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

Andreas K. Steib,[†] Olesya M. Kuzmina,[†] Sarah Fernandez,[†] Dietmar Flubacher,[‡] and Paul Knochel*[,†]

[†]Department of Chemistry, Ludwig-Maximilians-Universität, Butenandtstrasse 5-13, 81377 Munich, Germany
[‡]Novartis Pharma AG, Novartis Campus, 4056 Basel, Switzerland

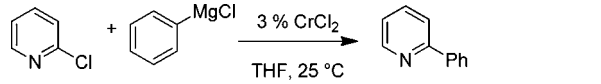
Supporting Information

ABSTRACT: Low-toxicity chromium(II) chloride catalyzes at 25 °C within minutes the coupling reactions of various (hetero)arylmagnesium 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 acceptably 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} for $NiCl_2$ = 105 mg/kg, for $PdCl_2$ = 2700 mg/kg, for $CoCl_2$ = 766 mg/kg, for $MnCl_2$ =1480 mg/kg, and for $FeCl_2$ = 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] Gas chromatographic 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] Solvent screening (THF, *n*-hexane, toluene, and *t*BuOMe) showed that THF was the optimal solvent. 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)



1a **2a** (2.3 equiv) **3a**: 90 % (less than 1 % of biphenyl)

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). 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*-dimethylamino)phenylmagnesium 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). 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 2-chloroquinoline (**1f**) and 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).

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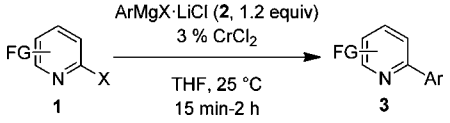
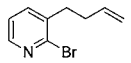
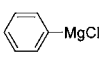
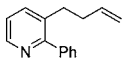
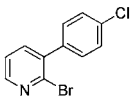
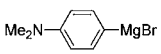
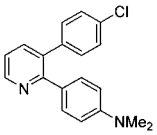
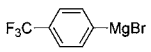
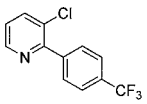
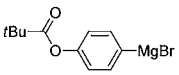
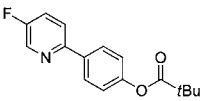
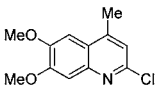
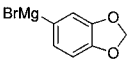
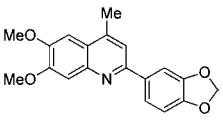
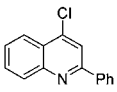
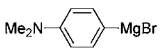
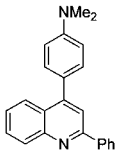
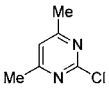
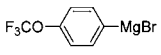
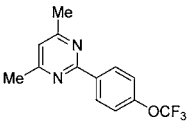
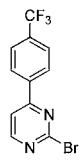
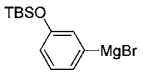
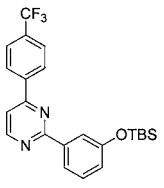
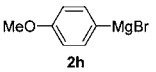
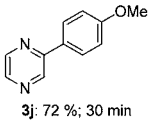
Table 1. Room-Temperature Cr-Catalyzed Cross-Coupling Reactions between N-Heterocyclic Halides and Arylmagnesium Reagents

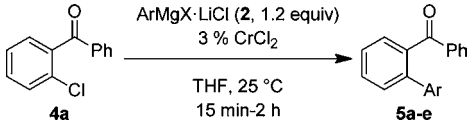


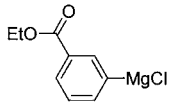
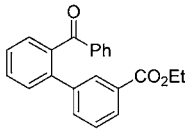
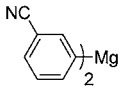
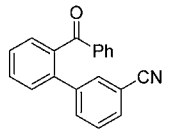
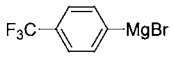
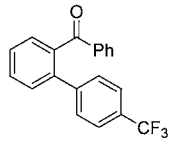
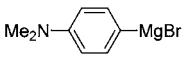
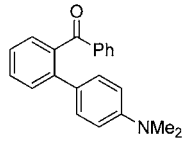
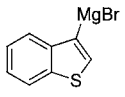
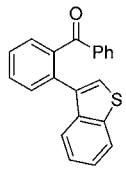
Entry	Starting Material	Grignard Reagent	Product[a]
1	 **1b**	 **2a**	 **3b**: 95 %; 15 min
2	 **1c**	 **2b**	 **3c**: 80 %; 90 min
3	 **1d**	 **2c**	 **3d**: 76 %; 15 min
4	 **1e**	 **2d**	 **3e**: 66 %; 15 min
5	 **1f**	 **2e**	 **3f**: 74 %; 1 h
6	 **1g**	 **2b**	 **3g**: 78 %; 15 min
7	 **1h**	 **2f**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

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**,**c**,**i**–**k**), yielding the corresponding polyfunctional ketones **5a**–**e** (71–94%; entries 1–5 of Table 2).

Table 2. Cr-Catalyzed Cross-Coupling Reactions between 2-Chlorobenzophenone (4a) and Phenylmagnesium Reagents



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** was used. [c]Reaction run at 50 °C for 2 h.

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 pyridyl ketone **5f** in 72% yield (Scheme 2).

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**,**h**,**l**) at 25 °C. Acidic workup 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.

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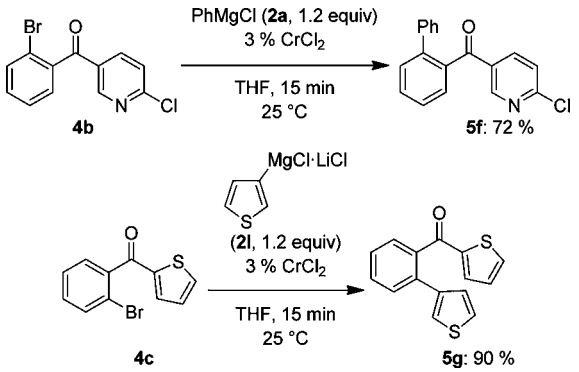
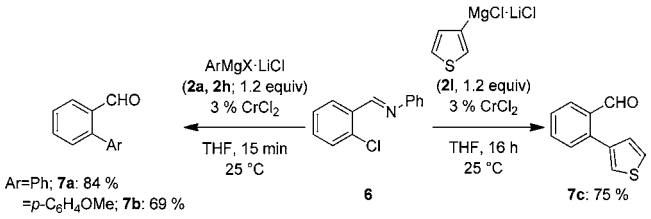
Scheme 2. Cr-Catalyzed Cross-Coupling Reactions between Heteroaryl-Substituted Ketones and Grignard Reagents

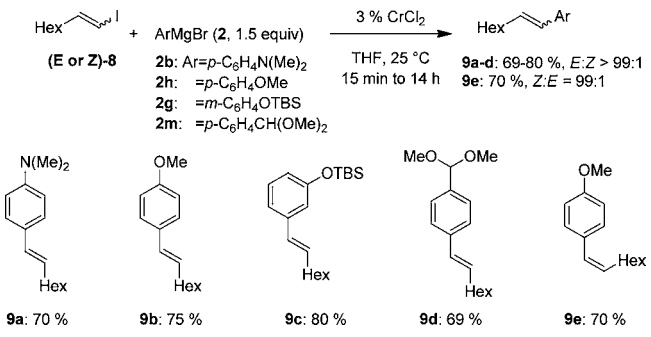


Scheme 3. Cr-Catalyzed Cross-Coupling Reactions between Imine-Protected Aldehyde 6 and Grignard Reagents



Finally, alkenyl iodides, such as (*E* or *Z*)-**8**, also undergo a stereoselective chromium-catalyzed arylation with a range of aryl Grignard reagents (**2b,g,h,m**), affording in all cases the functionalized styrenes **9a−e** in 69−80% yield (Scheme 4). For

Scheme 4. Cr-Catalyzed Cross-Coupling Reactions between Alkenyl Iodide (*E* or *Z*)-8 and Grignard Reagents 2



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).

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-toxicity chemical, in the same category as 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 1.2−1.5 equiv 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; ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

paul.knochel@cup.uni-muenchen.de

Notes

The authors declare no competing financial interest.

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