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Pd-Mediated Cross-Coupling of Aryl, Alkenyl, and Alkynyl Stannanes with Chiral 2-Bromo Oxazolines

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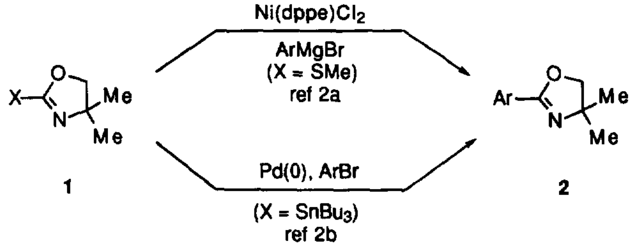
Abstract: *Chiral 2-bromo-2-oxazolines couple with appropriately substituted organostannanes mediated by Pd-catalysts to furnish 2-substituted oxazolines in good to moderate yields.*

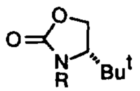
There are a number of methods available for the construction of 2-oxazolines.[1] Two methods have been described involving transition metal mediated cross coupling of intact, achiral 2-substituted oxazolines **1**.[2]



We have previously reported successful and efficient routes to the chiral 2-H oxazoline **3**[3] and found that we were unable to functionalize the 2-lithio derivative **4** with any tin, zinc, boron or silicon electrophiles. We then considered the transformation of an appropriate oxazoline **3** to species that would behave as electrophiles for palladium(0). We initially envisioned the formation

3, X = H
4, X = Li
8, X = OTf

5, G = Bu_3Sn
6, G = Br

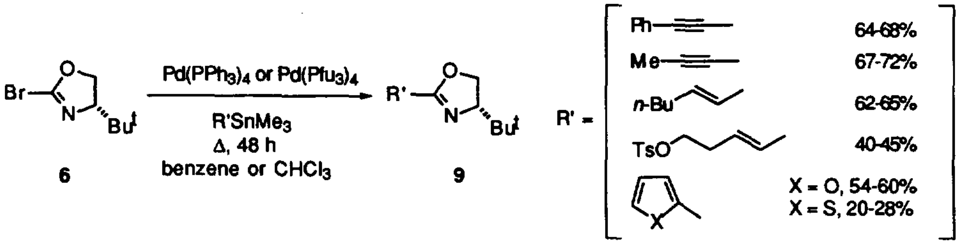


7, R = H, Tf

This paper is dedicated to Harry H. Wasserman in honor of his 75th birthday.

of the oxazoline triflate **8** from chiral oxazolidinone **7** (R = H) using standard protocol for generating enol triflates.[4] However, this resulted only in the recovery of the N-triflate **7** (R = Tf) in good yield.[5]

Finally, we found that lithiated oxazoline **4** (*t*-BuLi, THF, -78 °C) did react with 1,2-dibromotetrafluoroethane to give the bromo oxazoline **6** which could be obtained consistently in 50-70% yield.[6] Treatment of **6** with a variety of acetylenic, alkenyl and heterocyclic stannanes, using standard Pd(0) catalytic conditions produced the corresponding 2-substituted oxazolines, **9**.[7] $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ using either PPh_3 or $P(fu)_3$[8] as the ligand were both effective catalysts for the coupling reaction. Favorable results were obtained when benzene or chloroform were used as the solvent whereas no cross coupled product was obtained when THF, DME, DMF or NMP were employed. There was no evidence of catalyst decomposition, in the form of Pd(black) precipitation, even after extended reaction periods at elevated temperature.



Further applications for this cross coupling process will be reported in due course.

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5. Verified by X-ray crystal data analysis.
6. Procedure for the synthesis of **6**: A solution of **3** (1.0 g, 8.8 mM) was diluted with 90 mL anhydrous THF and cooled to -78 °C. Under an inert atmosphere, 1.1 equiv of *t*-BuLi (5.7 mL, 1.7 M) was added dropwise over 10 min. The bright yellow solution of the anion was allowed to stir at -78 °C for an additional 0.5 h prior to the addition, at once, of 1.1 equiv (9.7 mM, 3.2 g) dibromotetrafluoroethane. The mixture was allowed to warm *slowly* over 12 h after which time the volatiles were evaporated. The desired material was distilled directly from the residue (75-78 °C, 3 Torr) to give 1.36 g (57%) of **6**. ^1H NMR ($CDCl_3$): 0.89 (s, 9H), 3.89 (dd, J = 8.0, J = 10.1 Hz), 4.20 (t, J = 8.3 Hz), 4.36 (dd, J = 8.6, J = 10.0 Hz). IR (neat): 1624 cm^{-1}. Alternatively, the bromooxazoline may be purified by silica gel flash chromatography. The silica gel must be pretreated with 2% triethyl amine/hexanes and the oxazoline eluted using 2% ethyl acetate/hexanes. The product was stored as a matrix in benzene at -20 °C under N_2 or Ar.
7. General procedure for the cross coupling reaction: A solution of **6** was made approximately 0.5 M in the desired solvent. 1.05 equiv of the desired organostannane and 2-5 mole % of the desired catalytic reagent was added. The reaction was refluxed for 48 h after which time it was cooled and the volatiles evaporated. The residue was concentrated onto a small amount of silica gel and the product purified by silica gel flash chromatography using ethyl acetate and hexane mixtures of appropriate polarity.
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