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Tributylmagnesium ate complex-mediated bromine–magnesium exchange of bromoquinolines: a convenient access to functionalized quinolines

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Abstract—2-, 3- and 4-bromoquinolines were converted to the corresponding lithium tri(quinolyl)magnesates at −10°C by treatment with Bu_3MgLi in THF or toluene. The resulting organomagnesium derivatives were quenched by various electrophiles to afford functionalized quinolines.

The preparation of functional heterocycles is an important synthetic goal because of the multiple applications of these molecules.[1] Among the methods developed, lithiation is convenient to allow a number of polyfunctional azines (pyridines, quinolines...) and diazines syntheses since lithiated derivatives display a high reactivity towards many electrophilic functions.[2] Nevertheless, this methodology often requires low temperatures, which can be difficult to realize on an industrial scale. Moreover, halogen–lithium exchange is very sensitive to reaction temperature,[3] particularly in the quinoline series where derivatives are more prone to nucleophilic addition due to their lower LUMO levels.

Grignard reagents are of great importance, and numerous reports for the preparation of various organomagnesium compounds through direct metalation of organic halides with metallic magnesium, deprotonation, transmetallation, or halogen–magnesium exchange have been published.[4] We have been interested in the development of quinolylmagnesium reagents via bromine–magnesium exchange that could be subsequently involved in either electrophilic trapping or coupling reactions.[5]

Since a magnesium ate complex (R_3MgLi) was first published in 1951,[6] several investigations on its structure have been reported.[7] However, synthetic applications of magnesate reagents remained unexplored until very recently.[8] In 2001, the first halogen–magnesium exchanges via organomagnesium ate complexes were published by Oshima in the benzene, pyridine and thiophene series.[8i,l] The same year, the mono-exchange of dibromobenzenes and dibromoheteroarenes (pyridine and thiophene series) was reported by Iida and Mase using lithium tributylmagnesate.[8m]

Herein, we describe the bromine–magnesium exchange of 2-, 3- and 4-bromoquinolines using lithium tributylmagnesate.

Preliminary experiments on 3-bromoquinoline showed that reagents such as isopropylmagnesium chloride, *tert*-butylmagnesium chloride, di(isopropyl)magnesium, and isopropyl(2,2,6,6-tetramethyl-piperido)magnesium[9] could not be used to generate the corresponding 3-quinolylmagnesium derivatives, as observed in the case of pyridylmagnesium derivatives.[5c,f,g,i] Due to its lower LUMO level, quinoline is more prone to nucleophilic attack: addition of the base to the quinoline ring was favored over exchange reaction. So, we turned our attention to magnesium ate complexes.

First experiments were conducted on 3-bromoquinoline using lithium tributylmagnesate in toluene at −10°C, as described for the bromine–magnesium exchange of 2,6-dibromopyridine.[8m] Trapping the corresponding lithium tri(quinolyl)magnesate with benzaldehyde, dimethylformamide, iodine and diphenyl disulfide afforded alcohol **1a**,[3d] aldehyde **1b**,[10] iodide **1c**[11] and sulfide **1d**,[12] in medium to good yields (Scheme 1).

Keywords: quinoline; Grignard reagents; exchange reaction; ate complexes.

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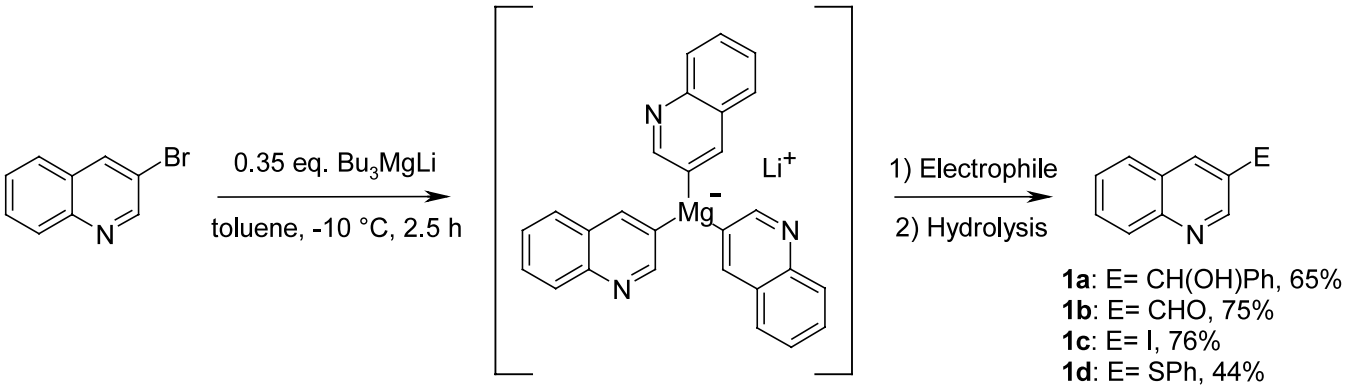


Scheme 1.

Note that the yields largely depend on the amount of magnesate used: 0% of **1a** with 1 equiv. of Bu_3MgLi, 5–10% with 0.66 equiv. and 65% with 0.35 equiv.! Butylated products obtained in the first and second cases could be formed through addition of the residual butylmagnesium species to the quinoline ring.

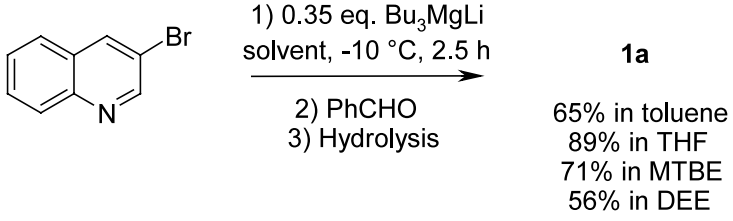
Since the main by-product is quinoline, the yields seem to depend on the trapping step with the electrophiles. Various polar solvents, such as tetrahydrofuran (THF), methyl-*tert*-butyl ether (MTBE) and diethyl ether (DEE), were then tested in order to optimize the reaction. THF was found to be the best solvent when benzaldehyde was used (Scheme 2).

The bromine–magnesium exchange reaction was then applied to 2-bromoquinoline[13] using THF as a solvent, under the same conditions. Reaction with benzaldehyde provided the alcohol **2a**[14] in 39% yield, the remaining 61% being a mixture of butylated quinolines, 2-bromoquinoline and 2,2′-biquinoline. In the case of enolizable 3-pentanone, a moderate yield of alcohol **2b**[15] was obtained. Trapping with iodine and diphenyl disulfide afforded iodide **2c**[16] and sulfide **2d**,[12] in low to medium yields (Scheme 3).

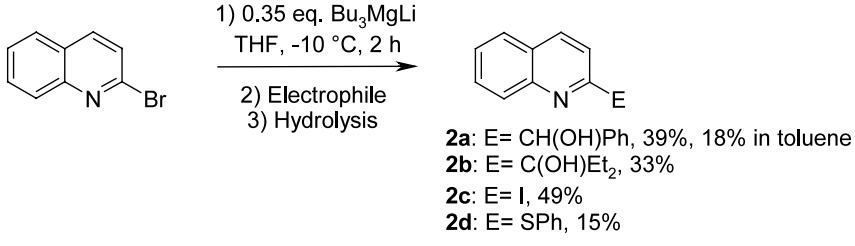
As previously observed in the pyridine series,[5i,8i,l,m] the bromine–magnesium exchange at C2 of the quinoline ring seems to be more difficult than the reaction at C3. Moreover, the lithium tri(2-quinolyl)magnesate could be less reactive than its 3-quinolyl analogue since the yields observed increase with the reactivity of the electrophile.

Bromine–magnesium exchange reaction was likewise observed with 4-bromoquinoline,[13] and the magnesate formed could be intercepted to produce the expected alcohol **3a**,[17] iodide **3b**,[11] sulfide **3c**[18] and carboxylic acid **3d**[10] in medium yields (Scheme 4).

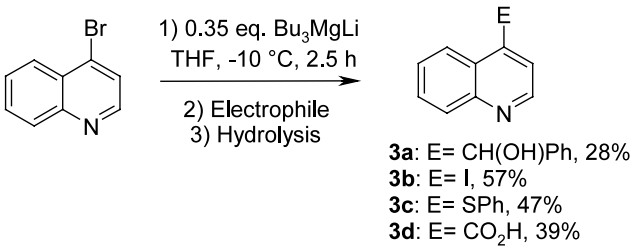
In conclusion, 2-, 3- and 4-substituted quinolines could be prepared from the corresponding bromo derivatives by bromine–magnesium exchange reaction. The main advantage of this methodology is the relative stability of these organometallic species: bromine–lithium exchange has to be performed at low temperature in



Scheme 2.



Scheme 3.



Scheme 4.

order to prevent side reactions while bromine–magnesium exchange proceeds at −10°C. Cross-coupling reactions involving the lithium tri(quinolyl)magnesates are currently underway.

Bromine–magnesium exchange; typical procedure: BuLi (1.6 M in hexanes, 1.3 mmol) was added to a solution of BuMgCl (2.0 M in ether, 0.65 mmol) in toluene (2 mL) at −10°C. After stirring for 1 h at −10°C, a solution of 3-bromoquinoline (0.23 mL, 1.7 mmol) in toluene (2 mL) was introduced at −30°C. After 2.5 h at −10°C, benzaldehyde (0.17 mL, 1.7 mmol) and, 1 h later, water (0.5 mL) were added. Dilution with AcOEt (50 mL), drying over $MgSO_4$ and column chromatography using CH_2Cl_2/AcOEt (80:20) as an eluent afforded alcohol **1a** (65% yield).

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