ChemPubSoc Europe

DOI: 10.1002/chem.201405275

CHEMISTRY A European Journal Full Paper

Synthetic Methods

Chemoselective Chromium(II)-Catalyzed Cross-Coupling Reactions of Dichlorinated Heteroaromatics with Functionalized Aryl Grignard Reagents

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Abstract: Chromium(II) chloride catalyzes the chemoselective cross-coupling reaction of dichloropyridines with a range of functionalized (hetero)aromatic Grignard reagents at room temperature. Functional groups, such as esters and acetals, are well tolerated in this transformation. Previously challenging substrates, quinolines and isoquinolines, participate in the selective Cr-catalyzed cross-coupling in cyclopentyl methyl ether (CPME) as the solvent. The effective purging of Cr salts is demonstrated by using various solid supports.

Introduction

Nitrogen-containing heterocyclic compounds are of significant interest to the pharmaceutical and agrochemical industries. Transition-metal-catalyzed cross-coupling reactions have become a cornerstone in the functionalization of such compounds. In general, cross-coupling-based methods to access complex molecules employ palladium or nickel catalysts.[1] The high cost of palladium and comparably higher toxicology of nickel salts have motivated the development of cross-coupling methods employing economical and readily available transition metals. Over the last few decades, iron salts have proven to be viable catalysts for cross-coupling reactions to form both sp^2–sp^2 and sp^2–sp^3 bonds.[2] Despite the promise of Fe-based cross-coupling reactions, the facility, with which certain aryl nucleophiles, such as aryl Grignard reagents, undergo homocoupling (to form symmetrical biaryls), has attenuated the utility of this transformation.[3] To address this challenge, Nakamura and co-workers have reported the use of N-heterocyclic carbene ligands for efficient biaryl formation.[4] Furthermore, isoquinoline can accelerate analogous Fe-catalyzed cross-coupling reactions, producing 2-arylated N-heterocyclic biaryls with low amounts of undesired homocoupled products.[5] To further improve this transformation, we have recently reported that unsymmetrical biaryls can be efficiently accessed using catalytic $CrCl_2$, in which the cross-coupling reaction between N-heterocyclic monochlorides and (hetero)aromatic Grignard reagents leads to the formation of the desired product with only trace amounts of homocoupled product.[6,7] The advantage of low oxidation state chromium salts is that they are more economical compared to palladium salts, but are also less toxic. According to the International Conference on Harmonization (ICH) guidelines, the permitted daily oral exposure for chromium(III) picolinate is approximately 10.7 mg day^{-1} compared to $Pd^{II}Cl_2$ at 0.1 mg day^{-1} and soluble Ni at 0.6 mg day^{-1}.[8]

An effective strategy to obtain highly functionalized heteroaromatic structural motifs involves the use of polyhalogenated starting materials that can be subsequently functionalized. Challenges in product selectivity with such systems have been addressed by utilizing differentially halogenated rings. Recently, high control in the differentiation of dihaloaromatics by using $Fe(acac)_3$ (acac = acetylacetonate) to form a range of alkylated N-heterocycles (sp^2–sp^3 coupling) has been demonstrated.[9] Unfortunately, employing this strategy in the formation of unsymmetrical biaryls led to the formation of significant amounts of homocoupled products employing various Fe, Co, and Mn catalysts. Given the utility of the transformation, we embarked on studying the chemoselective differentiation of dichloropyridines, quinolines, and isoquinolines in the context of biaryl coupling due to the prevalence of such motifs in drug-discovery programs. Herein, we report the development of a highly chemoselective Cr-catalyzed cross-coupling reaction and demonstrate the effective purging of chromium salts from the desired product using various solid supports.

Results and Discussion

Initial work utilizing 2,4-dichloropyridine (**1a**) with PhMgCl (**2a**) through a previously optimized Fe-catalysis protocol[5]

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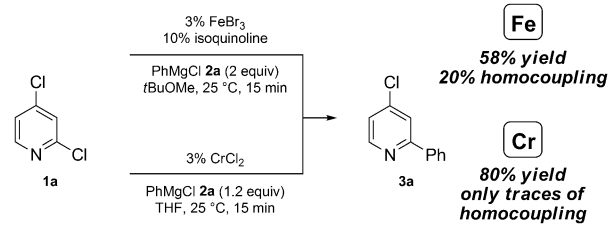
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201405275.

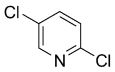
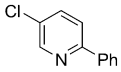
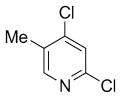
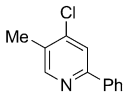
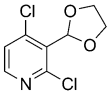
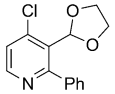
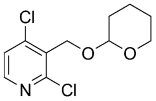
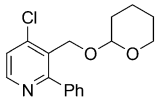


Scheme 1. Cross-coupling of 2,4-dichloropyridine (**1a**) with PhMgCl (**2a**): Fe versus Cr.

exclusively gave the 2-arylated product **3a** in 58% yield. In comparison, the chromium(II) chloride-catalyzed reaction using lower levels of **2a** (1.2 instead of 2 equiv) selectively gave pyridine **3a** in 80% yield with only trace amounts of the homocoupled product (Scheme 1).[10,11]

Evaluation of the scope of the chemoselective chromium-catalyzed cross-coupling reaction led to the arylation of a range of dichloro-N-heterocycles at room temperature (Table 1). Both 2,3-dichloropyridine (**1b**) and 2,5-dichloropyridine (**1c**) reacted with Grignard reagent **2a** within minutes to selectively form the 2-arylated products **3b** (76% yield, entry 1) and **3c** (87% yield, entry 2) respectively. Methyl substitution on the pyridine ring also led to high levels of selectivity,

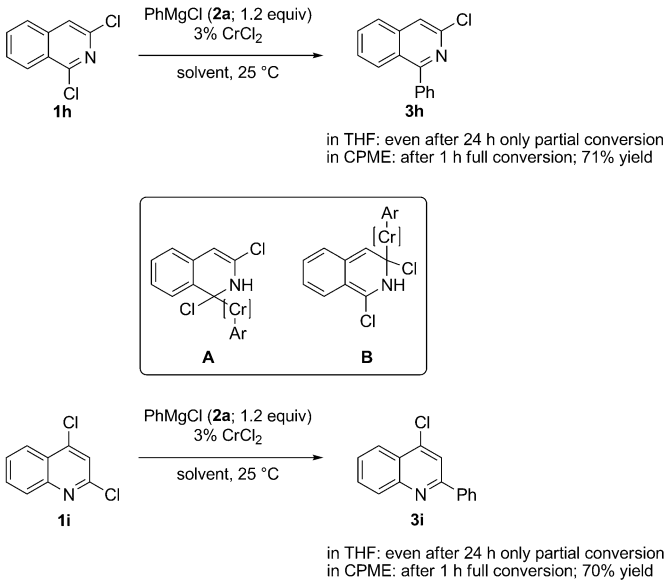
Table 1. Chemoselective Csp^2–Csp^2 cross-coupling reactions between dichlorinated pyridines (**1b**–**g**) and PhMgCl (**2a**).[a]

Entry[a]	Substrate	Product	Reaction time [min]	Yield [%]
				
1	**1b**	**3b**	15	76
				
2	**1c**	**3c**	15	87
				
3	**1d**	**3d**	15	85
				
4	**1e**	**3e**	15	88
				
5	**1f**	**3f**	30	67
				
6	**1g**	**3g**	30	76

[a] Reaction conditions: PhMgCl (**2a**; 1.2 equiv), dichlorinated pyridine (1 equiv), $CrCl_2$ (3 mol%) in THF at 25 °C.

in which 2,4-dichloropyridines **1d**–**e** react rapidly with **2a** to give phenylated products **3d**–**e** in high yields (85% for **3d** and 88% for **3e**, entries 3, 4). The sterically more demanding and coordinating acetal-containing 2,4-dichloropyridines **1f**–**g** also react rapidly to give products **3f**–**g** in 67% and 76% yields, respectively (entries 5–6).

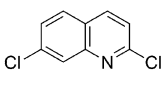
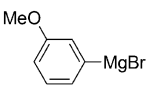
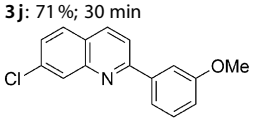
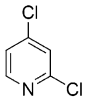
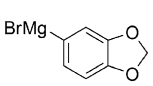
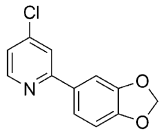
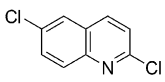
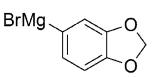
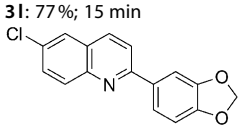
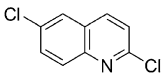
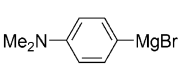
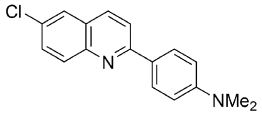
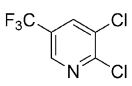
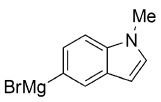
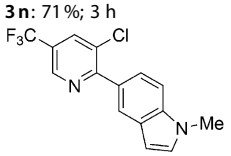
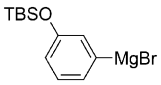
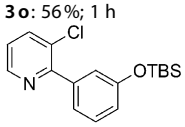
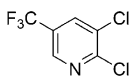
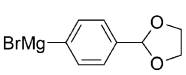
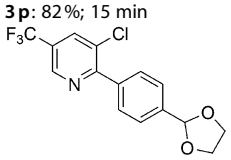
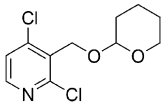
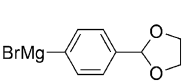
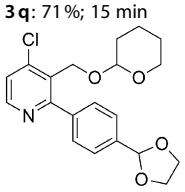
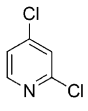
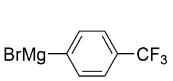
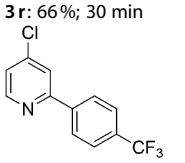
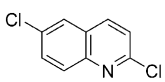
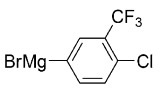
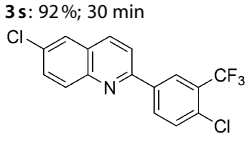
Chromium-catalyzed biaryl formation on 1,3-dichloroisoquinoline **1h** and 2,4-dichloroquinoline **1i** proved to be challenging. Although selective, the optimal conditions illustrated in Table 1 resulted in attenuated reactivity. Evaluation of coordinating and non-coordinating solvents with these fused aromatics revealed the superiority of cyclopentyl methyl ether (CPME) in the $CrCl_2$-catalyzed cross-coupling reaction. The desired coupling product **3h** was obtained in 71% yield after only 1 h reaction time at room temperature by using 3 mol% of $CrCl_2$ in CPME as solvent. The phenylation regioselectivity of **1h** at position one can be explained by formation of the more stable intermediate **A** that retains aromaticity. The competing arylation at position three does not occur because of loss of aromaticity in intermediate **B**. Analogously, the chemoselective coupling between quinoline **1i** and Grignard reagent **2a** gave the desired 2-arylated quinoline **3i** in 70% yield by using CPME (Scheme 2).



Scheme 2. Cr(II)-catalyzed cross-coupling reactions of isoquinoline **1h** and quinoline **1i** with PhMgCl (**2a**) by using cyclopentyl methyl ether as solvent and mechanistic aspects.

To further evaluate the utility of the chemoselective chromium(II)-catalyzed cross-coupling reaction, various aromatic Grignard reagents **2b**–**i** were employed (Table 2).[12] Electron-rich Grignard reagents, such as 3-(methoxyphenyl) magnesium bromide (**2b**), methylenedioxyarylmagnesium bromide **2c**, and 4-(dimethylamino)phenylmagnesium bromide (**2d**), reacted with dihalogenated pyridines **1a** and **c** and with quinolines **1j** and **k** resulting in the formation of the coupled products **3j**–**n** in 71–82% yield (entries 1–5). Notably, complete control in site

Table 2. Chemoselective Csp^2–Csp^2 cross-coupling reactions between dichlorinated heterocycles and various aromatic Grignard reagents.[a]

Entry	Substrate	Grignard reagent	Product
1	**1c** 	**2b** 	**3j**: 71%; 30 min 
2[b]	**1j** 	**2b** 	**3k**: 72%; 2 h 
3	**1a** 	**2c** 	**3l**: 77%; 15 min 
4[b]	**1k** 	**2c** 	**3m**: 82%; 1 h 
5	**1k** 	**2d** 	**3n**: 71%; 3 h 
6[c]	**1l** 	**2e** 	**3o**: 56%; 1 h 
7	**1b** 	**2f** 	**3p**: 82%; 15 min 
8	**1l** 	**2g** 	**3q**: 71%; 15 min 
9	**1g** 	**2g** 	**3r**: 66%; 30 min 
10	**1a** 	**2h** 	**3s**: 92%; 30 min 
11[b]	**1k**	**2i**	**3t**: 87%; 1 h

selectivity was obtained in these cross-coupling reactions. Heteroaromatic nucleophile 5-magnesiated indole **2e** reacts with 2,3-dichloro-5-(trifluoromethyl)pyridine (**1l**) within one hour to give the 2-arylated coupling product **3o** in 56% yield (entry 6). Silyl-protected 3-hydroxyphenyl magnesium bromide **2f** and acetal-substituted arylmagnesium derivative **2g** participated in the $CrCl_2$-catalyzed cross-coupling reaction with dichlorinated pyridines **1b**, **g**, and **l** selectively on C2, affording the desired products in 66–82% isolated yields (entries 7–9).

Electron-poor Grignard reagent 4-(trifluoromethyl)phenyl magnesium bromide (**2h**) was particularly effective in the Cr-catalyzed cross-coupling reaction. When this substrate was treated with pyridine **1a** in the presence of 3 mol% $CrCl_2$, the formation of heterocycle **3s** in 92% yield (entry 10) occurred.

Chloro-substituted Grignard reagent **2i**, when coupled with quinoline **1k** and trifluoromethylated 2,3-dichloropyridine **1l**, gave the desired products **3t** and **u** in 87 and 66% yield, respectively (entries 11 and 12).

The ability to conduct these experiments at room temperature poses a significant advantage. Thermally sensitive Grignard reagents, such as those containing an ester (**2j**) or 4-fluorophenylmagnesium bromide **2k**, undergo rapid cross-coupling reactions leading to trisubstituted pyridines **3v–w** in 70–79% yield (Scheme 3).[13] Ester **2j** has previously been used in Pd-catalyzed cross-coupling reactions on monohalogenated systems,[14] therefore, this method provides more practical means to access heterobiaryls that are commonly found in bioactive pharmaceuticals.

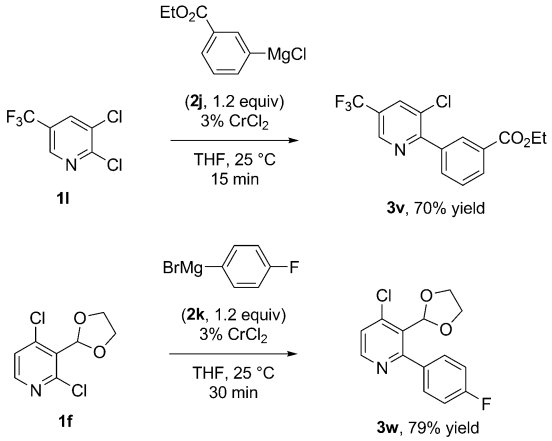
To rationalize the site selectivity in the Cr-catalyzed cross-coupling reactions we postulate a mechanism, in which the pyridine-ring nitrogen directs the attack of the low-valent phenyl–chromium organometallic onto the dihaloaromatic.[15,16] To support the notion of a directed delivery of the aryl nucleophile, treatment of 3,4-dichloropyridine **1m** (in which a ring nitrogen is not proximal to the C–Cl bond) with Grignard reagent **2a** in the presence of 3 mol% chromium chloride led to the exclusive formation of biphenyl, and none of the cross-coupled product was observed (Scheme 4). Furthermore, high selectivity for aryl incorporation proximal to the nitrogen with various 2,4- and 2,5-dichloropyridines supports the hypothesis of an N-directed addition.

Having demonstrated a wide substrate scope, we turned our attention to the removal of chromium. Despite the high permitted daily oral exposure for chromium(III) picolinate,[8] we sought to lower the overall chromium content from our reaction mixture prior to chromatography. Employing 2,4-dichloropyridine **1a** as a prototype, treatment with PhMgCl (**2a**) in the presence of 3 mol% $CrCl_2$, quenching unreacted Grignard reagent with an aqueous solution of ammonium chloride, separation and treatment of the organic layer using various solid supports was evaluated. As illustrated in Figure 1, several scavengers resulted in high recovery of arylated pyridine **3a** with remarkably low levels of chromium,[17] thereby enhancing the utility of this

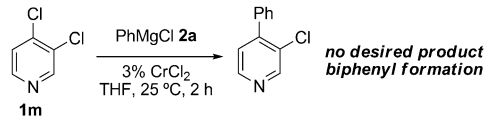
Table 2. (Continued)

Entry	Substrate	Grignard reagent	Product
12	**1l**	**2i**	**3u**: 66%; 30 min

[a] Reaction conditions: Grignard reagent (1.2 equiv), dichlorinated heterocycle of type **1** (1 equiv), $CrCl_2$ (3 mol%) in THF at room temperature. [b] CPME was used as solvent. [c] The reaction was performed at 50 °C.



Scheme 3. Regioselective Cr(II)-catalyzed cross-coupling reactions of pyridines **1f** and **l** with thermally sensitive Grignard reagents **2j**–**k**.



Scheme 4. Evidence for N-directed site selectivity.

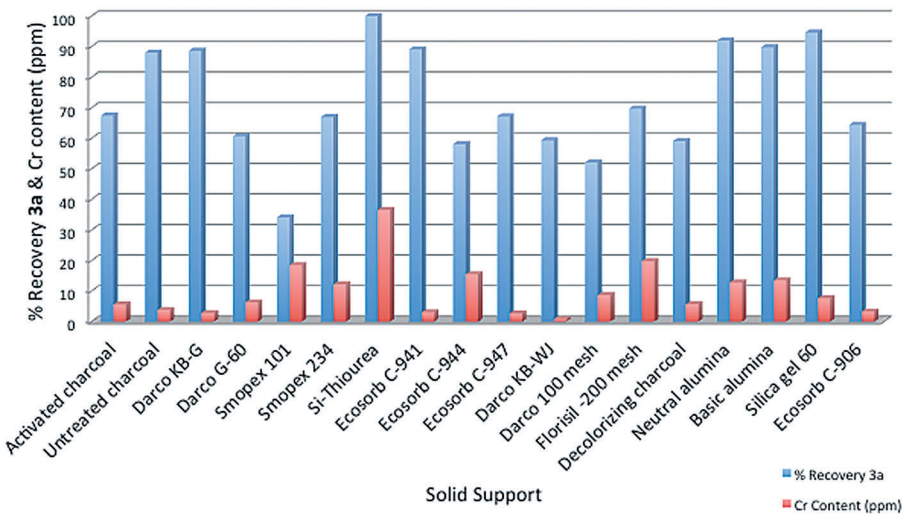


Figure 1. Treatment of pyridine **3a** with scavengers to evaluate recovery and chromium levels prior to chromatography.

methodology for pharmaceutical applications, in which low levels of concerning metals are critical.

Conclusion

We have reported a highly efficient regioselective Cr-catalyzed cross-coupling reaction of various dichloropyridines or -quinolines with a range of functionalized arylmagnesium reagents. Furthermore, we have demonstrated that chromium salts formed during the course of this reaction may be effectively removed prior to subsequent transformations.

Experimental Section

Typical procedure for the Cr-catalyzed cross-coupling reactions

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 1.2 mmol, 1.2 equiv) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and the aryl halide (1 mmol, 1.0 equiv) in, accordingly, THF or CPME (5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude compound, which was purified by column chromatography to give the final compound as an analytically pure substance.

Acknowledgements

The authors thank Desheng Wang for helping determine trace levels of chromium present after scavenging. The research leading to these results has received funding from the European Research Council under the European Community's Seventh Framework Programme (FP7/2007-2013; ERC grant agreement no. 227763).

Keywords: chromium · cross-coupling · magnesium · nitrogen heterocycles

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[17] Chromium concentration of the untreated organic layer after aqueous work-up was 34 ppm.

Received: September 15, 2014
Published online on December 2, 2014