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

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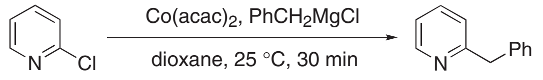
Treatment of 2-chloropyridine with benzylmagnesium chloride in the presence of a catalytic amount of cobalt(II) acetylacetonate in dioxane afforded the corresponding cross-coupling product in excellent yield. Trimethylsilylmethyl and phenyl Grignard reagents also participated in similar cross-coupling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

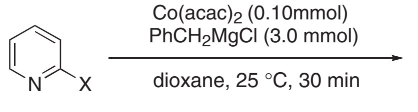
Treatment of 2-chloropyridine (**1**, 1.0 mmol) with benzylmagnesium chloride (3.0 mmol) in dioxane (3 mL) in the presence of cobalt(II) acetylacetonate (0.10 mmol) for 30 min at 25 °C afforded 2-benzylpyridine (**2**) in 81% yield (Eq. 1).[5,6] Use of 1.5 mmol of the Grignard reagent and 0.05 mmol of 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.



1 (1.0 mmol) **2** (1)

$Co(acac)_2$ (0.05 mmol), $PhCH_2MgCl$ (1.5 mmol): 73%
$Co(acac)_2$ (0.10 mmol), $PhCH_2MgCl$ (3.0 mmol): 81%

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.

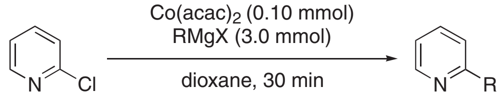


2 (2)

X=I, 45%; Br, 40%; OTs, 13%; F, 8%; CN, 0%; OTf, 0%

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



1 (1.0mmol)

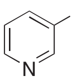
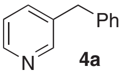
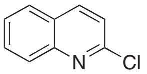
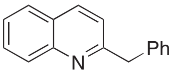
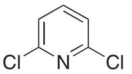
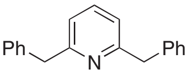
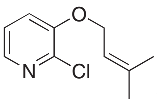
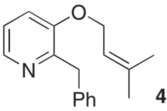
entry	RMgX	Temp/°C	Yield/%
1	$(CH_3)_3SiCH_2MgCl$	25	68
2	PhMgBr	25	17 (33% of **1**)
3	PhMgBr	50 (bath temp.)	73
4	$^{n}C_6H_{13}MgBr$	25	15
5	$CH_2{=}CHCH_2MgCl$	–20	complex mixture

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 dibenzylation occurred to yield **4c** in fair yield with contamination by a trace of the monobenzylated product (Table 2, Entry 3), whereas trimethylsilylmethylation led to selective conversion of the chlorine at the 2 position (Table 2, Entries 7 and 8).

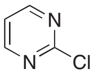
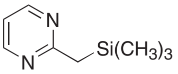
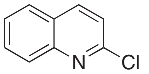
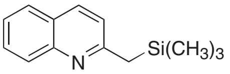
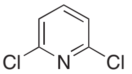
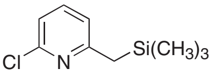
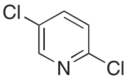
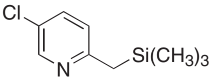
Interestingly, benzylation reactions of **3d** bearing an alkene moiety proceeded smoothly (Table 2, Entry 4), albeit the reactivity of **3d** is lower than that of **1**. Chloropyridine **3d** is a competent substrate for allylation to obtain **7** in 72% yield (Eq. 4). These facts stand in sharp contrast 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

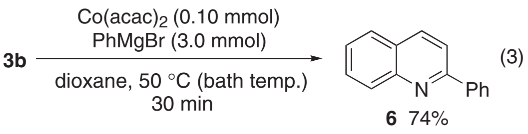
$$\text{Ar–Cl} \xrightarrow[\text{dioxane, 25 °C, 30 min}]{\substack{\text{Co(acac)}_2\text{ (0.10 mmol)} \\ \text{PhCH}_2\text{MgCl (3.0 mmol)}}} \text{Ar–CH}_2\text{Ph}$$

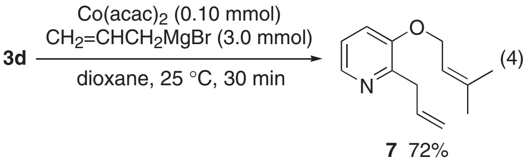
Entry	ArCl	Product	Yield/%
1	 **3a**	 **4a**	47
2	 **3b**	 **4b**	84
3	 **3c**	 **4c**	42
4	 **3d**	 **4d**	51

$$\text{Ar–Cl} \xrightarrow[\text{dioxane, 25 °C, 30 min}]{\substack{\text{Co(acac)}_2\text{ (0.10 mmol)} \\ \text{(CH}_3)_3\text{SiCH}_2\text{MgCl (3.0 mmol)}}} \text{Ar–CH}_2\text{Si(CH}_3)_3$$

Entry	Ar–Cl	Product	Yield/%
5	 **3e**	 **5a**	52
6	 **3b**	 **5b**	70
7	 **3c**	 **5c**	67
8	 **3f**	 **5d**	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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4 a) A. Fürstner and A. Leitner, *Angew. Chem., Int. Ed.*, **41**, 609 (2002). b) A. Fürstner, A. Leitner, M. Méndez, and H. Krause, *J. Am. Chem. Soc.*, **124**, 13856 (2002).

5 **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 × 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 benzylated product **2** (137 mg, 0.81 mmol) in 81% yield.

6 The utility of benzylic pyridines is documented. For instance, a) M. E. Angiolelli, A. L. Casalnuovo, and T. P. Selby, *Synlett*, **2000**, 905. b) W. Chai, A. Kwok, V. Wong, N. I. Carruthers, and J. Wu, *Synlett*, **2003**, 2086. c) F. Speiser, P. Braunstein, and L. Saussine, *Organometallics*, **23**, 2625 (2004).

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