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Room-Temperature Chromium(II)-Catalyzed Direct Arylation of Pyridines, Aryl Oxazolines, and Imines Using Arylmagnesium Reagents

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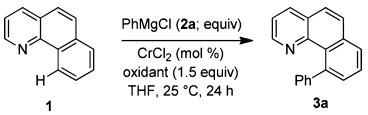
Supporting Information

ABSTRACT: We report a $CrCl_2$-catalyzed oxidative arylation of various pyridines, aryl oxazolines, and aryl imines using aromatic Grignard reagents in the presence of 2,3-dichlorobutane (DCB). Most of the reactions proceed rapidly at 25 °C and do not require any additional ligand. Benzo[*h*]quinoline, 2-arylpyridine, aryl oxazoline, and imines were successfully arylated in good yields under these conditions. A TMS-substituent was used to prevent double arylation. After oxidative cross-coupling the TMS-group was further converted to a second *ortho*-aryl substituent. Remarkably, inexpensive aryl *N*-butylimine derivatives are excellent substrates for this oxidative arylation.

The formation of C−C bonds involving a transition-metal catalyzed C−H activation has been widely developed in recent years.[1] A range of transition metals such as Pd,[2] Ru,[3] Rh,[4] Co,[5] and Fe[6,7] catalyze such cross-couplings. Iron and to some extent cobalt complexes are of special interest due to the moderate price and toxicity of these metals. The pioneering work of Nakamura and Yoshikai involving iron[6a,b,e] or cobalt catalysis[5a−f,h,j−l] and the recent modification of Wang and Shi[5g] have attracted much attention. Although very attractive, the large amounts of Grignard reagents required to reach full conversion, the long reaction times,[5g,6a,d] and the need for appropriate ligands (such as *cis*-1,2-bis(diphenylphosphino)-ethylene, 1,10-phenanthroline, 4,4′-di-*tert*-2,2-bipyridyl or *N*-heterocyclic carbenes)[5h−k,6a,b,7b] are drawbacks that make improvements still desirable.[7] Previously, we reported that $CrCl_2$ is an excellent catalyst for performing cross-couplings between aryl or heteroaryl halides and Grignard reagents.[8] The key feature of this cross-coupling is the very small amount of homocoupling product formed, implying that almost no excess of Grignard reagent is required. Furthermore, these chromium(II)-catalyzed cross-couplings are very fast reactions. These interesting features led us to examine directed C−H bond activation reactions involving $CrCl_2$.[9] Herein, we report the first Cr-catalyzed directed arylation of *N*-heterocycles,[2b,3c,5b,g,6a,7a−c] aryl oxazolines,[3c,e] and aryl imines,[5d,h,j,k,7a,c] which proceed usually rapidly at 25 °C and do not require any additional ligand. Thus, we have treated benzo[*h*]quinoline (**1**) with PhMgBr (**2a**, 1.5−4 equiv) in the presence of catalytic amounts of $CrCl_2$[10] and a 1,2-dichloroalkane acting as an oxidant at 25 °C for 24 h (Table 1). The use of 5 mol % of $CrCl_2$ led to the desired phenylated product in 57% yield, in the presence of 2,3-dichlorobutane (DCB)[5g] as an oxidant (entry 2). Using 10 mol % of $CrCl_2$ increased the yield of **3a** to 98% (calibrated GC-yield; entry 3). Lowering the amount of Grignard reagent to 1.5 or 2.5 equiv (instead of 4 equiv) decreased the yield respectively to 19% and 63% (entries 4 and 5).[11] Changing the nature of the oxidant from DCB[5g] to 1,2-dichloroethane or 1,2-dichloro-2-methylpropane[6a,7] led to lower yields (45−87%; entries 6 and 7). In the absence of an oxidant, only 10% of **3a** was obtained (entry 8). Treatment of benzo[*h*]quinoline (**1**) with PhMgBr (**2a**; 4 equiv) under the optimized conditions provided the arylated heterocycle **3a** in 95% isolated yield (entry 3). Similarly, other arylmagnesium reagents bearing either donor or acceptor substituents undergo a high yield arylation at position 10 furnishing the arylated benzo[*h*]quinolines **3b−f** in 66−90%

Table 1. Optimization of the Reaction of Benzo[*h*]quinoline (1) with PhMgBr (2a) Catalyzed by $CrCl_2$



entry	$CrCl_2$ (mol %)	PhMgBr (**2a**; equiv)	oxidant	yield of **3a** (%)[a]
1	0	4	2,3-dichlorobutane (DCB)	0
2	5	4	DCB	57
3	10	4	DCB	98 (95)[b]
4	10	1.5	DCB	19
5	10	2.5	DCB	63
6	10	4	1,2-dichloroethane	45
7	10	4	1,2-dichloro-2-methylpropane	87
8	10	4	without	10

[a]Yield determined after 24 h by integration of a GC chromatogram and comparison with undecane as a calibrated internal standart. [b]Yield of isolated product.

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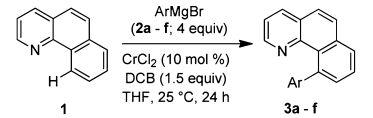
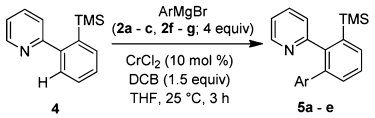
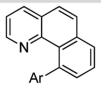
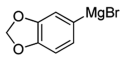
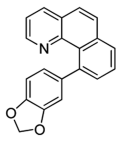
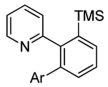
yield (entries 2–6 of Table 2). Using the same conditions, it was also possible to arylate 2-(2-trimethylsilylphenyl)pyridine (**4**) with various arylmagnesium reagents, affording the expected pyridines **5a–e** in 79–92% yield (entries 7–11 of Table 2).

Interestingly, these chromium(II)-catalyzed arylations proceed within a few hours at 25 °C. The role of the TMS-group (TMS = trimethylsilyl) at position 2 is to avoid a double arylation. This group can be further used to introduce a second different aryl substituent as shown in Scheme 1.

Table 2. Chromium-Catalyzed Arylation of Benzo[*h*]quinoline (1) and 2-(2-Trimethylsilylphenyl)pyridine (4)

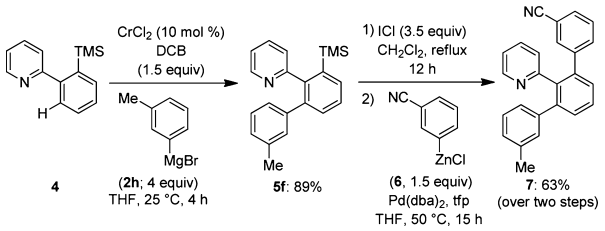




entry	ArMgBr	product yield (%)[a]
		
1	PhMgBr (**2a**)	**3a**: Ar = Ph; 95%[b]
2	3-MeO-C_6H_4MgBr (**2b**)	**3b**: Ar = 3-MeO-C_6H_4; 90%
3	4-Me_2N-C_6H_4MgBr (**2c**)	**3c**: Ar = 3-Me_2N-C_6H_4; 87%
		
4	**2d**	**3d**: 67%
5	4-F3C-C_6H_4MgBr (**2e**)	**3e**: Ar = 4-F3C-C_6H_4; 66%[c]
6	4-F-C_6H_4MgBr (**2f**)	**3f**: Ar = 4-F-C_6H_4; 86%
		
7	PhMgBr (**2a**)	**5a**: Ar = Ph; 92%
8	3-MeO-C_6H_4MgBr (**2b**)	**5b**: Ar = 3-MeO-C_6H_4; 79%
9	4-Me_2N-C_6H_4MgBr (**2c**)	**5c**: Ar = 3-Me_2N-C_6H_4; 85%[d]
10	3-TBSO-C_6H_4 (**2g**)	**5d**: Ar = 3-TBSO-C_6H_4; 83%
11	4-F-C_6H_4MgBr (**2f**)	**5e**: Ar = 4-F-C_6H_4; 84%

[a]Yield of isolated product after purification by flash column chromatography. [b]For entry 1, $CrCl_2$ (99.99%) was used. In all further experiments, $CrCl_2$ of 97% purity was used. [c]Reaction run for 38 h. [d]Reaction run for 4 h.

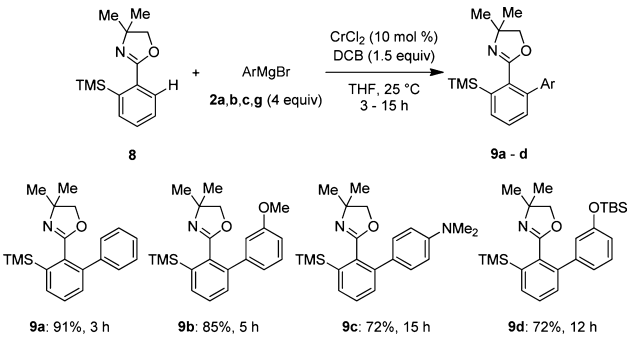
Scheme 1. Selective Bis-arylation of Phenylpyridine 4 Using Chromium and Palladium Catalysts



Thus, the treatment of **4** with 3-tolylmagnesium bromide (**2h**) in the presence of $CrCl_2$ (10 mol %; 97% purity) and DCB (1.5 equiv) afforded the arylated product **5f** in 89% yield. Treatment with ICl in refluxing CH_2Cl_2 for 12 h, followed by Negishi cross-coupling[12] with the cyano-substituted phenylzinc derivative **6** in the presence of 3 mol % $Pd(dba)_2$ (dba = dibenzylideneacetone) and 6 mol % tfp (tfp = tris(2-furyl)phosphine)[13] at 50 °C for 15 h, furnished the bis-arylated pyridine **7** in 63% yield over two steps (Scheme 1).

Aryl oxazolines are very popular substituents for directed C–H bond activation. Using the 2-TMS-phenyl oxazoline **8**, we have achieved an efficient C–H activation and arylation with various Grignard reagents as shown in Scheme 2. Functional groups such as a methoxy, a dimethylamino, or an OTBS group were well tolerated, and the *ortho*-arylated oxazolines **9a–d** were obtained in 72–91% yield (Scheme 2).

Scheme 2. Chromium-Catalyzed Arylation of 2-(2-Trimethylsilyl)phenyl)oxazoline (8) with Grignard Reagents 2



To convert the TMS group into a second aryl substituent, we have first arylated **8** with the Grignard reagent **2f** using 10 mol % $CrCl_2$ and DCB (1.5 equiv) and have obtained oxazoline **9e** in 87% yield (Scheme 3).

Treatment of **9e** with ICl in refluxing CH_2Cl_2 for 6 h, and subsequent Negishi cross-coupling with the ester-substituted phenylzinc derivative **10** in the presence of 3 mol % $Pd(dba)_2$ and 6 mol % tfp, furnishes the bis-arylated pyridine **11** in 89% yield over two steps (Scheme 3).

Also, we have found that imine-protected aldehydes **12** and **13** undergo this chromium-catalyzed C–H activation, furnishing the aldehydes **14a–f** in 61–88% yield (Scheme 4). Remarkably, the reaction time is strongly dependent on the nature of an aryl imine of type **12** or **13**. When the aryl *N*-(*p*-methoxy)phenyl

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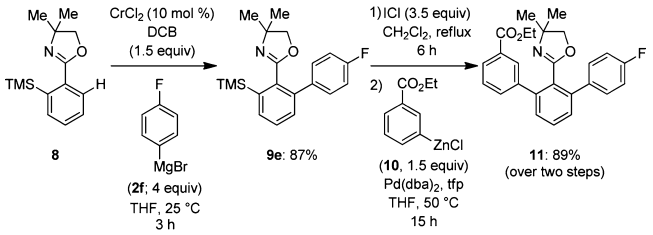
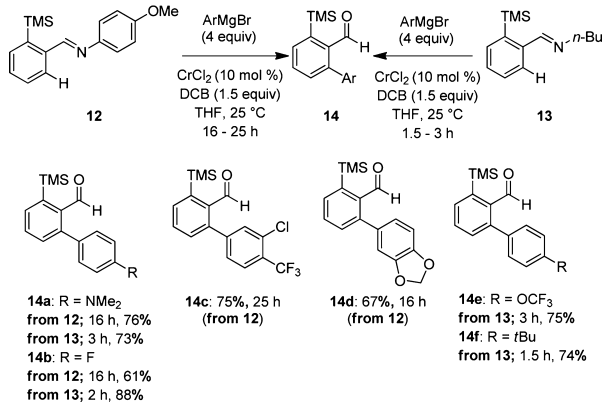
Scheme 3. Selective Bis-Arylation of the 2-(2-Trimethylsilyl)phenyl)oxazoline (8) Using Chromium and Palladium Catalysts



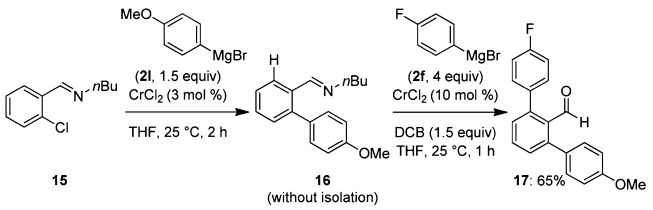
Scheme 4. Chromium-Catalyzed Arylation of Imines 12 and 13 with Grignard Reagents 2



imine **12** was used, the chromium-catalyzed arylation reactions using Grignard reagents **2c**, **2f**, **2d**, and (3-chloro-4-(trifluoromethyl)phenyl)magnesium bromide (**2i**) proceeded with reaction times of 16−25 h. On the other hand, the aryl *N*-butyl imine **13** reacted with Grignard reagents **2c**, **2f**, (4-(trifluoromethoxy)phenyl)magnesium bromide (**2j**) and (4-(*tert*-butyl)phenyl)magnesium bromide (**2k**) with much faster rates (1.5−3 h) giving after acidic workup the arylated aldehydes **14a−b** and **14e−f** in 73−88% yield (Scheme 4).

To show the practicability of this chromium C−H activation method, we have performed an unsymmetrical bis-arylation of the imine **15** derived from 2-chlorobenzaldehyde, via a one-pot Cr-catalyzed cross-coupling followed by a Cr-catalyzed oxidative arylation (Scheme 5).

Scheme 5. One-Pot Synthesis of Bis-Arylated Aldehyde 17 Using Chromium-Catalyzed Cross-Coupling and C−H Bond Activation Reactions



Thus, the Cr-catalyzed cross-coupling of **15** with the Grignard reagent (**2l**; 1.5 equiv) leads to the arylated imine **16**. Without isolation, a second Grignard reagent (**2f**; 4 equiv) was added and the desired C−H activation and cross-coupling is complete within 1 h at 25 °C, providing after acidic workup the unsymmetrically bis-arylated aldehyde **17** in 65% yield (Scheme 5).

In conclusion, we have shown that $CrCl_2$ is a very efficient catalyst for the performance of C−H activations of benzo[*h*]-quinoline, 2-phenylpyridine, phenyl oxazoline, and aryl imines using DCB as an oxidant. All these direct arylations proceed at 25 °C. The high catalytic activity of $CrCl_2$ avoids the use of additional ligands, and a broad reaction scope is achieved. Also, in the case of the direct arylation of imines, the use of *N*-butyl imines is possible for the first time (usually *N*-aryl imines are required). Further extensions of these Cr-catalyzed arylations are underway 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.

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Notes

The authors declare no competing financial interest.

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(10) For experiments of Table 1, 99.99% pure $CrCl_2$ has been used. All further experiments were performed with $CrCl_2$ (97%).

(11) The reaction theoretically requires 2 equiv of Grignard reagent (1 equiv for deprotonation and 1 equiv for coupling). Additionally some small amount of Grignard reagent is needed to reduce the $CrCl_2$ to its catalytically active species. Further optimizations are under investigation in our laboratories.

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