheme 1).[1d,2] One starts from 2-carboxylpyridines and chiral amino alcohols, in which several steps are needed and acid-sensitive functional groups cannot be tolerated. Another process begins with substituted 2-cyanopyridines and chiral amino alcohols, among which substituted 2-cyanopyridines are usually expensive and toxic cyano reagents are required during the preparation processes. Although these two methods have been widely used, the above-mentioned limitations and the ubiquity of this unit in various ligands call for the development of new synthetic processes to access chiral oxazoline ligands in an efficient and environmentally friendly manner.

Although the facile synthesis of simple chiral oxazolines was developed by Meyers in 1991,[3] to the best of our knowledge, efficient transformations from these compounds directly to variously valuable chiral ligands has not been well explored. Inspired from C−H arylation of heterocycles[4] for synthesis of racemic 2-aryloxazoline[5] and Chang's synthesis[6] of chiral 2-alkynyloxazoline, very recently we have reported a palladium-catalyzed C−H bond 2-pyridination[7] of chiral oxazoline for synthesis of chiral oxazoline iminopyridine[8] in which only a few examples have been reported and the yield of the reaction with less sterically hindered imines decreased dramatically.[8e] To explore the potential utility of simple chiral oxazolines and further develop protocols to synthesize chiral oxazoline ligands, we herein describe a general and efficient method for the synthesis of chiral oxazoline ligands via palladium-catalyzed C−H bond functionalization of chiral oxazolines using dppe as the ligand.

Scheme 1. Synthetic Strategies of 2-Pyridine Oxazoline



We chose acid-sensitive 2-bromo-6-iminopyridine **1a** as a substrate to react with chiral oxazoline **2a** in the presence of 2.5 mol % of $Pd(OAc)_2$ and Xantphos as a ligand. The reaction afforded chiral oxazoline iminopyridine **3a**. However, the yield was low (36%) (entry 1, Table 1). To improve the yield of this transformation, a variety of diphosphine ligands such as dppf, dppp, dppe, binap, and NiXantphos have been used instead of xantphos (entries 2−6). Simple dppe is found to be the best ligand for this transformation, and this 2-oxazolination was successfully scaled up without a decrease in yield (86% isolated yield). The use of monophosphine ligands give very low reactivity (entries 7 and

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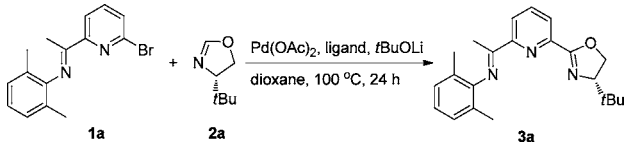
Table 1. Ligand Optimization of 2-Pyridination of Chiral Oxazoline[a]



entry	[Pd]	ligand	base	solvent	yield of 3a[b] (%)
1	$Pd(OAc)_2$	Xantphos	*t*BuOLi	dioxane	36
2	$Pd(OAc)_2$	NiXantphos	*t*BuOLi	dioxane	42
3	$Pd(OAc)_2$	dppf	*t*BuOLi	dioxane	38
4	$Pd(OAc)_2$	dppp	*t*BuOLi	dioxane	59
5	$Pd(OAc)_2$	dppe	*t*BuOLi	dioxane	86[c]
6	$Pd(OAc)_2$	BINAP	*t*BuOLi	dioxane	34
7	$Pd(OAc)_2$	PPh_3	*t*BuOLi	dioxane	10
8	$Pd(OAc)_2$	PCy_3	*t*BuOLi	dioxane	6
9	$Pd(OAc)_2$	dppe	*t*BuONa	dioxane	20
10	$Pd(OAc)_2$	dppe	*t*BuOK	dioxane	< 5
11	$Pd(OAc)_2$	dppe	*t*BuOLi	DME	46
12	$Pd(OAc)_2$	dppe	*t*BuOLi	DMF	40
13	$Pd(OAc)_2$	dppe	*t*BuOLi	toluene	28
14	$Pd(OAc)_2$	dppe	*t*BuOLi	THF	40
15	$Pd(dba)_2$	dppe	*t*BuOLi	dioxane	67
16	$Pd(PPh_3)_2Cl_2$	dppe	*t*BuOLi	dioxane	41

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), palladium source (2.5 mol %), ligand (2.8 mol %), base (2.0 mmol), solvent (6 mL). [b]Yields were determined by ^{1}H NMR spectroscopy using phenyltrimethylsilane as an internal standard. [c]Isolated yield.

8). Further optimization using various bases, solvents, and palladium catalysts revealed no further improvement for this transformation (entries 9−16, also see the Supporting Information).[9] The standard conditions are 2.5 mol % of $Pd(OAc)_2$ and 2.8 mol % of dppe, 2 equiv of *t*BuOLi, 1 equiv of halide, and 1.2 equiv of oxazoline in a solution of dioxane at 100 °C.

Having established the optimum reaction conditions, the scope and generality of this reaction were investigated as shown in Figure 1. 2-Bromo-6-iminopyridine can react with various chiral oxazolines (*t*Bu, *i*Pr, Bn, indenyl) to give chiral oxazoline iminopyridines **3a**−**g** in 71−89% yield without any racemization. The reaction with 2-chloropyridine would afford the pyridyl oxazoline **3h** in 66% yield, which is higher than the 55% yield obtained using 2-bromopyridine as the starting material. 2-Chloropyridine with a methyl group at different positions of the pyridyl ring did not significantly affect the yields (61−71%). The electron-deficient CF_3 group at the 4-position of the pyridyl rings could also be tolerated to give 72% yield of 4-(trifluoromethyl)-pyridyloxazoline **3m**. The free alcohol (in **3n**), which could potentially undergo further transformations, survived under the reaction conditions with 3 equiv of base. 2-Chloroquinoline was also suitable for the reaction to give **3o** in 81% yield. Other heteroaryl halides, such as 2-bromobenzothiophene, 2-chloropyrazine, and 2-chloropyrimidine, were also coupled with oxazoline to afford chiral *N*,*N*-ligands (**3p**−**r**) in 46−55% yields. 2-Bromobenzothiofuran reacted readily under standard conditions to give **3s**, a chiral *S*,*N*-ligand, in 95% yield. 2,2′-Dibromobispyridine could be converted into the monooxazoline *N*,*N*,*N*-ligand (**3t**) with high selectivity as the major product in a slightly low yield, with less than 2% of the dioxazolination side product. Aryl bromides with electron-donating and -withdrawing

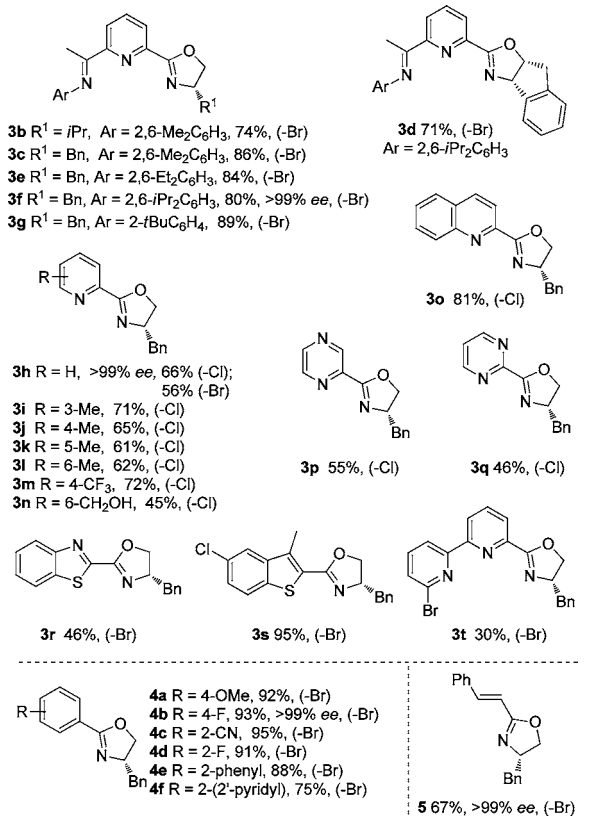
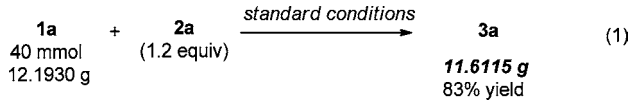


Figure 1. Scope of palladium-catalyzed synthesis of 2-substituted chiral oxazoline. Standard conditions: **1** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (2.5 mol %), dppe (2.8 mol %), *t*BuOLi (2.0 mmol), solvent (6 mL), 100 °C, 24 h.

substituents, even with sterically hindered 2-cyano, 2-fluoro, 2-phenyl, or 2-(2′pyridyl) groups, could serve as good partners to generate aryloxazolines efficiently in 75−95% yields (**4a**−**f**). The *E*-phenylvinyl bromide underwent the oxazolination reaction efficiently to give the desired 2-vinyl oxazoline **5** in 67% yield.

A 10-g scale reaction was readily conducted to give the oxazoline iminopyridine ligand **3a** in 83% yield (eq 1).



To demonstrate the potential application of the process to the synthesis of other various chiral ligands, the widely used phosphinooxazoline **6** (PHOX ligands),[10] 2-oxazolinyl phenol **7a**, 2-oxazolinylaniline **7b**, and pyridine-2,6-bis(oxazolino) **8** (PyBox ligand)[11] were easily prepared from known starting materials (Scheme 2).

To probe the mechanism of this reaction, H/D exchange[12] was performed in the presence of *t*BuOD to give **9** in 61% NMR yield with 68% D at C-2 of the oxazoline (Scheme 3, eq 2), which suggests that deprotonation of oxazoline at the 2-position could take place smoothly under the reaction conditions. A plausible catalytic cycle for this coupling reaction is depicted in Scheme 3. Oxidative addition of the halide to Pd(0) gives the organopalladium species **A**. The deprotonation of oxazoline at the 2-position in the presence of *t*BuOLi takes place to generate the lithium oxazoline intermediate, which can undergo transmetalation of organopalladium species **A** to give palladium

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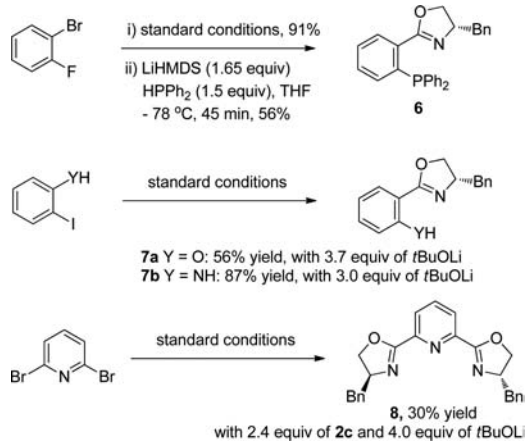
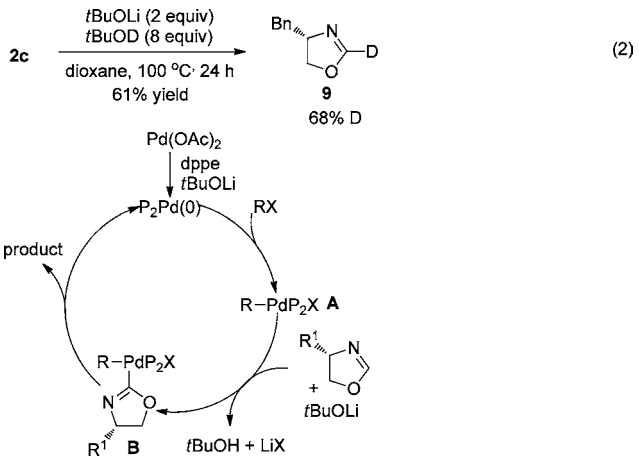
Scheme 2. Synthesis of Various Chiral Oxazoline Ligands



Scheme 3. Plausible Mechanism



oxazoline intermediate **B**. Finally, reductive elimination provides the product and regenerates the Pd(0) species.

In summary, we have developed a direct and practical method to install a chiral oxazoline unit onto aryl/heteroaryl rings via palladium-catalyzed C–H functionalization at the 2-positions of oxazolines with a variety of halides. The simple diphosphine ligand (dppe) could promote reactions efficiently. Pyridyl bromides or chlorides with a variety of functionalized groups, such as imino, free alcohols, and trifluoromethyl, were good partners and reacted with various oxazolines. Additionally, various of other heteroaryl halides as well as aryl halides participated. Vinyl bromide was also a good coupling partner. The reaction could be easily scaled up to 10 g scale. A plausible catalytic cycle for this coupling reaction is depicted based on the deuteration studies. Further studies on this transformation using base metal catalysts and applications in the new chiral ligand design are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03041.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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