

PALLADIUM-PHOSPHINE COMPLEX CATALYZED CROSS-COUPLING REACTION OF 1-METHYL-2-PYRROLYL-MAGNESIUM
BROMIDE AND -ZINC CHLORIDE WITH ORGANIC HALIDES

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Summary: 1-Methyl-2-pyrrolyl-magnesium bromide and -zinc chloride, which were prepared from 1-methyl-2-pyrrolyllithium with MgBr₂ and ZnCl₂ respectively, reacted with aryl- and hetero-aromatic halides to give the corresponding 2-substituted pyrroles in good to excellent yields in the presence of palladium-phosphine complexes as catalysts.

Introduction of organic groups on to heterocyclic compounds is one of the important pathways in organic synthesis. Reactions of readily obtainable lithiated heterocycles² with various electrophiles such as alkyl halides provide useful routes to substituted heterocyclic compounds.³ This methodology is, however, scarcely applicable to the coupling with aryl or heteroaryl halides.⁴ There have been only a limited number of methods for arylation and heteroarylation of heterocyclic compounds, which include the organocopper substitution reaction,⁵ nickel-phosphine complex catalyzed Grignard coupling reaction,⁶ and palladium-phosphine complex catalyzed coupling reaction of the organolithium reagents.⁷ For the pyrrole system which should afford a variety of compounds of pharmaceutical interest, however, the organocopper reaction does not always give a sole product in high yield,⁸ and the nickel catalyzed reaction gives unsatisfactory results.⁹

We now find that in the presence of a palladium-phosphine complex as a catalyst 1-methyl-2-pyrrolyl-magnesium bromide and -zinc chloride, prepared by transmetallation of 1-methyl-2-pyrrolyllithium¹⁰ with MgBr₂ and ZnCl₂¹¹ respectively, readily couple with aromatic and heterocyclic halides to give the corresponding substituted pyrroles in good to excellent yields.

While the reaction of 1-methyl-2-pyrrolyllithium with iodobenzene even in the presence of a palladium catalyst gave only a poor yield (29%) of the coupling product, the yield was dramatically improved by transmetallation from lithium to magnesium or zinc, as shown in

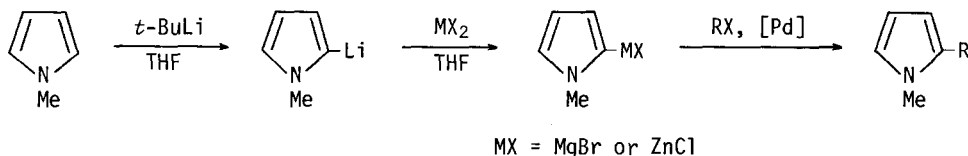


Table 1. Whereas the coupling of the Grignard reagent tends to depend upon the nature of the catalyst, the organozinc reagent gave the coupling product in fair to excellent yields, regardless of the catalyst employed. For both the organometallics, palladium complexes, especially the bidentate phosphine-palladium complexes, $\text{PdCl}_2(\text{dppb})^{12}$ or $\text{PdCl}_2(\text{dppf})^{12}$ showed higher catalytic activities than the nickel complex.

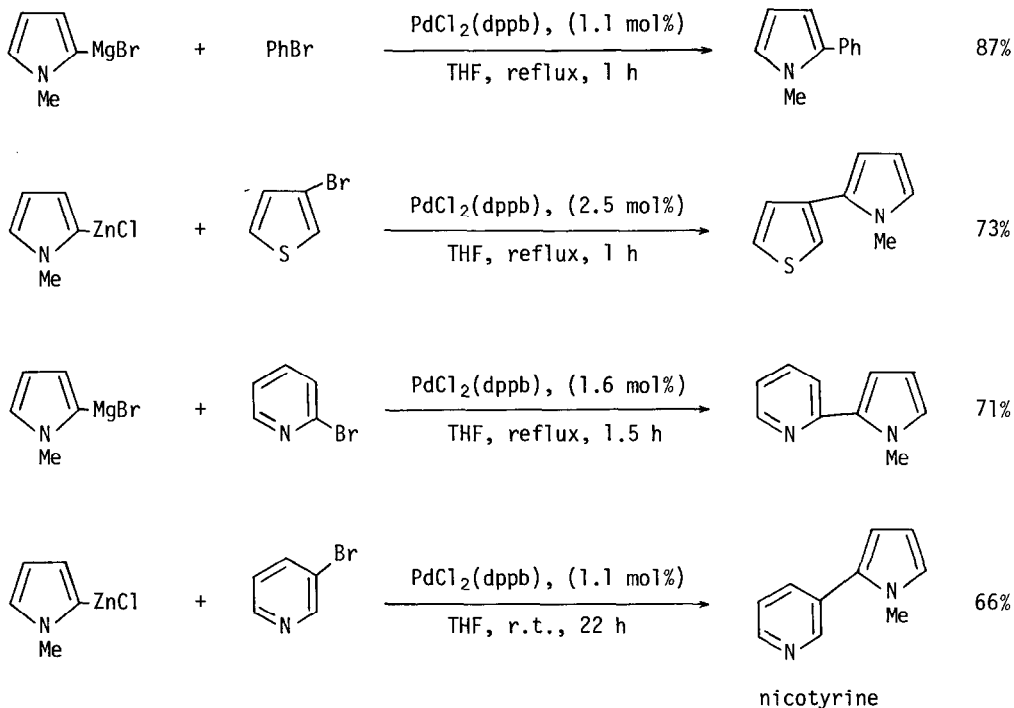
Similar coupling reaction proceeded efficiently with aromatic and heterocyclic bromides such as bromobenzene, 3-bromothiophene, and 2- and 3-bromopyridine to give coupling products, including nicotyrine,¹³ a constituent of the tobacco alkaloids.

Table 1. Comparison of Catalytic Activities for Coupling Reactions of 1-Methyl-2-Pyrrolyl-magnesium Bromide and -zinc Chloride with Iodobenzene^a

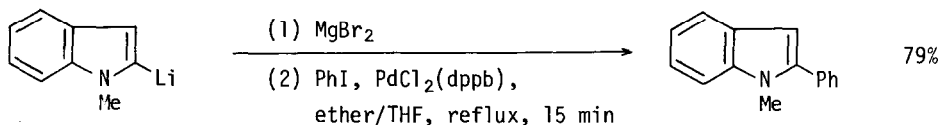
catalyst ^b	coupling product, yield (%) ^{c,d}	
	MX = MgBr	ZnCl
$\text{PdCl}_2(\text{dppb})$	93 (89)	95 (93) ^e
$\text{PdCl}_2(\text{dppf})$	79 (84)	68
$\text{PdCl}_2(\text{PPh}_3)_2$	53 (73)	85
$\text{NiCl}_2(\text{dppp})$	15 (66)	66

^a The reaction was carried out at room temperature on a 1~2.5 mmol scale; pyrrole / halide / catalyst = 1.5~2.5 / 1 / 0.01. ^b dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1'-bis(diphenylphosphino)ferrocene; dppp = 1,3-bis(diphenylphosphino)propane. ^c Yields were determined by GLC. ^d Numbers in parentheses show the yield under THF reflux for 15 min.

^e Under THF reflux for 40 min.



1-Methyl-2-indolylmagnesium bromide, prepared in the same manner,¹⁴ also coupled with iodobenzene in the presence of $\text{PdCl}_2(\text{dppb})$ to afford 1-methyl-2-phenylindole in 79% yield.



The present reaction may provide the most practical procedure for the introduction of 2-pyrrolyl or 2-indolyl group on to aromatic and heterocyclic compounds. It should be also mentioned that the present procedure does not require hardly accessible halogen derivatives of pyrrole and indole.

A typical procedure is as follows. 1-Methyl-2-pyrrolyllithium was prepared from 1-methylpyrrole (388 mg; 4.8 mmol) in THF (5 ml) by treatment with *t*-BuLi in pentane (4.8 mmol) at -78°C followed by stirring at room temperature for 0.5 h.¹⁰ This solution was added to a mixture of MgBr_2 (or dried ZnCl_2) (5.3 mmol) in THF (10 ml) at room temperature. The mixture was stirred at room temperature for 1 h. To a mixture of iodobenzene (540 mg; 2.6

mmol) and PdCl₂(dppb) (20 mg; 0.03 mmol) was added this THF solution of 1-methyl-2-pyrrolyl-magnesium bromide with stirring at room temperature under an argon atmosphere. After 20 h stirring, the mixture was hydrolyzed and made alkaline. GLC analysis of the organic layer showed the formation of 1-methyl-2-phenylpyrrole in 93% yield. The product was isolated by chromatography on silica gel (benzene / hexane = 1 / 3) to afford the pure product; 320 mg (78%), mp 47~48°C (lit.⁸ mp 51°C).

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