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Chromium(II)-Catalyzed Amination of N-Heterocyclic Chlorides with Magnesium Amides

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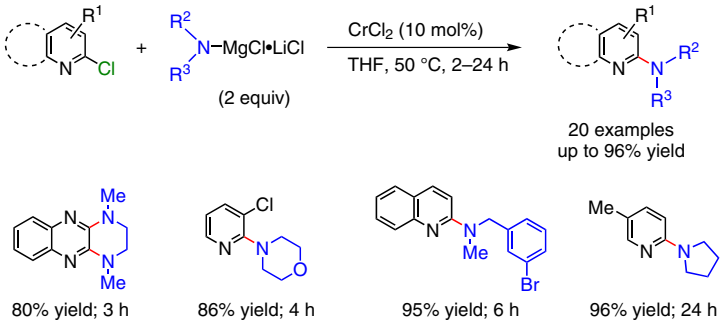

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Abstract We report a ligand-free chromium(II)-catalyzed amination reaction of various N-heterocyclic chlorides. $CrCl_2$ regioselectively catalyzes the reaction of chloropyridines and dichloropyridines, dichloroquinolines, dichloroisoquinolines and dichloroquinoxalines with a range of aliphatic, allylic, benzylic and saturated (hetero)cyclic magnesium amides in the presence of lithium chloride as additive. The reactions were performed at 50 °C in THF and led to the desired aminated products in 56–96% yield.

Key words chromium, amination, magnesium amides, heterocycles, pyridine

The syntheses of amino-substituted heterocycles are of the utmost importance for the pharmaceutical and agrochemical industries due to their high biological activity.[1] These molecules are generally prepared by nucleophilic aromatic substitution[2] but transition metal catalysts for aminations have also been intensively studied.[3] In 1983, Migita performed the coupling of aryl bromides with tin amides in the presence of a palladium catalyst.[4] More recently, since 1994, Buchwald[5] and Hartwig[6] have revolutionized this field by developing new classes of ligands and highly active palladium catalysts, which allowed a broad range of amination reactions.

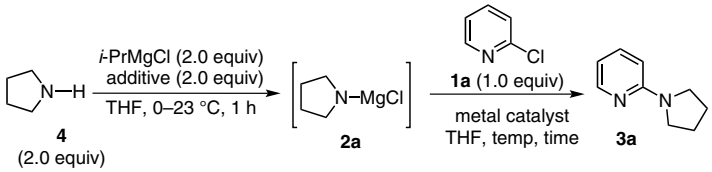
With the objective of replacing costly palladium and sensitive phosphine ligands, we studied economic, lowly toxic and readily available transition metals catalysts for amination reactions. Previously, we reported the chromium(II) chloride[7] catalyzed cross-couplings between (hetero)-aryl halides and (hetero)aryl Grignard reagents under mild and ligand-free conditions.[8] Additionally, direct arylation of pyridines, aryl oxazolines and imines with various arylmagnesium reagents was promoted by the presence of $CrCl_2$ as catalyst.[9]

Herein we report the chromium(II)-catalyzed amination of N-heterocyclic chlorides with magnesium amides affording a range of aminated pyridines, quinolines and quinoxalines.

In preliminary experiments, we examined the transition-metal-catalyzed amination of 2-chloropyridine (**1a**) with magnesium chloride pyrrolidin-1-ide (**2a**), which was prepared by the deprotonation of pyrrolidine (**4**) with *i*-PrMgCl in THF at 0 °C and was warmed to 23 °C over one hour (Table 1).[10] The resulting magnesium amide displayed a good thermic stability and a good solubility under the reaction conditions. In the absence of any catalyst, only 13% of the aminated product (**3a**) was observed at 23 °C after 20 hours of reaction time (entry 1).

However, when the Grignard reagent was prepared with an equimolar amount of lithium chloride as additive (use of *i*-PrMgCl·LiCl),[11] the conversion was increased and 27% of the pyridine **3a** was detected by calibrated GC analysis (entry 2). The use of 3% $FeBr_3$ or 3% $CoCl_2$ under the same conditions did not improve the amination (14–12%, entries 3 and 4). Nevertheless, in the presence of 3% $CrCl_2$, **3a** was obtained in 72% yield, which was improved to 77% using 10% of catalyst (entries 5 and 6). Performing the latter experiment without lithium chloride led to the formation of noticeably less product (64%, entry 7). In an attempt to further accelerate the reaction, the amination was then performed at 50 °C with 10 mol% of chromium(II) chloride. In the presence of 2.0 equivalents of LiCl, the aminated product **3a** was isolated in 95% yield, whereas **3a** was obtained in only 60% yield without additive (entries 8 and 9). Other chromium catalysts [$CrCp_2$,[12] $Cr(acac)_3$,[13] $CrBr_2$[14]] led to somewhat lower yields (45–81%, entries 10–13). Performing this reaction at 50 °C for three hours without catalyst in the presence of LiCl produced the aminated pyridine **3a** in 43% yield and, without LiCl, in 27% yield, confirming the importance

Table 1 Optimization of the Reaction Conditions[a]



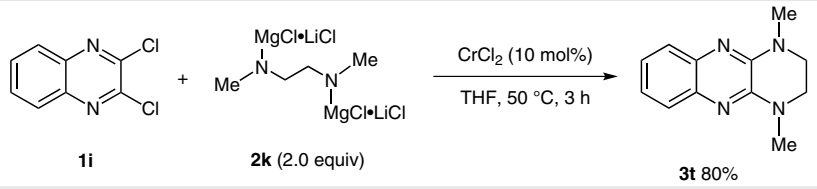
Entry	Catalyst	Amount of catalyst (mol%)	Additive	Temp (°C)	Time (h)	Yield (%)[b]
1	–	–	–	23	20	13
2	–	–	LiCl	23	20	27
3	$CoCl_2$	3	LiCl	23	20	14
4	$FeBr_3$	3	LiCl	23	20	12
5	$CrCl_2$	3	LiCl	23	24	72
6	$CrCl_2$	10	LiCl	23	20	77
7	$CrCl_2$	10	–	23	20	64
8	$CrCl_2$	10	LiCl	50	3	95
9	$CrCl_2$	10	–	50	3	60
10	$CrCp_2$	10	LiCl	50	3	45
11	$Cr(acac)_3$	10	LiCl	50	3	81
12	$CrBr_2$	10	LiCl	50	3	70
13	–	–	LiCl	50	3	43
14	–	–	–	50	3	27

[a] Reaction conditions: deprotonation of pyrrolidine (**4**; 2.0 mmol) with *i*-PrMgCl (with or without LiCl; 2.0 mmol) in THF at 0 °C to 23 °C in 1 h. Amination of 2-chloropyridine (**1a**; 1.0 mmol) with the prepared magnesium amide **2a** in THF at 23 °C or 50 °C with or without $CrCl_2$.
[b] Yields were determined by the integration of a gas chromatogram and comparison against undecane as a calibrated internal standard.

of the salt (entries 13 and 14).[15] Replacing 2-chloropyridine with the corresponding 2-bromopyridine led to slower substitution rates and incomplete conversion.

We have studied the reaction scope of this amination using various magnesium amides (Table 2).[16] First, 2-chloropyridine (**1a**) did also undergo an amination with magnesium chloride morpholin-4-ide (**2b**) or magnesium chloride dibutylamide (**2c**), leading to the formation of the aminated pyridines **3b** and **3c**, respectively, in 75% yield after 5–12 hours reaction time (entries 1 and 2). Substituted pyridines such as 2-chloro-5-methylpyridine (**1b**) usually reluctantly undergo amination with magnesium chloride pyrrolidin-1-ide (**2a**) and a full conversion was not observed even after three days at 50 °C without catalyst. In the presence of 10% $CrCl_2$, the aminated product **3d** was isolated in 96% yield after 24 hours (entry 3). A selective monoamination of 2,6-dichloropyridine (**1c**) with magnesium chloride pyrrolidin-1-ide (**2a**) was selectively achieved after seven hours to give the pyridine **3e** in 71% yield (entry 4).[17] 2,4-Dichloropyridine (**1d**) showed complete regioselectivity for the C2 position of the pyridine ring. Performing this amination reaction either with magnesium chloride dibenzylamide (**2d**) or with magnesium chloride indolin-1-ide (**2e**) led to the corresponding aminated pyridines **3f** and **3g**[18] in 50–54% yield after three hours of reaction time (entries 5 and 6). In the same way, 2,3-dichloropyridine (**1e**) underwent the desired selective amination with a range of aliphatic (**2c**), allylic (**2f**), benzylic (**2g**) and saturated heterocyclic (**2b**, **2h**) magnesium amides to provide the aminated pyridines **3h**–**l** in 71–86% yield (entries 7–11).

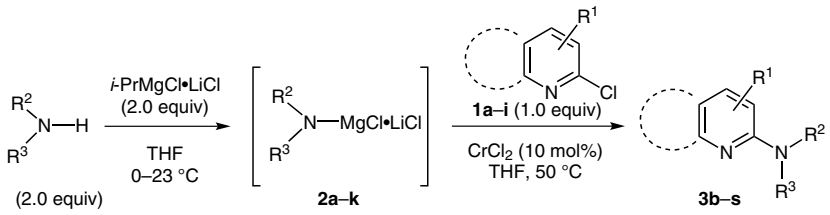
The amination of various other 2-chlorinated N-heterocycles was also examined. 2-Chloroquinoline (**1f**) was aminated with diverse saturated cyclic (**2i**) or heterocyclic (**2b**) magnesium amides, as well as with the magnesiated substituted benzylic amide **2j**, to afford the desired N-substituted quinolines **3m**–**o** in 85–95% yield after 6–23 hours of reaction time (entries 12–14). Also, the use of chromium(II) chloride dramatically increased the reaction rate and efficiency of 2-chloroquinoline (**1f**) with magnesium chloride pyrrolidin-1-ide (**2a**). Without catalyst, only 65% of the aminated quinoline **3p** was obtained after two days whereas 95% of **3p** was isolated after ten hours in the presence of 10% $CrCl_2$ (entry 15). The amination at the C1 position of 1-chloroisoquinoline (**1g**) was efficient using the saturated heterocyclic magnesium amides **2a** and **2b** and led to the isoquinolines **3q** and **3r**, respectively, after two hours of reaction time at 50 °C in 89–93% yield (entries 16 and 17).



1i 2k (2.0 equiv) 3t 80%

Scheme 1 $CrCl_2$-catalyzed diamination of 2,3-dichloroquinoxaline (**1i**)

Table 2 Cr(II)-Catalyzed Amination of the 2-Chlorinated Heterocycles **1a–i** with Magnesium Amides **2a–k**[a]



Entry	Substrate	Magnesium amide[b]	Product
1	**1a**	**2b**	**3b**: 12 h; 75%
2	**1a**	**2c**	**3c**: 5 h; 75%
3	**1b**	**2a**	**3d**: 24 h; 96%
4	**1c**	**2a**	**3e**: 7 h, 81%
5	**1d**	**2d**	**3f**: 3 h; 50%
6	**1d**	**2e**	**3g**: 3 h; 54%

Table 2 (continued)

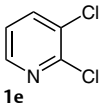
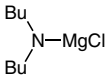
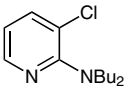
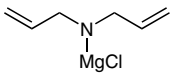
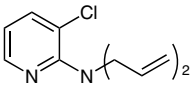
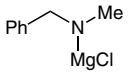
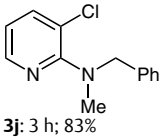
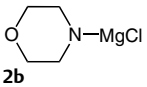
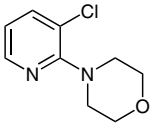
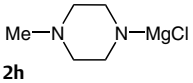
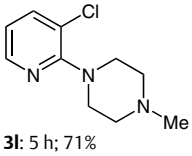
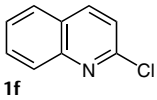
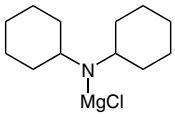
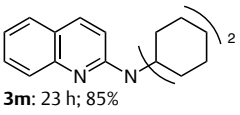
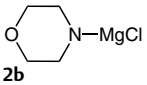
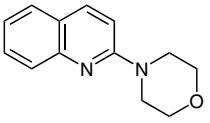
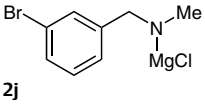
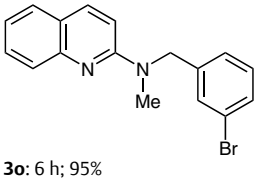
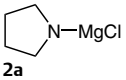
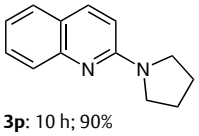
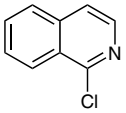
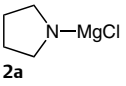
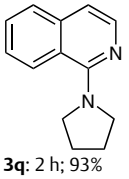
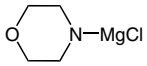
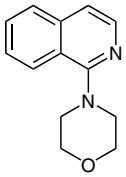
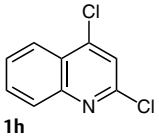
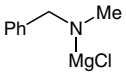
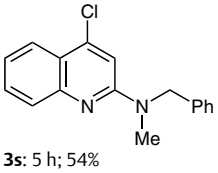
Entry	Substrate	Magnesium amide[b]	Product
7	 **1e**	 **2c**	 **3h**: 5 h; 71%
8	**1e**	 **2f**	 **3i**: 5 h; 82%
9	**1e**	 **2g**	 **3j**: 3 h; 83%
10	**1e**	 **2b**	 **3k**: 4 h; 86%
11	**1e**	 **2h**	 **3l**: 5 h; 71%
12	 **1f**	 **2i**	 **3m**: 23 h; 85%
13	**1f**	 **2b**	 **3n**: 8 h; 85%
14	**1f**	 **2j**	 **3o**: 6 h; 95%
15	**1f**	 **2a**	 **3p**: 10 h; 90%
16	 **1g**	 **2a**	 **3q**: 2 h; 93%

Table 2 (continued)

Entry	Substrate	Magnesium amide[b]	Product
17	**1g**	 **2b**	 **3r**: 2 h; 89%
18	 **1h**	 **2g**	 **3s**: 5 h; 54%

[a] Reaction conditions: $CrCl_2$ (10 mol%), chlorinated heterocycle **1a**–**i** (1.0 equiv), magnesium amide **2a**–**k** (2.0 equiv) in THF at 50 °C.
[b] LiCl was omitted for clarity.

Regioselective amination of 2,4-dichloroquinoline (**1h**) with the benzylic magnesium amide **2g** led to the aminated heterocycle **3s** (50 °C, 5 h) in 54% yield (entry 18).

The annelation of the quinoxaline scaffold was achieved by diamination of 2,3-dichloroquinoxaline (**1i**) with the bis-magnesium amide **2k** leading to the hydropyrazino[2,3-*b*]-quinoxaline **3t** in 80% yield (Scheme 1).

We propose that the Cr(II) catalysis may be a result of the Lewis acidity of Cr(II) as well as the higher ligand exchange rate of Cr(II) complexes compared to Cr(III) salts.

In summary, we have reported a selective chromium(II)-catalyzed amination of various N-heterocyclic mono- and dichlorides with a range of aliphatic, allylic, benzylic, and saturated (hetero)cyclic magnesium amides. All these straightforward aminations proceeded in the presence of lithium chloride as additive, at 50 °C, within short reaction times (in comparison with the amination without catalyst). No additional ligand was required and the desired 2-aminated heterocycles were obtained in high yields. This method represents an alternative to the use of expensive and sensitive phosphines and palladium salts by exploiting the catalytic activity of $CrCl_2$ in these amination reactions. The further expansion of these aminations is currently underway in our laboratories.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380178.

References and Notes

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(10) **Typical procedure for the formation of magnesium amides**: A dry and argon-flushed Schlenk tube was charged with the appropriate amine (2 equiv) and *i*-PrMgCl·LiCl (2 equiv, 1.2 M solution in THF) was added dropwise at 0 °C. This reaction mixture was warmed to r.t. (23 °C) and was stirred for approximately 1 h at this temperature in order to obtain full conversion to the corresponding magnesium amide.

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(12) $CrCp_2$ was purchased from Alfa Aesar (>97% purity) or prepared according to: Rohde, W.; Goertz, H.-H.; Handrich, U. Ger. Patent DE4337230A1, **1995**.

(13) $Cr(acac)_3$ was purchased from Sigma Aldrich (97% purity). The air-stable and cheap $Cr(acac)_3$ could be used in these aminations but led to either similar or, in most cases, to somewhat lower yields and/or longer reaction times.

(14) $CrBr_2$ was prepared according to: Concellón, J. M.; Rodríguez-Solla, H.; Blanco, E. G.; Villa-García, M. A.; Alvaredo, N.; García-Granda, S.; Díaz, M. R. *Adv. Synth. Catal.* **2009**, *351*, 2185.

(15) However, a longer reaction time (20 h at 50 °C) also led to full conversion.

(16) (a) **Typical procedure for the Cr-catalyzed amination using $CrCl_2$**: The previously prepared solution of the magnesium amide was transferred via syringe to a second dry and argon-flushed Schlenk tube, containing water-free $CrCl_2$ (0.1 equiv) and the N-heterocyclic halide in THF (1 equiv, 2 M in THF) at 23 °C. The resulting reaction mixture was stirred at 50 °C until the N-heterocyclic halide was consumed. The solvent was evaporated in vacuo and the crude product was purified on silica gel to afford the desired product. (b) **Typical procedure for the Cr-catalyzed amination using $Cr(acac)_3$**: The previously prepared solution of the magnesium amide was transferred via syringe to a second dry and argon-flushed Schlenk tube, containing $Cr(acac)_3$ (0.1 equiv) and the N-heterocyclic halide in THF (1 equiv, 2 M in THF) at 23 °C. The resulting reaction mixture was stirred at 50 °C until the N-heterocyclic halide was consumed. The solvent was evaporated in vacuo and the crude product was purified on silica gel to afford the desired product.

(17) No diamination product was observed in the aminations involving **1c**, **1d**, **1e** and **1h**.

(18) Magnesium chloride indolin-1-ide (**2e**) reacted rapidly with **1d** but the related magnesium chloride methylanilide underwent the amination reaction in only 32% yield, showing the limits of the $CrCl_2$ catalysis.