A Manganese-Catalyzed Cross-Coupling Reaction

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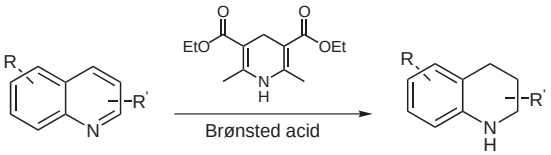
Abstract: A manganese-catalyzed cross-coupling reaction of heterocyclic chlorides with aryl- as well as alkylmagnesium halides has been developed. The reaction provides a variety of heterocyclic compounds under mild and practical reaction conditions using low amounts of manganese chloride as catalyst.

Key words: manganese catalysis, cross-coupling, arylation, alkylation, heterocycles, pyridine, quinoline

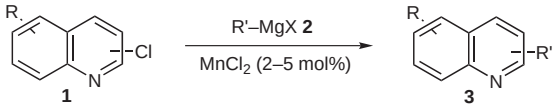
Transition-metal-catalyzed carbon–carbon bond-forming reactions are of great significance in the preparation of polyfunctional heterocylces.[1] This is especially true for cross-coupling reactions of chloro-substituted heterocycles with readily available alkyl- and aryl-Grignard reagents.[2] So far, these reactions have been performed with toxic or expensive nickel[3] and palladium[4] complexes or using more effective iron[5] or cobalt[6] catalysts.

Recently, we became interested in the synthesis of 1,2,3,4-tetrahydroquinoline derivatives, which are of great synthetic importance in the preparation of pharmaceuticals and agrochemicals, as well as in material sciences. In addition, many natural occurring alkaloids consist of this structural key element. Given the importance of this class of molecules, we recently developed a new Brønsted acid catalyzed partial reduction of quinolines (Scheme 1).[7]



Scheme 1 Brønsted acid catalyzed transfer hydrogenation

During the development of this hydrogenation procedure we required a practical, efficient and fast access to various substituted quinolines. Here we wish to report our results on the development of such a process, a manganese-catalyzed cross-coupling reaction of chloroquinolines with aryl- and alkylmagnesium halides (Scheme 2),[8] and the extension of this coupling procedure to other chloro-substituted heterocycles.



Scheme 2 Manganese-catalyzed cross-coupling reaction of chloroquinoline and Grignard reagents

Our initial experiments of the manganese-catalyzed cross-coupling reaction of chloroquinolines with aryl- and alkylmagnesium chlorides **2** concentrated on the evaluation of reaction parameters, such as solvent, temperature, catalyst loading and manganese salt. From these first experiments, we found that the test cross-coupling reaction of 4-chloroquinoline (**1a**) with phenyl magnesium chloride (**2a**) could best be performed in THF as solvent. The use of other solvents such as diethyl ether or DME also led to product formation, but yields of the corresponding isolated 4-phenyl quinoline (**3a**) were considerably lower. Among the commercially available manganese salts examined, manganese(II) chloride[9] showed the best catalytic activity and the use of 1 or 2 mol% resulted in complete conversion of the substrate **1a** after a short reaction time (1.5 h) at 0 °C. The corresponding product 4-phenyl quinoline (**3a**) was obtained in either 86% or 91% isolated yield, respectively, after column chromatography (Table 1, entry 1). Using these optimized reaction conditions, we explored the reaction of **1a** with different alkylmagnesium chlorides **2b**–**e** (Table 1, entry 2–7). The 4-alkyl-substituted quinolinines were again isolated in good yields (65–83%), however, in some cases we had to use 5 mol% of catalyst. The manganese-catalyzed cross-coupling reaction could also be performed with 2-chloro-, 2-chloro-4-alkyl-, and 4-chloro-2-phenylquinoline derivatives **1b**–**d**, as well as the 4,7-dichloroquinoline (**1e**). In the latter case the 4-substituted product **3l** was the major isolated product. However, some formation of double substituted product was additionally observed. Further examination of the reaction focused on variation of the heterocyclic system. Hence, performing the cross coupling of 1-chloroisoquinoline (**1f**) with phenyl- or *n*-butyl-magnesium chloride, the corresponding 2-alkyl- and 2-arylisoquinolines **3n**–**o** were obtained in satisfactory 77% and 84% yield, respectively (entry 17 and 18). Similarly, the manganese-catalyzed reaction of quinazoline, benzothiazole, purine, pyrimidine, quinoxaline, and pyridine derivatives **1g**–**l** resulted in the corresponding alkylated or arylated heterocyclic products **3p**–**v** (entry 19–25), although lower yields were obtained with the more

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electron-rich substrates. Interestingly, when comparing the manganese-catalyzed cross-coupling reactions of aryl- with alkylmagnesium chlorides, we found that the latter reactions generally proceeded more rapidly pointing to a faster transmetalation step and formation of the alkyl-manganese intermediates in the catalytic cycle.

Table 1 Manganese-Catalyzed Cross-Coupling Reaction of Various Heterocyclic Chlorides with Aryl- and Alkylmagnesium Chlorides[10]

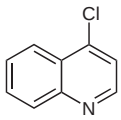
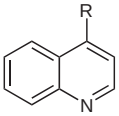
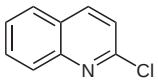
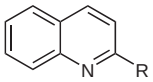
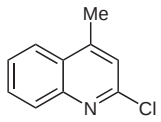
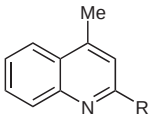
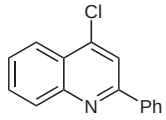
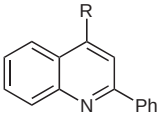
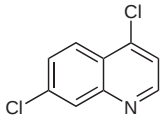
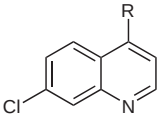
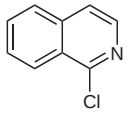
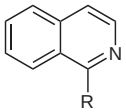
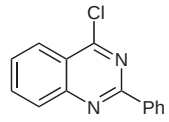
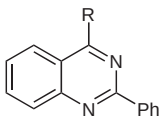
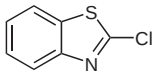
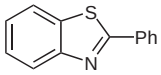
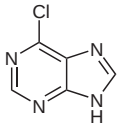
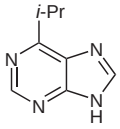
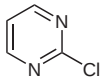
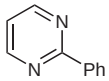
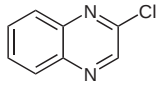
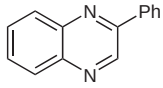
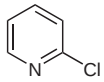
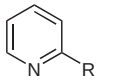
Entry	Ar–Cl	RMgCl **2** (equiv)	Catalyst amount (mol%)	Temp (°C)	Time (h)	Product **3**	Yield (%)[a]
1		PhMgCl (2) **2a**	1	0	1.5		86
2			2				91
	1a					**3a**: R = Ph	
3	**1a**	MeMgCl (2) **2b**	5	0	1.5	**3b**: R = Me	83
4	**1a**	*i*-PrMgCl (2) **2c**	1	0	1.5	**3c**: R = *i*-Pr	78
5			2				89
6	**1a**	*n*-BuMgCl (2) **2d**	5	0	1.5	**3d**: R = *n*-Bu	65
7	**1a**	*i*-BuMgCl (2) **2e**	5	0	5.0	**3e**: R = *i*-Bu	87
8		PhMgCl (2) **2a**	5	0 to r.t.	12		64
	1b					**3f**: R = Ph	
9	**1b**	*i*-PrMgCl (1.2) **2c**	5	0	1.5	**3g**: R = *i*-Pr	78
10		PhMgCl (4) **2a**	5	0 to r.t.	12		71
	1c					**3h**: R = Ph	
11	**1c**	*i*-PrMgCl (1.5) **2c**	2	0	4	**3i**: R = *i*-Pr	74
12			5				69
13		PhMgCl (4) **2a**	5	0 to r.t.	4		82
	1d					**3j**: R = Ph	
14	**1d**	*i*-PrMgCl (1.5) **2c**	2	0	4	**3k**: R = *i*-Pr	81
15		PhMgCl (2) **2a**	5	0 to r.t.	12		53
	1e					**3l**: R = Ph	
16	**1e**	*i*-PrMgCl (1.2) **2c**	5	0	2	**3m**: R = *i*-Pr	52
17		PhMgCl (4) **2a**	5	0	1.5		84
	1f					**3n**: R = Ph	
18	**1f**	*n*-BuMgCl (2) **2d**	5	0	2	**3o**: R = *n*-Bu	77

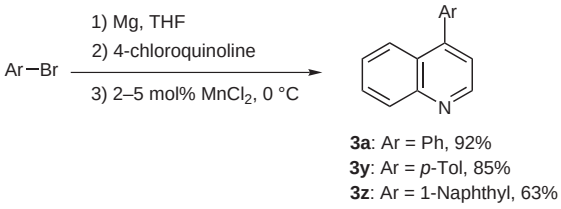
Table 1 Manganese-Catalyzed Cross-Coupling Reaction of Various Heterocyclic Chlorides with Aryl- and Alkylmagnesium Chlorides[10] (continued)

Entry	Ar–Cl	RMgCl **2** (equiv)	Catalyst amount (mol%)	Temp (°C)	Time (h)	Product **3**	Yield (%)[a]
19	 **1g**	PhMgCl (4) **2a**	5	0	1.5	 **3p**: R = Ph	71
20	**1g**	*i*-PrMgCl (2) **2c**	5	0	3	**3q**: R = *i*-Pr	50
21	 **1h**	PhMgCl (5) **2a**	5	0 to r.t.	3	 **3r**	47
22	 **1i**	*i*-PrMgCl (2.4) **2c**	5	0	2	 **3s**	46
23	 **1j**	PhMgCl (3) **2a**	5	0	3	 **3t**	40
24	 **1k**	PhMgCl (4) **2a**	5	–20	0.5	 **3u**	58
25	 **1l**	PhMgCl (2) **2a**	5	0 to r.t.	4	 **3v**	58

[a] Isolated yield after flash chromatography.

After having developed an efficient manganese-catalyzed cross-coupling reaction of aryl- and alkyl-Grignard reagents with a range of chloro-substituted heterocycles, we wondered whether it would be possible to extend this transformation to a one-pot procedure. Hence, we prepared the corresponding Grignard reagents and added subsequently a solution of 4-chloroquinoline (**1a**) and $MnCl_2$ to this mixture (Scheme 3). Following this protocol we were able to isolate the corresponding 4-substituted quinoline derivatives in good to excellent yields (63–92%).

In summary we have developed an efficient manganese-catalyzed cross-coupling reaction of a wide range of nitrogen-containing heteroaryl chlorides with aryl- as well as alkylmagnesium halides. Additionally, we were able to demonstrate that this transformation can be easily performed in a one-pot procedure to give the corresponding heterocyclic products in good to excellent isolated yields. The mild reaction conditions, the operational simplicity and practicability, as well as the low catalyst loading and the lower cost of manganese chloride, as compared to palladium or nickel salts, render this transformation an attractive alternative approach to various alkylated and arylated heterocycles.



Scheme 3 One-pot cross-coupling reaction of 4-chloroquinoline with aryl-Grignard reagents

Acknowledgment

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(9) For the reactions reported commercially available $MnCl_2$ salts were applied. $MnCl_2$ anhyd (Aldrich 99.999%), $MnCl_2 \cdot 4H_2O$ (Strem 99.999%) and $MnCl_2$ (Aldrich 98%) gave the same results in the cross-coupling reactions.
(10) **Typical Procedure: Preparation of 4-Isopropyl-2-phenylquinoline (3k).**
A two-necked round-bottomed flask was charged under Ar with 4-chloro-2-phenylquinoline (0.2397 g, 1.00 mmol), $MnCl_2$ (6.3 mg, 50 μmol) and THF (5mL) and cooled to 0 °C. The Grignard reagent *i*-PrMgCl (1.25 mL, 1.20 M in THF, 1.50 mmol) was added slowly via a syringe and the reaction mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched with sat. NH_4Cl (5 mL) and H_2O (5 mL) at 0 °C, extracted with EtOAc (3 × 25 mL), and dried over $Mg(SO_4)$. After removal of solvents in vacuo, the crude product was purified by column chromatography (hexane–EtOAc, 50:1) to give the product as a pale yellow oil (0.1887 g, 81%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 8.10–8.02 (m, 2 H, Ar*H*), 7.99 (d, *J* = 8.3 Hz, 1 H, Ar*H*), 7.68 (s, 1 H, Ar*H*), 7.64–7.55 (m, 1 H, Ar*H*), 7.47–7.32 (m, 4 H, Ar*H*), 3.68 [sept, *J* = 6.8 Hz, 1 H, $CH(CH_3)_2$], 1.35 [d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$]. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 157.4 (C), 155.0 (C), 148.6 (C), 140.3 (C), 130.7 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 127.7 (CH), 126.0 (CH), 125.9 (C), 123.0 (CH), 115.0 (CH), 28.6 (CH), 23.1 (CH_3). IR (neat): ν = 3061 (m), 2865 (s), 2930 (m), 2871 (w), 1596 (s), 1551 (s), 1508 (m), 1494 (s), 1460 (m), 1445 (m), 1414 (w), 1385 (m), 1364 (w), 1347 (s), 1234 (w), 1181 (w), 1071 (w), 1029 (w), 907 (w), 879 (m), 838 (w), 792 (m), 770 (s), 694 (s) cm^{-1}. ESI-MS: *m/z* = 248 $[M + H]^+$. Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.59; H, 7.04; N, 5.45.
Preparation of 4-(*p*-Tolyl)quinoline (3y).
A two-necked round-bottomed flask, equipped with a reflux condenser and dropping funnel, was charged with Mg (63.2 mg, 2.60 mmol) and THF (8 mL) under Ar and a solution of *p*-bromotoluene (0.4276 g, 2.50 mmol) in THF (5 mL) was added dropwise (15 min). Subsequently, the reaction mixture was refluxed for 1 h and cooled to 0 °C. A solution of 4-chloroquinoline (0.1636 g, 1.00 mmol) in THF (3 mL) was added via syringe to the reaction mixture and $MnCl_2$ (2.5 mg, 20 μmol) was quickly added. The resulting solution was stirred at 0 °C for 2 h, quenched with sat. NH_4Cl (5 mL) and H_2O (5 mL) at 0 °C, extracted with EtOAc (3 × 25 mL), and dried over $Mg(SO_4)$. After removal of solvents in vacuo, the crude product was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to provide the product as a pale yellow oil (0.1857 g, 85%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 8.79 (d, *J* = 4.5 Hz, 1 H, Ar*H*), 7.81 (d, *J* = 8.3 Hz, 1 H, Ar*H*), 7.61–7.78 (m, 1 H, Ar*H*), 7.37–7.28 (m, 1 H, Ar*H*), 7.28–7.14 (m, 5 H, Ar*H*), 2.31 (s, 3 H, CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 150.0 (CH), 148.8 (C), 148.5 (C), 138.4 (C), 135.1 (C), 129.9 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 126.9 (C), 126.5 (CH), 126.0 (CH), 121.3 (CH), 21.3 (CH_3). IR (neat): ν = 3027 (m), 2920 (m), 1614 (m), 1586 (s), 1569 (s), 1501 (s), 1459 (w), 1421 (m), 1389 (m), 1275 (w), 1112 (w), 1021 (w), 872 (w), 819 (s), 765 (s), 721 (w), 674 (m), 661 (w) cm^{-1}. ESI-MS: *m/z* = 220 $[M + H]^+$. Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.53; H, 6.15; N, 6.29.