

Cobalt-catalyzed Cross-coupling Reaction of Chloropyridines with Grignard Reagents

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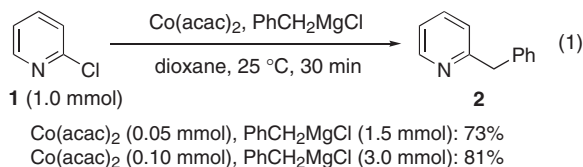
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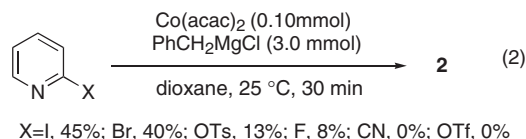
Treatment of 2-chloropyridine with benzylmagnesium chloride in the presence of a catalytic amount of cobalt(II) acetylacetonate in dioxane afforded the corresponding cross-coupling product in excellent yield. Trimethylsilylmethyl and phenyl Grignard reagents also participated in similar cross-coupling reactions.

Transition metal-catalyzed cross-coupling reactions are among the most important carbon–carbon bond forming reactions in organic synthesis.¹ Cobalt-catalyzed cross-coupling reactions have realized, without suffering from β -hydride elimination, the utilization of alkyl halides.^{2,3} In order to expand the scope of the cobalt-catalyzed reactions, we examined cross-coupling reactions of aryl halides with several Grignard reagents. Here we report a cobalt-catalyzed reaction of chloropyridine derivatives with Grignard reagents. Chloropyridines seem unlikely to undergo cross-coupling reaction, due to the strong carbon–chlorine bond.⁴

Treatment of 2-chloropyridine (**1**, 1.0 mmol) with benzylmagnesium chloride (3.0 mmol) in dioxane (3 mL) in the presence of cobalt(II) acetylacetonate (0.10 mmol) for 30 min at 25 °C afforded 2-benzylpyridine (**2**) in 81% yield (Eq. 1).^{5,6} Use of 1.5 mmol of the Grignard reagent and 0.05 mmol of the cobalt salt led to a slightly lower yet satisfactory yield of **2** (73%). Dioxane is a proper solvent, and reactions in ether or THF resulted in low conversions. Other cobalt salts such as CoCl_2 and CoCl_3 also catalyzed the reaction, although the yields were lower by ca. 10%. Neither lower nor higher temperatures improved the yield of **2**. The starting material **1** was completely recovered without any cobalt catalysts.



Surprisingly, the reaction of 2-iodopyridine afforded **2** in only 45% yield, where the starting material was completely consumed and a significant amount of 1,2-diphenylethane was obtained (Eq. 2). The bromo analogue was less reactive so that **2** was obtained in 40% yield, along with 19% recovery of the starting material. Seemingly promising leaving groups such as *p*-toluenesulfonate and trifluoromethanesulfonate resisted the reaction. Attempts to transform 2-fluoropyridine resulted in failure. Under the cobalt catalysis, 4-iodoanisole and 4-trifluoromethyl-1-chlorobenzene failed to react and both remained unchanged.



Trimethylsilylmethyl Grignard reagent also participated in a similar cross-coupling reaction to yield 2-pyridylmethyltrimethylsilane in 68% yield (Table 1, Entry 1). Phenylation at 25 °C resulted in low conversion (Entry 2) and required a higher temperature to proceed to completion (Entry 3). Installation of hexyl group was unsuccessful, competing with reduction that produced pyridine (Entry 4). The reaction with allylmagnesium chloride, even at –20 °C, failed to isolate 2-allylpyridine and yielded a complex mixture (Entry 5). Attempted methylation and vinylation left **1** intact. Reaction with 1-phenylethyl Grignard reagent afforded no trace of the corresponding coupling product, instead giving pyridine.

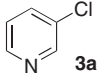
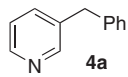
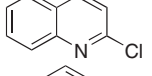
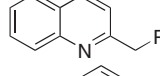
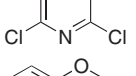
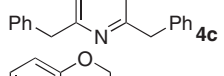
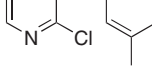
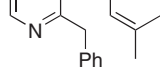
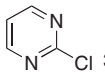
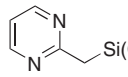
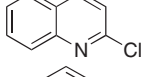
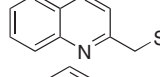
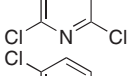
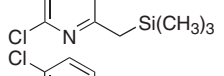
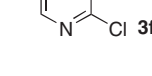
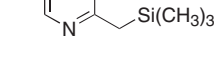
Table 1. Reaction of 2-chloropyridine (**1**) with various Grignard reagents

entry	RMgX	Temp/°C	Yield/%
1	(CH ₃) ₃ SiCH ₂ MgCl	25	68
2	PhMgBr	25	17 (33% of 1)
3	PhMgBr	50 (bath temp.)	73
4	"C ₆ H ₁₃ MgBr	25	15
5	CH ₂ =CHCH ₂ MgCl	–20	complex mixture

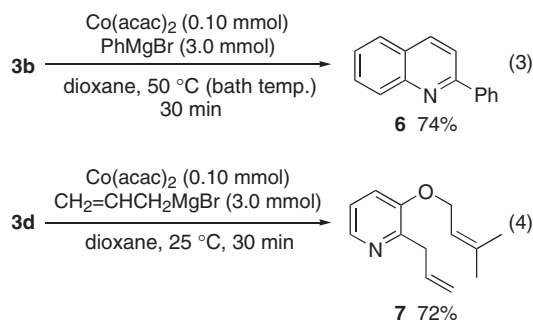
A variety of combinations of chloropyridine derivatives and Grignard reagents were surveyed (Table 2 and Eqs. 3 and 4). 3-Chloropyridine (**3a**) was transformed into 3-benzylpyridine (**4a**) in moderate yield (Table 2, Entry 1). Unfortunately, the reaction of 4-chloropyridine yielded no desired product. Benzylation was so efficient that dibenylation occurred to yield **4c** in fair yield with contamination by a trace of the monobenzylation product (Table 2, Entry 3), whereas trimethylsilylmethylation led to selective conversion of the chlorine at the 2 position (Table 2, Entries 7 and 8).

Interestingly, benzylation reactions of **3d** bearing an alkene moiety proceeded smoothly (Table 2, Entry 4), albeit the reactivity of **3d** is lower than that of **1**. Chloropyridine **3d** is a competent substrate for allylation to obtain **7** in 72% yield (Eq. 4). These facts stand in sharp contrast to the intramolecular 5-*exo-trig* cyclization reaction of 2-iodophenyl prenyl ether that was previously reported.⁷ The selective cross-coupling without

Table 2. Cobalt-catalyzed benzylation and trimethylsilylmethylation of chloropyridine derivatives

$\text{Ar-Cl} \xrightarrow[\text{dioxane, 25 } ^\circ\text{C, 30 min}]{\text{Co(acac)}_2 \text{ (0.10 mmol), PhCH}_2\text{MgCl (3.0 mmol)}} \text{Ar-CH}_2\text{Ph}$			
Entry	Ar-Cl	Product	Yield/%
1			47
2			84
3			42
4			51
$\text{Ar-Cl} \xrightarrow[\text{dioxane, 25 } ^\circ\text{C, 30 min}]{\text{Co(acac)}_2 \text{ (0.10 mmol), (CH}_3\text{)}_3\text{SiCH}_2\text{MgCl (3.0 mmol)}} \text{Ar-CH}_2\text{Si(CH}_3\text{)}_3$			
Entry	Ar-Cl	Product	Yield/%
5			52
6			70
7			67
8			78

the possible cyclization is suggestive of the absence of the 2-pyridylcobalt or 2-pyridyl radical intermediate. Alternatively, cobalt-mediated S_NAr reaction might be included. Exact reaction mechanism is not clear at this stage.



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References and Notes

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- Experimental Procedure:** Anhydrous cobalt(II) acetylacetonate (25.7 mg, 0.10 mmol) was placed in a 20-mL two-necked flask. Anhydrous dioxane (3 mL) was then added under argon. After the solution became red, benzylmagnesium chloride (0.98 M ether solution, 3.1 mL, 3.0 mmol) was added at 0 °C. The mixture was stirred for about 5 min at 25 °C. 2-Chloropyridine (**1**, 114 mg, 1.0 mmol) was added dropwise to the reaction mixture. After being stirred for 30 min at 25 °C, the reaction mixture was poured into water. The products were extracted with ethyl acetate (20 mL $\times$ 2). The combined organic layer was dried over sodium sulfate and concentrated. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in hexane) provided the corresponding benzylation product **2** (137 mg, 0.81 mmol) in 81% yield.
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