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Masked Multifunctionalization of Aromatics by Palladium-catalyzed Halogen-Oxazoline Exchange

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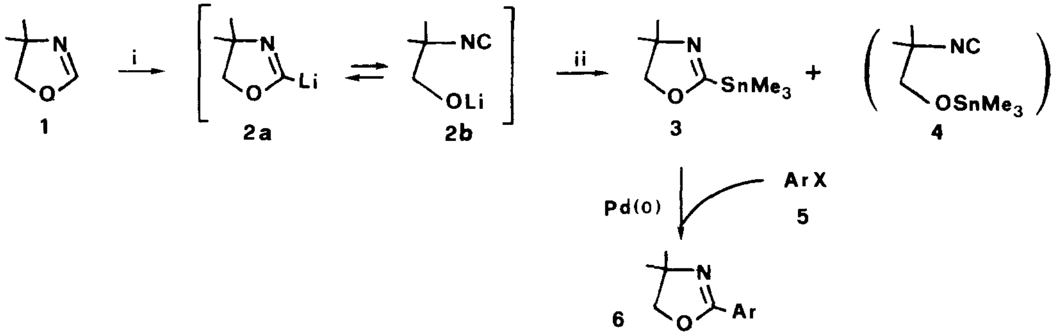
Abstract: The $(Ph_3P)_4$Pd-catalyzed cross-coupling of aryl and heteroaryl halides with 2-(trimethylstannyl)-4,4-dimethyl-2-oxazoline **3** affords aromatic 2-oxazolines **6** in very high yields.

The transition metal-catalyzed cross-coupling of aryl halides with organometallic species represents one of the most straightforward and versatile methods for carbon-carbon bond formation at aromatic rings.[1] The use of metalated heterocycles[2] in this methodology may provide a tool for aromatic functionalization in case the selected heterocycle is a masked functional group(s) equivalent. We report here the efficient palladium-catalyzed cross-coupling of a stannyloxazoline with aryl and heteroaryl halides to give the corresponding 2-oxazolines in very high yields. The synthetic utility of the 2-oxazolinyl group as a masked functionality (CHO, CO_2H) and director of metalation as well as nucleophilic and electrophilic aromatic substitutions has been amply demonstrated.[3] Common routes to aromatic oxazolines are based on the oxazoline ring closure at carboxylic acid derivatives;[3] a single method exists, limited in scope however, dealing with the cross-coupling of aryl Grignards and a 2-methylthiooxazoline.[4] The hitherto unreported 2-(trimethylstannyl)-4,4-dimethyl-2-oxazoline **3** (bp 78-80°C at 16 mmHg) was prepared (70-80% yield) by lithiation (BuLi) of 4,4-dimethyl-2-oxazoline **1** and then treatment with trimethyltin chloride (Scheme). Evidently almost exclusive quenching of lithio-oxazoline **2a** by the alkyltin chloride takes place since the O-trimethylstannyl isocyanide **4** arising from the open-chain lithium alkoxide **2b** was detected only by IR (2000 cm^{-1}) in the crude reaction mixture.[5] Cross-coupling reactions of the stannyloxazoline **3** (2.2 mmol) with the selected organic halide **5** (2 mmol) were carried out in refluxing benzene (15 mL, 12-20 h)



Scheme. Reagents and Conditions: i, BuLi (1.1 equiv.), -78°C in Et_2O ; ii, Me_3SnCl (1.1 equiv.); iii, $(Ph_3P)_4Pd$ (5% equiv.), C_6H_6, reflux.

under Argon atmosphere in the presence of 5% equiv. of tetrakis(triphenylphosphine)palladium(0). The resulting aryl and heteroaryl 2-oxazolines **6** were isolated by column chromatography (silica, diethyl ether : n-hexane 1:1) (Table). The wide scope of the method is evident when considering that besides giving products in very high yields it applies equally well to a variety of organic halides differing for the nature of the aromatic ring as well as the electron-donor or acceptor character of the substituent. As expected from reactivities of organic halides towards organostannanes,[1] aromatic iodides and bromides were quite efficient but a chloride was also successfully employed. Therefore this direct entry to aromatic oxazolines from organic halides nicely complements the Meyers methods[3] when the prerequisite carboxylic acids or nitriles are not available. The synthetic utility of this halogen-oxazoline exchange can be foreseen since it converts aryl and heteroaryl halides into masked carbonyl and carboxylic acid derivatives.

TABLE. Aromatic 2-oxazolines **6** from Cross-Coupling of Stannyloxazoline **3** and Organic Halides **5**

ArX **5**	2-Oxazoline **6**[a]	t/h	Yield %[b]
PhI	Ar = Ph	12	100
$MeOC_6H_4Br$-p	p-$MeOC_6H_4$	12	85
$MeSC_6H_4Br$-p	p-$MeSC_6H_4$	15	100
FC_6H_4Br-p	p-FC_6H_4	24	100
$MeCOC_6H_4Br$-p	p-$MeCOC_6H_4$	12	93
β-NaphBr[c]	β-Naph	12	95
2-BrPy[d]	2-Py	24	85
3-BrPy[d]	3-Py	24	62
2-ClQy[e]	2-Qy	12	75
3-BrQy[e]	3-Qy	12	90
4-BrQy-i[f]	4-Qy-i	12	92
3-BrThen[g]	3-Then	12	100
3-BrFur[h]	3-Fur	18	85

[a] All products were characterized by Mass and NMR spectra and showed identical properties to those of the literature. [b] Isolated yields. [c] β-Naph = β-naphtyl. [d] Py = pyridyl. [e] Qy = quinolyl. [f] Qy-i = isoquinolyl. [g] Then = thienyl. [h] Fur = furyl.

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5. By contrast, quenching the above equilibrium mixture with trimethylsilyl chloride gave exclusively O-trimethylsilyl β-hydroxyethylisocyanide. For a summary of the ambident chemistry of 2-lithio derivatives of oxazoles and 2-oxazolines see ref. 4 and A. Dondoni, T. Dall'Occo, G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, J. C. S. Chem. Commun., 258 (1984); A. Dondoni, Lect. in Heterocycl. Chem., **8**, 13 (1985).

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