PREPARATION AND ARYLATION OF 2-INDOLYLZINC DERIVATIVES

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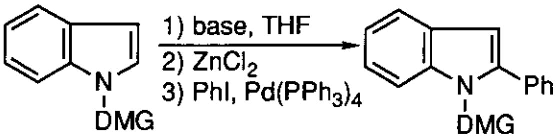
Abstract–2-Arylindoles were synthesized by the palladium-catalyzed reaction of aryl halides with 2-indolylzinc derivatives which were derived from the lithio derivatives.

The palladium-catalyzed reaction of arylzinc derivatives with aryl halides has been used as a general and highly chemoselective route to unsymmetrical biaryls.[1] The methodology has been expanded for the synthesis of biologically interesting unsymmetrical heterocyclic biaryls,[2] and heteroarylzinc compounds are usually easily accessible by the transmetallation of the corresponding heteroaryllithium with zinc chloride.

Introduction of carbon substituents into indoles is one of the most important processes in the indole chemistry, and a number of directed metallation groups (DMGs) at the 1-position of indoles have been developed for the functionalization at the 2-position[3]. In spite of the depth of DMGs study, the synthetic use of 2-indolylzinc derivatives has not yet been reported to our best knowledge.[4] We wish to report a convenient arylation of indoles using palladium-catalyzed reaction of 2-indolylzinc derivatives with aryl halides.

Firstly, some typical DMGs which are easily removable were chosen, and the transmetallation of the lithio derivatives with zinc chloride and the subsequent palladium-catalyzed reaction with iodobenzene was examined. As shown in Table I, *t*-butoxycarbonyl group gave the most satisfactory result whereas the reaction of the phenylsulfonylindole resulted in the complete recovery of the starting material.

Table I. Phenylation of 2-Indolylzinc Derivatives



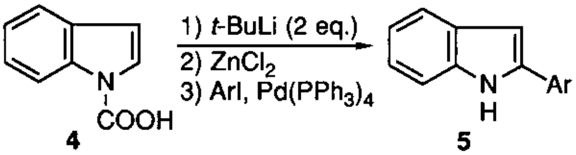
1 2

DMG	Base	Reaction time (h)	Yield (%)
SO_2Ph	LDA	13	recovery
CH_2OMe	*t*-BuLi	16	28
CH_2NMe_2	n-BuLi	15	15*
COO-*t*-Bu	*t*-BuLi	18	68

*: 3-Dimethylaminomethyl-2-phenylindole

From the structural relationship with *t*-butoxycarbonyl group, our next interest was focussed on the use of the 1-lithiocarboxyindole developed by Katritzky.[3e] Indole-1-carboxlic acid was treated with 2 equivalents of *t*-butyllithium to give the 2-lithio derivative which reacted with zinc chloride followed by palladium-catalyzed reaction with iodobenzene to give 2-phenylindole. Advantageous point of this procedure is that the DMG group is removable during the workup. Some other aryl iodides including heteroaryl iodides were subjected to the procedure, and 2-arylindoles were obtained in the yields shown in Table II.

Table II. Arylation via Indole-1-lithiocarboxylate



Ar	Reaction time (h)	Yield (%)
Ph	14	74
p-$EtOOCC_6H_4$	18	54
p-$O_2NC_6H_4$	15	55
p-$MeOC_6H_4$	17	25
2-thieny	18	56
2-pyridyl	13.5	29

Although analogous phenylation of 1-lithiocarboxypyrrole gave 2-phenylpyrrole in 39% yield, the application of the method to imidazole and pyrazole was not successful.

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5. Typical Procedure: **2-Phenylindole**–All operations were performed under an argon atmosphere. *t*-Butyllithium in pentane (15 mmol) was added to a solution of indole-1-carboxylic acid (805 mg, 5 mmol) in dry THF (220 ml) at the temperature below -65°C. The mixture was stirred at -70°C for 1 h followed by addition of an 1M THF solution of zinc chloride (12.5 ml, 12.5 mmol). The cooling bath was removed and the mixture was stirred for 1 h. To the mixture, iodobenzene (612 mg, 3 mmol) and $Pd(PPh_3)_4$ (0.25 mmol) was added. The whole mixture was refluxed for 14 h. The reaction mixture was diluted with H_2O and was extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was purified by silica gel column chromatography using hexane-AcOEt (19:1) as an eluent. The solid obtained was recrystallized from hexane-Et_2O to give colorless scales, mp 189°C (430 mg, 74%).

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