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Communication

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Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions between Csp^2-Centers

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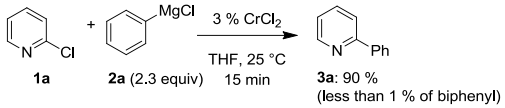
Supporting Information Placeholder

ABSTRACT: Low toxic chromium(II)-chloride catalyzes at 25°C within minutes the coupling reaction of various (hetero)aryl-magnesium reagents with *N*-heterocyclic halides, aromatic halogenated ketones or imines and alkenyl iodides. Remarkably, much lower amounts of homo-coupling side-products are obtained compared to related iron, cobalt or manganese cross-couplings.

Palladium- and nickel-catalyzed cross-coupling reactions between aromatic and heterocyclic groups are well established and have found many applications.[1] However, the prohibitively high price of palladium and the toxicity associated with nickel led to the search for alternative metals for these cross-couplings. For example, copper-catalyzed cross-couplings have been shown to be efficient for C-N bond formation.[2] Also, iron,[3] cobalt[4] and manganese[5] have proven to be possible alternatives for palladium and nickel. However, the scope of such Csp^2-Csp^2 cross-couplings is still limited, as these reactions often produce substantial amounts of homo-coupling side-products.[6] In the search for alternative metal catalysts having an acceptable low toxicity, we have examined the potential use of chromium salts.[7] Although Cr^{VI} is highly toxic (ORL-RAT LD_{50} = 50-150 mg/kg), Cr^{II} has a much lower toxicity (ORL-RAT LD_{50} = 1870 mg/kg), also compared to other metals: ORL-RAT $LD_{50}(NiCl_2)$ = 105 mg/kg, ($PdCl_2$) = 2700 mg/kg, ($CoCl_2$) = 766 mg/kg, ($MnCl_2$) =1480 mg/kg, ($FeCl_2$) = 450 mg/kg.[8]

Preliminary experiments showed that chromium-catalyzed cross-couplings between Csp^2-centers proceed quite smoothly and lead to significantly lower amounts of homo-coupling side-products compared to iron or cobalt.[9] Thus, the reaction of 2-chloropyridine (**1a**, 1.0 equiv) with PhMgCl (**2a**, 2.3 equiv) in THF in the presence of 3 % $CrCl_2$ (purity 99.99 %) is complete within 15 min at 25 °C, affording the desired cross-coupling product **3a** in 90 % yield.[10] GC-analysis of the crude reaction mixture indicated that less than 1 % of the homo-coupling product (biphenyl) is obtained (Scheme 1). Performing the same reaction with 3 % $FeBr_3$ or 3 % $CoCl_2$ under optimized conditions leads to about 15 % of the homo-coupling product.[11] A solvent screening (THF, *n*-hexane, toluene and *t*BuOMe) showed that THF was the optimal solvent. The optimization of the reagent stoichiometry indicated that only a small excess of Grignard reagent (1.2 equiv) was required. For all subsequent reactions standard grade $CrCl_2$ (purity 97 %) was used, since no difference with $CrCl_2$ (purity 99.99 %) was observed. Also, performing the cross-coupling with 5 % $MnCl_2$ leads, under optimum conditions, to only 58 % yield of **3a**[12] compared to 90 % yield obtained with 3 % $CrCl_2$.

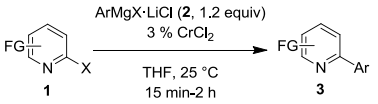
Scheme 1. Chromium-catalyzed cross-coupling between 2-chloropyridine (1a) and PhMgCl (2a)



The reaction scope of this new cross-coupling proved to be quite broad. Thus, a range of N-heterocyclic chlorides and bromides can be readily used (Table 1). PhMgCl (**2a**) also undergoes a smooth cross-coupling with 2-bromo-3-(but-3-en-1-yl)pyridine (**1b**; 25 °C, 15 min), leading to the 2,3-disubstituted pyridine **3b** in 95 % yield (entry 1 of Table 1). Interestingly, no radical cyclization product is observed in this cross-coupling (similar iron and cobalt cross-couplings produce 20 % of radical cyclization product).[11b] Both electron-rich and electron-poor Grignard reagents can be used for such cross-couplings.[13] Thus, the sterically hindered bromopyridine **1c** reacts with 4-*N*,*N*-dimethylaminophenylmagnesium bromide (**2b**) within 1.5 h at 25 °C, producing the 2,3-diarylated pyridine **3c** (80% yield; entry 2). Also, the electron-poor Grignard reagent **2c** reacts with 2-bromo-3-chloropyridine (**1d**) in 15 min at 25 °C, leading to the pyridine **3d** in 76 % yield (entry 3). The similar cross-coupling performed with 3 % of $FeBr_3$ gives only traces of product and significant amounts of homo-coupling. 2-Chloro-5-fluoropyridine (**1e**) also undergoes the cross-coupling reaction with the sensitive ester-substituted Grignard reagent **2d** to give the pyridine **3e** in 66 % yield (entry 4). Further N-heterocyclic halides, such as the 2-chloroquinoline (**1f**) and the 4-chloroquinoline **1g**, react well with Grignard reagents **2e** and **2b**, affording the expected products **3f** and **3g** (74-78 %; entries 5 and 6). In contrast, the corresponding iron-catalyzed cross-coupling with the 4-chloroquinoline **1g** fails, indicating that this Cr(II)-catalyzed cross-coupling may have a broader reaction scope than the corresponding Fe- and Co-catalyzed cross-couplings.[11] Halogenated diazenes, such as the 2-chloropyrimidines **1h-i** and the 2-chloropyrazine **1j**, rapidly react with the magnesium organometallics **2f-h** to provide the substituted diazenes **3h-j** (71-85 %; entries 7-9).

Remarkably, 2-halogenated aromatic ketones also undergo the chromium-catalyzed cross-coupling at room temperature within 15 min to 2 h (Table 2).[14] Thus, 2-chlorobenzophenone (**4a**) reacts with a range of aryl- and heteroarylmagnesium reagents (**2b, 2c, 2i-2k**) yielding the corresponding polyfunctional ketones **5a-5e** (71-94 %; entries 1-5 of Table 2).

Table 1. Room temperature Cr-catalyzed cross-coupling reactions between N-heterocyclic halides and arylmagnesium reagents



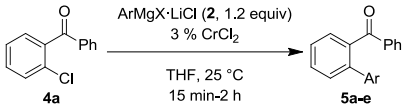
1 2 3

Entry	Starting Material	Grignard Reagent	Product[a]
1	**1b**	**2a**	**3b**: 95 %; 15 min
2	**1c**	**2b**	**3c**: 80 %; 90 min
3	**1d**	**2c**	**3d**: 76 %; 15 min
4	**1e**	**2d**	**3e**: 66 %; 15 min
5	**1f**	**2e**	**3f**: 74 %; 1 h
6	**1g**	**2b**	**3g**: 78 %; 15 min
7	**1h**	**2f**	**3h**: 71 %; 2 h
8	**1i**	**2g**	**3i**: 85 %; 15 min
9	**1j**	**2h**	**3j**: 72 %; 30 min

[a]Isolated yields of analytically pure products.

Interestingly, the (2-bromophenyl)(6-chloropyridin-3-yl)-methanone (**4b**) reacts with the Grignard reagent **2a** with complete regioselectivity (no chloride-substitution occurs) and gives the pyridylketone **5f** in 72 % yield (Scheme 2).

Table 2. Cr-catalyzed cross-coupling reactions between 2-chlorobenzophenone (4a) and phenylmagnesium reagents

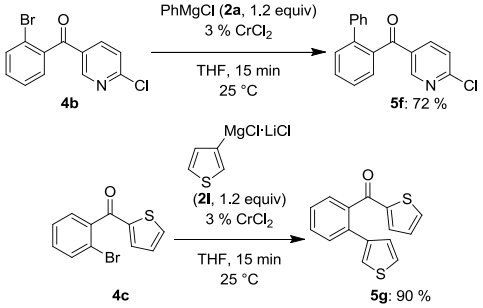


4a **5a-e**

Entry	Grignard Reagent	Product	Yield[a]
1	**2i**	**5a**	79 %; 15 min
2[b]	**2j**	**5b**	71 %; 2 h
3	**2c**	**5c**	93 %; 15 min
4	**2b**	**5d**	94 %; 15 min
5[c]	**2k**	**5e**	89 %; 2 h

[a]Isolated yields after purification by flash column chromatography. [b] 0.7 equiv of **2j** were used. [c] Reaction run at 50 °C for 2 h.

Scheme 2. Cr-catalyzed cross-coupling reactions between heteroaryl-substituted ketones and Grignard reagents

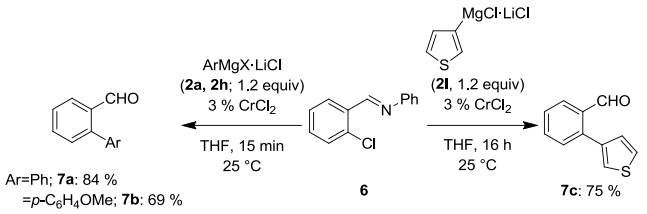


Heterocyclic ketones, such as **4c**, also cross-couple well with 3-thienylmagnesium chloride **2l**, affording the new ketone **5g** in 90 % yield (Scheme 2). These reactions show a remarkable functional group tolerance, since ester, nitriles and ketones are compatible with this Cr-catalyzed cross-coupling.[15]

Interestingly, the imine-protected 2-chlorobenzaldehyde **6** reacts readily with various Grignard reagents (**2a, 2h, 2l**) at 25 °C.

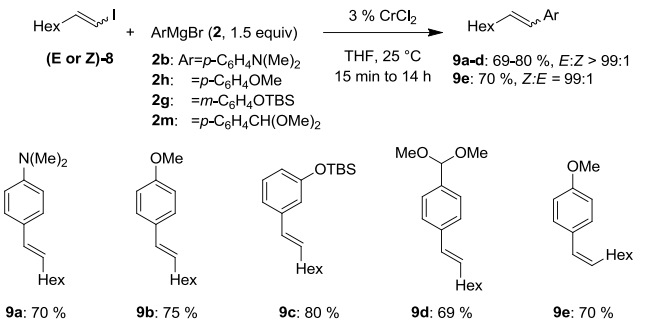
Acidic work-up provides the aldehydes **7a-c** in 69-84 % yield (Scheme 3). The presence of the sulfur-containing Grignard reagent **2l** extends considerably the reaction rate and 16 h reaction time is required to complete the cross-coupling leading to **7c**. Thus, this cross-coupling constitutes a simple way for functionalizing aromatic aldehydes in the *ortho*-position.

Scheme 3. Cr-catalyzed cross-coupling reactions between imine-protected aldehyde 6 and Grignard reagents



Finally, alkenyl iodides, such as **(E or Z)-8**, also undergo a stereoselective chromium-catalyzed arylation with a range of aryl Grignard reagents (**2b, 2g, 2h, 2m**), affording in all cases the functionalized styrenes **9a-e** in 69-80 % yield (Scheme 4). For the alkenyl iodide **(E)-8**, the reactions are completed in 15 min at 25 °C (E:Z ratio > 99:1), whereas a reaction time of 14 h is required for the coupling of **(Z)-8** (Z:E ratio = 99:1). Since no loss of stereochemistry is observed, a single electron transfer mechanism implying radical intermediates can be excluded, confirming the result obtained with the radical clock substrate (**1b**, entry 1 of Table 1).

Scheme 4. Cr-catalyzed cross-coupling reactions between alkenyl iodide (E or Z)-8 and Grignard reagents 2



In conclusion, we have reported a new transition metal-catalyzed cross-coupling reaction requiring only 3 % of chromium(II) chloride. This metal halide, as indicated in the introduction, has a moderate acute toxicity. Thus, major international suppliers classify chromium(II) chloride as a low toxic chemical, which is in the same category of toxicity like iron(II) chloride. Its price is comparable to the price of $CoCl_2$ or $FeCl_2$. Remarkably, these ligand-free cross-couplings proceed rapidly (usually less than 2 h) at 25 °C, require only 1.2 to 1.5 equivalents of Grignard reagent and produce significantly less homo-coupling side-products than the corresponding Fe- or Co-catalyzed cross-coupling reactions. $CrCl_2$ displays also a higher reactivity compared to similar Mn-catalyzed cross-couplings.

Based on all these features, chromium(II)-catalyzed cross-coupling should become attractive for research and development. Further explorations are under way in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, ^{1}H- and ^{13}C-NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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Graphical abstract :