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Iron-catalysed arylation of heteroaryl halides by Grignard reagents

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Abstract—Cross-coupling reaction of phenylmagnesium bromide with heteroaryl halides, in the presence of a catalytic amount of iron salts, is reported. Yields are moderate to good, and it is worth noting that this reaction has been applied to non-activate heteroaryl halides.

Several 2-alkyl-, 2-alkenyl-, and 2-phenylquinolines, the chimanines have been isolated from a Bolivian plant, *Galipea longiflora*,[1] and have shown very promising in vitro activity against several leishmania strains.[2] Few of them have shown in vivo, through oral administration, leismanicide properties.[3] Activity against *Plasmodium vinckei petteri* was also observed for some of them.[4] We have been involved in establishing a structure–activity relationship based on the nature of the chain branched at the 2 position of quinoline, and recently reported the cross-coupling reactions between multicomponent Grignard reagents with *N*-oxycarbonylisobutyloxyquinolinium chloride at low temperature to afford the desired 2-alkylquinolines in good yields.[5] Next we reported the iron-catalysed Grignard reduction-coupling reactions of 1,1-dibromo-2-(2-quinolyl)ethylene to afford 2-alkenyl quinolines.[6] To study the influence of the substitution position on the quinoline nucleus we prepared 3-phenylquinoline **2a** in 35% yield by coupling reaction of phenyl Grignard with 3-bromoquinoline **1a** in the presence of 5% M $Fe(acac)_3$.[7] It is worth noting that this was the first reported coupling reaction between a heteroaryl bromide and a Grignard reagent catalysed by an iron salt.[8]

Then Fürstner very recently reported the iron-catalysed reaction of alkyl-Grignard reagents with aryl chlorides,[9] and this prompted us to disclose our own results in this area. The aryl–aryl cross-coupling reaction is an extremely important reaction, and is usually catalysed by palladium or nickel complexes.[10] The use of cheap, non-toxic iron salts is particularly attractive in this field. Since our first report on the preparation of 3-phenylquinoline **2a** by coupling reaction between phenyl-Grignard and 3-bromoquinoline **1a** in the presence of $Fe(acac)_3$, in a 1:1 mixture of THF/NMP, we have re-examined the reaction conditions in order to improve the yield, and the results are summarised in Table 1. We first studied the influence of the solvent on the coupling of 2.2 equiv. of phenylmagnesium bromide to 3-bromoquinoline **1a** in the presence of 10% M $Fe(acac)_3$, and found that mixing more polar solvents (entries 1–6) or less polar solvents (entries 7 and 8) into the THF solution of **1a** did not allow us to increase the yield of 3-phenylquinoline **2a**, compared to the reaction run in THF alone (entry 9). This finding highlighted that this coupling reaction can be performed in THF alone (contrary to precedent reports[6,8,9]). Addition of NMP or other co-solvents, did not improve the yield but had a negative effect on the cross-coupling reaction. Then we checked the temperature effect (entries 9–14) and found that the best result (46%) was obtained at −30°C in 1 h. The remaining mass balance was composed of the starting material **1a** (16%) and the reduced quinoline **3a** (33%) (Scheme 1). After a prolonged reaction time (e.g. 3 or 20 h) the yield did not increase significantly, and adding some more catalyst during the reaction did not improve the result (results not shown). Finally, the desired 3-phenylquinoline **2a** was obtained after purification by flash chromatography on silica gel in 45% isolated yield[11] after 1 h at −30°C. When DMPU was used in equimolar quantity with **1a**, the yield was similar to the yield in THF alone (48%, entry 16, compare with entry 9). With only 1 equiv. of NMP, the yield decreased (29%, entry 15). We then tried to

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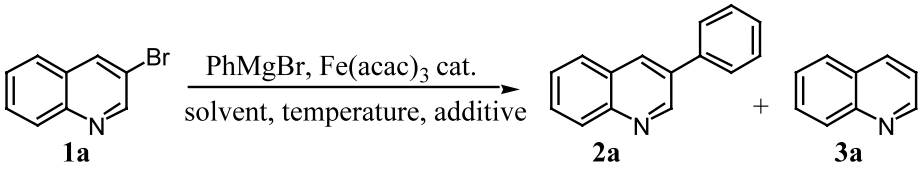
Table 1. Addition of 2 equiv. of PhMgBr to 3-bromoquinoline **1a** to afford 3-phenylquinoline **2a**

Entry	Cat. (10%)	Solvent	Additive (equiv.)	Temp. (°C)	Yield[a] (**2a**)	**1a**/**3a**
1	$Fe(acac)_3$	THF/NMP	None	−10	35[b]	ND
2	$Fe(acac)_3$	THF/TMEDA	None	−30	29	38/25
3	$Fe(acac)_3$	THF/sulfolane	None	−30	36	30/24
4	$Fe(acac)_3$	THF/dioxane	None	−30	29	51/15
5	$Fe(acac)_3$	THF/DMSO	None	−30	8	61/20
6	$Fe(acac)_3$	THF/DMPU	None	−30	13	63/24
7	$Fe(acac)_3$	Et_2O	None	−30	8	37/8
8	$Fe(acac)_3$	THF/toluene	None	−30	16	50/15
9	$Fe(acac)_3$	THF	None	−30	46 [45][b]	16/33
10	$Fe(acac)_3$	THF	None	−20	37	24/26
11	$Fe(acac)_3$	THF	None	−10	32	30/23
12	$Fe(acac)_3$	THF	None	0	32	16/30
13	$Fe(acac)_3$	THF	None	Rt	34	1/38
14	$Fe(acac)_3$	THF	None	−78	41	3/40
15	$Fe(acac)_3$	THF	NMP (1)	−30	29	49/19
16	$Fe(acac)_3$	THF	DMPU (1)	−30	48	18/42
17	$Fe(acac)_3$	THF	CH_3CN (1)	−30	16	26/43
18	$Fe(acac)_3$	THF	Bipyr (0.1)	−30	40	10/50
19	$Fe(acac)_3$	THF	Bipyr (0.3)	−30	4	83/5
20	$Fe(acac)_3$	THF	Me_2S (1)	−30	47	12/41
21	$Fe(acac)_3$	THF	Ph_3P (0.5)	−30	38	35/23
22	$Fe(acac)_3$	THF	$MnCl_2$ (0.2)	−30	9	66/19
23	$Fe(acac)_3$	THF	$ZnCl_2$ (0.2)	−30	8	75/6
24	$Fe(acac)_3$	THF	CuCN (0.2)	−30	8	73/13
25	$FeCl_3$	THF	None	−30	5	72/7
26	$FeCl_2$	THF	None	−30	9	64/7
27	$Co(acac)_2$	THF	None	−30	38	25/18

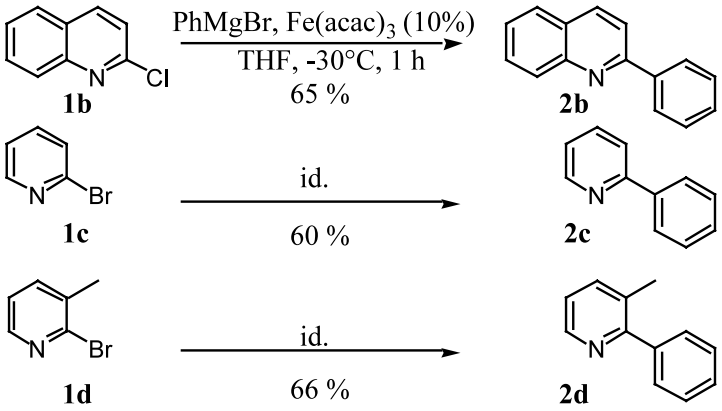
[a] GC yields % (after 1 h) with tetradecane as internal reference.
[b] Isolated yield; ND: not determined.



Scheme 1.

add some additive that could stabilise the low valent intermediate organoiron species (entries 17–21). We could never increase the yields but in the presence of either 0.1 equiv. of 2,2′-bipyridine or 1 equiv. of dimethylsulfide, **2a** was obtained in similar yields to THF alone (40 and 47% yield, respectively). Adding some co-catalyst (such as $MnCl_2$, $ZnCl_2$, CuCN) did not increase the yields but had a negative effect (entries 22–24). Surprisingly, $FeCl_3$ and $FeCl_2$ did not give the desired product in reasonable yields (entries 25 and 26). These results might be due to low solubility of these salts in THF at −30°C. However, $Co(acac)_2$ allowed us to obtain 3-phenylquinoline **2a** in 38% yield (entry 27). It is worthy of note that without any catalyst, no reaction occurred. It is interesting to note that our coupling reaction compares favourably with the nickel-catalysed reaction of heteroaryl-Grignard reagents with 3-bromoquinoline (reflux THF, 20 h, 44–57%).[12] We then applied this reaction to the cross-coupling of phenylmagnesium bromide with several heteroaryl halides (Scheme 2). When 2-chloroquinoline **1b** was treated with phenyl-Grignard in THF at −30°C for 1 h, the desired 2-phenylquinoline **2b** was obtained in 65% isolated yield.[11] Again it is interesting to note that **2b** was obtained by the palladium-catalyzed cross-coupling reaction of phenylboronic acid and 2-chloroquinoline (reflux THF, 2 h, 67%).[13] Next 2-bromopyridine **1c** was treated under the same reaction conditions, to afford 2-phenylpyridine **2c** in 60% isolated yield.[14] Finally, 3-methyl-2-bromopyridine **1d** led, under the same reaction conditions, to 3-methyl-2-phenylpyridine **2d** in 66% isolated yield.[14] In this example, it is noteworthy that *ortho* substitution on the aryl halide did not affect the yield.

In conclusion we report the first aryl–aryl cross-coupling reaction between phenyl-Grignard reagent and heteroaryl halides in the presence of iron salts with moderate to good yields. The reaction conditions are mild (THF, −30°C), which allows one to use a large variety of such organometallic species easily prepared by halogen–metal exchange.[15] Furthermore, the use of cheap and friendly iron catalysts favourably competes with nickel and palladium catalysis, and will probably



Scheme 2.

find industrial applications. We are now applying this procedure to the preparation of compounds of biological interest and the results will be reported elsewhere.

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11. 3-Phenylquinoline **2a**: ^{1}H NMR (200 MHz, δ ppm) 7.49 (m, 4H), 7.71 (m, 3H), 7.84 (d, $J=8.0$ Hz, 1H), 8.16 (d, $J=8.9$ Hz, 1H), 8.26 (d, $J=2.0$ Hz, 1H), 9.19 (d, $J=2.1$ Hz, 1H); ^{13}C NMR (50 MHz, δ ppm) 126.49, 126.89, 127.62, 128.68, 128.89, 132.62, 133.23, 137.26, 146.84, 149.33; ESI-MS (m/z) 228 ($M+Na^+$, 30), 206 (MH^+, 100); 2-phenylquinoline **2b**: ^{1}H NMR (200 MHz, δ ppm) 7.53 (m, 4H), 7.76 (m, 2H), 8.09 (d, $J=8.6$ Hz, 1H), 8.23 (m, 2H), 8.28 (d, $J=8.6$ Hz, 1H); ^{13}C NMR (50 MHz, δ ppm) 118.60, 125.96, 126.90, 127.22, 127.31, 128.57, 129.07, 129.36, 129.47, 136.44, 139.36, 148.03, 156.93; ESI-MS (m/z) 206 (MH^+, 100).
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