

Multiple Regioselective
Functionalizations of Quinolines via
Magnesiations

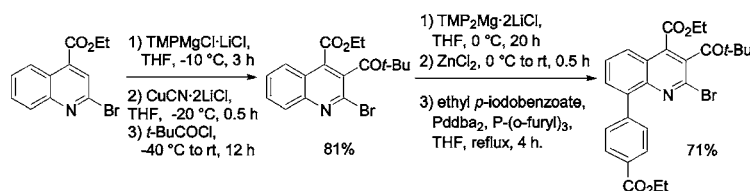
Nadège Boudet, Jennifer R. Lachs, and Paul Knochel*

Department Chemie und Biochemie, Ludwig-Maximilians-Universität, Butenandtstrasse
5-13, 81377 München, Germany

paul.knochel@cup.uni-muenchen.de

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ABSTRACT



A wide range of polyfunctionalized quinolines was prepared via chemo- and regioselective magnesiation reactions using appropriate Mg reagents, such as *i*-PrMgCl·LiCl, MesMgBr·LiCl, Mes₂Mg·2LiBr, TMPMgCl·LiCl, and TMP₂Mg·2LiCl. An application to the total synthesis of the biologically active compound talnetant was performed (six steps, 28%).

The preparation of polyfunctionalized quinolines is of great interest since this structural unit (Figure 1) is found in various

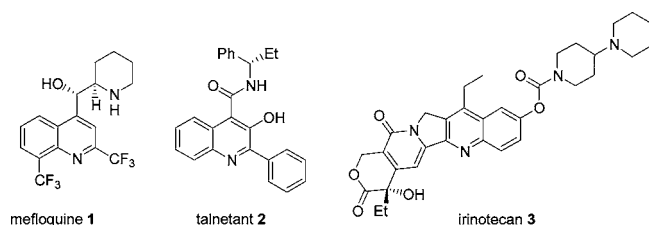


Figure 1. Drugs containing the quinoline skeleton.

drugs such as mefloquine (**1**), an antimalarial,¹ talnetant (**2**),² a potential NK3 receptor antagonist developed by GSK, or irinotecan (**3**),³ an anticancer drug, marketed by Pfizer. The

lithiation of quinolines via Br/Li exchange reactions or by using a lithium base has been reported.⁴ Mongin and Quéguiner described also Br/Mg exchange⁵ on monobrominated quinolines using Bu₃MgLi.⁶ These approaches are often complicated by a lack of regioselectivity and the propensity of lithium or magnesium reagents to undergo nucleophilic substitution at the C2 position. Recently, we have found that Br/Mg exchange reactions⁷ or the use of TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl)⁸ allows an efficient

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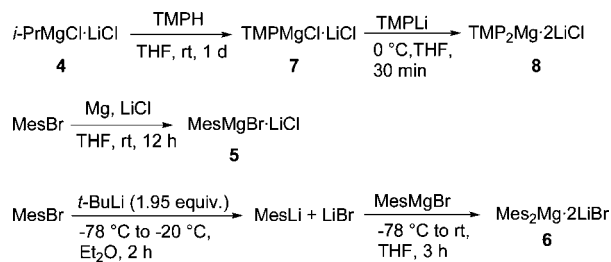
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direct magnesiation of various heterocycles. Herein, we wish to report chemo- and regioselective magnesiation of quinolines using Mg reagents (Scheme 1) such as *i*-PrMgCl·LiCl

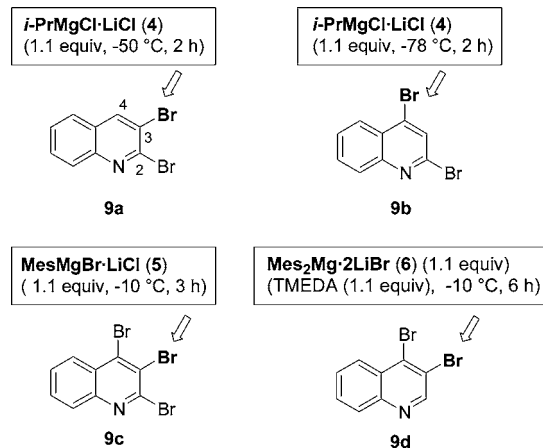
Scheme 1. Synthesis of the Magnesiation Reagents **5**, **6**, **7**, and **8**



(**4**),⁹ MesMgBr·LiCl (**5**, Mes = mesityl), Mes₂Mg·2LiBr (**6**), TMPMgCl·LiCl (**7**),⁸ and TMP₂Mg·2LiCl (**8**),¹⁰ starting from readily available polybrominated quinolines. The new Grignard reagents MesMgBr·LiCl and Mes₂Mg·2LiBr were readily prepared as indicated in Scheme 1. They proved to be highly selective for challenging Br/Mg exchanges.

Thus, the reaction of 2,3-dibromoquinoline (**9a**) with *i*-PrMgCl·LiCl (**4**, 1.1 equiv, −50 °C, 2 h, Scheme 2)

Scheme 2. Regioselective Br/Mg Exchange Reactions on Polybrominated Quinolines of Type **9**



provided quantitatively¹¹ and regioselectively¹² the corresponding 3-magnesiated 2-bromoquinoline (**10a**, Table 1). Similarly, starting from 2,4-dibromoquinoline (**9b**),¹³ the

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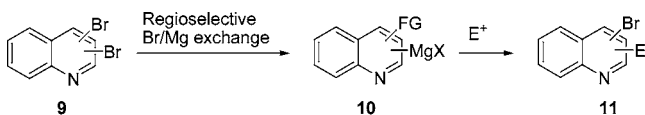
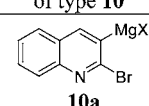
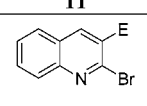
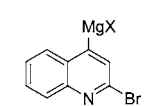
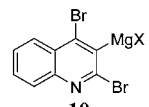

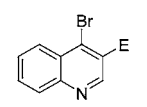
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(12) The regioselectivity of the Br/Mg exchange reaction was checked by ¹H NMR of the crude product quenched with saturated NH₄Cl (aqueous).

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Table 1. Regioselective Magnesiation via Br/Mg Exchange of Polybromoquinolines of Type **9** and Trapping with Electrophiles

				
entry	magnesium species of type 10 ^a	electrophile	product of type 11	yield (%) ^b
				
1	10a	TosCN	11a : E=CN	84
2	10a	C ₂ H ₅ CHO	11b : E=CH(OH)-C ₂ H ₅	76
3		PhSO ₂ SPh	11c : E=SPh	91
4	10b	TosCN	11d : E=CN	85
5	10b	LiHMDS; chloranil	11e : E=NH ₂	75 ^c
6		TosCN	11f : E=CN	88
7	10c	NC-CO ₂ Et	11g : E=CO ₂ Et	90
8		PhSO ₂ SMe	11h : E=SMe	79
9	10d		11i : E=	71 ^{e,f}

^a X = Cl·LiCl or Br·LiCl. ^b Isolated yield of analytically pure product.

^c Reaction performed after transmetalation with CuCl·2LiCl (1.2 equiv). ^d Ar = Mes·LiBr. ^e Reaction performed after transmetalation with ZnCl₂. ^f 2 mol % of Pddba₂ and 4 mol % of P-(*o*-furyl)₃ were added.

addition of **4** (1.1 equiv, −78 °C, 2 h) gave the corresponding 4-magnesiated 2-bromoquinoline (**10b**). In contrast, the reactions of 2,3,4-tribromoquinoline (**9c**) or 3,4-dibromoquinoline (**9d**)¹⁴ with *i*-PrMgCl·LiCl (**4**) were not selective and provided regioisomeric mixture of Grignard reagents. Related selectivity problems have been observed with dibromopyridines.^{15,16} However, using the sterically more demanding MesMgBr·LiCl (**5**, 1.1 equiv, −10 °C, 3 h), a complete regioselective magnesiation at the C3 position was observed for the 2,3,4-tribromoquinoline (**9c**), providing the corresponding intermediate **10c** (Table 1). The Grignard

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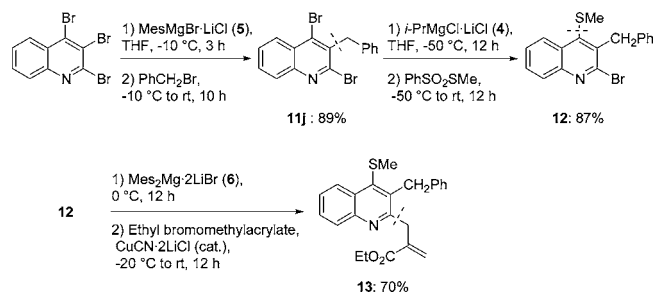
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reagent **5** was not reactive enough to perform an exchange in the case of the 3,4-dibromoquinoline (**9d**). However, by using the corresponding dimesitylmagnesium·2LiBr (1.1 equiv of **6**, 1.1 equiv of TMEDA,¹⁷ –10 °C, 6 h), a smooth regioselective magnesiation furnished the diaryl magnesium reagent **10d** (Table 1).

The Grignard compounds **10a–d** were trapped with various electrophiles as shown in Table 1. Thus, the C3-magnesiated 2-bromoquinoline **10a** was quenched with tosyl cyanide or propionaldehyde and gave 3-cyano-2-bromoquinoline (**11a**, 84%) or the corresponding alcohol (**11b**, 76%) (entries 1 and 2). Similarly, the Grignard intermediate **10b** afforded after quenching with PhSO₂SPh¹⁸ or tosyl cyanide the corresponding phenylsulfanyl quinoline (**11c**, 91%) or 4-cyano-2-bromoquinoline (**11d**, 85%) (entries 3 and 4). Interestingly, the transmetalation of the C4-magnesiated 2-bromoquinoline **10b** using CuCl·2LiCl (1.2 equiv, –50 °C, 1 h) followed by the addition of LiHMDS (2 equiv, –60 °C, 1 h) provided the corresponding amidocuprate¹⁹ which was oxidized using chloranil (1.2 equiv, –78 °C, 12 h) and then deprotected with TBAF (2.0 equiv, 25 °C, 15 min) leading to the 4-amino-2-bromoquinoline (**11e**, entry 5) in 75% yield. The reaction with C4-magnesiated 2,3-dibromoquinoline (**10c**) and tosyl cyanide afforded the corresponding quinoline **11f** (88%, entry 6). The Grignard intermediate **10c** was also quenched with ethyl cyanoformate giving the quinoline ester **11g** (90%, entry 7). The C3-magnesiated 4-bromoquinoline (**10d**) provided after trapping with PhSO₂SMe²⁰ the thioether **11h** (entry 8, 79% yield). Interestingly, the diarylmagnesium reagent **10d** underwent, after transmetalation with ZnCl₂, a Pd-catalyzed Negishi cross-coupling with 4-iodobenzonitrile and furnished the coupling product (**11i**) in 71% yield (entry 9). Remarkably, multiple selective exchanges can also be performed starting with the tribromoquinoline **9c**. Thus, the reaction of MesMgBr·LiCl (**5**, 1.1 equiv, –10 °C, 3 h) with **9c** provided, after quenching with benzyl bromide, the corresponding benzy-

Scheme 3. Successive Regioselective Br/Mg Exchange Reactions at the C3, C4, and C2 Positions



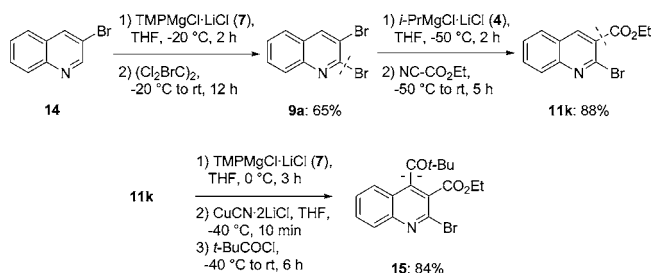
lated quinoline **11j** in 89% yield (Scheme 3). This product **11j** underwent a second Br/Mg exchange reaction using **4**

(1.1 equiv, –50 °C, 12 h) and led after quenching with PhSO₂SMe to the 3,4-functionalized 2-bromoquinoline **12** in 87% yield.

A third Br/Mg exchange was performed on **12** using Mes₂Mg·2LiBr (**6**, 1.2 equiv, 0 °C, 12 h), and a copper-catalyzed allylation with ethyl (2-bromomethyl)acrylate²¹ afforded the highly functionalized quinoline **13** in 70% yield. This last exchange reaction completed the sequence of successive functionalization at C4, C3, and C2 positions.

The direct magnesiation of quinolines using TMPMgCl·LiCl (**7**) and TMP₂Mg·2LiCl (**8**) further enhanced both the flexibility for regioselective magnesiations as well as the tolerance toward sensitive functional groups such as ketones or esters. Thus, successive magnesiations in positions C2, C3, and C4 could be achieved. Commercially available 3-bromoquinoline (**14**, Scheme 4) underwent a C2-deproto-

Scheme 4. Successive Regioselective Magnesiations at the C2, C3, and C4 Positions



nation using TMPMgCl·LiCl (**7**, 1.1 equiv, –20 °C, 2 h)⁸ and was quenched with 1,2-dibromo-1,1,2,2-tetrachloroethane, giving the 2,3-dibromoquinoline **9a** in 65% yield. The treatment of **9a** with *i*-PrMgCl·LiCl (**4**) provided, after reaction with ethyl cyanoformate, the 2-bromoquinoline-3-carboxylic acid ethyl ester **11k** in 88% yield. Addition of TMPMgCl·LiCl (**7**) to **11k** gave regioselectively the C4-magnesiated intermediate under mild conditions (0 °C, 3 h). Then, a smooth carboxylation in the presence of CuCN·2LiCl led to the quinoline **15** in 84% yield. Thus, the sequence of functionalization C2 > C3 > C4 was accomplished. The pertinent combination of Br/Mg exchanges and direct metalations allowed a regioselective functionalization of up to three new positions of the 2,4-dibromoquinoline (**9b**). Performing a Br/Mg exchange on **9b** using *i*-PrMgCl·LiCl (**4**, –78 °C, 2 h, Scheme 5) led, after reaction with ethyl cyanoformate, to the quinoline **11l** in 92% yield. Then, the regioselective deprotonation of **11l** at the C3 position using **7** (–10 °C, 3 h) followed by a copper-mediated acylation using pivaloyl chloride gave the quinoline derivative **16** in 81% yield. Remarkably, a second regioselective deprotona-

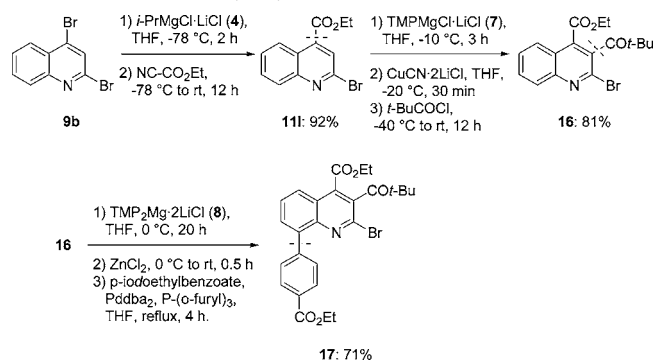
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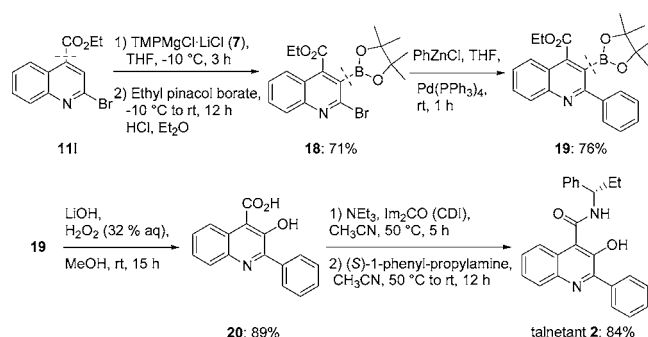
Scheme 5. Successive Regioselective Magnesiations at the C4, C3, and C8 Positions



tion on the quinoline **16** was performed at the C8 position (N-coordination), using the magnesium bisamide $\text{TMP}_2\text{Mg}\cdot\text{2LiCl}$ (**8**, Scheme 1)²² under mild conditions (0°C , 20 h). After transmetalation with ZnCl_2 , the corresponding diorganomagnesium species underwent a Pd-catalyzed Negishi cross-coupling using ethyl 4-iodobenzoate, furnishing the highly functionalized quinoline **17** in 71% yield.

As an application to our methodology, the total synthesis of talnetant **2** was performed (Scheme 6). The treatment of

Scheme 6. Successive Regioselective Functionalizations at the C4, C3, and C2 Positions



the 4-carbomethoxy-2-bromoquinoline **11** with $\text{TMPMgCl}\cdot\text{LiCl}$ (**7**, -10°C , 3 h) followed by quenching with ethyl pinacol borate²³ (1.5 equiv, -10°C to rt, 12 h) and acidic workup (1.2 equiv of HCl ²⁴ in Et_2O) furnished the corresponding pinacol boronic ester **18** in 71% yield. The Pd(0)-catalyzed

(22) $\text{TMPMgCl}\cdot\text{LiCl}$ (**7**) was found to be ineffective for this metalation.

cross-coupling of PhZnCl with **18** gave the corresponding functionalized boronic ester **19** in 76% yield. A basic oxidation using LiOH (6 equiv) and aq H_2O_2 (3 equiv) in MeOH (rt, 15 h) afforded the quinoline salicylic acid **20** in 89% yield. Treatment²⁵ of **20** with NEt_3 in acetonitrile (rt, 30 min) using CDI (1.1 equiv, 50°C , 5 h) and (*S*)-1-phenylpropylamine (1.1 equiv, 50°C to rt, 12 h) gave talnetant (**2**) in 84% yield.

By this method, we obtained a new sequence of functionalization, $\text{C4} > \text{C3} > \text{C2}$, and have found an alternative method to the Pfitzinger synthesis.²⁶

In summary, we have described various versatile regioselective functionalizations of quinolines using a combination of Br/Mg exchange reaction²⁷ and direct magnesiations. Several sensitive functionalities are tolerated such as an ester and a ketone. This approach opens a new route for the direct preparation of highly functionalized quinolines. Further extensions of this work are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via Internet at <http://pubs.acs.org>

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(27) **Typical procedure. Synthesis of 2-bromo-3-cyanoquinoline (11a).** A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 2,3-dibromoquinoline (**9a**) (1.23 g, 4.3 mmol) in dry THF (4 mL). $i\text{-PrMgCl}\cdot\text{LiCl}$ (**4**, 1.05 M in THF, 4.7 mmol, 1.1 equiv) was added slowly at -50°C , and the resulting mixture was stirred for 2 h to complete the bromine–magnesium exchange (checked by GC–MS analysis of reaction aliquots). Tosyl cyanide (1.02 g, 1.3 equiv) was then added dropwise at -50°C . The reaction mixture was warmed to rt for 12 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate ($3 \times 10 \text{ mL}$). The organic fractions were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether = 7:3) yielded 837 mg (84% yield) of **11a** as a colorless solid (mp $176.6\text{--}177.4^\circ\text{C}$).